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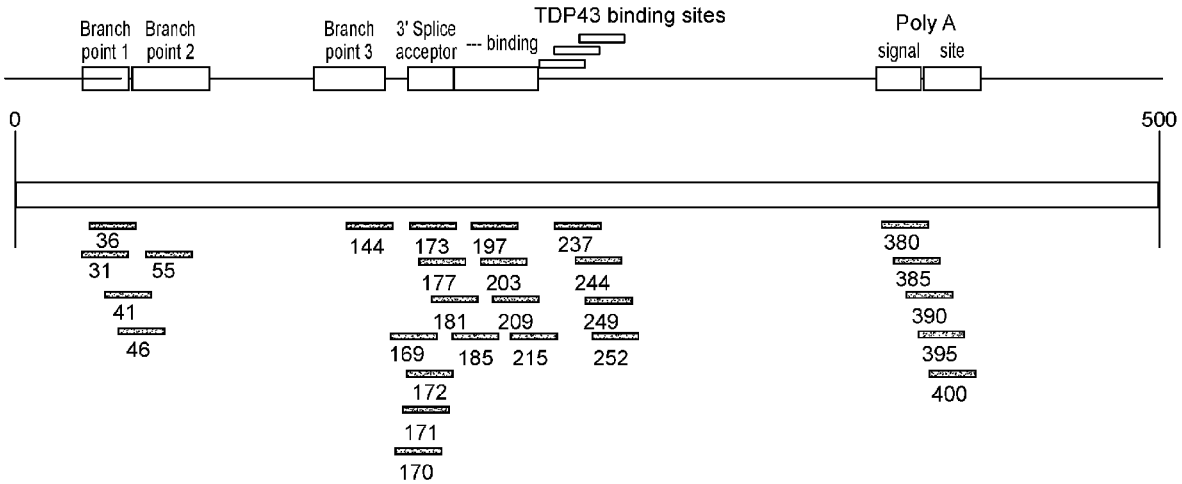

FIG. 1

(57) Abstract: Disclosed herein are oligonucleotides with one or more spacers or without a spacer. In various embodiments, STMN2, KCNQ2, UNC13A, or SMN2 oligonucleotides with spacer(s) reduce STMN2 transcripts with cryptic exons or reduce mis-spliced KCNQ2, UNC13A, or SMN2 transcripts and increase full length STMN2, KCNQ2, UNC13A, SMN transcripts, thereby imparting therapeutic efficacy against neurological diseases such as amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD) or spinal muscular atrophy (SMA).

[Continued on next page]

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SPLICE SWITCHER ANTISENSE OLIGONUCLEOTIDES WITH MODIFIED BACKBONE CHEMISTRIES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application No. 63/285,933 filed December 3, 2021, U.S. Provisional Patent Application No. 63/285,628 filed December 3, 2021, U.S. Provisional Patent Application No. 63/285,786 filed December 3, 2021, U.S. Provisional Patent Application No. 63/285,631 filed December 3, 2021, U.S. Provisional Patent Application No. 63/350,206 filed June 8, 2022, U.S. Provisional Patent Application No. 63/398,987 filed August 18, 2022, and U.S. Provisional Patent Application No. 63/398,992 filed August 18, 2022, the entire disclosure of each of which is hereby incorporated by reference in its entirety for all purposes.

BACKGROUND

[0001] Antisense oligonucleotides are nucleic acid-based compounds that can be used to inhibit expression of certain genes that are linked to diseases. Although antisense oligonucleotides can be generally designed to hybridize with target genes, conventional antisense oligonucleotides often exhibit poor efficacy. Thus, there is a need to develop modified antisense oligonucleotides that exhibit improved performance and efficacy for preventing, ameliorating, and treating diseases, examples of which include neurological diseases.

[0001] Thus, there is a pressing need to identify compounds and/or compositions capable of preventing, ameliorating, and treating neurological diseases such as: amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries (e.g., brachial plexus injuries), neuropathies (e.g., chemotherapy induced neuropathy), TDP43 proteinopathies (e.g., chronic traumatic encephalopathy, Perry Syndrome, Dementia with Lewy body in association with Alzheimer's disease, Parkinson's disease with or without dementia, and Limbic-predominant age-related TDP-43 encephalopathy (LATE)), Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, spinal muscular atrophy (SMA), and synaptic diseases like autism.

SUMMARY

[0002] Disclosed herein is a compound comprising a splice-switching oligonucleotide, and wherein the splice-switching oligonucleotide comprises a spacer. Additionally disclosed herein is a splice-switching oligonucleotide, wherein the splice-switching oligonucleotide comprises a spacer.

[0003] Additionally disclosed herein is a compound comprising a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

[0004] Additionally disclosed herein is a compound comprising a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript regulated by TDP-43, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

[0005] In various embodiments, the splice-switching oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

[0006] In various embodiments, the splice-switching oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

[0007] Additionally disclosed herein is a compound comprising a modified splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

[0008] In various embodiments, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof.

[0009] Additionally disclosed herein is a compound comprising a splice-switching oligonucleotide, wherein the splice-switching oligonucleotide comprises a spacer.

[0010] In various embodiments, the splice-switching oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease.

[0011] In various embodiments, the splice-switching oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript regulated by TDP-43, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

[0012] In various embodiments, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2. In various embodiments, the modified oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

[0013] Additionally disclosed herein is a compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

[0014] In various embodiments, the modified oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof.

[0015] Additionally disclosed herein is a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

[0016] Additionally disclosed herein is a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript regulated by TDP-43, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

[0017] In various embodiments, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one of STMN2, KCNQ2, UNC13A, or SMN2. In various embodiments, the modified oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

[0018] Additionally disclosed herein is a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one of STMN2, KCNQ2, UNC13A, or SMN2, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

[0019] In various embodiments, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

[0020] Additionally disclosed herein is a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage. In various embodiments, the oligonucleotide further comprises a spacer.

[0021] In various embodiments, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease.

[0022] In various embodiments, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript regulated by TDP-43, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

[0023] In various embodiments, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2. In various embodiments, the modified oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

[0024] Additionally disclosed herein is a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2, wherein at least one (i.e., one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

[0025] In various embodiments, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

[0026] Additionally disclosed herein is an oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

[0027] In various embodiments, the oligonucleotide comprises a segment with at most 11 linked nucleosides. In various embodiments, the oligonucleotide comprises a segment with at most 10, 9, or 8 linked nucleosides. In various embodiments, the oligonucleotide comprises a segment with at most 7 linked nucleosides. In various embodiments, the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides. In various embodiments, every segment of the oligonucleotide comprises at most 7 linked nucleosides.

[0028] In various embodiments, the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9603, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820.

[0029] In various embodiments, the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ

ID NOs: 9596-9603, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820.

[0030] In various embodiments, the oligonucleotide comprises a sequence that shares at least 95% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9603, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820.

[0031] In various embodiments, the oligonucleotide comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9603, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820.

[0032] In various embodiments, the oligonucleotide comprises a segment with at most 11 linked nucleosides or at most 7 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9603, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820. In various embodiments, the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9603, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820. In various embodiments, the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked

nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9603, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820.

[0033] In various embodiments, the oligonucleotide is at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 19 oligonucleotide units in length.

[0034] In various embodiments, the spacer is a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base. In various embodiments, the spacer is located between positions 10 and 15 of the oligonucleotide. In various embodiments, the spacer is located between positions 7 and 11 of the oligonucleotide.

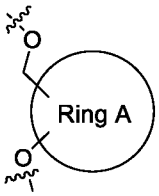
[0035] In various embodiments, the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide. In various embodiments, the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide. In various embodiments, the spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide. In various embodiments, the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide.

[0036] In various embodiments, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide. In various embodiments, the spacer is located between positions 2 and 5 of the oligonucleotide.

[0037] In various embodiments, the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides.

[0038] In various embodiments, at least two of the three spacers are adjacent to a guanine nucleobase. In various embodiments, each of the at least two of the three spacers immediately precede a guanine nucleobase. In various embodiments, each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal, hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

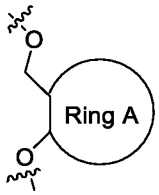
[0039] In various embodiments, each of the first, second or third spacers is independently represented by Formula (X), wherein:



Formula (X)

Ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group or a 4-8 member monocyclic heterocyclyl group, wherein the heterocyclyl group contains 1 or 2 heteroatoms selected from O, S and N, provided that A is not capable of forming a covalent bond to a nucleobase; and the symbol represents the point of connection to an internucleoside linkage.

[0040] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Xa), wherein:

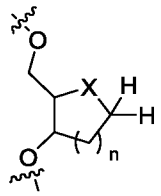


Formula (Xa).

[0041] In various embodiments, ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

[0042] In various embodiments, ring A is tetrahydrofuranyl. In various embodiments, ring A is tetrahydropyranyl.

[0043] In various embodiments, each of the first, second or third spacers is independently represented by Formula I, wherein:

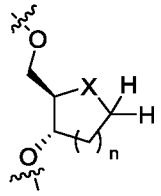


Formula (I)

X is selected from -CH_2- and -O-; and

n is 0, 1, 2 or 3.

[0044] In various embodiments, each of the first, second or third spacers is independently represented by Formula I', wherein:

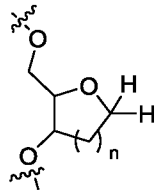


Formula (I')

X is selected from -CH_2- and -O-; and

n is 0, 1, 2 or 3.

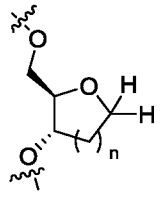
[0045] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

n is 0, 1, 2 or 3.

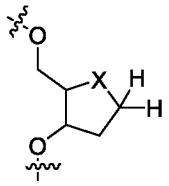
[0046] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia'); and

n is 0, 1, 2 or 3.

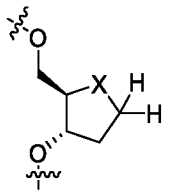
[0047] In various embodiments, each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

X is selected from -CH_2- and -O-.

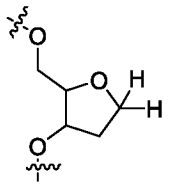
[0048] In various embodiments, each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

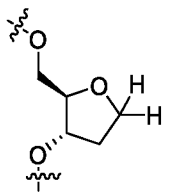
X is selected from -CH_2- and -O-.

[0049] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Iia), wherein:



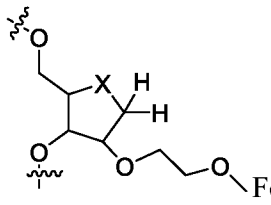
Formula (Iia).

[0050] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Iia'), wherein:



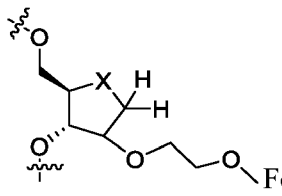
Formula (Iia').

[0051] In some embodiments, the spacer is represented by Formula (IIi), wherein:


Formula (IIi)

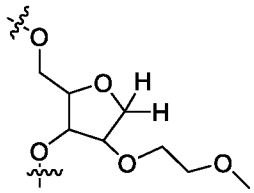
X is selected from -CH_2- and -O-.

[0052] In some embodiments, the spacer is represented by Formula (IIi'), wherein:

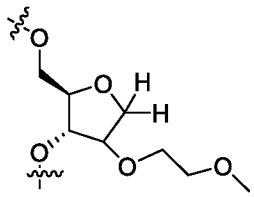

Formula (IIi')

X is selected from -CH_2-and -O.

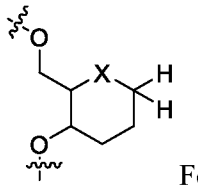
[0053] In some embodiments, the spacer is represented by Formula (IIib), wherein:


Formula (IIib).

[0054] In some embodiments, the spacer is represented by Formula (Iiib'), wherein:

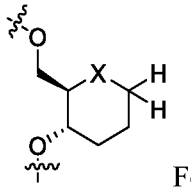

Formula (IIib').

[0055] In various embodiments, each of the first, second or third spacers is independently represented by Formula III, wherein:


Formula (III); and

X is selected from -CH_2- and -O-.

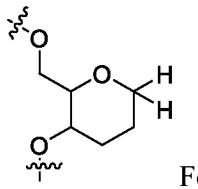
[0056] In various embodiments, each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

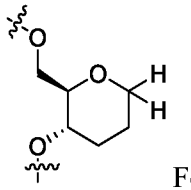
X is selected from -CH_2- and -O-.

[0057] In various embodiments, each of the first, second or third spacers is independently represented by Formula (IIIa), wherein:



Formula (IIIa).

[0058] In various embodiments, each of the first, second or third spacers is independently represented by Formula (IIIa'), wherein:



Formula (IIIa').

[0059] In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 10%. In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 20%. In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 25%. In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 30%. In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 40%. In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 50%. In various embodiments, the oligonucleotide is between 12 and 40 oligonucleotide units in length.

[0060] In various embodiments, at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a

methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[0061] In various embodiments, one or more nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages. In various embodiments, only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage. In various embodiments, nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages. In various embodiments, one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds. In various embodiments, only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond. In various embodiments, the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond.

[0062] In various embodiments, the oligonucleotide comprises a second spacer, wherein a base immediately preceding the second spacer is linked to a further preceding base through a phosphodiester bond. In various embodiments, one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds. In various embodiments, only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond. In various embodiments, two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds.

[0063] In various embodiments, one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the spacer in the oligonucleotide are linked through phosphodiester bonds. In various embodiments, one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds.

[0064] In various embodiments, the oligonucleotide includes a second spacer, and wherein one or more bases immediately preceding the second spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer in the oligonucleotide are linked through phosphodiester bonds. In various embodiments, one

base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.

[0065] In various embodiments, the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases. In various embodiments, the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases. In various embodiments, the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

[0066] In various embodiments, one or more internucleoside linkage of the oligonucleotide is a modified internucleoside linkage. In various embodiments, the modified internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. In various embodiments, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages. In various embodiments, the phosphorothioate linkage is in one of a *R*p configuration or a *S*p configuration.

[0067] In various embodiments, the oligonucleotide comprises at least one modified sugar moiety. In various embodiments, the modified sugar moiety is one of a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'-MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

[0068] In various embodiments, the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length STMN2, KCNQ2, UNC13A, or SMN2 protein. In various embodiments, the oligonucleotide exhibits at least a 100% increase of full length protein. In various embodiments, the oligonucleotide exhibits at least a 200% increase of full length protein. In various embodiments, the oligonucleotide exhibits at least a 300% increase of full length protein. In various embodiments, the oligonucleotide exhibits at least a 400% increase of full length protein.

[0069] In various embodiments, increase of the full length protein is measured in comparison to a reduced level of full length protein achieved using a TDP43 antisense oligonucleotide. In various embodiments, the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length protein. In various embodiments, the oligonucleotide exhibits at least a 50%, 60%, 70%, 80%, or 90% reduction of a mis-spliced transcript.

[0070] Additionally disclosed herein is a method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to the patient a compound or an oligonucleotide as disclosed herein.

[0071] In various embodiments, the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, tuberous sclerosis complex, Pick's Disease, tauopathies, primary age-related tauopathy, Down Syndrome, epilepsy/seizure disorder, depression, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), HIV-associated neurocognitive disorders (HAND), multisystem atrophy, amnestic mild cognitive impairment, corticobasal degeneration (CBD) and/or neuropathies such a chemotherapy induced neuropathy, Spinocerebellar ataxia (SCA), SCA type 2, Spinal Muscular Atrophy (SMA), Parkinsonism, Niemann-Pick disease type C (NPC), Charcot-Marie-Tooth Disease (CMT), Mucopolysaccharidosis type II (MPSIIA), Mucolipidosis IV, GM1 gangliosidosis, Sporadic inclusion body myositis (sIBM), Henoch-Schonlein purpura (HSP), Limbic-predominant age-related TDP-43 encephalopathy (LATE)), Cerebral Age-Related TDP-43 With Sclerosis (CARTS), Gaucher's disease, and facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, Perry disease, and synaptic diseases like autism. In various embodiments, the neurological disease is ALS. In various embodiments, the neurological disease is FTD. In various embodiments, the neurological disease is ALS with FTD. In various embodiments, the neurological disease is AD. In various embodiments, the neurological disease is PD. In various embodiments, the neurological disease is spinal muscular atrophy (SMA). In various embodiments, the neuropathy is chemotherapy induced neuropathy.

[0072] Additionally disclosed herein is a method of restoring axonal outgrowth and/or regeneration of a neuron, the method comprising exposing the neuron to a compound or an oligonucleotide as disclosed herein.

[0073] Additionally disclosed herein is a method of increasing, promoting, stabilizing, or maintaining any one of STMN2, KCNQ2, UNC13A, or SMN2 expression and/or function in a neuron, the method comprising exposing the cell to a compound or an oligonucleotide as disclosed herein. In various embodiments, the neuron is a motor neuron. In various embodiments, the neuron is a spinal cord neuron. In various embodiments, the neuron is a

neuron of a patient in need of treatment of a neurological disease and/or a neuropathy. In various embodiments, the neuropathy is chemotherapy induced neuropathy. In various embodiments, the exposing is performed *in vivo* or *ex vivo*. In various embodiments, the exposing comprises administering the oligonucleotide to a patient in need thereof.

[0074] In various embodiments, the oligonucleotide is administered topically, parenterally, intrathecally, intrathalamically, intracisternally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, intraduodenally, or intracerebroventricularly. In various embodiments, the oligonucleotide is administered orally. In various embodiments, a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically, intracerebroventricularly, or intracisternally. In various embodiments, the patient is a human.

[0075] Additionally disclosed herein is a pharmaceutical composition comprising the oligonucleotide disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0076] In various embodiments, the pharmaceutical composition is suitable for topical, intrathecal, intrathalamic, intracisternal, intracerebroventricular, parenteral, oral, pulmonary, intratracheal, intranasal, transdermal, rectal, buccal, sublingual, vaginal, or intraduodenal administration.

[0077] Additionally disclosed herein is a method of treating a neurological disease or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition disclosed herein.

[0078] In various embodiments, the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, tuberous sclerosis complex, Pick's Disease, tauopathies, primary age-related tauopathy, Down Syndrome, epilepsy/seizure disorder, depression, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), HIV-associated neurocognitive disorders (HAND), multisystem atrophy, amnestic mild cognitive impairment, corticobasal degeneration (CBD) and/or neuropathies such a chemotherapy induced neuropathy, Spinocerebellar ataxia (SCA), SCA type 2, Spinal Muscular Atrophy (SMA), Parkinsonism, Niemann-Pick disease type C (NPC), Charcot-Marie-Tooth Disease (CMT), Mucopolysaccharidosis type II (MPSIIA), Mucolipidosis IV, GM1

gangliosidosis, Sporadic inclusion body myositis (sIBM), Henoch-Schonlein purpura (HSP), Limbic-predominant age-related TDP-43 encephalopathy (LATE)), Cerebral Age-Related TDP-43 With Sclerosis (CARTS), Gaucher's disease, and facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, Perry disease, and synaptic diseases like autism.

[0079] In various embodiments, the neurological disease is ALS. In various embodiments, the neurological disease is FTD. In various embodiments, the neurological disease is ALS with FTD. In various embodiments, the neurological disease is AD. In various embodiments, the neurological disease is PD. In various embodiments, the neurological disease is spinal muscular atrophy (SMA). In various embodiments, the neuropathy is chemotherapy induced neuropathy.

[0080] In various embodiments, the pharmaceutical composition is administered topically, parenterally, orally, pulmonarily, rectally, buccally, sublingually, vaginally, intratracheally, intranasally, intracisternally, intrathecally, intrathalamically, transdermally, intraduodenally, or intracerebroventricularly. In various embodiments, the pharmaceutical composition is administered intrathecally, intrathalamically, or intracisternally. In various embodiments, a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally. In various embodiments, the patient is human.

[0081] Additionally disclosed herein is a method for treating a neurological disease in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein the oligonucleotide is at least 85% complementary to an equal length portion of a sequence from a transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

[0082] Additionally disclosed herein is a method for treating a neurological disease in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide is at least 85% complementary to a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

[0083] Additionally disclosed herein is a method for treating a neurological disease in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at

least 85% identity with any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9603, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

[0084] Additionally disclosed herein is a method for treating amyotrophic lateral sclerosis (ALS) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, or SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, or SEQ ID NOs; 9596-9603, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

[0085] Additionally disclosed herein is a method for treating Alzheimer's Disease (AD) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, or SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, or SEQ ID NOs; 9596-9603, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a

thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally, wherein the oligonucleotide further comprises a spacer

[0086] Additionally disclosed herein is a method for treating frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, or SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, or SEQ ID NOs; 9596-9603, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic

acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

[0087] Additionally disclosed herein is a method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, or SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, or SEQ ID NOs; 9596-9603, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

[0088] In various embodiments, nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages. In various embodiments, only one nucleoside

linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage. In various embodiments, nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages. In various embodiments, one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds. In various embodiments, only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond. In various embodiments, the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond. In various embodiments, the oligonucleotide comprises a second spacer, wherein a base immediately preceding the second spacer is linked to a further preceding base through a phosphodiester bond. In various embodiments, one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds. In various embodiments, only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond. In various embodiments, two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds. In various embodiments, one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the spacer in the oligonucleotide are linked through phosphodiester bonds. In various embodiments, one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds. In various embodiments, the oligonucleotide includes a second spacer, and wherein one or more bases immediately preceding the second spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer in the oligonucleotide are linked through phosphodiester bonds. In various embodiments, one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.

[0089] In various embodiments, the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases. In various embodiments, the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases. In various embodiments, the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

[0090] In various embodiments, the oligonucleotide is any one of a 19mer, 21mer, 23mer, or 25mer.

[0091] In various embodiments, at least one (*i.e.*, one or more) internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. In various embodiments, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

[0092] Additionally disclosed herein is an oligonucleotide and a pharmaceutically acceptable excipient, the oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707., a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, optionally wherein the oligonucleotide comprises a spacer and wherein the oligonucleotide is capable of increasing, restoring, or stabilizing expression of one or more of STMN2, KCNQ2, or UNC13A mRNA capable of translation of a functional protein in a cell or a human patient of an immune-mediated demyelinating disease, and wherein the level of increase, restoration, or stabilization of expression and/or activity and/or function is sufficient for use of the oligonucleotide as a medicament for the treatment of the immune-mediated demyelinating disease.

[0093] In various embodiments, the pharmaceutical composition disclosed herein, or the oligonucleotide disclosed herein, wherein the oligonucleotide comprises one or more chiral centers and/or double bonds.

[0094] In various embodiments, the pharmaceutical composition disclosed herein, or the oligonucleotide disclosed herein, wherein the oligonucleotide exist as stereoisomers selected from geometric isomers, enantiomers, and diastereomers.

[0095] Additionally disclosed herein is a method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition, in combination with a second therapeutic agent.

[0096] In various embodiments, the second therapeutic agent is selected from Riluzole (Rilutek), PrimeC, Edaravone (Radicava), rivastigmine, donepezil, galantamine, selective serotonin reuptake inhibitor, antipsychotic agents, cholinesterase inhibitors, memantine, benzodiazepine antianxiety drugs, AMX0035 (ELYBRIO), ZILUCOPLAN (RA101495), pridopidine, dual AON intrathecal administration (*e.g.*, BIIB067, BIIB078, and BIIB105), BIIB100, levodopa/carbidopa, dopaminergic agents (*e.g.*, ropinirole, pramipexole, rotigotine), medroxyprogesetrone, KCNQ2/KCNQ3 openers (e.g., retigabine, XEN1101, or QRL-101), bioactive scaffolds, anticonvulsants and psychostimulant agents, a therapy (*e.g.*, selected from breathing care, physical therapy, occupational therapy, speech therapy, nutritional support), deep

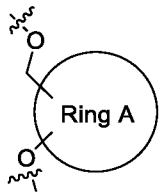
brain stimulation, levodopa and carbidopa (duopa, rytary, Sinemet, inbrija), istradefylline (nourianz), safinamide (xadago), pramipexole (Mirapex), rotigotine (neupro), ropinirole (requip), amantadine (gocovri, Symmetrel, osmolex), benztropine (Cogentin), trihexyphenidyl (artane), selegiline (eldepryl, zelapar), rasagiline, entacapone (comtan), opicapone (ongentys), tolcapone (tasmar), apomorphine (apokyn, kynmobi), exenatide, lingzhi, BIIB054, BIIB094, Caffeine, sarizotan, embryonic dopamine cell implantation, aducanamab (Aduhlem), memantine (Namenda), Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (razadyne), Namzeric, Suvorexant (belsomra), lecanemab, olanzapine (Zyprexa), quetiapine (Seroquel), SSRIs (citalopram (Cipramil), dapoxetine (Priligy), escitalopram (Cipralex), fluoxetine (Prozac or Oxactin), fluvoxamine (Faverin), paroxetine (Seroxat), sertraline (Lustral), vortioxetine (Brintellix)), divalproex sodium (Depakote), carbamazepine (Tegretol), medroxyprogestrone, Brivaracetam (briviact), cannabidiol (epidiolex), carbamazepine (carbatrol, Tegretol), cenobamate (xcopri), diazepam (valium), lorazepam (Ativan), clonazepam (klonopin), eslicarbazepine (aptiom), ethosuximide (zarontin), felbamate (felbatol), fenfluramine (fintepla), lacosamide (VIMPAT), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (oxtellar xr, Trileptal), perampanel (fycompa), phenobarbital, phenytoin (dilantin), pregabalin (lyrica), tiagabine (gabitril), topiramate (topamax), valproate (depakene, depakote), and/or zonisamide (zonegran), for treating said neurologic disease.

[0097] Additionally disclosed herein is a method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition, wherein at least one nucleoside linkage of the oligonucleotide is a non-natural linkage, optionally wherein the oligonucleotide comprises a spacer, and wherein the oligonucleotide further comprises a targeting or conjugate moiety selected from cholesterol, lipoic acid, panthothenic acid, polyethylene glycol, and an antibody for crossing the blood brain barrier.

[0098] In various embodiments, the spacer is a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base. In various embodiments, the spacer is located between positions 10 and 15 of the oligonucleotide. In various embodiments, the spacer is located between positions 7 and 11 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide. In various embodiments, the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide. In various embodiments, the spacer is located between

positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide. In various embodiments, the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide. In various embodiments, the spacer is located between positions 2 and 5 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides. In various embodiments, at least two of the three spacers are adjacent to a guanine nucleobase. In various embodiments, each of the at least two of the three spacers immediately precede a guanine nucleobase. In various embodiments, each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal, hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

[0099] In various embodiments, each of the first, second or third spacers is independently represented by Formula (X), wherein:

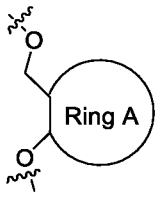


Formula (X)

Ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group or a 4-8 member monocyclic heterocyclyl group, wherein the heterocyclyl group contains 1 or 2 heteroatoms selected from O, S and N, provided that A is not capable of forming a covalent bond to a nucleobase; and

the symbol represents the point of connection to an internucleoside linkage.

[00100] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Xa), wherein:

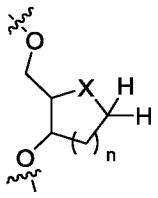


Formula (Xa).

[00101] In various embodiments, ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

[00102] In various embodiments, ring A is tetrahydrofuranyl. In various embodiments, ring A is tetrahydropyranyl.

[00103] In various embodiments, each of the first, second or third spacers is independently represented by Formula (I), wherein:

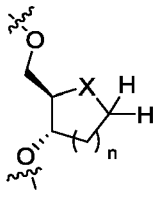


Formula (I)

X is selected from $-CH_2-$ and -O-; and

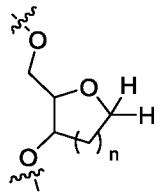
n is 0, 1, 2 or 3.

[00104] In various embodiments, each of the first, second or third spacers is independently represented by Formula (I'), wherein:



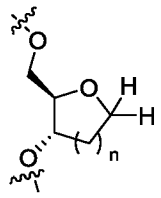
Formula (I').

[00105] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



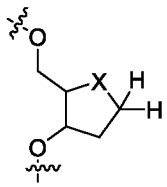
Formula (Ia).

[00106] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia').

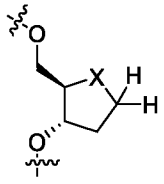
[00107] In various embodiments, each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

X is selected from -CH_2- and -O-.

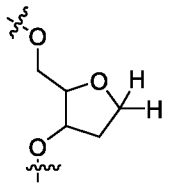
[00108] In various embodiments, each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

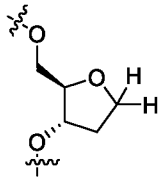
X is selected from -CH_2- and -O-.

[00109] In various embodiments, each of the first, second or third spacers is independently represented by Formula (IIa), wherein:



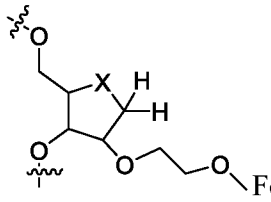
Formula (IIa).

[00110] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Iia'), wherein:



Formula (Iia').

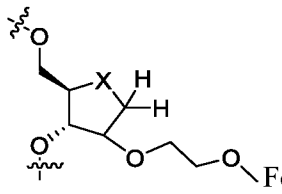
[00111] In some embodiments, the spacer is represented by Formula (IIi), wherein:



Formula (IIi)

X is selected from -CH_2- and -O-.

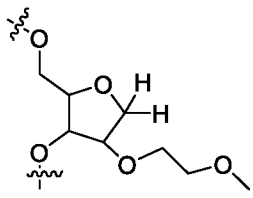
[00112] In some embodiments, the spacer is represented by Formula (IIi'), wherein:



Formula (IIi')

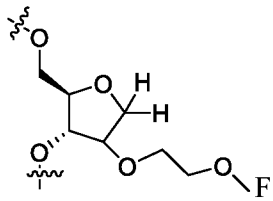
X is selected from -CH_2-and -O.

[00113] In some embodiments, the spacer is represented by Formula (IIib), wherein:

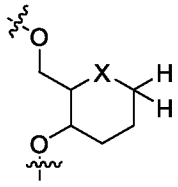


Formula (IIib).

[00114] In some embodiments, the spacer is represented by Formula (IIib'), wherein:

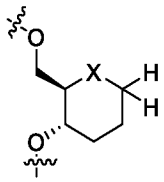

Formula (IIib').

[00115] In various embodiments, each of the first, second or third spacers is independently represented by Formula III, wherein:


Formula (III); and

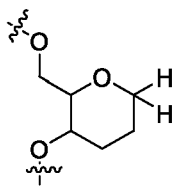
X is selected from -CH_2- and -O-.

[00116] T In various embodiments, each of the first, second or third spacers is independently represented by Formula III', wherein:

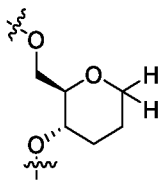

Formula (III'); and

X is selected from -CH_2- and -O-.

[00117] In various embodiments, each of the first, second or third spacers is independently represented by Formula (IIIa), wherein:


Formula (IIIa).

[00118] In various embodiments, each of the first, second or third spacers is independently represented by Formula (IIIa'), wherein:


Formula (IIIa').

[00119] In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 10%. In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 20%. In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 25%. In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 30%. In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 40%. In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 50%.

BRIEF DESCRIPTION OF THE DRAWINGS

[00120] FIG. 1 is a schematic depiction of portions of the STMN2 transcript and STMN2 antisense oligonucleotides that are designed to target certain portions of the STMN2 transcript.

[00121] FIG. 2 is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript in the presence of 6 different STMN2 parent oligonucleotides (SEQ ID NO: 36, SEQ ID NO: 55, SEQ ID NO: 177, SEQ ID NO: 203, SEQ ID NO: 244, and SEQ ID NO: 395).

[00122] FIG. 3 is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels in the presence of 6 different STMN2 parent oligonucleotides (SEQ ID NO: 173, SEQ ID NO: 181, SEQ ID NO: 197, SEQ ID NO: 215, SEQ ID NO: 385, and SEQ ID NO: 400).

[00123] FIG. 4 is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript in the presence of 6 different STMN2 parent oligonucleotides (SEQ ID NO: 173, SEQ ID NO: 181, SEQ ID NO: 197, SEQ ID NO: 215, SEQ ID NO: 385, and SEQ ID NO: 400).

[00124] FIG. 5A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels in the presence of 6 different STMN2 parent oligonucleotides (SEQ ID NO: 185, SEQ ID NO: 209, SEQ ID NO: 237, SEQ ID NO: 252, SEQ ID NO: 380, and SEQ ID NO: 390).

[00125] FIG. 5B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2

transcript in the presence of 6 different STMN2 parent oligonucleotides (SEQ ID NO: 185, SEQ ID NO: 209, SEQ ID NO: 237, SEQ ID NO: 252, SEQ ID NO: 380, and SEQ ID NO: 390).

[00126] FIG. 6A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels in the presence of 2 different STMN2 parent oligonucleotides (SEQ ID NO: 144 and SEQ ID NO: 237) over two duplicate experiments.

[00127] FIG. 6B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript in the presence of 2 different STMN2 parent oligonucleotides (SEQ ID NO: 144 and SEQ ID NO: 237) over two duplicate experiments.

[00128] FIG. 7A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels in the presence of 5 different STMN2 parent oligonucleotides (SEQ ID NO: 36, SEQ ID NO: 173, SEQ ID NO: 177, SEQ ID NO: 181, and SEQ ID NO: 185).

[00129] FIG. 7B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript in the presence of 5 different STMN2 parent oligonucleotides (SEQ ID NO: 36, SEQ ID NO: 173, SEQ ID NO: 177, SEQ ID NO: 181, and SEQ ID NO: 185).

[00130] FIG. 8A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels in the presence of 5 different STMN2 parent oligonucleotides (SEQ ID NO: 197, SEQ ID NO: 203, SEQ ID NO: 237, SEQ ID NO: 380, and SEQ ID NO: 395).

[00131] FIG. 8B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript in the presence of 5 different STMN2 parent oligonucleotides (SEQ ID NO: 197, SEQ ID NO: 203, SEQ ID NO: 237, SEQ ID NO: 380, and SEQ ID NO: 395).

[00132] FIG. 9A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels in the presence of 3 different STMN2 parent oligonucleotides (SEQ ID NO: 144, SEQ ID NO: 173, and SEQ ID NO: 237).

[00133] FIG. 9B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript in the presence of 3 different STMN2 parent oligonucleotides (SEQ ID NO: 144, SEQ ID NO: 173, and SEQ ID NO: 237).

[00134] FIG. 10A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of a SEQ ID NO: 181 STMN2 parent oligonucleotide.

[00135] FIG. 10B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of a SEQ ID NO: 181 STMN2 parent oligonucleotide.

[00136] FIG. 11A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of a SEQ ID NO: 185 STMN2 parent oligonucleotide.

[00137] FIG. 11B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of a SEQ ID NO: 185 STMN2 parent oligonucleotide.

[00138] FIG. 12A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of a SEQ ID NO: 197 STMN2 parent oligonucleotide.

[00139] FIG. 12B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of a SEQ ID NO: 197 STMN2 parent oligonucleotide.

[00140] FIG. 13A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of a SEQ ID NO: 144 STMN2 parent oligonucleotide.

[00141] FIG. 13B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of a SEQ ID NO: 144 STMN2 parent oligonucleotide.

[00142] FIG. 14A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of a SEQ ID NO: 173 STMN2 parent oligonucleotide.

[00143] FIG. 14B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of a SEQ ID NO: 173 STMN2 parent oligonucleotide.

[00144] FIG. 15A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of a SEQ ID NO: 237 STMN2 parent oligonucleotide.

[00145] FIG. 15B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of a SEQ ID NO: 237 STMN2 parent oligonucleotide.

[00146] FIG. 16 is a protein blot and quantified bar graph showing the normalized quantity of STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript for 2 different STMN2 parent oligonucleotides (SEQ ID NO: 173 and SEQ ID NO: 237).

[00147] FIG. 17A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different variants of a SEQ ID NO: 237 STMN2 parent oligonucleotide.

[00148] FIG. 17B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different variants of a SEQ ID NO: 237 STMN2 parent oligonucleotide.

[00149] FIG. 18A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different variants of a SEQ ID NO: 185 STMN2 parent oligonucleotide.

[00150] FIG. 18B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different variants of a SEQ ID NO: 185 STMN2 parent oligonucleotide.

[00151] FIG. 19A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different variants of a SEQ ID NO: 173 STMN2 parent oligonucleotide.

[00152] FIG. 19B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different variants of a SEQ ID NO: 173 STMN2 parent oligonucleotide.

[00153] FIG. 20A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different variants of a SEQ ID NO: 237 STMN2 parent oligonucleotide.

[00154] FIG. 20B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different variants of a SEQ ID NO: 237 STMN2 parent oligonucleotide.

[00155] FIG. 21A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different variants of a SEQ ID NO: 173 STMN2 parent oligonucleotide.

[00156] FIG. 21B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different variants of a SEQ ID NO: 173 STMN2 parent oligonucleotide.

[00157] FIG. 22A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different variants of a SEQ ID NO: 144 STMN2 parent oligonucleotide.

[00158] FIG. 22B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different variants of a SEQ ID NO: 144 STMN2 parent oligonucleotide.

[00159] FIG. 23 is a bar graph showing reversal of cryptic exon induction using SEQ ID NO: 237 STMN2 parent oligonucleotide even in view of increasing proteasome inhibition.

[00160] FIG. 24 shows the dose response curve illustrating increasing restoration of full length STMN2 transcript with increasing concentrations of STMN2 AON.

[00161] FIG. 25A shows a protein blot assay demonstrating the qualitative increase of full length STMN2 protein in response to higher concentrations of STMN2 AON.

[00162] FIG. 25B shows the quantitated levels of full length STMN2 protein normalized to GAPDH in response to different concentrations of STMN2 AON.

[00163] FIG. 26A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including a SEQ ID NO: 144 AON, a SEQ ID NO: 144 AON with two spacers (SEQ ID NO: 1589), a SEQ ID NO: 173 AON, a SEQ ID NO: 173 with two spacers (SEQ ID NO: 1590), a SEQ ID NO: 237 AON, and a SEQ ID NO: 237 AON with two spacers (SEQ ID NO: 1591).

[00164] FIG. 26B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs including a SEQ ID NO: 144 AON, a SEQ ID NO: 144 AON with two spacers (SEQ ID NO: 1589), a SEQ ID NO: 173 AON, a SEQ ID NO: 173 with two spacers (SEQ ID NO: 1590), a SEQ ID NO: 237 AON, and a SEQ ID NO: 237 AON with two spacers (SEQ ID NO: 1591).

[00165] FIG. 27A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 173, SEQ ID NO: 1608, SEQ ID NO: 1609, SEQ ID NO: 1610, SEQ ID

NO: 1611, SEQ ID NO: 1612, SEQ ID NO: 1613, SEQ ID NO: 1614, SEQ ID NO: 1615, SEQ ID NO: 1596, SEQ ID NO: 1597, and SEQ ID NO: 1418.

[00166] FIG. 27B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs including SEQ ID NO: 173, SEQ ID NO: 1608, SEQ ID NO: 1609, SEQ ID NO: 1610, SEQ ID NO: 1611, SEQ ID NO: 1612, SEQ ID NO: 1613, SEQ ID NO: 1614, SEQ ID NO: 1615, SEQ ID NO: 1596, SEQ ID NO: 1597, and SEQ ID NO: 1418.

[00167] FIG. 28A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 173, SEQ ID NO: 1632, SEQ ID NO: 1346, SEQ ID NO: 1631, SEQ ID NO: 1353, and SEQ ID NO: 1598.

[00168] FIG. 28B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs including SEQ ID NO: 173, SEQ ID NO: 1632, SEQ ID NO: 1346, SEQ ID NO: 1631, SEQ ID NO: 1353, and SEQ ID NO: 1598.

[00169] FIG. 29A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 173 and SEQ ID NO: 1610.

[00170] FIG. 29B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs including SEQ ID NO: 173 and SEQ ID NO: 1610.

[00171] FIG. 30A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 185 and SEQ ID NO: 1635.

[00172] FIG. 30B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs including SEQ ID NO: 185 and SEQ ID NO: 1635.

[00173] FIG. 31A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 1347, SEQ ID NO: 1633, and SEQ ID NO: 1634.

[00174] FIG. 31B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs including SEQ ID NO: 1347, SEQ ID NO: 1633, and SEQ ID NO: 1634.

[00175] FIG. 32A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 197, SEQ ID NO: 1617, SEQ ID NO: 1618, and SEQ ID NO: 1619.

[00176] FIG. 32B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs including SEQ ID NO: 197, SEQ ID NO: 1617, SEQ ID NO: 1618, and SEQ ID NO: 1619.

[00177] FIG. 33A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 252, SEQ ID NO: 1650, SEQ ID NO: 1434, SEQ ID NO: 1651, and SEQ ID NO: 1620.

[00178] FIG. 33B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs including SEQ ID NO: 252, SEQ ID NO: 1650, SEQ ID NO: 1434, SEQ ID NO: 1651, and SEQ ID NO: 1620.

[00179] FIG. 34A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 1434 and SEQ ID NO: 1620.

[00180] FIG. 34B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs including SEQ ID NO: 1434 and SEQ ID NO: 1620.

[00181] FIG. 35 is a bar graph showing normalized STMN2 protein levels following treatment with TDP43 antisense and restoration using STMN2 AONs including SEQ ID NO: 144, SEQ ID NO: 1589, SEQ ID NO: 173, SEQ ID NO: 1616, SEQ ID NO: 237, and SEQ ID NO: 1591.

DETAILED DESCRIPTION

[00182] The features and other details of the disclosure will now be more particularly described. Certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

[00183] Disclosed herein are oligonucleotides capable of targeting a region of a transcript transcribed from a gene. In various embodiments, such oligonucleotides target a STMN2 transcript. In various embodiments, such oligonucleotides target a KCNQ2 transcript. In various embodiments, such oligonucleotides target a UNC13A transcript. In various embodiments, such oligonucleotides target a SMN2 transcript. Additionally disclosed herein are oligonucleotides, including antisense oligonucleotide sequences, and methods for treating neurological diseases, such as amyotrophic lateral sclerosis and frontotemporal dementia, and/or neuropathies such as chemotherapy induced neuropathy, using same. In one embodiment, the oligonucleotides target a cryptic exon sequence of STMN2 transcripts, thereby reducing levels of STMN2 transcripts with the cryptic exon sequence. In various embodiments, the oligonucleotides target a sequence of KCNQ2 transcripts resulting in the reduction of levels of mis-spliced KCNQ2 transcripts. In various embodiments, the oligonucleotides target a sequence of UNC13A transcripts resulting in the reduction of levels of mis-spliced UNC13A transcripts. In various embodiments, the oligonucleotides target a sequence of SMN2 transcripts resulting in the reduction of levels of mis-spliced SMN2 transcripts. Also disclosed are pharmaceutical compositions comprising STMN2 oligonucleotides that target a region of STMN2 transcripts that comprise a cryptic exon, for treating neurological diseases and/or neuropathies; and manufacture of medicaments containing a disclosed STMN2 oligonucleotide that targets a region of STMN2 transcripts that comprise a cryptic exon to be used in treating a neurological disease and/or neuropathy. Also disclosed are pharmaceutical compositions comprising KCNQ2 oligonucleotides that target a region of KCNQ2 transcripts, for treating neurological diseases and/or neuropathies; and manufacture of medicaments containing a disclosed KCNQ2 oligonucleotide that targets a region

of KCNQ2 transcripts to be used in treating a neurological disease and/or neuropathy. Also disclosed are pharmaceutical compositions comprising UNC13A oligonucleotides that target a region of UNC13A transcripts, for treating neurological diseases and/or neuropathies; and manufacture of medicaments containing a disclosed UNC13A oligonucleotide that targets a region of UNC13A transcripts to be used in treating a neurological disease and/or neuropathy. Also disclosed are pharmaceutical compositions comprising SMN2 oligonucleotides that target a region of SMN2 transcripts, for treating neurological diseases and/or neuropathies; and manufacture of medicaments containing a disclosed SMN2 oligonucleotide that targets a region of SMN2 transcripts to be used in treating a neurological disease and/or neuropathy.

Definitions

[00184] The terms "treat," "treatment," "treating," and the like are used herein to generally mean obtaining a desired pharmacological and/or physiological effect. The effect may be therapeutic in terms of partially or completely curing a disease and/or adverse effect attributed to the disease. The term "treatment" as used herein covers any treatment of a disease in a mammal, particularly a human, and includes: (a) inhibiting the disease, *i.e.*, preventing the disease from increasing in severity or scope; (b) relieving the disease, *i.e.*, causing partial or complete amelioration of the disease; or (c) preventing relapse of the disease, *i.e.*, preventing the disease from returning to an active state following previous successful treatment of symptoms of the disease or treatment of the disease.

[00185] "Preventing" includes delaying the onset of clinical symptoms, complications, or biochemical indicia of the state, disorder, disease, or condition developing in a subject that may be afflicted with or predisposed to the state, disorder, disease, or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder, disease, or condition. "Preventing" includes prophylactically treating a state, disorder, disease, or condition in or developing in a subject, including prophylactically treating clinical symptoms, complications, or biochemical indicia of the state, disorder, disease, or condition in or developing in a subject.

[00186] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" as used herein interchangeably refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

[00187] The term "pharmaceutical composition" as used herein refers to a composition comprising at least one biologically active compound, for example, a STMN2 antisense oligonucleotide (AON), as disclosed herein formulated together with one or more pharmaceutically acceptable excipients.

[00188] "Individual," "patient," or "subject" are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or non-human primates, and most preferably humans. The compounds of the invention can be administered to a mammal, such as a human, but can also be other mammals such as an animal in need of veterinary treatment, *e.g.*, domestic animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, non-human primates, and the like). In some embodiments, the mammal treated in the methods of the invention is desirably a mammal in whom modulation of STMN2 expression and/or activity is desired. In some embodiments, the mammal treated in the methods of the invention is desirably a mammal in whom modulation of KCNQ2 expression and/or activity is desired. In some embodiments, the mammal treated in the methods of the invention is desirably a mammal in whom modulation of UNC13A expression and/or activity is desired. In some embodiments, the mammal treated in the methods of the invention is desirably a mammal in whom modulation of SMN2 expression and/or activity is desired.

[00189] As used herein, the phrase "regulated by TDP43" encompasses targets that are directly regulated and indirectly regulated by TDP43. Examples of targets that are directly regulated by TDP43 include STMN2 and UNC13A. An example of a target that is indirectly regulated by TDP43 includes KCNQ2.

[00190] As used herein, the term "antisense oligonucleotide" or "AON" encompasses antisense oligonucleotides that target genes or gene products of any of STMN2, KCNQ2, UNC13, and SMN2. "Antisense oligonucleotide" or "AON" encompass any of a parent oligonucleotide, an oligonucleotide variant, an oligonucleotide with one or more spacers, or an oligonucleotide variant with one or more spacers. Examples of antisense oligonucleotides include oligonucleotides comprising a sequence of any one of antisense oligonucleotide comprising any one of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NO: 3398-3899, SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NO: 7059-8322, SEQ ID NOs: 9596-9603, SEQ ID NOs: 9710-10141, SEQ

ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820.

[00191] The term "parent oligonucleotide" refers to an oligonucleotide that targets a transcript (e.g., a STMN2, KCNQ2, UNC13A, or SMN2 transcript) and is capable of increasing, restoring, or stabilizing full-length activity e.g., full length expression, for example, full length mRNA and/or full length protein expression. Parent oligonucleotides do not include a spacer. Examples of parent oligonucleotides include oligonucleotides comprising a sequence of any one of SEQ ID NOs: 1-446 and SEQ ID NOs: 893-1338, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, and SEQ ID NO: 4531-5794. As described hereafter, oligonucleotide with spacers and oligonucleotide variants are described in relation to a corresponding parent oligonucleotide.

[00192] The term "oligonucleotide variant" refers to an oligonucleotide that represents a modified version of a corresponding parent oligonucleotide. For example, an oligonucleotide variant represents a shortened version of a parent oligonucleotide. In various embodiments, an oligonucleotide variant is any one of a 15mer, 16mer, 17mer, 18mer 19mer, 20mer, 21mer, 22mer , 23mer, 24mer, 25mer, 26mer, or 27mer. Examples of oligonucleotide variants include oligonucleotides comprising a sequence of any one of SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1521, SEQ ID NOs: 3046-3221, SEQ ID NO: 3398-3899, SEQ ID NO: 7059-8322, and SEQ ID NOs: 9710-10141.

[00193] The term "oligonucleotide with one or more spacers" or "oligonucleotide comprising a spacer" refers to an oligonucleotide with at least one spacer. An oligonucleotide with one or more spacers can, in various embodiments, include one spacer, two spacers, three spacers, four spacer, five spacers, six spacers, seven spacers, eight spacers, nine spacers, or ten spacers. In various embodiments, an oligonucleotide comprising one or more spacers includes at least one segment with at most 7 linked nucleosides. For example, as described in a 5' to 3' direction, an oligonucleotide comprising a spacer can include a segment with 7 linked nucleosides, followed by a spacer, a second segment with 9 linked nucleosides, followed by a second spacer, and a third segment with 7 linked nucleosides. Here, the first segment of 7 linked nucleosides and the third segment of 7 linked nucleosides each represents segments with at most 7 linked nucleosides. As another example, an oligonucleotide comprising a spacer can include a segment with 10 linked nucleosides, followed by a spacer, a second segment with 10 linked nucleosides, followed by a second spacer, and a third segment with 3 linked nucleosides. Here, the third segment of 3 linked nucleosides represents the segment with at most 7 linked nucleosides. In various embodiments, an oligonucleotide with one or more spacers includes multiple segments with at most 7 linked

nucleosides. In various embodiments, every segment of an oligonucleotide with one or more spacers has at most 7 linked nucleosides. For example, the oligonucleotide may be a 23mer and include two spacers that divide the 23mer into three separate segments of 7 linked nucleosides each. Therefore, each segment of the oligonucleotide has at most 7 linked nucleosides.

[00194] Generally, oligonucleotides comprising one or more spacers are described in reference to a corresponding parent oligonucleotide or a corresponding oligonucleotide variant. Example oligonucleotides comprising one or spacers include any of SEQ ID NOs: 1417-1420, SEQ ID NOs: 1451-1664, SEQ ID NOs: 4402-4468, SEQ ID NOs: 4469-4476, SEQ ID NOs: 4477-4530, SEQ ID NOs: 9596-9696, SEQ ID NOs: 10574-10640, and SEQ ID NOs: 10644-10651.

STMN2

[00195] As used herein, "STMN2" (also known as Superior Cervical Ganglion-10 Protein, Stathmin-Like 2, SCGN10, SCG10, Neuronal Growth-Associated Protein, Neuron-Specific Growth-Associated Protein, or Protein SCG10 (Superior Cervical Ganglia NEAR Neural Specific 10) refers to the gene or gene products (*e.g.*, protein or mRNA transcript (including pre-mRNA) encoded by the gene) identified by Entrez Gene ID No. 11075 and allelic variants thereof, as well as orthologs found in non-human species (*e.g.*, non-human primates or mice).

[00196] The term "STMN2 transcript" refers to a STMN2 transcript comprising a cryptic exon. Such a STMN2 transcript comprising a cryptic exon can be a STMN2 pre-mRNA sequence or a STMN2 mature RNA sequence. The term "STMN2 transcript comprising a cryptic exon" refers to a STMN2 transcript that includes one or more cryptic exon sequences. STMN2 transcript sequences are shown to contain thymine (T), but one of skill in the art will appreciate that thymine (T) can generally be replaced with uracil (U) in RNA sequences.

[00197] The term "STMN2 oligonucleotide," "STMN2 antisense oligonucleotide," or "STMN2 AON" refers to an oligonucleotide that is capable of increasing, restoring, or stabilizing full-length STMN2 activity e.g., full length STMN2 expression, for example, full length STMN2 mRNA and/or full length STMN2 protein expression. Generally, a STMN2 oligonucleotide reduces the level of mature STMN2 transcripts with a cryptic exon by targeting a STMN2 transcript comprising a cryptic exon. For example, the STMN2 oligonucleotide reduces the level of mature STMN2 transcripts with a cryptic exon by repressing premature polyadenylation of STMN2 pre-mRNA and/or increasing, restoring, or stabilizing activity or function of STMN2. In various embodiments, a STMN2 oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a transcript comprising a sequence at least 90%

identity to SEQ ID NO: 1339 or SEQ ID NO: 1341, or a contiguous 15 to 50 nucleobase portion of SEQ ID NO: 1339 or SEQ ID NO: 1341. In various embodiments, a STMN2 oligonucleotide comprises a sequence that is between 85 and 98% complementary to an equal length portion of a transcript comprising a sequence at least 90% identity to SEQ ID NO: 1339 or SEQ ID NO: 1341, or a contiguous 15 to 50 nucleobase portion of SEQ ID NO: 1339 or SEQ ID NO: 1341. STMN2 target sequences are shown to contain thymine (T), but one of skill in the art will appreciate that thymine (T) can generally be replaced with uracil (U) in RNA sequences.

[00198] In various embodiments, STMN2 oligonucleotides are characterized by having one or more spacers, where each spacer divides up the STMN2 oligonucleotide into segments of linked nucleosides. In various embodiments, STMN2 oligonucleotides have two spacers. In one embodiment, STMN2 oligonucleotides have two segments of linked nucleosides separated by one spacer. In one embodiment, STMN2 oligonucleotides have three segments of linked nucleosides separated by two spacers. In such embodiments, STMN2 oligonucleotides have one segment with at most 7 linked nucleosides. For example, a STMN2 oligonucleotide may have, from the 5' to the 3' end, 5 linked nucleosides, followed by a spacer, 10 linked nucleosides, followed by a second spacer, and 8 linked nucleosides. Thus, the first segment of 5 linked nucleosides satisfies the one segment with at most 7 linked nucleosides. In various embodiments, STMN2 oligonucleotides have three spacers that divide the STMN2 oligonucleotide into four segments. In various embodiments, each of the four segments of the STMN2 oligonucleotide have at most 7 linked nucleosides.

[00199] As used herein, the term "STMN2 oligonucleotide" encompasses a "STMN2 parent oligonucleotide," a "STMN2 oligonucleotide with one or more spacers" (e.g., STMN2 oligonucleotide with two spacers or a STMN2 oligonucleotide with three spacers), a "STMN2 oligonucleotide variant with one or more spacers." Examples of STMN2 oligonucleotides include oligonucleotides comprising a sequence of any one of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669.

[00200] The term "STMN2 parent oligonucleotide" refers to an oligonucleotide that targets a STMN2 transcript with a cryptic exon and is capable of increasing, restoring, or stabilizing full-length STMN2 activity e.g., full length STMN2 expression, for example, full length STMN2 mRNA and/or full length STMN2 protein expression. STMN2 parent oligonucleotides do not include a spacer. Examples of STMN2 parent oligonucleotides include oligonucleotides comprising a sequence of any one of SEQ ID NOs: 1-446 and SEQ ID NOs: 893-1338. As

described hereafter, STMN2 oligonucleotide with spacers and STMN2 oligonucleotide variants are described in relation to a corresponding STMN2 parent oligonucleotide.

[00201] The term "STMN2 oligonucleotide variant" refers to a STMN2 oligonucleotide that represents a modified version of a corresponding STMN2 parent oligonucleotide. For example, a STMN2 oligonucleotide variant represents a shortened version of a STMN2 parent oligonucleotide. In various embodiments, a STMN2 oligonucleotide variant is any one of a 15mer, 16mer, 17mer, 18mer 19mer, 20mer, 21mer, 22mer, 23mer, 24mer, 25mer, 26mer, or 27mer. Examples of STMN2 oligonucleotide variants include oligonucleotides comprising a sequence of any one of SEQ ID NOs: 1342-1366 or SEQ ID NOs: 1392-1521. In various embodiments, STMN2 oligonucleotide variants comprise one or more spacers. Such STMN2 oligonucleotide variants comprise a sequence of any one of SEQ ID NOs: 1342-1366 and SEQ ID NOs: 1392-1416.

[00202] The term "STMN2 oligonucleotide with one or more spacers" or "STMN2 oligonucleotide comprising a spacer" refers to a STMN2 oligonucleotide with at least one spacer. An oligonucleotide with one or more spacers can, in various embodiments, include one spacer, two spacers, three spacers, four spacer, five spacers, six spacers, seven spacers, eight spacers, nine spacers, or ten spacers. In various embodiments, an oligonucleotide comprising one or more spacers includes at least one segment with at most 7 linked nucleosides. For example, as described in a 5' to 3' direction, an oligonucleotide comprising a spacer can include a segment with 7 linked nucleosides, followed by a spacer, a second segment with 9 linked nucleosides, followed by a second spacer, and a third segment with 7 linked nucleosides. Here, the first segment of 7 linked nucleosides and the third segment of 7 linked nucleosides each represents segments with at most 7 linked nucleosides. As another example, an oligonucleotide comprising a spacer can include a segment with 10 linked nucleosides, followed by a spacer, a second segment with 10 linked nucleosides, followed by a second spacer, and a third segment with 3 linked nucleosides. Here, the third segment of 3 linked nucleosides represents the segment with at most 7 linked nucleosides. In various embodiments, an oligonucleotide with one or more spacers includes multiple segments with at most 7 linked nucleosides. In various embodiments, every segment of an oligonucleotide with one or more spacers has at most 7 linked nucleosides. For example, the oligonucleotide may be a 23mer and include two spacers that divide the 23mer into three separate segments of 7 linked nucleosides each. Therefore, each segment of the oligonucleotide has at most 7 linked nucleosides.

[00203] Generally, STMN2 oligonucleotides comprising one or more spacers are described in reference to a corresponding STMN2 parent oligonucleotide or a corresponding STMN2 oligonucleotide variant. Example STMN2 oligonucleotides comprising one or spacers include any of SEQ ID NOs: 1417-1420 and SEQ ID NOs: 1451-1664.

[00204] The phrase "a STMN2 oligonucleotide that targets a STMN2 transcript" refers to a STMN2 oligonucleotide that binds to a STMN2 transcript. Example regions of a STMN2 transcript are shown in Table 1, which depicts sequences corresponding to regions of branch points (*e.g.*, branch point 1, 2, and 3) a 3' splice acceptor region, an ESE binding region, TDP43 binding sites, a cryptic exon, and a Poly A region. In various embodiments, the oligonucleotide binds to a region of a STMN2 transcript with a cryptic exon, the region being located less than 75 nucleobases upstream or downstream to any of the branch points (*e.g.*, branch point 1, 2, and 3) a 3' splice acceptor region, an ESE binding region, TDP43 binding sites, a cryptic exon, and a Poly A region.

KCNQ2

[00205] As used herein, "KCNQ2" (also known as Kv7.2, KCNA11, HNSPC, ENB1, BNFC, Potassium Channel, Voltage Gated KQT-Like Subfamily Q, Member 2, Neuroblastoma-Specific Potassium Channel Subunit Alpha KvLQT2, Potassium Voltage-Gated Channel Subfamily KQT Member 2) refers to the gene or gene products (*e.g.*, protein or mRNA transcript (including pre-mRNA) encoded by the gene) identified by any one of SEQ ID NOs: 3032-3043 and allelic variants thereof, as well as orthologs found in non-human species (*e.g.*, non-human primates or mice).

[00206] The term "KCNQ2 transcript" refers to a KCNQ2 transcript. Such a KCNQ2 transcript can be a KCNQ2 pre-mRNA sequence or a KCNQ2 mature RNA sequence. KCQN2 transcript sequences are shown to contain thymine (T), but one of skill in the art will appreciate that thymine (T) can generally be replaced with uracil (U) in RNA sequences.

[00207] The term "KCNQ2 oligonucleotide," "KCNQ2 antisense oligonucleotide," or "KCNQ2 AON" refers to an oligonucleotide that is capable of increasing, restoring, or stabilizing full-length KCNQ2 activity e.g., full length KCNQ2 expression, for example, full length KCNQ2 mRNA and/or full length KCNQ2 protein expression. Generally, a KCNQ2 oligonucleotide reduces the level of mis-spliced KCNQ2 transcripts by targeting a KCNQ2 transcript (e.g., KCNQ2 pre-mRNA or mis-spliced KCNQ2 with a target sequence). In various embodiments, a KCNQ2 oligonucleotide comprises a sequence that is at least 85% complementary to an equal

length portion of a transcript comprising a sequence at least 90% identity to any one of SEQ ID NOs: 3032-3045 or a contiguous 15 to 50 nucleobase portion to any one of SEQ ID NO: 3032-3043. In various embodiments, a KCNQ2 oligonucleotide comprises a sequence that is between 85 and 98% complementary to an equal length portion of a transcript comprising a sequence at least 90% identity to any one of SEQ ID NOs: 3032-3045, or a contiguous 15 to 50 nucleobase portion to any one of SEQ ID NOs: 3032-3045. KCQN2 target sequences are shown to contain thymine (T), but one of skill in the art will appreciate that thymine (T) can generally be replaced with uracil (U) in RNA sequences.

[00208] In various embodiments, KCNQ2 oligonucleotides are characterized by having one or more spacers, where each spacer divides up the KCNQ2 oligonucleotide into segments of linked nucleosides. In various embodiments, KCNQ2 oligonucleotides have two spacers. In one embodiment, KCNQ2 oligonucleotides have two segments of linked nucleosides separated by one spacer. In one embodiment, KCNQ2 oligonucleotides have three segments of linked nucleosides separated by two spacers. In such embodiments, KCNQ2 oligonucleotides have one segment with at most 7 linked nucleosides. For example, a KCNQ2 oligonucleotide may have, from the 5' to the 3' end, 5 linked nucleosides, followed by a spacer, 10 linked nucleosides, followed by a second spacer, and 8 linked nucleosides. Thus, the first segment of 5 linked nucleosides satisfies the one segment with at most 7 linked nucleosides. In various embodiments, KCNQ2 oligonucleotides have three spacers that divide the KCNQ2 oligonucleotide into four segments. In various embodiments, each of the four segments of the KCNQ2 oligonucleotide have at most 7 linked nucleosides.

[00209] As used herein, the term "KCNQ2 oligonucleotide" encompasses a "KCNQ2 parent oligonucleotide," a "KCNQ2 oligonucleotide with one or more spacers" (e.g., KCNQ2 oligonucleotide with two spacers or a KCNQ2 oligonucleotide with three spacers), a "KCNQ2 oligonucleotide variant with one or more spacers." Examples of KCNQ2 oligonucleotides include oligonucleotides comprising a sequence of any one of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NO: 3398-3899, and SEQ ID NOs: 4402-4530..

[00210] The term "KCNQ2 parent oligonucleotide" refers to an oligonucleotide that targets a KCNQ2 transcript and is capable of increasing, restoring, or stabilizing full-length KCNQ2 activity e.g., full length KCNQ2 expression, for example, full length KCNQ2 mRNA and/or full length KCNQ2 protein expression. KCNQ2 parent oligonucleotides do not include a spacer. Examples of KCNQ2 parent oligonucleotides include oligonucleotides comprising a sequence of

any one of SEQ ID NOs: 1676-1851and SEQ ID NOs: 2028-2529. As described hereafter, KCNQ2 oligonucleotide with spacers and KCNQ2 oligonucleotide variants are described in relation to a corresponding KCNQ2 parent oligonucleotide.

[00211] The term "KCNQ2 oligonucleotide variant" refers to a KCNQ2 oligonucleotide that represents a modified version of a corresponding KCNQ2 parent oligonucleotide. For example, a KCNQ2 oligonucleotide variant represents a shortened version of a KCNQ2 parent oligonucleotide. In various embodiments, a KCNQ2 oligonucleotide variant is any one of a 15mer, 16mer, 17mer, 18mer 19mer, 20mer, 21mer, 22mer, 23mer, 24mer, 25mer, 26mer, or 27mer. Examples of KCNQ2 oligonucleotide variants include oligonucleotides comprising a sequence of any one of SEQ ID NOs: 3046-3221, and SEQ ID NO: 3398-3899. In various embodiments, KCNQ2 oligonucleotide variants comprise one or more spacers. Such KCNQ2 oligonucleotide variants comprise a sequence of any one of SEQ ID NOs: 4469-4476, and SEQ ID NOs: 4477-4530.

[00212] Generally, KCNQ2 oligonucleotides comprising one or more spacers are described in reference to a corresponding KCNQ2 parent oligonucleotide or a corresponding KCNQ2 oligonucleotide variant. Example KCNQ2 oligonucleotides comprising one or spacers include any of SEQ ID NOs: 4402-4468, SEQ ID NOs: 4469-4476, and SEQ ID NOs: 4477-4530.

[00213] The phrase "a KCNQ2 oligonucleotide that targets a KCNQ2 transcript" refers to a KCNQ2 oligonucleotide that binds to a KCNQ2 transcript.

UNC13A

[00214] As used herein, "UNC13A" (also known as Unc-13 Homolog A, Munc13-1, KIAA1032, unc-13 homolog A (C. elegans), or Protein Unc-13 Homolog A) refers to the gene or gene products (*e.g.*, protein or mRNA transcript (including pre-mRNA) encoded by the gene) identified by Entrez Gene ID No. 23025 and allelic variants thereof, as well as orthologs found in non-human species (*e.g.*, non-human primates or mice). UNC13A transcript sequences are shown to contain thymine (T), but one of skill in the art will appreciate that thymine (T) can generally be replaced with uracil (U) in RNA sequences.

[00215] The term "UNC13A transcript" refers to a UNC13A transcript which can be a UNC13A pre-mRNA sequence or a UNC13A mature RNA sequence. The term "UNC13A oligonucleotide," "UNC13A antisense oligonucleotide," or "UNC13A AON" refers to an oligonucleotide that is capable of increasing, restoring, or stabilizing full-length UNC13A activity e.g., full length UNC13A expression, for example, full length UNC13A mRNA and/or

full length UNC13A protein expression. Generally, a UNC13A oligonucleotide reduces the level of mis-spliced UNC13A transcripts by targeting a UNC13A transcript (e.g., UNC13A pre-mRNA or mis-spliced UNC13A with a target sequence). In various embodiments, a UNC13A oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a transcript comprising a sequence at least 90% identity to SEQ ID NO: 9587-9595, or a contiguous 15 to 50 nucleobase portion of SEQ ID NO: 9587-9595. In various embodiments, a UNC13A oligonucleotide comprises a sequence that is between 85 and 98% complementary to an equal length portion of a transcript comprising a sequence at least 90% identity to any one of SEQ ID NO: 9587-9595, or a contiguous 15 to 50 nucleobase portion to any one of SEQ ID NO: 9587-9595. UNC13A target sequences are shown to contain thymine (T), but one of skill in the art will appreciate that thymine (T) can generally be replaced with uracil (U) in RNA sequences.

[00216] In various embodiments, UNC13A oligonucleotides are characterized by having one or more spacers, where each spacer divides up the UNC13A oligonucleotide into segments of linked nucleosides. In various embodiments, UNC13A oligonucleotides have two spacers. In one embodiment, UNC13A oligonucleotides have two segments of linked nucleosides separated by one spacer. In one embodiment, UNC13A oligonucleotides have three segments of linked nucleosides separated by two spacers. In such embodiments, UNC13A oligonucleotides have one segment with at most 7 linked nucleosides. For example, a UNC13A oligonucleotide may have, from the 5' to the 3' end, 5 linked nucleosides, followed by a spacer, 10 linked nucleosides, followed by a second spacer, and 8 linked nucleosides. Thus, the first segment of 5 linked nucleosides satisfies the one segment with at most 7 linked nucleosides. In various embodiments, UNC13A oligonucleotides have three spacers that divide the UNC13A oligonucleotide into four segments. In various embodiments, each of the four segments of the UNC13A oligonucleotide have at most 7 linked nucleosides.

[00217] As used herein, the term "UNC13A oligonucleotide" encompasses a "UNC13A parent oligonucleotide," a "UNC13A oligonucleotide with one or more spacers" (e.g., UNC13A oligonucleotide with two spacers or a UNC13A oligonucleotide with three spacers), a "UNC13A oligonucleotide variant with one or more spacers." Examples of UNC13A oligonucleotides include oligonucleotides comprising a sequence of any one of SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9696, and SEQ ID NOs: 10670-10779.

[00218] The term "UNC13A parent oligonucleotide" refers to an oligonucleotide that targets a UNC13A transcript and is capable of increasing, restoring, or stabilizing full-length UNC13A activity e.g., full length UNC13A expression, for example, full length UNC13A mRNA and/or

full length UNC13A protein expression. UNC13A parent oligonucleotides do not include a spacer. Examples of UNC13A parent oligonucleotides include oligonucleotides comprising a sequence of any one of SEQ ID NO: 4531-5794. As described hereafter, UNC13A oligonucleotide with spacers and UNC13A oligonucleotide variants are described in relation to a corresponding UNC13A parent oligonucleotide.

[00219] The term "UNC13A oligonucleotide variant" refers to a UNC13A oligonucleotide that represents a modified version of a corresponding UNC13A parent oligonucleotide. For example, a UNC13A oligonucleotide variant represents a shortened version of a UNC13A parent oligonucleotide. In various embodiments, a UNC13A oligonucleotide variant is any one of a 15mer, 16mer, 17mer, 18mer 19mer, 20mer, 21mer, 22mer 23mer, or 24mer. Examples of UNC13A oligonucleotide variants include oligonucleotides comprising a sequence of any one of SEQ ID NO: 7059-8322. In various embodiments, UNC13A oligonucleotide variants comprise one or more spacers. Such UNC13A oligonucleotide variants comprise a sequence of any one of SEQ ID NO: 9596-9696.

[00220] Generally, UNC13A oligonucleotides comprising one or more spacers are described in reference to a corresponding UNC13A parent oligonucleotide or a corresponding UNC13A oligonucleotide variant. Example UNC13A oligonucleotides comprising one or spacers include any of SEQ ID NOs: 9596-9696.

[00221] The phrase "a UNC13A oligonucleotide that targets a UNC13A transcript" refers to a UNC13A oligonucleotide that binds to a UNC13A transcript

SMN2

[00222] As used herein, "SMN2" (also known as Survival of Motor Neuron 2, SMNC, TRD16B, BCD541, GEMINI1, Survival Motor Neuron Protein, Tudor Domain Containing 16B, Component of Gems 1, Gemin-1, C-BCD541, SMNT, SMN) refers to the gene or gene products (*e.g.*, protein or mRNA transcript (including pre-mRNA) encoded by the gene) identified by any one of SEQ ID NOs: 9698-9709 and allelic variants thereof, as well as orthologs found in non-human species (*e.g.*, non-human primates or mice).

[00223] The term "SMN2 transcript" refers to a SMN2 transcript. Such a SMN2 transcript can be a SMN2 pre-mRNA sequence or a SMN2 mature RNA sequence. SMN2 transcript sequences are shown to contain thymine (T), but one of skill in the art will appreciate that thymine (T) can generally be replaced with uracil (U) in RNA sequences.

[00224] The term "SMN2 oligonucleotide," "SMN2 antisense oligonucleotide," or "SMN2 AON" refers to an oligonucleotide that is capable of increasing, restoring, or stabilizing full-length SMN2 activity e.g., full length SMN2 expression, for example, full length SMN2 mRNA and/or full length SMN2 protein expression. Generally, a SMN2 oligonucleotide reduces the level of mis-spliced SMN2 transcripts by targeting a SMN2 transcript (e.g., SMN2 pre-mRNA or mis-spliced SMN2 with a target sequence). In various embodiments, a SMN2 oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a transcript comprising a sequence at least 90% identity to any one of SEQ ID NOs: 9698-9709 or a contiguous 15 to 50 nucleobase portion to any one of SEQ ID NO: 9698-9709. In various embodiments, a SMN2 oligonucleotide comprises a sequence that is between 85 and 98% complementary to an equal length portion of a transcript comprising a sequence at least 90% identity to any one of SEQ ID NOs: 9698-9709, or a contiguous 15 to 50 nucleobase portion to any one of SEQ ID NOs: 9698-9709. SMN2 target sequences are shown to contain thymine (T), but one of skill in the art will appreciate that thymine (T) can generally be replaced with uracil (U) in RNA sequences.

[00225] In various embodiments, SMN2 oligonucleotides are characterized by having one or more spacers, where each spacer divides up the SMN2 oligonucleotide into segments of linked nucleosides. In various embodiments, SMN2 oligonucleotides have two spacers. In one embodiment, SMN2 oligonucleotides have two segments of linked nucleosides separated by one spacer. In one embodiment, SMN2 oligonucleotides have three segments of linked nucleosides separated by two spacers. In such embodiments, SMN2 oligonucleotides have one segment with at most 7 linked nucleosides. For example, a SMN2 oligonucleotide may have, from the 5' to the 3' end, 5 linked nucleosides, followed by a spacer, 10 linked nucleosides, followed by a second spacer, and 8 linked nucleosides. Thus, the first segment of 5 linked nucleosides satisfies the one segment with at most 7 linked nucleosides. In various embodiments, SMN2 oligonucleotides have three spacers that divide the SMN2 oligonucleotide into four segments. In various embodiments, each of the four segments of the SMN2 oligonucleotide have at most 7 linked nucleosides.

[00226] As used herein, the term "SMN2 oligonucleotide" encompasses a "SMN2 parent oligonucleotide," a "SMN2 oligonucleotide with one or more spacers" (e.g., SMN2 oligonucleotide with two spacers or a SMN2 oligonucleotide with three spacers), a "SMN2 oligonucleotide variant with one or more spacers." Examples of SMN2 oligonucleotides include

oligonucleotides comprising a sequence of any one of SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, and SEQ ID NOs: 10783-10808.

[00227] The term "SMN2 parent oligonucleotide" refers to an oligonucleotide that targets a SMN2 transcript and is capable of increasing, restoring, or stabilizing full-length SMN2 activity e.g., full length SMN2 expression, for example, full length SMN2 mRNA and/or full length SMN2 protein expression. SMN2 parent oligonucleotides do not include a spacer. As described hereafter, SMN2 oligonucleotide with spacers and SMN2 oligonucleotide variants are described in relation to a corresponding SMN2 parent oligonucleotide.

[00228] The term "SMN2 oligonucleotide variant" refers to a SMN2 oligonucleotide that represents a modified version of a corresponding SMN2 parent oligonucleotide. For example, a SMN2 oligonucleotide variant represents a shortened version of a SMN2 parent oligonucleotide. In various embodiments, a SMN2 oligonucleotide variant is any one of a 15mer, 16mer, 17mer, 18mer 19mer, 20mer, 21mer, 22mer, 23mer, or 24mer. Examples of SMN2 oligonucleotide variants include oligonucleotides comprising a sequence of any one of SEQ ID NOs: 9710-10141. In various embodiments, SMN2 oligonucleotide variants comprise one or more spacers. In various embodiments, SMN2 oligonucleotide variants may comprise a sequence of any one of SEQ ID NOs: 10574-10643 and SEQ ID NOs: 10644-10651.

[00229] Generally, SMN2 oligonucleotides comprising one or more spacers are described in reference to a corresponding SMN2 parent oligonucleotide or a corresponding SMN2 oligonucleotide variant. Example SMN2 oligonucleotides comprising one or spacers include any of SEQ ID NOs: 10574-10640 and SEQ ID NOs: 10644-10651.

[00230] In various embodiments, one or more spacers may be located at one or more positions of an oligonucleotide. A spacer may be located between a first position and a second position of the oligonucleotide. As used herein, a spacer located between a first position and second position encompasses the spacer being located at the first position, located at the second position, or located at any position of the oligonucleotide sandwiched by the first position and the second position.

[00231] In the present specification, the term "therapeutically effective amount" means the amount of an oligonucleotide that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor, or other clinician. In some embodiments, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a transcript comprising a sequence at least

90% identity to SEQ ID NO: 1339 or SEQ ID NO: 1341, or a contiguous 15 to 50 nucleobase portion of SEQ ID NO: 1339 or SEQ ID NO: 1341. In some embodiments, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a transcript comprising a sequence at least 90% identity to a sequence at least 90% identity to any one of SEQ ID NO: 3032-3045, or a contiguous 15 to 50 nucleobase portion to any one of SEQ ID NO: 3032-3045. In some embodiments, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a transcript comprising a sequence at least 90% identity to a sequence that is at least 85% complementary to an equal length portion of a transcript comprising a sequence at least 90% identity to SEQ ID NO: 9587-9595, or a contiguous 15 to 50 nucleobase portion of SEQ ID NO: 9587-9595. In some embodiments, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a transcript comprising a sequence at least 90% identity to any one of SEQ ID NO: 9698-9709, or a contiguous 15 to 50 nucleobase portion to any one of SEQ ID NO: 9698-9709. The oligonucleotide is administered in therapeutically effective amounts to treat and/or prevent a disease, condition, disorder, or state, for example, a neurological disease and/or a neuropathy. Alternatively, a therapeutically effective amount of an oligonucleotide is the quantity required to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in the prevention of or a decrease in the symptoms associated with a disease associated with reduced STMN2 activity in the motor neurons, an amount which results in the prevention of or a decrease in the symptoms associated with a disease associated with reduced KCNQ2 activity in the motor neurons, an amount which results in the prevention of or a decrease in the symptoms associated with a disease associated with reduced UNC13A activity in the motor neurons, and/or an amount which results in the prevention of or a decrease in the symptoms associated with a disease associated with reduced SMN2 activity in the motor neurons.

[00232] The term "pharmaceutically acceptable salt(s)" as used herein refers to salts of acidic or basic groups that may be present in a STMN2 oligonucleotide used in the present compositions, a KCNQ2 oligonucleotide used in the present compositions, a UNC13A oligonucleotide used in the present compositions, and/or a SMN2 oligonucleotide used in the present compositions. A STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable

anions, including but not limited to malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. A STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide included in the present compositions that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. Pharmaceutically acceptable salts of the disclosure include, for example, pharmaceutically acceptable salts of STMN2 oligonucleotides that include a sequence of any of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669; pharmaceutically acceptable salts of KCNQ2 oligonucleotides that include a sequence of any of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NO: 3398-3899, and SEQ ID NOs: 4402-4530; pharmaceutically acceptable salts of UNC13A oligonucleotides that include a sequence of any of SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9696, and SEQ ID NOs: 10670-10779; and pharmaceutically acceptable salts of SMN2 oligonucleotides that include a sequence of any of SEQ ID NOs: 9710-10141 and SEQ ID NOs: 10574-10651.

[00233] A STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide of the disclosure may contain one or more chiral centers, groups, linkages, and/or double bonds and, therefore, exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers. The term "stereoisomers" when used herein consist of all geometric isomers, enantiomers or diastereomers. These compounds may be designated by the symbols "R" or "S" (or "R*p*" or "S*p*") depending on the configuration of substituents around the stereogenic atom, for example, a stereogenic carbon, phosphorous, or sulfur atom. In some embodiments, one or more linkages of the compound may have a Rp or Sp configuration (*e.g.*, one or more phosphorothioate linkages have either a Rp or Sp configuration). The configuration of each phosphorothioate linkage may be independent of another phosphorothioate linkage (*e.g.*, one phosphorothioate linkage has a Rp configuration and a second phosphorothioate linkage has

a Sp configuration). In various embodiments, the STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide can have a mixed configuration of phosphorothioate linkages. For example, the STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide may have five phosphorothioate linkages in a R*p* configuration, followed by fifteen phosphorothioate linkages in a S*p* configuration, followed by five phosphorothioate linkages in a R*p* configuration. The present invention encompasses various stereoisomers of these compounds and mixtures thereof. Stereoisomers include enantiomers and diastereomers. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

[00234] Individual stereoisomers of a STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide of the present invention can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, or (3) direct separation of the mixture of optical enantiomers on chiral chromatographic columns. Stereoisomeric mixtures can also be resolved into their component stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase super critical fluid chromatography, chiral-phase simulated moving bed chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Stereoisomers can also be obtained from stereomerically-pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

[00235] The STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms.

[00236] The disclosure also embraces fluorescently labeled compounds of the invention. The disclosure also embraces isotopically labeled compounds of the invention (*i.e.*, isotopically labeled STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or

SMN2 oligonucleotide) which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number abundantly found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{33}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

[00237] Certain isotopically labeled disclosed compounds (*e.g.*, those labeled with ^{3}H, ^{14}C, or ^{35}S) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^{3}H), carbon-14 (*i.e.*, ^{14}C), or ^{35}S isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances.

[00238] As used herein, "2'-*O*-(2-methoxyethyl)" (also 2'-MOE and 2'-$O(CH_2)_2OCH_3$ and MOE) refers to an *O*-methoxyethyl modification of the 2' position of a furanose ring. A 2'-O-(2-methoxyethyl) is used interchangeably as "2'-*O*-methoxyethyl" in the present disclosure. A sugar moiety in a nucleoside modified with 2'-MOE is a modified sugar.

[00239] As used herein, "2'-MOE nucleoside" (also 2'-*O*-(2-methoxyethyl) nucleoside) means a nucleoside comprising a 2'-MOE modified sugar moiety.

[00240] As used herein, "2'-substituted nucleoside" means a nucleoside comprising a substituent at the 2'-position of the furanose ring other than H or OH. In certain embodiments, 2' substituted nucleosides include nucleosides with bicyclic sugar modifications.

[00241] As used herein, "5-methyl cytosine" (5-MeC) means a cytosine modified with a methyl group attached to the 5 position. A 5-methyl cytosine (5-MeC) is a modified nucleobase.

[00242] As used herein, "bicyclic sugar" means a furanose ring modified by the bridging of two atoms. A bicyclic sugar is a modified sugar.

[00243] As used herein, "bicyclic nucleoside" (also BNA) means a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4'-carbon and the 2'-carbon of the sugar ring.

[00244] As used herein, "cap structure" or "terminal cap moiety" means chemical modifications, which have been incorporated at either terminus of an antisense compound.

[00245] As used herein, "cEt" or "constrained ethyl" means a bicyclic nucleoside having a sugar moiety comprising a bridge connecting the 4'-carbon and the 2'-carbon, wherein the bridge has the formula: 4'-CH(CH_3)—*O*-2'.

[00246] As used herein, "constrained ethyl nucleoside" (also cEt nucleoside) means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-CH(CH_3)—*O*-2' bridge. In some embodiments, cEt can be modified. In some embodiments, the cEt can be *S*-cEt (in an *S*-constrained ethyl 2'-4'-bridged nucleic acid). In some other embodiments, the cEt can be *R*-cEt.

[00247] As used herein, "internucleoside linkage" refers to the covalent linkage between adjacent nucleosides in an oligonucleotide. In some embodiments, as used herein, "non-natural linkage" refers to a "modified internucleoside linkage."

[00248] As used herein, "contiguous" in the context of an oligonucleotide refers to nucleosides, nucleobases, sugar moieties, or internucleoside linkages that are immediately adjacent to each other. For example, "contiguous nucleobases" means nucleobases that are immediately adjacent to each other in a sequence. As an example to the contrary, two nucleosides separated by a spacer are not contiguous.

[00249] As used herein, "locked nucleic acid" or "LNA" or "LNA nucleosides" means nucleic acid monomers having a bridge (*e.g.*, methylene, ethylene, aminooxy, or oxyimino bridge) connecting two carbon atoms between the 4' and 2' position of the nucleoside sugar unit, thereby forming a bicyclic sugar. Examples of such bicyclic sugar include, but are not limited to (A) α-L-Methyleneoxy (4'-CH_2—O-2') LNA, (B) β-D-Methyleneoxy (4'-CH_2—O-2') LNA, (C) Ethyleneoxy (4'-$(CH_2)_2$—O-2') LNA, (D) Aminooxy (4'-CH_2—O—N(R)-2') LNA and (E) Oxyamino (4'-CH_2—N(R)—O-2') LNA; wherein R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008).

[00250] As used herein, LNA compounds include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the sugar wherein each of the bridges independently comprises 1 or from 2 to 4 linked groups independently selected from —$[C(R_1)(R_2)]_n$ —, —$C(R_1)$=$C(R_2)$—, —$C(R_1)$=N—, —C(=NR_1)—, —C(=O)—, —C(=S)—, —O—, —$Si(R_1)_2$—, —$S(=O)_x$— and —$N(R_1)$ —; wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; each R_1 and R_2 is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, a heterocycle radical, a substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O) —H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl

(S(=O)- J_1); and each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(=O) —H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1-C_{12} aminoalkyl, substituted C_1-C_{12} aminoalkyl or a protecting group.

[00251] Examples of 4'-2' bridging groups encompassed within the definition of LNA include, but are not limited to one of formulae: —$[C(R_1)(R_2)]_n$ —, — $[C(R_1)(R_2)]_n$—O—, — $C(R_1R_2)$—$N(R_1)$—O— or —$C(R_1R_2)$—O—$N(R_1)$—. Furthermore, other bridging groups encompassed with the definition of LNA are 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2—O-2', 4'-$(CH_2)_2$—O-2', 4'- CH_2—O—$N(R_1)$-2' and 4'- CH_2—$N(R_1)$—O-2'- bridges, wherein each R_1 and R_2 is, independently, H, a protecting group or C_1-C_{12} alkyl.

[00252] Also included within the definition of LNA according to the invention are LNAs in which the 2'-hydroxyl group of the ribosyl sugar ring is connected to the 4' carbon atom of the sugar ring, thereby forming a bridge to form the bicyclic sugar moiety. The bridge can be a methylene (—CH_2—) group connecting the 2' oxygen atom and the 4' carbon atom, for which the term methyleneoxy (4'-CH_2—O-2') LNA is used. Furthermore, in the case of the bicyclic sugar moiety having an ethylene bridging group in this position, the term ethyleneoxy (4'-CH_2CH_2—O-2') LNA is used.

[00253] As used herein, a "spacer" refers to a nucleoside-replacement group (*e.g.*, a non-nucleoside group that replaces a nucleoside present in a STMN2 parent oligonucleotide, KCNQ2 parent oligonucleotide, UNC13A parent oligonucleotide, and/or SMN2 parent oligonucleotide). The spacer is characterized by the lack of a nucleotide base and by the replacement of the nucleoside sugar moiety with a non-sugar substitute. The non-sugar substitute group of a spacer lacks an aldehyde, ketone, acetal, ketal, hemiacetal or hemiketal group. The non-sugar substitute group of a spacer is thus capable of connecting to the 3' and 5' positions of the nucleosides adjacent to the spacer through an internucleoside linker as described herein, but not capable of forming a covalent bond with a nucleotide base (*i.e.*, not capable of linking a nucleobase to another group, such as an internucleoside linkage, conjugate group, or terminal group in an oligonucleotide). Generally, a STMN2 oligonucleotide with a spacer is described in relation to a STMN2 parent oligonucleotide, wherein the spacer replaces a nucleoside of the STMN2 parent oligonucleotide. Generally, a KCNQ2 oligonucleotide with a spacer is described in relation to a KCNQ2 parent oligonucleotide, wherein the spacer replaces a nucleoside of the KCNQ2 parent oligonucleotide. Generally, a UNC13A oligonucleotide with a spacer is described in relation to a UNC13A parent oligonucleotide, wherein the spacer replaces a nucleoside of the UNC13A

parent oligonucleotide. Generally, a SMN2 oligonucleotide with a spacer is described in relation to a SMN2 parent oligonucleotide, wherein the spacer replaces a nucleoside of the SMN2 parent oligonucleotide. In all embodiments of the present disclosure, a spacer cannot hybridize to a nucleoside comprising a nucleobase at the corresponding position of a STMN2 transcript, KCNQ2 transcript, UNC13A transcript, and/or SMN2 transcript, within the numerical order of the length of the AON oligonucleotide (*i.e.*, if the spacer is positioned after nucleoside 4 of an AON (*i.e.*, at position 5 from the 5'-end), the spacer is not complementary to the nucleoside (A, C, G, or U) at the same corresponding position of the target STMN2 transcript, KCNQ2 transcript, UNC13A transcript, and/or SMN2 transcript).

[00254] As used herein, "mismatch" or a "non-complementary group" refers to the case when a group (e.g., nucleobase) of a first nucleic acid is not capable of pairing with the corresponding group (e.g., nucleobase) of a second or target nucleic acid.

[00255] As used herein, "modified internucleoside linkage" refers to a substitution or any change from a naturally occurring internucleoside linkage (*e.g.*, a phosphodiester internucleoside bond).

[00256] As used herein, "modified nucleobase" means any nucleobase other than adenine, cytosine, guanine, thymine, or uracil. Examples of a modified nucleobase include 5-methyl cytosine, pseudouridine, or 5-methoxyuridine. An "unmodified nucleobase" means the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C), and uracil (U).

[00257] As used herein, a "modified nucleoside" means a nucleoside having, independently, a modified sugar moiety and/or modified nucleobase. A universal base is a modified nucleobase that can pair with any one of the five unmodified nucleobases. Modified nucleosides include abasic nucleosides, which lack a nucleobase. However, modified nucleosides do not include spacers or other groups that are incapable of linking a nucleobase.

[00258] As used herein, "linked nucleosides" are nucleosides that are connected in a contiguous sequence (*i.e.*, no additional nucleosides are presented between those that are linked). In various embodiments, an oligonucleotide may have different segments of linked nucleosides connected through a spacer. Here, the spacer (*i.e.*, nucleoside replacement) is not considered a nucleoside and therefore, divides up the oligonucleotide into two segments of linked nucleosides. The oligonucleotide may have a first segment of Y linked nucleosides (*e.g.*, Y nucleosides that are connected in a contiguous sequence), followed by a spacer, and then a second segment of Z linked nucleosides. Here, the Y and Z linked nucleosides is described in either the 5' to 3' direction or the 3' to 5' direction. In various embodiments, the first segment consists of 7 or

fewer linked nucleosides (e.g., Y = 7 or fewer) whereas the second segment comprises 8 or more linked nucleosides (*e.g.*, Z = 8 or more).

[00259] As used herein, "modified oligonucleotide" means an oligonucleotide comprising at least one (*i.e.*, one or more) modified internucleoside linkage, modified sugar, and/or modified nucleobase.

[00260] As used herein, "modified sugar" or "modified sugar moiety" means a modified furanosyl sugar moiety or a modified sugar moiety having other than a furanosyl moiety that can link a nucleobase to another group, such as an internucleoside linkage, conjugate group, or terminal group in an oligonucleotide.

[00261] As used herein, "monomer" means a single unit of an oligomer. Monomers include, but are not limited to, nucleosides and nucleotides, whether naturally occurring or modified.

[00262] As used herein, "motif" means the pattern of unmodified and modified nucleosides in an antisense compound.

[00263] As used herein, "natural sugar moiety" means a sugar moiety found in DNA (2'-H) or RNA (2'-OH).

[00264] As used herein, "naturally occurring internucleoside linkage" means a 3' to 5' phosphodiester linkage.

[00265] As used herein, "non-complementary nucleobases" refers to a pair of nucleobases that do not form hydrogen bonds with one another or otherwise support hybridization.

[00266] As used herein, "nucleic acid" refers to molecules composed of monomeric nucleotides. A nucleic acid includes, but is not limited to, ribonucleic acids (RNA), deoxyribonucleic acids (DNA), single-stranded nucleic acids, double-stranded nucleic acids, non-coding RNA, small interfering ribonucleic acids (siRNA), short-hairpin RNA (shRNA), and microRNAs (miRNA).

[00267] As used herein, "nucleobase" means a heterocyclic moiety capable of base pairing with a base of another nucleic acid.

[00268] As used herein, "nucleobase complementarity" refers to a nucleobase that is capable of base pairing with another nucleobase. For example, in DNA, adenine (A) is complementary to thymine (T). For example, in RNA, adenine (A) is complementary to uracil (U). In certain embodiments, complementary nucleobase refers to a nucleobase of an antisense compound that is capable of base pairing with a corresponding nucleobase of its target nucleic acid. For example, if a nucleobase at a certain position of an antisense compound is capable of hydrogen bonding with a nucleobase at a certain position of a target nucleic acid, then the position of hydrogen

bonding between the oligonucleotide and the target nucleic acid is considered to be complementary at that nucleobase pair.

[00269] As used herein, "nucleobase sequence" means the order of nucleobases independent of any sugar, linkage, and/or nucleobase modification.

[00270] As used herein, "nucleoside" refers to a nucleobase linked to a sugar. The term "nucleoside" also includes a "modified nucleoside" which has independently, a modified sugar moiety and/or modified nucleobase.

[00271] As used herein, "nucleoside mimetic" includes those structures used to replace the sugar, the sugar and the base, or the base and not necessarily the linkage at one or more positions of an oligomeric compound such as for example nucleoside mimetics having morpholino, cyclohexenyl, cyclohexyl, tetrahydropyranyl, bicyclo, or tricyclo sugar mimetics, *e.g.*, non-furanose sugar units. Nucleotide mimetic includes those structures used to replace the nucleoside and the linkage at one or more positions of an oligomeric compound such as for example peptide nucleic acids or morpholinos (morpholinos linked by a phosphorodiamidate or other non-phosphodiester linkage). Sugar surrogate overlaps with the slightly broader term nucleoside mimetic but is intended to indicate replacement of the sugar unit (furanose ring) only. The tetrahydropyranyl rings provided herein are illustrative of an example of a sugar surrogate wherein the furanose sugar group has been replaced with a tetrahydropyranyl ring system. "Mimetic" refers to groups that are substituted for a sugar, a nucleobase, and/or internucleoside linkage. Generally, a mimetic is used in place of the sugar or sugar-internucleoside linkage combination, and the nucleobase is maintained for hybridization to a selected target.

[00272] As used herein, "nucleotide" means a nucleoside having a phosphate group covalently linked to the sugar portion of the nucleoside.

[00273] As used herein, "oligomeric compound" or "oligomer" means a polymer of linked monomeric subunits which is capable of hybridizing to at least a region of a nucleic acid molecule.

[00274] As used herein, "oligonucleotide" means a polymer of one or more segments of linked nucleosides each of which can be modified or unmodified, independent one from another.

[00275] As used herein, "hotspot region" is a range of nucleobases on a target nucleic acid amenable to oligomeric compound-mediated modulation of the splicing of the target nucleic acid.

[00276] As used herein, "hybridization" means the pairing or annealing of complementary oligonucleotides and/or nucleic acids. While not limited to a particular mechanism, the most

common mechanism of hybridization involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding between complementary nucleobases.

[00277] As used herein, "increasing the amount of activity" refers to more transcriptional expression, more accurate splicing resulting in full length mature mRNA and/or protein expression, and/or more activity relative to the transcriptional expression or activity in an untreated or control sample.

Antisense Therapeutics

[00278] Antisense therapeutics are a class of nucleic acid-based compounds that can be used to modulate a transcript, such as mRNA. In various embodiments, antisense therapeutics comprise one or more spacers and can be used to modulate a transcript that is transcribed from a gene, such as a STMN2 pre-mRNA comprising a cryptic exon, a KCNQ2 pre-mRNA, a UNC13A pre-mRNA, and/or a SMN2 pre-mRNA.

[00279] Antisense therapeutics may be single- or double-stranded deoxyribonucleic acid (DNA)-based, ribonucleic acid (RNA)-based, or DNA/RNA chemical analogue compounds. In general, antisense therapeutics are designed to include a sequence that is complementary or nearly complementary to an mRNA or pre-mRNA sequence transcribed from a given gene in order to promote binding between the antisense therapeutic and the pre-mRNA or mRNA. In certain embodiments, antisense therapeutics act by binding to an mRNA or pre-mRNA, thereby inhibiting protein translation, altering pre-mRNA splicing into mature mRNA (*e.g.,* by preventing appropriate proteins such as splicing activator proteins from binding), and/or causing destruction of mRNA. In certain embodiments, the antisense therapeutic sequence is complementary to a portion of a targeted gene's or mRNA's sense sequence. In certain embodiments, antisense therapeutics described herein are oligonucleotide-based compounds that include an oligonucleotide sequence complementary to a pre-mRNA sense, or a portion thereof, and one or more spacers. In certain embodiments, antisense therapeutics described herein can also be nucleotide chemical analog-based compounds.

[00280] In certain embodiments, an oligonucleotide, such as disclosed herein, may be an oligonucleotide sequence of 5 to 100 oligonucleotide units in length, for example, 10 to 60 oligonucleotide units in length, for example, 12 to 50 oligonucleotide units in length, 14 to 40 oligonucleotide units in length, 10 to 30 oligonucleotide units in length, for example, 14 to 30 oligonucleotide units in length, for example, 14 to 25 or 15 to 22 oligonucleotide units in length, or 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27 oligonucleotide units in length. As used herein, an

"oligonucleotide unit" refers to either a nucleoside (e.g., a nucleoside which includes a sugar and/or a nucleobase) or a nucleoside-replacement group (e.g., a spacer) of the oligonucleotide.

[00281] In particular embodiments, the oligonucleotides are 25 oligonucleotide units in length. In particular embodiments, the oligonucleotides are 23 oligonucleotide units in length. In particular embodiments, the oligonucleotides are 21 oligonucleotide units in length. In particular embodiments, the oligonucleotides are 19 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 18 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 19 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 20 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 21 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 22 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 23 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 24 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 25 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 26 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 27 oligonucleotide units in length.

[00282] In certain embodiments, AONs may include chemically modified nucleosides (for example, 2'-O-methylated nucleosides or 2'-O-(2-methoxyethyl) nucleosides) as well as modified internucleoside linkages (for example, phosphorothioate linkages). In certain embodiments, AONs described herein include oligonucleotide sequences that are complementary to RNA sequences, such as STMN2 mRNA sequences. In certain embodiments, AONs described herein can include chemically modified nucleosides and modified internucleoside linkages (for example, phosphorothioate linkages). In particular embodiments, AONs described herein include one or more spacers.

[00283] In various embodiments, the oligonucleotides comprise one or more spacers. In particular embodiments, the oligonucleotides comprise one spacer. In various embodiments, the oligonucleotides comprise two spacers. For example, the oligonucleotide includes 23 oligonucleotide units with 21 nucleobases and two nucleoside replacement groups (e.g., two spacers). Further embodiments of oligonucleotides with one spacer and oligonucleotides with two spacers are described herein. In various embodiments, the oligonucleotides comprise three spacers.

[00284] In some embodiments, an antisense oligonucleotide can be, but is not limited to, inhibitors of a gene transcript (for example, shRNAs, siRNAs, PNAs, LNAs, 2'-*O*-methyl (2'OMe) antisense oligonucleotide (AON), 2'-*O*-(2-methoxyethyl) (MOE) AON, or morpholino oligomers (*e.g.*, phosphorodiamidate morpholino (PMO))), or compositions that include such compounds. In some embodiments an oligonucleotide is an antisense oligonucleotide (AON) comprising 2'OMe (*e.g.*, a AON comprising one or more 2'OMe modified sugar), MOE (*e.g.*, a AON comprising one or more MOE modified sugar), peptide nucleic acids (*e.g.*, a AON comprising one or more *N*-(2-aminoethyl)-glycine units linked by amide bonds or carbonyl methylene linkage as repeating units in place of a sugar-phosphate backbone), locked nucleic acids (*e.g.*, a AON comprising one or more locked ribose, and can be a mixture of 2'-deoxy nucleotides or 2'OMe nucleotides), c-ET (*e.g.*, a AON comprising one or more cET sugar), constrained methoxyethyl (cMOE) (*e.g.*, a AON comprising one or more cMOE sugar), morpholino oligomer (*e.g.*, a AON comprising a backbone comprising one or more PMO), deoxy-2'-fluoro nucleoside (*e.g.*, a AON comprising one or more 2'-fluoro-β-D-arabinonucleoside), tricyclo-DNAs (tcDNA) (*e.g.*, a AON comprising one or more tcDNA modified sugar), 2'-O,4'-C-Ethylene-bridged nucleic acid (ENA) (*e.g.*, a AON comprising one or more ENA modified sugar), or hexitol nucleic acids (HNA) (*e.g.*, a AON comprising one or more HNA modified sugar). In some embodiments, a AON comprises one or more internucleoside linkage independently selected from a phosphorothioate linkage, phosphodiester linkage, phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, phosphorodiamidate morpholino (PMO) (morpholino) linkage, PNA linkage, or any combination of phosphorothioate linkage, phosphodiester linkage, a phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, a phosphoramidothioate linkage, thiophosphorodiamidate linkage, phosphorodiamidate morpholino (PMO) (morpholino) linkage, and PNA linkage. In some embodiments, a STMN2 AON, a KCNQ2 AON a UNC13A AON, or a SMN2 AON comprises one or more phosphorothioate linkage, phosphodiester linkage, or a combination of phosphorothioate and phosphodiester linkages.

[00285] Peptide nucleic acids (PNAs) are short, artificially synthesized polymers with a structure that mimics DNA or RNA. PNAs include a backbone composed of repeating N-(2-aminoethyl)-glycine units linked by peptide bonds. In certain embodiments, PNAs described herein can be used as antisense therapeutics that bind to RNA sequences with high specificity and increase,

restore, and/or stabilize levels (*e.g.*, full length UNC13A mRNA or protein levels) and/or activity (*e.g.*, biological activity, for example, UNC13A activity).

[00286] Locked nucleic acids (LNAs) are oligonucleotide sequences that include one or more modified RNA nucleotides in which the ribose moiety is modified with an extra bridge connecting the 2' oxygen and 4' carbon. LNAs are believed to have higher Tm's than analogous oligonucleotide sequences. In certain embodiments, LNAs described herein can be used as antisense therapeutics that bind to RNA sequences with high specificity. For example, LNAs can bind to STMN2 pre-RNA and repress premature polyadenylation of STMN2 pre-mRNA, and increase, restore, and/or stabilize STMN2 levels (*e.g.*, STMN2 mRNA or protein levels) and/or activity (*e.g.*, biological activity, for example, STMN2 activity); LNAs can bind to KCNQ2 pre-RNA and reduce mis-splicing of KCNQ2 pre-mRNA, and increase, restore, and/or stabilize KCNQ2 levels (*e.g.*, KCNQ2 mRNA or protein levels) and/or activity (*e.g.*, biological activity, for example, KCNQ2 activity); LNAs can bind to UNC13A pre-mRNA and prevent mis-splicing of UNC13A pre-mRNA, and increase, restore, and/or stabilize UNC13A levels (*e.g.*, UNC13A mRNA or protein levels) and/or activity (*e.g.*, biological activity, for example, UNC13A activity); and/or LNAs can bind to SMN2 pre-RNA and reduce mis-splicing of SMN2 pre-mRNA, and increase, restore, and/or stabilize SMN2 levels (*e.g.*, SMN2 mRNA or protein levels) and/or activity (*e.g.*, biological activity, for example, SMN2 activity).

[00287] Morpholino oligomers are oligonucleotide compounds that include bases attached to a backbone of methylenemorpholine rings linked through phosphorodiamidate groups. In certain embodiments, morpholino oligomers of the present invention can be designed to bind to specific pre-mRNA sequence of interest.

STMN2 Oligonucleotides Complementary to STMN2 Transcript with a Cryptic Exon

[00288] In some embodiments, a STMN2 AON includes a sequence that is at least 85% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a STMN2 transcript that includes a cryptic exon (e.g., SEQ ID NO: 1339 or SEQ ID NO: 1341). In some embodiments, a STMN2 AON includes a sequence that is between 85 and 98% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a STMN2 transcript that includes a cryptic exon (e.g., SEQ ID NO: 1339 or SEQ ID NO: 1341). In some embodiments, a STMN2 AON includes a sequence that is between 90-95% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a STMN2 transcript that includes a

cryptic exon (e.g., SEQ ID NO: 1339 or SEQ ID NO: 1341). In particular embodiments, a STMN2 AON includes a sequence that is at least 85% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a STMN2 transcript that includes a cryptic exon (e.g., SEQ ID NO: 1339 or SEQ ID NO: 1341). In particular embodiments, a STMN2 AON includes a sequence that is between 84% to 88% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a STMN2 transcript that includes a cryptic exon (e.g., SEQ ID NO: 1339 or SEQ ID NO: 1341). In particular embodiments, a STMN2 AON includes a sequence that is between 89% to 92% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a STMN2 transcript that includes a cryptic exon (e.g., SEQ ID NO: 1339 or SEQ ID NO: 1341). In particular embodiments, a STMN2 AON includes a sequence that is between 94% to 96% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a STMN2 transcript that includes a cryptic exon (e.g., SEQ ID NO: 1339 or SEQ ID NO: 1341).

[00289] In various embodiments, a STMN2 AON comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669. In various embodiments, a STMN2 AON comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669.

[00290] In various embodiments, the region of the STMN2 transcript targeted by the STMN2 AON is the cryptic exon sequence. In various embodiments, the region of the STMN2 transcript targeted by the STMN2 AON is a sequence located upstream or downstream (e.g., 100 or 200 bases upstream or downstream) of the cryptic exon sequence. In some embodiments, the STMN2 AON comprises a spacer and has a segment having at most 7 linked nucleosides. In some embodiments, the STMN2 AON comprises a spacer and has a segment having at most 6, 5, 4, 3, or 2 linked nucleosides.

[00291] STMN2 AON binding specificity can be assessed via measurement of parameters such as dissociation constant, melting temperature, or other criteria such as changes in protein or RNA expression levels or other assays that measure STMN2 activity or expression.

[00292] In some embodiments, a STMN2 AON can include a non-duplexed oligonucleotide. In some embodiments, a STMN2 AON can include a duplex of two oligonucleotides where the first

oligonucleotide includes a nucleobase sequence that is completely or almost completely complementary to a STMN2 pre-mRNA sequence and the second oligonucleotide includes a nucleobase sequence that is complementary to the nucleobase sequence of the first oligonucleotide.

[00293] In some embodiments, a STMN2 AON can target STMN2 pre-mRNAs that include a cryptic exon produced from STMN2 genes of one or more species. For example, a STMN2 AON can target a STMN2 pre-mRNA, which includes a cryptic exon, of a mammalian STMN2 gene, for example, a human (*i.e.*, *Homo sapiens*) STMN2 gene. In particular embodiments, the STMN2 AON targets a human STMN2 pre-mRNA, which includes a cryptic exon. In some embodiments, the STMN2 AON includes a nucleobase sequence that is complementary to a nucleobase sequence of a STMN2 gene or a STMN2 pre-mRNA, which includes a cryptic exon, or a portion thereof.

[00294] STMN2 AONs described herein include antisense oligonucleotides comprising the oligonucleotide sequences listed in Table 1 below:

Table 1. STMN2 AON Sequences, in each one or more spacers described in the present disclosure are incorporated for generation of an oligonucleotide of the present invention

SEQ ID NO:	AON Sequence* (5' → 3')	Region	SEQ ID NO:	Target Sequence (5' → 3')
1	GGAGGGATACCTGTATATTACAAGT		447	ACTTGTAATATACAGGTATCCCTCC
2	AGGAGGGATACCTGTATATTACAAG		448	CTTGTAATATACAGGTATCCCTCCT
3	CAGGAGGGATACCTGTATATTACAA		449	TTGTAATATACAGGTATCCCTCCTG
4	CCAGGAGGGATACCTGTATATTACA		450	TGTAATATACAGGTATCCCTCCTGG
5	ACCAGGAGGGATACCTGTATATTAC		451	GTAATATACAGGTATCCCTCCTGGT
6	TACCAGGAGGGATACCTGTATATTA		452	TAATATACAGGTATCCCTCCTGGTA
7	TTACCAGGAGGGATACCTGTATATT		453	AATATACAGGTATCCCTCCTGGTAA
8	CTTACCAGGAGGGATACCTGTATAT		454	ATATACAGGTATCCCTCCTGGTAAG
9	GCTTACCAGGAGGGATACCTGTATA		455	TATACAGGTATCCCTCCTGGTAAGC
10	AGCTTACCAGGAGGGATACCTGTAT		456	ATACAGGTATCCCTCCTGGTAAGCT
11	GAGCTTACCAGGAGGGATACCTGTA		457	TACAGGTATCCCTCCTGGTAAGCTC
12	AGAGCTTACCAGGAGGGATACCTGT		458	ACAGGTATCCCTCCTGGTAAGCTCT
13	CAGAGCTTACCAGGAGGGATACCTG		459	CAGGTATCCCTCCTGGTAAGCTCTG
14	CCAGAGCTTACCAGGAGGGATACCT		460	AGGTATCCCTCCTGGTAAGCTCTGG
15	ACCAGAGCTTACCAGGAGGGATACC		461	GGTATCCCTCCTGGTAAGCTCTGGT
16	TACCAGAGCTTACCAGGAGGGATAC		462	GTATCCCTCCTGGTAAGCTCTGGTA
17	ATACCAGAGCTTACCAGGAGGGATA		463	TATCCCTCCTGGTAAGCTCTGGTAT
18	AATACCAGAGCTTACCAGGAGGGAT		464	ATCCCTCCTGGTAAGCTCTGGTATT

19	TAATACCAGAGCTTACCAGGAGGGA		465	TCCCTCCTGGTAAGCTCTGGTATTA
20	ATAATACCAGAGCTTACCAGGAGGG		466	CCCTCCTGGTAAGCTCTGGTATTAT
21	CATAATACCAGAGCTTACCAGGAGG		467	CCTCCTGGTAAGCTCTGGTATTATG
22	ACATAATACCAGAGCTTACCAGGAG		468	CTCCTGGTAAGCTCTGGTATTATGT
23	GACATAATACCAGAGCTTACCAGGA		469	TCCTGGTAAGCTCTGGTATTATGTC
24	AGACATAATACCAGAGCTTACCAGG		470	CCTGGTAAGCTCTGGTATTATGTCT
25	AAGACATAATACCAGAGCTTACCAG		471	CTGGTAAGCTCTGGTATTATGTCTT
26	TAAGACATAATACCAGAGCTTACCA		472	TGGTAAGCTCTGGTATTATGTCTTA
27	TTAAGACATAATACCAGAGCTTACC		473	GGTAAGCTCTGGTATTATGTCTTAA
28	GTTAAGACATAATACCAGAGCTTAC		474	GTAAGCTCTGGTATTATGTCTTAAC
29	TGTTAAGACATAATACCAGAGCTTA		475	TAAGCTCTGGTATTATGTCTTAACA
30	ATGTTAAGACATAATACCAGAGCTT	branch point 1	476	AAGCTCTGGTATTATGTCTTAACAT
31	AATGTTAAGACATAATACCAGAGCT	branch point 1	477	AGCTCTGGTATTATGTCTTAACATT
32	AAATGTTAAGACATAATACCAGAGC	branch point 1	478	GCTCTGGTATTATGTCTTAACATTT
33	AAAATGTTAAGACATAATACCAGAG	branch point 1	479	CTCTGGTATTATGTCTTAACATTTT
34	AAAAATGTTAAGACATAATACCAGA	branch point 1	480	TCTGGTATTATGTCTTAACATTTTT
35	TAAAAATGTTAAGACATAATACCAG	branch point 1	481	CTGGTATTATGTCTTAACATTTTTA
36	TTAAAAATGTTAAGACATAATACCA	branch point 1	482	TGGTATTATGTCTTAACATTTTTAA
37	TTTAAAAATGTTAAGACATAATACC	branch point 1	483	GGTATTATGTCTTAACATTTTTAAA
38	ATTTAAAAATGTTAAGACATAATAC	branch point 1	484	GTATTATGTCTTAACATTTTTAAAT
39	GATTTAAAAATGTTAAGACATAATA	branch point 1	485	TATTATGTCTTAACATTTTTAAATC
40	AGATTTAAAAATGTTAAGACATAAT	branch point 1	486	ATTATGTCTTAACATTTTTAAATCT
41	TAGATTTAAAAATGTTAAGACATAA	branch point 1	487	TTATGTCTTAACATTTTTAAATCTA
42	ATAGATTTAAAAATGTTAAGACATA	branch point 1	488	TATGTCTTAACATTTTTAAATCTAT
43	CATAGATTTAAAAATGTTAAGACAT	branch point 1	489	ATGTCTTAACATTTTTAAATCTATG
44	CCATAGATTTAAAAATGTTAAGACA	branch point 1	490	TGTCTTAACATTTTTAAATCTATGG
45	ACCATAGATTTAAAAATGTTAAGAC	branch point 1	491	GTCTTAACATTTTTAAATCTATGGT
46	TACCATAGATTTAAAAATGTTAAGA	branch point 1	492	TCTTAACATTTTTAAATCTATGGTA
47	TTACCATAGATTTAAAAATGTTAAG		493	CTTAACATTTTTAAATCTATGGTAA
48	ATTACCATAGATTTAAAAATGTTAA		494	TTAACATTTTTAAATCTATGGTAAT
49	GATTACCATAGATTTAAAAATGTTA		495	TAACATTTTTAAATCTATGGTAATC

50	AGATTACCATAGATTTAAAAATGTT	Branch point 2	496	AACATTTTTAAATCTATGGTAATCT
51	AAGATTACCATAGATTTAAAAATGT	Branch point 2	497	ACATTTTTAAATCTATGGTAATCTT
52	AAAGATTACCATAGATTTAAAAATG	Branch point 2	498	CATTTTTAAATCTATGGTAATCTTT
53	TAAAGATTACCATAGATTTAAAAAT	Branch point 2	499	ATTTTTAAATCTATGGTAATCTTTA
54	GTAAAGATTACCATAGATTTAAAAA	Branch point 2	500	TTTTTAAATCTATGGTAATCTTTAC
55	TGTAAAGATTACCATAGATTTAAAA	Branch point 2	501	TTTTAAATCTATGGTAATCTTTACA
56	TTGTAAAGATTACCATAGATTTAAA	Branch point 2	502	TTTAAATCTATGGTAATCTTTACAA
57	TTTGTAAAGATTACCATAGATTTAA	Branch point 2	503	TTAAATCTATGGTAATCTTTACAAA
58	TTTTGTAAAGATTACCATAGATTTA	Branch point 2	504	TAAATCTATGGTAATCTTTACAAAA
59	ATTTTGTAAAGATTACCATAGATTT	Branch point 2	505	AAATCTATGGTAATCTTTACAAAAT
60	TATTTTGTAAAGATTACCATAGATT	Branch point 2	506	AATCTATGGTAATCTTTACAAAATA
61	ATATTTTGTAAAGATTACCATAGAT	Branch point 2	507	ATCTATGGTAATCTTTACAAAATAT
62	AATATTTTGTAAAGATTACCATAGA	Branch point 2	508	TCTATGGTAATCTTTACAAAATATT
63	AAATATTTTGTAAAGATTACCATAG	Branch point 2	509	CTATGGTAATCTTTACAAAATATTT
64	AAAATATTTTGTAAAGATTACCATA	Branch point 2	510	TATGGTAATCTTTACAAAATATTTT
65	TAAAATATTTTGTAAAGATTACCAT	Branch point 2	511	ATGGTAATCTTTACAAAATATTTTA
66	GTAAAATATTTTGTAAAGATTACCA	Branch point 2	512	TGGTAATCTTTACAAAATATTTTAC
67	AGTAAAATATTTTGTAAAGATTACC		513	GGTAATCTTTACAAAATATTTTACT
68	AAGTAAAATATTTTGTAAAGATTAC		514	GTAATCTTTACAAAATATTTTACTT
69	GAAGTAAAATATTTTGTAAAGATTA		515	TAATCTTTACAAAATATTTTACTTC
70	GGAAGTAAAATATTTTGTAAAGATT		516	AATCTTTACAAAATATTTTACTTCC
71	CGGAAGTAAAATATTTTGTAAAGAT		517	ATCTTTACAAAATATTTTACTTCCG
72	TCGGAAGTAAAATATTTTGTAAAGA		518	TCTTTACAAAATATTTTACTTCCGA
73	TTCGGAAGTAAAATATTTTGTAAAG		519	CTTTACAAAATATTTTACTTCCGAA
74	GTTCGGAAGTAAAATATTTTGTAAA		520	TTTACAAAATATTTTACTTCCGAAC
75	AGTTCGGAAGTAAAATATTTTGTAA		521	TTACAAAATATTTTACTTCCGAACT
76	GAGTTCGGAAGTAAAATATTTTGTA		522	TACAAAATATTTTACTTCCGAACTC
77	TGAGTTCGGAAGTAAAATATTTTGT		523	ACAAAATATTTTACTTCCGAACTCA
78	ATGAGTTCGGAAGTAAAATATTTTG		524	CAAAATATTTTACTTCCGAACTCAT
79	TATGAGTTCGGAAGTAAAATATTTT		525	AAAATATTTTACTTCCGAACTCATA
80	ATATGAGTTCGGAAGTAAAATATTT		526	AAATATTTTACTTCCGAACTCATAT

81	TATATGAGTTCGGAAGTAAAATATT		527	AATATTTTACTTCCGAACTCATATA
82	GTATATGAGTTCGGAAGTAAAATAT		528	ATATTTTACTTCCGAACTCATATAC
83	GGTATATGAGTTCGGAAGTAAAATA		529	TATTTTACTTCCGAACTCATATACC
84	AGGTATATGAGTTCGGAAGTAAAAT		530	ATTTTACTTCCGAACTCATATACCT
85	CAGGTATATGAGTTCGGAAGTAAAA		531	TTTTACTTCCGAACTCATATACCTG
86	CCAGGTATATGAGTTCGGAAGTAAA		532	TTTACTTCCGAACTCATATACCTGG
87	CCCAGGTATATGAGTTCGGAAGTAA		533	TTACTTCCGAACTCATATACCTGGG
88	CCCCAGGTATATGAGTTCGGAAGTA		534	TACTTCCGAACTCATATACCTGGGG
89	TCCCCAGGTATATGAGTTCGGAAGT		535	ACTTCCGAACTCATATACCTGGGGA
90	ATCCCCAGGTATATGAGTTCGGAAG		536	CTTCCGAACTCATATACCTGGGGAT
91	AATCCCCAGGTATATGAGTTCGGAA		537	TTCCGAACTCATATACCTGGGGATT
92	AAATCCCCAGGTATATGAGTTCGGA		538	TCCGAACTCATATACCTGGGGATTT
93	AAAATCCCCAGGTATATGAGTTCGG		539	CCGAACTCATATACCTGGGGATTTT
94	TAAAATCCCCAGGTATATGAGTTCG		540	CGAACTCATATACCTGGGGATTTTA
95	ATAAAATCCCCAGGTATATGAGTTC		541	GAACTCATATACCTGGGGATTTTAT
96	AATAAAATCCCCAGGTATATGAGTT		542	AACTCATATACCTGGGGATTTTATT
97	TAATAAAATCCCCAGGTATATGAGT		543	ACTCATATACCTGGGGATTTTATTA
98	GTAATAAAATCCCCAGGTATATGAG		544	CTCATATACCTGGGGATTTTATTAC
99	AGTAATAAAATCCCCAGGTATATGA		545	TCATATACCTGGGGATTTTATTACT
100	GAGTAATAAAATCCCCAGGTATATG		546	CATATACCTGGGGATTTTATTACTC
101	AGAGTAATAAAATCCCCAGGTATAT		547	ATATACCTGGGGATTTTATTACTCT
102	CAGAGTAATAAAATCCCCAGGTATA		548	TATACCTGGGGATTTTATTACTCTG
103	CCAGAGTAATAAAATCCCCAGGTAT		549	ATACCTGGGGATTTTATTACTCTGG
104	CCCAGAGTAATAAAATCCCCAGGTA		550	TACCTGGGGATTTTATTACTCTGGG
105	TCCCAGAGTAATAAAATCCCCAGGT		551	ACCTGGGGATTTTATTACTCTGGGA
106	TTCCCAGAGTAATAAAATCCCCAGG		552	CCTGGGGATTTTATTACTCTGGGAA
107	ATTCCCAGAGTAATAAAATCCCCAG		553	CTGGGGATTTTATTACTCTGGGAAT
108	AATTCCCAGAGTAATAAAATCCCCA		554	TGGGGATTTTATTACTCTGGGAATT
109	TAATTCCCAGAGTAATAAAATCCCC		555	GGGGATTTTATTACTCTGGGAATTA
110	ATAATTCCCAGAGTAATAAAATCCC		556	GGGATTTTATTACTCTGGGAATTAT
111	CATAATTCCCAGAGTAATAAAATCC		557	GGATTTTATTACTCTGGGAATTATG
112	ACATAATTCCCAGAGTAATAAAATC		558	GATTTTATTACTCTGGGAATTATGT
113	CACATAATTCCCAGAGTAATAAAAT		559	ATTTTATTACTCTGGGAATTATGTG
114	ACACATAATTCCCAGAGTAATAAAA		560	TTTTATTACTCTGGGAATTATGTGT
115	AACACATAATTCCCAGAGTAATAAA		561	TTTATTACTCTGGGAATTATGTGTT
116	GAACACATAATTCCCAGAGTAATAA		562	TTATTACTCTGGGAATTATGTGTTC
117	AGAACACATAATTCCCAGAGTAATA		563	TATTACTCTGGGAATTATGTGTTCT
118	CAGAACACATAATTCCCAGAGTAAT		564	ATTACTCTGGGAATTATGTGTTCTG
119	GCAGAACACATAATTCCCAGAGTAA		565	TTACTCTGGGAATTATGTGTTCTGC
120	GGCAGAACACATAATTCCCAGAGTA		566	TACTCTGGGAATTATGTGTTCTGCC
121	GGGCAGAACACATAATTCCCAGAGT		567	ACTCTGGGAATTATGTGTTCTGCCC
122	GGGGCAGAACACATAATTCCCAGAG		568	CTCTGGGAATTATGTGTTCTGCCCC

123	TGGGGCAGAACACATAATTCCCAGA		569	TCTGGGAATTATGTGTTCTGCCCCA
124	ATGGGGCAGAACACATAATTCCCAG		570	CTGGGAATTATGTGTTCTGCCCCAT
125	GATGGGGCAGAACACATAATTCCCA		571	TGGGAATTATGTGTTCTGCCCCATC
126	TGATGGGGCAGAACACATAATTCCC		572	GGGAATTATGTGTTCTGCCCCATCA
127	GTGATGGGGCAGAACACATAATTCC		573	GGAATTATGTGTTCTGCCCCATCAC
128	AGTGATGGGGCAGAACACATAATTC		574	GAATTATGTGTTCTGCCCCATCACT
129	GAGTGATGGGGCAGAACACATAATT	Branch point 3	575	AATTATGTGTTCTGCCCCATCACTC
130	AGAGTGATGGGGCAGAACACATAAT	Branch point 3	576	ATTATGTGTTCTGCCCCATCACTCT
131	GAGAGTGATGGGGCAGAACACATAA	Branch point 3	577	TTATGTGTTCTGCCCCATCACTCTC
132	AGAGAGTGATGGGGCAGAACACATA	Branch point 3	578	TATGTGTTCTGCCCCATCACTCTCT
133	GAGAGAGTGATGGGGCAGAACACAT	Branch point 3	579	ATGTGTTCTGCCCCATCACTCTCTC
134	AGAGAGAGTGATGGGGCAGAACACA	Branch point 3	580	TGTGTTCTGCCCCATCACTCTCTCT
135	AAGAGAGAGTGATGGGGCAGAACAC	Branch point 3	581	GTGTTCTGCCCCATCACTCTCTCTT
136	TAAGAGAGAGTGATGGGGCAGAACA	Branch point 3	582	TGTTCTGCCCCATCACTCTCTCTTA
137	TTAAGAGAGAGTGATGGGGCAGAAC	Branch point 3	583	GTTCTGCCCCATCACTCTCTCTTAA
138	ATTAAGAGAGAGTGATGGGGCAGAA	Branch point 3	584	TTCTGCCCCATCACTCTCTCTTAAT
139	AATTAAGAGAGAGTGATGGGGCAGA	Branch point 3	585	TCTGCCCCATCACTCTCTCTTAATT
140	CAATTAAGAGAGAGTGATGGGGCAG	Branch point 3	586	CTGCCCCATCACTCTCTCTTAATTG
141	CCAATTAAGAGAGAGTGATGGGGCA	Branch point 3	587	TGCCCCATCACTCTCTCTTAATTGG
142	TCCAATTAAGAGAGAGTGATGGGGC	Branch point 3	588	GCCCCATCACTCTCTCTTAATTGGA
143	ATCCAATTAAGAGAGAGTGATGGGG	Branch point 3	589	CCCCATCACTCTCTCTTAATTGGAT
144	AATCCAATTAAGAGAGAGTGATGGG	Branch point 3	590	CCCATCACTCTCTCTTAATTGGATT
145	AAATCCAATTAAGAGAGAGTGATGG	Branch point 3	591	CCATCACTCTCTCTTAATTGGATTT
146	AAAATCCAATTAAGAGAGAGTGATG		592	CATCACTCTCTCTTAATTGGATTTT
147	AAAAATCCAATTAAGAGAGAGTGAT		593	ATCACTCTCTCTTAATTGGATTTTT
148	TAAAAATCCAATTAAGAGAGAGTGA		594	TCACTCTCTCTTAATTGGATTTTTA
149	TTAAAAATCCAATTAAGAGAGAGTG		595	CACTCTCTCTTAATTGGATTTTTAA
150	TTTAAAAATCCAATTAAGAGAGAGT		596	ACTCTCTCTTAATTGGATTTTTAAA
151	TTTTAAAAATCCAATTAAGAGAGAG		597	CTCTCTCTTAATTGGATTTTTAAAA
152	ATTTTAAAAATCCAATTAAGAGAGA		598	TCTCTCTTAATTGGATTTTTAAAAT
153	AATTTTAAAAATCCAATTAAGAGAG		599	CTCTCTTAATTGGATTTTTAAAATT

154	TAATTTTAAAAATCCAATTAAGAGA		600	TCTCTTAATTGGATTTTTAAAATTA
155	ATAATTTTAAAAATCCAATTAAGAG		601	CTCTTAATTGGATTTTTAAAATTAT
156	TATAATTTTAAAAATCCAATTAAGA		602	TCTTAATTGGATTTTTAAAATTATA
157	ATATAATTTTAAAAATCCAATTAAG		603	CTTAATTGGATTTTTAAAATTATAT
158	AATATAATTTTAAAAATCCAATTAA		604	TTAATTGGATTTTTAAAATTATATT
159	GAATATAATTTTAAAAATCCAATTA		605	TAATTGGATTTTTAAAATTATATTC
160	TGAATATAATTTTAAAAATCCAATT		606	AATTGGATTTTTAAAATTATATTCA
161	ATGAATATAATTTTAAAAATCCAAT		607	ATTGGATTTTTAAAATTATATTCAT
162	TATGAATATAATTTTAAAAATCCAA		608	TTGGATTTTTAAAATTATATTCATA
163	ATATGAATATAATTTTAAAAATCCA		609	TGGATTTTTAAAATTATATTCATAT
164	AATATGAATATAATTTTAAAAATCC		610	GGATTTTTAAAATTATATTCATATT
165	CAATATGAATATAATTTTAAAAATC		611	GATTTTTAAAATTATATTCATATTG
166	GCAATATGAATATAATTTTAAAAAT		612	ATTTTTAAAATTATATTCATATTGC
167	TGCAATATGAATATAATTTTAAAAA		613	TTTTTAAAATTATATTCATATTGCA
168	CTGCAATATGAATATAATTTTAAAA		614	TTTTAAAATTATATTCATATTGCAG
169	CCTGCAATATGAATATAATTTTAAA		615	TTTAAAATTATATTCATATTGCAGG
170	TCCTGCAATATGAATATAATTTTAA		616	TTAAAATTATATTCATATTGCAGGA
171	GTCCTGCAATATGAATATAATTTTA	Acceptor site	617	TAAAATTATATTCATATTGCAGGAC
172	AGTCCTGCAATATGAATATAATTTT	Acceptor site	618	AAAATTATATTCATATTGCAGGACT
173	GAGTCCTGCAATATGAATATAATTT	Acceptor site	619	AAATTATATTCATATTGCAGGACTC
174	CGAGTCCTGCAATATGAATATAATT	Acceptor site	620	AATTATATTCATATTGCAGGACTCG
175	CCGAGTCCTGCAATATGAATATAAT	Acceptor site	621	ATTATATTCATATTGCAGGACTCGG
176	GCCGAGTCCTGCAATATGAATATAA	Acceptor site	622	TTATATTCATATTGCAGGACTCGGC
177	TGCCGAGTCCTGCAATATGAATATA	Acceptor site	623	TATATTCATATTGCAGGACTCGGCA
178	CTGCCGAGTCCTGCAATATGAATAT	Acceptor site	624	ATATTCATATTGCAGGACTCGGCAG
179	TCTGCCGAGTCCTGCAATATGAATA	Acceptor site	625	TATTCATATTGCAGGACTCGGCAGA
180	TTCTGCCGAGTCCTGCAATATGAAT	Acceptor site	626	ATTCATATTGCAGGACTCGGCAGAA
181	CTTCTGCCGAGTCCTGCAATATGAA	Acceptor site	627	TTCATATTGCAGGACTCGGCAGAAG
182	TCTTCTGCCGAGTCCTGCAATATGA	Acceptor site	628	TCATATTGCAGGACTCGGCAGAAGA
183	GTCTTCTGCCGAGTCCTGCAATATG	Acceptor site	629	CATATTGCAGGACTCGGCAGAAGAC
184	GGTCTTCTGCCGAGTCCTGCAATAT	Acceptor site	630	ATATTGCAGGACTCGGCAGAAGACC
185	AGGTCTTCTGCCGAGTCCTGCAATA	Acceptor site	631	TATTGCAGGACTCGGCAGAAGACCT

186	AAGGTCTTCTGCCGAGTCCTGCAAT	Acceptor site	632	ATTGCAGGACTCGGCAGAAGACCTT
187	GAAGGTCTTCTGCCGAGTCCTGCAA	Acceptor site	633	TTGCAGGACTCGGCAGAAGACCTTC
188	CGAAGGTCTTCTGCCGAGTCCTGCA	Acceptor site	634	TGCAGGACTCGGCAGAAGACCTTCG
189	TCGAAGGTCTTCTGCCGAGTCCTGC	Acceptor site	635	GCAGGACTCGGCAGAAGACCTTCGA
190	CTCGAAGGTCTTCTGCCGAGTCCTG	Acceptor site	636	CAGGACTCGGCAGAAGACCTTCGAG
191	TCTCGAAGGTCTTCTGCCGAGTCCT	ESE Binding	637	AGGACTCGGCAGAAGACCTTCGAGA
192	CTCTCGAAGGTCTTCTGCCGAGTCC	ESE Binding	638	GGACTCGGCAGAAGACCTTCGAGAG
193	TCTCTCGAAGGTCTTCTGCCGAGTC	ESE Binding	639	GACTCGGCAGAAGACCTTCGAGAGA
194	TTCTCTCGAAGGTCTTCTGCCGAGT	ESE Binding	640	ACTCGGCAGAAGACCTTCGAGAGAA
195	TTTCTCTCGAAGGTCTTCTGCCGAG	ESE Binding	641	CTCGGCAGAAGACCTTCGAGAGAAA
196	CTTTCTCTCGAAGGTCTTCTGCCGA	ESE Binding	642	TCGGCAGAAGACCTTCGAGAGAAAG
197	CCTTTCTCTCGAAGGTCTTCTGCCG	ESE Binding	643	CGGCAGAAGACCTTCGAGAGAAAGG
198	ACCTTTCTCTCGAAGGTCTTCTGCC	ESE Binding	644	GGCAGAAGACCTTCGAGAGAAAGGT
199	TACCTTTCTCTCGAAGGTCTTCTGC	ESE Binding	645	GCAGAAGACCTTCGAGAGAAAGGTA
200	CTACCTTTCTCTCGAAGGTCTTCTG	ESE Binding	646	CAGAAGACCTTCGAGAGAAAGGTAG
201	TCTACCTTTCTCTCGAAGGTCTTCT	ESE Binding	647	AGAAGACCTTCGAGAGAAAGGTAGA
202	TTCTACCTTTCTCTCGAAGGTCTTC	ESE Binding	648	GAAGACCTTCGAGAGAAAGGTAGAA
203	TTTCTACCTTTCTCTCGAAGGTCTT	ESE Binding	649	AAGACCTTCGAGAGAAAGGTAGAAA
204	TTTTCTACCTTTCTCTCGAAGGTCT	ESE Binding	650	AGACCTTCGAGAGAAAGGTAGAAAA
205	ATTTTCTACCTTTCTCTCGAAGGTC	ESE Binding	651	GACCTTCGAGAGAAAGGTAGAAAAT
206	TATTTTCTACCTTTCTCTCGAAGGT	ESE Binding	652	ACCTTCGAGAGAAAGGTAGAAAATA
207	TTATTTTCTACCTTTCTCTCGAAGG	ESE Binding	653	CCTTCGAGAGAAAGGTAGAAAATAA
208	CTTATTTTCTACCTTTCTCTCGAAG	ESE Binding	654	CTTCGAGAGAAAGGTAGAAAATAAG
209	TCTTATTTTCTACCTTTCTCTCGAA	ESE Binding	655	TTCGAGAGAAAGGTAGAAAATAAGA
210	TTCTTATTTTCTACCTTTCTCTCGA	ESE Binding	656	TCGAGAGAAAGGTAGAAAATAAGAA

211	ATTCTTATTTTCTACCTTTCTCTCG	ESE Binding	657	CGAGAGAAAGGTAGAAAATAAGAAT
212	AATTCTTATTTTCTACCTTTCTCTC	ESE Binding	658	GAGAGAAAGGTAGAAAATAAGAATT
213	AAATTCTTATTTTCTACCTTTCTCT	ESE Binding	659	AGAGAAAGGTAGAAAATAAGAATTT
214	CAAATTCTTATTTTCTACCTTTCTC	ESE Binding	660	GAGAAAGGTAGAAAATAAGAATTTG
215	CCAAATTCTTATTTTCTACCTTTCT	ESE Binding	661	AGAAAGGTAGAAAATAAGAATTTGG
216	GCCAAATTCTTATTTTCTACCTTTC	ESE Binding	662	GAAAGGTAGAAAATAAGAATTTGGC
217	AGCCAAATTCTTATTTTCTACCTTT	ESE Binding	663	AAAGGTAGAAAATAAGAATTTGGCT
218	GAGCCAAATTCTTATTTTCTACCTT	ESE Binding	664	AAGGTAGAAAATAAGAATTTGGCTC
219	AGAGCCAAATTCTTATTTTCTACCT	ESE Binding	665	AGGTAGAAAATAAGAATTTGGCTCT
220	GAGAGCCAAATTCTTATTTTCTACC	ESE Binding	666	GGTAGAAAATAAGAATTTGGCTCTC
221	AGAGAGCCAAATTCTTATTTTCTAC	ESE Binding	667	GTAGAAAATAAGAATTTGGCTCTCT
222	CAGAGAGCCAAATTCTTATTTTCTA		668	TAGAAAATAAGAATTTGGCTCTCTG
223	ACAGAGAGCCAAATTCTTATTTTCT		669	AGAAAATAAGAATTTGGCTCTCTGT
224	CACAGAGAGCCAAATTCTTATTTTC		670	GAAAATAAGAATTTGGCTCTCTGTG
225	ACACAGAGAGCCAAATTCTTATTTT		671	AAAATAAGAATTTGGCTCTCTGTGT
226	CACACAGAGAGCCAAATTCTTATTT	Overlaps TDP-43 site 1	672	AAATAAGAATTTGGCTCTCTGTGTG
227	TCACACAGAGAGCCAAATTCTTATT	Overlaps TDP-43 site 1	673	AATAAGAATTTGGCTCTCTGTGTGA
228	CTCACACAGAGAGCCAAATTCTTAT	Overlaps TDP-43 site 1	674	ATAAGAATTTGGCTCTCTGTGTGAG
229	GCTCACACAGAGAGCCAAATTCTTA	Overlaps TDP-43 site 1	675	TAAGAATTTGGCTCTCTGTGTGAGC
230	TGCTCACACAGAGAGCCAAATTCTT	Overlaps TDP-43 site 1	676	AAGAATTTGGCTCTCTGTGTGAGCA
231	ATGCTCACACAGAGAGCCAAATTCT	Overlaps TDP-43 site 1	677	AGAATTTGGCTCTCTGTGTGAGCAT
232	CATGCTCACACAGAGAGCCAAATTC	Overlaps TDP-43 site 1	678	GAATTTGGCTCTCTGTGTGAGCATG
233	ACATGCTCACACAGAGAGCCAAATT	Overlaps TDP-43 site 1	679	AATTTGGCTCTCTGTGTGAGCATGT

234	CACATGCTCACACAGAGAGCCAAAT	Overlaps TDP-43 site 1	680	ATTTGGCTCTCTGTGTGAGCATGTG
235	ACACATGCTCACACAGAGAGCCAAA	Overlaps TDP-43 site 1	681	TTTGGCTCTCTGTGTGAGCATGTGT
236	CACACATGCTCACACAGAGAGCCAA	Overlaps TDP-43 site 1 & 2	682	TTGGCTCTCTGTGTGAGCATGTGTG
237	GCACACATGCTCACACAGAGAGCCA	Overlaps TDP-43 site 1 & 2	683	TGGCTCTCTGTGTGAGCATGTGTGC
238	CGCACACATGCTCACACAGAGAGCC	Overlaps TDP-43 site 1 & 2	684	GGCTCTCTGTGTGAGCATGTGTGCG
239	ACGCACACATGCTCACACAGAGAGC	Overlaps TDP-43 site 1 & 2	685	GCTCTCTGTGTGAGCATGTGTGCGT
240	CACGCACACATGCTCACACAGAGAG	Overlaps TDP-43 site 1 & 2	686	CTCTCTGTGTGAGCATGTGTGCGTG
241	ACACGCACACATGCTCACACAGAGA	Overlaps TDP-43 site 1 & 2	687	TCTCTGTGTGAGCATGTGTGCGTGT
242	CACACGCACACATGCTCACACAGAG	Overlaps TDP-43 site 1 & 2	688	CTCTGTGTGAGCATGTGTGCGTGTG
243	ACACACGCACACATGCTCACACAGA	Overlaps TDP-43 site 1 & 2	689	TCTGTGTGAGCATGTGTGCGTGTGT
244	CACACACGCACACATGCTCACACAG	Overlaps TDP-43 site 1 & 2 & 3	690	CTGTGTGAGCATGTGTGCGTGTGTG
245	GCACACACGCACACATGCTCACACA	Overlaps TDP-43 site 1 & 2 & 3	691	TGTGTGAGCATGTGTGCGTGTGTGC
246	CGCACACACGCACACATGCTCACAC	Overlaps TDP-43 site 2 & 3	692	GTGTGAGCATGTGTGCGTGTGTGCG

247	TCGCACACACGCACACATGCTCACA	Overlaps TDP-43 site 2 & 3	693	TGTGAGCATGTGTGCGTGTGTGCGA
248	CTCGCACACACGCACACATGCTCAC	Overlaps TDP-43 site 2 & 3	694	GTGAGCATGTGTGCGTGTGTGCGAG
249	TCTCGCACACACGCACACATGCTCA	Overlaps TDP-43 site 2 & 3	695	TGAGCATGTGTGCGTGTGTGCGAGA
250	CTCTCGCACACACGCACACATGCTC	Overlaps TDP-43 site 2 & 3	696	GAGCATGTGTGCGTGTGTGCGAGAG
251	TCTCTCGCACACACGCACACATGCT	Overlaps TDP-43 site 2 & 3	697	AGCATGTGTGCGTGTGTGCGAGAGA
252	CTCTCTCGCACACACGCACACATGC	Overlaps TDP-43 site 2 & 3	698	GCATGTGTGCGTGTGTGCGAGAGAG
253	TCTCTCTCGCACACACGCACACATG	Overlaps TDP-43 site 2 & 3	699	CATGTGTGCGTGTGTGCGAGAGAGA
254	CTCTCTCTCGCACACACGCACACAT	Overlaps TDP-43 site 2 & 3	700	ATGTGTGCGTGTGTGCGAGAGAGAG
255	TCTCTCTCTCGCACACACGCACACA	Overlaps TDP-43 site 2 & 3	701	TGTGTGCGTGTGTGCGAGAGAGAGA
256	CTCTCTCTCTCGCACACACGCACAC	Overlaps TDP-43 site 3	702	GTGTGCGTGTGTGCGAGAGAGAGAG
257	TCTCTCTCTCTCGCACACACGCACA	Overlaps TDP-43 site 3	703	TGTGCGTGTGTGCGAGAGAGAGAGA
258	GTCTCTCTCTCTCGCACACACGCAC	Overlaps TDP-43 site 3	704	GTGCGTGTGTGCGAGAGAGAGAGAC
259	TGTCTCTCTCTCTCGCACACACGCA	Overlaps TDP-43 site 3	705	TGCGTGTGTGCGAGAGAGAGAGACA
260	CTGTCTCTCTCTCTCGCACACACGC	Overlaps TDP-43 site 3	706	GCGTGTGTGCGAGAGAGAGAGACAG

261	TCTGTCTCTCTCTCTCGCACACACG	Overlaps TDP-43 site 3	707	CGTGTGTGCGAGAGAGAGAGACAGA
262	GTCTGTCTCTCTCTCTCGCACACAC	Overlaps TDP-43 site 3	708	GTGTGTGCGAGAGAGAGAGACAGAC
263	TGTCTGTCTCTCTCTCTCGCACACA	Overlaps TDP-43 site 3	709	TGTGTGCGAGAGAGAGAGACAGACA
264	CTGTCTGTCTCTCTCTCTCGCACAC		710	GTGTGCGAGAGAGAGAGACAGACAG
265	GCTGTCTGTCTCTCTCTCTCGCACA		711	TGTGCGAGAGAGAGAGACAGACAGC
266	GGCTGTCTGTCTCTCTCTCTCGCAC		712	GTGCGAGAGAGAGAGACAGACAGCC
267	AGGCTGTCTGTCTCTCTCTCTCGCA		713	TGCGAGAGAGAGAGACAGACAGCCT
268	CAGGCTGTCTGTCTCTCTCTCTCGC		714	GCGAGAGAGAGAGACAGACAGCCTG
269	GCAGGCTGTCTGTCTCTCTCTCTCG		715	CGAGAGAGAGAGACAGACAGCCTGC
270	GGCAGGCTGTCTGTCTCTCTCTCTC		716	GAGAGAGAGAGACAGACAGCCTGCC
271	AGGCAGGCTGTCTGTCTCTCTCTCT		717	AGAGAGAGAGACAGACAGCCTGCCT
272	TAGGCAGGCTGTCTGTCTCTCTCTC		718	GAGAGAGAGACAGACAGCCTGCCTA
273	TTAGGCAGGCTGTCTGTCTCTCTCT		719	AGAGAGAGACAGACAGCCTGCCTAA
274	CTTAGGCAGGCTGTCTGTCTCTCTC		720	GAGAGAGACAGACAGCCTGCCTAAG
275	TCTTAGGCAGGCTGTCTGTCTCTCT		721	AGAGAGACAGACAGCCTGCCTAAGA
276	TTCTTAGGCAGGCTGTCTGTCTCTC		722	GAGAGACAGACAGCCTGCCTAAGAA
277	CTTCTTAGGCAGGCTGTCTGTCTCT		723	AGAGACAGACAGCCTGCCTAAGAAG
278	TCTTCTTAGGCAGGCTGTCTGTCTC		724	GAGACAGACAGCCTGCCTAAGAAGA
279	TTCTTCTTAGGCAGGCTGTCTGTCT		725	AGACAGACAGCCTGCCTAAGAAGAA
280	TTTCTTCTTAGGCAGGCTGTCTGTC		726	GACAGACAGCCTGCCTAAGAAGAAA
281	ATTTCTTCTTAGGCAGGCTGTCTGT		727	ACAGACAGCCTGCCTAAGAAGAAAT
282	CATTTCTTCTTAGGCAGGCTGTCTG		728	CAGACAGCCTGCCTAAGAAGAAATG
283	TCATTTCTTCTTAGGCAGGCTGTCT		729	AGACAGCCTGCCTAAGAAGAAATGA
284	TTCATTTCTTCTTAGGCAGGCTGTC		730	GACAGCCTGCCTAAGAAGAAATGAA
285	ATTCATTTCTTCTTAGGCAGGCTGT		731	ACAGCCTGCCTAAGAAGAAATGAAT
286	CATTCATTTCTTCTTAGGCAGGCTG		732	CAGCCTGCCTAAGAAGAAATGAATG
287	ACATTCATTTCTTCTTAGGCAGGCT		733	AGCCTGCCTAAGAAGAAATGAATGT
288	CACATTCATTTCTTCTTAGGCAGGC		734	GCCTGCCTAAGAAGAAATGAATGTG
289	TCACATTCATTTCTTCTTAGGCAGG		735	CCTGCCTAAGAAGAAATGAATGTGA
290	TTCACATTCATTTCTTCTTAGGCAG		736	CTGCCTAAGAAGAAATGAATGTGAA
291	ATTCACATTCATTTCTTCTTAGGCA		737	TGCCTAAGAAGAAATGAATGTGAAT
292	CATTCACATTCATTTCTTCTTAGGC		738	GCCTAAGAAGAAATGAATGTGAATG
293	GCATTCACATTCATTTCTTCTTAGG		739	CCTAAGAAGAAATGAATGTGAATGC
294	CGCATTCACATTCATTTCTTCTTAG		740	CTAAGAAGAAATGAATGTGAATGCG
295	CCGCATTCACATTCATTTCTTCTTA		741	TAAGAAGAAATGAATGTGAATGCGG
296	GCCGCATTCACATTCATTTCTTCTT		742	AAGAAGAAATGAATGTGAATGCGGC
297	AGCCGCATTCACATTCATTTCTTCT		743	AGAAGAAATGAATGTGAATGCGGCT

298	AAGCCGCATTCACATTCATTTCTTC		744	GAAGAAATGAATGTGAATGCGGCTT
299	CAAGCCGCATTCACATTCATTTCTT		745	AAGAAATGAATGTGAATGCGGCTTG
300	ACAAGCCGCATTCACATTCATTTCT		746	AGAAATGAATGTGAATGCGGCTTGT
301	CACAAGCCGCATTCACATTCATTTC		747	GAAATGAATGTGAATGCGGCTTGTG
302	CCACAAGCCGCATTCACATTCATTT		748	AAATGAATGTGAATGCGGCTTGTGG
303	GCCACAAGCCGCATTCACATTCATT		749	AATGAATGTGAATGCGGCTTGTGGC
304	TGCCACAAGCCGCATTCACATTCAT		750	ATGAATGTGAATGCGGCTTGTGGCA
305	GTGCCACAAGCCGCATTCACATTCA		751	TGAATGTGAATGCGGCTTGTGGCAC
306	TGTGCCACAAGCCGCATTCACATTC		752	GAATGTGAATGCGGCTTGTGGCACA
307	CTGTGCCACAAGCCGCATTCACATT		753	AATGTGAATGCGGCTTGTGGCACAG
308	ACTGTGCCACAAGCCGCATTCACAT		754	ATGTGAATGCGGCTTGTGGCACAGT
309	AACTGTGCCACAAGCCGCATTCACA		755	TGTGAATGCGGCTTGTGGCACAGTT
310	CAACTGTGCCACAAGCCGCATTCAC		756	GTGAATGCGGCTTGTGGCACAGTTG
311	TCAACTGTGCCACAAGCCGCATTCA		757	TGAATGCGGCTTGTGGCACAGTTGA
312	GTCAACTGTGCCACAAGCCGCATTC		758	GAATGCGGCTTGTGGCACAGTTGAC
313	TGTCAACTGTGCCACAAGCCGCATT		759	AATGCGGCTTGTGGCACAGTTGACA
314	TTGTCAACTGTGCCACAAGCCGCAT		760	ATGCGGCTTGTGGCACAGTTGACAA
315	CTTGTCAACTGTGCCACAAGCCGCA		761	TGCGGCTTGTGGCACAGTTGACAAG
316	CCTTGTCAACTGTGCCACAAGCCGC		762	GCGGCTTGTGGCACAGTTGACAAGG
317	TCCTTGTCAACTGTGCCACAAGCCG		763	CGGCTTGTGGCACAGTTGACAAGGA
318	ATCCTTGTCAACTGTGCCACAAGCC		764	GGCTTGTGGCACAGTTGACAAGGAT
319	CATCCTTGTCAACTGTGCCACAAGC		765	GCTTGTGGCACAGTTGACAAGGATG
320	TCATCCTTGTCAACTGTGCCACAAG		766	CTTGTGGCACAGTTGACAAGGATGA
321	ATCATCCTTGTCAACTGTGCCACAA		767	TTGTGGCACAGTTGACAAGGATGAT
322	TATCATCCTTGTCAACTGTGCCACA		768	TGTGGCACAGTTGACAAGGATGATA
323	TTATCATCCTTGTCAACTGTGCCAC		769	GTGGCACAGTTGACAAGGATGATAA
324	TTTATCATCCTTGTCAACTGTGCCA		770	TGGCACAGTTGACAAGGATGATAAA
325	ATTTATCATCCTTGTCAACTGTGCC		771	GGCACAGTTGACAAGGATGATAAAT
326	GATTTATCATCCTTGTCAACTGTGC		772	GCACAGTTGACAAGGATGATAAATC
327	TGATTTATCATCCTTGTCAACTGTG		773	CACAGTTGACAAGGATGATAAATCA
328	TTGATTTATCATCCTTGTCAACTGT		774	ACAGTTGACAAGGATGATAAATCAA
329	ATTGATTTATCATCCTTGTCAACTG		775	CAGTTGACAAGGATGATAAATCAAT
330	TATTGATTTATCATCCTTGTCAACT		776	AGTTGACAAGGATGATAAATCAATA
331	TTATTGATTTATCATCCTTGTCAAC		777	GTTGACAAGGATGATAAATCAATAA
332	ATTATTGATTTATCATCCTTGTCAA		778	TTGACAAGGATGATAAATCAATAAT
333	CATTATTGATTTATCATCCTTGTCA		779	TGACAAGGATGATAAATCAATAATG
334	GCATTATTGATTTATCATCCTTGTC		780	GACAAGGATGATAAATCAATAATGC
335	TGCATTATTGATTTATCATCCTTGT		781	ACAAGGATGATAAATCAATAATGCA
336	TTGCATTATTGATTTATCATCCTTG		782	CAAGGATGATAAATCAATAATGCAA
337	CTTGCATTATTGATTTATCATCCTT		783	AAGGATGATAAATCAATAATGCAAG
338	GCTTGCATTATTGATTTATCATCCT		784	AGGATGATAAATCAATAATGCAAGC
339	AGCTTGCATTATTGATTTATCATCC		785	GGATGATAAATCAATAATGCAAGCT

340	AAGCTTGCATTATTGATTTATCATC		786	GATGATAAATCAATAATGCAAGCTT
341	TAAGCTTGCATTATTGATTTATCAT		787	ATGATAAATCAATAATGCAAGCTTA
342	GTAAGCTTGCATTATTGATTTATCA		788	TGATAAATCAATAATGCAAGCTTAC
343	AGTAAGCTTGCATTATTGATTTATC		789	GATAAATCAATAATGCAAGCTTACT
344	TAGTAAGCTTGCATTATTGATTTAT		790	ATAAATCAATAATGCAAGCTTACTA
345	ATAGTAAGCTTGCATTATTGATTTA		791	TAAATCAATAATGCAAGCTTACTAT
346	GATAGTAAGCTTGCATTATTGATTT		792	AAATCAATAATGCAAGCTTACTATC
347	TGATAGTAAGCTTGCATTATTGATT		793	AATCAATAATGCAAGCTTACTATCA
348	ATGATAGTAAGCTTGCATTATTGAT		794	ATCAATAATGCAAGCTTACTATCAT
349	AATGATAGTAAGCTTGCATTATTGA		795	TCAATAATGCAAGCTTACTATCATT
350	AAATGATAGTAAGCTTGCATTATTG		796	CAATAATGCAAGCTTACTATCATTT
351	TAAATGATAGTAAGCTTGCATTATT		797	AATAATGCAAGCTTACTATCATTTA
352	ATAAATGATAGTAAGCTTGCATTAT		798	ATAATGCAAGCTTACTATCATTTAT
353	CATAAATGATAGTAAGCTTGCATTA		799	TAATGCAAGCTTACTATCATTTATG
354	TCATAAATGATAGTAAGCTTGCATT		800	AATGCAAGCTTACTATCATTTATGA
355	TTCATAAATGATAGTAAGCTTGCAT		801	ATGCAAGCTTACTATCATTTATGAA
356	ATTCATAAATGATAGTAAGCTTGCA		802	TGCAAGCTTACTATCATTTATGAAT
357	TATTCATAAATGATAGTAAGCTTGC		803	GCAAGCTTACTATCATTTATGAATA
358	CTATTCATAAATGATAGTAAGCTTG		804	CAAGCTTACTATCATTTATGAATAG
359	GCTATTCATAAATGATAGTAAGCTT		805	AAGCTTACTATCATTTATGAATAGC
360	TGCTATTCATAAATGATAGTAAGCT		806	AGCTTACTATCATTTATGAATAGCA
361	TTGCTATTCATAAATGATAGTAAGC		807	GCTTACTATCATTTATGAATAGCAA
362	ATTGCTATTCATAAATGATAGTAAG		808	CTTACTATCATTTATGAATAGCAAT
363	TATTGCTATTCATAAATGATAGTAA		809	TTACTATCATTTATGAATAGCAATA
364	GTATTGCTATTCATAAATGATAGTA		810	TACTATCATTTATGAATAGCAATAC
365	AGTATTGCTATTCATAAATGATAGT		811	ACTATCATTTATGAATAGCAATACT
366	CAGTATTGCTATTCATAAATGATAG		812	CTATCATTTATGAATAGCAATACTG
367	TCAGTATTGCTATTCATAAATGATA		813	TATCATTTATGAATAGCAATACTGA
368	TTCAGTATTGCTATTCATAAATGAT		814	ATCATTTATGAATAGCAATACTGAA
369	CTTCAGTATTGCTATTCATAAATGA		815	TCATTTATGAATAGCAATACTGAAG
370	TCTTCAGTATTGCTATTCATAAATG		816	CATTTATGAATAGCAATACTGAAGA
371	TTCTTCAGTATTGCTATTCATAAAT		817	ATTTATGAATAGCAATACTGAAGAA
372	TTTCTTCAGTATTGCTATTCATAAA		818	TTTATGAATAGCAATACTGAAGAAA
373	ATTTCTTCAGTATTGCTATTCATAA		819	TTATGAATAGCAATACTGAAGAAAT
374	AATTTCTTCAGTATTGCTATTCATA		820	TATGAATAGCAATACTGAAGAAATT
375	TAATTTCTTCAGTATTGCTATTCAT		821	ATGAATAGCAATACTGAAGAAATTA
376	TTAATTTCTTCAGTATTGCTATTCA		822	TGAATAGCAATACTGAAGAAATTAA
377	TTTAATTTCTTCAGTATTGCTATTC	polyA signal	823	GAATAGCAATACTGAAGAAATTAAA
378	TTTTAATTTCTTCAGTATTGCTATT	polyA signal	824	AATAGCAATACTGAAGAAATTAAAA
379	GTTTTAATTTCTTCAGTATTGCTAT	polyA signal	825	ATAGCAATACTGAAGAAATTAAAAC

380	TGTTTTAATTTCTTCAGTATTGCTA	polyA signal	826	TAGCAATACTGAAGAAATTAAAACA
381	TTGTTTTAATTTCTTCAGTATTGCT	polyA signal	827	AGCAATACTGAAGAAATTAAAACAA
382	TTTGTTTTAATTTCTTCAGTATTGC	polyA signal	828	GCAATACTGAAGAAATTAAAACAAA
383	TTTTGTTTTAATTTCTTCAGTATTG	polyA signal	829	CAATACTGAAGAAATTAAAACAAAA
384	CTTTTGTTTTAATTTCTTCAGTATT	polyA signal	830	AATACTGAAGAAATTAAAACAAAAG
385	TCTTTTGTTTTAATTTCTTCAGTAT	polyA signal	831	ATACTGAAGAAATTAAAACAAAAGA
386	ATCTTTTGTTTTAATTTCTTCAGTA	polyA signal	832	TACTGAAGAAATTAAAACAAAAGAT
387	AATCTTTTGTTTTAATTTCTTCAGT	polyA signal	833	ACTGAAGAAATTAAAACAAAAGATT
388	CAATCTTTTGTTTTAATTTCTTCAG	polyA signal	834	CTGAAGAAATTAAAACAAAAGATTG
389	GCAATCTTTTGTTTTAATTTCTTCA	polyA signal	835	TGAAGAAATTAAAACAAAAGATTGC
390	AGCAATCTTTTGTTTTAATTTCTTC	polyA signal	836	GAAGAAATTAAAACAAAAGATTGCT
391	CAGCAATCTTTTGTTTTAATTTCTT	polyA signal	837	AAGAAATTAAAACAAAAGATTGCTG
392	ACAGCAATCTTTTGTTTTAATTTCT	polyA signal	838	AGAAATTAAAACAAAAGATTGCTGT
393	GACAGCAATCTTTTGTTTTAATTTC	polyA signal	839	GAAATTAAAACAAAAGATTGCTGTC
394	AGACAGCAATCTTTTGTTTTAATTT	polyA signal	840	AAATTAAAACAAAAGATTGCTGTCT
395	GAGACAGCAATCTTTTGTTTTAATT	polyA signal and site	841	AATTAAAACAAAAGATTGCTGTCTC
396	TGAGACAGCAATCTTTTGTTTTAAT	polyA signal and site	842	ATTAAAACAAAAGATTGCTGTCTCA
397	TTGAGACAGCAATCTTTTGTTTTAA	polyA site	843	TTAAAACAAAAGATTGCTGTCTCAA
398	ATTGAGACAGCAATCTTTTGTTTTA	polyA site	844	TAAAACAAAAGATTGCTGTCTCAAT
399	TATTGAGACAGCAATCTTTTGTTTT	polyA site	845	AAAACAAAAGATTGCTGTCTCAATA
400	ATATTGAGACAGCAATCTTTTGTTT	polyA site	846	AAACAAAAGATTGCTGTCTCAATAT
401	TATATTGAGACAGCAATCTTTTGTT	polyA site	847	AACAAAAGATTGCTGTCTCAATATA
402	ATATATTGAGACAGCAATCTTTTGT	polyA site	848	ACAAAAGATTGCTGTCTCAATATAT
403	GATATATTGAGACAGCAATCTTTTG	polyA site	849	CAAAAGATTGCTGTCTCAATATATC

404	AGATATATTGAGACAGCAATCTTTT	polyA site	850	AAAAGATTGCTGTCTCAATATATCT
405	AAGATATATTGAGACAGCAATCTTT	polyA site	851	AAAGATTGCTGTCTCAATATATCTT
406	TAAGATATATTGAGACAGCAATCTT	polyA site	852	AAGATTGCTGTCTCAATATATCTTA
407	ATAAGATATATTGAGACAGCAATCT	polyA site	853	AGATTGCTGTCTCAATATATCTTAT
408	TATAAGATATATTGAGACAGCAATC	polyA site	854	GATTGCTGTCTCAATATATCTTATA
409	ATATAAGATATATTGAGACAGCAAT	polyA site	855	ATTGCTGTCTCAATATATCTTATAT
410	AATATAAGATATATTGAGACAGCAA	polyA site	856	TTGCTGTCTCAATATATCTTATATT
411	AAATATAAGATATATTGAGACAGCA	polyA site	857	TGCTGTCTCAATATATCTTATATTT
412	TAAATATAAGATATATTGAGACAGC	polyA site	858	GCTGTCTCAATATATCTTATATTTA
413	ATAAATATAAGATATATTGAGACAG		859	CTGTCTCAATATATCTTATATTTAT
414	AATAAATATAAGATATATTGAGACA		860	TGTCTCAATATATCTTATATTTATT
415	TAATAAATATAAGATATATTGAGAC		861	GTCTCAATATATCTTATATTTATTA
416	ATAATAAATATAAGATATATTGAGA		862	TCTCAATATATCTTATATTTATTAT
417	AATAATAAATATAAGATATATTGAG		863	CTCAATATATCTTATATTTATTATT
418	AAATAATAAATATAAGATATATTGA		864	TCAATATATCTTATATTTATTATTT
419	TAAATAATAAATATAAGATATATTG		865	CAATATATCTTATATTTATTATTTA
420	GTAAATAATAAATATAAGATATATT		866	AATATATCTTATATTTATTATTTAC
421	GGTAAATAATAAATATAAGATATAT		867	ATATATCTTATATTTATTATTTACC
422	TGGTAAATAATAAATATAAGATATA		868	TATATCTTATATTTATTATTTACCA
423	TTGGTAAATAATAAATATAAGATAT		869	ATATCTTATATTTATTATTTACCAA
424	TTTGGTAAATAATAAATATAAGATA		870	TATCTTATATTTATTATTTACCAAA
425	ATTTGGTAAATAATAAATATAAGAT		871	ATCTTATATTTATTATTTACCAAAT
426	AATTTGGTAAATAATAAATATAAGA		872	TCTTATATTTATTATTTACCAAATT
427	TAATTTGGTAAATAATAAATATAAG		873	CTTATATTTATTATTTACCAAATTA
428	ATAATTTGGTAAATAATAAATATAA		874	TTATATTTATTATTTACCAAATTAT
429	AATAATTTGGTAAATAATAAATATA		875	TATATTTATTATTTACCAAATTATT
430	GAATAATTTGGTAAATAATAAATAT		876	ATATTTATTATTTACCAAATTATTC
431	AGAATAATTTGGTAAATAATAAATA		877	TATTTATTATTTACCAAATTATTCT
432	TAGAATAATTTGGTAAATAATAAAT		878	ATTTATTATTTACCAAATTATTCTA
433	TTAGAATAATTTGGTAAATAATAAA		879	TTTATTATTTACCAAATTATTCTAA
434	CTTAGAATAATTTGGTAAATAATAA		880	TTATTATTTACCAAATTATTCTAAG
435	TCTTAGAATAATTTGGTAAATAATA		881	TATTATTTACCAAATTATTCTAAGA
436	CTCTTAGAATAATTTGGTAAATAAT		882	ATTATTTACCAAATTATTCTAAGAG
437	ACTCTTAGAATAATTTGGTAAATAA		883	TTATTTACCAAATTATTCTAAGAGT
438	TACTCTTAGAATAATTTGGTAAATA		884	TATTTACCAAATTATTCTAAGAGTA
439	ATACTCTTAGAATAATTTGGTAAAT		885	ATTTACCAAATTATTCTAAGAGTAT

440	AATACTCTTAGAATAATTTGGTAAA		886	TTTACCAAATTATTCTAAGAGTATT
441	AAATACTCTTAGAATAATTTGGTAA		887	TTACCAAATTATTCTAAGAGTATTT
442	GAAATACTCTTAGAATAATTTGGTA		888	TACCAAATTATTCTAAGAGTATTTC
443	AGAAATACTCTTAGAATAATTTGGT		889	ACCAAATTATTCTAAGAGTATTTCT
444	AAGAAATACTCTTAGAATAATTTGG		890	CCAAATTATTCTAAGAGTATTTCTT
445	GAAGAAATACTCTTAGAATAATTTG		891	CAAATTATTCTAAGAGTATTTCTTC
446	GGAAGAAATACTCTTAGAATAATTT		892	AAATTATTCTAAGAGTATTTCTTCC

* At least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide sequence is independently selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00295] Table 2 below identifies additional STMN2 AON sequences:

Table 2. Additional STMN2 AON Sequences (corresponding to SEQ ID NOs: 1-446 but with thymine bases replaced with uracil bases)

SEQ ID NO:	AON Sequence* (5' → 3')
893	GGAGGGAUACCUGUAUAUUACAAGU
894	AGGAGGGAUACCUGUAUAUUACAAG
895	CAGGAGGGAUACCUGUAUAUUACAA
896	CCAGGAGGGAUACCUGUAUAUUACA
897	ACCAGGAGGGAUACCUGUAUAUUAC
898	UACCAGGAGGGAUACCUGUAUAUUA
899	UUACCAGGAGGGAUACCUGUAUAUU
900	CUUACCAGGAGGGAUACCUGUAUAU
901	GCUUACCAGGAGGGAUACCUGUAUA
902	AGCUUACCAGGAGGGAUACCUGUAU
903	GAGCUUACCAGGAGGGAUACCUGUA
904	AGAGCUUACCAGGAGGGAUACCUGU
905	CAGAGCUUACCAGGAGGGAUACCUG
906	CCAGAGCUUACCAGGAGGGAUACCU
907	ACCAGAGCUUACCAGGAGGGAUACC
908	UACCAGAGCUUACCAGGAGGGAUAC

909	AUACCAGAGCUUACCAGGAGGGAUA
910	AAUACCAGAGCUUACCAGGAGGGAU
911	UAAUACCAGAGCUUACCAGGAGGGA
912	AUAAUACCAGAGCUUACCAGGAGGG
913	CAUAAUACCAGAGCUUACCAGGAGG
914	ACAUAAUACCAGAGCUUACCAGGAG
915	GACAUAAUACCAGAGCUUACCAGGA
916	AGACAUAAUACCAGAGCUUACCAGG
917	AAGACAUAAUACCAGAGCUUACCAG
918	UAAGACAUAAUACCAGAGCUUACCA
919	UUAAGACAUAAUACCAGAGCUUACC
920	GUUAAGACAUAAUACCAGAGCUUAC
921	UGUUAAGACAUAAUACCAGAGCUUA
922	AUGUUAAGACAUAAUACCAGAGCUU
923	AAUGUUAAGACAUAAUACCAGAGCU
924	AAAUGUUAAGACAUAAUACCAGAGC
925	AAAAUGUUAAGACAUAAUACCAGAG
926	AAAAAUGUUAAGACAUAAUACCAGA
927	UAAAAAUGUUAAGACAUAAUACCAG
928	UUAAAAAUGUUAAGACAUAAUACCA
929	UUUAAAAAUGUUAAGACAUAAUACC
930	AUUUAAAAAUGUUAAGACAUAAUAC
931	GAUUUAAAAAUGUUAAGACAUAAUA
932	AGAUUUAAAAAUGUUAAGACAUAAU
933	UAGAUUUAAAAAUGUUAAGACAUAA
934	AUAGAUUUAAAAAUGUUAAGACAUA
935	CAUAGAUUUAAAAAUGUUAAGACAU
936	CCAUAGAUUUAAAAAUGUUAAGACA
937	ACCAUAGAUUUAAAAAUGUUAAGAC
938	UACCAUAGAUUUAAAAAUGUUAAGA
939	UUACCAUAGAUUUAAAAAUGUUAAG
940	AUUACCAUAGAUUUAAAAAUGUUAA
941	GAUUACCAUAGAUUUAAAAAUGUUA
942	AGAUUACCAUAGAUUUAAAAAUGUU
943	AAGAUUACCAUAGAUUUAAAAAUGU
944	AAAGAUUACCAUAGAUUUAAAAAUG
945	UAAAGAUUACCAUAGAUUUAAAAAU
946	GUAAAGAUUACCAUAGAUUUAAAAA
947	UGUAAAGAUUACCAUAGAUUUAAAA
948	UUGUAAAGAUUACCAUAGAUUUAAA
949	UUUGUAAAGAUUACCAUAGAUUUAA
950	UUUUGUAAAGAUUACCAUAGAUUUA

951	AUUUUGUAAAGAUUACCAUAGAUUU
952	UAUUUUGUAAAGAUUACCAUAGAUU
953	AUAUUUUGUAAAGAUUACCAUAGAU
954	AAUAUUUUGUAAAGAUUACCAUAGA
955	AAAUAUUUUGUAAAGAUUACCAUAG
956	AAAAUAUUUUGUAAAGAUUACCAUA
957	UAAAAUAUUUUGUAAAGAUUACCAU
958	GUAAAAUAUUUUGUAAAGAUUACCA
959	AGUAAAAUAUUUUGUAAAGAUUACC
960	AAGUAAAAUAUUUUGUAAAGAUUAC
961	GAAGUAAAAUAUUUUGUAAAGAUUA
962	GGAAGUAAAAUAUUUUGUAAAGAUU
963	CGGAAGUAAAAUAUUUUGUAAAGAU
964	UCGGAAGUAAAAUAUUUUGUAAAGA
965	UUCGGAAGUAAAAUAUUUUGUAAAG
966	GUUCGGAAGUAAAAUAUUUUGUAAA
967	AGUUCGGAAGUAAAAUAUUUUGUAA
968	GAGUUCGGAAGUAAAAUAUUUUGUA
969	UGAGUUCGGAAGUAAAAUAUUUUGU
970	AUGAGUUCGGAAGUAAAAUAUUUUG
971	UAUGAGUUCGGAAGUAAAAUAUUUU
972	AUAUGAGUUCGGAAGUAAAAUAUUU
973	UAUAUGAGUUCGGAAGUAAAAUAUU
974	GUAUAUGAGUUCGGAAGUAAAAUAU
975	GGUAUAUGAGUUCGGAAGUAAAAUA
976	AGGUAUAUGAGUUCGGAAGUAAAAU
977	CAGGUAUAUGAGUUCGGAAGUAAAA
978	CCAGGUAUAUGAGUUCGGAAGUAAA
979	CCCAGGUAUAUGAGUUCGGAAGUAA
980	CCCCAGGUAUAUGAGUUCGGAAGUA
981	UCCCCAGGUAUAUGAGUUCGGAAGU
982	AUCCCCAGGUAUAUGAGUUCGGAAG
983	AAUCCCCAGGUAUAUGAGUUCGGAA
984	AAAUCCCCAGGUAUAUGAGUUCGGA
985	AAAAUCCCCAGGUAUAUGAGUUCGG
986	UAAAAUCCCCAGGUAUAUGAGUUCG
987	AUAAAAUCCCCAGGUAUAUGAGUUC
988	AAUAAAAUCCCCAGGUAUAUGAGUU
989	UAAUAAAAUCCCCAGGUAUAUGAGU
990	GUAAUAAAAUCCCCAGGUAUAUGAG
991	AGUAAUAAAAUCCCCAGGUAUAUGA
992	GAGUAAUAAAAUCCCCAGGUAUAUG

993	AGAGUAAUAAAAUCCCCAGGUAUAU
994	CAGAGUAAUAAAAUCCCCAGGUAUA
995	CCAGAGUAAUAAAAUCCCCAGGUAU
996	CCCAGAGUAAUAAAAUCCCCAGGUA
997	UCCCAGAGUAAUAAAAUCCCCAGGU
998	UUCCCAGAGUAAUAAAAUCCCCAGG
999	AUUCCCAGAGUAAUAAAAUCCCCAG
1000	AAUUCCCAGAGUAAUAAAAUCCCCA
1001	UAAUUCCCAGAGUAAUAAAAUCCCC
1002	AUAAUUCCCAGAGUAAUAAAAUCCC
1003	CAUAAUUCCCAGAGUAAUAAAAUCC
1004	ACAUAAUUCCCAGAGUAAUAAAAUC
1005	CACAUAAUUCCCAGAGUAAUAAAAU
1006	ACACAUAAUUCCCAGAGUAAUAAAA
1007	AACACAUAAUUCCCAGAGUAAUAAA
1008	GAACACAUAAUUCCCAGAGUAAUAA
1009	AGAACACAUAAUUCCCAGAGUAAUA
1010	CAGAACACAUAAUUCCCAGAGUAAU
1011	GCAGAACACAUAAUUCCCAGAGUAA
1012	GGCAGAACACAUAAUUCCCAGAGUA
1013	GGGCAGAACACAUAAUUCCCAGAGU
1014	GGGGCAGAACACAUAAUUCCCAGAG
1015	UGGGGCAGAACACAUAAUUCCCAGA
1016	AUGGGGCAGAACACAUAAUUCCCAG
1017	GAUGGGGCAGAACACAUAAUUCCCA
1018	UGAUGGGGCAGAACACAUAAUUCCC
1019	GUGAUGGGGCAGAACACAUAAUUCC
1020	AGUGAUGGGGCAGAACACAUAAUUC
1021	GAGUGAUGGGGCAGAACACAUAAUU
1022	AGAGUGAUGGGGCAGAACACAUAAU
1023	GAGAGUGAUGGGGCAGAACACAUAA
1024	AGAGAGUGAUGGGGCAGAACACAUA
1025	GAGAGAGUGAUGGGGCAGAACACAU
1026	AGAGAGAGUGAUGGGGCAGAACACA
1027	AAGAGAGAGUGAUGGGGCAGAACAC
1028	UAAGAGAGAGUGAUGGGGCAGAACA
1029	UUAAGAGAGAGUGAUGGGGCAGAAC
1030	AUUAAGAGAGAGUGAUGGGGCAGAA
1031	AAUUAAGAGAGAGUGAUGGGGCAGA
1032	CAAUUAAGAGAGAGUGAUGGGGCAG
1033	CCAAUUAAGAGAGAGUGAUGGGGCA
1034	UCCAAUUAAGAGAGAGUGAUGGGGC

1035	AUCCAAUUAAGAGAGAGUGAUGGGG
1036	AAUCCAAUUAAGAGAGAGUGAUGGG
1037	AAAUCCAAUUAAGAGAGAGUGAUGG
1038	AAAAUCCAAUUAAGAGAGAGUGAUG
1039	AAAAAUCCAAUUAAGAGAGAGUGAU
1040	UAAAAAUCCAAUUAAGAGAGAGUGA
1041	UUAAAAAUCCAAUUAAGAGAGAGUG
1042	UUUAAAAAUCCAAUUAAGAGAGAGU
1043	UUUUAAAAAUCCAAUUAAGAGAGAG
1044	AUUUUAAAAAUCCAAUUAAGAGAGA
1045	AAUUUUAAAAAUCCAAUUAAGAGAG
1046	UAAUUUUAAAAAUCCAAUUAAGAGA
1047	AUAAUUUUAAAAAUCCAAUUAAGAG
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1049	AUAUAAUUUUAAAAAUCCAAUUAAG
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1051	GAAUAUAAUUUUAAAAAUCCAAUUA
1052	UGAAUAUAAUUUUAAAAAUCCAAUU
1053	AUGAAUAUAAUUUUAAAAAUCCAAU
1054	UAUGAAUAUAAUUUUAAAAAUCCAA
1055	AUAUGAAUAUAAUUUUAAAAAUCCA
1056	AAUAUGAAUAUAAUUUUAAAAAUCC
1057	CAAUAUGAAUAUAAUUUUAAAAAUC
1058	GCAAUAUGAAUAUAAUUUUAAAAAU
1059	UGCAAUAUGAAUAUAAUUUUAAAAA
1060	CUGCAAUAUGAAUAUAAUUUUAAAA
1061	CCUGCAAUAUGAAUAUAAUUUUAAA
1062	UCCUGCAAUAUGAAUAUAAUUUUAA
1063	GUCCUGCAAUAUGAAUAUAAUUUUA
1064	AGUCCUGCAAUAUGAAUAUAAUUUU
1065	GAGUCCUGCAAUAUGAAUAUAAUUU
1066	CGAGUCCUGCAAUAUGAAUAUAAUU
1067	CCGAGUCCUGCAAUAUGAAUAUAAU
1068	GCCGAGUCCUGCAAUAUGAAUAUAA
1069	UGCCGAGUCCUGCAAUAUGAAUAUA
1070	CUGCCGAGUCCUGCAAUAUGAAUAU
1071	UCUGCCGAGUCCUGCAAUAUGAAUA
1072	UUCUGCCGAGUCCUGCAAUAUGAAU
1073	CUUCUGCCGAGUCCUGCAAUAUGAA
1074	UCUUCUGCCGAGUCCUGCAAUAUGA
1075	GUCUUCUGCCGAGUCCUGCAAUAUG
1076	GGUCUUCUGCCGAGUCCUGCAAUAU

1077	AGGUCUUCUGCCGAGUCCUGCAAUA
1078	AAGGUCUUCUGCCGAGUCCUGCAAU
1079	GAAGGUCUUCUGCCGAGUCCUGCAA
1080	CGAAGGUCUUCUGCCGAGUCCUGCA
1081	UCGAAGGUCUUCUGCCGAGUCCUGC
1082	CUCGAAGGUCUUCUGCCGAGUCCUG
1083	UCUCGAAGGUCUUCUGCCGAGUCCU
1084	CUCUCGAAGGUCUUCUGCCGAGUCC
1085	UCUCUCGAAGGUCUUCUGCCGAGUC
1086	UUCUCUCGAAGGUCUUCUGCCGAGU
1087	UUUCUCUCGAAGGUCUUCUGCCGAG
1088	CUUUCUCUCGAAGGUCUUCUGCCGA
1089	CCUUUCUCUCGAAGGUCUUCUGCCG
1090	ACCUUUCUCUCGAAGGUCUUCUGCC
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1100	CUUAUUUUCUACCUUUCUCUCGAAG
1101	UCUUAUUUUCUACCUUUCUCUCGAA
1102	UUCUUAUUUUCUACCUUUCUCUCGA
1103	AUUCUUAUUUUCUACCUUUCUCUCG
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1105	AAAUUCUUAUUUUCUACCUUUCUCU
1106	CAAAUUCUUAUUUUCUACCUUUCUC
1107	CCAAAUUCUUAUUUUCUACCUUUCU
1108	GCCAAAUUCUUAUUUUCUACCUUUC
1109	AGCCAAAUUCUUAUUUUCUACCUUU
1110	GAGCCAAAUUCUUAUUUUCUACCUU
1111	AGAGCCAAAUUCUUAUUUUCUACCU
1112	GAGAGCCAAAUUCUUAUUUUCUACC
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1115	ACAGAGAGCCAAAUUCUUAUUUUCU
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1117	ACACAGAGAGCCAAAUUCUUAUUUU
1118	CACACAGAGAGCCAAAUUCUUAUUU

1119	UCACACAGAGAGCCAAAUUCUUAUU
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1121	GCUCACACAGAGAGCCAAAUUCUUA
1122	UGCUCACACAGAGAGCCAAAUUCUU
1123	AUGCUCACACAGAGAGCCAAAUUCU
1124	CAUGCUCACACAGAGAGCCAAAUUC
1125	ACAUGCUCACACAGAGAGCCAAAUU
1126	CACAUGCUCACACAGAGAGCCAAAU
1127	ACACAUGCUCACACAGAGAGCCAAA
1128	CACACAUGCUCACACAGAGAGCCAA
1129	GCACACAUGCUCACACAGAGAGCCA
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1131	ACGCACACAUGCUCACACAGAGAGC
1132	CACGCACACAUGCUCACACAGAGAG
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1140	CUCGCACACACGCACACAUGCUCAC
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1146	CUCUCUCUCGCACACACGCACACAU
1147	UCUCUCUCUCGCACACACGCACACA
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1163	AGGCAGGCUGUCUGUCUCUCUCUCU
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1169	CUUCUUAGGCAGGCUGUCUGUCUCU
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1172	UUUCUUCUUAGGCAGGCUGUCUGUC
1173	AUUUCUUCUUAGGCAGGCUGUCUGU
1174	CAUUUCUUCUUAGGCAGGCUGUCUG
1175	UCAUUUCUUCUUAGGCAGGCUGUCU
1176	UUCAUUUCUUCUUAGGCAGGCUGUC
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1178	CAUUCAUUUCUUCUUAGGCAGGCUG
1179	ACAUUCAUUUCUUCUUAGGCAGGCU
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1181	UCACAUUCAUUUCUUCUUAGGCAGG
1182	UUCACAUUCAUUUCUUCUUAGGCAG
1183	AUUCACAUUCAUUUCUUCUUAGGCA
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1187	CCGCAUUCACAUUCAUUUCUUCUUA
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1189	AGCCGCAUUCACAUUCAUUUCUUCU
1190	AAGCCGCAUUCACAUUCAUUUCUUC
1191	CAAGCCGCAUUCACAUUCAUUUCUU
1192	ACAAGCCGCAUUCACAUUCAUUUCU
1193	CACAAGCCGCAUUCACAUUCAUUUC
1194	CCACAAGCCGCAUUCACAUUCAUUU
1195	GCCACAAGCCGCAUUCACAUUCAUU
1196	UGCCACAAGCCGCAUUCACAUUCAU
1197	GUGCCACAAGCCGCAUUCACAUUCA
1198	UGUGCCACAAGCCGCAUUCACAUUC
1199	CUGUGCCACAAGCCGCAUUCACAUU
1200	ACUGUGCCACAAGCCGCAUUCACAU
1201	AACUGUGCCACAAGCCGCAUUCACA
1202	CAACUGUGCCACAAGCCGCAUUCAC

1203	UCAACUGUGCCACAAGCCGCAUUCA
1204	GUCAACUGUGCCACAAGCCGCAUUC
1205	UGUCAACUGUGCCACAAGCCGCAUU
1206	UUGUCAACUGUGCCACAAGCCGCAU
1207	CUUGUCAACUGUGCCACAAGCCGCA
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1209	UCCUUGUCAACUGUGCCACAAGCCG
1210	AUCCUUGUCAACUGUGCCACAAGCC
1211	CAUCCUUGUCAACUGUGCCACAAGC
1212	UCAUCCUUGUCAACUGUGCCACAAG
1213	AUCAUCCUUGUCAACUGUGCCACAA
1214	UAUCAUCCUUGUCAACUGUGCCACA
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1216	UUUAUCAUCCUUGUCAACUGUGCCA
1217	AUUUAUCAUCCUUGUCAACUGUGCC
1218	GAUUUAUCAUCCUUGUCAACUGUGC
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1220	UUGAUUUAUCAUCCUUGUCAACUGU
1221	AUUGAUUUAUCAUCCUUGUCAACUG
1222	UAUUGAUUUAUCAUCCUUGUCAACU
1223	UUAUUGAUUUAUCAUCCUUGUCAAC
1224	AUUAUUGAUUUAUCAUCCUUGUCAA
1225	CAUUAUUGAUUUAUCAUCCUUGUCA
1226	GCAUUAUUGAUUUAUCAUCCUUGUC
1227	UGCAUUAUUGAUUUAUCAUCCUUGU
1228	UUGCAUUAUUGAUUUAUCAUCCUUG
1229	CUUGCAUUAUUGAUUUAUCAUCCUU
1230	GCUUGCAUUAUUGAUUUAUCAUCCU
1231	AGCUUGCAUUAUUGAUUUAUCAUCC
1232	AAGCUUGCAUUAUUGAUUUAUCAUC
1233	UAAGCUUGCAUUAUUGAUUUAUCAU
1234	GUAAGCUUGCAUUAUUGAUUUAUCA
1235	AGUAAGCUUGCAUUAUUGAUUUAUC
1236	UAGUAAGCUUGCAUUAUUGAUUUAU
1237	AUAGUAAGCUUGCAUUAUUGAUUUA
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1246	UCAUAAAUGAUAGUAAGCUUGCAUU
1247	UUCAUAAAUGAUAGUAAGCUUGCAU
1248	AUUCAUAAAUGAUAGUAAGCUUGCA
1249	UAUUCAUAAAUGAUAGUAAGCUUGC
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1254	AUUGCUAUUCAUAAAUGAUAGUAAG
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1260	UUCAGUAUUGCUAUUCAUAAAUGAU
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1265	AUUUCUUCAGUAUUGCUAUUCAUAA
1266	AAUUUCUUCAGUAUUGCUAUUCAUA
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1269	UUUAAUUUCUUCAGUAUUGCUAUUC
1270	UUUUAAUUUCUUCAGUAUUGCUAUU
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1272	UGUUUUAAUUUCUUCAGUAUUGCUA
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1274	UUUGUUUUAAUUUCUUCAGUAUUGC
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1276	CUUUUGUUUUAAUUUCUUCAGUAUU
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1279	AAUCUUUUGUUUUAAUUUCUUCAGU
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1283	CAGCAAUCUUUUGUUUUAAUUUCUU
1284	ACAGCAAUCUUUUGUUUUAAUUUCU
1285	GACAGCAAUCUUUUGUUUUAAUUUC
1286	AGACAGCAAUCUUUUGUUUUAAUUU

1287	GAGACAGCAAUCUUUUGUUUUAAUU
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1291	UAUUGAGACAGCAAUCUUUUGUUUU
1292	AUAUUGAGACAGCAAUCUUUUGUUU
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1294	AUAUAUUGAGACAGCAAUCUUUUGU
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1296	AGAUAUAUUGAGACAGCAAUCUUUU
1297	AAGAUAUAUUGAGACAGCAAUCUUU
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1299	AUAAGAUAUAUUGAGACAGCAAUCU
1300	UAUAAGAUAUAUUGAGACAGCAAUC
1301	AUAUAAGAUAUAUUGAGACAGCAAU
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1303	AAAUAUAAGAUAUAUUGAGACAGCA
1304	UAAAUAUAAGAUAUAUUGAGACAGC
1305	AUAAAUAUAAGAUAUAUUGAGACAG
1306	AAUAAAUAUAAGAUAUAUUGAGACA
1307	UAAUAAAUAUAAGAUAUAUUGAGAC
1308	AUAAUAAAUAUAAGAUAUAUUGAGA
1309	AAUAAUAAAUAUAAGAUAUAUUGAG
1310	AAAUAAUAAAUAUAAGAUAUAUUGA
1311	UAAAUAAUAAAUAUAAGAUAUAUUG
1312	GUAAAUAAUAAAUAUAAGAUAUAUU
1313	GGUAAAUAAUAAAUAUAAGAUAUAU
1314	UGGUAAAUAAUAAAUAUAAGAUAUA
1315	UUGGUAAAUAAUAAAUAUAAGAUAU
1316	UUUGGUAAAUAAUAAAUAUAAGAUA
1317	AUUUGGUAAAUAAUAAAUAUAAGAU
1318	AAUUUGGUAAAUAAUAAAUAUAAGA
1319	UAAUUUGGUAAAUAAUAAAUAUAAG
1320	AUAAUUUGGUAAAUAAUAAAUAUAA
1321	AAUAAUUUGGUAAAUAAUAAAUAUA
1322	GAAUAAUUUGGUAAAUAAUAAAUAU
1323	AGAAUAAUUUGGUAAAUAAUAAAUA
1324	UAGAAUAAUUUGGUAAAUAAUAAAU
1325	UUAGAAUAAUUUGGUAAAUAAUAAA
1326	CUUAGAAUAAUUUGGUAAAUAAUAA
1327	UCUUAGAAUAAUUUGGUAAAUAAUA
1328	CUCUUAGAAUAAUUUGGUAAAUAAU

1329	ACUCUUAGAAUAAUUUGGUAAAUAA
1330	UACUCUUAGAAUAAUUUGGUAAAUA
1331	AUACUCUUAGAAUAAUUUGGUAAAU
1332	AAUACUCUUAGAAUAAUUUGGUAAA
1333	AAAUACUCUUAGAAUAAUUUGGUAA
1334	GAAAUACUCUUAGAAUAAUUUGGUA
1335	AGAAAUACUCUUAGAAUAAUUUGGU
1336	AAGAAAUACUCUUAGAAUAAUUUGG
1337	GAAGAAAUACUCUUAGAAUAAUUUG
1338	GGAAGAAAUACUCUUAGAAUAAUUU

* At least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide sequence is independently selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00296] Table 3 below identifies exemplary STMN2 AON sequences:

Table 3. Exemplary STMN2 AON Sequences, in each one or more spacers described in the present disclosure are incorporated for generation of an oligonucleotide of the present invention

SEQ ID NO: (legacy ID*)	Oligonucleotide sequence (5'→3')
SEQ ID NO: 31	AATGTTAAGACATAATACCAGAGCT
SEQ ID NO: 36	TTAAAAATGTTAAGACATAATACCA
SEQ ID NO: 41	TAGATTTAAAAATGTTAAGACATAA
SEQ ID NO: 46	TACCATAGATTTAAAAATGTTAAGA
SEQ ID NO: 55	TGTAAAGATTACCATAGATTTAAAA
SEQ ID NO: 144	AATCCAATTAAGAGAGAGTGATGGG
SEQ ID NO: 146	AAAATCCAATTAAGAGAGAGTGATG
SEQ ID NO: 150	TTTAAAAATCCAATTAAGAGAGAGT
SEQ ID NO: 169	CCTGCAATATGAATATAATTTTAAA
SEQ ID NO: 170	TCCTGCAATATGAATATAATTTTAA
SEQ ID NO: 171	GTCCTGCAATATGAATATAATTTTA

SEQ ID NO: 172	AGTCCTGCAATATGAATATAATTTT
SEQ ID NO: 173	GAGTCCTGCAATATGAATATAATTT
SEQ ID NO: 177	TGCCGAGTCCTGCAATATGAATATA
SEQ ID NO: 181	CTTCTGCCGAGTCCTGCAATATGAA
SEQ ID NO: 185	AGGTCTTCTGCCGAGTCCTGCAATA
SEQ ID NO: 197	CCTTTCTCTCGAAGGTCTTCTGCCG
SEQ ID NO: 203	TTTCTACCTTTCTCTCGAAGGTCTT
SEQ ID NO: 209	TCTTATTTTCTACCTTTCTCTCGAA
SEQ ID NO: 215	CCAAATTCTTATTTTCTACCTTTCT
SEQ ID NO: 237	GCACACATGCTCACACAGAGAGCCA
SEQ ID NO: 244	CACACACGCACACATGCTCACACAG
SEQ ID NO: 249	TCTCGCACACACGCACACATGCTCA
SEQ ID NO: 252	CTCTCTCGCACACACGCACACATGC
SEQ ID NO: 380	TGTTTTAATTTCTTCAGTATTGCTA
SEQ ID NO: 385	TCTTTTGTTTTAATTTCTTCAGTAT
SEQ ID NO: 390	AGCAATCTTTTGTTTTAATTTCTTC
SEQ ID NO: 395	GAGACAGCAATCTTTTGTTTTAATT
SEQ ID NO: 400	ATATTGAGACAGCAATCTTTTGTTT

* At least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide sequence is independently selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00297] In some embodiments, all internucleoside linkages of the STMN2 AON oligonucleotides listed in Table 3 are phosphorothioate linkages (except when a spacer is present, the linkage may or may not be a phosphorothioate linkage), and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the STMN2 AON oligonucleotides listed in Table 3 are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC.

[00298] Table 4 below identifies additional exemplary STMN2 AON sequences:

Table 4. Additional Exemplary STMN2 AON Sequences (corresponding to AONs shown in Table 3 but with thymine bases replaced with uracil bases)

SEQ ID NO:	Oligonucleotide sequence (5'→3')
SEQ ID NO: 923	AAUGUUAAGACAUAAUACCAGAGCU
SEQ ID NO: 928	UUAAAAAUGUUAAGACAUAAUACCA
SEQ ID NO: 933	UAGAUUUAAAAAUGUUAAGACAUAA
SEQ ID NO: 938	UACCAUAGAUUUAAAAAUGUUAAGA
SEQ ID NO: 947	UGUAAAGAUUACCAUAGAUUUAAAA
SEQ ID NO: 1036	AAUCCAAUUAAGAGAGAGUGAUGGG
SEQ ID NO: 1038	AAAAUCCAAUUAAGAGAGAGUGAUG
SEQ ID NO: 1042	UUUAAAAAUCCAAUUAAGAGAGAGU
SEQ ID NO: 1061	CCUGCAAUAUGAAUAUAAUUUUAAA
SEQ ID NO: 1062	UCCUGCAAUAUGAAUAUAAUUUUAA
SEQ ID NO: 1063	GUCCUGCAAUAUGAAUAUAAUUUUA
SEQ ID NO: 1064	AGUCCUGCAAUAUGAAUAUAAUUUU
SEQ ID NO: 1065	GAGUCCUGCAAUAUGAAUAUAAUUU
SEQ ID NO: 1077	AGGUCUUCUGCCGAGUCCUGCAAUA
SEQ ID NO: 1089	CCUUUCUCUCGAAGGUCUUCUGCCG
SEQ ID NO: 1095	UUUCUACCUUUCUCUCGAAGGUCUU
SEQ ID NO: 1101	UCUUAUUUUCUACCUUUCUCUCGAA
SEQ ID NO: 1107	CCAAAUUCUUAUUUUCUACCUUUCU
SEQ ID NO: 1129	GCACACAUGCUCACACAGAGAGCCA
SEQ ID NO: 1136	CACACACGCACACAUGCUCACACAG
SEQ ID NO: 1141	UCUCGCACACACGCACACAUGCUCA
SEQ ID NO: 1144	CUCUCUCGCACACACGCACACAUGC
SEQ ID NO: 1272	UGUUUUAAUUUCUUCAGUAUUGCUA
SEQ ID NO: 1277	UCUUUUGUUUUAAUUUCUUCAGUAU
SEQ ID NO: 1282	AGCAAUCUUUUGUUUUAAUUUCUUC
SEQ ID NO: 1287	GAGACAGCAAUCUUUUGUUUUAAUU
SEQ ID NO: 1292	AUAUUGAGACAGCAAUCUUUUGUUU

STMN2 Transcript with a Cryptic Exon

[00299] In one embodiment, a STMN2 AON targets a region of a STMN2 transcript comprising a cryptic exon sequence, the STMN2 transcript comprising the sequence provided as SEQ ID NO: 1339.

ACTTGTAATATACAGGTATCCCTCCTGGTAAGCTCTGGTATTATGTCTTAACATTTTT
AAATCTATGGTAATCTTTACAAAATATTTTACTTCCGAACTCATATACCTGGGGATTT

TATTACTCTGGGAATTATGTGTTCTGCCCCATCACTCTCTCTTAATTGGATTTTTAAA
ATTATATTCATATTGCAGGACTCGGCAGAAGACCTTCGAGAGAAAGGTAGAAAATA
AGAATTTGGCTCTCTGTGTGAGCATGTGTGCGTGTGTGCGAGAGAGAGAGACAGAC
AGCCTGCCTAAGAAGAAATGAATGTGAATGCGGCTTGTGGCACAGTTGACAAGGAT
GATAAATCAATAATGCAAGCTTACTATCATTTATGAATAGCAATACTGAAGAAATTA
AAACAAAAGATTGCTGTCTCAATATATCTTATATTTATTATTTACCAAATTATTCTAA
GAGTATTTCTTCC
(SEQ ID NO: 1339)

[00300] A cryptic exon sequence within the STMN2 transcript is provided as SEQ ID NO: 1340.

GACTCGGCAGAAGACCTTCGAGAGAAAGGTAGAAAATAAGAATTTGGCTCTCTGTG
TGAGCATGTGTGCGTGTGTGCGAGAGAGAGAGACAGACAGCCTGCCTAAGAAGAAA
TGAATGTGAATGCGGCTTGTGGCACAGTTGACAAGGATGATAAATCAATAATGCAA
GCTTACTATCATTTATGAATAGCAATACTGAAGAAATTAAAACAAAAGATTGCTGTC
TC
(SEQ ID NO: 1340) (Source: NCBI Reference Sequence: NC_000008.11).

[00301] In various embodiments, the STMN2 transcript with a cryptic exon shares between 90-100% identity with SEQ ID NO: 1339. In various embodiments, the STMN2 transcript with a cryptic exon shares at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity with SEQ ID NO: 1341.

[00302] In one embodiment, a STMN2 transcript with a cryptic exon can comprise a pre-mRNA STMN2 transcript. In one embodiment, a STMN2 transcript with a cryptic exon can comprise the sequence provided as SEQ ID NO: 1341.

AGCTCCTAGGAAGCTTCAGGGCTTAAAGCTCCACTCTACTTGGACTGTACTATCAGG
CCCCCAAAATGGGGGGAGCCGACAGGGAAGGACTGATTTCCATTTCAAACTGCATTC
TGGTACTTTGTACTCCAGCACCATTGGCCGATCAATATTTAATGCTTGGAGATTCTGA
CTCTGCGGGAGTCATGTCAGGGGACCTTGGGAGCCAATCTGCTTGAGCTTCTGAGTG
ATAATTATTCATGGGCTCCTGCCTCTTGCTCTTTCTCTAGCACGGTCCCACTCTGCAG
ACTCAGTGCCTTATTCAGTCTTCTCTCTCGCTCTCTCCGCTGCTGTAGCCGGACCCTTT
GCCTTCGCCACTGCTCAGCGTCTGCACATCCCTACAATGGCTAAAACAGCAATGGTA
AGGCACTGCGCCTCGTTCTCCGTCGGCTCTACCTGGAGCCCACCTCTCACCTCCTCTC
TTGAGCTCTAGAAGCATTCAGAGATATTTTATAAAGAAAAAGATGTTAATGGTAACA
CAGGACCAGGAAGGACAGGGCAGTTCTGGGGGAGGTGGGAGGGCAGAGAAGAGGT
CTATGGAAATCTAAAGCGAAGAATTTCTTTTAAAAGGTAGAAGCGGGTAAGTTGCCC
TCCTATGGGTAGAGAATTTATTCTGTTTCCATATTTAAAATTAGGACTCAATCGTGAG
GGGAGGAAGCTACCTTAACTGTTTGCCTTAAATGGGCTTAAGGGACATTTTGGAAAG
TGCTTTATAACGACCTTTTTTTTTTTTATTTCTTCTCTAGTTTAAGAAGAAAATAGGAA
AGGGGTAAAGGGAAGGTGGGAGAAAGGAAAAAGAAAATTGCAAAGTCAAAGCGGT
CCCATCCCGCTGTTTGAAAGATGGGTGGAGACGGGGGGAGGGGATGGAGAGAACTG
GGCACATTTTACGGTATTGTCTCGTCGAAGAAACCGCTAGTCCTGGGGTGCGGTGCA
GGGAGGTAAGACGGCGGGGGACAGGGTGGGGGTAGGACCTCCGCTCCTTTGTTTTA
GGGCAAGGGAGGGGAAGGAGAGAGGAAGTCGCGGAGGGCGTGGAGGGCGCGGGTG
GGCAGCTGCAGGGGCGGGGAAGCGCGCGGCAGGGAGGGGTGGAGGGACAGCGGCT
TCGAAGGCGCTGGGGTGGGGTTTCTTTGTGTGCGGACCAGCGGTCCCGGGGGGAGG
CACCTGCAGCGCTGGGCGCACAATGCGGACAGCCCCACCCAGTGCGGAACCGCGCA

GCCCCGCCCCCCCGCCCGGTGCTGCATCTTCATTCGAAAGGGGGTCGGGTGGGGAGC
GCAGCGTGACACCCAGGAGCCCAACCCTGCGGGGACAGCGGCGCCACGCCCCGCGC
TCCCCGCTCCCGACTCCCCGCCGCGGCTTCCAAGAGAGACCTGACCACTGACCCCGC
CCTCCCCACGCTGGCCTCATTGTTCTGCTTTTAAGAGAGATGGGAAAAGTGGGTTAA
CATTTTTCTTTTCGGAAGCAAATTACATAGAGTGTTTAGACATAGACACAGATAAAG
GGTTCTTTGAAGACCTTTGATCGTTTGCGGGAAAAGCTTCTAGAACCTAGACATGTG
TATGTATAATAATAGAGATGACATGAAATCGTATATAAAGCAAAAGAGGTCAAAGT
CTTAAGTTAAGCCACGCGAAATTTCCGTTTTGTGGGTCAGACAGTGCCAAATATCGG
CAATTTCATAAGCTCAGAGAGACAAGACAGTGGAGACACAGGATGACCGGAAAAGA
TTCTGGATTCAGGGCCTTCATCCGCAATTGGTCTTGTGCCTTGAGTGCCCACGGTTCT
GGCGCTCAGTGGCCCCGGGGTGAAAAGGCAGGGTGGGGCCTGGGGTCCTGTGGCAG
CTGGAAGCACGTGTCCCCCGGGACTTGGTTGCAGGATGCGGAGACAGGGAAAGCTG
CCGAAAGGACTCCATCTGCGCGGCTCCGCCCTGCCCTACCCTCCCCGCGGAGCCGGG
GAGACCTCAGGCTCCGAGACTGGCGGGGAAGAGGAATATGGGAGGGGCAGTTGAGC
TGTATGCAGTCCTGGAACCTCTTTTTTCAGCCCCGCAGTCCACAACGGCCCGAGCAC
CCCTTGATGTGCGCAGACCCCCGGCGTGGCTCTCAGCCCCAGCACCGAGCCCCTCCC
AGCCAAGCGGGTGGCTCTGCAGAAAAGCTGGCTCGAGCCCCGCCCGGCCACACAAA
GGCGCGGCCCCACCCAGCCCGGGCGCGAGACCGCAGAGGTGACCCCCTTCCCAGGG
ATTCAGGGAGGGCTGTCTCTTCTCGCCCACCCACGGTCCGCGGAGCTCGGGGCTTTT
TTTCCCCCAGCCCAAGCCCCCCGCCCACCCTCTGTTCTCTATGATTTTCCAGAATGGA
GACCCCGCGAGGGGCTTCTCTAAGGGAGACCCTCGCTCCTCCAGCGGGGCGCGGCTC
GGCCCCACCCCTCCCAGCTGAGGCCCAGAGCCGCCTACCGCTGGCCGGGTGGGGGC
GCACGTGGCGACTGGGTGTGTGGAGCGCAGCCAGCCCTGCAGAGCCCCGCGCCGCG
CCCTGCGCTCCCCTCCCCGGAGTTGGGCGCTCGCCCCCGCGGTGCAGCCGGGGAGAC
CGGTTTCTGCGCAGTGTCCTGAGCTACCCCCGCTTTCCACAATTCGCAGTTCACTCGC
ACGTCCAGAAAGGTTCTGAGAATGGGTGGTGGGGGCGATCTCGCCTCGCTTTCTGCA
CCCCTCAGAAAGGTTTCCGCTGCAGGCTAGTGGCTGCAAACTCATCGTCATCATCAG
TATTATTATCATTTCAAATCGTTGTTATTATTTAATGATTCAGTAGCCTTGTTTGTTCT
CATTTGTTCAAAAGGGACGTGGATTGCTCTTGGTTAAGGATTAACCCTTGTTGCGTTC
GCTTTGCTTCCTCCTAATTGCCCTCATCCCTTTCCCCCACAAAAAGGTAAATTTGTCT
CCAGTTGTTCATTTTAAGTTATAAAGCAAATATATTTTTGCTTCCTGCCAGGATTATG
TATGTTCATGTGGCTAAGATACATGTGCAAGTGCTTGCTAAGAGCAGGGTTTGTGTG
CCAACGATTGCTGGAAAATTCTCTGCAAAGAATTGTTTGTGGCTGCAATGGGTGAGA
ATACACATATATAATTGAGATGATCTTCAACATAAGGTTATATCTATAAATATATAA
ATATAGTTTATGCACAAAATTTTAAGTTTTTTCCCCTGAAACTGTTCTTCCAACTGCT
GATTCTTGATACAGCCTCAATCCTACACAGATACATGGATCGTGAAATGGTAGCCGC
CATCCAAATAAAAATCCCACCCCAAATATGACAAACGCAAGCATCCTTTCTGGCCAT
AATTTAACTGCATTTGCAAATCATGAAAAAAACACTACTTCTGCAGTATTAAAATAA
TAGATTTTGAAATTAATTCCAATTTCAAAGATAATTAATTATCAGGGCGAGTGCTTTT
TTCCTGATTCATTAAACAATTATGTATTCAGCATGATTGTAAGAGGTGCATATAATAT
TCCCCATTATCTTTTCTAATGAAGTGGGCACCTTCTGAATGGATATATAAGTAACTAG
AAATGAAAAGCTGAGGATTTGGTCAGAATTTCAGGATAAAACTGAAAGAAATGGCA
GTAGTTTATCAATTAATCTCATGTATTTAGTTTATACCAGGTGAGTAAGCTGAGCCTG
CAATAAACACTCTCTGTCCCAGTGTAACACGTCGCAGGTAGCTAGAATGATAGGATA
AATTAATAGACCTTGTGGTGTTTGTCTATGCACGTTAAAATTCTCTGAGAGAAAGTA
TATTTTAAAATGATAATTAAGATTGGACATTTGTGCTATTAAAATCTACAACTTTAGT
CAAAATTCACAATGGTTTTTTTTTACAATAATGTGACTTACAGATTTGTAGTAAATTA
TTCTATTCTAAAAGAGAAATGAGTGTTTTTATTGTTACAGCTATTACCTCATTAATAT
TTTTAGCAAACTTTTATTTGTTGCATTGAAAGCAGTTTTAATTACTTTGGGTTTTTATT

TTTCAAATTACTAATGGATAGATGGTGGAATAAGCATTTAATCATTTGGCACAATAT
GACTTCCATCAAATAGCTCATTCTCAGTGATTAAAAAATGCTACAAGAGGCTACAAT
TTACTCAGATTCAGGAAATGTCCTTTCAGAGTGCCATAAGGCTGATTCATATAATAA
AATAGTTTTCTTCCCTATAATTTAAGATCAAATAGTTACTTAGTTCTGTGAATACCTA
GCAGTAGCTATCAAACAGAATTTTAAAGTTAAATCTGTACAACTAACAATGAAGTGG
AGGATGAATCGATACATATTGAATGGAAGACTTTGTCATTGATAAATTCAGGCCATC
TTTAGGAAAATTCCGGATTTATCAATCACCATTATTTTTTACTTCAACTGAGTGTGAC
TGATCACATGCTCAGGCTACCTTGGTAGCTCATTGCTCACAGGAGGCTGAAAAAAGC
TGGCCTCCGAGCAGGAGGAAGCTCAGAGCACAAACCTAGGCCTGGGCGTGGCCACT
GGGAGCTGCTGATAGCGAACCCCAGCTCACACCAGTTTCTTTTTTGGTCGTGGGAAG
AAAAACACATATTATCCTGTTGTCACAAGATCTGTGACCTTATATGAAAAAATGCTA
GAATTTTTTCATTAAAAAAGAAAATACTGAACTAGCCAGTGACCCAGATGTTTTCAG
AACCTAGACTGGTTCTGTCCATTGGAAAACCTCGGTGTCTGCATTAACTTTTCACCAC
ACTAGAGGGCAATCATGTTCTCTAAAAAAGCAGATGATTGATGTAAACCTAGTTCCA
AATATTAACTGTTTAATAAAATCTTTTCTTTTACCAGGAACATTCAAGTGTTTATTCA
ATAAGCTGATGCCATGCTTTACCCTAGTGGATGAACAGAGCTTGTACAATTTTCAAG
GAGACAGGATGAAATGAGTGGTCATAATCTGAAAGTAGATACACGCCCTGGTTAAT
TATTCCCTGATGGTTTTACTTCTCAGTTTTATTACATTGTTATTATAATACCATTTATG
TTACTTCTGAGATTTTGTAGTGGATAAATAGTAGAAAAATGTCAGTAGTAATAGCAA
AGTTATTTAGCAGCCGAATATTTTAATGCTTAAAAATAAAGGAATAAATTAAAGAAA
ATCATTGTTTACTTCTTCATCGATTGAAATGTGCCCCCTGTTCAGAGCACATCTGAAT
ATCAGAGTCTCCACCTGCAGAGAACATGCAGCTTAGCGAGTAAAACAGGCAGGTAT
GTGATACTGAGGAGGTGTACCAAAAACTGACTGCTGTTATTTTTCCCATCTTCTAAGT
CTGTCTTTCTTTTCCATTTAAAGATACCTTTTTAAATCTAATCCAATGTGATTTCAATC
TAGTTTTATCAGATTTCAACAATTATTGAGCATCTCCTTGTAGTGGTTTTCTGTTTATT
AGAAAATCGATGTTAATTTTAACGAAGTAAGAAGAAATATATAAGTATAAACTAATT
TTGGGTATCATCAAAAGTGGATTTTTTAAATATGCATTGATAGAATTATTTTTTGATT
ACATTTTATGTAATTCTAATCCAGCTATAAAATATTTAATAGTGTCATATTACTGTGT
TCCTCAAACTTTGATGTGCATATGAATTACCTTTGATTTTCATTAAAATGCAAATTCT
GATTCAATACATCTGGCTTGAGGCAGACATTCTGTCTTCCGAACAAGCTCCCAGATG
ATGCTGATTCTGACCACTAAACACATCAGTTTTAGGGATATTAACTTGTAATATACA
GGTATCCCTCCTGGTAAGCTCTGGTATTATGTCTTAACATTTTTAAATCTATGGTAAT
CTTTACAAAATATTTTACTTCCGAACTCATATACCTGGGGATTTTATTACTCTGGGAA
TTATGTGTTCTGCCCCATCACTCTCTCTTAATTGGATTTTTAAAATTATATTCATATTG
CAGGACTCGGCAGAAGACCTTCGAGAGAAAGGTAGAAAATAAGAATTTGGCTCTCT
GTGTGAGCATGTGTGCGTGTGTGCGAGAGAGAGAGACAGACAGCCTGCCTAAGAAG
AAATGAATGTGAATGCGGCTTGTGGCACAGTTGACAAGGATGATAAATCAATAATG
CAAGCTTACTATCATTTATGAATAGCAATACTGAAGAAATTAAAACAAAAGATTGCT
GTCTCAATATATCTTATATTTATTATTTACCAAATTATTCTAAGAGTATTTCTTCCTGA
ATACCATGTGAGAAAATTCTTAAGAATTTATTGAGTATGACTGTATATTTGAAAAGA
GTGTTTTCTTCTGCTTATCTAAGCCAATAAAGGATCTTCATTATTCAATTCTAACTTTC
TAAGGAAGTCAACCTACAGATCAGAAAGAGGATCTTCAAGGAATAGCATCAAAGAC
ATAGTCAGGTCTCCCATGCAGTGACTGGCTGACCATGCAGCCATTACCACCTTTCTG
GAAATATTATGCTGCAAAAATGATACAATACACGAAATATCTCAAATTAAAAAATAT
AACATTTCCCAAATAGGGCACTAAAAACATGATCCCAAATAAAACTAGCTTCAGGGT
TTGCAGAATATACTGTTACTCAACACAAAGTTGGACTAAGTCTCAAAGTTAGCCATT
CAGTTGTTGTTAACAGTTCATTTCAGGGTCTCTCAGAAGCTGGGAAACTTTCCATTTT
TGCAATTTCTTGTACATTGAAGGAAAGGAAGACACACTTAAGACAGCATTACAAAA
GTAATTCATGTTTTAAATGTTTAATTCTGGCAGTCGGGCAGGGCTCTCTGTATAACCT

CATTTGGAGATGACAAAAATCTAAACTTGAGGGCCTCGAGCCAATAAGTCTTCCTAT
TTCTTTACTCAAACATTTTCCCGCAATGGTGCTTTCTTTCAACTGTTTTTCTGGTGTAT
TCATAAATTCCAGATTCTCTATGGGAAGTAACTTTTATTGATTGATTTAACCCTTGTA
TAGCACATATAACATGCAAGGCATTGTTCTAAGAACTTTCCACATATTAACTGTGTT
AATCACTTAATAATCCTAAGTAGGTTCTATTACAGATATGGAAACTGAGGCACAGAA
AGTTGAAGTATCTTACTCAAGGTCACACAGTTAGTCAGATCCAGAATTTGGGCCCAG
GCCATCTGGCTTCGGAATCCATCTTTCACCGATTGCTGCTAGTCTCATATCTGTTCCA
TGTTAGAGGTGAGCTCCCATTGCAGAGGTCACACCTGTGATATCACCATTTTATTTAA
ACAGACCAGAGATGGTCTTCTCCTTTCTGATCACAGACTCACCTTGAAGAGAAAATA
CTTCCAAATTGATGCCTAGTTTTAATAGCTTACCTGGGGCTTATTCAAATAATTGCCA
TGATTTAGGCTTTGGGAGAAAGAGAGCTATGAGGCCGTGTGGGTTGTAACGTATGAG
ACACATGGCGTTCTGCAGGCTCAGCACAGCATCGATTTCTGGTGGGAACACACTCTG
ATGACCAGTTCCAGAAATAACATTGACTTAATCTCCTCAGTCCCATCATGGTTAGCA
CATTTCAAAATGCCTCCTTAACTACTTCCATAGGCCAGAGATATTTAGTTTTAACATT
TTGTTGAATAAAATAAATTTACACATTCACATTTAATATAACTATTAGATGTTATTTC
AAGATTCTCTTCATATTACCATCAAAGCAGGCAGGCAGGCAGGAGAGAACTGTAGG
AAGGTTTTGAATCCCTTGTGAAACATTTTTAATTATCTTTTAATAAAGGAATCAGGCC
CTGTCATTTGTCAAGGAGACATTTGCAGTAGTAAAGCTTGTGTTTATAATATCCATTT
TTATTAGTCATGATTAAAGATAACATTTGTGTACATTTGTTCTCACAAAACACTTTTA
TATGAGTGTAAAGGTTAATTAATGCATTTCAGCCATCATTTTGCTGGTCATGTGGAA
ATATAGCTTCTTTAGGAATTGTACTTAGAGTAGGAGCCACATATTATACTATAAAAC
CATAACAAAAATATTTTAAGTTTGTTCTCACTTGTTGTTGACCTCCAGAGTAAAATAT
TTAATACTCTGGAAAGTTATGGGTTTCAAAATTTATTTTATGGCAAGAAATAGATAA
TTACAGTTCTCATAGAGCACATTTAAAATAATTTATTTTTATAGGGCAAAAATATTGC
CTAGGACTGAATGATTTTTTTTTTTTACAAAGATTGTAAAGCAACGCCTGCAAGAGT
GCCCATTTAGCAGTTATTCTTCTGGAATAATTGTATTTTGGATGTTGGAGTTCGCACA
TTAACCATTAGTACAAGTACCCAATATAACAATAGATCATCAGGATAATAAATCTGT
CCATCTTTTAGTTGTATGTCTTTATATCAGGATAAAGAGAATTGAGTGAAATTTATCT
AAACCTAGTCCCACAAATACTTTTACAAGAGAGCATGTTAAAGTGTAAATTAAATTT
TTATTAGCATTCTACTCTGTCTTTGGAAGTTTTTTTTCCTTATGAAATGCAGCCATAA
AGTTTAACTTCCATTAACAAAGCTGCTCACAGTAAACCTATTATAATAATAGTTTCCC
AGTTTGGGCTTCCTAGTGAGGAGCAACCTAACTCACACGAAACAACCCCAACTTATA
ATATATTGACTGTTACAAAACTGAGACCAGAAAATCCCATCAAGATGGTACTGTTAT
CATTTCCAGACTCTCGGGAAGAACATTAATCATCTCAGGCACTTTTAGGATAGACTT
ATTGCAGCCTCCCTGGGAACTCTGCTTCAGAACATAATTATTTTTATTAATGCAGAGT
TACTTTTTATTTCCAACAAAAATATCTATTGTTATTATTTAAGTCTTACAGCTTTATCT
GAGAAATTCCAATTAGCACCCTTCTCATAATAAATATTCAAACACATGAAAAATTAC
CAAAGTTGTTCTAGTCTTTTAATGACATATTACATGATCCTGCACTCTTGTCACTTTA
AAAATTATCTTTTTATTATATTTCTGATGATTTTTTTCTTATATAGTTTTTTAAAAGGA
GCAGGCAAGCATAGAAGACTAAAAAATGTTCAAAAGAAAAATTAAATCGCATGATC
TATCTATATGGGACCTTGTCATTTTTAGAAAACATTCACCTGCTTCATCCTTTTGAAT
CTTCATATAATCCCTCTGAGATGGGCATACTATACAAGTTGTCTTATTTAAAGATTGG
TAAATTTAAGCTCAAATAATTTATTCAGTGGCAAGCCTCAGAGGCAGACTCGGAACA
CAGGTCTAATATATATTATATATATATTATAACATATAATATATATATTACATATAAT
AAAGTTGTGTATATTATTTACCTATCAAAATATTTATATGTAATATATAAATATGTTA
TATATCATGTATGTGCCTATTTCATACATATATACACATTCATGCAAAATAAGGTTTA
GCACTCCCTCCACTGTCCTGTAATAAAACATGCACAGTGAGAATAGTCATACACGAG
GCATATTTGTCTTCAGTTTAAAGTCATTGATAGTCAGTGTCACTAACTAAAGTAAAAT
AGATTGGAGCACCAACTTTGTTCTGAAGCCTGTGCCAGGTATTATGAGAACAAAAAT

AAAAATGTTCCTCACCCTTGGTGGATTTAGTCTTTTGCAGAAAAAAAGATCCTGTAC
ATGTCAGAAAGTTCAATAGTAATAATGGTAATTTATAACTATAAATGGAAGTCACCA
TCTCACAATTTCACCATCTTAACAATTTTGTTAAACTGCCCTACAATATTACAAGATA
GTACATAATGATACACTAGTAACATCAACTAGGAAGTACCAAGATCCACCAAAAGG
CTGAAAAATTTAAATATTTAATGAGTCCATCAACCAATCTGGCCAGAGAATTCTTTA
ATTAAAATGCTTCCCAAATTTTACTGAGAATCAGCAGCGTTTGAGGAGCTAGCCTCC
ACCCCCAGAGGTTCTCACTCTATTAGGTCTGAAGCAGGTCCCATGGATTTGCATTTCT
AACAAGCTCCCAGGTGGTGCTGATGAGGCTGATTCAGAACCACACTTGGAGTAGAC
CTAAAACAGCAGTGACCTGTAGGGTCCCCAAGCAGCAGGCCAGGACAGCATGTGAG
TTACGTCCTCTGTGGAGCTCTGCAACAAGGCGTCAAGAGGTCAGAGTCTAAGTCCCC
ATCAGCTCTGCCCTTCTCCACCAGTGCTGCTGGTGCTGCATGGAAGGAAGAGCCCAG
AAGGGATTCTGAGTTTCAGTCTTTACTCTTGCTGACGCACCTTGGTCAGGTCAATTTT
CCTGTTTGTTCCTCTAATTCAGCATCTGTAAAATAGCCATGTGAACTGCCTTGTCCAT
ATCAGAGGGTCTTTTTCAGACTCAAGGAAAAAAACGTGAAAGTGATTAGTGTCTGTC
AAGTAGTATATAAATGCAAGAAGTTGAGTTTTTAAATTGTCATTAGATATAAATACC
CATGTGCATGCATTTAGAATGAGTAAAGAGGGAACAAGGAGCGCAATCAAAAACTG
CGTCATTTGCTTTTTGAAAAATACTTTCTATGTAATGAAAAGTGAAATAAAATGTTA
ATTGAGTCCCTCTGACAACAGCATCAGACGTTTTGCAGTTCTTGTGATTAGAACCCA
CCTGGCCAGCCCTTCTTCCTCCTAAAGAAGAGCCTTCTTCTTCTTAAATGAAGGTTGG
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CGAGCGAGAAGTCCTTCAGAAGGCTTTGGAGGAGAACAACAACTTCAGCAAGATGG
CGGAGGAAAAGCTGATCCTGAAAATGGAACAAATTAAGGAAAACCGTGAGGCTAAT
CTAGCTGCTATTATTGAACGTCTGCAGGAAAAGGTAATCTCAGCAGAGTCCTGAGCA
GATGGATATATTCATATGCAGCACAGCTGGGTGAACTTCCATATGCCTGAGCACAGA
GACGAAGTCAAAATTTGCTGCAGGTGTGAGGACAACTAACTCCCATGGGCAGGGTC
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TGTACATCTGCACACCACTTTTCCTGCAAATAATCAACCCAAAGAGTGCTTAAAATT
CCTGACATCAACCCACAGAATCTCCAAGGATGGGACCCAGCATCCATACATTTTAAA
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AGACCCTGTCTCTAAAATAAAAAGAAAAAAAAAAGATGACCACTTCTGAAATGACAC
CTATCAATGAGTTAATCATTCAATGAATATGTATTGAGTCCCTACTATATGCTTAGGA
ACCTTTGTAATATCATTACCAACCATGTCTTTCCCAATACAGACAATACAAAATTCA
GCAATAAATAATATAGCACCAACAATTAGAGAATAAGACAACATGTAGTATGGTCC
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TCTAATATTTAGCCGTGGTTGAGAACCACTGTGCTAAATGTTTCTTAAATATGCTTTG
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TTCCTCCAAAGAAGAATGTTACACTCATTTCTTATTTCAGTTTCCTGTTTTCATAGCA
CCTCATCTTAACACTCCAGGCTATTATATAGAAAAGAATCAAATGTGGAGAAGGCTG
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GAGGGGAAGAGAGGAAGATGAGAGAAAGGAAAGAGAGGGGGAAACACCTGTTCTT
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TCTTTTCTTGCCATTATTCACACTTATGTCACATTAGCTATGATTTGCAGTTTTAATTT
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TTTAACTCTTTAGTTATAGATTCCAGCTATTATCAATTTACACCTATTGCATTCTTCTC
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GCTTTTGATGTTGTGTCTTTCCACTCAAATGAATTTGCTAGGTCTGTTCTTTTTGAAGC
TCCCCATGTCTAACTCCATTCCAAAAGAAAAATGAGGTCAGTAGACAGTCTATGGTG
CTAGAAACCCACCATTGCCTAATGACCTAGAAGGCTTTGTTGTCTCTGAGCTTGACT
AAGACCATACCTAGATCACAGGTATTATGACTCCACATGAACCTTCACATTTGTTCG

CTCATAATCTACTTACTGCCTAAAAACTACAAAACCAGGCTAAGAAATACCACCAGT
CATAGCATTTACTTCTGCTTCTCCTGGATTATGTGCTACAAATGTGCTTTGGCTTTAG
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GAACCTTTTAAAGTGCTGAACACAAATCCAAATTCGAATGGTTCAAGCAGCCGTGAA
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GCTCTTACCTATAGTACAAGTACATGATGCTACTGAATATTTTTCCACTTGGAAACTG
TGAGCTGGTTGTTGCATTAAAACACACATACAAACAAAATCAAAAACACTGCGGAC
TTTCACTCAAGCTGGTCTTTCTTCCCCAGTGTAAGGCAATCCTGCCTACTAACAACAC
CAACAACAAAACACTCCATCTGTGAAGCTGACGCAGTTAAGGGGGCTAGGCAGGGC
ATTTGTGCCAACTAAGAATCACCAGATACCCACCATAAGTACCTATCGCAGTTTTGA
AGTCGTTTCTCCCCAACTCCCAACTCCTGAAGGTTGCTGCCTGCATATTTACTCTTCA
TTAGTGCTATTTTCCTGTATGTCATTGTGAGCAAGCTGTGATTAATAAAGAATTGGAG
TTCTGTGAACTAATAAAGGTTTGGTCTGTT

(SEQ ID NO: 1341)

STMN2 Oligonucleotides Targeting Regions of the STMN2 Transcript

[00303] In various embodiments, STMN2 AON disclosed herein are complementary to specific regions of STMN2 transcripts (for example, a STMN2 pre-mRNA comprising a cryptic exon) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 1341. In some embodiments, a STMN2 AON comprises a sequence that is complementary to a specific region of the STMN2 transcript (for example, a STMN2 pre-mRNA comprising a cryptic exon) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 1339 or SEQ ID NO: 1341. In some embodiments, a STMN2 AON comprises a sequence that is at least 85% complementary to a specific region of the STMN2 transcript. In some embodiments, a STMN2 AON comprises a sequence that is 90 to 95% complementary to a specific region of the STMN2 transcript.

[00304] In some embodiments, the STMN2 AON (e.g., STMN2 AON) has a segment that has, at most, 7 linked nucleosides. In some embodiments, the STMN2 AON has a segment that has, at most, 6, 5, 4, 3, or 2 linked nucleosides. The segments of the STMN2 AON may be separated from other segments of the STMN2 AON through a spacer. The segment of the STMN2 AON is complementary to a specific region of the STMN2 transcript (for example, a STMN2 transcript comprising a cryptic exon) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 1339 or SEQ ID NO: 1341.

[00305] In some embodiments, a STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript comprising any one of positions 144-168,

173-197, 185-209, or 237-261 of SEQ ID NO: 1339. In some embodiments, a STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript comprising any one of positions 121-144, 146-170, 150-170, 150-172, 150-170, 150-172, 150-174, 169-193, 170-194, 171-195, 172-196, 197-221, 249-273, 252-276, or 276-300. In some embodiments, a STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript comprising any one of positions 144-164, 144-166, 145-167, 146-166, 146-168, 147-165, or 148-168 of SEQ ID NO: 1339. In some embodiments, a STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript comprising any one of positions 173-191, 173-193, 173-195, 173-197, 175-195, 175-197, 177-197, or 179-197 of SEQ ID NO: 1339. In some embodiments, a STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript comprising any one of positions 185-205, 187-209, 189-209, or 191-209 of SEQ ID NO: 1339. In some embodiments, a STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript comprising any one of positions 237-255, 237-259, 239-259, 239-261, 241-261, or 243-261 of SEQ ID NO: 1339.

[00306] In some embodiments, a STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript consisting of any one of positions 144-168, 173-197, 185-209, or 237-261 of SEQ ID NO: 1339. In some embodiments, a STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript consisting of any one of positions 144-164, 144-166, 145-167, 146-166, 146-168, 147-165, or 148-168 of SEQ ID NO: 1339. In some embodiments, a STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript consisting of any one of positions 173-191, 173-193, 173-195, 173-197, 175-195, 175-197, 177-197, or 179-197 of SEQ ID NO: 1339. In some embodiments, a STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript consisting of any one of positions 185-205, 187-209, 189-209, or 191-209 of SEQ ID NO: 1339. In some embodiments, a STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript consisting of any one of positions 237-255, 237-259, 239-259, 239-261, 241-261, or 243-261 of SEQ ID NO: 1339.

STMN2 Oligonucleotide Variants

[00307] In various embodiments, STMN2 AONs include different variants, hereafter referred to as STMN2 AON variants. A STMN2 AON variant may be an oligonucleotide sequence of 5 to 100 nucleobases in length, for example, 10 to 40 nucleobases in length, for example, 14 to 40

nucleobases in length, 10 to 30 nucleobases in length, for example, 14 to 30 nucleobases in length, for example, 16 to 28 nucleobases in length, for example, 19 to 23 nucleobases in length, for example, 21 to 23 nucleobases in length, for example, or 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleobases in length. A STMN2 AON variant may be an oligonucleotide sequence complementary to a portion of a STMN2 pre-mRNA sequence or a STMN2 gene sequence.

[00308] In various embodiments, a STMN2 AON variant represents a modified version of a corresponding STMN2 parent oligonucleotide that includes a nucleobase sequence selected from any one of SEQ ID NOs: 1-446 or SEQ ID NOs: 893-1338. In some embodiments, a STMN2 AON variant includes a nucleobase sequence that represents a shortened version of a nucleobase sequence of a STMN2 AON selected from any one of SEQ ID NOs: 1-446 or SEQ ID NOs: 893-1338. As one example, if a STMN2 parent oligonucleotide includes a 25mer (*e.g.*, 25 nucleotide bases in length) a variant (*e.g.*, a STMN2 variant) may include a shorter version (*e.g.*, 15mer, 17mer, 19mer, 21mer, or 23mer) of the 25mer STMN2 parent oligonucleotide. In one embodiment, a nucleobase sequence of a STMN2 AON variant differs from a corresponding nucleobase sequence of a STMN2 parent oligonucleotide in that 1, 2, 3, 4, 5, or 6 nucleotide bases are removed from one or both of the 3' and 5' ends of the nucleobase sequence of the STMN2 parent oligonucleotide. In one embodiment, the corresponding STMN2 AON variant may include a 23mer where two nucleotide bases were removed from one of the 3' or 5' end of a 25mer included in the STMN2 parent oligonucleotide. In one embodiment, the corresponding STMN2 AON variant may include a 23mer where one nucleotide base is removed from each of the 3' and 5' ends of the 25mer included in the STMN2 parent oligonucleotide. In one embodiment, the corresponding STMN2 AON variant may include a 21mer where two nucleotide bases are removed from each of the 3' and 5' ends of the 25mer included in the STMN2 parent oligonucleotide. In one embodiment, the corresponding STMN2 AON variant may include a 21mer where four nucleotide bases are removed from either the 3' or 5' end of the 25mer included in the STMN2 parent oligonucleotide. In one embodiment, the corresponding STMN2 AON variant may include a 19mer where three nucleotide bases are removed from each of the 3' and 5' ends of the 25mer included in the STMN2 parent oligonucleotide. In one embodiment, the corresponding STMN2 AON variant may include a 19mer where six nucleotide bases are removed from either the 3' or 5' end of the 25mer included in the STMN2 parent oligonucleotide.

[00309] Example sequences of STMN2 AON variants are shown below in Tables 5A and 5B.

Table 5A. STMN2 Oligonucleotide Variant Sequences

SEQ ID NO:	AON Sequence* (5' → 3')	SEQ ID NO:	Target Sequence (5' → 3')
1342	ATCCAATTAAGAGAGAGTGATGG	1367	CCATCACTCTCTCTTAATTGGAT
1343	AATCCAATTAAGAGAGAGTGATG	1368	CATCACTCTCTCTTAATTGGATT
1344	TCCAATTAAGAGAGAGTGATGGG	1369	CCCATCACTCTCTCTTAATTGGA
1345	GAGTCCTGCAATATGAATATAAT	1370	ATTATATTCATATTGCAGGACTC
1346	GTCCTGCAATATGAATATAATTT	1371	AAATTATATTCATATTGCAGGAC
1347	GTCTTCTGCCGAGTCCTGCAATA	1372	TATTGCAGGACTCGGCAGAAGAC
1348	GCACACATGCTCACACAGAGAGC	1373	GCTCTCTGTGTGAGCATGTGTGC
1349	ACACATGCTCACACAGAGAGCCA	1374	TGGCTCTCTGTGTGAGCATGTGT
1350	TCCAATTAAGAGAGAGTGATG	1375	CATCACTCTCTCTTAATTGGA
1351	AATCCAATTAAGAGAGAGTGA	1376	TCACTCTCTCTTAATTGGATT
1352	CAATTAAGAGAGAGTGATGGG	1377	CCCATCACTCTCTCTTAATTG
1353	GTCCTGCAATATGAATATAAT	1378	ATTATATTCATATTGCAGGAC
1354	GAGTCCTGCAATATGAATATA	1379	TATATTCATATTGCAGGACTC
1355	CCTGCAATATGAATATAATTT	1380	AAATTATATTCATATTGCAGG
1356	AGGTCTTCTGCCGAGTCCTGC	1381	GCAGGACTCGGCAGAAGACCT
1357	CTTCTGCCGAGTCCTGCAATA	1382	TATTGCAGGACTCGGCAGAAG
1358	ACACATGCTCACACAGAGAGC	1383	GCTCTCTGTGTGAGCATGTGT
1359	GCACACATGCTCACACAGAGA	1384	TCTCTGTGTGAGCATGTGTGC
1360	ACATGCTCACACAGAGAGCCA	1385	TGGCTCTCTGTGTGAGCATGT
1361	CCAATTAAGAGAGAGTGAT	1386	ATCACTCTCTCTTAATTGG
1362	GAGTCCTGCAATATGAATA	1387	TATTCATATTGCAGGACTC
1363	TGCAATATGAATATAATTT	1388	AAATTATATTCATATTGCA
1364	TCTGCCGAGTCCTGCAATA	1389	TATTGCAGGACTCGGCAGA
1365	GCACACATGCTCACACAGA	1390	TCTGTGTGAGCATGTGTGC
1366	ATGCTCACACAGAGAGCCA	1391	TGGCTCTCTGTGTGAGCAT

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a

thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

Table 5B: Additional STMN2 Oligonucleotide Variant Sequences

SEQ ID NO:	AON Sequence* (5' → 3')
1421	CCTGCAATATGAATATAATTTTA
1422	TGCAATATGAATATAATTTTAAA
1423	CTGCAATATGAATATAATTTTAA
1424	TGCAATATGAATATAATTTTA
1425	TCCTGCAATATGAATATAATTTT
1426	CTGCAATATGAATATAATTTT
1427	AGTCCTGCAATATGAATATAATT
1428	TCCTGCAATATGAATATAATT
1429	TTTCTCTCGAAGGTCTTCTGCCG
1430	CCTTTCTCTCGAAGGTCTTCTGC
1431	CTTTCTCTCGAAGGTCTTCTGCC
1432	CTCTCGCACACACGCACACATGC
1433	CTCTCTCGCACACACGCACACAT
1434	TCTCTCGCACACACGCACACATG
1435	CTCTCGCACACACGCACACAT

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00310] Table 6 below identifies additional variants of STMN2 AON sequences:

Table 6. Additional STMN2 Oligonucleotide Variant Sequences

SEQ ID NO:	AON Sequence* (5' → 3')
1392	AUCCAAUUAAGAGAGAGUGAUGG

1393	AAUCCAAUUAAGAGAGAGUGAUG
1394	UCCAAUUAAGAGAGAGUGAUGGG
1395	GAGUCCUGCAAUAUGAAUAUAAU
1396	GUCCUGCAAUAUGAAUAUAAUUU
1397	GUCUUCUGCCGAGUCCUGCAAUA
1398	GCACACAUGCUCACACAGAGAGC
1399	ACACAUGCUCACACAGAGAGCCA
1400	UCCAAUUAAGAGAGAGUGAUG
1401	AAUCCAAUUAAGAGAGAGUGA
1402	CAAUUAAGAGAGAGUGAUGGG
1403	GUCCUGCAAUAUGAAUAUAAU
1404	GAGUCCUGCAAUAUGAAUAUA
1405	CCUGCAAUAUGAAUAUAAUUU
1406	AGGUCUUCUGCCGAGUCCUGC
1407	CUUCUGCCGAGUCCUGCAAUA
1408	ACACAUGCUCACACAGAGAGC
1409	GCACACAUGCUCACACAGAGA
1410	ACAUGCUCACACAGAGAGCCA
1411	CCAAUUAAGAGAGAGUGAU
1412	GAGUCCUGCAAUAUGAAUA
1413	UGCAAUAUGAAUAUAAUUU
1414	UCUGCCGAGUCCUGCAAUA
1415	GCACACAUGCUCACACAGA
1416	AUGCUCACACAGAGAGCCA
1436	CCUGCAAUAUGAAUAUAAUUUUA
1437	UGCAAUAUGAAUAUAAUUUUAAA
1438	CUGCAAUAUGAAUAUAAUUUUAA
1439	UGCAAUAUGAAUAUAAUUUUA
1440	UCCUGCAAUAUGAAUAUAAUUUU
1441	CUGCAAUAUGAAUAUAAUUUU
1442	AGUCCUGCAAUAUGAAUAUAAUU
1443	UCCUGCAAUAUGAAUAUAAUU
1444	UUUCUCUCGAAGGUCUUCUGCCG
1445	CCUUUCUCUCGAAGGUCUUCUGC
1446	CUUUCUCUCGAAGGUCUUCUGCC
1447	CUCUCGCACACACGCACACAUGC
1448	CUCUCUCGCACACACGCACACAU
1449	UCUCUCGCACACACGCACACAUG
1450	CUCUCGCACACACGCACACAU

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate

linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

KCNQ2 Oligonucleotides Complementary to KCNQ2 Transcript

[00311] In some embodiments, a KCNQ2 AON includes a sequence that is at least 85% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a KCNQ2 transcript (e.g., any one of SEQ ID NOs: 3032-3045). In some embodiments, a KCNQ2 AON includes a sequence that is between 90-95% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a KCNQ2 transcript.(e. g., any one of SEQ ID NOs: 3032-3043). In particular embodiments, a KCNQ2 AON includes a sequence that is between 85% and 90% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a KCNQ2 transcript (e.g., any one of SEQ ID NOs: 3032-3043). In particular embodiments, a KCNQ2 AON includes a sequence that is between 84% to 88% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a KCNQ2 transcript (e.g., any one of SEQ ID NOs: 3032-3043). In particular embodiments, a KCNQ2 AON includes a sequence that is between 89% to 92% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a KCNQ2 transcript (e.g., any one of SEQ ID NOs: 3032-3043). In particular embodiments, a KCNQ2 AON includes a sequence that is between 94% to 96% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a KCNQ2 transcript e.g., SEQ ID NOs: 3032-3043).

[00312] In various embodiments, a KCNQ2 AON comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NO: 3398-3899, and SEQ ID NOs: 4402-4530. In various embodiments, a KCNQ2 AON comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NO: 3398-3899, and SEQ ID NOs: 4402-4530.

[00313] In some embodiments, the KCNQ2 AON comprises a spacer and has a segment having at most 7 linked nucleosides. In some embodiments, the KCNQ2 AON comprises a spacer and has a segment having at most 6, 5, 4, 3, or 2 linked nucleosides.

[00314] KCNQ2 AON binding specificity can be assessed via measurement of parameters such as dissociation constant, melting temperature or other criteria such as changes in protein or RNA expression levels or other assays that measure KCNQ2 activity or expression.

[00315] In some embodiments, a KCNQ2 AON can include a non-duplexed oligonucleotide. In some embodiments, a KCNQ2 AON can include a duplex of two oligonucleotides where the first oligonucleotide includes a nucleobase sequence that is completely or almost completely complementary to a KCNQ2 pre-mRNA sequence and the second oligonucleotide includes a nucleobase sequence that is complementary to the nucleobase sequence of the first oligonucleotide.

[00316] In some embodiments, a KCNQ2 AON can target KCNQ2 mRNAs of one or more isoforms. In some embodiments, the KCNQ2 AON includes a nucleobase sequence that is complementary to a nucleobase sequence of a KCNQ2 gene or a KCNQ2 mRNA.

[00317] KCNQ2 AONs described herein include antisense oligonucleotides comprising the oligonucleotide sequences listed in Table 7A and 7B below:

Table 7A. Example KCNQ2 AON Sequences complementary to a sequence in the Intron 4 region of a KCNQ2 transcript.

SEQ ID NO:	AON Sequence* (5' → 3')	SEQ ID NO:	Target Sequence (5' → 3')
1676	CGCCAGCCTTGGGGCCGTGACTCAC	1852	GTGAGTCACGGCCCCAAGGCTGGCG
1677	CCGCCAGCCTTGGGGCCGTGACTCA	1853	TGAGTCACGGCCCCAAGGCTGGCGG
1678	ACCGCCAGCCTTGGGGCCGTGACTC	1854	GAGTCACGGCCCCAAGGCTGGCGGT
1679	CACCGCCAGCCTTGGGGCCGTGACT	1855	AGTCACGGCCCCAAGGCTGGCGGTG
1680	CCACCGCCAGCCTTGGGGCCGTGAC	1856	GTCACGGCCCCAAGGCTGGCGGTGG
1681	CCCACCGCCAGCCTTGGGGCCGTGA	1857	TCACGGCCCCAAGGCTGGCGGTGGG
1682	GCCCACCGCCAGCCTTGGGGCCGTG	1858	CACGGCCCCAAGGCTGGCGGTGGGC
1683	CGCCCACCGCCAGCCTTGGGGCCGT	1859	ACGGCCCCAAGGCTGGCGGTGGGCG
1684	GCGCCCACCGCCAGCCTTGGGGCCG	1860	CGGCCCCAAGGCTGGCGGTGGGCGC
1685	GGCGCCCACCGCCAGCCTTGGGGCC	1861	GGCCCCAAGGCTGGCGGTGGGCGCC

1686	GGGCGCCCACCGCCAGCCTTGGGGC	1862	GCCCCAAGGCTGGCGGTGGGCGCCC
1687	GGGGCGCCCACCGCCAGCCTTGGGG	1863	CCCCAAGGCTGGCGGTGGGCGCCCC
1688	GGGGGCGCCCACCGCCAGCCTTGGG	1864	CCCAAGGCTGGCGGTGGGCGCCCCC
1689	TGGGGGCGCCCACCGCCAGCCTTGG	1865	CCAAGGCTGGCGGTGGGCGCCCCCA
1690	CTGGGGGCGCCCACCGCCAGCCTTG	1866	CAAGGCTGGCGGTGGGCGCCCCCAG
1691	GCTGGGGGCGCCCACCGCCAGCCTT	1867	AAGGCTGGCGGTGGGCGCCCCCAGC
1692	GGCTGGGGGCGCCCACCGCCAGCCT	1868	AGGCTGGCGGTGGGCGCCCCCAGCC
1693	TGGCTGGGGGCGCCCACCGCCAGCC	1869	GGCTGGCGGTGGGCGCCCCCAGCCA
1694	CTGGCTGGGGGCGCCCACCGCCAGC	1870	GCTGGCGGTGGGCGCCCCCAGCCAG
1695	GCTGGCTGGGGGCGCCCACCGCCAG	1871	CTGGCGGTGGGCGCCCCCAGCCAGC
1696	CGCTGGCTGGGGGCGCCCACCGCCA	1872	TGGCGGTGGGCGCCCCCAGCCAGCG
1697	TCGCTGGCTGGGGGCGCCCACCGCC	1873	GGCGGTGGGCGCCCCCAGCCAGCGA
1698	CTCGCTGGCTGGGGGCGCCCACCGC	1874	GCGGTGGGCGCCCCCAGCCAGCGAG
1699	TCTCGCTGGCTGGGGGCGCCCACCG	1875	CGGTGGGCGCCCCCAGCCAGCGAGA
1700	CTCTCGCTGGCTGGGGGCGCCCACC	1876	GGTGGGCGCCCCCAGCCAGCGAGAG
1701	ACTCTCGCTGGCTGGGGGCGCCCAC	1877	GTGGGCGCCCCCAGCCAGCGAGAGT
1702	GACTCTCGCTGGCTGGGGGCGCCCA	1878	TGGGCGCCCCCAGCCAGCGAGAGTC
1703	GGACTCTCGCTGGCTGGGGGCGCCC	1879	GGGCGCCCCCAGCCAGCGAGAGTCC
1704	AGGACTCTCGCTGGCTGGGGGCGCC	1880	GGCGCCCCCAGCCAGCGAGAGTCCT
1705	CAGGACTCTCGCTGGCTGGGGGCGC	1881	GCGCCCCCAGCCAGCGAGAGTCCTG
1706	CCAGGACTCTCGCTGGCTGGGGGCG	1882	CGCCCCCAGCCAGCGAGAGTCCTGG
1707	GCCAGGACTCTCGCTGGCTGGGGGC	1883	GCCCCCAGCCAGCGAGAGTCCTGGC
1708	GGCCAGGACTCTCGCTGGCTGGGGG	1884	CCCCCAGCCAGCGAGAGTCCTGGCC
1709	GGGCCAGGACTCTCGCTGGCTGGGG	1885	CCCCAGCCAGCGAGAGTCCTGGCCC
1710	TGGGCCAGGACTCTCGCTGGCTGGG	1886	CCCAGCCAGCGAGAGTCCTGGCCCA
1711	CTGGGCCAGGACTCTCGCTGGCTGG	1887	CCAGCCAGCGAGAGTCCTGGCCCAG
1712	TCTGGGCCAGGACTCTCGCTGGCTG	1888	CAGCCAGCGAGAGTCCTGGCCCAGA
1713	GTCTGGGCCAGGACTCTCGCTGGCT	1889	AGCCAGCGAGAGTCCTGGCCCAGAC
1714	GGTCTGGGCCAGGACTCTCGCTGGC	1890	GCCAGCGAGAGTCCTGGCCCAGACC

1715	CGGTCTGGGCCAGGACTCTCGCTGG	1891	CCAGCGAGAGTCCTGGCCCAGACCG
1716	CCGGTCTGGGCCAGGACTCTCGCTG	1892	CAGCGAGAGTCCTGGCCCAGACCGG
1717	CCCGGTCTGGGCCAGGACTCTCGCT	1893	AGCGAGAGTCCTGGCCCAGACCGGG
1718	GCCCGGTCTGGGCCAGGACTCTCGC	1894	GCGAGAGTCCTGGCCCAGACCGGGC
1719	GGCCCGGTCTGGGCCAGGACTCTCG	1895	CGAGAGTCCTGGCCCAGACCGGGCC
1720	GGGCCCGGTCTGGGCCAGGACTCTC	1896	GAGAGTCCTGGCCCAGACCGGGCCC
1721	GGGGCCCGGTCTGGGCCAGGACTCT	1897	AGAGTCCTGGCCCAGACCGGGCCCC
1722	TGGGGCCCGGTCTGGGCCAGGACTC	1898	GAGTCCTGGCCCAGACCGGGCCCCA
1723	GTGGGGCCCGGTCTGGGCCAGGACT	1899	AGTCCTGGCCCAGACCGGGCCCCAC
1724	GGTGGGGCCCGGTCTGGGCCAGGAC	1900	GTCCTGGCCCAGACCGGGCCCCACC
1725	GGGTGGGGCCCGGTCTGGGCCAGGA	1901	TCCTGGCCCAGACCGGGCCCCACCC
1726	GGGGTGGGGCCCGGTCTGGGCCAGG	1902	CCTGGCCCAGACCGGGCCCCACCCC
1727	AGGGGTGGGGCCCGGTCTGGGCCAG	1903	CTGGCCCAGACCGGGCCCCACCCCT
1728	CAGGGGTGGGGCCCGGTCTGGGCCA	1904	TGGCCCAGACCGGGCCCCACCCCTG
1729	GCAGGGGTGGGGCCCGGTCTGGGCC	1905	GGCCCAGACCGGGCCCCACCCCTGC
1730	GGCAGGGGTGGGGCCCGGTCTGGGC	1906	GCCCAGACCGGGCCCCACCCCTGCC
1731	AGGCAGGGGTGGGGCCCGGTCTGGG	1907	CCCAGACCGGGCCCCACCCCTGCCT
1732	CAGGCAGGGGTGGGGCCCGGTCTGG	1908	CCAGACCGGGCCCCACCCCTGCCTG
1733	CCAGGCAGGGGTGGGGCCCGGTCTG	1909	CAGACCGGGCCCCACCCCTGCCTGG
1734	CCCAGGCAGGGGTGGGGCCCGGTCT	1910	AGACCGGGCCCCACCCCTGCCTGGG
1735	CCCCAGGCAGGGGTGGGGCCCGGTC	1911	GACCGGGCCCCACCCCTGCCTGGGG
1736	ACCCCAGGCAGGGGTGGGGCCCGGT	1912	ACCGGGCCCCACCCCTGCCTGGGGT
1737	AACCCCAGGCAGGGGTGGGGCCCGG	1913	CCGGGCCCCACCCCTGCCTGGGGTT
1738	AAACCCCAGGCAGGGGTGGGGCCCG	1914	CGGGCCCCACCCCTGCCTGGGGTTT
1739	CAAACCCCAGGCAGGGGTGGGGCCC	1915	GGGCCCCACCCCTGCCTGGGGTTTG
1740	GCAAACCCCAGGCAGGGGTGGGGCC	1916	GGCCCCACCCCTGCCTGGGGTTTGC
1741	AGCAAACCCCAGGCAGGGGTGGGGC	1917	GCCCCACCCCTGCCTGGGGTTTGCT
1742	AAGCAAACCCCAGGCAGGGGTGGGG	1918	CCCCACCCCTGCCTGGGGTTTGCTT
1743	GAAGCAAACCCCAGGCAGGGGTGGG	1919	CCCACCCCTGCCTGGGGTTTGCTTC

1744	TGAAGCAAACCCCAGGCAGGGGTGG	1920	CCACCCCTGCCTGGGGTTTGCTTCA
1745	TTGAAGCAAACCCCAGGCAGGGGTG	1921	CACCCCTGCCTGGGGTTTGCTTCAA
1746	CTTGAAGCAAACCCCAGGCAGGGGT	1922	ACCCCTGCCTGGGGTTTGCTTCAAG
1747	TCTTGAAGCAAACCCCAGGCAGGGG	1923	CCCCTGCCTGGGGTTTGCTTCAAGA
1748	CTCTTGAAGCAAACCCCAGGCAGGG	1924	CCCTGCCTGGGGTTTGCTTCAAGAG
1749	GCTCTTGAAGCAAACCCCAGGCAGG	1925	CCTGCCTGGGGTTTGCTTCAAGAGC
1750	GGCTCTTGAAGCAAACCCCAGGCAG	1926	CTGCCTGGGGTTTGCTTCAAGAGCC
1751	GGGCTCTTGAAGCAAACCCCAGGCA	1927	TGCCTGGGGTTTGCTTCAAGAGCCC
1752	AGGGCTCTTGAAGCAAACCCCAGGC	1928	GCCTGGGGTTTGCTTCAAGAGCCCT
1753	CAGGGCTCTTGAAGCAAACCCCAGG	1929	CCTGGGGTTTGCTTCAAGAGCCCTG
1754	CCAGGGCTCTTGAAGCAAACCCCAG	1930	CTGGGGTTTGCTTCAAGAGCCCTGG
1755	CCCAGGGCTCTTGAAGCAAACCCCA	1931	TGGGGTTTGCTTCAAGAGCCCTGGG
1756	ACCCAGGGCTCTTGAAGCAAACCCC	1932	GGGGTTTGCTTCAAGAGCCCTGGGT
1757	CACCCAGGGCTCTTGAAGCAAACCC	1933	GGGTTTGCTTCAAGAGCCCTGGGTG
1758	CCACCCAGGGCTCTTGAAGCAAACC	1934	GGTTTGCTTCAAGAGCCCTGGGTGG
1759	TCCACCCAGGGCTCTTGAAGCAAAC	1935	GTTTGCTTCAAGAGCCCTGGGTGGA
1760	CTCCACCCAGGGCTCTTGAAGCAAA	1936	TTTGCTTCAAGAGCCCTGGGTGGAG
1761	CCTCCACCCAGGGCTCTTGAAGCAA	1937	TTGCTTCAAGAGCCCTGGGTGGAGG
1762	CCCTCCACCCAGGGCTCTTGAAGCA	1938	TGCTTCAAGAGCCCTGGGTGGAGGG
1763	TCCCTCCACCCAGGGCTCTTGAAGC	1939	GCTTCAAGAGCCCTGGGTGGAGGGA
1764	ATCCCTCCACCCAGGGCTCTTGAAG	1940	CTTCAAGAGCCCTGGGTGGAGGGAT
1765	CATCCCTCCACCCAGGGCTCTTGAA	1941	TTCAAGAGCCCTGGGTGGAGGGATG
1766	CCATCCCTCCACCCAGGGCTCTTGA	1942	TCAAGAGCCCTGGGTGGAGGGATGG
1767	TCCATCCCTCCACCCAGGGCTCTTG	1943	CAAGAGCCCTGGGTGGAGGGATGGA
1768	CTCCATCCCTCCACCCAGGGCTCTT	1944	AAGAGCCCTGGGTGGAGGGATGGAG
1769	ACTCCATCCCTCCACCCAGGGCTCT	1945	AGAGCCCTGGGTGGAGGGATGGAGT
1770	GACTCCATCCCTCCACCCAGGGCTC	1946	GAGCCCTGGGTGGAGGGATGGAGTC
1771	TGACTCCATCCCTCCACCCAGGGCT	1947	AGCCCTGGGTGGAGGGATGGAGTCA
1772	CTGACTCCATCCCTCCACCCAGGGC	1948	GCCCTGGGTGGAGGGATGGAGTCAG

1773	ACTGACTCCATCCCTCCACCCAGGG	1949	CCCTGGGTGGAGGGATGGAGTCAGT
1774	CACTGACTCCATCCCTCCACCCAGG	1950	CCTGGGTGGAGGGATGGAGTCAGTG
1775	CCACTGACTCCATCCCTCCACCCAG	1951	CTGGGTGGAGGGATGGAGTCAGTGG
1776	ACCACTGACTCCATCCCTCCACCCA	1952	TGGGTGGAGGGATGGAGTCAGTGGT
1777	CACCACTGACTCCATCCCTCCACCC	1953	GGGTGGAGGGATGGAGTCAGTGGTG
1778	CCACCACTGACTCCATCCCTCCACC	1954	GGTGGAGGGATGGAGTCAGTGGTGG
1779	GCCACCACTGACTCCATCCCTCCAC	1955	GTGGAGGGATGGAGTCAGTGGTGGC
1780	AGCCACCACTGACTCCATCCCTCCA	1956	TGGAGGGATGGAGTCAGTGGTGGCT
1781	GAGCCACCACTGACTCCATCCCTCC	1957	GGAGGGATGGAGTCAGTGGTGGCTC
1782	AGAGCCACCACTGACTCCATCCCTC	1958	GAGGGATGGAGTCAGTGGTGGCTCT
1783	CAGAGCCACCACTGACTCCATCCCT	1959	AGGGATGGAGTCAGTGGTGGCTCTG
1784	CCAGAGCCACCACTGACTCCATCCC	1960	GGGATGGAGTCAGTGGTGGCTCTGG
1785	GCCAGAGCCACCACTGACTCCATCC	1961	GGATGGAGTCAGTGGTGGCTCTGGC
1786	AGCCAGAGCCACCACTGACTCCATC	1962	GATGGAGTCAGTGGTGGCTCTGGCT
1787	CAGCCAGAGCCACCACTGACTCCAT	1963	ATGGAGTCAGTGGTGGCTCTGGCTG
1788	CCAGCCAGAGCCACCACTGACTCCA	1964	TGGAGTCAGTGGTGGCTCTGGCTGG
1789	TCCAGCCAGAGCCACCACTGACTCC	1965	GGAGTCAGTGGTGGCTCTGGCTGGA
1790	CTCCAGCCAGAGCCACCACTGACTC	1966	GAGTCAGTGGTGGCTCTGGCTGGAG
1791	GCTCCAGCCAGAGCCACCACTGACT	1967	AGTCAGTGGTGGCTCTGGCTGGAGC
1792	GGCTCCAGCCAGAGCCACCACTGAC	1968	GTCAGTGGTGGCTCTGGCTGGAGCC
1793	GGGCTCCAGCCAGAGCCACCACTGA	1969	TCAGTGGTGGCTCTGGCTGGAGCCC
1794	TGGGCTCCAGCCAGAGCCACCACTG	1970	CAGTGGTGGCTCTGGCTGGAGCCCA
1795	ATGGGCTCCAGCCAGAGCCACCACT	1971	AGTGGTGGCTCTGGCTGGAGCCCAT
1796	GATGGGCTCCAGCCAGAGCCACCAC	1972	GTGGTGGCTCTGGCTGGAGCCCATC
1797	TGATGGGCTCCAGCCAGAGCCACCA	1973	TGGTGGCTCTGGCTGGAGCCCATCA
1798	CTGATGGGCTCCAGCCAGAGCCACC	1974	GGTGGCTCTGGCTGGAGCCCATCAG
1799	CCTGATGGGCTCCAGCCAGAGCCAC	1975	GTGGCTCTGGCTGGAGCCCATCAGG
1800	ACCTGATGGGCTCCAGCCAGAGCCA	1976	TGGCTCTGGCTGGAGCCCATCAGGT
1801	CACCTGATGGGCTCCAGCCAGAGCC	1977	GGCTCTGGCTGGAGCCCATCAGGTG

1802	ACACCTGATGGGCTCCAGCCAGAGC	1978	GCTCTGGCTGGAGCCCATCAGGTGT
1803	CACACCTGATGGGCTCCAGCCAGAG	1979	CTCTGGCTGGAGCCCATCAGGTGTG
1804	TCACACCTGATGGGCTCCAGCCAGA	1980	TCTGGCTGGAGCCCATCAGGTGTGA
1805	TTCACACCTGATGGGCTCCAGCCAG	1981	CTGGCTGGAGCCCATCAGGTGTGAA
1806	GTTCACACCTGATGGGCTCCAGCCA	1982	TGGCTGGAGCCCATCAGGTGTGAAC
1807	CGTTCACACCTGATGGGCTCCAGCC	1983	GGCTGGAGCCCATCAGGTGTGAACG
1808	TCGTTCACACCTGATGGGCTCCAGC	1984	GCTGGAGCCCATCAGGTGTGAACGA
1809	CTCGTTCACACCTGATGGGCTCCAG	1985	CTGGAGCCCATCAGGTGTGAACGAG
1810	GCTCGTTCACACCTGATGGGCTCCA	1986	TGGAGCCCATCAGGTGTGAACGAGC
1811	GGCTCGTTCACACCTGATGGGCTCC	1987	GGAGCCCATCAGGTGTGAACGAGCC
1812	AGGCTCGTTCACACCTGATGGGCTC	1988	GAGCCCATCAGGTGTGAACGAGCCT
1813	GAGGCTCGTTCACACCTGATGGGCT	1989	AGCCCATCAGGTGTGAACGAGCCTC
1814	GGAGGCTCGTTCACACCTGATGGGC	1990	GCCCATCAGGTGTGAACGAGCCTCC
1815	GGGAGGCTCGTTCACACCTGATGGG	1991	CCCATCAGGTGTGAACGAGCCTCCC
1816	AGGGAGGCTCGTTCACACCTGATGG	1992	CCATCAGGTGTGAACGAGCCTCCCT
1817	GAGGGAGGCTCGTTCACACCTGATG	1993	CATCAGGTGTGAACGAGCCTCCCTC
1818	GGAGGGAGGCTCGTTCACACCTGAT	1994	ATCAGGTGTGAACGAGCCTCCCTCC
1819	GGGAGGGAGGCTCGTTCACACCTGA	1995	TCAGGTGTGAACGAGCCTCCCTCCC
1820	GGGGAGGGAGGCTCGTTCACACCTG	1996	CAGGTGTGAACGAGCCTCCCTCCCC
1821	AGGGGAGGGAGGCTCGTTCACACCT	1997	AGGTGTGAACGAGCCTCCCTCCCCT
1822	AAGGGGAGGGAGGCTCGTTCACACC	1998	GGTGTGAACGAGCCTCCCTCCCCTT
1823	AAAGGGGAGGGAGGCTCGTTCACAC	1999	GTGTGAACGAGCCTCCCTCCCCTTT
1824	GAAAGGGGAGGGAGGCTCGTTCACA	2000	TGTGAACGAGCCTCCCTCCCCTTTC
1825	AGAAAGGGGAGGGAGGCTCGTTCAC	2001	GTGAACGAGCCTCCCTCCCCTTTCT
1826	AAGAAAGGGGAGGGAGGCTCGTTCA	2002	TGAACGAGCCTCCCTCCCCTTTCTT
1827	GAAGAAAGGGGAGGGAGGCTCGTTC	2003	GAACGAGCCTCCCTCCCCTTTCTTC
1828	AGAAGAAAGGGGAGGGAGGCTCGTT	2004	AACGAGCCTCCCTCCCCTTTCTTCT
1829	GAGAAGAAAGGGGAGGGAGGCTCGT	2005	ACGAGCCTCCCTCCCCTTTCTTCTC
1830	CGAGAAGAAAGGGGAGGGAGGCTCG	2006	CGAGCCTCCCTCCCCTTTCTTCTCG

1831	CCGAGAAGAAAGGGGAGGGAGGCTC	2007	GAGCCTCCCTCCCCTTTCTTCTCGG
1832	ACCGAGAAGAAAGGGGAGGGAGGCT	2008	AGCCTCCCTCCCCTTTCTTCTCGGT
1833	CACCGAGAAGAAAGGGGAGGGAGGC	2009	GCCTCCCTCCCCTTTCTTCTCGGTG
1834	GCACCGAGAAGAAAGGGGAGGGAGG	2010	CCTCCCTCCCCTTTCTTCTCGGTGC
1835	AGCACCGAGAAGAAAGGGGAGGGAG	2011	CTCCCTCCCCTTTCTTCTCGGTGCT
1836	AAGCACCGAGAAGAAAGGGGAGGGA	2012	TCCCTCCCCTTTCTTCTCGGTGCTT
1837	GAAGCACCGAGAAGAAAGGGGAGGG	2013	CCCTCCCCTTTCTTCTCGGTGCTTC
1838	AGAAGCACCGAGAAGAAAGGGGAGG	2014	CCTCCCCTTTCTTCTCGGTGCTTCT
1839	AAGAAGCACCGAGAAGAAAGGGGAG	2015	CTCCCCTTTCTTCTCGGTGCTTCTT
1840	GAAGAAGCACCGAGAAGAAAGGGGA	2016	TCCCCTTTCTTCTCGGTGCTTCTTC
1841	AGAAGAAGCACCGAGAAGAAAGGGG	2017	CCCCTTTCTTCTCGGTGCTTCTTCT
1842	GAGAAGAAGCACCGAGAAGAAAGGG	2018	CCCTTTCTTCTCGGTGCTTCTTCTC
1843	CGAGAAGAAGCACCGAGAAGAAAGG	2019	CCTTTCTTCTCGGTGCTTCTTCTCG
1844	ACGAGAAGAAGCACCGAGAAGAAAG	2020	CTTTCTTCTCGGTGCTTCTTCTCGT
1845	CACGAGAAGAAGCACCGAGAAGAAA	2021	TTTCTTCTCGGTGCTTCTTCTCGTG
1846	TCACGAGAAGAAGCACCGAGAAGAA	2022	TTCTTCTCGGTGCTTCTTCTCGTGA
1847	GTCACGAGAAGAAGCACCGAGAAGA	2023	TCTTCTCGGTGCTTCTTCTCGTGAC
1848	AGTCACGAGAAGAAGCACCGAGAAG	2024	CTTCTCGGTGCTTCTTCTCGTGACT
1849	AAGTCACGAGAAGAAGCACCGAGAA	2025	TTCTCGGTGCTTCTTCTCGTGACTT
1850	CAAGTCACGAGAAGAAGCACCGAGA	2026	TCTCGGTGCTTCTTCTCGTGACTTG
1851	CCAAGTCACGAGAAGAAGCACCGAG	2027	CTCGGTGCTTCTTCTCGTGACTTGG

* At least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide sequence is independently selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a

thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

Table 7B. Example KCNQ2 AON Sequences complementary to a sequence of a KCNQ2 transcript.

SEQ ID NO:	AON Sequence* (5' → 3')	SEQ ID NO:	Target Sequence (5' → 3')
2028	TCACCACCACCACCACCATCATCAC	2530	GTGATGATGGTGGTGGTGGTGGTGA
2029	ATCACCACCACCACCACCATCATCA	2531	TGATGATGGTGGTGGTGGTGGTGAT
2030	CATCACCACCACCACCACCATCATC	2532	GATGATGGTGGTGGTGGTGGTGATG
2031	CCATCACCACCACCACCACCATCAT	2533	ATGATGGTGGTGGTGGTGGTGATGG
2032	ACCATCACCACCACCACCACCATCA	2534	TGATGGTGGTGGTGGTGGTGATGGT
2033	CACCATCACCACCACCACCACCATC	2535	GATGGTGGTGGTGGTGGTGATGGTG
2034	TCACCATCACCACCACCACCACCAT	2536	ATGGTGGTGGTGGTGGTGATGGTGA
2035	ATCACCATCACCACCACCACCACCA	2537	TGGTGGTGGTGGTGGTGATGGTGAT
2036	CATCACCATCACCACCACCACCACC	2538	GGTGGTGGTGGTGGTGATGGTGATG
2037	CCATCACCATCACCACCACCACCAC	2539	GTGGTGGTGGTGGTGATGGTGATGG
2038	ACCATCACCATCACCACCACCACCA	2540	TGGTGGTGGTGGTGATGGTGATGGT
2039	CACCATCACCATCACCACCACCACC	2541	GGTGGTGGTGGTGATGGTGATGGTG
2040	CCACCATCACCATCACCACCACCAC	2542	GTGGTGGTGGTGATGGTGATGGTGG
2041	ACCACCATCACCATCACCACCACCA	2543	TGGTGGTGGTGATGGTGATGGTGGT
2042	CACCACCATCACCATCACCACCACC	2544	GGTGGTGGTGATGGTGATGGTGGTG
2043	TCACCACCATCACCATCACCACCAC	2545	GTGGTGGTGATGGTGATGGTGGTGA
2044	ATCACCACCATCACCATCACCACCA	2546	TGGTGGTGATGGTGATGGTGGTGAT
2045	CATCACCACCATCACCATCACCACC	2547	GGTGGTGATGGTGATGGTGGTGATG
2046	CCATCACCACCATCACCATCACCAC	2548	GTGGTGATGGTGATGGTGGTGATGG
2047	ACCATCACCACCATCACCATCACCA	2549	TGGTGATGGTGATGGTGGTGATGGT
2048	CACCATCACCACCATCACCATCACC	2550	GGTGATGGTGATGGTGGTGATGGTG
2049	TCACCATCACCACCATCACCATCAC	2551	GTGATGGTGATGGTGGTGATGGTGA
2050	ATCACCATCACCACCATCACCATCA	2552	TGATGGTGATGGTGGTGATGGTGAT
2051	CATCACCATCACCACCATCACCATC	2553	GATGGTGATGGTGGTGATGGTGATG
2052	CCATCACCATCACCACCATCACCAT	2554	ATGGTGATGGTGGTGATGGTGATGG
2053	ACCATCACCATCACCACCATCACCA	2555	TGGTGATGGTGGTGATGGTGATGGT
2054	CACCATCACCATCACCACCATCACC	2556	GGTGATGGTGGTGATGGTGATGGTG
2055	CCACCATCACCATCACCACCATCAC	2557	GTGATGGTGGTGATGGTGATGGTGG
2056	ACCACCATCACCATCACCACCATCA	2558	TGATGGTGGTGATGGTGATGGTGGT
2057	CACCACCATCACCATCACCACCATC	2559	GATGGTGGTGATGGTGATGGTGGTG
2058	CCACCACCATCACCATCACCACCAT	2560	ATGGTGGTGATGGTGATGGTGGTGG
2059	ACCACCACCATCACCATCACCACCA	2561	TGGTGGTGATGGTGATGGTGGTGGT
2060	CACCACCACCATCACCATCACCACC	2562	GGTGGTGATGGTGATGGTGGTGGTG
2061	CCACCACCACCATCACCATCACCAC	2563	GTGGTGATGGTGATGGTGGTGGTGG
2062	ACCACCACCACCATCACCATCACCA	2564	TGGTGATGGTGATGGTGGTGGTGGT
2063	CACCACCACCACCATCACCATCACC	2565	GGTGATGGTGATGGTGGTGGTGGTG

2064	CCACCACCACCACCATCACCATCAC	2566	GTGATGGTGATGGTGGTGGTGGTGG
2065	ACCACCACCACCACCATCACCATCA	2567	TGATGGTGATGGTGGTGGTGGTGGT
2066	CACCACCACCACCACCATCACCATC	2568	GATGGTGATGGTGGTGGTGGTGGTG
2067	CCACCACCACCACCACCATCACCAT	2569	ATGGTGATGGTGGTGGTGGTGGTGG
2068	ACCACCACCACCACCACCATCACCA	2570	TGGTGATGGTGGTGGTGGTGGTGGT
2069	CACCACCACCACCACCACCATCACC	2571	GGTGATGGTGGTGGTGGTGGTGGTG
2070	CCACCACCACCACCACCACCATCAC	2572	GTGATGGTGGTGGTGGTGGTGGTGG
2071	ACCACCACCACCACCACCACCATCA	2573	TGATGGTGGTGGTGGTGGTGGTGGT
2072	CACCACCACCACCACCACCACCATC	2574	GATGGTGGTGGTGGTGGTGGTGGTG
2073	TCACCACCACCACCACCACCACCAT	2575	ATGGTGGTGGTGGTGGTGGTGGTGA
2074	ATCACCACCACCACCACCACCACCA	2576	TGGTGGTGGTGGTGGTGGTGGTGAT
2075	CATCACCACCACCACCACCACCACC	2577	GGTGGTGGTGGTGGTGGTGGTGATG
2076	CCATCACCACCACCACCACCACCAC	2578	GTGGTGGTGGTGGTGGTGGTGATGG
2077	ACCATCACCACCACCACCACCACCA	2579	TGGTGGTGGTGGTGGTGGTGATGGT
2078	CACCATCACCACCACCACCACCACC	2580	GGTGGTGGTGGTGGTGGTGATGGTG
2079	CCACCATCACCACCACCACCACCAC	2581	GTGGTGGTGGTGGTGGTGATGGTGG
2080	ACCACCATCACCACCACCACCACCA	2582	TGGTGGTGGTGGTGGTGATGGTGGT
2081	CACCACCATCACCACCACCACCACC	2583	GGTGGTGGTGGTGGTGATGGTGGTG
2082	CCACCACCATCACCACCACCACCAC	2584	GTGGTGGTGGTGGTGATGGTGGTGG
2083	ACCACCACCATCACCACCACCACCA	2585	TGGTGGTGGTGGTGATGGTGGTGGT
2084	CACCACCACCATCACCACCACCACC	2586	GGTGGTGGTGGTGATGGTGGTGGTG
2085	TCACCACCACCATCACCACCACCAC	2587	GTGGTGGTGGTGATGGTGGTGGTGA
2086	ATCACCACCACCATCACCACCACCA	2588	TGGTGGTGGTGATGGTGGTGGTGAT
2087	CATCACCACCACCATCACCACCACC	2589	GGTGGTGGTGATGGTGGTGGTGATG
2088	CCATCACCACCACCATCACCACCAC	2590	GTGGTGGTGATGGTGGTGGTGATGG
2089	ACCATCACCACCACCATCACCACCA	2591	TGGTGGTGATGGTGGTGGTGATGGT
2090	AACCATCACCACCACCATCACCACC	2592	GGTGGTGATGGTGGTGGTGATGGTT
2091	AAACCATCACCACCACCATCACCAC	2593	GTGGTGATGGTGGTGGTGATGGTTT
2092	AAAACCATCACCACCACCATCACCA	2594	TGGTGATGGTGGTGGTGATGGTTTT
2093	CAAAACCATCACCACCACCATCACC	2595	GGTGATGGTGGTGGTGATGGTTTTG
2094	CCAAAACCATCACCACCACCATCAC	2596	GTGATGGTGGTGGTGATGGTTTTGG
2095	ACCAAAACCATCACCACCACCATCA	2597	TGATGGTGGTGGTGATGGTTTTGGT
2096	CACCAAAACCATCACCACCACCATC	2598	GATGGTGGTGGTGATGGTTTTGGTG
2097	CCACCAAAACCATCACCACCACCAT	2599	ATGGTGGTGGTGATGGTTTTGGTGG
2098	ACCACCAAAACCATCACCACCACCA	2600	TGGTGGTGGTGATGGTTTTGGTGGT
2099	CACCACCAAAACCATCACCACCACC	2601	GGTGGTGGTGATGGTTTTGGTGGTG
2100	CCACCACCAAAACCATCACCACCAC	2602	GTGGTGGTGATGGTTTTGGTGGTGG
2101	ACCACCACCAAAACCATCACCACCA	2603	TGGTGGTGATGGTTTTGGTGGTGGT
2102	CACCACCACCAAAACCATCACCACC	2604	GGTGGTGATGGTTTTGGTGGTGGTG
2103	TCACCACCACCAAAACCATCACCAC	2605	GTGGTGATGGTTTTGGTGGTGGTGA
2104	ATCACCACCACCAAAACCATCACCA	2606	TGGTGATGGTTTTGGTGGTGGTGAT
2105	CATCACCACCACCAAAACCATCACC	2607	GGTGATGGTTTTGGTGGTGGTGATG
2106	CCATCACCACCACCAAAACCATCAC	2608	GTGATGGTTTTGGTGGTGGTGATGG
2107	ACCATCACCACCACCAAAACCATCA	2609	TGATGGTTTTGGTGGTGGTGATGGT
2108	CACCATCACCACCACCAAAACCATC	2610	GATGGTTTTGGTGGTGGTGATGGTG
2109	CCACCATCACCACCACCAAAACCAT	2611	ATGGTTTTGGTGGTGGTGATGGTGG
2110	ACCACCATCACCACCACCAAAACCA	2612	TGGTTTTGGTGGTGGTGATGGTGGT
2111	GACCACCATCACCACCACCAAAACC	2613	GGTTTTGGTGGTGGTGATGGTGGTC

2112	TGACCACCATCACCACCACCAAAAC	2614	GTTTTGGTGGTGGTGATGGTGGTCA
2113	ATGACCACCATCACCACCACCAAAA	2615	TTTTGGTGGTGGTGATGGTGGTCAT
2114	CATGACCACCATCACCACCACCAAA	2616	TTTGGTGGTGGTGATGGTGGTCATG
2115	CCATGACCACCATCACCACCACCAA	2617	TTGGTGGTGGTGATGGTGGTCATGG
2116	ACCATGACCACCATCACCACCACCA	2618	TGGTGGTGGTGATGGTGGTCATGGT
2117	CACCATGACCACCATCACCACCACC	2619	GGTGGTGGTGATGGTGGTCATGGTG
2118	ACACCATGACCACCATCACCACCAC	2620	GTGGTGGTGATGGTGGTCATGGTGT
2119	AACACCATGACCACCATCACCACCA	2621	TGGTGGTGATGGTGGTCATGGTGTT
2120	CAACACCATGACCACCATCACCACC	2622	GGTGGTGATGGTGGTCATGGTGTTG
2121	TCAACACCATGACCACCATCACCAC	2623	GTGGTGATGGTGGTCATGGTGTTGA
2122	ATCAACACCATGACCACCATCACCA	2624	TGGTGATGGTGGTCATGGTGTTGAT
2123	CATCAACACCATGACCACCATCACC	2625	GGTGATGGTGGTCATGGTGTTGATG
2124	ACATCAACACCATGACCACCATCAC	2626	GTGATGGTGGTCATGGTGTTGATGT
2125	CACATCAACACCATGACCACCATCA	2627	TGATGGTGGTCATGGTGTTGATGTG
2126	TCACATCAACACCATGACCACCATC	2628	GATGGTGGTCATGGTGTTGATGTGA
2127	ATCACATCAACACCATGACCACCAT	2629	ATGGTGGTCATGGTGTTGATGTGAT
2128	CATCACATCAACACCATGACCACCA	2630	TGGTGGTCATGGTGTTGATGTGATG
2129	CCATCACATCAACACCATGACCACC	2631	GGTGGTCATGGTGTTGATGTGATGG
2130	ACCATCACATCAACACCATGACCAC	2632	GTGGTCATGGTGTTGATGTGATGGT
2131	CACCATCACATCAACACCATGACCA	2633	TGGTCATGGTGTTGATGTGATGGTG
2132	CCACCATCACATCAACACCATGACC	2634	GGTCATGGTGTTGATGTGATGGTGG
2133	ACCACCATCACATCAACACCATGAC	2635	GTCATGGTGTTGATGTGATGGTGGT
2134	CACCACCATCACATCAACACCATGA	2636	TCATGGTGTTGATGTGATGGTGGTG
2135	CCACCACCATCACATCAACACCATG	2637	CATGGTGTTGATGTGATGGTGGTGG
2136	ACCACCACCATCACATCAACACCAT	2638	ATGGTGTTGATGTGATGGTGGTGGT
2137	CACCACCACCATCACATCAACACCA	2639	TGGTGTTGATGTGATGGTGGTGGTG
2138	ACACCACCACCATCACATCAACACC	2640	GGTGTTGATGTGATGGTGGTGGTGT
2139	AACACCACCACCATCACATCAACAC	2641	GTGTTGATGTGATGGTGGTGGTGTT
2140	CAACACCACCACCATCACATCAACA	2642	TGTTGATGTGATGGTGGTGGTGTTG
2141	CCAACACCACCACCATCACATCAAC	2643	GTTGATGTGATGGTGGTGGTGTTGG
2142	ACCAACACCACCACCATCACATCAA	2644	TTGATGTGATGGTGGTGGTGTTGGT
2143	CACCAACACCACCACCATCACATCA	2645	TGATGTGATGGTGGTGGTGTTGGTG
2144	CCACCAACACCACCACCATCACATC	2646	GATGTGATGGTGGTGGTGTTGGTGG
2145	ACCACCAACACCACCACCATCACAT	2647	ATGTGATGGTGGTGGTGTTGGTGGT
2146	CACCACCAACACCACCACCATCACA	2648	TGTGATGGTGGTGGTGTTGGTGGTG
2147	CCACCACCAACACCACCACCATCAC	2649	GTGATGGTGGTGGTGTTGGTGGTGG
2148	ACCACCACCAACACCACCACCATCA	2650	TGATGGTGGTGGTGTTGGTGGTGGT
2149	CACCACCACCAACACCACCACCATC	2651	GATGGTGGTGGTGTTGGTGGTGGTG
2150	TCACCACCACCAACACCACCACCAT	2652	ATGGTGGTGGTGTTGGTGGTGGTGA
2151	ATCACCACCACCAACACCACCACCA	2653	TGGTGGTGGTGTTGGTGGTGGTGAT
2152	CATCACCACCACCAACACCACCACC	2654	GGTGGTGGTGTTGGTGGTGGTGATG
2153	CCATCACCACCACCAACACCACCAC	2655	GTGGTGGTGTTGGTGGTGGTGATGG
2154	ACCATCACCACCACCAACACCACCA	2656	TGGTGGTGTTGGTGGTGGTGATGGT
2155	CACCATCACCACCACCAACACCACC	2657	GGTGGTGTTGGTGGTGGTGATGGTG
2156	TCACCATCACCACCACCAACACCAC	2658	GTGGTGTTGGTGGTGGTGATGGTGA
2157	ATCACCATCACCACCACCAACACCA	2659	TGGTGTTGGTGGTGGTGATGGTGAT
2158	CATCACCATCACCACCACCAACACC	2660	GGTGTTGGTGGTGGTGATGGTGATG
2159	GCATCACCATCACCACCACCAACAC	2661	GTGTTGGTGGTGGTGATGGTGATGC

2160	AGCATCACCATCACCACCACCAACA	2662	TGTTGGTGGTGGTGATGGTGATGCT
2161	AAGCATCACCATCACCACCACCAAC	2663	GTTGGTGGTGGTGATGGTGATGCTT
2162	GAAGCATCACCATCACCACCACCAA	2664	TTGGTGGTGGTGATGGTGATGCTTC
2163	AGAAGCATCACCATCACCACCACCA	2665	TGGTGGTGGTGATGGTGATGCTTCT
2164	CAGAAGCATCACCATCACCACCACC	2666	GGTGGTGGTGATGGTGATGCTTCTG
2165	CCAGAAGCATCACCATCACCACCAC	2667	GTGGTGGTGATGGTGATGCTTCTGG
2166	ACCAGAAGCATCACCATCACCACCA	2668	TGGTGGTGATGGTGATGCTTCTGGT
2167	CACCAGAAGCATCACCATCACCACC	2669	GGTGGTGATGGTGATGCTTCTGGTG
2168	TCACCAGAAGCATCACCATCACCAC	2670	GTGGTGATGGTGATGCTTCTGGTGA
2169	ATCACCAGAAGCATCACCATCACCA	2671	TGGTGATGGTGATGCTTCTGGTGAT
2170	CATCACCAGAAGCATCACCATCACC	2672	GGTGATGGTGATGCTTCTGGTGATG
2171	CCATCACCAGAAGCATCACCATCAC	2673	GTGATGGTGATGCTTCTGGTGATGG
2172	ACCATCACCAGAAGCATCACCATCA	2674	TGATGGTGATGCTTCTGGTGATGGT
2173	CACCATCACCAGAAGCATCACCATC	2675	GATGGTGATGCTTCTGGTGATGGTG
2174	CCACCATCACCAGAAGCATCACCAT	2676	ATGGTGATGCTTCTGGTGATGGTGG
2175	ACCACCATCACCAGAAGCATCACCA	2677	TGGTGATGCTTCTGGTGATGGTGGT
2176	GACCACCATCACCAGAAGCATCACC	2678	GGTGATGCTTCTGGTGATGGTGGTC
2177	TGACCACCATCACCAGAAGCATCAC	2679	GTGATGCTTCTGGTGATGGTGGTCA
2178	ATGACCACCATCACCAGAAGCATCA	2680	TGATGCTTCTGGTGATGGTGGTCAT
2179	CATGACCACCATCACCAGAAGCATC	2681	GATGCTTCTGGTGATGGTGGTCATG
2180	TCATGACCACCATCACCAGAAGCAT	2682	ATGCTTCTGGTGATGGTGGTCATGA
2181	ATCATGACCACCATCACCAGAAGCA	2683	TGCTTCTGGTGATGGTGGTCATGAT
2182	CATCATGACCACCATCACCAGAAGC	2684	GCTTCTGGTGATGGTGGTCATGATG
2183	CCATCATGACCACCATCACCAGAAG	2685	CTTCTGGTGATGGTGGTCATGATGG
2184	ACCATCATGACCACCATCACCAGAA	2686	TTCTGGTGATGGTGGTCATGATGGT
2185	CACCATCATGACCACCATCACCAGA	2687	TCTGGTGATGGTGGTCATGATGGTG
2186	CCACCATCATGACCACCATCACCAG	2688	CTGGTGATGGTGGTCATGATGGTGG
2187	ACCACCATCATGACCACCATCACCA	2689	TGGTGATGGTGGTCATGATGGTGGT
2188	CACCACCATCATGACCACCATCACC	2690	GGTGATGGTGGTCATGATGGTGGTG
2189	GCACCACCATCATGACCACCATCAC	2691	GTGATGGTGGTCATGATGGTGGTGC
2190	GGCACCACCATCATGACCACCATCA	2692	TGATGGTGGTCATGATGGTGGTGCC
2191	CGGCACCACCATCATGACCACCATC	2693	GATGGTGGTCATGATGGTGGTGCCG
2192	ACGGCACCACCATCATGACCACCAT	2694	ATGGTGGTCATGATGGTGGTGCCGT
2193	GACGGCACCACCATCATGACCACCA	2695	TGGTGGTCATGATGGTGGTGCCGTC
2194	AGACGGCACCACCATCATGACCACC	2696	GGTGGTCATGATGGTGGTGCCGTCT
2195	CAGACGGCACCACCATCATGACCAC	2697	GTGGTCATGATGGTGGTGCCGTCTG
2196	GCAGACGGCACCACCATCATGACCA	2698	TGGTCATGATGGTGGTGCCGTCTGC
2197	GGCAGACGGCACCACCATCATGACC	2699	GGTCATGATGGTGGTGCCGTCTGCC
2198	AGGCAGACGGCACCACCATCATGAC	2700	GTCATGATGGTGGTGCCGTCTGCCT
2199	GAGGCAGACGGCACCACCATCATGA	2701	TCATGATGGTGGTGCCGTCTGCCTC
2200	AGAGGCAGACGGCACCACCATCATG	2702	CATGATGGTGGTGCCGTCTGCCTCT
2201	GAGAGGCAGACGGCACCACCATCAT	2703	ATGATGGTGGTGCCGTCTGCCTCTC
2202	TGAGAGGCAGACGGCACCACCATCA	2704	TGATGGTGGTGCCGTCTGCCTCTCA
2203	CTGAGAGGCAGACGGCACCACCATC	2705	GATGGTGGTGCCGTCTGCCTCTCAG
2204	CCTGAGAGGCAGACGGCACCACCAT	2706	ATGGTGGTGCCGTCTGCCTCTCAGG
2205	TCCTGAGAGGCAGACGGCACCACCA	2707	TGGTGGTGCCGTCTGCCTCTCAGGA
2206	CTCCTGAGAGGCAGACGGCACCACC	2708	GGTGGTGCCGTCTGCCTCTCAGGAG
2207	GCTCCTGAGAGGCAGACGGCACCAC	2709	GTGGTGCCGTCTGCCTCTCAGGAGC

2208	AGCTCCTGAGAGGCAGACGGCACCA	2710	TGGTGCCGTCTGCCTCTCAGGAGCT
2209	CAGCTCCTGAGAGGCAGACGGCACC	2711	GGTGCCGTCTGCCTCTCAGGAGCTG
2210	CCAGCTCCTGAGAGGCAGACGGCAC	2712	GTGCCGTCTGCCTCTCAGGAGCTGG
2211	ACCAGCTCCTGAGAGGCAGACGGCA	2713	TGCCGTCTGCCTCTCAGGAGCTGGT
2212	GACCAGCTCCTGAGAGGCAGACGGC	2714	GCCGTCTGCCTCTCAGGAGCTGGTC
2213	TGACCAGCTCCTGAGAGGCAGACGG	2715	CCGTCTGCCTCTCAGGAGCTGGTCA
2214	GTGACCAGCTCCTGAGAGGCAGACG	2716	CGTCTGCCTCTCAGGAGCTGGTCAC
2215	AGTGACCAGCTCCTGAGAGGCAGAC	2717	GTCTGCCTCTCAGGAGCTGGTCACT
2216	CAGTGACCAGCTCCTGAGAGGCAGA	2718	TCTGCCTCTCAGGAGCTGGTCACTG
2217	GCAGTGACCAGCTCCTGAGAGGCAG	2719	CTGCCTCTCAGGAGCTGGTCACTGC
2218	GGCAGTGACCAGCTCCTGAGAGGCA	2720	TGCCTCTCAGGAGCTGGTCACTGCC
2219	AGGCAGTGACCAGCTCCTGAGAGGC	2721	GCCTCTCAGGAGCTGGTCACTGCCT
2220	CAGGCAGTGACCAGCTCCTGAGAGG	2722	CCTCTCAGGAGCTGGTCACTGCCTG
2221	CCAGGCAGTGACCAGCTCCTGAGAG	2723	CTCTCAGGAGCTGGTCACTGCCTGG
2222	ACCAGGCAGTGACCAGCTCCTGAGA	2724	TCTCAGGAGCTGGTCACTGCCTGGT
2223	TACCAGGCAGTGACCAGCTCCTGAG	2725	CTCAGGAGCTGGTCACTGCCTGGTA
2224	GTACCAGGCAGTGACCAGCTCCTGA	2726	TCAGGAGCTGGTCACTGCCTGGTAC
2225	TGTACCAGGCAGTGACCAGCTCCTG	2727	CAGGAGCTGGTCACTGCCTGGTACA
2226	ATGTACCAGGCAGTGACCAGCTCCT	2728	AGGAGCTGGTCACTGCCTGGTACAT
2227	GATGTACCAGGCAGTGACCAGCTCC	2729	GGAGCTGGTCACTGCCTGGTACATC
2228	CGATGTACCAGGCAGTGACCAGCTC	2730	GAGCTGGTCACTGCCTGGTACATCG
2229	CCGATGTACCAGGCAGTGACCAGCT	2731	AGCTGGTCACTGCCTGGTACATCGG
2230	GCCGATGTACCAGGCAGTGACCAGC	2732	GCTGGTCACTGCCTGGTACATCGGC
2231	AGCCGATGTACCAGGCAGTGACCAG	2733	CTGGTCACTGCCTGGTACATCGGCT
2232	AAGCCGATGTACCAGGCAGTGACCA	2734	TGGTCACTGCCTGGTACATCGGCTT
2233	GAAGCCGATGTACCAGGCAGTGACC	2735	GGTCACTGCCTGGTACATCGGCTTC
2234	GGAAGCCGATGTACCAGGCAGTGAC	2736	GTCACTGCCTGGTACATCGGCTTCC
2235	AGGAAGCCGATGTACCAGGCAGTGA	2737	TCACTGCCTGGTACATCGGCTTCCT
2236	AAGGAAGCCGATGTACCAGGCAGTG	2738	CACTGCCTGGTACATCGGCTTCCTT
2237	AAAGGAAGCCGATGTACCAGGCAGT	2739	ACTGCCTGGTACATCGGCTTCCTTT
2238	CAAAGGAAGCCGATGTACCAGGCAG	2740	CTGCCTGGTACATCGGCTTCCTTTG
2239	ACAAAGGAAGCCGATGTACCAGGCA	2741	TGCCTGGTACATCGGCTTCCTTTGT
2240	GACAAAGGAAGCCGATGTACCAGGC	2742	GCCTGGTACATCGGCTTCCTTTGTC
2241	AGACAAAGGAAGCCGATGTACCAGG	2743	CCTGGTACATCGGCTTCCTTTGTCT
2242	GAGACAAAGGAAGCCGATGTACCAG	2744	CTGGTACATCGGCTTCCTTTGTCTC
2243	TGAGACAAAGGAAGCCGATGTACCA	2745	TGGTACATCGGCTTCCTTTGTCTCA
2244	ATGAGACAAAGGAAGCCGATGTACC	2746	GGTACATCGGCTTCCTTTGTCTCAT
2245	GATGAGACAAAGGAAGCCGATGTAC	2747	GTACATCGGCTTCCTTTGTCTCATC
2246	GGATGAGACAAAGGAAGCCGATGTA	2748	TACATCGGCTTCCTTTGTCTCATCC
2247	AGGATGAGACAAAGGAAGCCGATGT	2749	ACATCGGCTTCCTTTGTCTCATCCT
2248	CAGGATGAGACAAAGGAAGCCGATG	2750	CATCGGCTTCCTTTGTCTCATCCTG
2249	CCAGGATGAGACAAAGGAAGCCGAT	2751	ATCGGCTTCCTTTGTCTCATCCTGG
2250	GCCAGGATGAGACAAAGGAAGCCGA	2752	TCGGCTTCCTTTGTCTCATCCTGGC
2251	GGCCAGGATGAGACAAAGGAAGCCG	2753	CGGCTTCCTTTGTCTCATCCTGGCC
2252	AGGCCAGGATGAGACAAAGGAAGCC	2754	GGCTTCCTTTGTCTCATCCTGGCCT
2253	GAGGCCAGGATGAGACAAAGGAAGC	2755	GCTTCCTTTGTCTCATCCTGGCCTC
2254	CGAGGCCAGGATGAGACAAAGGAAG	2756	CTTCCTTTGTCTCATCCTGGCCTCG
2255	ACGAGGCCAGGATGAGACAAAGGAA	2757	TTCCTTTGTCTCATCCTGGCCTCGT

2256	AACGAGGCCAGGATGAGACAAAGGA	2758	TCCTTTGTCTCATCCTGGCCTCGTT
2257	GAACGAGGCCAGGATGAGACAAAGG	2759	CCTTTGTCTCATCCTGGCCTCGTTC
2258	GGAACGAGGCCAGGATGAGACAAAG	2760	CTTTGTCTCATCCTGGCCTCGTTCC
2259	AGGAACGAGGCCAGGATGAGACAAA	2761	TTTGTCTCATCCTGGCCTCGTTCCT
2260	CAGGAACGAGGCCAGGATGAGACAA	2762	TTGTCTCATCCTGGCCTCGTTCCTG
2261	CCAGGAACGAGGCCAGGATGAGACA	2763	TGTCTCATCCTGGCCTCGTTCCTGG
2262	ACCAGGAACGAGGCCAGGATGAGAC	2764	GTCTCATCCTGGCCTCGTTCCTGGT
2263	CACCAGGAACGAGGCCAGGATGAGA	2765	TCTCATCCTGGCCTCGTTCCTGGTG
2264	ACACCAGGAACGAGGCCAGGATGAG	2766	CTCATCCTGGCCTCGTTCCTGGTGT
2265	TACACCAGGAACGAGGCCAGGATGA	2767	TCATCCTGGCCTCGTTCCTGGTGTA
2266	GTACACCAGGAACGAGGCCAGGATG	2768	CATCCTGGCCTCGTTCCTGGTGTAC
2267	AGTACACCAGGAACGAGGCCAGGAT	2769	ATCCTGGCCTCGTTCCTGGTGTACT
2268	AAGTACACCAGGAACGAGGCCAGGA	2770	TCCTGGCCTCGTTCCTGGTGTACTT
2269	CAAGTACACCAGGAACGAGGCCAGG	2771	CCTGGCCTCGTTCCTGGTGTACTTG
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2271	GCCAAGTACACCAGGAACGAGGCCA	2773	TGGCCTCGTTCCTGGTGTACTTGGC
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2274	TCTGCCAAGTACACCAGGAACGAGG	2776	CCTCGTTCCTGGTGTACTTGGCAGA
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2276	TCTCTGCCAAGTACACCAGGAACGA	2778	TCGTTCCTGGTGTACTTGGCAGAGA
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2285	TCTCCCCCTTCTCTGCCAAGTACAC	2787	GTGTACTTGGCAGAGAAGGGGGAGA
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2288	CGTTCTCCCCCTTCTCTGCCAAGTA	2790	TACTTGGCAGAGAAGGGGGAGAACG
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2291	GGTCGTTCTCCCCCTTCTCTGCCAA	2793	TTGGCAGAGAAGGGGGAGAACGACC
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2295	AAGTGGTCGTTCTCCCCCTTCTCTG	2797	CAGAGAAGGGGGAGAACGACCACTT
2296	AAAGTGGTCGTTCTCCCCCTTCTCT	2798	AGAGAAGGGGGAGAACGACCACTTT
2297	CAAAGTGGTCGTTCTCCCCCTTCTC	2799	GAGAAGGGGGAGAACGACCACTTTG
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2299	GTCAAAGTGGTCGTTCTCCCCCTTC	2801	GAAGGGGGAGAACGACCACTTTGAC
2300	TGTCAAAGTGGTCGTTCTCCCCCTT	2802	AAGGGGGAGAACGACCACTTTGACA
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2302	GGTGTCAAAGTGGTCGTTCTCCCCC	2804	GGGGGAGAACGACCACTTTGACACC
2303	AGGTGTCAAAGTGGTCGTTCTCCCC	2805	GGGGAGAACGACCACTTTGACACCT

2304	TAGGTGTCAAAGTGGTCGTTCTCCC	2806	GGGAGAACGACCACTTTGACACCTA
2305	GTAGGTGTCAAAGTGGTCGTTCTCC	2807	GGAGAACGACCACTTTGACACCTAC
2306	CGTAGGTGTCAAAGTGGTCGTTCTC	2808	GAGAACGACCACTTTGACACCTACG
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2332	CACCAGGCCCCACCAGAGTGCATCC	2834	GGATGCACTCTGGTGGGGCCTGGTG
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2335	ACTCACCAGGCCCCACCAGAGTGCA	2837	TGCACTCTGGTGGGGCCTGGTGAGT
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2525	AGCCCTCCCCACCCACTCCCCCGCC	3027	GGCGGGGGAGTGGGTGGGGAGGGCT
2526	CAGCCCTCCCCACCCACTCCCCCGC	3028	GCGGGGGAGTGGGTGGGGAGGGCTG
2527	CCAGCCCTCCCCACCCACTCCCCCG	3029	CGGGGGAGTGGGTGGGGAGGGCTGG
2528	CCCAGCCCTCCCCACCCACTCCCCC	3030	GGGGGAGTGGGTGGGGAGGGCTGGG
2529	GCCCAGCCCTCCCCACCCACTCCCC	3031	GGGGAGTGGGTGGGGAGGGCTGGGC

* At least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide sequence is independently selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a

thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

KCNQ2 Transcript

[00318] In various embodiments, a KCNQ2 transcript comprises the sequence provided as SEQ ID NO: 3032.

AGGCGCCGAGGTGCGCGCGGAGCGAGGTGGCCGCAGCGTCTCCGCGCGCGGCCCAA
GCCCGGCAGGAGTGCGGAACCGCCGCCTCGGCCATGCGGCTCCCGGCCGGGGGGCC
TGGGCTGGGGCCCGCGCCGCCCCCCGCGCTCCGCCCCCGCTGAGCCTGAGCCCGACC
CGGGGCGCCTCCCGCCAGGCACCATGGTGCAGAAGTCGCGCAACGGCGGCGTATAC
CCCGGCCCGAGCGGGGAGAAGAAGCTGAAGGTGGGCTTCGTGGGGCTGGACCCCGG
CGCGCCCGACTCCACCCGGGACGGGGCGCTGCTGATCGCCGGCTCCGAGGCCCCCA
AGCGCGGCAGCATCCTCAGCAAACCTCGCGCGGGCGGCGCGGGCGCCGGGAAGCCC
CCCAAGCGCAACGCCTTCTACCGCAAGCTGCAGAATTTCCTCTACAACGTGCTGGAG
CGGCCGCGCGGCTGGGCGTTCATCTACCACGCCTACGTGTTCCTCCTGGTTTTCTCCT
GCCTCGTGCTGTCTGTGTTTTCCACCATCAAGGAGTATGAGAAGAGCTCGGAGGGGG
CCCTCTACATCCTGGAAATCGTGACTATCGTGGTGTTTGGCGTGGAGTACTTCGTGCG
GATCTGGGCCGCAGGCTGCTGCTGCCGGTACCGTGGCTGGAGGGGGCGGCTCAAGTT
TGCCCGGAAACCGTTCTGTGTGATTGACATCATGGTGCTCATCGCCTCCATTGCGGTG
CTGGCCGCCGGCTCCCAGGGCAACGTCTTTGCCACATCTGCGCTCCGGAGCCTGCGC
TTCCTGCAGATTCTGCGGATGATCCGCATGGACCGGCGGGGAGGCACCTGGAAGCTG
CTGGGCTCTGTGGTCTATGCCCACAGCAAGGAGCTGGTCACTGCCTGGTACATCGGC
TTCCTTTGTCTCATCCTGGCCTCGTTCCTGGTGTACTTGGCAGAGAAGGGGGAGAAC
GACCACTTTGACACCTACGCGGATGCACTCTGGTGGGGCCTGATCACGCTGACCACC
ATTGGCTACGGGGACAAGTACCCCCAGACCTGGAACGGCAGGCTCCTTGCGGCAAC
CTTCACCCTCATCGGTGTCTCCTTCTTCGCGCTGCCTGCAGGCATCTTGGGGTCTGGG
TTTGCCCTGAAGGTTCAGGAGCAGCACAGGCAGAAGCACTTTGAGAAGAGGCGGAA
CCCGGCAGCAGGCCTGATCCAGTCGGCCTGGAGATTCTACGCCACCAACCTCTCGCG
CACAGACCTGCACTCCACGTGGCAGTACTACGAGCGAACGGTCACCGTGCCCATGTA
CAGTTCGCAAACTCAAACCTACGGGGCCTCCAGACTTATCCCCCCGCTGAACCAGCT
GGAGCTGCTGAGGAACCTCAAGAGTAAATCTGGACTCGCTTTCAGGAAGGACCCCC
CGCCGGAGCCGTCTCCAAGCCAGAAGGTCAGTTTGAAAGATCGTGTCTTCTCCAGCC
CCCGAGGCGTGGCTGCCAAGGGGAAGGGGTCCCCGCAGGCCCAGACTGTGAGGCGG
TCACCCAGCGCCGACCAGAGCCTCGAGGACAGCCCCAGCAAGGTGCCCAAGAGCTG
GAGCTTCGGGGACCGCAGCCGGGCACGCCAGGCTTTCCGCATCAAGGGTGCCGCGT
CACGGCAGAACTCAGAAGAAGCAAGCCTCCCCGGAGAGGACATTGTGGATGACAAG
AGCTGCCCCTGCGAGTTTGTGACCGAGGACCTGACCCCGGGCCTCAAAGTCAGCATC
AGAGCCGTGTGTGTCATGCGGTTCCTGGTGTCCAAGCGGAAGTTCAAGGAGAGCCTG
CGGCCCTACGACGTGATGGACGTCATCGAGCAGTACTCAGCCGGCCACCTGGACAT
GCTGTCCCGAATTAAGAGCCTGCAGTCCAGGATAGATATGATTGTGGGTCCCCCGCC
CCCTTCAACTCCCCGGCACAAGAAGTACCCCACCAAAGGACCCACGGCCCCTCCGA
GAGAGTCACCCCAGTACTCACCTAGAGTGGACCAGATCGTGGGGCGGGGCCCAGCG
ATCACGGACAAGGACCGCACCAAGGGCCCGGCCGAGGCGGAGCTGCCCGAGGACCC
CAGCATGATGGGACGGCTCGGGAAGGTGGAGAAGCAGGTCTTGTCCATGGAGAAGA
AGCTGGACTTCCTGGTGAATATCTACATGCAGCGGATGGGCATCCCCCCGACAGAGA
CCGAGGCCTACTTTGGGGCCAAAGAGCCGGAGCCGGCGCCGCCGTACCACAGCCCG
GAAGACAGCCGGGAGCATGTCGACAGGCACGGCTGCATTGTCAAGATCGTGCGCTC

CAGCAGCTCCACGGGCCAGAAGAACTTCTCGGCGCCCCCGGCCGCGCCCCCTGTCCA
GTGTCCGCCCTCCACCTCCTGGCAGCCACAGAGCCACCCGCGCCAGGGCCACGGCAC
CTCCCCCGTGGGGGACCACGGCTCCCTGGTGCGCATCCCGCCGCCGCCTGCCCACGA
GCGGTCGCTGTCCGCCTACGGCGGGGGCAACCGCGCCAGCATGGAGTTCCTGCGGC
AGGAGGACACCCCGGGCTGCAGGCCCCCCGAGGGGAACCTGCGGGACAGCGACAC
GTCCATCTCCATCCCGTCCGTGGACCACGAGGAGCTGGAGCGTTCCTTCAGCGGCTT
CAGCATCTCCCAGTCCAAGGAGAACCTGGATGCTCTCAACAGCTGCTACGCGGCCGT
GGCGCCTTGTGCCAAAGTCAGGCCCTACATTGCGGAGGGAGAGTCAGACACCGACT
CCGACCTCTGTACCCCGTGCGGGCCCCCGCCACGCTCGGCCACCGGCGAGGGTCCCT
TTGGTGACGTGGGCTGGGCCGGGCCCAGGAAGTGAGGCGGCGCTGGGCCAGTGGAC
CCGCCCGCGGCCCTCCTCAGCACGGTGCCTCCGAGGTTTTGAGGCGGGAACCCTCTG
GGGCCCTTTTCTTACAGTAACTGAGTGTGGCGGGAAGGGTGGGCCCTGGAGGGGCCC
ATGTGGGCTGAAGGATGGGGGCTCCTGGCAGTGACCTTTTACAAAAGTTATTTTCCA
ACAGGGGCTGGAGGGCTGGGCAGGGCCCTGTGGCTCCAGGAGCAGCGTGCAGGAGC
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GGGGCGGGAGTGATGACGGGGTGTTGCCAGCGTGGCAACAGGCGGGGGGTTGTCTC
AGCCGAGCCCAGGGGAGGCACAAAGGGCAGGCCTGTTCCCTGAGGACCTGCGCAAA
GGGCGGGCCTGTTTGGTGAGGACCTGCGGCCTTGGGTCCCGGTGGGGTTTCCGGGCA
GCTACAGGCGGGTGTGGCCGGCCGCTGTGCGTGGCCTCTGCCTTCACACCTGACCTG
CCCGGCGGGCTTTCCTGTTCCCCACCTCAGGGGCGCCCAAATACAGAGCTATTGGTT
GGCGTCTTCTCCCTGTACCTTCTGGGATCTGAGGGCTCTTTCCATGGAAGCCAGCCCC
GAGGTGGAGACCTTCGCCTGCAGCCGAGGAGCGGGTGGGGCCTGGGAACCAAACTG
GAGCCAGAGTGGACGTCCAGCCCTCTGGTCTTGGCCTCCAGAGGGAGGGCCTGGCTC
ACGGTGGGGCCAGGGAGCCGGCTCCAAAGGGTCTTCAAAAAGGGGGTCCTTGGGGG
CTCCAGCTGCCTCGCCCTGGCCTTTCTGTGGGTGCGTGAGAGCCAGCAGCACCCCAG
CCTTGGAGACCGGGGGGGCAGGACCCCAAGTCCTCCCCTCTCTCCTGACTGCCCTGG
CCGGGTGCCGGCACTGCGAGACCCACCTGGTGAGCAGGCCTCACAGTTCTTAGCCAG
GGCCCCACCTCGCCTGTGTCCCACCAGTGCCCCGACAGACCTGGGGCAGGGCTGGGC
CATGATGCAGCGGGCCAGGATAGCCTCCACCGTCAGCACAGGGCCGCCCTCCCCGC
CTTTCCGGAGGAAACCACTCCCACCTCAGCCCAGCTGTGCGCCCTCCCTAGCTCTCCT
GCCCCCTGGAGCTGATGGCCCCTTCTCCACTGACCGATTCCTTAGCGGGGCCTCTTG
GGGTCTCGGGCCTCGGGTGCACCGTCCCATGCCCGTCCTGTTGTGGGCACCGTGGCC
CTTGGGGCAGGCGGCTCTAATGCGGGAGCGAGTCCCTAGCTCCAGACTTAAGAACC
AGACCCCGGGAGCATCTGGCATTTGGCGTGACGGCGTCGCAGGCGGGCCTGGGCTC
CCTGGAGAGTGGCCTCCCTGGGAGTGAGCAGGGCTGGGGTCGTGGGCGCAAATACT
CCTGCAGAGCAAGTGCAGGGGAGTCCTGGGCCCGTTTCTCCTCCACCTGCGTTTTCA
GTGCACTTGGCTTGGCTGGGAGGTCCTGAGGCCCTGAGGCCAGCAGGGGAACCAGT
CCTGAGGGAGAGGACTTTGAAAGCAGCATTTGAGGGTCGTACGCCCCTGGCTGGTG
GGGGTCCTGGCGCTCAGGGTGTTCGGGGAGCCATGTCTGGCGTCCATTGTGGGGAGC
TGCTGCCCTGGCCTCTCTGCCTACCCCCAGCCCGGCCAGGGCACTCCCAGGCCCTGT
CGCCATTGAGGTGCCTCCGCTGGGCTGTCTCCTCACCCCTCCCTGTGCTGGAGCCTGT
CCCAAAAAGGTGCCAACTGGGAGGCCTCGGAAGCCACTGTCCAGGCTCCCACTGCC
TGTCTGCTCTGTTCCCAAAGGCAGCGTGTGTGGCCTCGGGCCCTGCGGTGGCATGAA
GCATCCCTTCTGGTGTGGGCATCGCTACGTGTTTTGGGGGCAGCGTTTCACGGCGGT
GCCCTTGCTGTCTCCCTTGGGCTGGCTCGAGCCTGGGGTCCATGTCCCTTTGCCGTCC
CGTCATGGGGCAGGGAATCCATAGCGGGGCCCACAGGCAGGGGTATGAGTGCGTCC
CACCCAACGCAGCACCAGCCCCGGCCACCGCTCCCCGTGTCCCCAGTTCCGTCTCAG
CTACCTGGACTCCAGGACCCTGGAGAAGGGAGACCTGGCAGTGGAGGGAGGCTGTG
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CCCCGCCTGCTCTTTCCTCCCCCACCAGTATGGCCCCACCTGCTCTTTCCTCCCCCCC
CAAGGTGTGGCCCCACCTGTTCTTTCCTCCCCTGCCGAGGTGTGACCCCACCTGCTCT
TTCCTCCCTCCCAGTATGGCCCCACCTGCTCTTTCCTCCCCCGAGGTGAGGCCCCGCC
TGCTCTTTCCTCCCATGGGGCCGCTGAGGCATGAGCACCTGGGCACAGGTTGGGGCT
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AGGAGGGACTGAGGCCAGACTCATGTCCAGCAAGGAACGTGTGGTGTGTCCCCTGG
GAAGTCTCTGGGCCCTGGGAAGAGGGAAGGTGCACGTCCTGGGATGGTTGCGGGGC
CCTGTTTTGGGAGACAAAGGGGTAGAGGGTCTGTCTTGGGCCCCCCCAGACTCTAGC
CTGAGCAGTGCAGCCACCTACTGCCCCACCTCAGAGAAGTGCAGCGGGAAGGAGGC
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TGCACGCTTACATGTACACGTGCACAGATCACACACATGCACACACGTGTAGCTCAC
ACACAGTATACACATACACAAGTGCACAGACCACACACAGCACTAACACATGCACA
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GTGATGCTGGAATGTCAAGCGCCGTCGTGGGGTATCCGACTGTCCGGGCTCCTGGTC
CGCAGTGGCAGAGCGCCAGGCAGAGCCCAATCAGGGTCTCGTGCTGCCCTTCCCTCC
CACAGCCTGGCAGCCATCCAGAGGAGGGGCTCTACCAGATGCCAAGGTGCCCCGGT
GTCTGTATGGGTGTCCGGTTGGGTCCTGTGTTTGGTCTGCCCTGGAGGTGCTGGGCCC
TCCTGGGATGGGTGGCTCAGCCTCGAATCCCAGGCCCCAGCCCAGGCAGGTGCTGCT
GCCTGTTGTGGTTTCCTGGCCCAGCTTCTCCTTCTCCCTCTGCATAAAATCACAGTCC
GTGAGTCTTCCAGCTGCCACCACGGCTGGGACACGCTGGGGGAGGGCTCCTCCCATG
CCTCCTGCACACAGCCGTCTGAGCAGGGCAGGTGCCCAACACCCCCCACCGGAGGA
CACGCTGCCCCTCAGCGATGCCCCTACCTTTTGGGGGGCCTCGTCTCAAGCCCCCCCT
TGGAGGCTGAAATCACCCCAGGCACTGTGAGGGCTTCTCCAGGGGGCACCCTTTGAG
CTGTGGGTCTGATCACCCCAAGTCCCGCCCGGAGGAGAGGCACAGCCAGGGCGTGT
GGTTTAATGTTTGCCCCCTTCGGGGCTGGAGGTCTCAGTGTTTCTAGATTCCAGACCC
TGCTGCCAGAGAGACCTGCTGCCGGAGAGAAGGGGAGGAGGACTCCAGCTGGGCTC
GGTCCCCCACAGTCAGGGACCCCCATAAAGGACACCCCCTTCTCTCTAGAAAGAGCT
GGGCTCTCAGCTATTTCTAGTTGCTTCCCAGAAGCCGAGGAGCAGAAGGAGCTGTGA
GAGCTTTGCAGAAACGCCCTTGTCCCCGCCCTCCTGAGCTATGAATGCCGTACAGAG
CAGAGGCTGGGGCATTGGCAAGATCACAGGTTGATGCTGCACAGCCCCATTGACAC
AAACCCTCAAAGCAGACGTGAGAGGGACGGTTCACAAAGCTCGGACCTGCCGTGGA
GGGTGCCCGGCAGACGTGGCGTGAGAGGGACGGCTCACGAGGCTTGGACCTGCTGT
GGAGGGTGCCCAGCAGACGTGGTGTGAGAGGAACGGCTCACGAGACTTGGACCTGG
TGGAGGGTGCCCAGCAGACGTGGTGTGAGAGGGACGGCTCACAGGGCTTGGACCTG
CCATGGAGGGTGCCCGGCAGACGTGGTGTGAGAGGGATGGTTCACAGGGCTTGGAC
CTGCCATGGAGGGTGCCCGGCAGATGTGGTGGGAGAGAGATGGCTCATGAGGCTTG
GACCTGCCGTGGAGGGTGCCCAGCAGACGTGGTATGAGAGGGATGGCTCACGAGGC
TTGGACCTGGTGGAGGGTGCCCGGCAGACGTGTGAGAGGGACGGTTCACAAGGCTT
GGACCTGCCATGGAGGGTGCCCAGCAGACGTGGTGTGAGAGGGACAGCTCACGAGG
CTTGGACCTGCTGTGGAGGGTGCCCAGCAGGGGGCTGAGCTCTGAGGGGTGGGTGC
TCAGTGCACGGGTGCCCCCAGTGTCCTCTGATCCTGTCCGGTGCCTCCCCCAACCCCC
ACACCCATGCAGAACTCCCAGGTCACATGCACGTATGTCCAGGGCATGGGGGTGGC

GTGAAGAGGCCTGGTCAGGGCCTTTAGGGGCTGCAGGACGGAATGGCCGCCTGGGG
AGCCTGTGTGGCTGTGCCGGGCAGCCATCCTGCATTCCCACCCAGCGCGCAGTCTCC
ACCTCGGCCCCAGCAAAGCGCTAAGCAGCCGGAGAGACAGCCAGGGCGGCTTCCTG
AAGGATGTGGGATGGTGGACTCCGGGGTCGAGGGAATACGCAGGTTCCTGTCCCTCC
GGGAGACCTAGAGAAGCTGCACACCCAGGAGCTTTCCATGACCCGGGAGCATGAGT
GAATGGGGGTTCCAGTTTGCTGAACTTTGCCGTCTTGTAAGGGTGGGGGCTGACGGC
CGACCCTGGGAGGAGGTGACATCGCCGGGGGAGGTTGTGGGCAACGGTGGAGGAGG
AGAGACGGGAGGGGACCATTTGGGATGGAGGGGCCTCTTCAGAGTTTTAAAAGGCG
TTTGTGGGGTGGAGTTGAGTGTGCTCTGGGCTTGGACACTTGCCGTGGTGCCCCTGG
CTGGCCGAGGAGACTGGCTCTGGCCAGGGGCCCCGTCCTGAGAGGTCCTCAGCGTCT
GACTCTCGGCCAGGCGCCAGCAAGGAGGGGCCGGTCCCCGGGGCTACCAGGCAGGC
ACGTGCACATCGCCATCGCCACACGCCAACTCCGCCTGGGTTTTACAAAGTCGTTGC
CTTAATGCATGTGGACAGGAACTCCCTGAGGTCGCCCCATGCCCCCTGGCTGTGCCA
GGTACGGACGCCCTGGACCCTGCGAACAGGTGGGGCGGGCGAGGGGCCCAAGGGA
CGGGCTCCAGAGACACGCGCAGGGCAGGAGGGGTCTCACGGAGGGGTCTCGCACTG
AGGCGCCCAGAGCTGGTGGTCCCGCTGGACGCCATCCCTCTGCCCGGGATCCACACG
GCCCACGTGTGCCCGCCATGCCCGCGCCCCACGCCATTGCAGTCTGCCATCCTCTGG
CCGTGACGGTGGCTGCAGCTTCCCCATTTGCGCCGTTGCCTCTGGCTGTCTGCACTTT
TGTTCATGCTCCAAAGAACATTTCATAATGCCTTCAGTACCGACGTACACTTCTGACC
ATTTTGTATGTGTCCTTGTGCCGTAGTGACCAGGCCTTTTTTTGGTGGATGTGTTACC
CCGCACACTTCAATCTCAACTTTGTGCACCGTCCATTTTCTAGGGATAGACGCCCAG
GGAATGAACTCTAGTTTTCTAACAGATTAGCTGAGATATTAACTTACTCACACGGAC
AGGTTGATGCCAGAGCCGTAAGAATGCGCCAGTGCGGGTTTGCGGGGGACTTCGGG
TGTGGGGTCCTGCGGCCGCGATGGCCGTGGAAGGTTCTGGGGATCCCTGCTGCCACG
GGGACGAGTTCGGACGCCAGGTGGACCTGTGCACTCAGTAAAACGCAGTGATTCAA
CCTGGA

(SEQ ID NO: 3032 (SOURCE NCBI REFERENCE NO: NM_001382235.1)

[00319] In various embodiments, a KCNQ2 mRNA transcript comprises the sequence provided as SEQ ID NO: 3033.

AGGCGCCGAGGTGCGCGCGGAGCGAGGTGGCCGCAGCGTCTCCGCGCGCGGCCCAA
GCCCGGCAGGAGTGCGGAACCGCCGCCTCGGCCATGCGGCTCCCGGCCGGGGGGCC
TGGGCTGGGGCCCGCGCCGCCCCCCGCGCTCCGCCCCCGCTGAGCCTGAGCCCGACC
CGGGGCGCCTCCCGCCAGGCACCATGGTGCAGAAGTCGCGCAACGGCGGCGTATAC
CCCGGCCCGAGCGGGGAGAAGAAGCTGAAGGTGGGCTTCGTGGGGCTGGACCCCGG
CGCGCCCGACTCCACCCGGGACGGGGCGCTGCTGATCGCCGGCTCCGAGGCCCCCA
AGCGCGGCAGCATCCTCAGCAAACCTCGCGCGGGCGGCGCGGGCGCCGGGAAGCCC
CCCAAGCGCAACGCCTTCTACCGCAAGCTGCAGAATTTCCTCTACAACGTGCTGGAG
CGGCCGCGCGGCTGGGCGTTCATCTACCACGCCTACGTGTTCCTCCTGGTTTTCTCCT
GCCTCGTGCTGTCTGTGTTTTCCACCATCAAGGAGTATGAGAAGAGCTCGGAGGGGG
CCCTCTACATCCTGGAAATCGTGACTATCGTGGTGTTTGGCGTGGAGTACTTCGTGCG
GATCTGGGCCGCAGGCTGCTGCTGCCGGTACCGTGGCTGGAGGGGGCGGCTCAAGTT
TGCCCGGAAACCGTTCTGTGTGATTGACATCATGGTGCTCATCGCCTCCATTGCGGTG
CTGGCCGCCGGCTCCCAGGGCAACGTCTTTGCCACATCTGCGCTCCGGAGCCTGCGC
TTCCTGCAGATTCTGCGGATGATCCGCATGGACCGGCGGGGAGGCACCTGGAAGCTG
CTGGGCTCTGTGGTCTATGCCCACAGCAAGGAGCTGGTCACTGCCTGGTACATCGGC
TTCCTTTGTCTCATCCTGGCCTCGTTCCTGGTGTACTTGGCAGAGAAGGGGGAGAAC
GACCACTTTGACACCTACGCGGATGCACTCTGGTGGGGCCTGATCACGCTGACCACC
ATTGGCTACGGGGACAAGTACCCCCAGACCTGGAACGGCAGGCTCCTTGCGGCAAC

CTTCACCCTCATCGGTGTCTCCTTCTTCGCGCTGCCTGCAGGCATCTTGGGGTCTGGG
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CCCGGCAGCAGGCCTGATCCAGTCGGCCTGGAGATTCTACGCCACCAACCTCTCGCG
CACAGACCTGCACTCCACGTGGCAGTACTACGAGCGAACGGTCACCGTGCCCATGTA
CAGACTTATCCCCCCGCTGAACCAGCTGGAGCTGCTGAGGAACCTCAAGAGTAAATC
TGGACTCGCTTTCAGGAAGGACCCCCCGCCGGAGCCGTCTCCAAGCCAGAAGGTCA
GTTTGAAAGATCGTGTCTTCTCCAGCCCCCGAGGCGTGGCTGCCAAGGGGAAGGGGT
CCCCGCAGGCCCAGACTGTGAGGCGGTCACCCAGCGCCGACCAGAGCCTCGAGGAC
AGCCCCAGCAAGGTGCCCAAGAGCTGGAGCTTCGGGGACCGCAGCCGGGCACGCCA
GGCTTTCCGCATCAAGGGTGCCGCGTCACGGCAGAACTCAGAAGAAGCAAGCCTCC
CCGGAGAGGACATTGTGGATGACAAGAGCTGCCCCTGCGAGTTTGTGACCGAGGAC
CTGACCCCGGGCCTCAAAGTCAGCATCAGAGCCGTGTGTGTCATGCGGTTCCTGGTG
TCCAAGCGGAAGTTCAAGGAGAGCCTGCGGCCCTACGACGTGATGGACGTCATCGA
GCAGTACTCAGCCGGCCACCTGGACATGCTGTCCCGAATTAAGAGCCTGCAGTCCAG
AGTGGACCAGATCGTGGGGCGGGGCCCAGCGATCACGGACAAGGACCGCACCAAG
GGCCCGGCCGAGGCGGAGCTGCCCGAGGACCCCAGCATGATGGGACGGCTCGGGAA
GGTGGAGAAGCAGGTCTTGTCCATGGAGAAGAAGCTGGACTTCCTGGTGAATATCTA
CATGCAGCGGATGGGCATCCCCCCGACAGAGACCGAGGCCTACTTTGGGGCCAAAG
AGCCGGAGCCGGCGCCGCCGTACCACAGCCCGGAAGACAGCCGGGAGCATGTCGAC
AGGCACGGCTGCATTGTCAAGATCGTGCGCTCCAGCAGCTCCACGGGCCAGAAGAA
CTTCTCGGCGCCCCCGGCCGCGCCCCCTGTCCAGTGTCCGCCCTCCACCTCCTGGCAG
CCACAGAGCCACCCGCGCCAGGGCCACGGCACCTCCCCCGTGGGGGACCACGGCTC
CCTGGTGCGCATCCCGCCGCCGCCTGCCCACGAGCGGTCGCTGTCCGCCTACGGCGG
GGGCAACCGCGCCAGCATGGAGTTCCTGCGGCAGGAGGACACCCCGGGCTGCAGGC
CCCCCGAGGGGAACCTGCGGGACAGCGACACGTCCATCTCCATCCCGTCCGTGGACC
ACGAGGAGCTGGAGCGTTCCTTCAGCGGCTTCAGCATCTCCCAGTCCAAGGAGAACC
TGGATGCTCTCAACAGCTGCTACGCGGCCGTGGCGCCTTGTGCCAAAGTCAGGCCCT
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GTGGCGGGAAGGGTGGGCCCTGGAGGGGCCCATGTGGGCTGAAGGATGGGGGCTCC
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GGCCGCGGCCGACATCAGCCCGGTGTGAGGAGGGGCGGGAGTGATGACGGGGTGTT
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AAAGGGTCTTCAAAAAGGGGGTCCTTGGGGGCTCCAGCTGCCTCGCCCTGGCCTTTC
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CTCCACCGTCAGCACAGGGCCGCCCTCCCCGCCTTTCCGGAGGAAACCACTCCCACC

TCAGCCCAGCTGTGCGCCCTCCCTAGCTCTCCTGCCCCCTGGAGCTGATGGCCCCTTC
TCCACTGACCGATTCCTTAGCGGGGCCTCTTGGGGTCTCGGGCCTCGGGTGCACCGT
CCCATGCCCGTCCTGTTGTGGGCACCGTGGCCCTTGGGGCAGGCGGCTCTAATGCGG
GAGCGAGTCCCTAGCTCCAGACTTAAGAACCAGACCCCGGGAGCATCTGGCATTTGG
CGTGACGGCGTCGCAGGCGGGCCTGGGCTCCCTGGAGAGTGGCCTCCCTGGGAGTG
AGCAGGGCTGGGGTCGTGGGCGCAAATACTCCTGCAGAGCAAGTGCAGGGGAGTCC
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GAGGCCCTGAGGCCAGCAGGGGAACCAGTCCTGAGGGAGAGGACTTTGAAAGCAGC
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AGCCATGTCTGGCGTCCATTGTGGGGAGCTGCTGCCCTGGCCTCTCTGCCTACCCCC
AGCCCGGCCAGGGCACTCCCAGGCCCTGTCGCCATTGAGGTGCCTCCGCTGGGCTGT
CTCCTCACCCCTCCCTGTGCTGGAGCCTGTCCCAAAAAGGTGCCAACTGGGAGGCCT
CGGAAGCCACTGTCCAGGCTCCCACTGCCTGTCTGCTCTGTTCCCAAAGGCAGCGTG
TGTGGCCTCGGGCCCTGCGGTGGCATGAAGCATCCCTTCTGGTGTGGGCATCGCTAC
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GCCCACAGGCAGGGGTATGAGTGCGTCCCACCCAACGCAGCACCAGCCCCGGCCAC
CGCTCCCCGTGTCCCCAGTTCCGTCTCAGCTACCTGGACTCCAGGACCCTGGAGAAG
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CCCTGCCGAGGTGTGACCCCACCTGCTCTTTCCTCCCTCCCAGTATGGCCCCACCTGC
TCTTTCCTCCCCCGAGGTGAGGCCCCGCCTGCTCTTTCCTCCCATGGGGCCGCTGAGG
CATGAGCACCTGGGCACAGGTTGGGGCTCTGCAGGATGAGGAAGACAGGCCAATCC
CTTCCCTCCCAGAAGCTGGCCGCCCAGCAGGAGGGACTGAGGCCAGACTCATGTCC
AGCAAGGAACGTGTGGTGTGTCCCCTGGGAAGTCTCTGGGCCCTGGGAAGAGGGAA
GGTGCACGTCCTGGGATGGTTGCGGGGCCCTGTTTTGGGAGACAAAGGGGTAGAGG
GTCTGTCTTGGGCCCCCCCAGACTCTAGCCTGAGCAGTGCAGCCACCTACTGCCCCA
CCTCAGAGAAGTGCAGCGGGAAGGAGGCTGGAGGTGGTGCGGCGCTGCCTCGGGTG
TCTGCGTGAATGAGCGTGGCCAAGGACCAGTGCCACCTCATGGCAAAGAGCTCCCG
CAGTGTTTGTTAGAGTGCACATCCCTACGTGCCCACTGGCACACACACGTGCTCACA
TACATGTCCGCATACAGGCGTACACATGCACGCTTGCACACATGCACACAGACCACA
TAGCACACATGTGCACTGACCACACCTGTATAGACCATGCACAGTACACATACGTGC
ATACACATGCCTGCATACAGGCATACACATGCACGCTTACATGTACACGTGCACAGA
TCACACACATGCACACACGTGTAGCTCACACACAGTATACACATACACAAGTGCAC
AGACCACACACAGCACTAACACATGCACACACAAAGTGCATAGGCCACACAGCACA
TGCACACAGGTGCACAGACCACACAGCACACACAAGTGCACAGAGCACACTGCACA
CATGCACACACACACGCGTGCATGCACACTCCTCGCACTTCCAGCCTTGGAGCCCTT
CTGTCTCTGGTCTTTCTCTTTGACCCTGCTGAGTGTAAGCTGCCTGGGGAGGGGCTAC
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GGGGTATCCGACTGTCCGGGCTCCTGGTCCGCAGTGGCAGAGCGCCAGGCAGAGCC
CAATCAGGGTCTCGTGCTGCCCTTCCCTCCCACAGCCTGGCAGCCATCCAGAGGAGG
GGCTCTACCAGATGCCAAGGTGCCCCGGTGTCTGTATGGGTGTCCGGTTGGGTCCTG
TGTTTGGTCTGCCCTGGAGGTGCTGGGCCCTCCTGGGATGGGTGGCTCAGCCTCGAA
TCCCAGGCCCCAGCCCAGGCAGGTGCTGCTGCCTGTTGTGGTTTCCTGGCCCAGCTT
CTCCTTCTCCCTCTGCATAAAATCACAGTCCGTGAGTCTTCCAGCTGCCACCACGGCT
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GGCAGGTGCCCAACACCCCCCACCGGAGGACACGCTGCCCCTCAGCGATGCCCCTA
CCTTTTGGGGGGCCTCGTCTCAAGCCCCCCCTTGGAGGCTGAAATCACCCCAGGCAC

TGTGAGGGCTTCTCCAGGGGGCACCCTTTGAGCTGTGGGTCTGATCACCCCAAGTCC
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GACCTGTGCACTCAGTAAAACGCAGTGATTCAACCTGGA

(SEQ ID NO: 3033) (Source: NCBI Reference Sequence: NM_004518.6).

[00320] In various embodiments, a KCNQ2 mRNA transcript comprises the sequence provided as SEQ ID NO: 3034.

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CACGGGGACGAGTTCGGACGCCAGGTGGACCTGTGCACTCAGTAAAACGCAGTGAT
TCAACCTGGA

(SEQ ID NO: 3034) (Source: NCBI Reference Sequence: NM_172106.3).

[00321] In various embodiments, a KCNQ2 mRNA transcript comprises the sequence provided as SEQ ID NO: 3035.

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AGCTGCTGCCCTGGCCTCTCTGCCTACCCCCAGCCCGGCCAGGGCACTCCCAGGCCC
TGTCGCCATTGAGGTGCCTCCGCTGGGCTGTCTCCTCACCCCTCCCTGTGCTGGAGCC
TGTCCCAAAAAGGTGCCAACTGGGAGGCCTCGGAAGCCACTGTCCAGGCTCCCACT
GCCTGTCTGCTCTGTTCCCAAAGGCAGCGTGTGTGGCCTCGGGCCCTGCGGTGGCAT
GAAGCATCCCTTCTGGTGTGGGCATCGCTACGTGTTTTGGGGGCAGCGTTTCACGGC
GGTGCCCTTGCTGTCTCCCTTGGGCTGGCTCGAGCCTGGGGTCCATGTCCCTTTGCCG
TCCCGTCATGGGGCAGGGAATCCATAGCGGGGCCCACAGGCAGGGGTATGAGTGCG
TCCCACCCAACGCAGCACCAGCCCCGGCCACCGCTCCCCGTGTCCCCAGTTCCGTCT
CAGCTACCTGGACTCCAGGACCCTGGAGAAGGGAGACCTGGCAGTGGAGGGAGGCT
GTGCTGTGTGTCCCCCTGCAGGTGTGACCCCGCCTGCTCTTTCCTCCCCCGCCAGGTG
TGGCCCCGCCTGCTCTTTCCTCCCCCACCAGTATGGCCCCACCTGCTCTTTCCTCCCC
CCCCAAGGTGTGGCCCCACCTGTTCTTTCCTCCCCTGCCGAGGTGTGACCCCACCTGC
TCTTTCCTCCCTCCCAGTATGGCCCCACCTGCTCTTTCCTCCCCCGAGGTGAGGCCCC
GCCTGCTCTTTCCTCCCATGGGGCCGCTGAGGCATGAGCACCTGGGCACAGGTTGGG
GCTCTGCAGGATGAGGAAGACAGGCCAATCCCTTCCCTCCCAGAAGCTGGCCGCCC
AGCAGGAGGGACTGAGGCCAGACTCATGTCCAGCAAGGAACGTGTGGTGTGTCCCC
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GGCCCTGTTTTGGGAGACAAAGGGGTAGAGGGTCTGTCTTGGGCCCCCCCAGACTCT
AGCCTGAGCAGTGCAGCCACCTACTGCCCCACCTCAGAGAAGTGCAGCGGGAAGGA
GGCTGGAGGTGGTGCGGCGCTGCCTCGGGTGTCTGCGTGAATGAGCGTGGCCAAGG
ACCAGTGCCACCTCATGGCAAAGAGCTCCCGCAGTGTTTGTTAGAGTGCACATCCCT
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TGCACGCTTGCACACATGCACACAGACCACATAGCACACATGTGCACTGACCACACC
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ACATGCACGCTTACATGTACACGTGCACAGATCACACACATGCACACACGTGTAGCT
CACACACAGTATACACATACACAAGTGCACAGACCACACACAGCACTAACACATGC
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TCCCACAGCCTGGCAGCCATCCAGAGGAGGGGCTCTACCAGATGCCAAGGTGCCCC
GGTGTCTGTATGGGTGTCCGGTTGGGTCCTGTGTTTGGTCTGCCCTGGAGGTGCTGGG
CCCTCCTGGGATGGGTGGCTCAGCCTCGAATCCCAGGCCCCAGCCCAGGCAGGTGCT
GCTGCCTGTTGTGGTTTCCTGGCCCAGCTTCTCCTTCTCCCTCTGCATAAAATCACAG
TCCGTGAGTCTTCCAGCTGCCACCACGGCTGGGACACGCTGGGGGAGGGCTCCTCCC
ATGCCTCCTGCACACAGCCGTCTGAGCAGGGCAGGTGCCCAACACCCCCCACCGGA
GGACACGCTGCCCCTCAGCGATGCCCCTACCTTTTGGGGGGCCTCGTCTCAAGCCCC
CCCTTGGAGGCTGAAATCACCCCAGGCACTGTGAGGGCTTCTCCAGGGGGCACCCTT
TGAGCTGTGGGTCTGATCACCCCAAGTCCCGCCCGGAGGAGAGGCACAGCCAGGGC
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AGCTGGGCTCTCAGCTATTTCTAGTTGCTTCCCAGAAGCCGAGGAGCAGAAGGAGCT
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CTGGTGGAGGGTGCCCAGCAGACGTGGTGTGAGAGGGACGGCTCACAGGGCTTGGA
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GGACCTGCCATGGAGGGTGCCCGGCAGATGTGGTGGGAGAGAGATGGCTCATGAGG
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AGGCTTGGACCTGGTGGAGGGTGCCCGGCAGACGTGTGAGAGGGACGGTTCACAAG
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GAGGCTTGGACCTGCTGTGGAGGGTGCCCAGCAGGGGGCTGAGCTCTGAGGGGTGG
GTGCTCAGTGCACGGGTGCCCCCAGTGTCCTCTGATCCTGTCCGGTGCCTCCCCCAA
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CCTCCGGGAGACCTAGAGAAGCTGCACACCCAGGAGCTTTCCATGACCCGGGAGCA
TGAGTGAATGGGGGTTCCAGTTTGCTGAACTTTGCCGTCTTGTAAGGGTGGGGGCTG
ACGGCCGACCCTGGGAGGAGGTGACATCGCCGGGGGAGGTTGTGGGCAACGGTGGA
GGAGGAGAGACGGGAGGGGACCATTTGGGATGGAGGGGCCTCTTCAGAGTTTTAAA
AGGCGTTTGTGGGGTGGAGTTGAGTGTGCTCTGGGCTTGGACACTTGCCGTGGTGCC
CCTGGCTGGCCGAGGAGACTGGCTCTGGCCAGGGGCCCCGTCCTGAGAGGTCCTCA
GCGTCTGACTCTCGGCCAGGCGCCAGCAAGGAGGGGCCGGTCCCCGGGGCTACCAG
GCAGGCACGTGCACATCGCCATCGCCACACGCCAACTCCGCCTGGGTTTTACAAAGT
CGTTGCCTTAATGCATGTGGACAGGAACTCCCTGAGGTCGCCCCATGCCCCCTGGCT
GTGCCAGGTACGGACGCCCTGGACCCTGCGAACAGGTGGGGCGGGCGAGGGGCCCA
AGGGACGGGCTCCAGAGACACGCGCAGGGCAGGAGGGGTCTCACGGAGGGGTCTCG
CACTGAGGCGCCCAGAGCTGGTGGTCCCGCTGGACGCCATCCCTCTGCCCGGGATCC
ACACGGCCCACGTGTGCCCGCCATGCCCGCGCCCCACGCCATTGCAGTCTGCCATCC
TCTGGCCGTGACGGTGGCTGCAGCTTCCCCATTTGCGCCGTTGCCTCTGGCTGTCTGC
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TGACCATTTTGTATGTGTCCTTGTGCCGTAGTGACCAGGCCTTTTTTTGGTGGATGTG
TTACCCCGCACACTTCAATCTCAACTTTGTGCACCGTCCATTTTCTAGGGATAGACGC
CCAGGGAATGAACTCTAGTTTTCTAACAGATTAGCTGAGATATTAACTTACTCACAC
GGACAGGTTGATGCCAGAGCCGTAAGAATGCGCCAGTGCGGGTTTGCGGGGGACTT
CGGGTGTGGGGTCCTGCGGCCGCGATGGCCGTGGAAGGTTCTGGGGATCCCTGCTGC
CACGGGGACGAGTTCGGACGCCAGGTGGACCTGTGCACTCAGTAAAACGCAGTGAT
TCAACCTGGA

(SEQ ID NO: 3035) (Source: NCBI Reference Sequence: NM_172107.4).

[00322] In various embodiments, a KCNQ2 mRNA transcript comprises the sequence provided as SEQ ID NO: 3036.

AGGCGCCGAGGTGCGCGCGGAGCGAGGTGGCCGCAGCGTCTCCGCGCGCGGCCCAA
GCCCGGCAGGAGTGCGGAACCGCCGCCTCGGCCATGCGGCTCCCGGCCGGGGGGCC
TGGGCTGGGGCCCGCGCCGCCCCCCGCGCTCCGCCCCCGCTGAGCCTGAGCCCGACC

CGGGGCGCCTCCCGCCAGGCACCATGGTGCAGAAGTCGCGCAACGGCGGCGTATAC
CCCGGCCCGAGCGGGGAGAAGAAGCTGAAGGTGGGCTTCGTGGGGCTGGACCCCGG
CGCGCCCGACTCCACCCGGGACGGGGCGCTGCTGATCGCCGGCTCCGAGGCCCCCA
AGCGCGGCAGCATCCTCAGCAAACCTCGCGCGGGCGGCGCGGGCGCCGGGAAGCCC
CCCAAGCGCAACGCCTTCTACCGCAAGCTGCAGAATTTCCTCTACAACGTGCTGGAG
CGGCCGCGCGGCTGGGCGTTCATCTACCACGCCTACGTGTTCCTCCTGGTTTTCTCCT
GCCTCGTGCTGTCTGTGTTTTCCACCATCAAGGAGTATGAGAAGAGCTCGGAGGGGG
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GATCTGGGCCGCAGGCTGCTGCTGCCGGTACCGTGGCTGGAGGGGGCGGCTCAAGTT
TGCCCGGAAACCGTTCTGTGTGATTGACATCATGGTGCTCATCGCCTCCATTGCGGTG
CTGGCCGCCGGCTCCCAGGGCAACGTCTTTGCCACATCTGCGCTCCGGAGCCTGCGC
TTCCTGCAGATTCTGCGGATGATCCGCATGGACCGGCGGGGAGGCACCTGGAAGCTG
CTGGGCTCTGTGGTCTATGCCCACAGCAAGGAGCTGGTCACTGCCTGGTACATCGGC
TTCCTTTGTCTCATCCTGGCCTCGTTCCTGGTGTACTTGGCAGAGAAGGGGGAGAAC
GACCACTTTGACACCTACGCGGATGCACTCTGGTGGGGCCTGATCACGCTGACCACC
ATTGGCTACGGGGACAAGTACCCCCAGACCTGGAACGGCAGGCTCCTTGCGGCAAC
CTTCACCCTCATCGGTGTCTCCTTCTTCGCGCTGCCTGCAGGCATCTTGGGGTCTGGG
TTTGCCCTGAAGGTTCAGGAGCAGCACAGGCAGAAGCACTTTGAGAAGAGGCGGAA
CCCGGCAGCAGGCCTGATCCAGTCGGCCTGGAGATTCTACGCCACCAACCTCTCGCG
CACAGACCTGCACTCCACGTGGCAGTACTACGAGCGAACGGTCACCGTGCCCATGTA
CAGTTCGCAAACTCAAACCTACGGGGCCTCCAGACTTATCCCCCCGCTGAACCAGCT
GGAGCTGCTGAGGAACCTCAAGAGTAAATCTGGACTCGCTTTCAGGAAGGACCCCC
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AGCAGGTCTTGTCCATGGAGAAGAAGCTGGACTTCCTGGTGAATATCTACATGCAGC
GGATGGGCATCCCCCCGACAGAGACCGAGGCCTACTTTGGGGCCAAAGAGCCGGAG
CCGGCGCCGCCGTACCACAGCCCGGAAGACAGCCGGGAGCATGTCGACAGGCACGG
CTGCATTGTCAAGATCGTGCGCTCCAGCAGCTCCACGGGCCAGAAGAACTTCTCGGC
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CCACCCGCGCCAGGGCCACGGCACCTCCCCCGTGGGGGACCACGGCTCCCTGGTGC
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GCGCCAGCATGGAGTTCCTGCGGCAGGAGGACACCCCGGGCTGCAGGCCCCCCGAG
GGGAACCTGCGGGACAGCGACACGTCCATCTCCATCCCGTCCGTGGACCACGAGGA
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GACCTTTTACAAAAGTTATTTTCCAACAGGGGCTGGAGGGCTGGGCAGGGCCCTGTG

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GGCTGGGGTCGTGGGCGCAAATACTCCTGCAGAGCAAGTGCAGGGGAGTCCTGGGC
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AGGGTCGTACGCCCCTGGCTGGTGGGGGTCCTGGCGCTCAGGGTGTTCGGGGAGCCA
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CAGGCAGGGGTATGAGTGCGTCCCACCCAACGCAGCACCAGCCCCGGCCACCGCTC
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CCGAGGTGTGACCCCACCTGCTCTTTCCTCCCTCCCAGTATGGCCCCACCTGCTCTTT
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CCTCCCAGAAGCTGGCCGCCCAGCAGGAGGGACTGAGGCCAGACTCATGTCCAGCA
AGGAACGTGTGGTGTGTCCCCTGGGAAGTCTCTGGGCCCTGGGAAGAGGGAAGGTG
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CACAGGTGCACAGACCACACAGCACACACAAGTGCACAGAGCACACTGCACACATG
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GGTGCCCAACACCCCCCACCGGAGGACACGCTGCCCCTCAGCGATGCCCCTACCTTT
TGGGGGGCCTCGTCTCAAGCCCCCCCTTGGAGGCTGAAATCACCCCAGGCACTGTGA
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GGACACCCCCTTCTCTCTAGAAAGAGCTGGGCTCTCAGCTATTTCTAGTTGCTTCCCA
GAAGCCGAGGAGCAGAAGGAGCTGTGAGAGCTTTGCAGAAACGCCCTTGTCCCCGC
CCTCCTGAGCTATGAATGCCGTACAGAGCAGAGGCTGGGGCATTGGCAAGATCACA
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GTGGTATGAGAGGGATGGCTCACGAGGCTTGGACCTGGTGGAGGGTGCCCGGCAGA
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CGTGGTGTGAGAGGGACAGCTCACGAGGCTTGGACCTGCTGTGGAGGGTGCCCAGC
AGGGGGCTGAGCTCTGAGGGGTGGGTGCTCAGTGCACGGGTGCCCCCAGTGTCCTCT
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GCACGTATGTCCAGGGCATGGGGGTGGCGTGAAGAGGCCTGGTCAGGGCCTTTAGG
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CAACTCCGCCTGGGTTTTACAAAGTCGTTGCCTTAATGCATGTGGACAGGAACTCCC
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GGACGCCATCCCTCTGCCCGGGATCCACACGGCCCACGTGTGCCCGCCATGCCCGCG
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TGACCAGGCCTTTTTTTGGTGGATGTGTTACCCCGCACACTTCAATCTCAACTTTGTG
CACCGTCCATTTTCTAGGGATAGACGCCCAGGGAATGAACTCTAGTTTTCTAACAGA
TTAGCTGAGATATTAACTTACTCACACGGACAGGTTGATGCCAGAGCCGTAAGAATG
CGCCAGTGCGGGTTTGCGGGGGACTTCGGGTGTGGGGTCCTGCGGCCGCGATGGCCG
TGGAAGGTTCTGGGGATCCCTGCTGCCACGGGGACGAGTTCGGACGCCAGGTGGAC
CTGTGCACTCAGTAAAACGCAGTGATTCAACCTGGA
(SEQ ID NO: 3036) (Source: NCBI Reference Sequence: NM_172108.5).

[00323] In various embodiments, KCNQ2 mRNA transcript comprises the sequence provided as SEQ ID NO: 3037.

AGGCGCCGAGGTGCGCGCGGAGCGAGGTGGCCGCAGCGTCTCCGCGCGCGGCCCAA
GCCCGGCAGGAGTGCGGAACCGCCGCCTCGGCCATGCGGCTCCCGGCCGGGGGGCC
TGGGCTGGGGCCCGCGCCGCCCCCCGCGCTCCGCCCCCGCTGAGCCTGAGCCCGACC
CGGGGCGCCTCCCGCCAGGCACCATGGTGCAGAAGTCGCGCAACGGCGGCGTATAC
CCCGGCCCGAGCGGGGAGAAGAAGCTGAAGGTGGGCTTCGTGGGGCTGGACCCCGG
CGCGCCCGACTCCACCCGGGACGGGGCGCTGCTGATCGCCGGCTCCGAGGCCCCCA
AGCGCGGCAGCATCCTCAGCAAACCTCGCGCGGGCGGCGCGGGCGCCGGGAAGCCC
CCCAAGCGCAACGCCTTCTACCGCAAGCTGCAGAATTTCCTCTACAACGTGCTGGAG
CGGCCGCGCGGCTGGGCGTTCATCTACCACGCCTACGTGTTCCTCCTGGTTTTCTCCT
GCCTCGTGCTGTCTGTGTTTTCCACCATCAAGGAGTATGAGAAGAGCTCGGAGGGGG
CCCTCTACATCCTGGAAATCGTGACTATCGTGGTGTTTGGCGTGGAGTACTTCGTGCG
GATCTGGGCCGCAGGCTGCTGCTGCCGGTACCGTGGCTGGAGGGGGCGGCTCAAGTT
TGCCCGGAAACCGTTCTGTGTGATTGACATCATGGTGCTCATCGCCTCCATTGCGGTG
CTGGCCGCCGGCTCCCAGGGCAACGTCTTTGCCACATCTGCGCTCCGGAGCCTGCGC
TTCCTGCAGATTCTGCGGATGATCCGCATGGACCGGCGGGGAGGCACCTGGAAGCTG
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TTCCTTTGTCTCATCCTGGCCTCGTTCCTGGTGTACTTGGCAGAGAAGGGGGAGAAC
GACCACTTTGACACCTACGCGGATGCACTCTGGTGGGGCCTGATCACGCTGACCACC
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CTTCACCCTCATCGGTGTCTCCTTCTTCGCGCTGCCTGCAGGCATCTTGGGGTCTGGG
TTTGCCCTGAAGGTTCAGGAGCAGCACAGGCAGAAGCACTTTGAGAAGAGGCGGAA
CCCGGCAGCAGGCCTGATCCAGTCGGCCTGGAGATTCTACGCCACCAACCTCTCGCG
CACAGACCTGCACTCCACGTGGCAGTACTACGAGCGAACGGTCACCGTGCCCATGTA
CAGGTACCGCCGCCGGGCACCTGCCACCAAGCAACTGTTTCATTTTTTATTTTCCATT
TGTTCTTAAACCCCACTTTTTGTTGTTCATTATTTTGATTGATTTTTTTTCTTTAAAATG
TATTTTTCACAAAGGA
(SEQ ID NO: 3037) (Source: NCBI Reference Sequence: NM_172109.3).

[00324] In various embodiments, a KCNQ2 mRNA transcript comprises the sequence provided as SEQ ID NO: 3038.

AGCGTCTCCGCGCGCGGCCCAAGCCCGGCAGGAGTGCGGAACCGCCGCCTCGGCCA
TGCGGCTCCCGGCCGGGGGGCCTGGGCTGGGGCCCGCGCCGCCCCCCGCGCTCCGCC
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GTCGCGCAACGGCGGCGTATACCCCGGCCCGAGCGGGGAGAAGAAGCTGAAGGTGG
GCTTCGTGGGGCTGGACCCCGGCGCGCCCGACTCCACCCGGGACGGGGCGCTGCTG
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CGGCGCGGGCGCCGGGAAGCCCCCCAAGCGCAACGCCTTCTACCGCAAGCTGCAGA
ATTTCCTCTACAACGTGCTGGAGCGGCCGCGCGGCTGGGCGTTCATCTACCACGCCT
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GTATGAGAAGAGCTCGGAGGGGGCCCTCTACATCCTGGAAATCGTGACTATCGTGGT
GTTTGGCGTGGAGTACTTCGTGCGGATCTGGGCCGCAGGCTGCTGCTGCCGGTACCG
TGGCTGGAGGGGGCGGCTCAAGTTTGCCCGGAAACCGTTCTGTGTGATTGACATCAT
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(SEQ ID NO: 3038) (Source: NCBI Reference Sequence: XM_011528811.2))

[00325] In various embodiments, a KCNQ2 mRNA transcript comprises the sequence provided as SEQ ID NO: 3039.

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ATGGAGGGGCCTCTTCAGAGTTTTAAAAGGCGTTTGTGGGGTGGAGTTGAGTGTGCT
CTGGGCTTGGACACTTGCCGTGGTGCCCCTGGCTGGCCGAGGAGACTGGCTCTGGCC
AGGGGCCCCGTCCTGAGAGGTCCTCAGCGTCTGACTCTCGGCCAGGCGCCAGCAAG
GAGGGGCCGGTCCCCGGGGCTACCAGGCAGGCACGTGCACATCGCCATCGCCACAC
GCCAACTCCGCCTGGGTTTTACAAAGTCGTTGCCTTAATGCATGTGGACAGGAACTC
CCTGAGGTCGCCCCATGCCCCCTGGCTGTGCCAGGTACGGACGCCCTGGACCCTGCG
AACAGGTGGGGCGGGCGAGGGGCCCAAGGGACGGGCTCCAGAGACACGCGCAGGG
CAGGAGGGGTCTCACGGAGGGGTCTCGCACTGAGGCGCCCAGAGCTGGTGGTCCCG
CTGGACGCCATCCCTCTGCCCGGGATCCACACGGCCCACGTGTGCCCGCCATGCCCG
CGCCCCACGCCATTGCAGTCTGCCATCCTCTGGCCGTGACGGTGGCTGCAGCTTCCC
CATTTGCGCCGTTGCCTCTGGCTGTCTGCACTTTTGTTCATGCTCCAAAGAACATTTC
ATAATGCCTTCAGTACCGACGTACACTTCTGACCATTTTGTATGTGTCCTTGTGCCGT
AGTGACCAGGCCTTTTTTTGGTGGATGTGTTACCCCGCACACTTCAATCTCAACTTTG
TGCACCGTCCATTTTCTAGGGATAGACGCCCAGGGAATGAACTCTAGTTTTCTAACA
GATTAGCTGAGATATTAACTTACTCACACGGACAGGTTGATGCCAGAGCCGTAAGAA
TGCGCCAGTGCGGGTTTGCGGGGGACTTCGGGTGTGGGGTCCTGCGGCCGCGATGGC
CGTGGAAGGTTCTGGGGATCCCTGCTGCCACGGGGACGAGTTCGGACGCCAGGTGG
ACCTGTGCACTCAGTAAAACGCAGTGATTCAACCTGGA
(SEQ ID NO: 3039) (Source: NCBI Reference Sequence: XM_017027844.2)

[00326] In various embodiments, a KCNQ2 mRNA transcript comprises the sequence provided as SEQ ID NO: 3040.

AGCGTCTCCGCGCGCGGCCCAAGCCCGGCAGGAGTGCGGAACCGCCGCCTCGGCCA
TGCGGCTCCCGGCCGGGGGGCCTGGGCTGGGGCCCGCGCCGCCCCCCGCGCTCCGCC
CCCGCTGAGCCTGAGCCCGACCCGGGGCGCCTCCCGCCAGGCACCATGGTGCAGAA
GTCGCGCAACGGCGGCGTATACCCCGGCCCGAGCGGGGAGAAGAAGCTGAAGGTGG
GCTTCGTGGGGCTGGACCCCGGCGCGCCCGACTCCACCCGGGACGGGGCGCTGCTG
ATCGCCGGCTCCGAGGCCCCCAAGCGCGGCAGCATCCTCAGCAAACCTCGCGCGGG
CGGCGCGGGCGCCGGGAAGCCCCCCAAGCGCAACGCCTTCTACCGCAAGCTGCAGA
ATTTCCTCTACAACGTGCTGGAGCGGCCGCGCGGCTGGGCGTTCATCTACCACGCCT

ACGTGTTCCTCCTGGTTTTCTCCTGCCTCGTGCTGTCTGTGTTTTCCACCATCAAGGA
GTATGAGAAGAGCTCGGAGGGGGCCCTCTACATCCTGGAAATCGTGACTATCGTGGT
GTTTGGCGTGGAGTACTTCGTGCGGATCTGGGCCGCAGGCTGCTGCTGCCGGTACCG
TGGCTGGAGGGGGCGGCTCAAGTTTGCCCGGAAACCGTTCTGTGTGATTGACATCAT
GGTGCTCATCGCCTCCATTGCGGTGCTGGCCGCCGGCTCCCAGGGCAACGTCTTTGC
CACATCTGCGCTCCGGAGCCTGCGCTTCCTGCAGATTCTGCGGATGATCCGCATGGA
CCGGCGGGGAGGCACCTGGAAGCTGCTGGGCTCTGTGGTCTATGCCCACAGCAAGG
AGCTGGTCACTGCCTGGTACATCGGCTTCCTTTGTCTCATCCTGGCCTCGTTCCTGGT
GTACTTGGCAGAGAAGGGGGAGAACGACCACTTTGACACCTACGCGGATGCACTCT
GGTGGGGCCTGATCACGCTGACCACCATTGGCTACGGGGACAAGTACCCCCAGACC
TGGAACGGCAGGCTCCTTGCGGCAACCTTCACCCTCATCGGTGTCTCCTTCTTCGCGC
TGCCTGCAGGCATCTTGGGGTCTGGGTTTGCCCTGAAGGTTCAGGAGCAGCACAGGC
AGAAGCACTTTGAGAAGAGGCGGAACCCGGCAGCAGGCCTGATCCAGTCGGCCTGG
AGATTCTACGCCACCAACCTCTCGCGCACAGACCTGCACTCCACGTGGCAGTACTAC
GAGCGAACGGTCACCGTGCCCATGTACAGTTCGCAAACTCAAACCTACGGGGCCTCC
AGACTTATCCCCCCGCTGAACCAGCTGGAGCTGCTGAGGAACCTCAAGAGTAAATCT
GGACTCGCTTTCAGGAAGGACCCCCCGCCGGAGCCGTCTCCAAGCCAGAAGGTCAG
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GATATGATTGTGGGTCCCCCGCCCCCTTCAACTCCCCGGCACAAGAAGTACCCCACC
AAAGGACCCACGGCCCCTCCGAGAGAGTCACCCCAGTACTCACCTAGAGTGGACCA
GATCGTGGGGCGGGGCCCAGCGATCACGGACAAGGACCGCACCAAGGGCCCGGCCG
AGGCGGAGCTGCCCGAGGACCCCAGCATGATGGGACGGCTCGGGAAGGTGGAGAA
GCAGGTCTTGTCCATGGAGAAGAAGCTGGACTTCCTGGTGAATATCTACATGCAGCG
GATGGGCATCCCCCCGACAGAGACCGAGGCCTACTTTGGGGCCAAAGAGCCGGAGC
CGGCGCCGCCGTACCACAGCCCGGAAGACAGCCGGGAGCATGTCGACAGGCACGGC
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GACCTTTTACAAAAGTTATTTTCCAACAGGGGCTGGAGGGCTGGGCAGGGCCCTGTG
GCTCCAGGAGCAGCGTGCAGGAGCAAGGCTGCCCTGTCCACTCTGCTCAGGGCCGC
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GCCTGTTCCCTGAGGACCTGCGCAAAGGGCGGGCCTGTTTGGTGAGGACCTGCGGCC
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GGCTGGGGTCGTGGGCGCAAATACTCCTGCAGAGCAAGTGCAGGGGAGTCCTGGGC
CCGTTTCTCCTCCACCTGCGTTTTCAGTGCACTTGGCTTGGCTGGGAGGTCCTGAGGC
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AGGGTCGTACGCCCCTGGCTGGTGGGGGTCCTGGCGCTCAGGGTGTTCGGGGAGCCA
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CCGAGGTGTGACCCCACCTGCTCTTTCCTCCCTCCCAGTATGGCCCCACCTGCTCTTT
CCTCCCCCGAGGTGAGGCCCCGCCTGCTCTTTCCTCCCATGGGGCCGCTGAGGCATG
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CCTCCCAGAAGCTGGCCGCCCAGCAGGAGGGACTGAGGCCAGACTCATGTCCAGCA
AGGAACGTGTGGTGTGTCCCCTGGGAAGTCTCTGGGCCCTGGGAAGAGGGAAGGTG
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TCTACCAGATGCCAAGGTGCCCCGGTGTCTGTATGGGTGTCCGGTTGGGTCCTGTGTT
TGGTCTGCCCTGGAGGTGCTGGGCCCTCCTGGGATGGGTGGCTCAGCCTCGAATCCC
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CACGCTGGGGGAGGGCTCCTCCCATGCCTCCTGCACACAGCCGTCTGAGCAGGGCA
GGTGCCCAACACCCCCCACCGGAGGACACGCTGCCCCTCAGCGATGCCCCTACCTTT
TGGGGGGCCTCGTCTCAAGCCCCCCCTTGGAGGCTGAAATCACCCCAGGCACTGTGA
GGGCTTCTCCAGGGGGCACCCTTTGAGCTGTGGGTCTGATCACCCCAAGTCCCGCCC
GGAGGAGAGGCACAGCCAGGGCGTGTGGTTTAATGTTTGCCCCCTTCGGGGCTGGA
GGTCTCAGTGTTTCTAGATTCCAGACCCTGCTGCCAGAGAGACCTGCTGCCGGAGAG
AAGGGGAGGAGGACTCCAGCTGGGCTCGGTCCCCCACAGTCAGGGACCCCCATAAA
GGACACCCCCTTCTCTCTAGAAAGAGCTGGGCTCTCAGCTATTTCTAGTTGCTTCCCA
GAAGCCGAGGAGCAGAAGGAGCTGTGAGAGCTTTGCAGAAACGCCCTTGTCCCCGC
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CGTGTGAGAGGGACGGTTCACAAGGCTTGGACCTGCCATGGAGGGTGCCCAGCAGA
CGTGGTGTGAGAGGGACAGCTCACGAGGCTTGGACCTGCTGTGGAGGGTGCCCAGC
AGGGGGCTGAGCTCTGAGGGGTGGGTGCTCAGTGCACGGGTGCCCCCAGTGTCCTCT
GATCCTGTCCGGTGCCTCCCCCAACCCCCACACCCATGCAGAACTCCCAGGTCACAT
GCACGTATGTCCAGGGCATGGGGGTGGCGTGAAGAGGCCTGGTCAGGGCCTTTAGG
GGCTGCAGGACGGAATGGCCGCCTGGGGAGCCTGTGTGGCTGTGCCGGGCAGCCAT
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CCGGAGAGACAGCCAGGGCGGCTTCCTGAAGGATGTGGGATGGTGGACTCCGGGGT
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GGAGCTTTCCATGACCCGGGAGCATGAGTGAATGGGGGTTCCAGTTTGCTGAACTTT
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GGGGAGGTTGTGGGCAACGGTGGAGGAGGAGAGACGGGAGGGGACCATTTGGGAT
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GGGCCCCGTCCTGAGAGGTCCTCAGCGTCTGACTCTCGGCCAGGCGCCAGCAAGGA
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CAACTCCGCCTGGGTTTTACAAAGTCGTTGCCTTAATGCATGTGGACAGGAACTCCC
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CAGGTGGGGCGGGCGAGGGGCCCAAGGGACGGGCTCCAGAGACACGCGCAGGGCA
GGAGGGGTCTCACGGAGGGGTCTCGCACTGAGGCGCCCAGAGCTGGTGGTCCCGCT
GGACGCCATCCCTCTGCCCGGGATCCACACGGCCCACGTGTGCCCGCCATGCCCGCG

CCCCACGCCATTGCAGTCTGCCATCCTCTGGCCGTGACGGTGGCTGCAGCTTCCCCA
TTTGCGCCGTTGCCTCTGGCTGTCTGCACTTTTGTTCATGCTCCAAAGAACATTTCAT
AATGCCTTCAGTACCGACGTACACTTCTGACCATTTTGTATGTGTCCTTGTGCCGTAG
TGACCAGGCCTTTTTTTGGTGGATGTGTTACCCCGCACACTTCAATCTCAACTTTGTG
CACCGTCCATTTTCTAGGGATAGACGCCCAGGGAATGAACTCTAGTTTTCTAACAGA
TTAGCTGAGATATTAACTTACTCACACGGACAGGTTGATGCCAGAGCCGTAAGAATG
CGCCAGTGCGGGTTTGCGGGGGACTTCGGGTGTGGGGTCCTGCGGCCGCGATGGCCG
TGGAAGGTTCTGGGGATCCCTGCTGCCACGGGGACGAGTTCGGACGCCAGGTGGAC
CTGTGCACTCAGTAAAACGCAGTGATTCAACCTGGA
(SEQ ID NO: 3040) (Source: NCBI Reference Sequence: XM_017027841.2)

[00327] In various embodiments, a KCNQ2 mRNA transcript comprises the sequence provided as SEQ ID NO: 3041.

AGCGTCTCCGCGCGCGGCCCAAGCCCGGCAGGAGTGCGGAACCGCCGCCTCGGCCA
TGCGGCTCCCGGCCGGGGGGCCTGGGCTGGGGCCCGCGCCGCCCCCCGCGCTCCGCC
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GTCGCGCAACGGCGGCGTATACCCCGGCCCGAGCGGGGAGAAGAAGCTGAAGGTGG
GCTTCGTGGGGCTGGACCCCGGCGCGCCCGACTCCACCCGGGACGGGGCGCTGCTG
ATCGCCGGCTCCGAGGCCCCCAAGCGCGGCAGCATCCTCAGCAAACCTCGCGCGGG
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ATTTCCTCTACAACGTGCTGGAGCGGCCGCGCGGCTGGGCGTTCATCTACCACGCCT
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GTATGAGAAGAGCTCGGAGGGGGCCCTCTACATCCTGGAAATCGTGACTATCGTGGT
GTTTGGCGTGGAGTACTTCGTGCGGATCTGGGCCGCAGGCTGCTGCTGCCGGTACCG
TGGCTGGAGGGGGCGGCTCAAGTTTGCCCGGAAACCGTTCTGTGTGATTGACATCAT
GGTGCTCATCGCCTCCATTGCGGTGCTGGCCGCCGGCTCCCAGGGCAACGTCTTTGC
CACATCTGCGCTCCGGAGCCTGCGCTTCCTGCAGATTCTGCGGATGATCCGCATGGA
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GTACTTGGCAGAGAAGGGGGAGAACGACCACTTTGACACCTACGCGGATGCACTCT
GGTGGGGCCTGATCACGCTGACCACCATTGGCTACGGGGACAAGTACCCCCAGACC
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GCCCCAGCAAGGTGCCCAAGAGCTGGAGCTTCGGGGACCGCAGCCGGGCACGCCAG
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CGGAGAGGACATTGTGGATGACAAGAGCTGCCCCTGCGAGTTTGTGACCGAGGACC
TGACCCCGGGCCTCAAAGTCAGCATCAGAGCCGTGTGTGTCATGCGGTTCCTGGTGT
CCAAGCGGAAGTTCAAGGAGAGCCTGCGGCCCTACGACGTGATGGACGTCATCGAG
CAGTACTCAGCCGGCCACCTGGACATGCTGTCCCGAATTAAGAGCCTGCAGTCCAGG
CAAGAGCCCCGCCTGCCTGTCCAGCAGGGGACAAGAACGGGAGTGGACCAGATCGT
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GAGCTGCCCGAGGACCCCAGCATGATGGGACGGCTCGGGAAGGTGGAGAAGCAGGT
CTTGTCCATGGAGAAGAAGCTGGACTTCCTGGTGAATATCTACATGCAGCGGATGGG
CATCCCCCCGACAGAGACCGAGGCCTACTTTGGGGCCAAAGAGCCGGAGCCGGCGC
CGCCGTACCACAGCCCGGAAGACAGCCGGGAGCATGTCGACAGGCACGGCTGCATT
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CCCCACCTGCTCTTTCCTCCCTCCCAGTATGGCCCCACCTGCTCTTTCCTCCCCCGAG
GTGAGGCCCCGCCTGCTCTTTCCTCCCATGGGGCCGCTGAGGCATGAGCACCTGGGC
ACAGGTTGGGGCTCTGCAGGATGAGGAAGACAGGCCAATCCCTTCCCTCCCAGAAG
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ACGTGTAGCTCACACACAGTATACACATACACAAGTGCACAGACCACACACAGCAC
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GACCACACAGCACACACAAGTGCACAGAGCACACTGCACACATGCACACACACACG
CGTGCATGCACACTCCTCGCACTTCCAGCCTTGGAGCCCTTCTGTCTCTGGTCTTTCT
CTTTGACCCTGCTGAGTGTAAGCTGCCTGGGGAGGGGCTACAAGGAGTAATTGTGGC
TTTAGGGGTCGTGGTGATGCTGGAATGTCAAGCGCCGTCGTGGGGTATCCGACTGTC
CGGGCTCCTGGTCCGCAGTGGCAGAGCGCCAGGCAGAGCCCAATCAGGGTCTCGTG
CTGCCCTTCCCTCCCACAGCCTGGCAGCCATCCAGAGGAGGGGCTCTACCAGATGCC
AAGGTGCCCCGGTGTCTGTATGGGTGTCCGGTTGGGTCCTGTGTTTGGTCTGCCCTGG
AGGTGCTGGGCCCTCCTGGGATGGGTGGCTCAGCCTCGAATCCCAGGCCCCAGCCCA
GGCAGGTGCTGCTGCCTGTTGTGGTTTCCTGGCCCAGCTTCTCCTTCTCCCTCTGCAT
AAAATCACAGTCCGTGAGTCTTCCAGCTGCCACCACGGCTGGGACACGCTGGGGGA
GGGCTCCTCCCATGCCTCCTGCACACAGCCGTCTGAGCAGGGCAGGTGCCCAACACC
CCCCACCGGAGGACACGCTGCCCCTCAGCGATGCCCCTACCTTTTGGGGGGCCTCGT
CTCAAGCCCCCCCTTGGAGGCTGAAATCACCCCAGGCACTGTGAGGGCTTCTCCAGG
GGGCACCCTTTGAGCTGTGGGTCTGATCACCCCAAGTCCCGCCCGGAGGAGAGGCA
CAGCCAGGGCGTGTGGTTTAATGTTTGCCCCCTTCGGGGCTGGAGGTCTCAGTGTTTC
TAGATTCCAGACCCTGCTGCCAGAGAGACCTGCTGCCGGAGAGAAGGGGAGGAGGA
CTCCAGCTGGGCTCGGTCCCCCACAGTCAGGGACCCCCATAAAGGACACCCCCTTCT
CTCTAGAAAGAGCTGGGCTCTCAGCTATTTCTAGTTGCTTCCCAGAAGCCGAGGAGC
AGAAGGAGCTGTGAGAGCTTTGCAGAAACGCCCTTGTCCCCGCCCTCCTGAGCTATG
AATGCCGTACAGAGCAGAGGCTGGGGCATTGGCAAGATCACAGGTTGATGCTGCAC
AGCCCCATTGACACAAACCCTCAAAGCAGACGTGAGAGGGACGGTTCACAAAGCTC
GGACCTGCCGTGGAGGGTGCCCGGCAGACGTGGCGTGAGAGGGACGGCTCACGAGG
CTTGGACCTGCTGTGGAGGGTGCCCAGCAGACGTGGTGTGAGAGGAACGGCTCACG
AGACTTGGACCTGGTGGAGGGTGCCCAGCAGACGTGGTGTGAGAGGGACGGCTCAC
AGGGCTTGGACCTGCCATGGAGGGTGCCCGGCAGACGTGGTGTGAGAGGGATGGTT
CACAGGGCTTGGACCTGCCATGGAGGGTGCCCGGCAGATGTGGTGGGAGAGAGATG
GCTCATGAGGCTTGGACCTGCCGTGGAGGGTGCCCAGCAGACGTGGTATGAGAGGG
ATGGCTCACGAGGCTTGGACCTGGTGGAGGGTGCCCGGCAGACGTGTGAGAGGGAC

GGTTCACAAGGCTTGGACCTGCCATGGAGGGTGCCCAGCAGACGTGGTGTGAGAGG
GACAGCTCACGAGGCTTGGACCTGCTGTGGAGGGTGCCCAGCAGGGGGCTGAGCTC
TGAGGGGTGGGTGCTCAGTGCACGGGTGCCCCCAGTGTCCTCTGATCCTGTCCGGTG
CCTCCCCCAACCCCCACACCCATGCAGAACTCCCAGGTCACATGCACGTATGTCCAG
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ATGGCCGCCTGGGGAGCCTGTGTGGCTGTGCCGGGCAGCCATCCTGCATTCCCACCC
AGCGCGCAGTCTCCACCTCGGCCCCAGCAAAGCGCTAAGCAGCCGGAGAGACAGCC
AGGGCGGCTTCCTGAAGGATGTGGGATGGTGGACTCCGGGGTCGAGGGAATACGCA
GGTTCCTGTCCCTCCGGGAGACCTAGAGAAGCTGCACACCCAGGAGCTTTCCATGAC
CCGGGAGCATGAGTGAATGGGGGTTCCAGTTTGCTGAACTTTGCCGTCTTGTAAGGG
TGGGGGCTGACGGCCGACCCTGGGAGGAGGTGACATCGCCGGGGGAGGTTGTGGGC
AACGGTGGAGGAGGAGAGACGGGAGGGGACCATTTGGGATGGAGGGGCCTCTTCAG
AGTTTTAAAAGGCGTTTGTGGGGTGGAGTTGAGTGTGCTCTGGGCTTGGACACTTGC
CGTGGTGCCCCTGGCTGGCCGAGGAGACTGGCTCTGGCCAGGGGCCCCGTCCTGAG
AGGTCCTCAGCGTCTGACTCTCGGCCAGGCGCCAGCAAGGAGGGGCCGGTCCCCGG
GGCTACCAGGCAGGCACGTGCACATCGCCATCGCCACACGCCAACTCCGCCTGGGTT
TTACAAAGTCGTTGCCTTAATGCATGTGGACAGGAACTCCCTGAGGTCGCCCCATGC
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AGGGGCCCAAGGGACGGGCTCCAGAGACACGCGCAGGGCAGGAGGGGTCTCACGG
AGGGGTCTCGCACTGAGGCGCCCAGAGCTGGTGGTCCCGCTGGACGCCATCCCTCTG
CCCGGGATCCACACGGCCCACGTGTGCCCGCCATGCCCGCGCCCCACGCCATTGCAG
TCTGCCATCCTCTGGCCGTGACGGTGGCTGCAGCTTCCCCATTTGCGCCGTTGCCTCT
GGCTGTCTGCACTTTTGTTCATGCTCCAAAGAACATTTCATAATGCCTTCAGTACCGA
CGTACACTTCTGACCATTTTGTATGTGTCCTTGTGCCGTAGTGACCAGGCCTTTTTTT
GGTGGATGTGTTACCCCGCACACTTCAATCTCAACTTTGTGCACCGTCCATTTTCTAG
GGATAGACGCCCAGGGAATGAACTCTAGTTTTCTAACAGATTAGCTGAGATATTAAC
TTACTCACACGGACAGGTTGATGCCAGAGCCGTAAGAATGCGCCAGTGCGGGTTTGC
GGGGGACTTCGGGTGTGGGGTCCTGCGGCCGCGATGGCCGTGGAAGGTTCTGGGGA
TCCCTGCTGCCACGGGGACGAGTTCGGACGCCAGGTGGACCTGTGCACTCAGTAAAA
CGCAGTGATTCAACCTGGA

(SEQ ID NO: 3041) (Source: NCBI Reference Sequence: XM_017027842.2)

[00328] In various embodiments, a KCNQ2 mRNA transcript comprises the sequence provided as SEQ ID NO: 3042.

CTCCTAGGCCCAAGCTGTCCTCCTGCCTCGGCCTCGCCAAGCTCTGGGAGTACAGGC
GTGGCCGCCGGGCCTGGCCTGTTTGCTTCGGATGTTTCGTGTAAGTGGAGTTGTCATC
GTGGTGCCGTTTTGTGCCTGGCTTTCCTTGCCGAGCCTGCCCTCAGGTTCCTTCGTGT
TTAGGGTACTCCTTCATCCTCTCCGTGTCTGGGGGCCGCTGCCTCGTCCTTCCTGTGG
CCGCACGGACGGACCTCAGTTTATCTACCCACCCACCAACTGGATGTTGGGTTGCGT
CTGCCGTGAGGCTGCTGTGGACACGCGGTTCCTCCTGGTTTTCTCCTGCCTCGTGCTG
TCTGTGTTTTCCACCATCAAGGAGTATGAGAAGAGCTCGGAGGGGGCCCTCTACATC
CTGGAAATCGTGACTATCGTGGTGTTTGGCGTGGAGTACTTCGTGCGGATCTGGGCC
GCAGGCTGCTGCTGCCGGTACCGTGGCTGGAGGGGGCGGCTCAAGTTTGCCCGGAA
ACCGTTCTGTGTGATTGACATCATGGTGCTCATCGCCTCCATTGCGGTGCTGGCCGCC
GGCTCCCAGGGCAACGTCTTTGCCACATCTGCGCTCCGGAGCCTGCGCTTCCTGCAG
ATTCTGCGGATGATCCGCATGGACCGGCGGGGAGGCACCTGGAAGCTGCTGGGCTCT
GTGGTCTATGCCCACAGCAAGGAGCTGGTCACTGCCTGGTACATCGGCTTCCTTTGT

CTCATCCTGGCCTCGTTCCTGGTGTACTTGGCAGAGAAGGGGGAGAACGACCACTTT
GACACCTACGCGGATGCACTCTGGTGGGGCCTGATCACGCTGACCACCATTGGCTAC
GGGGACAAGTACCCCCAGACCTGGAACGGCAGGCTCCTTGCGGCAACCTTCACCCTC
ATCGGTGTCTCCTTCTTCGCGCTGCCTGCAGGCATCTTGGGGTCTGGGTTTGCCCTGA
AGGTTCAGGAGCAGCACAGGCAGAAGCACTTTGAGAAGAGGCGGAACCCGGCAGC
AGGCCTGATCCAGTCGGCCTGGAGATTCTACGCCACCAACCTCTCGCGCACAGACCT
GCACTCCACGTGGCAGTACTACGAGCGAACGGTCACCGTGCCCATGTACAGTTCGCA
AACTCAAACCTACGGGGCCTCCAGACTTATCCCCCCGCTGAACCAGCTGGAGCTGCT
GAGGAACCTCAAGAGTAAATCTGGACTCGCTTTCAGGAAGGACCCCCCGCCGGAGC
CGTCTCCAAGCCAGAAGGTCAGTTTGAAAGATCGTGTCTTCTCCAGCCCCCGAGGCG
TGGCTGCCAAGGGGAAGGGGTCCCCGCAGGCCCAGACTGTGAGGCGGTCACCCAGC
GCCGACCAGAGCCTCGAGGACAGCCCCAGCAAGGTGCCCAAGAGCTGGAGCTTCGG
GGACCGCAGCCGGGCACGCCAGGCTTTCCGCATCAAGGGTGCCGCGTCACGGCAGA
ACTCAGAAGAAGCAAGCCTCCCCGGAGAGGACATTGTGGATGACAAGAGCTGCCCC
TGCGAGTTTGTGACCGAGGACCTGACCCCGGGCCTCAAAGTCAGCATCAGAGCCGTG
TGTGTCATGCGGTTCCTGGTGTCCAAGCGGAAGTTCAAGGAGAGCCTGCGGCCCTAC
GACGTGATGGACGTCATCGAGCAGTACTCAGCCGGCCACCTGGACATGCTGTCCCGA
ATTAAGAGCCTGCAGTCCAGGATAGATATGATTGTGGGTCCCCCGCCCCCTTCAACT
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CCAGTACTCACCTAGAGTGGACCAGATCGTGGGGCGGGGCCCAGCGATCACGGACA
AGGACCGCACCAAGGGCCCGGCCGAGGCGGAGCTGCCCGAGGACCCCAGCATGATG
GGACGGCTCGGGAAGGTGGAGAAGCAGGTCTTGTCCATGGAGAAGAAGCTGGACTT
CCTGGTGAATATCTACATGCAGCGGATGGGCATCCCCCCGACAGAGACCGAGGCCT
ACTTTGGGGCCAAAGAGCCGGAGCCGGCGCCGCCGTACCACAGCCCGGAAGACAGC
CGGGAGCATGTCGACAGGCACGGCTGCATTGTCAAGATCGTGCGCTCCAGCAGCTCC
ACGGGCCAGAAGAACTTCTCGGCGCCCCCGGCCGCGCCCCCTGTCCAGTGTCCGCCC
TCCACCTCCTGGCAGCCACAGAGCCACCCGCGCCAGGGCCACGGCACCTCCCCCGTG
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TCCGCCTACGGCGGGGGCAACCGCGCCAGCATGGAGTTCCTGCGGCAGGAGGACAC
CCCGGGCTGCAGGCCCCCCGAGGGGAACCTGCGGGACAGCGACACGTCCATCTCCA
TCCCGTCCGTGGACCACGAGGAGCTGGAGCGTTCCTTCAGCGGCTTCAGCATCTCCC
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CCTCCTCAGCACGGTGCCTCCGAGGTTTTGAGGCGGGAACCCTCTGGGGCCCTTTTCT
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AGGGCTGGGCAGGGCCCTGTGGCTCCAGGAGCAGCGTGCAGGAGCAAGGCTGCCCT
GTCCACTCTGCTCAGGGCCGCGGCCGACATCAGCCCGGTGTGAGGAGGGGCGGGAG
TGATGACGGGGTGTTGCCAGCGTGGCAACAGGCGGGGGGTTGTCTCAGCCGAGCCC
AGGGGAGGCACAAAGGGCAGGCCTGTTCCCTGAGGACCTGCGCAAAGGGCGGGCCT
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GGTGTGGCCGGCCGCTGTGCGTGGCCTCTGCCTTCACACCTGACCTGCCCGGCGGGC
TTTCCTGTTCCCCACCTCAGGGGCGCCCAAATACAGAGCTATTGGTTGGCGTCTTCTC
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CCTTCGCCTGCAGCCGAGGAGCGGGTGGGGCCTGGGAACCAAACTGGAGCCAGAGT
GGACGTCCAGCCCTCTGGTCTTGGCCTCCAGAGGGAGGGCCTGGCTCACGGTGGGGC
CAGGGAGCCGGCTCCAAAGGGTCTTCAAAAAGGGGGTCCTTGGGGGCTCCAGCTGC

CTCGCCCTGGCCTTTCTGTGGGTGCGTGAGAGCCAGCAGCACCCCAGCCTTGGAGAC
CGGGGGGGCAGGACCCCAAGTCCTCCCCTCTCTCCTGACTGCCCTGGCCGGGTGCCG
GCACTGCGAGACCCACCTGGTGAGCAGGCCTCACAGTTCTTAGCCAGGGCCCCACCT
CGCCTGTGTCCCACCAGTGCCCCGACAGACCTGGGGCAGGGCTGGGCCATGATGCA
GCGGGCCAGGATAGCCTCCACCGTCAGCACAGGGCCGCCCTCCCCGCCTTTCCGGAG
GAAACCACTCCCACCTCAGCCCAGCTGTGCGCCCTCCCTAGCTCTCCTGCCCCCTGG
AGCTGATGGCCCCTTCTCCACTGACCGATTCCTTAGCGGGGCCTCTTGGGGTCTCGG
GCCTCGGGTGCACCGTCCCATGCCCGTCCTGTTGTGGGCACCGTGGCCCTTGGGGCA
GGCGGCTCTAATGCGGGAGCGAGTCCCTAGCTCCAGACTTAAGAACCAGACCCCGG
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GGCCTCCCTGGGAGTGAGCAGGGCTGGGGTCGTGGGCGCAAATACTCCTGCAGAGC
AAGTGCAGGGGAGTCCTGGGCCCGTTTCTCCTCCACCTGCGTTTTCAGTGCACTTGGC
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GGACTTTGAAAGCAGCATTTGAGGGTCGTACGCCCCTGGCTGGTGGGGGTCCTGGCG
CTCAGGGTGTTCGGGGAGCCATGTCTGGCGTCCATTGTGGGGAGCTGCTGCCCTGGC
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GCCTCCGCTGGGCTGTCTCCTCACCCCTCCCTGTGCTGGAGCCTGTCCCAAAAAGGT
GCCAACTGGGAGGCCTCGGAAGCCACTGTCCAGGCTCCCACTGCCTGTCTGCTCTGT
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CCCTTGGGCTGGCTCGAGCCTGGGGTCCATGTCCCTTTGCCGTCCCGTCATGGGGCA
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CAGGACCCTGGAGAAGGGAGACCTGGCAGTGGAGGGAGGCTGTGCTGTGTGTCCCC
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CACCTGTTCTTTCCTCCCCTGCCGAGGTGTGACCCCACCTGCTCTTTCCTCCCTCCCA
GTATGGCCCCACCTGCTCTTTCCTCCCCCGAGGTGAGGCCCCGCCTGCTCTTTCCTCC
CATGGGGCCGCTGAGGCATGAGCACCTGGGCACAGGTTGGGGCTCTGCAGGATGAG
GAAGACAGGCCAATCCCTTCCCTCCCAGAAGCTGGCCGCCCAGCAGGAGGGACTGA
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CCTGGGAAGAGGGAAGGTGCACGTCCTGGGATGGTTGCGGGGCCCTGTTTTGGGAG
ACAAAGGGGTAGAGGGTCTGTCTTGGGCCCCCCCAGACTCTAGCCTGAGCAGTGCA
GCCACCTACTGCCCCACCTCAGAGAAGTGCAGCGGGAAGGAGGCTGGAGGTGGTGC
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TGCACACAGACCACATAGCACACATGTGCACTGACCACACCTGTATAGACCATGCAC
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GTACACGTGCACAGATCACACACATGCACACACGTGTAGCTCACACACAGTATACA
CATACACAAGTGCACAGACCACACACAGCACTAACACATGCACACACAAAGTGCAT
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GCGCCAGGCAGAGCCCAATCAGGGTCTCGTGCTGCCCTTCCCTCCCACAGCCTGGCA
GCCATCCAGAGGAGGGGCTCTACCAGATGCCAAGGTGCCCCGGTGTCTGTATGGGTG
TCCGGTTGGGTCCTGTGTTTGGTCTGCCCTGGAGGTGCTGGGCCCTCCTGGGATGGGT

GGCTCAGCCTCGAATCCCAGGCCCCAGCCCAGGCAGGTGCTGCTGCCTGTTGTGGTT
TCCTGGCCCAGCTTCTCCTTCTCCCTCTGCATAAAATCACAGTCCGTGAGTCTTCCAG
CTGCCACCACGGCTGGGACACGCTGGGGGAGGGCTCCTCCCATGCCTCCTGCACACA
GCCGTCTGAGCAGGGCAGGTGCCCAACACCCCCCACCGGAGGACACGCTGCCCCTC
AGCGATGCCCCTACCTTTTGGGGGGCCTCGTCTCAAGCCCCCCCTTGGAGGCTGAAA
TCACCCCAGGCACTGTGAGGGCTTCTCCAGGGGGCACCCTTTGAGCTGTGGGTCTGA
TCACCCCAAGTCCCGCCCGGAGGAGAGGCACAGCCAGGGCGTGTGGTTTAATGTTTG
CCCCCTTCGGGGCTGGAGGTCTCAGTGTTTCTAGATTCCAGACCCTGCTGCCAGAGA
GACCTGCTGCCGGAGAGAAGGGGAGGAGGACTCCAGCTGGGCTCGGTCCCCCACAG
TCAGGGACCCCCATAAAGGACACCCCCTTCTCTCTAGAAAGAGCTGGGCTCTCAGCT
ATTTCTAGTTGCTTCCCAGAAGCCGAGGAGCAGAAGGAGCTGTGAGAGCTTTGCAGA
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CATTGGCAAGATCACAGGTTGATGCTGCACAGCCCCATTGACACAAACCCTCAAAGC
AGACGTGAGAGGGACGGTTCACAAAGCTCGGACCTGCCGTGGAGGGTGCCCGGCAG
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CAGACGTGGTGTGAGAGGAACGGCTCACGAGACTTGGACCTGGTGGAGGGTGCCCA
GCAGACGTGGTGTGAGAGGGACGGCTCACAGGGCTTGGACCTGCCATGGAGGGTGC
CCGGCAGACGTGGTGTGAGAGGGATGGTTCACAGGGCTTGGACCTGCCATGGAGGG
TGCCCGGCAGATGTGGTGGGAGAGAGATGGCTCATGAGGCTTGGACCTGCCGTGGA
GGGTGCCCAGCAGACGTGGTATGAGAGGGATGGCTCACGAGGCTTGGACCTGGTGG
AGGGTGCCCGGCAGACGTGTGAGAGGGACGGTTCACAAGGCTTGGACCTGCCATGG
AGGGTGCCCAGCAGACGTGGTGTGAGAGGGACAGCTCACGAGGCTTGGACCTGCTG
TGGAGGGTGCCCAGCAGGGGGCTGAGCTCTGAGGGGTGGGTGCTCAGTGCACGGGT
GCCCCCAGTGTCCTCTGATCCTGTCCGGTGCCTCCCCCAACCCCCACACCCATGCAG
AACTCCCAGGTCACATGCACGTATGTCCAGGGCATGGGGGTGGCGTGAAGAGGCCT
GGTCAGGGCCTTTAGGGGCTGCAGGACGGAATGGCCGCCTGGGGAGCCTGTGTGGC
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GCAAAGCGCTAAGCAGCCGGAGAGACAGCCAGGGCGGCTTCCTGAAGGATGTGGGA
TGGTGGACTCCGGGGTCGAGGGAATACGCAGGTTCCTGTCCCTCCGGGAGACCTAGA
GAAGCTGCACACCCAGGAGCTTTCCATGACCCGGGAGCATGAGTGAATGGGGGTTC
CAGTTTGCTGAACTTTGCCGTCTTGTAAGGGTGGGGGCTGACGGCCGACCCTGGGAG
GAGGTGACATCGCCGGGGGAGGTTGTGGGCAACGGTGGAGGAGGAGAGACGGGAG
GGGACCATTTGGGATGGAGGGGCCTCTTCAGAGTTTTAAAAGGCGTTTGTGGGGTGG
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ACTGGCTCTGGCCAGGGGCCCCGTCCTGAGAGGTCCTCAGCGTCTGACTCTCGGCCA
GGCGCCAGCAAGGAGGGGCCGGTCCCCGGGGCTACCAGGCAGGCACGTGCACATCG
CCATCGCCACACGCCAACTCCGCCTGGGTTTTACAAAGTCGTTGCCTTAATGCATGT
GGACAGGAACTCCCTGAGGTCGCCCCATGCCCCCTGGCTGTGCCAGGTACGGACGCC
CTGGACCCTGCGAACAGGTGGGGCGGGCGAGGGGCCCAAGGGACGGGCTCCAGAG
ACACGCGCAGGGCAGGAGGGGTCTCACGGAGGGGTCTCGCACTGAGGCGCCCAGAG
CTGGTGGTCCCGCTGGACGCCATCCCTCTGCCCGGGATCCACACGGCCCACGTGTGC
CCGCCATGCCCGCGCCCCACGCCATTGCAGTCTGCCATCCTCTGGCCGTGACGGTGG
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AAGAACATTTCATAATGCCTTCAGTACCGACGTACACTTCTGACCATTTTGTATGTGT
CCTTGTGCCGTAGTGACCAGGCCTTTTTTTGGTGGATGTGTTACCCCGCACACTTCAA
TCTCAACTTTGTGCACCGTCCATTTTCTAGGGATAGACGCCCAGGGAATGAACTCTA
GTTTTCTAACAGATTAGCTGAGATATTAACTTACTCACACGGACAGGTTGATGCCAG
AGCCGTAAGAATGCGCCAGTGCGGGTTTGCGGGGGACTTCGGGTGTGGGGTCCTGC

GGCCGCGATGGCCGTGGAAGGTTCTGGGGATCCCTGCTGCCACGGGGACGAGTTCG
GACGCCAGGTGGACCTGTGCACTCAGTAAAACGCAGTGATTCAACCTGGA
(SEQ ID NO: 3042) (Source: NCBI Reference Sequence: XM_017027843.1)

[00329] In various embodiments, a KCNQ2 mRNA transcript comprises the sequence provided as SEQ ID NO: 3043.

GTTCTTGGTGATTGGTTTCATTTTTTGCTTAATCATTTGCACATTGTGATGCAGAGCT
AAATCGCCAGGGTTTTTGGGGAGATTCTTGGGAAAACGTTCCGTGTTTTCTGAGCCTT
TTCTAAGGAACGCCCCGGCGGGGAGCTGCGCTCCTGAAGGGCTTCACAATGAGGGG
ATCCACTGAGCCCCAACGTGACTGTCCTCAGGGGAGCCCTTGAACCCCCAGATAGCC
ATGCCTGCAGTGGCAGCCACGCCTCCTGGGTAAACCGAGACCCACCTCCAACTGGG
GGACTGGCTGGCATGGCCAAACGTCGCCGATTGGTTTGCAAAGCGGGACAACTGCA
CGTTTTCCTCTCTCAAATGTGTGTGCTTCACACCCACGCCCTTTCCCGGGGTCACGTC
CTTCCCAAGCAGGGCTTCTGCGGCGTCTGAGGCCACATGTATTATTGTTTTGTCAGCA
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GTGCCTCAGTTTCCCTGCTCCCGGCCGTGTGCTGTTGCCGGCGCCCAGGACTAACTGT
GCTCTCCTCATTTCCAGTAAAGGCAGCCCGTGCAGAGGGCCCCTGTGTGGATGCTGC
CCCGGACGCTCTAGCCAGAAGGTCAGTTTGAAAGATCGTGTCTTCTCCAGCCCCCGA
GGCGTGGCTGCCAAGGGGAAGGGGTCCCCGCAGGCCCAGACTGTGAGGCGGTCACC
CAGCGCCGACCAGAGCCTCGAGGACAGCCCCAGCAAGGTGCCCAAGAGCTGGAGCT
TCGGGGACCGCAGCCGGGCACGCCAGGCTTTCCGCATCAAGGGTGCCGCGTCACGG
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CCCCTGCGAGTTTGTGACCGAGGACCTGACCCCGGGCCTCAAAGTCAGCATCAGAGC
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CCGAATTAAGAGCCTGCAGTCCAGGATAGATATGATTGTGGGTCCCCCGCCCCCTTC
AACTCCCCGGCACAAGAAGTACCCCACCAAAGGACCCACGGCCCCTCCGAGAGAGT
CACCCCAGTACTCACCTAGAGTGGACCAGATCGTGGGGCGGGGCCCAGCGATCACG
GACAAGGACCGCACCAAGGGCCCGGCCGAGGCGGAGCTGCCCGAGGACCCCAGCAT
GATGGGACGGCTCGGGAAGGTGGAGAAGCAGGTCTTGTCCATGGAGAAGAAGCTGG
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CCTACTTTGGGGCCAAAGAGCCGGAGCCGGCGCCGCCGTACCACAGCCCGGAAGAC
AGCCGGGAGCATGTCGACAGGCACGGCTGCATTGTCAAGATCGTGCGCTCCAGCAG
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GCCCTCCACCTCCTGGCAGCCACAGAGCCACCCGCGCCAGGGCCACGGCACCTCCCC
CGTGGGGGACCACGGCTCCCTGGTGCGCATCCCGCCGCCGCCTGCCCACGAGCGGTC
GCTGTCCGCCTACGGCGGGGGCAACCGCGCCAGCATGGAGTTCCTGCGGCAGGAGG
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CTGTACCCCGTGCGGGCCCCCGCCACGCTCGGCCACCGGCGAGGGTCCCTTTGGTGA
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CGGCCCTCCTCAGCACGGTGCCTCCGAGGTTTTGAGGCGGGAACCCTCTGGGGCCCT

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GCTGGAGGGCTGGGCAGGGCCCTGTGGCTCCAGGAGCAGCGTGCAGGAGCAAGGCT
GCCCTGTCCACTCTGCTCAGGGCCGCGGCCGACATCAGCCCGGTGTGAGGAGGGGC
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GGAGACCTTCGCCTGCAGCCGAGGAGCGGGTGGGGCCTGGGAACCAAACTGGAGCC
AGAGTGGACGTCCAGCCCTCTGGTCTTGGCCTCCAGAGGGAGGGCCTGGCTCACGGT
GGGGCCAGGGAGCCGGCTCCAAAGGGTCTTCAAAAAGGGGGTCCTTGGGGGCTCCA
GCTGCCTCGCCCTGGCCTTTCTGTGGGTGCGTGAGAGCCAGCAGCACCCCAGCCTTG
GAGACCGGGGGGGCAGGACCCCAAGTCCTCCCCTCTCTCCTGACTGCCCTGGCCGGG
TGCCGGCACTGCGAGACCCACCTGGTGAGCAGGCCTCACAGTTCTTAGCCAGGGCCC
CACCTCGCCTGTGTCCCACCAGTGCCCCGACAGACCTGGGGCAGGGCTGGGCCATGA
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GGAGGAAACCACTCCCACCTCAGCCCAGCTGTGCGCCCTCCCTAGCTCTCCTGCCCC
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GAGCAAGTGCAGGGGAGTCCTGGGCCCGTTTCTCCTCCACCTGCGTTTTCAGTGCAC
TTGGCTTGGCTGGGAGGTCCTGAGGCCCTGAGGCCAGCAGGGGAACCAGTCCTGAG
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TGAGGTGCCTCCGCTGGGCTGTCTCCTCACCCCTCCCTGTGCTGGAGCCTGTCCCAAA
AAGGTGCCAACTGGGAGGCCTCGGAAGCCACTGTCCAGGCTCCCACTGCCTGTCTGC
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(SEQ ID NO: 3043) (Source: NCBI Reference Sequence: XM_017027845.1)

[00330] In various embodiments, a KCNQ2 transcript is a KCNQ2 pre-mRNA transcript. In various embodiments, a KCNQ2 pre-mRNA transcript comprises a sequence provided as SEQ ID NO: 3044.

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CCCCCCTCCCATCAGAGGCAGGTAGGGCAGCCCAGTGGCAGGAAGTCCCGCCCCCATCAGA
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CGCCCCCATCAGAGGCAGGTAGGGCAGCCCAGTGGCAGGAAGTCCCTCCCCCACCATCAGA
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GGTCCTGCTCAGCCACACCCCGTCTTGAGCTGCCCTTGTCCAGCTGGGCTTTTGTAGACTTAC
TGCAGGGTCTTTGTTTCCAAGTGAGTTCCCACGTAGCTGCAGGCCTCAGCGCACACCCACCGT
GGTGGCCCCTGCCAGCCCAGCAGTGGCCGTGACTCTGTGGATACCAGACTGGTCAGAAGCCC
CCGTCCCTGAGGGCAAAGGAGCCTCCCTCCCTTCTTATTGTCATGAGTGACCTGTGGCCTCAT
TGGAGATCAGCTCAGCTGAATTCTGCATCCTACACACACACATGCACACACGCAAACGTGCA
CACTCTTGCACACATGAACACATGCACACGCGTGCACACAGAAACTTGTGCAATGCACATGA
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TCCCCTCTTCTGGTTTGTGCGTTGGTTCCTGTGCTGCTCTGGGCCTTCTCTCCTTGTCCTGGTG
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GTCCCCATCAGACCCGGTGGGGCCGACGGCTTCAGTGGCACATTACGTAGGAGTAAAGCTCC
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GCAGGAGCAGAACCTCACGGTGCCAGAAGACGGGCTGAGAACGGGGCGCACCCCGTCCATC
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CACTGTGGCCTGGTCCAGGAGGAGAGGGCAGGGGCCCTGCTGCACCCACCCGAACTCATGCT
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CCCGTCCTGTTGTGGGCACCGTGGCCCTTGGGGCAGGCGGCTCTAATGCGGGAGCGAGTCCC
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GAGGCTGGGGCATTGGCAAGATCACAGGTTGATGCTGCACAGCCCCATTGACACAAACCCTC
AAAGCAGACGTGAGAGGGACGGTTCACAAAGCTCGGACCTGCCGTGGAGGGTGCCCGGCAG
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TGAGAGGGATGGTTCACAGGGCTTGGACCTGCCATGGAGGGTGCCCGGCAGATGTGGTGGG
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AGGGATGGCTCACGAGGCTTGGACCTGGTGGAGGGTGCCCGGCAGACGTGTGAGAGGGACG
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TCACGAGGCTTGGACCTGCTGTGGAGGGTGCCCAGCAGGGGGCTGAGCTCTGAGGGGTGGG
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GGAGCTTTCCATGACCCGGGAGCATGAGTGAATGGGGGTTCCAGTTTGCTGAACTTTGCCGT
CTTGTAAGGGTGGGGGCTGACGGCCGACCCTGGGAGGAGGTGACATCGCCGGGGGAGGTTG
TGGGCAACGGTGGAGGAGGAGAGACGGGAGGGGACCATTTGGGATGGAGGGGCCTCTTCAG
AGTTTTAAAAGGCGTTTGTGGGGTGGAGTTGAGTGTGCTCTGGGCTTGGACACTTGCCGTGG
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GTCTGACTCTCGGCCAGGCGCCAGCAAGGAGGGGCCGGTCCCCGGGGCTACCAGGCAGGCA
CGTGCACATCGCCATCGCCACACGCCAACTCCGCCTGGGTTTTACAAAGTCGTTGCCTTAATG
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CTGGACCCTGCGAACAGGTGGGGCGGGCGAGGGGCCCAAGGGACGGGCTCCAGAGACACGC
GCAGGGCAGGAGGGGTCTCACGGAGGGGTCTCGCACTGAGGCGCCCAGAGCTGGTGGTCCC
GCTGGACGCCATCCCTCTGCCCGGGATCCACACGGCCCACGTGTGCCCGCCATGCCCGCGCC
CCACGCCATTGCAGTCTGCCATCCTCTGGCCGTGACGGTGGCTGCAGCTTCCCCATTTGCGCC
GTTGCCTCTGGCTGTCTGCACTTTTGTTCATGCTCCAAAGAACATTTCATAATGCCTTCAGTA
CCGACGTACACTTCTGACCATTTTGTATGTGTCCTTGTGCCGTAGTGACCAGGCCTTTTTTTGG
TGGATGTGTTACCCCGCACACTTCAATCTCAACTTTGTGCACCGTCCATTTTCTAGGGATAGA
CGCCCAGGGAATGAACTCTAGTTTTCTAACAGATTAGCTGAGATATTAACTTACTCACACGG

ACAGGTTGATGCCAGAGCCGTAAGAATGCGCCAGTGCGGGTTTGCGGGGGACTTCGGGTGTG
GGGTCCTGCGGCCGCGATGGCCGTGGAAGGTTCTGGGGATCCCTGCTGCCACGGGGACGAGT
TCGGACGCCAGGTGGACCTGTGCACTCAGTAAAACGCAGTGATTCAACCTGGA

NCBI Reference Sequence NG_009004.2 is SEQ ID NO: 3044.

[00331] In various embodiments, a KCNQ2 pre-mRNA transcript comprises a sequence provided as SEQ ID NO: 3045. NCBI Reference Sequence NC_000020.11 Reference GRCh38.p13 Primary Assembly is SEQ ID NO: 3045.

[00332] In various embodiments, the KCNQ2 transcript shares between 90-100% identity with any one of SEQ ID NO: 3032-3043 or shares between 90-100% identity to a KCNQ2 pre-mRNA transcript comprising SEQ ID NO: 3044 or SEQ ID NO: 3045. In various embodiments, the KCNQ2 transcript shares at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity with SEQ ID NO: 3032-3043or shares at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity with a KCNQ2 pre-mRNA transcript transcribed from SEQ ID NO: 3044 or SEQ ID NO: 3045.

[00333] In various embodiments, KCNQ2 is indirectly regulated by TDP43, and as such is encompassed by the phrase "regulated by TDP43".

KCNQ2 Oligonucleotides Targeting Regions of the KCNQ2 Transcript

[00334] In various embodiments, KCNQ2 AON disclosed herein are complementary to specific regions of KCNQ2 transcripts (for example, a KCNQ2 transcript) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 3032-3045. In some embodiments, a KCNQ2 AON comprises a sequence that is complementary to a specific region of the KCNQ2 transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 3032-3045. In some embodiments, a KCNQ2 AON comprises a sequence that is at least 85% complementary to a specific region of the KCNQ2 transcript. In some embodiments, a KCNQ2 AON comprises a sequence that is at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% complementary to a specific region of the KCNQ2 transcript. In some embodiments, a KCNQ2 AON comprises a sequence that is 90 to 99% complementary to a specific region of the KCNQ2 transcript. In some embodiments, a KCNQ2 AON comprises a sequence that is 90 to 95% complementary to a specific region of the KCNQ2 transcript. In some embodiments, a KCNQ2 AON comprises a sequence that is 95 to 99% complementary to a

specific region of the KCNQ2 transcript. In various embodiments, the KCQN2 transcript is a pre-mRNA transcript and the specific region is intron 4 of the KCNQ2 pre-mRNA transcript. In various embodiments, the KCQN2 transcript is a pre-mRNA transcript and the specific region is intron 5 of the KCNQ2 pre-mRNA transcript. In various embodiments, the specific region is exon 5 of the KCNQ2 pre-mRNA transcript.

[00335] In some embodiments, the KCNQ2 AON (e.g., KCNQ2 AON) has a segment that has, at most, 7 linked nucleosides. In some embodiments, the KCNQ2 AON has a segment that has, at most, 6, 5, 4, 3, or 2 linked nucleosides. The segments of the KCNQ2 AON may be separated from other segments of the KCNQ2 AON through a spacer. The segment of the KCNQ2 AON is complementary to a specific region of the KCNQ2 transcript (for example, a KCNQ2 transcript) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 3032-3045.

KCNQ2 Oligonucleotide Variants

[00336] In various embodiments, KCNQ2 AONs include different variants, hereafter referred to as KCNQ2 AON variants. A KCNQ2 AON variant may be an oligonucleotide sequence of 5 to 100 nucleobases in length, for example, 10 to 40 nucleobases in length, for example, 14 to 40 nucleobases in length, 10 to 30 nucleobases in length, for example, 14 to 30 nucleobases in length, for example, 16 to 28 nucleobases in length, for example, 19 to 23 nucleobases in length, for example, 21 to 23 nucleobases in length, for example, or 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleobases in length. A KCNQ2 AON variant may be an oligonucleotide sequence complementary to a portion of a KCNQ2 pre-mRNA sequence or a KCNQ2 gene sequence. Example KCNQ2 AON variants include a nucleobase sequence selected from any one of SEQ ID NOs: SEQ ID NOs: 4402-4468, SEQ ID NOs: 4469-4476, or SEQ ID NOs: 4477-4530.

[00337] In various embodiments, a KCNQ2 AON variant represents a modified version of a corresponding KCNQ2 parent oligonucleotide that includes a nucleobase sequence selected from any one of SEQ ID NOs: 1676-1851and SEQ ID NOs: 2028-2529. In some embodiments, a KCNQ2 AON variant includes a nucleobase sequence that represents a shortened version of a nucleobase sequence of a KCNQ2 AON selected from any one of SEQ ID NOs: 1676-1851and SEQ ID NOs: 2028-2529. As one example, if a KCNQ2 parent oligonucleotide includes a 25mer (*e.g.*, 25 nucleotide bases in length) a variant (*e.g.*, a KCNQ2 variant) may include a shorter version (*e.g.*, 15mer, 17mer, 19mer, 21mer, or 23mer) of the 25mer KCNQ2 parent oligonucleotide. In one embodiment, a nucleobase sequence of a KCNQ2 AON variant differs

from a corresponding nucleobase sequence of a KCNQ2 parent oligonucleotide in that 1, 2, 3, 4, 5, or 6 nucleotide bases are removed from one or both of the 3' and 5' ends of the nucleobase sequence of the KCNQ2 parent oligonucleotide. In one embodiment, the corresponding KCNQ2 AON variant may include a 23mer where two nucleotide bases were removed from one of the 3' or 5' end of a 25mer included in the KCNQ2 parent oligonucleotide. In one embodiment, the corresponding KCNQ2 AON variant may include a 23mer where one nucleotide base is removed from each of the 3' and 5' ends of the 25mer included in the KCNQ2 parent oligonucleotide. In one embodiment, the corresponding KCNQ2 AON variant may include a 21mer where two nucleotide bases are removed from each of the 3' and 5' ends of the 25mer included in the KCNQ2 parent oligonucleotide. In one embodiment, the corresponding KCNQ2 AON variant may include a 21mer where four nucleotide bases are removed from either the 3' or 5' end of the 25mer included in the KCNQ2 parent oligonucleotide. In one embodiment, the corresponding KCNQ2 AON variant may include a 19mer where three nucleotide bases are removed from each of the 3' and 5' ends of the 25mer included in the KCNQ2 parent oligonucleotide. In one embodiment, the corresponding KCNQ2 AON variant may include a 19mer where six nucleotide bases are removed from either the 3' or 5' end of the 25mer included in the KCNQ2 parent oligonucleotide.

[00338] Example sequences of KCNQ2 AON variants are shown below in Tables 8A and 8B.

Table 8A. KCNQ2 Oligonucleotide Variant Sequences complementary to a sequence of a KCNQ2 transcript

SEQ ID NO:	AON Sequence* (5' → 3')	SEQ ID NO:	Target Sequence (5' → 3')
3046	CGCCAGCCTTGGGGCCGTGACTC	3222	GAGTCACGGCCCCAAGGCTGGCG
3047	CCGCCAGCCTTGGGGCCGTGACT	3223	AGTCACGGCCCCAAGGCTGGCGG
3048	ACCGCCAGCCTTGGGGCCGTGAC	3224	GTCACGGCCCCAAGGCTGGCGGT
3049	CACCGCCAGCCTTGGGGCCGTGA	3225	TCACGGCCCCAAGGCTGGCGGTG
3050	CCACCGCCAGCCTTGGGGCCGTG	3226	CACGGCCCCAAGGCTGGCGGTGG
3051	CCCACCGCCAGCCTTGGGGCCGT	3227	ACGGCCCCAAGGCTGGCGGTGGG
3052	GCCCACCGCCAGCCTTGGGGCCG	3228	CGGCCCCAAGGCTGGCGGTGGGC
3053	CGCCCACCGCCAGCCTTGGGGCC	3229	GGCCCCAAGGCTGGCGGTGGGCG
3054	GCGCCCACCGCCAGCCTTGGGGC	3230	GCCCCAAGGCTGGCGGTGGGCGC
3055	GGCGCCCACCGCCAGCCTTGGGG	3231	CCCCAAGGCTGGCGGTGGGCGCC
3056	GGGCGCCCACCGCCAGCCTTGGG	3232	CCCAAGGCTGGCGGTGGGCGCCC
3057	GGGGCGCCCACCGCCAGCCTTGG	3233	CCAAGGCTGGCGGTGGGCGCCCC
3058	GGGGGCGCCCACCGCCAGCCTTG	3234	CAAGGCTGGCGGTGGGCGCCCCC

3059	TGGGGGCGCCCACCGCCAGCCTT	3235	AAGGCTGGCGGTGGGCGCCCCCA
3060	CTGGGGGCGCCCACCGCCAGCCT	3236	AGGCTGGCGGTGGGCGCCCCCAG
3061	GCTGGGGGCGCCCACCGCCAGCC	3237	GGCTGGCGGTGGGCGCCCCCAGC
3062	GGCTGGGGGCGCCCACCGCCAGC	3238	GCTGGCGGTGGGCGCCCCCAGCC
3063	TGGCTGGGGGCGCCCACCGCCAG	3239	CTGGCGGTGGGCGCCCCCAGCCA
3064	CTGGCTGGGGGCGCCCACCGCCA	3240	TGGCGGTGGGCGCCCCCAGCCAG
3065	GCTGGCTGGGGGCGCCCACCGCC	3241	GGCGGTGGGCGCCCCCAGCCAGC
3066	CGCTGGCTGGGGGCGCCCACCGC	3242	GCGGTGGGCGCCCCCAGCCAGCG
3067	TCGCTGGCTGGGGGCGCCCACCG	3243	CGGTGGGCGCCCCCAGCCAGCGA
3068	CTCGCTGGCTGGGGGCGCCCACC	3244	GGTGGGCGCCCCCAGCCAGCGAG
3069	TCTCGCTGGCTGGGGGCGCCCAC	3245	GTGGGCGCCCCCAGCCAGCGAGA
3070	CTCTCGCTGGCTGGGGGCGCCCA	3246	TGGGCGCCCCCAGCCAGCGAGAG
3071	ACTCTCGCTGGCTGGGGGCGCCC	3247	GGGCGCCCCCAGCCAGCGAGAGT
3072	GACTCTCGCTGGCTGGGGGCGCC	3248	GGCGCCCCCAGCCAGCGAGAGTC
3073	GGACTCTCGCTGGCTGGGGGCGC	3249	GCGCCCCCAGCCAGCGAGAGTCC
3074	AGGACTCTCGCTGGCTGGGGGCG	3250	CGCCCCCAGCCAGCGAGAGTCCT
3075	CAGGACTCTCGCTGGCTGGGGGC	3251	GCCCCCAGCCAGCGAGAGTCCTG
3076	CCAGGACTCTCGCTGGCTGGGGG	3252	CCCCCAGCCAGCGAGAGTCCTGG
3077	GCCAGGACTCTCGCTGGCTGGGG	3253	CCCCAGCCAGCGAGAGTCCTGGC
3078	GGCCAGGACTCTCGCTGGCTGGG	3254	CCCAGCCAGCGAGAGTCCTGGCC
3079	GGGCCAGGACTCTCGCTGGCTGG	3255	CCAGCCAGCGAGAGTCCTGGCCC
3080	TGGGCCAGGACTCTCGCTGGCTG	3256	CAGCCAGCGAGAGTCCTGGCCCA
3081	CTGGGCCAGGACTCTCGCTGGCT	3257	AGCCAGCGAGAGTCCTGGCCCAG
3082	TCTGGGCCAGGACTCTCGCTGGC	3258	GCCAGCGAGAGTCCTGGCCCAGA
3083	GTCTGGGCCAGGACTCTCGCTGG	3259	CCAGCGAGAGTCCTGGCCCAGAC
3084	GGTCTGGGCCAGGACTCTCGCTG	3260	CAGCGAGAGTCCTGGCCCAGACC
3085	CGGTCTGGGCCAGGACTCTCGCT	3261	AGCGAGAGTCCTGGCCCAGACCG
3086	CCGGTCTGGGCCAGGACTCTCGC	3262	GCGAGAGTCCTGGCCCAGACCGG
3087	CCCGGTCTGGGCCAGGACTCTCG	3263	CGAGAGTCCTGGCCCAGACCGGG
3088	GCCCGGTCTGGGCCAGGACTCTC	3264	GAGAGTCCTGGCCCAGACCGGGC
3089	GGCCCGGTCTGGGCCAGGACTCT	3265	AGAGTCCTGGCCCAGACCGGGCC
3090	GGGCCCGGTCTGGGCCAGGACTC	3266	GAGTCCTGGCCCAGACCGGGCCC
3091	GGGGCCCGGTCTGGGCCAGGACT	3267	AGTCCTGGCCCAGACCGGGCCCC
3092	TGGGGCCCGGTCTGGGCCAGGAC	3268	GTCCTGGCCCAGACCGGGCCCCA
3093	GTGGGGCCCGGTCTGGGCCAGGA	3269	TCCTGGCCCAGACCGGGCCCCAC
3094	GGTGGGGCCCGGTCTGGGCCAGG	3270	CCTGGCCCAGACCGGGCCCCACC
3095	GGGTGGGGCCCGGTCTGGGCCAG	3271	CTGGCCCAGACCGGGCCCCACCC
3096	GGGGTGGGGCCCGGTCTGGGCCA	3272	TGGCCCAGACCGGGCCCCACCCC
3097	AGGGGTGGGGCCCGGTCTGGGCC	3273	GGCCCAGACCGGGCCCCACCCCT
3098	CAGGGGTGGGGCCCGGTCTGGGC	3274	GCCCAGACCGGGCCCCACCCCTG
3099	GCAGGGGTGGGGCCCGGTCTGGG	3275	CCCAGACCGGGCCCCACCCCTGC
3100	GGCAGGGGTGGGGCCCGGTCTGG	3276	CCAGACCGGGCCCCACCCCTGCC

3101	AGGCAGGGGTGGGGCCCGGTCTG	3277	CAGACCGGGCCCCACCCCTGCCT
3102	CAGGCAGGGGTGGGGCCCGGTCT	3278	AGACCGGGCCCCACCCCTGCCTG
3103	CCAGGCAGGGGTGGGGCCCGGTC	3279	GACCGGGCCCCACCCCTGCCTGG
3104	CCCAGGCAGGGGTGGGGCCCGGT	3280	ACCGGGCCCCACCCCTGCCTGGG
3105	CCCCAGGCAGGGGTGGGGCCCGG	3281	CCGGGCCCCACCCCTGCCTGGGG
3106	ACCCCAGGCAGGGGTGGGGCCCG	3282	CGGGCCCCACCCCTGCCTGGGGT
3107	AACCCCAGGCAGGGGTGGGGCCC	3283	GGGCCCCACCCCTGCCTGGGGTT
3108	AAACCCCAGGCAGGGGTGGGGCC	3284	GGCCCCACCCCTGCCTGGGGTTT
3109	CAAACCCCAGGCAGGGGTGGGGC	3285	GCCCCACCCCTGCCTGGGGTTTG
3110	GCAAACCCCAGGCAGGGGTGGGG	3286	CCCCACCCCTGCCTGGGGTTTGC
3111	AGCAAACCCCAGGCAGGGGTGGG	3287	CCCACCCCTGCCTGGGGTTTGCT
3112	AAGCAAACCCCAGGCAGGGGTGG	3288	CCACCCCTGCCTGGGGTTTGCTT
3113	GAAGCAAACCCCAGGCAGGGGTG	3289	CACCCCTGCCTGGGGTTTGCTTC
3114	TGAAGCAAACCCCAGGCAGGGGT	3290	ACCCCTGCCTGGGGTTTGCTTCA
3115	TTGAAGCAAACCCCAGGCAGGGG	3291	CCCCTGCCTGGGGTTTGCTTCAA
3116	CTTGAAGCAAACCCCAGGCAGGG	3292	CCCTGCCTGGGGTTTGCTTCAAG
3117	TCTTGAAGCAAACCCCAGGCAGG	3293	CCTGCCTGGGGTTTGCTTCAAGA
3118	CTCTTGAAGCAAACCCCAGGCAG	3294	CTGCCTGGGGTTTGCTTCAAGAG
3119	GCTCTTGAAGCAAACCCCAGGCA	3295	TGCCTGGGGTTTGCTTCAAGAGC
3120	GGCTCTTGAAGCAAACCCCAGGC	3296	GCCTGGGGTTTGCTTCAAGAGCC
3121	GGGCTCTTGAAGCAAACCCCAGG	3297	CCTGGGGTTTGCTTCAAGAGCCC
3122	AGGGCTCTTGAAGCAAACCCCAG	3298	CTGGGGTTTGCTTCAAGAGCCCT
3123	CAGGGCTCTTGAAGCAAACCCCA	3299	TGGGGTTTGCTTCAAGAGCCCTG
3124	CCAGGGCTCTTGAAGCAAACCCC	3300	GGGGTTTGCTTCAAGAGCCCTGG
3125	CCCAGGGCTCTTGAAGCAAACCC	3301	GGGTTTGCTTCAAGAGCCCTGGG
3126	ACCCAGGGCTCTTGAAGCAAACC	3302	GGTTTGCTTCAAGAGCCCTGGGT
3127	CACCCAGGGCTCTTGAAGCAAAC	3303	GTTTGCTTCAAGAGCCCTGGGTG
3128	CCACCCAGGGCTCTTGAAGCAAA	3304	TTTGCTTCAAGAGCCCTGGGTGG
3129	TCCACCCAGGGCTCTTGAAGCAA	3305	TTGCTTCAAGAGCCCTGGGTGGA
3130	CTCCACCCAGGGCTCTTGAAGCA	3306	TGCTTCAAGAGCCCTGGGTGGAG
3131	CCTCCACCCAGGGCTCTTGAAGC	3307	GCTTCAAGAGCCCTGGGTGGAGG
3132	CCCTCCACCCAGGGCTCTTGAAG	3308	CTTCAAGAGCCCTGGGTGGAGGG
3133	TCCCTCCACCCAGGGCTCTTGAA	3309	TTCAAGAGCCCTGGGTGGAGGGA
3134	ATCCCTCCACCCAGGGCTCTTGA	3310	TCAAGAGCCCTGGGTGGAGGGAT
3135	CATCCCTCCACCCAGGGCTCTTG	3311	CAAGAGCCCTGGGTGGAGGGATG
3136	CCATCCCTCCACCCAGGGCTCTT	3312	AAGAGCCCTGGGTGGAGGGATGG
3137	TCCATCCCTCCACCCAGGGCTCT	3313	AGAGCCCTGGGTGGAGGGATGGA
3138	CTCCATCCCTCCACCCAGGGCTC	3314	GAGCCCTGGGTGGAGGGATGGAG
3139	ACTCCATCCCTCCACCCAGGGCT	3315	AGCCCTGGGTGGAGGGATGGAGT
3140	GACTCCATCCCTCCACCCAGGGC	3316	GCCCTGGGTGGAGGGATGGAGTC
3141	TGACTCCATCCCTCCACCCAGGG	3317	CCCTGGGTGGAGGGATGGAGTCA
3142	CTGACTCCATCCCTCCACCCAGG	3318	CCTGGGTGGAGGGATGGAGTCAG

3143	ACTGACTCCATCCCTCCACCCAG	3319	CTGGGTGGAGGGATGGAGTCAGT
3144	CACTGACTCCATCCCTCCACCCA	3320	TGGGTGGAGGGATGGAGTCAGTG
3145	CCACTGACTCCATCCCTCCACCC	3321	GGGTGGAGGGATGGAGTCAGTGG
3146	ACCACTGACTCCATCCCTCCACC	3322	GGTGGAGGGATGGAGTCAGTGGT
3147	CACCACTGACTCCATCCCTCCAC	3323	GTGGAGGGATGGAGTCAGTGGTG
3148	CCACCACTGACTCCATCCCTCCA	3324	TGGAGGGATGGAGTCAGTGGTGG
3149	GCCACCACTGACTCCATCCCTCC	3325	GGAGGGATGGAGTCAGTGGTGGC
3150	AGCCACCACTGACTCCATCCCTC	3326	GAGGGATGGAGTCAGTGGTGGCT
3151	GAGCCACCACTGACTCCATCCCT	3327	AGGGATGGAGTCAGTGGTGGCTC
3152	AGAGCCACCACTGACTCCATCCC	3328	GGGATGGAGTCAGTGGTGGCTCT
3153	CAGAGCCACCACTGACTCCATCC	3329	GGATGGAGTCAGTGGTGGCTCTG
3154	CCAGAGCCACCACTGACTCCATC	3330	GATGGAGTCAGTGGTGGCTCTGG
3155	GCCAGAGCCACCACTGACTCCAT	3331	ATGGAGTCAGTGGTGGCTCTGGC
3156	AGCCAGAGCCACCACTGACTCCA	3332	TGGAGTCAGTGGTGGCTCTGGCT
3157	CAGCCAGAGCCACCACTGACTCC	3333	GGAGTCAGTGGTGGCTCTGGCTG
3158	CCAGCCAGAGCCACCACTGACTC	3334	GAGTCAGTGGTGGCTCTGGCTGG
3159	TCCAGCCAGAGCCACCACTGACT	3335	AGTCAGTGGTGGCTCTGGCTGGA
3160	CTCCAGCCAGAGCCACCACTGAC	3336	GTCAGTGGTGGCTCTGGCTGGAG
3161	GCTCCAGCCAGAGCCACCACTGA	3337	TCAGTGGTGGCTCTGGCTGGAGC
3162	GGCTCCAGCCAGAGCCACCACTG	3338	CAGTGGTGGCTCTGGCTGGAGCC
3163	GGGCTCCAGCCAGAGCCACCACT	3339	AGTGGTGGCTCTGGCTGGAGCCC
3164	TGGGCTCCAGCCAGAGCCACCAC	3340	GTGGTGGCTCTGGCTGGAGCCCA
3165	ATGGGCTCCAGCCAGAGCCACCA	3341	TGGTGGCTCTGGCTGGAGCCCAT
3166	GATGGGCTCCAGCCAGAGCCACC	3342	GGTGGCTCTGGCTGGAGCCCATC
3167	TGATGGGCTCCAGCCAGAGCCAC	3343	GTGGCTCTGGCTGGAGCCCATCA
3168	CTGATGGGCTCCAGCCAGAGCCA	3344	TGGCTCTGGCTGGAGCCCATCAG
3169	CCTGATGGGCTCCAGCCAGAGCC	3345	GGCTCTGGCTGGAGCCCATCAGG
3170	ACCTGATGGGCTCCAGCCAGAGC	3346	GCTCTGGCTGGAGCCCATCAGGT
3171	CACCTGATGGGCTCCAGCCAGAG	3347	CTCTGGCTGGAGCCCATCAGGTG
3172	ACACCTGATGGGCTCCAGCCAGA	3348	TCTGGCTGGAGCCCATCAGGTGT
3173	CACACCTGATGGGCTCCAGCCAG	3349	CTGGCTGGAGCCCATCAGGTGTG
3174	TCACACCTGATGGGCTCCAGCCA	3350	TGGCTGGAGCCCATCAGGTGTGA
3175	TTCACACCTGATGGGCTCCAGCC	3351	GGCTGGAGCCCATCAGGTGTGAA
3176	GTTCACACCTGATGGGCTCCAGC	3352	GCTGGAGCCCATCAGGTGTGAAC
3177	CGTTCACACCTGATGGGCTCCAG	3353	CTGGAGCCCATCAGGTGTGAACG
3178	TCGTTCACACCTGATGGGCTCCA	3354	TGGAGCCCATCAGGTGTGAACGA
3179	CTCGTTCACACCTGATGGGCTCC	3355	GGAGCCCATCAGGTGTGAACGAG
3180	GCTCGTTCACACCTGATGGGCTC	3356	GAGCCCATCAGGTGTGAACGAGC
3181	GGCTCGTTCACACCTGATGGGCT	3357	AGCCCATCAGGTGTGAACGAGCC
3182	AGGCTCGTTCACACCTGATGGGC	3358	GCCCATCAGGTGTGAACGAGCCT
3183	GAGGCTCGTTCACACCTGATGGG	3359	CCCATCAGGTGTGAACGAGCCTC
3184	GGAGGCTCGTTCACACCTGATGG	3360	CCATCAGGTGTGAACGAGCCTCC

3185	GGGAGGCTCGTTCACACCTGATG	3361	CATCAGGTGTGAACGAGCCTCCC
3186	AGGGAGGCTCGTTCACACCTGAT	3362	ATCAGGTGTGAACGAGCCTCCCT
3187	GAGGGAGGCTCGTTCACACCTGA	3363	TCAGGTGTGAACGAGCCTCCCTC
3188	GGAGGGAGGCTCGTTCACACCTG	3364	CAGGTGTGAACGAGCCTCCCTCC
3189	GGGAGGGAGGCTCGTTCACACCT	3365	AGGTGTGAACGAGCCTCCCTCCC
3190	GGGGAGGGAGGCTCGTTCACACC	3366	GGTGTGAACGAGCCTCCCTCCCC
3191	AGGGGAGGGAGGCTCGTTCACAC	3367	GTGTGAACGAGCCTCCCTCCCCT
3192	AAGGGGAGGGAGGCTCGTTCACA	3368	TGTGAACGAGCCTCCCTCCCCTT
3193	AAAGGGGAGGGAGGCTCGTTCAC	3369	GTGAACGAGCCTCCCTCCCCTTT
3194	GAAAGGGGAGGGAGGCTCGTTCA	3370	TGAACGAGCCTCCCTCCCCTTTC
3195	AGAAAGGGGAGGGAGGCTCGTTC	3371	GAACGAGCCTCCCTCCCCTTTCT
3196	AAGAAAGGGGAGGGAGGCTCGTT	3372	AACGAGCCTCCCTCCCCTTTCTT
3197	GAAGAAAGGGGAGGGAGGCTCGT	3373	ACGAGCCTCCCTCCCCTTTCTTC
3198	AGAAGAAAGGGGAGGGAGGCTCG	3374	CGAGCCTCCCTCCCCTTTCTTCT
3199	GAGAAGAAAGGGGAGGGAGGCTC	3375	GAGCCTCCCTCCCCTTTCTTCTC
3200	CGAGAAGAAAGGGGAGGGAGGCT	3376	AGCCTCCCTCCCCTTTCTTCTCG
3201	CCGAGAAGAAAGGGGAGGGAGGC	3377	GCCTCCCTCCCCTTTCTTCTCGG
3202	ACCGAGAAGAAAGGGGAGGGAGG	3378	CCTCCCTCCCCTTTCTTCTCGGT
3203	CACCGAGAAGAAAGGGGAGGGAG	3379	CTCCCTCCCCTTTCTTCTCGGTG
3204	GCACCGAGAAGAAAGGGGAGGGA	3380	TCCCTCCCCTTTCTTCTCGGTGC
3205	AGCACCGAGAAGAAAGGGGAGGG	3381	CCCTCCCCTTTCTTCTCGGTGCT
3206	AAGCACCGAGAAGAAAGGGGAGG	3382	CCTCCCCTTTCTTCTCGGTGCTT
3207	GAAGCACCGAGAAGAAAGGGGAG	3383	CTCCCCTTTCTTCTCGGTGCTTC
3208	AGAAGCACCGAGAAGAAAGGGGA	3384	TCCCCTTTCTTCTCGGTGCTTCT
3209	AAGAAGCACCGAGAAGAAAGGGG	3385	CCCCTTTCTTCTCGGTGCTTCTT
3210	GAAGAAGCACCGAGAAGAAAGGG	3386	CCCTTTCTTCTCGGTGCTTCTTC
3211	AGAAGAAGCACCGAGAAGAAAGG	3387	CCTTTCTTCTCGGTGCTTCTTCT
3212	GAGAAGAAGCACCGAGAAGAAAG	3388	CTTTCTTCTCGGTGCTTCTTCTC
3213	CGAGAAGAAGCACCGAGAAGAAA	3389	TTTCTTCTCGGTGCTTCTTCTCG
3214	ACGAGAAGAAGCACCGAGAAGAA	3390	TTCTTCTCGGTGCTTCTTCTCGT
3215	CACGAGAAGAAGCACCGAGAAGA	3391	TCTTCTCGGTGCTTCTTCTCGTG
3216	TCACGAGAAGAAGCACCGAGAAG	3392	CTTCTCGGTGCTTCTTCTCGTGA
3217	GTCACGAGAAGAAGCACCGAGAA	3393	TTCTCGGTGCTTCTTCTCGTGAC
3218	AGTCACGAGAAGAAGCACCGAGA	3394	TCTCGGTGCTTCTTCTCGTGACT
3219	AAGTCACGAGAAGAAGCACCGAG	3395	CTCGGTGCTTCTTCTCGTGACTT
3220	CAAGTCACGAGAAGAAGCACCGA	3396	TCGGTGCTTCTTCTCGTGACTTG
3221	CCAAGTCACGAGAAGAAGCACCG	3397	CGGTGCTTCTTCTCGTGACTTGG

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate

linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

Table 8B: Additional KCNQ2 Oligonucleotide Variant Sequences complementary to a sequence a KCNQ2 transcript

SEQ ID NO:	AON Sequence* (5' → 3')	SEQ ID NO:	Target Sequence (5' → 3')
3398	TCACCACCACCACCACCATCATC	3900	GATGATGGTGGTGGTGGTGGTGA
3399	ATCACCACCACCACCACCATCAT	3901	ATGATGGTGGTGGTGGTGGTGAT
3400	CATCACCACCACCACCACCATCA	3902	TGATGGTGGTGGTGGTGGTGATG
3401	CCATCACCACCACCACCACCATC	3903	GATGGTGGTGGTGGTGGTGATGG
3402	ACCATCACCACCACCACCACCAT	3904	ATGGTGGTGGTGGTGGTGATGGT
3403	CACCATCACCACCACCACCACCA	3905	TGGTGGTGGTGGTGGTGATGGTG
3404	TCACCATCACCACCACCACCACC	3906	GGTGGTGGTGGTGGTGATGGTGA
3405	ATCACCATCACCACCACCACCAC	3907	GTGGTGGTGGTGGTGATGGTGAT
3406	CATCACCATCACCACCACCACCA	3908	TGGTGGTGGTGGTGATGGTGATG
3407	CCATCACCATCACCACCACCACC	3909	GGTGGTGGTGGTGATGGTGATGG
3408	ACCATCACCATCACCACCACCAC	3910	GTGGTGGTGGTGATGGTGATGGT
3409	CACCATCACCATCACCACCACCA	3911	TGGTGGTGGTGATGGTGATGGTG
3410	CCACCATCACCATCACCACCACC	3912	GGTGGTGGTGATGGTGATGGTGG
3411	ACCACCATCACCATCACCACCAC	3913	GTGGTGGTGATGGTGATGGTGGT
3412	CACCACCATCACCATCACCACCA	3914	TGGTGGTGATGGTGATGGTGGTG
3413	TCACCACCATCACCATCACCACC	3915	GGTGGTGATGGTGATGGTGGTGA
3414	ATCACCACCATCACCATCACCAC	3916	GTGGTGATGGTGATGGTGGTGAT
3415	CATCACCACCATCACCATCACCA	3917	TGGTGATGGTGATGGTGGTGATG
3416	CCATCACCACCATCACCATCACC	3918	GGTGATGGTGATGGTGGTGATGG
3417	ACCATCACCACCATCACCATCAC	3919	GTGATGGTGATGGTGGTGATGGT
3418	CACCATCACCACCATCACCATCA	3920	TGATGGTGATGGTGGTGATGGTG
3419	TCACCATCACCACCATCACCATC	3921	GATGGTGATGGTGGTGATGGTGA
3420	ATCACCATCACCACCATCACCAT	3922	ATGGTGATGGTGGTGATGGTGAT
3421	CATCACCATCACCACCATCACCA	3923	TGGTGATGGTGGTGATGGTGATG
3422	CCATCACCATCACCACCATCACC	3924	GGTGATGGTGGTGATGGTGATGG
3423	ACCATCACCATCACCACCATCAC	3925	GTGATGGTGGTGATGGTGATGGT
3424	CACCATCACCATCACCACCATCA	3926	TGATGGTGGTGATGGTGATGGTG
3425	CCACCATCACCATCACCACCATC	3927	GATGGTGGTGATGGTGATGGTGG
3426	ACCACCATCACCATCACCACCAT	3928	ATGGTGGTGATGGTGATGGTGGT
3427	CACCACCATCACCATCACCACCA	3929	TGGTGGTGATGGTGATGGTGGTG
3428	CCACCACCATCACCATCACCACC	3930	GGTGGTGATGGTGATGGTGGTGG

3429	ACCACCACCATCACCATCACCAC	3931	GTGGTGATGGTGATGGTGGTGGT
3430	CACCACCACCATCACCATCACCA	3932	TGGTGATGGTGATGGTGGTGGTG
3431	CCACCACCACCATCACCATCACC	3933	GGTGATGGTGATGGTGGTGGTGG
3432	ACCACCACCACCATCACCATCAC	3934	GTGATGGTGATGGTGGTGGTGGT
3433	CACCACCACCACCATCACCATCA	3935	TGATGGTGATGGTGGTGGTGGTG
3434	CCACCACCACCACCATCACCATC	3936	GATGGTGATGGTGGTGGTGGTGG
3435	ACCACCACCACCACCATCACCAT	3937	ATGGTGATGGTGGTGGTGGTGGT
3436	CACCACCACCACCACCATCACCA	3938	TGGTGATGGTGGTGGTGGTGGTG
3437	CCACCACCACCACCACCATCACC	3939	GGTGATGGTGGTGGTGGTGGTGG
3438	ACCACCACCACCACCACCATCAC	3940	GTGATGGTGGTGGTGGTGGTGGT
3439	CACCACCACCACCACCACCATCA	3941	TGATGGTGGTGGTGGTGGTGGTG
3440	CCACCACCACCACCACCACCATC	3942	GATGGTGGTGGTGGTGGTGGTGG
3441	ACCACCACCACCACCACCACCAT	3943	ATGGTGGTGGTGGTGGTGGTGGT
3442	CACCACCACCACCACCACCACCA	3944	TGGTGGTGGTGGTGGTGGTGGTG
3443	TCACCACCACCACCACCACCACC	3945	GGTGGTGGTGGTGGTGGTGGTGA
3444	ATCACCACCACCACCACCACCAC	3946	GTGGTGGTGGTGGTGGTGGTGAT
3445	CATCACCACCACCACCACCACCA	3947	TGGTGGTGGTGGTGGTGGTGATG
3446	CCATCACCACCACCACCACCACC	3948	GGTGGTGGTGGTGGTGGTGATGG
3447	ACCATCACCACCACCACCACCAC	3949	GTGGTGGTGGTGGTGGTGATGGT
3448	CACCATCACCACCACCACCACCA	3950	TGGTGGTGGTGGTGGTGATGGTG
3449	CCACCATCACCACCACCACCACC	3951	GGTGGTGGTGGTGGTGATGGTGG
3450	ACCACCATCACCACCACCACCAC	3952	GTGGTGGTGGTGGTGATGGTGGT
3451	CACCACCATCACCACCACCACCA	3953	TGGTGGTGGTGGTGATGGTGGTG
3452	CCACCACCATCACCACCACCACC	3954	GGTGGTGGTGGTGATGGTGGTGG
3453	ACCACCACCATCACCACCACCAC	3955	GTGGTGGTGGTGATGGTGGTGGT
3454	CACCACCACCATCACCACCACCA	3956	TGGTGGTGGTGATGGTGGTGGTG
3455	TCACCACCACCATCACCACCACC	3957	GGTGGTGGTGATGGTGGTGGTGA
3456	ATCACCACCACCATCACCACCAC	3958	GTGGTGGTGATGGTGGTGGTGAT
3457	CATCACCACCACCATCACCACCA	3959	TGGTGGTGATGGTGGTGGTGATG
3458	CCATCACCACCACCATCACCACC	3960	GGTGGTGATGGTGGTGGTGATGG
3459	ACCATCACCACCACCATCACCAC	3961	GTGGTGATGGTGGTGGTGATGGT
3460	AACCATCACCACCACCATCACCA	3962	TGGTGATGGTGGTGGTGATGGTT
3461	AAACCATCACCACCACCATCACC	3963	GGTGATGGTGGTGGTGATGGTTT
3462	AAAACCATCACCACCACCATCAC	3964	GTGATGGTGGTGGTGATGGTTTT
3463	CAAAACCATCACCACCACCATCA	3965	TGATGGTGGTGGTGATGGTTTTG
3464	CCAAAACCATCACCACCACCATC	3966	GATGGTGGTGGTGATGGTTTTGG
3465	ACCAAAACCATCACCACCACCAT	3967	ATGGTGGTGGTGATGGTTTTGGT
3466	CACCAAAACCATCACCACCACCA	3968	TGGTGGTGGTGATGGTTTTGGTG
3467	CCACCAAAACCATCACCACCACC	3969	GGTGGTGGTGATGGTTTTGGTGG
3468	ACCACCAAAACCATCACCACCAC	3970	GTGGTGGTGATGGTTTTGGTGGT
3469	CACCACCAAAACCATCACCACCA	3971	TGGTGGTGATGGTTTTGGTGGTG
3470	CCACCACCAAAACCATCACCACC	3972	GGTGGTGATGGTTTTGGTGGTGG
3471	ACCACCACCAAAACCATCACCAC	3973	GTGGTGATGGTTTTGGTGGTGGT
3472	CACCACCACCAAAACCATCACCA	3974	TGGTGATGGTTTTGGTGGTGGTG
3473	TCACCACCACCAAAACCATCACC	3975	GGTGATGGTTTTGGTGGTGGTGA
3474	ATCACCACCACCAAAACCATCAC	3976	GTGATGGTTTTGGTGGTGGTGAT
3475	CATCACCACCACCAAAACCATCA	3977	TGATGGTTTTGGTGGTGGTGATG
3476	CCATCACCACCACCAAAACCATC	3978	GATGGTTTTGGTGGTGGTGATGG

3477	ACCATCACCACCACCAAAACCAT	3979	ATGGTTTTGGTGGTGGTGATGGT
3478	CACCATCACCACCACCAAAACCA	3980	TGGTTTTGGTGGTGGTGATGGTG
3479	CCACCATCACCACCACCAAAACC	3981	GGTTTTGGTGGTGGTGATGGTGG
3480	ACCACCATCACCACCACCAAAAC	3982	GTTTTGGTGGTGGTGATGGTGGT
3481	GACCACCATCACCACCACCAAAA	3983	TTTTGGTGGTGGTGATGGTGGTC
3482	TGACCACCATCACCACCACCAAA	3984	TTTGGTGGTGGTGATGGTGGTCA
3483	ATGACCACCATCACCACCACCAA	3985	TTGGTGGTGGTGATGGTGGTCAT
3484	CATGACCACCATCACCACCACCA	3986	TGGTGGTGGTGATGGTGGTCATG
3485	CCATGACCACCATCACCACCACC	3987	GGTGGTGGTGATGGTGGTCATGG
3486	ACCATGACCACCATCACCACCAC	3988	GTGGTGGTGATGGTGGTCATGGT
3487	CACCATGACCACCATCACCACCA	3989	TGGTGGTGATGGTGGTCATGGTG
3488	ACACCATGACCACCATCACCACC	3990	GGTGGTGATGGTGGTCATGGTGT
3489	AACACCATGACCACCATCACCAC	3991	GTGGTGATGGTGGTCATGGTGTT
3490	CAACACCATGACCACCATCACCA	3992	TGGTGATGGTGGTCATGGTGTTG
3491	TCAACACCATGACCACCATCACC	3993	GGTGATGGTGGTCATGGTGTTGA
3492	ATCAACACCATGACCACCATCAC	3994	GTGATGGTGGTCATGGTGTTGAT
3493	CATCAACACCATGACCACCATCA	3995	TGATGGTGGTCATGGTGTTGATG
3494	ACATCAACACCATGACCACCATC	3996	GATGGTGGTCATGGTGTTGATGT
3495	CACATCAACACCATGACCACCAT	3997	ATGGTGGTCATGGTGTTGATGTG
3496	TCACATCAACACCATGACCACCA	3998	TGGTGGTCATGGTGTTGATGTGA
3497	ATCACATCAACACCATGACCACC	3999	GGTGGTCATGGTGTTGATGTGAT
3498	CATCACATCAACACCATGACCAC	4000	GTGGTCATGGTGTTGATGTGATG
3499	CCATCACATCAACACCATGACCA	4001	TGGTCATGGTGTTGATGTGATGG
3500	ACCATCACATCAACACCATGACC	4002	GGTCATGGTGTTGATGTGATGGT
3501	CACCATCACATCAACACCATGAC	4003	GTCATGGTGTTGATGTGATGGTG
3502	CCACCATCACATCAACACCATGA	4004	TCATGGTGTTGATGTGATGGTGG
3503	ACCACCATCACATCAACACCATG	4005	CATGGTGTTGATGTGATGGTGGT
3504	CACCACCATCACATCAACACCAT	4006	ATGGTGTTGATGTGATGGTGGTG
3505	CCACCACCATCACATCAACACCA	4007	TGGTGTTGATGTGATGGTGGTGG
3506	ACCACCACCATCACATCAACACC	4008	GGTGTTGATGTGATGGTGGTGGT
3507	CACCACCACCATCACATCAACAC	4009	GTGTTGATGTGATGGTGGTGGTG
3508	ACACCACCACCATCACATCAACA	4010	TGTTGATGTGATGGTGGTGGTGT
3509	AACACCACCACCATCACATCAAC	4011	GTTGATGTGATGGTGGTGGTGTT
3510	CAACACCACCACCATCACATCAA	4012	TTGATGTGATGGTGGTGGTGTTG
3511	CCAACACCACCACCATCACATCA	4013	TGATGTGATGGTGGTGGTGTTGG
3512	ACCAACACCACCACCATCACATC	4014	GATGTGATGGTGGTGGTGTTGGT
3513	CACCAACACCACCACCATCACAT	4015	ATGTGATGGTGGTGGTGTTGGTG
3514	CCACCAACACCACCACCATCACA	4016	TGTGATGGTGGTGGTGTTGGTGG
3515	ACCACCAACACCACCACCATCAC	4017	GTGATGGTGGTGGTGTTGGTGGT
3516	CACCACCAACACCACCACCATCA	4018	TGATGGTGGTGGTGTTGGTGGTG
3517	CCACCACCAACACCACCACCATC	4019	GATGGTGGTGGTGTTGGTGGTGG
3518	ACCACCACCAACACCACCACCAT	4020	ATGGTGGTGGTGTTGGTGGTGGT
3519	CACCACCACCAACACCACCACCA	4021	TGGTGGTGGTGTTGGTGGTGGTG
3520	TCACCACCACCAACACCACCACC	4022	GGTGGTGGTGTTGGTGGTGGTGA
3521	ATCACCACCACCAACACCACCAC	4023	GTGGTGGTGTTGGTGGTGGTGAT
3522	CATCACCACCACCAACACCACCA	4024	TGGTGGTGTTGGTGGTGGTGATG
3523	CCATCACCACCACCAACACCACC	4025	GGTGGTGTTGGTGGTGGTGATGG
3524	ACCATCACCACCACCAACACCAC	4026	GTGGTGTTGGTGGTGGTGATGGT

3525	CACCATCACCACCACCAACACCA	4027	TGGTGTTGGTGGTGGTGATGGTG
3526	TCACCATCACCACCACCAACACC	4028	GGTGTTGGTGGTGGTGATGGTGA
3527	ATCACCATCACCACCACCAACAC	4029	GTGTTGGTGGTGGTGATGGTGAT
3528	CATCACCATCACCACCACCAACA	4030	TGTTGGTGGTGGTGATGGTGATG
3529	GCATCACCATCACCACCACCAAC	4031	GTTGGTGGTGGTGATGGTGATGC
3530	AGCATCACCATCACCACCACCAA	4032	TTGGTGGTGGTGATGGTGATGCT
3531	AAGCATCACCATCACCACCACCA	4033	TGGTGGTGGTGATGGTGATGCTT
3532	GAAGCATCACCATCACCACCACC	4034	GGTGGTGGTGATGGTGATGCTTC
3533	AGAAGCATCACCATCACCACCAC	4035	GTGGTGGTGATGGTGATGCTTCT
3534	CAGAAGCATCACCATCACCACCA	4036	TGGTGGTGATGGTGATGCTTCTG
3535	CCAGAAGCATCACCATCACCACC	4037	GGTGGTGATGGTGATGCTTCTGG
3536	ACCAGAAGCATCACCATCACCAC	4038	GTGGTGATGGTGATGCTTCTGGT
3537	CACCAGAAGCATCACCATCACCA	4039	TGGTGATGGTGATGCTTCTGGTG
3538	TCACCAGAAGCATCACCATCACC	4040	GGTGATGGTGATGCTTCTGGTGA
3539	ATCACCAGAAGCATCACCATCAC	4041	GTGATGGTGATGCTTCTGGTGAT
3540	CATCACCAGAAGCATCACCATCA	4042	TGATGGTGATGCTTCTGGTGATG
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3546	GACCACCATCACCAGAAGCATCA	4048	TGATGCTTCTGGTGATGGTGGTC
3547	TGACCACCATCACCAGAAGCATC	4049	GATGCTTCTGGTGATGGTGGTCA
3548	ATGACCACCATCACCAGAAGCAT	4050	ATGCTTCTGGTGATGGTGGTCAT
3549	CATGACCACCATCACCAGAAGCA	4051	TGCTTCTGGTGATGGTGGTCATG
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3551	ATCATGACCACCATCACCAGAAG	4053	CTTCTGGTGATGGTGGTCATGAT
3552	CATCATGACCACCATCACCAGAA	4054	TTCTGGTGATGGTGGTCATGATG
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3555	CACCATCATGACCACCATCACCA	4057	TGGTGATGGTGGTCATGATGGTG
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3557	ACCACCATCATGACCACCATCAC	4059	GTGATGGTGGTCATGATGGTGGT
3558	CACCACCATCATGACCACCATCA	4060	TGATGGTGGTCATGATGGTGGTG
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3560	GGCACCACCATCATGACCACCAT	4062	ATGGTGGTCATGATGGTGGTGCC
3561	CGGCACCACCATCATGACCACCA	4063	TGGTGGTCATGATGGTGGTGCCG
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3563	GACGGCACCACCATCATGACCAC	4065	GTGGTCATGATGGTGGTGCCGTC
3564	AGACGGCACCACCATCATGACCA	4066	TGGTCATGATGGTGGTGCCGTCT
3565	CAGACGGCACCACCATCATGACC	4067	GGTCATGATGGTGGTGCCGTCTG
3566	GCAGACGGCACCACCATCATGAC	4068	GTCATGATGGTGGTGCCGTCTGC
3567	GGCAGACGGCACCACCATCATGA	4069	TCATGATGGTGGTGCCGTCTGCC
3568	AGGCAGACGGCACCACCATCATG	4070	CATGATGGTGGTGCCGTCTGCCT
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3603	GAAGCCGATGTACCAGGCAGTGA	4105	TCACTGCCTGGTACATCGGCTTC
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3613	TGAGACAAAGGAAGCCGATGTAC	4115	GTACATCGGCTTCCTTTGTCTCA
3614	ATGAGACAAAGGAAGCCGATGTA	4116	TACATCGGCTTCCTTTGTCTCAT
3615	GATGAGACAAAGGAAGCCGATGT	4117	ACATCGGCTTCCTTTGTCTCATC
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3617	AGGATGAGACAAAGGAAGCCGAT	4119	ATCGGCTTCCTTTGTCTCATCCT
3618	CAGGATGAGACAAAGGAAGCCGA	4120	TCGGCTTCCTTTGTCTCATCCTG
3619	CCAGGATGAGACAAAGGAAGCCG	4121	CGGCTTCCTTTGTCTCATCCTGG
3620	GCCAGGATGAGACAAAGGAAGCC	4122	GGCTTCCTTTGTCTCATCCTGGC

3621	GGCCAGGATGAGACAAAGGAAGC	4123	GCTTCCTTTGTCTCATCCTGGCC
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3624	CGAGGCCAGGATGAGACAAAGGA	4126	TCCTTTGTCTCATCCTGGCCTCG
3625	ACGAGGCCAGGATGAGACAAAGG	4127	CCTTTGTCTCATCCTGGCCTCGT
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3627	GAACGAGGCCAGGATGAGACAAA	4129	TTTGTCTCATCCTGGCCTCGTTC
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3663	GTGGTCGTTCTCCCCCTTCTCTG	4165	CAGAGAAGGGGGAGAACGACCAC
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3806	CCCCAAAGAGATGTATGGAGCAG	4308	CTGCTCCATACATCTCTTTGGGG
3807	GCCCCAAAGAGATGTATGGAGCA	4309	TGCTCCATACATCTCTTTGGGGC
3808	GGCCCCAAAGAGATGTATGGAGC	4310	GCTCCATACATCTCTTTGGGGCC
3809	TGGCCCCAAAGAGATGTATGGAG	4311	CTCCATACATCTCTTTGGGGCCA
3810	GTGGCCCCAAAGAGATGTATGGA	4312	TCCATACATCTCTTTGGGGCCAC
3811	GGTGGCCCCAAAGAGATGTATGG	4313	CCATACATCTCTTTGGGGCCACC
3812	AGGTGGCCCCAAAGAGATGTATG	4314	CATACATCTCTTTGGGGCCACCT

3813	CAGGTGGCCCCAAAGAGATGTAT	4315	ATACATCTCTTTGGGGCCACCTG
3814	GCAGGTGGCCCCAAAGAGATGTA	4316	TACATCTCTTTGGGGCCACCTGC
3815	AGCAGGTGGCCCCAAAGAGATGT	4317	ACATCTCTTTGGGGCCACCTGCT
3816	CAGCAGGTGGCCCCAAAGAGATG	4318	CATCTCTTTGGGGCCACCTGCTG
3817	CCAGCAGGTGGCCCCAAAGAGAT	4319	ATCTCTTTGGGGCCACCTGCTGG
3818	GCCAGCAGGTGGCCCCAAAGAGA	4320	TCTCTTTGGGGCCACCTGCTGGC
3819	AGCCAGCAGGTGGCCCCAAAGAG	4321	CTCTTTGGGGCCACCTGCTGGCT
3820	CAGCCAGCAGGTGGCCCCAAAGA	4322	TCTTTGGGGCCACCTGCTGGCTG
3821	GCAGCCAGCAGGTGGCCCCAAAG	4323	CTTTGGGGCCACCTGCTGGCTGC
3822	GGCAGCCAGCAGGTGGCCCCAAA	4324	TTTGGGGCCACCTGCTGGCTGCC
3823	GGGCAGCCAGCAGGTGGCCCCAA	4325	TTGGGGCCACCTGCTGGCTGCCC
3824	CGGGCAGCCAGCAGGTGGCCCCA	4326	TGGGGCCACCTGCTGGCTGCCCG
3825	ACGGGCAGCCAGCAGGTGGCCCC	4327	GGGGCCACCTGCTGGCTGCCCGT
3826	CACGGGCAGCCAGCAGGTGGCCC	4328	GGGCCACCTGCTGGCTGCCCGTG
3827	CCACGGGCAGCCAGCAGGTGGCC	4329	GGCCACCTGCTGGCTGCCCGTGG
3828	ACCACGGGCAGCCAGCAGGTGGC	4330	GCCACCTGCTGGCTGCCCGTGGT
3829	GACCACGGGCAGCCAGCAGGTGG	4331	CCACCTGCTGGCTGCCCGTGGTC
3830	TGACCACGGGCAGCCAGCAGGTG	4332	CACCTGCTGGCTGCCCGTGGTCA
3831	ATGACCACGGGCAGCCAGCAGGT	4333	ACCTGCTGGCTGCCCGTGGTCAT
3832	CATGACCACGGGCAGCCAGCAGG	4334	CCTGCTGGCTGCCCGTGGTCATG
3833	TCATGACCACGGGCAGCCAGCAG	4335	CTGCTGGCTGCCCGTGGTCATGA
3834	ATCATGACCACGGGCAGCCAGCA	4336	TGCTGGCTGCCCGTGGTCATGAT
3835	CATCATGACCACGGGCAGCCAGC	4337	GCTGGCTGCCCGTGGTCATGATG
3836	CCATCATGACCACGGGCAGCCAG	4338	CTGGCTGCCCGTGGTCATGATGG
3837	GCCATCATGACCACGGGCAGCCA	4339	TGGCTGCCCGTGGTCATGATGGC
3838	AGCCATCATGACCACGGGCAGCC	4340	GGCTGCCCGTGGTCATGATGGCT
3839	AAGCCATCATGACCACGGGCAGC	4341	GCTGCCCGTGGTCATGATGGCTT
3840	CAAGCCATCATGACCACGGGCAG	4342	CTGCCCGTGGTCATGATGGCTTG
3841	ACAAGCCATCATGACCACGGGCA	4343	TGCCCGTGGTCATGATGGCTTGT
3842	CACAAGCCATCATGACCACGGGC	4344	GCCCGTGGTCATGATGGCTTGTG
3843	CCACAAGCCATCATGACCACGGG	4345	CCCGTGGTCATGATGGCTTGTGG
3844	ACCACAAGCCATCATGACCACGG	4346	CCGTGGTCATGATGGCTTGTGGT
3845	GACCACAAGCCATCATGACCACG	4347	CGTGGTCATGATGGCTTGTGGTC
3846	CGACCACAAGCCATCATGACCAC	4348	GTGGTCATGATGGCTTGTGGTCG
3847	TCGACCACAAGCCATCATGACCA	4349	TGGTCATGATGGCTTGTGGTCGA
3848	CTCGACCACAAGCCATCATGACC	4350	GGTCATGATGGCTTGTGGTCGAG
3849	CCTCGACCACAAGCCATCATGAC	4351	GTCATGATGGCTTGTGGTCGAGG
3850	GCCTCGACCACAAGCCATCATGA	4352	TCATGATGGCTTGTGGTCGAGGC
3851	CGCCTCGACCACAAGCCATCATG	4353	CATGATGGCTTGTGGTCGAGGCG
3852	CCGCCTCGACCACAAGCCATCAT	4354	ATGATGGCTTGTGGTCGAGGCGG
3853	CCCGCCTCGACCACAAGCCATCA	4355	TGATGGCTTGTGGTCGAGGCGGG
3854	CCCCGCCTCGACCACAAGCCATC	4356	GATGGCTTGTGGTCGAGGCGGGG
3855	ACCCCGCCTCGACCACAAGCCAT	4357	ATGGCTTGTGGTCGAGGCGGGGT
3856	CACCCCGCCTCGACCACAAGCCA	4358	TGGCTTGTGGTCGAGGCGGGGTG
3857	CCACCCCGCCTCGACCACAAGCC	4359	GGCTTGTGGTCGAGGCGGGGTGG
3858	ACCACCCCGCCTCGACCACAAGC	4360	GCTTGTGGTCGAGGCGGGGTGGT
3859	CACCACCCCGCCTCGACCACAAG	4361	CTTGTGGTCGAGGCGGGGTGGTG
3860	CCACCACCCCGCCTCGACCACAA	4362	TTGTGGTCGAGGCGGGGTGGTGG

3861	ACCACCACCCCGCCTCGACCACA	4363	TGTGGTCGAGGCGGGGTGGTGGT
3862	AACCACCACCCCGCCTCGACCAC	4364	GTGGTCGAGGCGGGGTGGTGGTT
3863	CAACCACCACCCCGCCTCGACCA	4365	TGGTCGAGGCGGGGTGGTGGTTG
3864	GCAACCACCACCCCGCCTCGACC	4366	GGTCGAGGCGGGGTGGTGGTTGC
3865	GGCAACCACCACCCCGCCTCGAC	4367	GTCGAGGCGGGGTGGTGGTTGCC
3866	TGGCAACCACCACCCCGCCTCGA	4368	TCGAGGCGGGGTGGTGGTTGCCA
3867	TTGGCAACCACCACCCCGCCTCG	4369	CGAGGCGGGGTGGTGGTTGCCAA
3868	CTTGGCAACCACCACCCCGCCTC	4370	GAGGCGGGGTGGTGGTTGCCAAG
3869	GCTTGGCAACCACCACCCCGCCT	4371	AGGCGGGGTGGTGGTTGCCAAGC
3870	AGCTTGGCAACCACCACCCCGCC	4372	GGCGGGGTGGTGGTTGCCAAGCT
3871	CAGCTTGGCAACCACCACCCCGC	4373	GCGGGGTGGTGGTTGCCAAGCTG
3872	CCAGCTTGGCAACCACCACCCCG	4374	CGGGGTGGTGGTTGCCAAGCTGG
3873	GCCAGCTTGGCAACCACCACCCC	4375	GGGGTGGTGGTTGCCAAGCTGGC
3874	CGCCAGCTTGGCAACCACCACCC	4376	GGGTGGTGGTTGCCAAGCTGGCG
3875	CCGCCAGCTTGGCAACCACCACC	4377	GGTGGTGGTTGCCAAGCTGGCGG
3876	CCCGCCAGCTTGGCAACCACCAC	4378	GTGGTGGTTGCCAAGCTGGCGGG
3877	CCCCGCCAGCTTGGCAACCACCA	4379	TGGTGGTTGCCAAGCTGGCGGGG
3878	CCCCCGCCAGCTTGGCAACCACC	4380	GGTGGTTGCCAAGCTGGCGGGGG
3879	TCCCCCGCCAGCTTGGCAACCAC	4381	GTGGTTGCCAAGCTGGCGGGGGA
3880	CTCCCCCGCCAGCTTGGCAACCA	4382	TGGTTGCCAAGCTGGCGGGGGAG
3881	ACTCCCCCGCCAGCTTGGCAACC	4383	GGTTGCCAAGCTGGCGGGGGAGT
3882	CACTCCCCCGCCAGCTTGGCAAC	4384	GTTGCCAAGCTGGCGGGGGAGTG
3883	CCACTCCCCCGCCAGCTTGGCAA	4385	TTGCCAAGCTGGCGGGGGAGTGG
3884	CCCACTCCCCCGCCAGCTTGGCA	4386	TGCCAAGCTGGCGGGGGAGTGGG
3885	ACCCACTCCCCCGCCAGCTTGGC	4387	GCCAAGCTGGCGGGGGAGTGGGT
3886	CACCCACTCCCCCGCCAGCTTGG	4388	CCAAGCTGGCGGGGGAGTGGGTG
3887	CCACCCACTCCCCCGCCAGCTTG	4389	CAAGCTGGCGGGGGAGTGGGTGG
3888	CCCACCCACTCCCCCGCCAGCTT	4390	AAGCTGGCGGGGGAGTGGGTGGG
3889	CCCCACCCACTCCCCCGCCAGCT	4391	AGCTGGCGGGGGAGTGGGTGGGG
3890	TCCCCACCCACTCCCCCGCCAGC	4392	GCTGGCGGGGGAGTGGGTGGGGA
3891	CTCCCCACCCACTCCCCCGCCAG	4393	CTGGCGGGGGAGTGGGTGGGGAG
3892	CCTCCCCACCCACTCCCCCGCCA	4394	TGGCGGGGGAGTGGGTGGGGAGG
3893	CCCTCCCCACCCACTCCCCCGCC	4395	GGCGGGGGAGTGGGTGGGGAGGG
3894	GCCCTCCCCACCCACTCCCCCGC	4396	GCGGGGGAGTGGGTGGGGAGGGC
3895	AGCCCTCCCCACCCACTCCCCCG	4397	CGGGGGAGTGGGTGGGGAGGGCT
3896	CAGCCCTCCCCACCCACTCCCCC	4398	GGGGGAGTGGGTGGGGAGGGCTG
3897	CCAGCCCTCCCCACCCACTCCCC	4399	GGGGAGTGGGTGGGGAGGGCTGG
3898	CCCAGCCCTCCCCACCCACTCCC	4400	GGGAGTGGGTGGGGAGGGCTGGG
3899	GCCCAGCCCTCCCCACCCACTCC	4401	GGAGTGGGTGGGGAGGGCTGGGC

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate

linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

UNC13A Oligonucleotides Complementary to UNC13A Transcript

[00339] In some embodiments, a UNC13A AON includes a sequence that is at least 85% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a UNC13A transcript (e.g., SEQ ID NO: 9587-9595). In some embodiments, a UNC13A AON includes a sequence that is between 90-95% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a UNC13A transcript (e.g., SEQ ID NO: 9587-9595). In particular embodiments, a UNC13A AON includes a sequence that is between 85% and 90% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a UNC13A transcript (e.g., SEQ ID NO: 9587-9595). In particular embodiments, a UNC13A AON includes a sequence that is between 84% to 88% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a UNC13A transcript (e.g., SEQ ID NO: 9587-9595). In particular embodiments, a UNC13A AON includes a sequence that is between 89% to 92% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a mis-spliced UNC13A transcript (e.g., SEQ ID NO: 9587-9595). In particular embodiments, a UNC13A AON includes a sequence that is between 94% to 96% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a UNC13A transcript (e.g., SEQ ID NO: 9587-9595).

[00340] In various embodiments, a UNC13A AON comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9696, and SEQ ID NOs: 10670-10779. In various embodiments, a UNC13A AON comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9696, and SEQ ID NOs: 10670-10779.

[00341] In some embodiments, the UNC13A AON comprises a spacer and has a segment having at most 7 linked nucleosides. In some embodiments, the UNC13A AON comprises a spacer and has a segment having at most 6, 5, 4, 3, or 2 linked nucleosides.

[00342] UNC13A AON binding specificity can be assessed via measurement of parameters such as dissociation constant, melting temperature, or other criteria such as changes in protein or RNA expression levels or other assays that measure UNC13A activity or expression.

[00343] In some embodiments, a UNC13A AON can include a non-duplexed oligonucleotide. In some embodiments, a UNC13A AON can include a duplex of two oligonucleotides where the first oligonucleotide includes a nucleobase sequence that is completely or almost completely complementary to a UNC13A pre-mRNA sequence and the second oligonucleotide includes a nucleobase sequence that is complementary to the nucleobase sequence of the first oligonucleotide.

[00344] In some embodiments, a UNC13A AON can target UNC13A pre-mRNAs produced from UNC13A genes of one or more species. For example, a UNC13A AON can target a UNC13A pre-mRNA of a mammalian UNC13A gene, for example, a human (*i.e.*, *Homo sapiens*) UNC13A gene. In particular embodiments, the UNC13A AON targets a human UNC13A pre-mRNA. In some embodiments, the UNC13A AON includes a nucleobase sequence that is complementary to a nucleobase sequence of a UNC13A gene or a UNC13A pre-mRNA or a portion thereof.

[00345] UNC13A AONs described herein include antisense oligonucleotides comprising the oligonucleotide sequences listed in Table 9 below:

Table 9. Example UNC13A AON Sequences.

SEQ ID NO:	AON Sequence* (5' → 3')	SEQ ID NO:	Target Sequence (5' → 3')
4531	GGAGGGGCCGAGCAATGACCCTCAC	5795	GTGAGGGTCATTGCTCGGCCCCTCC
4532	GGGAGGGGCCGAGCAATGACCCTCA	5796	TGAGGGTCATTGCTCGGCCCCTCCC
4533	TGGGAGGGGCCGAGCAATGACCCTC	5797	GAGGGTCATTGCTCGGCCCCTCCCA
4534	ATGGGAGGGGCCGAGCAATGACCCT	5798	AGGGTCATTGCTCGGCCCCTCCCAT
4535	CATGGGAGGGGCCGAGCAATGACCC	5799	GGGTCATTGCTCGGCCCCTCCCATG
4536	GCATGGGAGGGGCCGAGCAATGACC	5800	GGTCATTGCTCGGCCCCTCCCATGC
4537	GGCATGGGAGGGGCCGAGCAATGAC	5801	GTCATTGCTCGGCCCCTCCCATGCC
4538	TGGCATGGGAGGGGCCGAGCAATGA	5802	TCATTGCTCGGCCCCTCCCATGCCA
4539	GTGGCATGGGAGGGGCCGAGCAATG	5803	CATTGCTCGGCCCCTCCCATGCCAC
4540	AGTGGCATGGGAGGGGCCGAGCAAT	5804	ATTGCTCGGCCCCTCCCATGCCACT
4541	AAGTGGCATGGGAGGGGCCGAGCAA	5805	TTGCTCGGCCCCTCCCATGCCACTT
4542	GAAGTGGCATGGGAGGGGCCGAGCA	5806	TGCTCGGCCCCTCCCATGCCACTTC
4543	GGAAGTGGCATGGGAGGGGCCGAGC	5807	GCTCGGCCCCTCCCATGCCACTTCC
4544	TGGAAGTGGCATGGGAGGGGCCGAG	5808	CTCGGCCCCTCCCATGCCACTTCCA
4545	GTGGAAGTGGCATGGGAGGGGCCGA	5809	TCGGCCCCTCCCATGCCACTTCCAC

4546	AGTGGAAGTGGCATGGGAGGGGCCG	5810	CGGCCCCTCCCATGCCACTTCCACT
4547	GAGTGGAAGTGGCATGGGAGGGGCC	5811	GGCCCCTCCCATGCCACTTCCACTC
4548	TGAGTGGAAGTGGCATGGGAGGGGC	5812	GCCCCTCCCATGCCACTTCCACTCA
4549	GTGAGTGGAAGTGGCATGGGAGGGG	5813	CCCCTCCCATGCCACTTCCACTCAC
4550	GGTGAGTGGAAGTGGCATGGGAGGG	5814	CCCTCCCATGCCACTTCCACTCACC
4551	TGGTGAGTGGAAGTGGCATGGGAGG	5815	CCTCCCATGCCACTTCCACTCACCA
4552	ATGGTGAGTGGAAGTGGCATGGGAG	5816	CTCCCATGCCACTTCCACTCACCAT
4553	AATGGTGAGTGGAAGTGGCATGGGA	5817	TCCCATGCCACTTCCACTCACCATT
4554	GAATGGTGAGTGGAAGTGGCATGGG	5818	CCCATGCCACTTCCACTCACCATTC
4555	GGAATGGTGAGTGGAAGTGGCATGG	5819	CCATGCCACTTCCACTCACCATTCC
4556	AGGAATGGTGAGTGGAAGTGGCATG	5820	CATGCCACTTCCACTCACCATTCCT
4557	CAGGAATGGTGAGTGGAAGTGGCAT	5821	ATGCCACTTCCACTCACCATTCCTG
4558	GCAGGAATGGTGAGTGGAAGTGGCA	5822	TGCCACTTCCACTCACCATTCCTGC
4559	GGCAGGAATGGTGAGTGGAAGTGGC	5823	GCCACTTCCACTCACCATTCCTGCC
4560	AGGCAGGAATGGTGAGTGGAAGTGG	5824	CCACTTCCACTCACCATTCCTGCCT
4561	CAGGCAGGAATGGTGAGTGGAAGTG	5825	CACTTCCACTCACCATTCCTGCCTG
4562	GCAGGCAGGAATGGTGAGTGGAAGT	5826	ACTTCCACTCACCATTCCTGCCTGC
4563	GGCAGGCAGGAATGGTGAGTGGAAG	5827	CTTCCACTCACCATTCCTGCCTGCC
4564	GGGCAGGCAGGAATGGTGAGTGGAA	5828	TTCCACTCACCATTCCTGCCTGCCC
4565	TGGGCAGGCAGGAATGGTGAGTGGA	5829	TCCACTCACCATTCCTGCCTGCCCA
4566	CTGGGCAGGCAGGAATGGTGAGTGG	5830	CCACTCACCATTCCTGCCTGCCCAG
4567	GCTGGGCAGGCAGGAATGGTGAGTG	5831	CACTCACCATTCCTGCCTGCCCAGC
4568	AGCTGGGCAGGCAGGAATGGTGAGT	5832	ACTCACCATTCCTGCCTGCCCAGCT
4569	GAGCTGGGCAGGCAGGAATGGTGAG	5833	CTCACCATTCCTGCCTGCCCAGCTC
4570	AGAGCTGGGCAGGCAGGAATGGTGA	5834	TCACCATTCCTGCCTGCCCAGCTCT
4571	AAGAGCTGGGCAGGCAGGAATGGTG	5835	CACCATTCCTGCCTGCCCAGCTCTT
4572	GAAGAGCTGGGCAGGCAGGAATGGT	5836	ACCATTCCTGCCTGCCCAGCTCTTC
4573	GGAAGAGCTGGGCAGGCAGGAATGG	5837	CCATTCCTGCCTGCCCAGCTCTTCC
4574	AGGAAGAGCTGGGCAGGCAGGAATG	5838	CATTCCTGCCTGCCCAGCTCTTCCT
4575	GAGGAAGAGCTGGGCAGGCAGGAAT	5839	ATTCCTGCCTGCCCAGCTCTTCCTC
4576	AGAGGAAGAGCTGGGCAGGCAGGAA	5840	TTCCTGCCTGCCCAGCTCTTCCTCT
4577	AAGAGGAAGAGCTGGGCAGGCAGGA	5841	TCCTGCCTGCCCAGCTCTTCCTCTT
4578	AAAGAGGAAGAGCTGGGCAGGCAGG	5842	CCTGCCTGCCCAGCTCTTCCTCTTT
4579	GAAAGAGGAAGAGCTGGGCAGGCAG	5843	CTGCCTGCCCAGCTCTTCCTCTTTC
4580	AGAAAGAGGAAGAGCTGGGCAGGCA	5844	TGCCTGCCCAGCTCTTCCTCTTTCT
4581	CAGAAAGAGGAAGAGCTGGGCAGGC	5845	GCCTGCCCAGCTCTTCCTCTTTCTG
4582	CCAGAAAGAGGAAGAGCTGGGCAGG	5846	CCTGCCCAGCTCTTCCTCTTTCTGG
4583	GCCAGAAAGAGGAAGAGCTGGGCAG	5847	CTGCCCAGCTCTTCCTCTTTCTGGC
4584	GGCCAGAAAGAGGAAGAGCTGGGCA	5848	TGCCCAGCTCTTCCTCTTTCTGGCC
4585	TGGCCAGAAAGAGGAAGAGCTGGGC	5849	GCCCAGCTCTTCCTCTTTCTGGCCA
4586	GTGGCCAGAAAGAGGAAGAGCTGGG	5850	CCCAGCTCTTCCTCTTTCTGGCCAC
4587	TGTGGCCAGAAAGAGGAAGAGCTGG	5851	CCAGCTCTTCCTCTTTCTGGCCACA

4588	GTGTGGCCAGAAAGAGGAAGAGCTG	5852	CAGCTCTTCCTCTTTCTGGCCACAC
4589	GGTGTGGCCAGAAAGAGGAAGAGCT	5853	AGCTCTTCCTCTTTCTGGCCACACC
4590	TGGTGTGGCCAGAAAGAGGAAGAGC	5854	GCTCTTCCTCTTTCTGGCCACACCA
4591	ATGGTGTGGCCAGAAAGAGGAAGAG	5855	CTCTTCCTCTTTCTGGCCACACCAT
4592	GATGGTGTGGCCAGAAAGAGGAAGA	5856	TCTTCCTCTTTCTGGCCACACCATC
4593	GGATGGTGTGGCCAGAAAGAGGAAG	5857	CTTCCTCTTTCTGGCCACACCATCC
4594	TGGATGGTGTGGCCAGAAAGAGGAA	5858	TTCCTCTTTCTGGCCACACCATCCA
4595	GTGGATGGTGTGGCCAGAAAGAGGA	5859	TCCTCTTTCTGGCCACACCATCCAC
4596	TGTGGATGGTGTGGCCAGAAAGAGG	5860	CCTCTTTCTGGCCACACCATCCACA
4597	GTGTGGATGGTGTGGCCAGAAAGAG	5861	CTCTTTCTGGCCACACCATCCACAC
4598	AGTGTGGATGGTGTGGCCAGAAAGA	5862	TCTTTCTGGCCACACCATCCACACT
4599	GAGTGTGGATGGTGTGGCCAGAAAG	5863	CTTTCTGGCCACACCATCCACACTC
4600	AGAGTGTGGATGGTGTGGCCAGAAA	5864	TTTCTGGCCACACCATCCACACTCT
4601	GAGAGTGTGGATGGTGTGGCCAGAA	5865	TTCTGGCCACACCATCCACACTCTC
4602	GGAGAGTGTGGATGGTGTGGCCAGA	5866	TCTGGCCACACCATCCACACTCTCC
4603	AGGAGAGTGTGGATGGTGTGGCCAG	5867	CTGGCCACACCATCCACACTCTCCT
4604	CAGGAGAGTGTGGATGGTGTGGCCA	5868	TGGCCACACCATCCACACTCTCCTG
4605	CCAGGAGAGTGTGGATGGTGTGGCC	5869	GGCCACACCATCCACACTCTCCTGG
4606	GCCAGGAGAGTGTGGATGGTGTGGC	5870	GCCACACCATCCACACTCTCCTGGC
4607	GGCCAGGAGAGTGTGGATGGTGTGG	5871	CCACACCATCCACACTCTCCTGGCC
4608	GGGCCAGGAGAGTGTGGATGGTGTG	5872	CACACCATCCACACTCTCCTGGCCC
4609	AGGGCCAGGAGAGTGTGGATGGTGT	5873	ACACCATCCACACTCTCCTGGCCCT
4610	GAGGGCCAGGAGAGTGTGGATGGTG	5874	CACCATCCACACTCTCCTGGCCCTC
4611	AGAGGGCCAGGAGAGTGTGGATGGT	5875	ACCATCCACACTCTCCTGGCCCTCT
4612	CAGAGGGCCAGGAGAGTGTGGATGG	5876	CCATCCACACTCTCCTGGCCCTCTG
4613	TCAGAGGGCCAGGAGAGTGTGGATG	5877	CATCCACACTCTCCTGGCCCTCTGA
4614	CTCAGAGGGCCAGGAGAGTGTGGAT	5878	ATCCACACTCTCCTGGCCCTCTGAG
4615	TCTCAGAGGGCCAGGAGAGTGTGGA	5879	TCCACACTCTCCTGGCCCTCTGAGA
4616	GTCTCAGAGGGCCAGGAGAGTGTGG	5880	CCACACTCTCCTGGCCCTCTGAGAC
4617	AGTCTCAGAGGGCCAGGAGAGTGTG	5881	CACACTCTCCTGGCCCTCTGAGACT
4618	CAGTCTCAGAGGGCCAGGAGAGTGT	5882	ACACTCTCCTGGCCCTCTGAGACTG
4619	GCAGTCTCAGAGGGCCAGGAGAGTG	5883	CACTCTCCTGGCCCTCTGAGACTGC
4620	GGCAGTCTCAGAGGGCCAGGAGAGT	5884	ACTCTCCTGGCCCTCTGAGACTGCC
4621	GGGCAGTCTCAGAGGGCCAGGAGAG	5885	CTCTCCTGGCCCTCTGAGACTGCCC
4622	CGGGCAGTCTCAGAGGGCCAGGAGA	5886	TCTCCTGGCCCTCTGAGACTGCCCG
4623	GCGGGCAGTCTCAGAGGGCCAGGAG	5887	CTCCTGGCCCTCTGAGACTGCCCGC
4624	GGCGGGCAGTCTCAGAGGGCCAGGA	5888	TCCTGGCCCTCTGAGACTGCCCGCC
4625	TGGCGGGCAGTCTCAGAGGGCCAGG	5889	CCTGGCCCTCTGAGACTGCCCGCCA
4626	ATGGCGGGCAGTCTCAGAGGGCCAG	5890	CTGGCCCTCTGAGACTGCCCGCCAT
4627	CATGGCGGGCAGTCTCAGAGGGCCA	5891	TGGCCCTCTGAGACTGCCCGCCATG
4628	GCATGGCGGGCAGTCTCAGAGGGCC	5892	GGCCCTCTGAGACTGCCCGCCATGC
4629	GGCATGGCGGGCAGTCTCAGAGGGC	5893	GCCCTCTGAGACTGCCCGCCATGCC

4630	TGGCATGGCGGGCAGTCTCAGAGGG	5894	CCCTCTGAGACTGCCCGCCATGCCA
4631	ATGGCATGGCGGGCAGTCTCAGAGG	5895	CCTCTGAGACTGCCCGCCATGCCAT
4632	AATGGCATGGCGGGCAGTCTCAGAG	5896	CTCTGAGACTGCCCGCCATGCCATT
4633	GAATGGCATGGCGGGCAGTCTCAGA	5897	TCTGAGACTGCCCGCCATGCCATTC
4634	GGAATGGCATGGCGGGCAGTCTCAG	5898	CTGAGACTGCCCGCCATGCCATTCC
4635	GGGAATGGCATGGCGGGCAGTCTCA	5899	TGAGACTGCCCGCCATGCCATTCCC
4636	AGGGAATGGCATGGCGGGCAGTCTC	5900	GAGACTGCCCGCCATGCCATTCCCT
4637	AAGGGAATGGCATGGCGGGCAGTCT	5901	AGACTGCCCGCCATGCCATTCCCTT
4638	AAAGGGAATGGCATGGCGGGCAGTC	5902	GACTGCCCGCCATGCCATTCCCTTT
4639	TAAAGGGAATGGCATGGCGGGCAGT	5903	ACTGCCCGCCATGCCATTCCCTTTA
4640	GTAAAGGGAATGGCATGGCGGGCAG	5904	CTGCCCGCCATGCCATTCCCTTTAC
4641	GGTAAAGGGAATGGCATGGCGGGCA	5905	TGCCCGCCATGCCATTCCCTTTACC
4642	AGGTAAAGGGAATGGCATGGCGGGC	5906	GCCCGCCATGCCATTCCCTTTACCT
4643	CAGGTAAAGGGAATGGCATGGCGGG	5907	CCCGCCATGCCATTCCCTTTACCTG
4644	CCAGGTAAAGGGAATGGCATGGCGG	5908	CCGCCATGCCATTCCCTTTACCTGG
4645	TCCAGGTAAAGGGAATGGCATGGCG	5909	CGCCATGCCATTCCCTTTACCTGGA
4646	TTCCAGGTAAAGGGAATGGCATGGC	5910	GCCATGCCATTCCCTTTACCTGGAA
4647	TTTCCAGGTAAAGGGAATGGCATGG	5911	CCATGCCATTCCCTTTACCTGGAAA
4648	TTTTCCAGGTAAAGGGAATGGCATG	5912	CATGCCATTCCCTTTACCTGGAAAA
4649	GTTTTCCAGGTAAAGGGAATGGCAT	5913	ATGCCATTCCCTTTACCTGGAAAAC
4650	AGTTTTCCAGGTAAAGGGAATGGCA	5914	TGCCATTCCCTTTACCTGGAAAACT
4651	GAGTTTTCCAGGTAAAGGGAATGGC	5915	GCCATTCCCTTTACCTGGAAAACTC
4652	GGAGTTTTCCAGGTAAAGGGAATGG	5916	CCATTCCCTTTACCTGGAAAACTCC
4653	AGGAGTTTTCCAGGTAAAGGGAATG	5917	CATTCCCTTTACCTGGAAAACTCCT
4654	GAGGAGTTTTCCAGGTAAAGGGAAT	5918	ATTCCCTTTACCTGGAAAACTCCTC
4655	GGAGGAGTTTTCCAGGTAAAGGGAA	5919	TTCCCTTTACCTGGAAAACTCCTCC
4656	GGGAGGAGTTTTCCAGGTAAAGGGA	5920	TCCCTTTACCTGGAAAACTCCTCCC
4657	AGGGAGGAGTTTTCCAGGTAAAGGG	5921	CCCTTTACCTGGAAAACTCCTCCCT
4658	TAGGGAGGAGTTTTCCAGGTAAAGG	5922	CCTTTACCTGGAAAACTCCTCCCTA
4659	ATAGGGAGGAGTTTTCCAGGTAAAG	5923	CTTTACCTGGAAAACTCCTCCCTAT
4660	GATAGGGAGGAGTTTTCCAGGTAAA	5924	TTTACCTGGAAAACTCCTCCCTATC
4661	GGATAGGGAGGAGTTTTCCAGGTAA	5925	TTACCTGGAAAACTCCTCCCTATCC
4662	TGGATAGGGAGGAGTTTTCCAGGTA	5926	TACCTGGAAAACTCCTCCCTATCCA
4663	ATGGATAGGGAGGAGTTTTCCAGGT	5927	ACCTGGAAAACTCCTCCCTATCCAT
4664	GATGGATAGGGAGGAGTTTTCCAGG	5928	CCTGGAAAACTCCTCCCTATCCATC
4665	TGATGGATAGGGAGGAGTTTTCCAG	5929	CTGGAAAACTCCTCCCTATCCATCA
4666	TTGATGGATAGGGAGGAGTTTTCCA	5930	TGGAAAACTCCTCCCTATCCATCAA
4667	TTTGATGGATAGGGAGGAGTTTTCC	5931	GGAAAACTCCTCCCTATCCATCAAA
4668	CTTTGATGGATAGGGAGGAGTTTTC	5932	GAAAACTCCTCCCTATCCATCAAAG
4669	ACTTTGATGGATAGGGAGGAGTTTT	5933	AAAACTCCTCCCTATCCATCAAAGT
4670	GACTTTGATGGATAGGGAGGAGTTT	5934	AAACTCCTCCCTATCCATCAAAGTC
4671	GGACTTTGATGGATAGGGAGGAGTT	5935	AACTCCTCCCTATCCATCAAAGTCC

4672	TGGACTTTGATGGATAGGGAGGAGT	5936	ACTCCTCCCTATCCATCAAAGTCCA
4673	CTGGACTTTGATGGATAGGGAGGAG	5937	CTCCTCCCTATCCATCAAAGTCCAG
4674	TCTGGACTTTGATGGATAGGGAGGA	5938	TCCTCCCTATCCATCAAAGTCCAGA
4675	ATCTGGACTTTGATGGATAGGGAGG	5939	CCTCCCTATCCATCAAAGTCCAGAT
4676	AATCTGGACTTTGATGGATAGGGAG	5940	CTCCCTATCCATCAAAGTCCAGATT
4677	GAATCTGGACTTTGATGGATAGGGA	5941	TCCCTATCCATCAAAGTCCAGATTC
4678	TGAATCTGGACTTTGATGGATAGGG	5942	CCCTATCCATCAAAGTCCAGATTCA
4679	CTGAATCTGGACTTTGATGGATAGG	5943	CCTATCCATCAAAGTCCAGATTCAG
4680	CCTGAATCTGGACTTTGATGGATAG	5944	CTATCCATCAAAGTCCAGATTCAGG
4681	CCCTGAATCTGGACTTTGATGGATA	5945	TATCCATCAAAGTCCAGATTCAGGG
4682	ACCCTGAATCTGGACTTTGATGGAT	5946	ATCCATCAAAGTCCAGATTCAGGGT
4683	GACCCTGAATCTGGACTTTGATGGA	5947	TCCATCAAAGTCCAGATTCAGGGTC
4684	TGACCCTGAATCTGGACTTTGATGG	5948	CCATCAAAGTCCAGATTCAGGGTCA
4685	GTGACCCTGAATCTGGACTTTGATG	5949	CATCAAAGTCCAGATTCAGGGTCAC
4686	GGTGACCCTGAATCTGGACTTTGAT	5950	ATCAAAGTCCAGATTCAGGGTCACC
4687	AGGTGACCCTGAATCTGGACTTTGA	5951	TCAAAGTCCAGATTCAGGGTCACCT
4688	GAGGTGACCCTGAATCTGGACTTTG	5952	CAAAGTCCAGATTCAGGGTCACCTC
4689	GGAGGTGACCCTGAATCTGGACTTT	5953	AAAGTCCAGATTCAGGGTCACCTCC
4690	AGGAGGTGACCCTGAATCTGGACTT	5954	AAGTCCAGATTCAGGGTCACCTCCT
4691	GAGGAGGTGACCCTGAATCTGGACT	5955	AGTCCAGATTCAGGGTCACCTCCTC
4692	AGAGGAGGTGACCCTGAATCTGGAC	5956	GTCCAGATTCAGGGTCACCTCCTCT
4693	CAGAGGAGGTGACCCTGAATCTGGA	5957	TCCAGATTCAGGGTCACCTCCTCTG
4694	CCAGAGGAGGTGACCCTGAATCTGG	5958	CCAGATTCAGGGTCACCTCCTCTGG
4695	CCCAGAGGAGGTGACCCTGAATCTG	5959	CAGATTCAGGGTCACCTCCTCTGGG
4696	TCCCAGAGGAGGTGACCCTGAATCT	5960	AGATTCAGGGTCACCTCCTCTGGGA
4697	TTCCCAGAGGAGGTGACCCTGAATC	5961	GATTCAGGGTCACCTCCTCTGGGAA
4698	CTTCCCAGAGGAGGTGACCCTGAAT	5962	ATTCAGGGTCACCTCCTCTGGGAAG
4699	GCTTCCCAGAGGAGGTGACCCTGAA	5963	TTCAGGGTCACCTCCTCTGGGAAGC
4700	GGCTTCCCAGAGGAGGTGACCCTGA	5964	TCAGGGTCACCTCCTCTGGGAAGCC
4701	GGGCTTCCCAGAGGAGGTGACCCTG	5965	CAGGGTCACCTCCTCTGGGAAGCCC
4702	TGGGCTTCCCAGAGGAGGTGACCCT	5966	AGGGTCACCTCCTCTGGGAAGCCCA
4703	GTGGGCTTCCCAGAGGAGGTGACCC	5967	GGGTCACCTCCTCTGGGAAGCCCAC
4704	GGTGGGCTTCCCAGAGGAGGTGACC	5968	GGTCACCTCCTCTGGGAAGCCCACC
4705	AGGTGGGCTTCCCAGAGGAGGTGAC	5969	GTCACCTCCTCTGGGAAGCCCACCT
4706	AAGGTGGGCTTCCCAGAGGAGGTGA	5970	TCACCTCCTCTGGGAAGCCCACCTT
4707	CAAGGTGGGCTTCCCAGAGGAGGTG	5971	CACCTCCTCTGGGAAGCCCACCTTG
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4709	GCCAAGGTGGGCTTCCCAGAGGAGG	5973	CCTCCTCTGGGAAGCCCACCTTGGC
4710	GGCCAAGGTGGGCTTCCCAGAGGAG	5974	CTCCTCTGGGAAGCCCACCTTGGCC
4711	AGGCCAAGGTGGGCTTCCCAGAGGA	5975	TCCTCTGGGAAGCCCACCTTGGCCT
4712	GAGGCCAAGGTGGGCTTCCCAGAGG	5976	CCTCTGGGAAGCCCACCTTGGCCTC
4713	GGAGGCCAAGGTGGGCTTCCCAGAG	5977	CTCTGGGAAGCCCACCTTGGCCTCC

4714	TGGAGGCCAAGGTGGGCTTCCCAGA	5978	TCTGGGAAGCCCACCTTGGCCTCCA
4715	CTGGAGGCCAAGGTGGGCTTCCCAG	5979	CTGGGAAGCCCACCTTGGCCTCCAG
4716	CCTGGAGGCCAAGGTGGGCTTCCCA	5980	TGGGAAGCCCACCTTGGCCTCCAGG
4717	ACCTGGAGGCCAAGGTGGGCTTCCC	5981	GGGAAGCCCACCTTGGCCTCCAGGT
4718	AACCTGGAGGCCAAGGTGGGCTTCC	5982	GGAAGCCCACCTTGGCCTCCAGGTT
4719	CAACCTGGAGGCCAAGGTGGGCTTC	5983	GAAGCCCACCTTGGCCTCCAGGTTG
4720	TCAACCTGGAGGCCAAGGTGGGCTT	5984	AAGCCCACCTTGGCCTCCAGGTTGA
4721	GTCAACCTGGAGGCCAAGGTGGGCT	5985	AGCCCACCTTGGCCTCCAGGTTGAC
4722	AGTCAACCTGGAGGCCAAGGTGGGC	5986	GCCCACCTTGGCCTCCAGGTTGACT
4723	GAGTCAACCTGGAGGCCAAGGTGGG	5987	CCCACCTTGGCCTCCAGGTTGACTC
4724	AGAGTCAACCTGGAGGCCAAGGTGG	5988	CCACCTTGGCCTCCAGGTTGACTCT
4725	GAGAGTCAACCTGGAGGCCAAGGTG	5989	CACCTTGGCCTCCAGGTTGACTCTC
4726	TGAGAGTCAACCTGGAGGCCAAGGT	5990	ACCTTGGCCTCCAGGTTGACTCTCA
4727	GTGAGAGTCAACCTGGAGGCCAAGG	5991	CCTTGGCCTCCAGGTTGACTCTCAC
4728	AGTGAGAGTCAACCTGGAGGCCAAG	5992	CTTGGCCTCCAGGTTGACTCTCACT
4729	TAGTGAGAGTCAACCTGGAGGCCAA	5993	TTGGCCTCCAGGTTGACTCTCACTA
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4732	GAGTAGTGAGAGTCAACCTGGAGGC	5996	GCCTCCAGGTTGACTCTCACTACTC
4733	TGAGTAGTGAGAGTCAACCTGGAGG	5997	CCTCCAGGTTGACTCTCACTACTCA
4734	ATGAGTAGTGAGAGTCAACCTGGAG	5998	CTCCAGGTTGACTCTCACTACTCAT
4735	GATGAGTAGTGAGAGTCAACCTGGA	5999	TCCAGGTTGACTCTCACTACTCATC
4736	TGATGAGTAGTGAGAGTCAACCTGG	6000	CCAGGTTGACTCTCACTACTCATCA
4737	ATGATGAGTAGTGAGAGTCAACCTG	6001	CAGGTTGACTCTCACTACTCATCAT
4738	GATGATGAGTAGTGAGAGTCAACCT	6002	AGGTTGACTCTCACTACTCATCATC
4739	TGATGATGAGTAGTGAGAGTCAACC	6003	GGTTGACTCTCACTACTCATCATCA
4740	CTGATGATGAGTAGTGAGAGTCAAC	6004	GTTGACTCTCACTACTCATCATCAG
4741	CCTGATGATGAGTAGTGAGAGTCAA	6005	TTGACTCTCACTACTCATCATCAGG
4742	ACCTGATGATGAGTAGTGAGAGTCA	6006	TGACTCTCACTACTCATCATCAGGT
4743	AACCTGATGATGAGTAGTGAGAGTC	6007	GACTCTCACTACTCATCATCAGGTT
4744	GAACCTGATGATGAGTAGTGAGAGT	6008	ACTCTCACTACTCATCATCAGGTTC
4745	AGAACCTGATGATGAGTAGTGAGAG	6009	CTCTCACTACTCATCATCAGGTTCT
4746	AAGAACCTGATGATGAGTAGTGAGA	6010	TCTCACTACTCATCATCAGGTTCTT
4747	GAAGAACCTGATGATGAGTAGTGAG	6011	CTCACTACTCATCATCAGGTTCTTC
4748	GGAAGAACCTGATGATGAGTAGTGA	6012	TCACTACTCATCATCAGGTTCTTCC
4749	AGGAAGAACCTGATGATGAGTAGTG	6013	CACTACTCATCATCAGGTTCTTCCT
4750	AAGGAAGAACCTGATGATGAGTAGT	6014	ACTACTCATCATCAGGTTCTTCCTT
4751	GAAGGAAGAACCTGATGATGAGTAG	6015	CTACTCATCATCAGGTTCTTCCTTC
4752	AGAAGGAAGAACCTGATGATGAGTA	6016	TACTCATCATCAGGTTCTTCCTTCT
4753	TAGAAGGAAGAACCTGATGATGAGT	6017	ACTCATCATCAGGTTCTTCCTTCTA
4754	ATAGAAGGAAGAACCTGATGATGAG	6018	CTCATCATCAGGTTCTTCCTTCTAT
4755	AATAGAAGGAAGAACCTGATGATGA	6019	TCATCATCAGGTTCTTCCTTCTATT

4756	GAATAGAAGGAAGAACCTGATGATG	6020	CATCATCAGGTTCTTCCTTCTATTC
4757	GGAATAGAAGGAAGAACCTGATGAT	6021	ATCATCAGGTTCTTCCTTCTATTCC
4758	TGGAATAGAAGGAAGAACCTGATGA	6022	TCATCAGGTTCTTCCTTCTATTCCA
4759	CTGGAATAGAAGGAAGAACCTGATG	6023	CATCAGGTTCTTCCTTCTATTCCAG
4760	GCTGGAATAGAAGGAAGAACCTGAT	6024	ATCAGGTTCTTCCTTCTATTCCAGC
4761	GGCTGGAATAGAAGGAAGAACCTGA	6025	TCAGGTTCTTCCTTCTATTCCAGCC
4762	GGGCTGGAATAGAAGGAAGAACCTG	6026	CAGGTTCTTCCTTCTATTCCAGCCC
4763	AGGGCTGGAATAGAAGGAAGAACCT	6027	AGGTTCTTCCTTCTATTCCAGCCCT
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4766	GTTAGGGCTGGAATAGAAGGAAGAA	6030	TTCTTCCTTCTATTCCAGCCCTAAC
4767	GGTTAGGGCTGGAATAGAAGGAAGA	6031	TCTTCCTTCTATTCCAGCCCTAACC
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4774	CCTGAGTGGTTAGGGCTGGAATAGA	6038	TCTATTCCAGCCCTAACCACTCAGG
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4783	CGGCCCAATCCTGAGTGGTTAGGGC	6047	GCCCTAACCACTCAGGATTGGGCCG
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4792	AGACACAAACGGCCCAATCCTGAGT	6056	ACTCAGGATTGGGCCGTTTGTGTCT
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4795	CCCAGACACAAACGGCCCAATCCTG	6059	CAGGATTGGGCCGTTTGTGTCTGGG
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4798	ATACCCAGACACAAACGGCCCAATC	6062	GATTGGGCCGTTTGTGTCTGGGTAT
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4804	AGAGACATACCCAGACACAAACGGC	6068	GCCGTTTGTGTCTGGGTATGTCTCT
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4806	GAAGAGACATACCCAGACACAAACG	6070	CGTTTGTGTCTGGGTATGTCTCTTC
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4809	CTGGAAGAGACATACCCAGACACAA	6073	TTGTGTCTGGGTATGTCTCTTCCAG
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4814	GGCAGCTGGAAGAGACATACCCAGA	6078	TCTGGGTATGTCTCTTCCAGCTGCC
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4842	GGGATAAGAGTTCTTTCCAGGAAAC	6106	GTTTCCTGGAAAGAACTCTTATCCC
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4897	CATCTGTTCAATCATTCATTCATTC	6161	GAATGAATGAATGATTGAACAGATG
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4903	CTCATTCATCTGTTCAATCATTCAT	6167	ATGAATGATTGAACAGATGAATGAG
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4907	ATCACTCATTCATCTGTTCAATCAT	6171	ATGATTGAACAGATGAATGAGTGAT
4908	CATCACTCATTCATCTGTTCAATCA	6172	TGATTGAACAGATGAATGAGTGATG
4909	TCATCACTCATTCATCTGTTCAATC	6173	GATTGAACAGATGAATGAGTGATGA
4910	CTCATCACTCATTCATCTGTTCAAT	6174	ATTGAACAGATGAATGAGTGATGAG
4911	ACTCATCACTCATTCATCTGTTCAA	6175	TTGAACAGATGAATGAGTGATGAGT
4912	TACTCATCACTCATTCATCTGTTCA	6176	TGAACAGATGAATGAGTGATGAGTA
4913	CTACTCATCACTCATTCATCTGTTC	6177	GAACAGATGAATGAGTGATGAGTAG
4914	TCTACTCATCACTCATTCATCTGTT	6178	AACAGATGAATGAGTGATGAGTAGA
4915	ATCTACTCATCACTCATTCATCTGT	6179	ACAGATGAATGAGTGATGAGTAGAT
4916	TATCTACTCATCACTCATTCATCTG	6180	CAGATGAATGAGTGATGAGTAGATA
4917	TTATCTACTCATCACTCATTCATCT	6181	AGATGAATGAGTGATGAGTAGATAA
4918	TTTATCTACTCATCACTCATTCATC	6182	GATGAATGAGTGATGAGTAGATAAA
4919	TTTTATCTACTCATCACTCATTCAT	6183	ATGAATGAGTGATGAGTAGATAAAA
4920	CTTTTATCTACTCATCACTCATTCA	6184	TGAATGAGTGATGAGTAGATAAAAG
4921	CCTTTTATCTACTCATCACTCATTC	6185	GAATGAGTGATGAGTAGATAAAAGG
4922	TCCTTTTATCTACTCATCACTCATT	6186	AATGAGTGATGAGTAGATAAAAGGA
4923	ATCCTTTTATCTACTCATCACTCAT	6187	ATGAGTGATGAGTAGATAAAAGGAT

4924	CATCCTTTTATCTACTCATCACTCA	6188	TGAGTGATGAGTAGATAAAAGGATG
4925	CCATCCTTTTATCTACTCATCACTC	6189	GAGTGATGAGTAGATAAAAGGATGG
4926	TCCATCCTTTTATCTACTCATCACT	6190	AGTGATGAGTAGATAAAAGGATGGA
4927	ATCCATCCTTTTATCTACTCATCAC	6191	GTGATGAGTAGATAAAAGGATGGAT
4928	CATCCATCCTTTTATCTACTCATCA	6192	TGATGAGTAGATAAAAGGATGGATG
4929	CCATCCATCCTTTTATCTACTCATC	6193	GATGAGTAGATAAAAGGATGGATGG
4930	TCCATCCATCCTTTTATCTACTCAT	6194	ATGAGTAGATAAAAGGATGGATGGA
4931	CTCCATCCATCCTTTTATCTACTCA	6195	TGAGTAGATAAAAGGATGGATGGAG
4932	TCTCCATCCATCCTTTTATCTACTC	6196	GAGTAGATAAAAGGATGGATGGAGA
4933	CTCTCCATCCATCCTTTTATCTACT	6197	AGTAGATAAAAGGATGGATGGAGAG
4934	TCTCTCCATCCATCCTTTTATCTAC	6198	GTAGATAAAAGGATGGATGGAGAGA
4935	ATCTCTCCATCCATCCTTTTATCTA	6199	TAGATAAAAGGATGGATGGAGAGAT
4936	CATCTCTCCATCCATCCTTTTATCT	6200	AGATAAAAGGATGGATGGAGAGATG
4937	CCATCTCTCCATCCATCCTTTTATC	6201	GATAAAAGGATGGATGGAGAGATGG
4938	CCCATCTCTCCATCCATCCTTTTAT	6202	ATAAAAGGATGGATGGAGAGATGGG
4939	ACCCATCTCTCCATCCATCCTTTTA	6203	TAAAAGGATGGATGGAGAGATGGGT
4940	CACCCATCTCTCCATCCATCCTTTT	6204	AAAAGGATGGATGGAGAGATGGGTG
4941	TCACCCATCTCTCCATCCATCCTTT	6205	AAAGGATGGATGGAGAGATGGGTGA
4942	CTCACCCATCTCTCCATCCATCCTT	6206	AAGGATGGATGGAGAGATGGGTGAG
4943	ACTCACCCATCTCTCCATCCATCCT	6207	AGGATGGATGGAGAGATGGGTGAGT
4944	TACTCACCCATCTCTCCATCCATCC	6208	GGATGGATGGAGAGATGGGTGAGTA
4945	GTACTCACCCATCTCTCCATCCATC	6209	GATGGATGGAGAGATGGGTGAGTAC
4946	TGTACTCACCCATCTCTCCATCCAT	6210	ATGGATGGAGAGATGGGTGAGTACA
4947	ATGTACTCACCCATCTCTCCATCCA	6211	TGGATGGAGAGATGGGTGAGTACAT
4948	CATGTACTCACCCATCTCTCCATCC	6212	GGATGGAGAGATGGGTGAGTACATG
4949	CCATGTACTCACCCATCTCTCCATC	6213	GATGGAGAGATGGGTGAGTACATGG
4950	TCCATGTACTCACCCATCTCTCCAT	6214	ATGGAGAGATGGGTGAGTACATGGA
4951	ATCCATGTACTCACCCATCTCTCCA	6215	TGGAGAGATGGGTGAGTACATGGAT
4952	CATCCATGTACTCACCCATCTCTCC	6216	GGAGAGATGGGTGAGTACATGGATG
4953	CCATCCATGTACTCACCCATCTCTC	6217	GAGAGATGGGTGAGTACATGGATGG
4954	TCCATCCATGTACTCACCCATCTCT	6218	AGAGATGGGTGAGTACATGGATGGA
4955	ATCCATCCATGTACTCACCCATCTC	6219	GAGATGGGTGAGTACATGGATGGAT
4956	TATCCATCCATGTACTCACCCATCT	6220	AGATGGGTGAGTACATGGATGGATA
4957	CTATCCATCCATGTACTCACCCATC	6221	GATGGGTGAGTACATGGATGGATAG
4958	TCTATCCATCCATGTACTCACCCAT	6222	ATGGGTGAGTACATGGATGGATAGA
4959	ATCTATCCATCCATGTACTCACCCA	6223	TGGGTGAGTACATGGATGGATAGAT
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4962	TCCATCTATCCATCCATGTACTCAC	6226	GTGAGTACATGGATGGATAGATGGA
4963	ATCCATCTATCCATCCATGTACTCA	6227	TGAGTACATGGATGGATAGATGGAT
4964	CATCCATCTATCCATCCATGTACTC	6228	GAGTACATGGATGGATAGATGGATG
4965	TCATCCATCTATCCATCCATGTACT	6229	AGTACATGGATGGATAGATGGATGA

4966	CTCATCCATCTATCCATCCATGTAC	6230	GTACATGGATGGATAGATGGATGAG
4967	ACTCATCCATCTATCCATCCATGTA	6231	TACATGGATGGATAGATGGATGAGT
4968	AACTCATCCATCTATCCATCCATGT	6232	ACATGGATGGATAGATGGATGAGTT
4969	CAACTCATCCATCTATCCATCCATG	6233	CATGGATGGATAGATGGATGAGTTG
4970	CCAACTCATCCATCTATCCATCCAT	6234	ATGGATGGATAGATGGATGAGTTGG
4971	ACCAACTCATCCATCTATCCATCCA	6235	TGGATGGATAGATGGATGAGTTGGT
4972	CACCAACTCATCCATCTATCCATCC	6236	GGATGGATAGATGGATGAGTTGGTG
4973	CCACCAACTCATCCATCTATCCATC	6237	GATGGATAGATGGATGAGTTGGTGG
4974	CCCACCAACTCATCCATCTATCCAT	6238	ATGGATAGATGGATGAGTTGGTGGG
4975	ACCCACCAACTCATCCATCTATCCA	6239	TGGATAGATGGATGAGTTGGTGGGT
4976	TACCCACCAACTCATCCATCTATCC	6240	GGATAGATGGATGAGTTGGTGGGTA
4977	CTACCCACCAACTCATCCATCTATC	6241	GATAGATGGATGAGTTGGTGGGTAG
4978	TCTACCCACCAACTCATCCATCTAT	6242	ATAGATGGATGAGTTGGTGGGTAGA
4979	ATCTACCCACCAACTCATCCATCTA	6243	TAGATGGATGAGTTGGTGGGTAGAT
4980	AATCTACCCACCAACTCATCCATCT	6244	AGATGGATGAGTTGGTGGGTAGATT
4981	GAATCTACCCACCAACTCATCCATC	6245	GATGGATGAGTTGGTGGGTAGATTC
4982	CGAATCTACCCACCAACTCATCCAT	6246	ATGGATGAGTTGGTGGGTAGATTCG
4983	ACGAATCTACCCACCAACTCATCCA	6247	TGGATGAGTTGGTGGGTAGATTCGT
4984	CACGAATCTACCCACCAACTCATCC	6248	GGATGAGTTGGTGGGTAGATTCGTG
4985	CCACGAATCTACCCACCAACTCATC	6249	GATGAGTTGGTGGGTAGATTCGTGG
4986	GCCACGAATCTACCCACCAACTCAT	6250	ATGAGTTGGTGGGTAGATTCGTGGC
4987	AGCCACGAATCTACCCACCAACTCA	6251	TGAGTTGGTGGGTAGATTCGTGGCT
4988	TAGCCACGAATCTACCCACCAACTC	6252	GAGTTGGTGGGTAGATTCGTGGCTA
4989	CTAGCCACGAATCTACCCACCAACT	6253	AGTTGGTGGGTAGATTCGTGGCTAG
4990	TCTAGCCACGAATCTACCCACCAAC	6254	GTTGGTGGGTAGATTCGTGGCTAGA
4991	ATCTAGCCACGAATCTACCCACCAA	6255	TTGGTGGGTAGATTCGTGGCTAGAT
4992	CATCTAGCCACGAATCTACCCACCA	6256	TGGTGGGTAGATTCGTGGCTAGATG
4993	CCATCTAGCCACGAATCTACCCACC	6257	GGTGGGTAGATTCGTGGCTAGATGG
4994	TCCATCTAGCCACGAATCTACCCAC	6258	GTGGGTAGATTCGTGGCTAGATGGA
4995	ATCCATCTAGCCACGAATCTACCCA	6259	TGGGTAGATTCGTGGCTAGATGGAT
4996	CATCCATCTAGCCACGAATCTACCC	6260	GGGTAGATTCGTGGCTAGATGGATG
4997	TCATCCATCTAGCCACGAATCTACC	6261	GGTAGATTCGTGGCTAGATGGATGA
4998	ATCATCCATCTAGCCACGAATCTAC	6262	GTAGATTCGTGGCTAGATGGATGAT
4999	CATCATCCATCTAGCCACGAATCTA	6263	TAGATTCGTGGCTAGATGGATGATG
5000	CCATCATCCATCTAGCCACGAATCT	6264	AGATTCGTGGCTAGATGGATGATGG
5001	TCCATCATCCATCTAGCCACGAATC	6265	GATTCGTGGCTAGATGGATGATGGA
5002	ATCCATCATCCATCTAGCCACGAAT	6266	ATTCGTGGCTAGATGGATGATGGAT
5003	CATCCATCATCCATCTAGCCACGAA	6267	TTCGTGGCTAGATGGATGATGGATG
5004	CCATCCATCATCCATCTAGCCACGA	6268	TCGTGGCTAGATGGATGATGGATGG
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5006	ATCCATCCATCATCCATCTAGCCAC	6270	GTGGCTAGATGGATGATGGATGGAT
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5008	CCATCCATCCATCATCCATCTAGCC	6272	GGCTAGATGGATGATGGATGGATGG
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5015	CATCTGTCCATCCATCCATCATCCA	6279	TGGATGATGGATGGATGGACAGATG
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5017	TCCATCTGTCCATCCATCCATCATC	6281	GATGATGGATGGATGGACAGATGGA
5018	ATCCATCTGTCCATCCATCCATCAT	6282	ATGATGGATGGATGGACAGATGGAT
5019	CATCCATCTGTCCATCCATCCATCA	6283	TGATGGATGGATGGACAGATGGATG
5020	CCATCCATCTGTCCATCCATCCATC	6284	GATGGATGGATGGACAGATGGATGG
5021	TCCATCCATCTGTCCATCCATCCAT	6285	ATGGATGGATGGACAGATGGATGGA
5022	ATCCATCCATCTGTCCATCCATCCA	6286	TGGATGGATGGACAGATGGATGGAT
5023	TATCCATCCATCTGTCCATCCATCC	6287	GGATGGATGGACAGATGGATGGATA
5024	ATATCCATCCATCTGTCCATCCATC	6288	GATGGATGGACAGATGGATGGATAT
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5048	CTATACTTTCAATAGTTCAATCATA	6312	TATGATTGAACTATTGAAAGTATAG
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5095	CTCATCCATCATCTAACAATTACCC	6359	GGGTAATTGTTAGATGATGGATGAG
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5164	CCCAGTCAATCATCTATCCAGCAAT	6428	ATTGCTGGATAGATGATTGACTGGG
5165	ACCCAGTCAATCATCTATCCAGCAA	6429	TTGCTGGATAGATGATTGACTGGGT
5166	CACCCAGTCAATCATCTATCCAGCA	6430	TGCTGGATAGATGATTGACTGGGTG
5167	CCACCCAGTCAATCATCTATCCAGC	6431	GCTGGATAGATGATTGACTGGGTGG
5168	TCCACCCAGTCAATCATCTATCCAG	6432	CTGGATAGATGATTGACTGGGTGGA
5169	ATCCACCCAGTCAATCATCTATCCA	6433	TGGATAGATGATTGACTGGGTGGAT
5170	TATCCACCCAGTCAATCATCTATCC	6434	GGATAGATGATTGACTGGGTGGATA
5171	CTATCCACCCAGTCAATCATCTATC	6435	GATAGATGATTGACTGGGTGGATAG
5172	TCTATCCACCCAGTCAATCATCTAT	6436	ATAGATGATTGACTGGGTGGATAGA
5173	ATCTATCCACCCAGTCAATCATCTA	6437	TAGATGATTGACTGGGTGGATAGAT
5174	CATCTATCCACCCAGTCAATCATCT	6438	AGATGATTGACTGGGTGGATAGATG
5175	TCATCTATCCACCCAGTCAATCATC	6439	GATGATTGACTGGGTGGATAGATGA

5176	TTCATCTATCCACCCAGTCAATCAT	6440	ATGATTGACTGGGTGGATAGATGAA
5177	TTTCATCTATCCACCCAGTCAATCA	6441	TGATTGACTGGGTGGATAGATGAAA
5178	ATTTCATCTATCCACCCAGTCAATC	6442	GATTGACTGGGTGGATAGATGAAAT
5179	CATTTCATCTATCCACCCAGTCAAT	6443	ATTGACTGGGTGGATAGATGAAATG
5180	ACATTTCATCTATCCACCCAGTCAA	6444	TTGACTGGGTGGATAGATGAAATGT
5181	AACATTTCATCTATCCACCCAGTCA	6445	TGACTGGGTGGATAGATGAAATGTT
5182	CAACATTTCATCTATCCACCCAGTC	6446	GACTGGGTGGATAGATGAAATGTTG
5183	CCAACATTTCATCTATCCACCCAGT	6447	ACTGGGTGGATAGATGAAATGTTGG
5184	TCCAACATTTCATCTATCCACCCAG	6448	CTGGGTGGATAGATGAAATGTTGGA
5185	ATCCAACATTTCATCTATCCACCCA	6449	TGGGTGGATAGATGAAATGTTGGAT
5186	CATCCAACATTTCATCTATCCACCC	6450	GGGTGGATAGATGAAATGTTGGATG
5187	TCATCCAACATTTCATCTATCCACC	6451	GGTGGATAGATGAAATGTTGGATGA
5188	CTCATCCAACATTTCATCTATCCAC	6452	GTGGATAGATGAAATGTTGGATGAG
5189	GCTCATCCAACATTTCATCTATCCA	6453	TGGATAGATGAAATGTTGGATGAGC
5190	TGCTCATCCAACATTTCATCTATCC	6454	GGATAGATGAAATGTTGGATGAGCA
5191	CTGCTCATCCAACATTTCATCTATC	6455	GATAGATGAAATGTTGGATGAGCAG
5192	TCTGCTCATCCAACATTTCATCTAT	6456	ATAGATGAAATGTTGGATGAGCAGA
5193	ATCTGCTCATCCAACATTTCATCTA	6457	TAGATGAAATGTTGGATGAGCAGAT
5194	AATCTGCTCATCCAACATTTCATCT	6458	AGATGAAATGTTGGATGAGCAGATT
5195	TAATCTGCTCATCCAACATTTCATC	6459	GATGAAATGTTGGATGAGCAGATTA
5196	TTAATCTGCTCATCCAACATTTCAT	6460	ATGAAATGTTGGATGAGCAGATTAA
5197	CTTAATCTGCTCATCCAACATTTCA	6461	TGAAATGTTGGATGAGCAGATTAAG
5198	ACTTAATCTGCTCATCCAACATTTC	6462	GAAATGTTGGATGAGCAGATTAAGT
5199	AACTTAATCTGCTCATCCAACATTT	6463	AAATGTTGGATGAGCAGATTAAGTT
5200	CAACTTAATCTGCTCATCCAACATT	6464	AATGTTGGATGAGCAGATTAAGTTG
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5202	TACAACTTAATCTGCTCATCCAACA	6466	TGTTGGATGAGCAGATTAAGTTGTA
5203	ATACAACTTAATCTGCTCATCCAAC	6467	GTTGGATGAGCAGATTAAGTTGTAT
5204	AATACAACTTAATCTGCTCATCCAA	6468	TTGGATGAGCAGATTAAGTTGTATT
5205	CAATACAACTTAATCTGCTCATCCA	6469	TGGATGAGCAGATTAAGTTGTATTG
5206	CCAATACAACTTAATCTGCTCATCC	6470	GGATGAGCAGATTAAGTTGTATTGG
5207	TCCAATACAACTTAATCTGCTCATC	6471	GATGAGCAGATTAAGTTGTATTGGA
5208	ATCCAATACAACTTAATCTGCTCAT	6472	ATGAGCAGATTAAGTTGTATTGGAT
5209	CATCCAATACAACTTAATCTGCTCA	6473	TGAGCAGATTAAGTTGTATTGGATG
5210	CCATCCAATACAACTTAATCTGCTC	6474	GAGCAGATTAAGTTGTATTGGATGG
5211	CCCATCCAATACAACTTAATCTGCT	6475	AGCAGATTAAGTTGTATTGGATGGG
5212	TCCCATCCAATACAACTTAATCTGC	6476	GCAGATTAAGTTGTATTGGATGGGA
5213	ATCCCATCCAATACAACTTAATCTG	6477	CAGATTAAGTTGTATTGGATGGGAT
5214	CATCCCATCCAATACAACTTAATCT	6478	AGATTAAGTTGTATTGGATGGGATG
5215	CCATCCCATCCAATACAACTTAATC	6479	GATTAAGTTGTATTGGATGGGATGG
5216	TCCATCCCATCCAATACAACTTAAT	6480	ATTAAGTTGTATTGGATGGGATGGA
5217	ATCCATCCCATCCAATACAACTTAA	6481	TTAAGTTGTATTGGATGGGATGGAT

5218	CATCCATCCCATCCAATACAACTTA	6482	TAAGTTGTATTGGATGGGATGGATG
5219	CCATCCATCCCATCCAATACAACTT	6483	AAGTTGTATTGGATGGGATGGATGG
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5222	CTTCCATCCATCCCATCCAATACAA	6486	TTGTATTGGATGGGATGGATGGAAG
5223	ACTTCCATCCATCCCATCCAATACA	6487	TGTATTGGATGGGATGGATGGAAGT
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5228	ACCACACTTCCATCCATCCCATCCA	6492	TGGATGGGATGGATGGAAGTGTGGT
5229	AACCACACTTCCATCCATCCCATCC	6493	GGATGGGATGGATGGAAGTGTGGTT
5230	CAACCACACTTCCATCCATCCCATC	6494	GATGGGATGGATGGAAGTGTGGTTG
5231	TCAACCACACTTCCATCCATCCCAT	6495	ATGGGATGGATGGAAGTGTGGTTGA
5232	CTCAACCACACTTCCATCCATCCCA	6496	TGGGATGGATGGAAGTGTGGTTGAG
5233	ACTCAACCACACTTCCATCCATCCC	6497	GGGATGGATGGAAGTGTGGTTGAGT
5234	AACTCAACCACACTTCCATCCATCC	6498	GGATGGATGGAAGTGTGGTTGAGTT
5235	TAACTCAACCACACTTCCATCCATC	6499	GATGGATGGAAGTGTGGTTGAGTTA
5236	ATAACTCAACCACACTTCCATCCAT	6500	ATGGATGGAAGTGTGGTTGAGTTAT
5237	AATAACTCAACCACACTTCCATCCA	6501	TGGATGGAAGTGTGGTTGAGTTATT
5238	TAATAACTCAACCACACTTCCATCC	6502	GGATGGAAGTGTGGTTGAGTTATTA
5239	CTAATAACTCAACCACACTTCCATC	6503	GATGGAAGTGTGGTTGAGTTATTAG
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5241	TTCTAATAACTCAACCACACTTCCA	6505	TGGAAGTGTGGTTGAGTTATTAGAA
5242	CTTCTAATAACTCAACCACACTTCC	6506	GGAAGTGTGGTTGAGTTATTAGAAG
5243	CCTTCTAATAACTCAACCACACTTC	6507	GAAGTGTGGTTGAGTTATTAGAAGG
5244	TCCTTCTAATAACTCAACCACACTT	6508	AAGTGTGGTTGAGTTATTAGAAGGA
5245	TTCCTTCTAATAACTCAACCACACT	6509	AGTGTGGTTGAGTTATTAGAAGGAA
5246	CTTCCTTCTAATAACTCAACCACAC	6510	GTGTGGTTGAGTTATTAGAAGGAAG
5247	TCTTCCTTCTAATAACTCAACCACA	6511	TGTGGTTGAGTTATTAGAAGGAAGA
5248	ATCTTCCTTCTAATAACTCAACCAC	6512	GTGGTTGAGTTATTAGAAGGAAGAT
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5250	CAATCTTCCTTCTAATAACTCAACC	6514	GGTTGAGTTATTAGAAGGAAGATTG
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5252	CTCAATCTTCCTTCTAATAACTCAA	6516	TTGAGTTATTAGAAGGAAGATTGAG
5253	ACTCAATCTTCCTTCTAATAACTCA	6517	TGAGTTATTAGAAGGAAGATTGAGT
5254	TACTCAATCTTCCTTCTAATAACTC	6518	GAGTTATTAGAAGGAAGATTGAGTA
5255	CTACTCAATCTTCCTTCTAATAACT	6519	AGTTATTAGAAGGAAGATTGAGTAG
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5258	TATCTACTCAATCTTCCTTCTAATA	6522	TATTAGAAGGAAGATTGAGTAGATA
5259	CTATCTACTCAATCTTCCTTCTAAT	6523	ATTAGAAGGAAGATTGAGTAGATAG

5260	CCTATCTACTCAATCTTCCTTCTAA	6524	TTAGAAGGAAGATTGAGTAGATAGG
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5262	CACCTATCTACTCAATCTTCCTTCT	6526	AGAAGGAAGATTGAGTAGATAGGTG
5263	TCACCTATCTACTCAATCTTCCTTC	6527	GAAGGAAGATTGAGTAGATAGGTGA
5264	TTCACCTATCTACTCAATCTTCCTT	6528	AAGGAAGATTGAGTAGATAGGTGAA
5265	ATTCACCTATCTACTCAATCTTCCT	6529	AGGAAGATTGAGTAGATAGGTGAAT
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5268	CAAATTCACCTATCTACTCAATCTT	6532	AAGATTGAGTAGATAGGTGAATTTG
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5271	CAACAAATTCACCTATCTACTCAAT	6535	ATTGAGTAGATAGGTGAATTTGTTG
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5273	ATCAACAAATTCACCTATCTACTCA	6537	TGAGTAGATAGGTGAATTTGTTGAT
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5275	CTATCAACAAATTCACCTATCTACT	6539	AGTAGATAGGTGAATTTGTTGATAG
5276	ACTATCAACAAATTCACCTATCTAC	6540	GTAGATAGGTGAATTTGTTGATAGT
5277	GACTATCAACAAATTCACCTATCTA	6541	TAGATAGGTGAATTTGTTGATAGTC
5278	TGACTATCAACAAATTCACCTATCT	6542	AGATAGGTGAATTTGTTGATAGTCA
5279	CTGACTATCAACAAATTCACCTATC	6543	GATAGGTGAATTTGTTGATAGTCAG
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5286	TACCCATCTGACTATCAACAAATTC	6550	GAATTTGTTGATAGTCAGATGGGTA
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5300	TCCATCTACCTATCTACCCATCTGA	6564	TCAGATGGGTAGATAGGTAGATGGA
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5417	CAGAAATTATGAACCCAATTATCAA	6681	TTGATAATTGGGTTCATAATTTCTG
5418	TCAGAAATTATGAACCCAATTATCA	6682	TGATAATTGGGTTCATAATTTCTGA
5419	TTCAGAAATTATGAACCCAATTATC	6683	GATAATTGGGTTCATAATTTCTGAA
5420	ATTCAGAAATTATGAACCCAATTAT	6684	ATAATTGGGTTCATAATTTCTGAAT
5421	TATTCAGAAATTATGAACCCAATTA	6685	TAATTGGGTTCATAATTTCTGAATA
5422	ATATTCAGAAATTATGAACCCAATT	6686	AATTGGGTTCATAATTTCTGAATAT
5423	AATATTCAGAAATTATGAACCCAAT	6687	ATTGGGTTCATAATTTCTGAATATT
5424	AAATATTCAGAAATTATGAACCCAA	6688	TTGGGTTCATAATTTCTGAATATTT
5425	TAAATATTCAGAAATTATGAACCCA	6689	TGGGTTCATAATTTCTGAATATTTA
5426	CTAAATATTCAGAAATTATGAACCC	6690	GGGTTCATAATTTCTGAATATTTAG
5427	TCTAAATATTCAGAAATTATGAACC	6691	GGTTCATAATTTCTGAATATTTAGA

5428	ATCTAAATATTCAGAAATTATGAAC	6692	GTTCATAATTTCTGAATATTTAGAT
5429	CATCTAAATATTCAGAAATTATGAA	6693	TTCATAATTTCTGAATATTTAGATG
5430	CCATCTAAATATTCAGAAATTATGA	6694	TCATAATTTCTGAATATTTAGATGG
5431	TCCATCTAAATATTCAGAAATTATG	6695	CATAATTTCTGAATATTTAGATGGA
5432	ATCCATCTAAATATTCAGAAATTAT	6696	ATAATTTCTGAATATTTAGATGGAT
5433	CATCCATCTAAATATTCAGAAATTA	6697	TAATTTCTGAATATTTAGATGGATG
5434	CCATCCATCTAAATATTCAGAAATT	6698	AATTTCTGAATATTTAGATGGATGG
5435	ACCATCCATCTAAATATTCAGAAAT	6699	ATTTCTGAATATTTAGATGGATGGT
5436	AACCATCCATCTAAATATTCAGAAA	6700	TTTCTGAATATTTAGATGGATGGTT
5437	CAACCATCCATCTAAATATTCAGAA	6701	TTCTGAATATTTAGATGGATGGTTG
5438	ACAACCATCCATCTAAATATTCAGA	6702	TCTGAATATTTAGATGGATGGTTGT
5439	CACAACCATCCATCTAAATATTCAG	6703	CTGAATATTTAGATGGATGGTTGTG
5440	TCACAACCATCCATCTAAATATTCA	6704	TGAATATTTAGATGGATGGTTGTGA
5441	CTCACAACCATCCATCTAAATATTC	6705	GAATATTTAGATGGATGGTTGTGAG
5442	ACTCACAACCATCCATCTAAATATT	6706	AATATTTAGATGGATGGTTGTGAGT
5443	CACTCACAACCATCCATCTAAATAT	6707	ATATTTAGATGGATGGTTGTGAGTG
5444	CCACTCACAACCATCCATCTAAATA	6708	TATTTAGATGGATGGTTGTGAGTGG
5445	GCCACTCACAACCATCCATCTAAAT	6709	ATTTAGATGGATGGTTGTGAGTGGC
5446	AGCCACTCACAACCATCCATCTAAA	6710	TTTAGATGGATGGTTGTGAGTGGCT
5447	CAGCCACTCACAACCATCCATCTAA	6711	TTAGATGGATGGTTGTGAGTGGCTG
5448	CCAGCCACTCACAACCATCCATCTA	6712	TAGATGGATGGTTGTGAGTGGCTGG
5449	ACCAGCCACTCACAACCATCCATCT	6713	AGATGGATGGTTGTGAGTGGCTGGT
5450	CACCAGCCACTCACAACCATCCATC	6714	GATGGATGGTTGTGAGTGGCTGGTG
5451	CCACCAGCCACTCACAACCATCCAT	6715	ATGGATGGTTGTGAGTGGCTGGTGG
5452	TCCACCAGCCACTCACAACCATCCA	6716	TGGATGGTTGTGAGTGGCTGGTGGA
5453	GTCCACCAGCCACTCACAACCATCC	6717	GGATGGTTGTGAGTGGCTGGTGGAC
5454	TGTCCACCAGCCACTCACAACCATC	6718	GATGGTTGTGAGTGGCTGGTGGACA
5455	CTGTCCACCAGCCACTCACAACCAT	6719	ATGGTTGTGAGTGGCTGGTGGACAG
5456	TCTGTCCACCAGCCACTCACAACCA	6720	TGGTTGTGAGTGGCTGGTGGACAGA
5457	GTCTGTCCACCAGCCACTCACAACC	6721	GGTTGTGAGTGGCTGGTGGACAGAC
5458	CGTCTGTCCACCAGCCACTCACAAC	6722	GTTGTGAGTGGCTGGTGGACAGACG
5459	TCGTCTGTCCACCAGCCACTCACAA	6723	TTGTGAGTGGCTGGTGGACAGACGA
5460	TTCGTCTGTCCACCAGCCACTCACA	6724	TGTGAGTGGCTGGTGGACAGACGAA
5461	TTTCGTCTGTCCACCAGCCACTCAC	6725	GTGAGTGGCTGGTGGACAGACGAAA
5462	TTTTCGTCTGTCCACCAGCCACTCA	6726	TGAGTGGCTGGTGGACAGACGAAAA
5463	TTTTTCGTCTGTCCACCAGCCACTC	6727	GAGTGGCTGGTGGACAGACGAAAAA
5464	ATTTTTCGTCTGTCCACCAGCCACT	6728	AGTGGCTGGTGGACAGACGAAAAAT
5465	CATTTTTCGTCTGTCCACCAGCCAC	6729	GTGGCTGGTGGACAGACGAAAAATG
5466	CCATTTTTCGTCTGTCCACCAGCCA	6730	TGGCTGGTGGACAGACGAAAAATGG
5467	TCCATTTTTCGTCTGTCCACCAGCC	6731	GGCTGGTGGACAGACGAAAAATGGA
5468	ATCCATTTTTCGTCTGTCCACCAGC	6732	GCTGGTGGACAGACGAAAAATGGAT
5469	CATCCATTTTTCGTCTGTCCACCAG	6733	CTGGTGGACAGACGAAAAATGGATG

5470	CCATCCATTTTTCGTCTGTCCACCA	6734	TGGTGGACAGACGAAAAATGGATGG
5471	ACCATCCATTTTTCGTCTGTCCACC	6735	GGTGGACAGACGAAAAATGGATGGT
5472	AACCATCCATTTTTCGTCTGTCCAC	6736	GTGGACAGACGAAAAATGGATGGTT
5473	CAACCATCCATTTTTCGTCTGTCCA	6737	TGGACAGACGAAAAATGGATGGTTG
5474	CCAACCATCCATTTTTCGTCTGTCC	6738	GGACAGACGAAAAATGGATGGTTGG
5475	TCCAACCATCCATTTTTCGTCTGTC	6739	GACAGACGAAAAATGGATGGTTGGA
5476	ATCCAACCATCCATTTTTCGTCTGT	6740	ACAGACGAAAAATGGATGGTTGGAT
5477	TATCCAACCATCCATTTTTCGTCTG	6741	CAGACGAAAAATGGATGGTTGGATA
5478	TTATCCAACCATCCATTTTTCGTCT	6742	AGACGAAAAATGGATGGTTGGATAA
5479	TTTATCCAACCATCCATTTTTCGTC	6743	GACGAAAAATGGATGGTTGGATAAA
5480	ATTTATCCAACCATCCATTTTTCGT	6744	ACGAAAAATGGATGGTTGGATAAAT
5481	AATTTATCCAACCATCCATTTTTCG	6745	CGAAAAATGGATGGTTGGATAAATT
5482	CAATTTATCCAACCATCCATTTTTC	6746	GAAAAATGGATGGTTGGATAAATTG
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5484	ATCAATTTATCCAACCATCCATTTT	6748	AAAATGGATGGTTGGATAAATTGAT
5485	CATCAATTTATCCAACCATCCATTT	6749	AAATGGATGGTTGGATAAATTGATG
5486	CCATCAATTTATCCAACCATCCATT	6750	AATGGATGGTTGGATAAATTGATGG
5487	CCCATCAATTTATCCAACCATCCAT	6751	ATGGATGGTTGGATAAATTGATGGG
5488	ACCCATCAATTTATCCAACCATCCA	6752	TGGATGGTTGGATAAATTGATGGGT
5489	CACCCATCAATTTATCCAACCATCC	6753	GGATGGTTGGATAAATTGATGGGTG
5490	CCACCCATCAATTTATCCAACCATC	6754	GATGGTTGGATAAATTGATGGGTGG
5491	TCCACCCATCAATTTATCCAACCAT	6755	ATGGTTGGATAAATTGATGGGTGGA
5492	ATCCACCCATCAATTTATCCAACCA	6756	TGGTTGGATAAATTGATGGGTGGAT
5493	CATCCACCCATCAATTTATCCAACC	6757	GGTTGGATAAATTGATGGGTGGATG
5494	CCATCCACCCATCAATTTATCCAAC	6758	GTTGGATAAATTGATGGGTGGATGG
5495	TCCATCCACCCATCAATTTATCCAA	6759	TTGGATAAATTGATGGGTGGATGGA
5496	ATCCATCCACCCATCAATTTATCCA	6760	TGGATAAATTGATGGGTGGATGGAT
5497	CATCCATCCACCCATCAATTTATCC	6761	GGATAAATTGATGGGTGGATGGATG
5498	CCATCCATCCACCCATCAATTTATC	6762	GATAAATTGATGGGTGGATGGATGG
5499	ACCATCCATCCACCCATCAATTTAT	6763	ATAAATTGATGGGTGGATGGATGGT
5500	AACCATCCATCCACCCATCAATTTA	6764	TAAATTGATGGGTGGATGGATGGTT
5501	CAACCATCCATCCACCCATCAATTT	6765	AAATTGATGGGTGGATGGATGGTTG
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5503	ACCAACCATCCATCCACCCATCAAT	6767	ATTGATGGGTGGATGGATGGTTGGT
5504	AACCAACCATCCATCCACCCATCAA	6768	TTGATGGGTGGATGGATGGTTGGTT
5505	CAACCAACCATCCATCCACCCATCA	6769	TGATGGGTGGATGGATGGTTGGTTG
5506	ACAACCAACCATCCATCCACCCATC	6770	GATGGGTGGATGGATGGTTGGTTGT
5507	TACAACCAACCATCCATCCACCCAT	6771	ATGGGTGGATGGATGGTTGGTTGTA
5508	ATACAACCAACCATCCATCCACCCA	6772	TGGGTGGATGGATGGTTGGTTGTAT
5509	CATACAACCAACCATCCATCCACCC	6773	GGGTGGATGGATGGTTGGTTGTATG
5510	TCATACAACCAACCATCCATCCACC	6774	GGTGGATGGATGGTTGGTTGTATGA
5511	TTCATACAACCAACCATCCATCCAC	6775	GTGGATGGATGGTTGGTTGTATGAA

5512	TTTCATACAACCAACCATCCATCCA	6776	TGGATGGATGGTTGGTTGTATGAAA
5513	CTTTCATACAACCAACCATCCATCC	6777	GGATGGATGGTTGGTTGTATGAAAG
5514	TCTTTCATACAACCAACCATCCATC	6778	GATGGATGGTTGGTTGTATGAAAGA
5515	TTCTTTCATACAACCAACCATCCAT	6779	ATGGATGGTTGGTTGTATGAAAGAA
5516	ATTCTTTCATACAACCAACCATCCA	6780	TGGATGGTTGGTTGTATGAAAGAAT
5517	CATTCTTTCATACAACCAACCATCC	6781	GGATGGTTGGTTGTATGAAAGAATG
5518	TCATTCTTTCATACAACCAACCATC	6782	GATGGTTGGTTGTATGAAAGAATGA
5519	TTCATTCTTTCATACAACCAACCAT	6783	ATGGTTGGTTGTATGAAAGAATGAA
5520	ATTCATTCTTTCATACAACCAACCA	6784	TGGTTGGTTGTATGAAAGAATGAAT
5521	CATTCATTCTTTCATACAACCAACC	6785	GGTTGGTTGTATGAAAGAATGAATG
5522	TCATTCATTCTTTCATACAACCAAC	6786	GTTGGTTGTATGAAAGAATGAATGA
5523	ATCATTCATTCTTTCATACAACCAA	6787	TTGGTTGTATGAAAGAATGAATGAT
5524	AATCATTCATTCTTTCATACAACCA	6788	TGGTTGTATGAAAGAATGAATGATT
5525	CAATCATTCATTCTTTCATACAACC	6789	GGTTGTATGAAAGAATGAATGATTG
5526	CCAATCATTCATTCTTTCATACAAC	6790	GTTGTATGAAAGAATGAATGATTGG
5527	CCCAATCATTCATTCTTTCATACAA	6791	TTGTATGAAAGAATGAATGATTGGG
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5536	ATCCACCTACCCAATCATTCATTCT	6800	AGAATGAATGATTGGGTAGGTGGAT
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5538	TAATCCACCTACCCAATCATTCATT	6802	AATGAATGATTGGGTAGGTGGATTA
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5547	TCCGCAACTTAATCCACCTACCCAA	6811	TTGGGTAGGTGGATTAAGTTGCGGA
5548	ATCCGCAACTTAATCCACCTACCCA	6812	TGGGTAGGTGGATTAAGTTGCGGAT
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5550	TGATCCGCAACTTAATCCACCTACC	6814	GGTAGGTGGATTAAGTTGCGGATCA
5551	TTGATCCGCAACTTAATCCACCTAC	6815	GTAGGTGGATTAAGTTGCGGATCAA
5552	ATTGATCCGCAACTTAATCCACCTA	6816	TAGGTGGATTAAGTTGCGGATCAAT
5553	CATTGATCCGCAACTTAATCCACCT	6817	AGGTGGATTAAGTTGCGGATCAATG

5554	ACATTGATCCGCAACTTAATCCACC	6818	GGTGGATTAAGTTGCGGATCAATGT
5555	TACATTGATCCGCAACTTAATCCAC	6819	GTGGATTAAGTTGCGGATCAATGTA
5556	ATACATTGATCCGCAACTTAATCCA	6820	TGGATTAAGTTGCGGATCAATGTAT
5557	CATACATTGATCCGCAACTTAATCC	6821	GGATTAAGTTGCGGATCAATGTATG
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5561	ATCCCATACATTGATCCGCAACTTA	6825	TAAGTTGCGGATCAATGTATGGGAT
5562	CATCCCATACATTGATCCGCAACTT	6826	AAGTTGCGGATCAATGTATGGGATG
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5593	AACCACACATCCATCCATCCATCCA	6857	TGGATGGATGGATGGATGTGTGGTT
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5598	AATTCAACCACACATCCATCCATCC	6862	GGATGGATGGATGTGTGGTTGAATT
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5601	AGTAATTCAACCACACATCCATCCA	6865	TGGATGGATGTGTGGTTGAATTACT
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5603	TCAGTAATTCAACCACACATCCATC	6867	GATGGATGTGTGGTTGAATTACTGA
5604	TTCAGTAATTCAACCACACATCCAT	6868	ATGGATGTGTGGTTGAATTACTGAA
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5606	CTTTCAGTAATTCAACCACACATCC	6870	GGATGTGTGGTTGAATTACTGAAAG
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5633	CAAATTTCACCCATCCACTCTTCCA	6897	TGGAAGAGTGGATGGGTGAAATTTG
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5643	CTAACTACCCCAAATTTCACCCATC	6907	GATGGGTGAAATTTGGGGTAGTTAG
5644	TCTAACTACCCCAAATTTCACCCAT	6908	ATGGGTGAAATTTGGGGTAGTTAGA
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5647	CCATCTAACTACCCCAAATTTCACC	6911	GGTGAAATTTGGGGTAGTTAGATGG
5648	CCCATCTAACTACCCCAAATTTCAC	6912	GTGAAATTTGGGGTAGTTAGATGGG
5649	ACCCATCTAACTACCCCAAATTTCA	6913	TGAAATTTGGGGTAGTTAGATGGGT
5650	CACCCATCTAACTACCCCAAATTTC	6914	GAAATTTGGGGTAGTTAGATGGGTG
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5655	ACACCCACCCATCTAACTACCCCAA	6919	TTGGGGTAGTTAGATGGGTGGGTGT
5656	CACACCCACCCATCTAACTACCCCA	6920	TGGGGTAGTTAGATGGGTGGGTGTG
5657	ACACACCCACCCATCTAACTACCCC	6921	GGGGTAGTTAGATGGGTGGGTGTGT
5658	CACACACCCACCCATCTAACTACCC	6922	GGGTAGTTAGATGGGTGGGTGTGTG
5659	CCACACACCCACCCATCTAACTACC	6923	GGTAGTTAGATGGGTGGGTGTGTGG
5660	TCCACACACCCACCCATCTAACTAC	6924	GTAGTTAGATGGGTGGGTGTGTGGA
5661	ATCCACACACCCACCCATCTAACTA	6925	TAGTTAGATGGGTGGGTGTGTGGAT
5662	CATCCACACACCCACCCATCTAACT	6926	AGTTAGATGGGTGGGTGTGTGGATG
5663	CCATCCACACACCCACCCATCTAAC	6927	GTTAGATGGGTGGGTGTGTGGATGG
5664	TCCATCCACACACCCACCCATCTAA	6928	TTAGATGGGTGGGTGTGTGGATGGA
5665	ATCCATCCACACACCCACCCATCTA	6929	TAGATGGGTGGGTGTGTGGATGGAT
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5667	TTATCCATCCACACACCCACCCATC	6931	GATGGGTGGGTGTGTGGATGGATAA
5668	TTTATCCATCCACACACCCACCCAT	6932	ATGGGTGGGTGTGTGGATGGATAAA
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5670	CTTTTATCCATCCACACACCCACCC	6934	GGGTGGGTGTGTGGATGGATAAAAG
5671	TCTTTTATCCATCCACACACCCACC	6935	GGTGGGTGTGTGGATGGATAAAAGA
5672	CTCTTTTATCCATCCACACACCCAC	6936	GTGGGTGTGTGGATGGATAAAAGAG
5673	ACTCTTTTATCCATCCACACACCCA	6937	TGGGTGTGTGGATGGATAAAAGAGT
5674	TACTCTTTTATCCATCCACACACCC	6938	GGGTGTGTGGATGGATAAAAGAGTA
5675	CTACTCTTTTATCCATCCACACACC	6939	GGTGTGTGGATGGATAAAAGAGTAG
5676	TCTACTCTTTTATCCATCCACACAC	6940	GTGTGTGGATGGATAAAAGAGTAGA
5677	ATCTACTCTTTTATCCATCCACACA	6941	TGTGTGGATGGATAAAAGAGTAGAT
5678	CATCTACTCTTTTATCCATCCACAC	6942	GTGTGGATGGATAAAAGAGTAGATG
5679	TCATCTACTCTTTTATCCATCCACA	6943	TGTGGATGGATAAAAGAGTAGATGA

5680	TTCATCTACTCTTTTATCCATCCAC	6944	GTGGATGGATAAAAGAGTAGATGAA
5681	ATTCATCTACTCTTTTATCCATCCA	6945	TGGATGGATAAAAGAGTAGATGAAT
5682	CATTCATCTACTCTTTTATCCATCC	6946	GGATGGATAAAAGAGTAGATGAATG
5683	TCATTCATCTACTCTTTTATCCATC	6947	GATGGATAAAAGAGTAGATGAATGA
5684	TTCATTCATCTACTCTTTTATCCAT	6948	ATGGATAAAAGAGTAGATGAATGAA
5685	ATTCATTCATCTACTCTTTTATCCA	6949	TGGATAAAAGAGTAGATGAATGAAT
5686	AATTCATTCATCTACTCTTTTATCC	6950	GGATAAAAGAGTAGATGAATGAATT
5687	TAATTCATTCATCTACTCTTTTATC	6951	GATAAAAGAGTAGATGAATGAATTA
5688	TTAATTCATTCATCTACTCTTTTAT	6952	ATAAAAGAGTAGATGAATGAATTAA
5689	ATTAATTCATTCATCTACTCTTTTA	6953	TAAAAGAGTAGATGAATGAATTAAT
5690	CATTAATTCATTCATCTACTCTTTT	6954	AAAAGAGTAGATGAATGAATTAATG
5691	TCATTAATTCATTCATCTACTCTTT	6955	AAAGAGTAGATGAATGAATTAATGA
5692	TTCATTAATTCATTCATCTACTCTT	6956	AAGAGTAGATGAATGAATTAATGAA
5693	ATTCATTAATTCATTCATCTACTCT	6957	AGAGTAGATGAATGAATTAATGAAT
5694	TATTCATTAATTCATTCATCTACTC	6958	GAGTAGATGAATGAATTAATGAATA
5695	TTATTCATTAATTCATTCATCTACT	6959	AGTAGATGAATGAATTAATGAATAA
5696	TTTATTCATTAATTCATTCATCTAC	6960	GTAGATGAATGAATTAATGAATAAA
5697	GTTTATTCATTAATTCATTCATCTA	6961	TAGATGAATGAATTAATGAATAAAC
5698	TGTTTATTCATTAATTCATTCATCT	6962	AGATGAATGAATTAATGAATAAACA
5699	CTGTTTATTCATTAATTCATTCATC	6963	GATGAATGAATTAATGAATAAACAG
5700	CCTGTTTATTCATTAATTCATTCAT	6964	ATGAATGAATTAATGAATAAACAGG
5701	GCCTGTTTATTCATTAATTCATTCA	6965	TGAATGAATTAATGAATAAACAGGC
5702	TGCCTGTTTATTCATTAATTCATTC	6966	GAATGAATTAATGAATAAACAGGCA
5703	CTGCCTGTTTATTCATTAATTCATT	6967	AATGAATTAATGAATAAACAGGCAG
5704	TCTGCCTGTTTATTCATTAATTCAT	6968	ATGAATTAATGAATAAACAGGCAGA
5705	ATCTGCCTGTTTATTCATTAATTCA	6969	TGAATTAATGAATAAACAGGCAGAT
5706	CATCTGCCTGTTTATTCATTAATTC	6970	GAATTAATGAATAAACAGGCAGATG
5707	CCATCTGCCTGTTTATTCATTAATT	6971	AATTAATGAATAAACAGGCAGATGG
5708	TCCATCTGCCTGTTTATTCATTAAT	6972	ATTAATGAATAAACAGGCAGATGGA
5709	ATCCATCTGCCTGTTTATTCATTAA	6973	TTAATGAATAAACAGGCAGATGGAT
5710	CATCCATCTGCCTGTTTATTCATTA	6974	TAATGAATAAACAGGCAGATGGATG
5711	TCATCCATCTGCCTGTTTATTCATT	6975	AATGAATAAACAGGCAGATGGATGA
5712	ATCATCCATCTGCCTGTTTATTCAT	6976	ATGAATAAACAGGCAGATGGATGAT
5713	CATCATCCATCTGCCTGTTTATTCA	6977	TGAATAAACAGGCAGATGGATGATG
5714	ACATCATCCATCTGCCTGTTTATTC	6978	GAATAAACAGGCAGATGGATGATGT
5715	TACATCATCCATCTGCCTGTTTATT	6979	AATAAACAGGCAGATGGATGATGTA
5716	TTACATCATCCATCTGCCTGTTTAT	6980	ATAAACAGGCAGATGGATGATGTAA
5717	CTTACATCATCCATCTGCCTGTTTA	6981	TAAACAGGCAGATGGATGATGTAAG
5718	GCTTACATCATCCATCTGCCTGTTT	6982	AAACAGGCAGATGGATGATGTAAGC
5719	AGCTTACATCATCCATCTGCCTGTT	6983	AACAGGCAGATGGATGATGTAAGCT
5720	CAGCTTACATCATCCATCTGCCTGT	6984	ACAGGCAGATGGATGATGTAAGCTG
5721	GCAGCTTACATCATCCATCTGCCTG	6985	CAGGCAGATGGATGATGTAAGCTGC

5722	GGCAGCTTACATCATCCATCTGCCT	6986	AGGCAGATGGATGATGTAAGCTGCC
5723	GGGCAGCTTACATCATCCATCTGCC	6987	GGCAGATGGATGATGTAAGCTGCCC
5724	GGGGCAGCTTACATCATCCATCTGC	6988	GCAGATGGATGATGTAAGCTGCCCC
5725	TGGGGCAGCTTACATCATCCATCTG	6989	CAGATGGATGATGTAAGCTGCCCCA
5726	CTGGGGCAGCTTACATCATCCATCT	6990	AGATGGATGATGTAAGCTGCCCCAG
5727	TCTGGGGCAGCTTACATCATCCATC	6991	GATGGATGATGTAAGCTGCCCCAGA
5728	GTCTGGGGCAGCTTACATCATCCAT	6992	ATGGATGATGTAAGCTGCCCCAGAC
5729	GGTCTGGGGCAGCTTACATCATCCA	6993	TGGATGATGTAAGCTGCCCCAGACC
5730	GGGTCTGGGGCAGCTTACATCATCC	6994	GGATGATGTAAGCTGCCCCAGACCC
5731	AGGGTCTGGGGCAGCTTACATCATC	6995	GATGATGTAAGCTGCCCCAGACCCT
5732	CAGGGTCTGGGGCAGCTTACATCAT	6996	ATGATGTAAGCTGCCCCAGACCCTG
5733	CCAGGGTCTGGGGCAGCTTACATCA	6997	TGATGTAAGCTGCCCCAGACCCTGG
5734	CCCAGGGTCTGGGGCAGCTTACATC	6998	GATGTAAGCTGCCCCAGACCCTGGG
5735	TCCCAGGGTCTGGGGCAGCTTACAT	6999	ATGTAAGCTGCCCCAGACCCTGGGA
5736	GTCCCAGGGTCTGGGGCAGCTTACA	7000	TGTAAGCTGCCCCAGACCCTGGGAC
5737	GGTCCCAGGGTCTGGGGCAGCTTAC	7001	GTAAGCTGCCCCAGACCCTGGGACC
5738	AGGTCCCAGGGTCTGGGGCAGCTTA	7002	TAAGCTGCCCCAGACCCTGGGACCT
5739	GAGGTCCCAGGGTCTGGGGCAGCTT	7003	AAGCTGCCCCAGACCCTGGGACCTC
5740	AGAGGTCCCAGGGTCTGGGGCAGCT	7004	AGCTGCCCCAGACCCTGGGACCTCT
5741	CAGAGGTCCCAGGGTCTGGGGCAGC	7005	GCTGCCCCAGACCCTGGGACCTCTG
5742	TCAGAGGTCCCAGGGTCTGGGGCAG	7006	CTGCCCCAGACCCTGGGACCTCTGA
5743	GTCAGAGGTCCCAGGGTCTGGGGCA	7007	TGCCCCAGACCCTGGGACCTCTGAC
5744	GGTCAGAGGTCCCAGGGTCTGGGGC	7008	GCCCCAGACCCTGGGACCTCTGACC
5745	GGGTCAGAGGTCCCAGGGTCTGGGG	7009	CCCCAGACCCTGGGACCTCTGACCC
5746	GGGGTCAGAGGTCCCAGGGTCTGGG	7010	CCCAGACCCTGGGACCTCTGACCCC
5747	GGGGGTCAGAGGTCCCAGGGTCTGG	7011	CCAGACCCTGGGACCTCTGACCCCC
5748	CGGGGGTCAGAGGTCCCAGGGTCTG	7012	CAGACCCTGGGACCTCTGACCCCCG
5749	CCGGGGGTCAGAGGTCCCAGGGTCT	7013	AGACCCTGGGACCTCTGACCCCCGG
5750	GCCGGGGGTCAGAGGTCCCAGGGTC	7014	GACCCTGGGACCTCTGACCCCCGGC
5751	CGCCGGGGGTCAGAGGTCCCAGGGT	7015	ACCCTGGGACCTCTGACCCCCGGCG
5752	TCGCCGGGGGTCAGAGGTCCCAGGG	7016	CCCTGGGACCTCTGACCCCCGGCGA
5753	GTCGCCGGGGGTCAGAGGTCCCAGG	7017	CCTGGGACCTCTGACCCCCGGCGAC
5754	GGTCGCCGGGGGTCAGAGGTCCCAG	7018	CTGGGACCTCTGACCCCCGGCGACC
5755	GGGTCGCCGGGGGTCAGAGGTCCCA	7019	TGGGACCTCTGACCCCCGGCGACCC
5756	GGGGTCGCCGGGGGTCAGAGGTCCC	7020	GGGACCTCTGACCCCCGGCGACCCC
5757	AGGGGTCGCCGGGGGTCAGAGGTCC	7021	GGACCTCTGACCCCCGGCGACCCCT
5758	AAGGGGTCGCCGGGGGTCAGAGGTC	7022	GACCTCTGACCCCCGGCGACCCCTT
5759	CAAGGGGTCGCCGGGGGTCAGAGGT	7023	ACCTCTGACCCCCGGCGACCCCTTG
5760	GCAAGGGGTCGCCGGGGGTCAGAGG	7024	CCTCTGACCCCCGGCGACCCCTTGC
5761	TGCAAGGGGTCGCCGGGGGTCAGAG	7025	CTCTGACCCCCGGCGACCCCTTGCA
5762	GTGCAAGGGGTCGCCGGGGGTCAGA	7026	TCTGACCCCCGGCGACCCCTTGCAC
5763	AGTGCAAGGGGTCGCCGGGGGTCAG	7027	CTGACCCCCGGCGACCCCTTGCACT

5764	GAGTGCAAGGGGTCGCCGGGGGTCA	7028	TGACCCCCGGCGACCCCTTGCACTC
5765	AGAGTGCAAGGGGTCGCCGGGGGTC	7029	GACCCCCGGCGACCCCTTGCACTCT
5766	GAGAGTGCAAGGGGTCGCCGGGGGT	7030	ACCCCCGGCGACCCCTTGCACTCTC
5767	GGAGAGTGCAAGGGGTCGCCGGGGG	7031	CCCCCGGCGACCCCTTGCACTCTCC
5768	TGGAGAGTGCAAGGGGTCGCCGGGG	7032	CCCCGGCGACCCCTTGCACTCTCCA
5769	ATGGAGAGTGCAAGGGGTCGCCGGG	7033	CCCGGCGACCCCTTGCACTCTCCAT
5770	CATGGAGAGTGCAAGGGGTCGCCGG	7034	CCGGCGACCCCTTGCACTCTCCATG
5771	TCATGGAGAGTGCAAGGGGTCGCCG	7035	CGGCGACCCCTTGCACTCTCCATGA
5772	GTCATGGAGAGTGCAAGGGGTCGCC	7036	GGCGACCCCTTGCACTCTCCATGAC
5773	TGTCATGGAGAGTGCAAGGGGTCGC	7037	GCGACCCCTTGCACTCTCCATGACA
5774	GTGTCATGGAGAGTGCAAGGGGTCG	7038	CGACCCCTTGCACTCTCCATGACAC
5775	AGTGTCATGGAGAGTGCAAGGGGTC	7039	GACCCCTTGCACTCTCCATGACACT
5776	AAGTGTCATGGAGAGTGCAAGGGGT	7040	ACCCCTTGCACTCTCCATGACACTT
5777	AAAGTGTCATGGAGAGTGCAAGGGG	7041	CCCCTTGCACTCTCCATGACACTTT
5778	GAAAGTGTCATGGAGAGTGCAAGGG	7042	CCCTTGCACTCTCCATGACACTTTC
5779	AGAAAGTGTCATGGAGAGTGCAAGG	7043	CCTTGCACTCTCCATGACACTTTCT
5780	GAGAAAGTGTCATGGAGAGTGCAAG	7044	CTTGCACTCTCCATGACACTTTCTC
5781	AGAGAAAGTGTCATGGAGAGTGCAA	7045	TTGCACTCTCCATGACACTTTCTCT
5782	GAGAGAAAGTGTCATGGAGAGTGCA	7046	TGCACTCTCCATGACACTTTCTCTC
5783	GGAGAGAAAGTGTCATGGAGAGTGC	7047	GCACTCTCCATGACACTTTCTCTCC
5784	GGGAGAGAAAGTGTCATGGAGAGTG	7048	CACTCTCCATGACACTTTCTCTCCC
5785	TGGGAGAGAAAGTGTCATGGAGAGT	7049	ACTCTCCATGACACTTTCTCTCCCA
5786	ATGGGAGAGAAAGTGTCATGGAGAG	7050	CTCTCCATGACACTTTCTCTCCCAT
5787	CATGGGAGAGAAAGTGTCATGGAGA	7051	TCTCCATGACACTTTCTCTCCCATG
5788	CCATGGGAGAGAAAGTGTCATGGAG	7052	CTCCATGACACTTTCTCTCCCATGG
5789	ACCATGGGAGAGAAAGTGTCATGGA	7053	TCCATGACACTTTCTCTCCCATGGT
5790	CACCATGGGAGAGAAAGTGTCATGG	7054	CCATGACACTTTCTCTCCCATGGTG
5791	CCACCATGGGAGAGAAAGTGTCATG	7055	CATGACACTTTCTCTCCCATGGTGG
5792	GCCACCATGGGAGAGAAAGTGTCAT	7056	ATGACACTTTCTCTCCCATGGTGGC
5793	TGCCACCATGGGAGAGAAAGTGTCA	7057	TGACACTTTCTCTCCCATGGTGGCA
5794	CTGCCACCATGGGAGAGAAAGTGTC	7058	GACACTTTCTCTCCCATGGTGGCAG

* At least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide sequence is independently selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a

thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

UNC13A Transcript

[00346] In various embodiments, an UNC13A mRNA transcript comprises the sequence provided as SEQ ID NO: 9587.

GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCC
GGGAGATGCCCCAGCCCAGCGGCCGCTGAGCCCGACCCGACAGAGCCGGCCCGGCCGCCTCCGGCCCACC
TGCGAGCTCGGAGACATGTCTCTGCTTTGCGTTGGAGTCAAAAAAGCCAAGTTTGATGGTGCCCAAGAGA
AATTCAACACGTACGTGACCCTGAAAGTGCAGAATGTCAAGAGCACGACCATCGCGGTGCGGGGCAGCCA
GCCCAGCTGGGAGCAGGATTTCATGTTCGAGATTAACCGTCTGGATTTGGGACTGACGGTGGAGGTGTGG
AATAAGGGTCTCATCTGGGACACAATGGTGGGCACTGTGTGGATCCCACTGAGGACCATCCGCCAGTCCA
ATGAGGAGGGCCCTGGAGAGTGGCTGACGCTGGACTCCCAGGTCATCATGGCAGACAGTGAGATCTGTGG
CACCAAGGACCCCACCTTCCACCGCATCCTCCTGGACACGCGCTTTGAGCTACCCTTAGACATTCCTGAA
GAGGAGGCTCGCTACTGGGCCAAGAAGCTGGAGCAGCTCAATGCTATGCGGGACCAGGATGAATATTCGT
TCCAAGATGAGCAAGACAAGCCTCTGCCTGTCCCCAGCAACCAGTGCTGCAACTGGAATTATTTTGGCTG
GGGTGAGCAGCACAACGATGACCCCGACAGTGCAGTGGATGATCGTGACAGTGACTACCGCAGTGAAACG
AGCAACAGCATCCCGCCGCCCTATTATACTACGTCACAACCCAACGCCTCAGTCCACCAATATTCTGTTC
GCCCACCACCCCTGGGCTCCCGGGAGTCCTACAGTGACTCCATGCACAGTTACGAGGAGTTCTCTGAGCC
ACAAGCCCTCAGCCCCACGGGTAGCAGCCGCTATGCCTCTTCCGGGGAGCTGAGCCAGGGAAGCTCTCAG
CTGAGCGAGGACTTCGACCCTGACGAGCACAGCCTGCAGGGCTCCGACATGGAGGATGAGCGGGACCGGG
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AGAGCTGGAGGAGGACCTGGAGGACTTCCTGGAGGAGGAGGAGCTGCCTGAAGATGAGGAGGAGCTGGAG
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CAGATCCCTGAGGCTGAGCCACCCAAGGACGAGGAGAGTTTCAGGCCGAGAGAGGATGAGGAAGGCCAGG
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CAAGGATCACATGGTACGAGAAGAAGCCAAGAGCTTGACCCCAAAGCAGTGCGCGGTTGTTGAGTTGGCC
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GAGGACTCTCAGGACCCCCAACTTTACCTAGCACAGGCTGGGCACAAGTGGGTGACAGGGAGTCTACGCC
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GAGAGTGGACATGGCTGAGACACGGACAGAGAAAAGACAAGGAGTCCAGGGGGCTGAAAGCCTTTTGAAA
TCAGGAAGTTCCTGTATTGGCAGAACAAAGCCCAGAGAGGAGCAGGGCTTTCCTCAACGCCACCCAGCAA
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GCTGGCCCCACATTTCCATGAATCGGGGAAACAGCACAAGAAGGTTGGCCTGTGGCAGGGCAAGGGTTAA
AGGGGTGACATTGAGGGATGCCTCAGAGTCAAAGTCCCCTGACCAAGAGGAATAGAGTAGAAAACACAGA
GACAGAGGGTGAGATCACGCCCCGATGAGGACGGAGAGAGACAGAGATGGAGAGAGACATAGAGGTGGAA
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CACACCCCCAATTCCTCTCTCAGGCCCCAGAGCCTGAGACCTCACCATGCCCCCATCAGAGATGCAAAAA
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GAAGTTGGGGGAGGGCCTTAGTCCCGGATCACAACCCCGTCTGCTCCCCAGAATCCTTTCCTAAGAATCG
TTGAGGACCAAAGTTGTCTTTGCTGACACGTGTTGCTTTTCTCTTTGCCTTTTATTGTTTCAGAGAAAAA
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CGGTCCAGTGTCTGCACAGACGCCTTCATTTCTCTGTAAATATGTGACTTGGAACAAATGTTTAACACAA
ACGAGAAGTGGTCATGAATGCATGGTGTTGAGATGTTTTGCACTATTCTGACTTTTTGGTCTCTGTAAAA
ATATTTTATTAACAGCAGACATTAAAAAAAGAAAAACCACACACA

(**SEQ ID NO: 9587** (SOURCE NCBI Reference Sequence NM_001080421.3)).

[00347] In various embodiments, an UNC13A mRNA transcript comprises the sequence provided as SEQ ID NO: 9588.

GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCC
GGGAGATGCCCCAGCCCAGCGGCCGCTGAGCCCGACCCGACAGAGCCGGCCCGGCCGCCTCCGGCCCACC
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GCCCAGCTGGGAGCAGGATTTCATGTTCGAGATTAACCGTCTGGATTTGGGACTGACGGTGGAGGTGTGG
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CAGCAGACATTAAAAAAAGAAAAACCACACACA

(**SEQ ID NO: 9588** (SOURCE NCBI Reference Sequence NM_001387021.1)).

[00348] In various embodiments, an UNC13A mRNA transcript comprises the sequence provided as SEQ ID NO: 9589.

GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCC
GGGAGATGCCCCAGCCCAGCGGCCGCTGAGCCCGACCCGACAGAGCCGGCCCGGCCGCCTCCGGCCCACC
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(**SEQ ID NO: 9589** (SOURCE NCBI Reference Sequence NM_001387022.1)).

[00349] In various embodiments, an UNC13A mRNA transcript comprises the sequence provided as SEQ ID NO: 9590.

GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCC
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ACAGCAGACATTAAAAAAAGAAAAACCACACACA

(SEQ ID NO: 9590 (SOURCE NCBI Reference Sequence NM_001387023.1)).

[00350] In various embodiments, an UNC13A mRNA transcript comprises the sequence provided as SEQ ID NO: 9591.

CTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCCGGGAGATGCC
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(SEQ ID NO: 9591 (SOURCE NCBI Reference Sequence XM_011527810.2)).

[00351] In various embodiments, an UNC13A mRNA transcript comprises the sequence provided as SEQ ID NO: 9592.

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ATGAATGCATGGTGTTGAGATGTTTTGCACTATTCTGACTTTTTGGTCTCTGTAAAAATATTTTATTAAC
AGCAGACATTAAAAAAAGAAAAACCACACACAGCCTTGGA

(**SEQ ID NO: 9592** (SOURCE (NCBI Reference Sequence XM_017026502.1)).

[00352] In various embodiments, an UNC13A mRNA transcript comprises the sequence provided as SEQ ID NO: 9593.

CTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCCGGGAGATGCC

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TAACAGCAGACATTAAAAAAAGAAAAACCACACACAGCCTTGGA

(**SEQ ID NO: 9593** (SOURCE NCBI Reference Sequence XM_011527811.2)).

[00353] In various embodiments, a UNC13A transcript is a pre-mRNA UNC13A transcript. In various embodiments, a UNC13A pre-mRNA transcript comprises a sequence provided as SEQ ID NO: 9594.

CAGTGGCTCACACCTGTAATCCCAGCACTTTGGGAGGCCGAGGTGGGTGGATCACTTGAGGTCAGGAGTT
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GCCATGGGACTGGGGGTTTCTCTGTCCAGCTCTGTTTCTCCCAGACTGGGGTCTGAGGACTCTCAGGACC

CCCAACTTTACCTAGCACAGGCTGGGCACAAGTGGGTGACAGGGAGTCTACGCCTAGTGGAATTATGTAT
TGGGGCAGGGTCAGTGTGAGAATACACATCCGCATGCATGTCTGTCCATGTCTGTCCGTACCAACCTTCC
CCTTCCACACGGACCTGGGCACATAGGAGGTGTCTGAGCCTGACACATGGGACAGAGAGTGGACATGGCT
GAGACACGGACAGAGAAAAGACAAGGAGTCCAGGGGGCTGAAAGCCTTTTGAAATCAGGAAGTTCCTGTA
TTGGCAGAACAAAGCCCAGAGAGGAGCAGGGCTTTCCTCAACGCCACCCAGCAAGTGGACACAGAGCCCG
GCCTTGGATGACACCTCCAGGGTTCTGAACCCTGGACCTCGCTTTATGCAAGGAGCTGGCCCCACATTTC
CATGAATCGGGGAAACAGCACAAGAAGGTTGGCCTGTGGCAGGGCAAGGGTTAAAGGGGTGACATTGAGG
GATGCCTCAGAGTCAAAGTCCCCTGACCAAGAGGAATAGAGTAGAAAACACAGAGACAGAGGGTGAGATC
ACGCCCCGATGAGGACGGAGAGAGACAGAGATGGAGAGAGACATAGAGGTGGAAATATACAGAGAAAGAT
AAATGCAGAGACCAAGGCAGGGAGTGTCGGGGGAAGTAAAGAGGGTGTCCTGAAGAAAGAAGGATCTGTT
CACTCTTACCAGTCTGTCCTCGAATGATTTGCATAAAATGAGGAGGTGCCTGTCCACACCCCCAATTCCT
CTCTCAGGCCCCAGAGCCTGAGACCTCACCATGCCCCCATCAGAGATGCAAAAAACTAAACACCCAACTA
GAAATCCTTGGGACCTCTCTCGGCTGGGATCTCAGAGCCTTTCTGTCCCCTACCCCTACCCCATGTGCTG
TCGATTTTGCAGATGGGGACAACCTGGGGCCTCCCGGAACTCTGCCACCCTGGGGAAGTTGGGGGAGGGC
CTTAGTCCCGGATCACAACCCCGTCTGCTCCCCAGAATCCTTTCCTAAGAATCGTTGAGGACCAAAGTTG
TCTTTGCTGACACGTGTTGCTTTTCTCTTTGCCTTTTATTGTTTCAGAGAAAAATCAAGTTGACTGTGTC
AAGTAACACCCCACCCCTTACCCCCGTCCAGCCATAGTGGCTCTCTGGAGACACAGGTCACAGGCGGAGG
GTCCCCTGATCATCCCCAACCACACAGCCAGGGGGACTTGACCCCTGTCCACCCCTGTCTCGTGCTCCCT
CAGACCCCCACAAACCGGCCAAGCAGTCCGGGGAGGCTTCCCCTCCACACAACTCTTAGCATGTGATTGC
AGATGTGAAATCAAAACGTTGTTTGTTTTTTGTTTTGTTTTGATTCTACCCCGTCGGTCCAGTGTCTGCA
CAGACGCCTTCATTTCTCTGTAAATATGTGACTTGGAACAAATGTTTAACACAAACGAGAAGTGGTCATG
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AGACATTAAAAAAAGAAAAACCACACACAGCCTTGGACACGTGGTTGCCTCCTCCTTGCATTCCTTTATC
AGCAAAAAAACAAAAACAAAAACCTCACGTACGATTAGCACCTACTAGGTAGGCGCAGACTCAGTAGAAC
ACACTGCTTGCCCATGAACGCGGCTCATCCGCAACTGGAGTCATCCCCATTTTACAGAGAAGGAAACTGA
AGTACAGAGAGACAAGATCTTGCTCAGATCACATAGCCAGGAAGAGATGGAGCTGGGACTTGAACTCAGA
ACATTTGCAACCATTGCTTTTTTTTTTTTTTTTTGAGATGAAGTCTCTGTTGCCCAGGCTGGAATGCAGT
GGTGCAATCTCAGCTCACTGCAATCTCCACCTCCCAGATTCAAGCGATTCTCCTGCCTTAGCCTCCTGAG
TAGCTGGGATTACAGGCGCCCGCCACCTTGCCTGGCTAATTTTTGTATTTTTAGTAGAGATAGGATTTCA
CCATGTTGGCCAGGCTGGTCGCGAACCCCTGACCTCAGGTGATCCACTCCCTCGGCCTCCCAAAGTGCTG
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ACTGCATCCTCAACCTCCCAGGCTCAGGTGATCCTCCCACCTCAGCCTCCTGAGTAGTGTGCACCACCAC
ACCTGGCTAATTTGTGTATTTTTTGTAGTGATAGGATGTCGCCATGTTGCCCAGACTGCTCTCGAACTCC
TCACTTTGGGCAATCCTCTCTCCTCAGCCCTCCAAAGTGTTGGGATTACAGGCGTGAGCCACTGTGCCTG
GCCATGTCTGTTTTAAATGTAGCAGCTGGGGCCAGGCGCAGTGGCTCACGCCTGTAATCCCAGCACTTTA
GGAGGCCGAGGCGGGTGGATCACGAGGTCAGGAGATCGAGACCATCCTGGCTAACACGGTGAAACCCCGT
CTCTACTAAAAGTACCAAAAATTAGCCGGGCACGGTGGCAGGCACCTGTAGTTCCAGCTACTCGGGAGGC
TGAGGCAGGAGAATGGTGTGAACTGGGGAGGCGGAGCTTGCAGTGAGCCAAGATCACGCCACTGCATTCC
AGCCTGGGTGACGGAGCGAGACTCCATCTCAAAAAAAAAAAAAAGAAAAAAAAGTAGCAGCTGGGAATCTC
ATTTCATAAACTCAGATGTGTGAGGAATGAAACTCCATTTTCCAACAGCTGAATTTAATTTCTGTTTTGA
GTCTCCATCCCACGAGGAAGCAGAAATGGAATCTCATTCAGCCCAGTTTCCTCGGTAAATTCCGAAATTC
CCCTCCTTATGTCTGGGGTTATTTCTACATTTGAGCGGACAGGACGGGAGCTGCGGGATCCACCACCAGG
AGTGGGTTCAGTGAGTGCTTTTGGTTGCAAGTAACAGACAGCAGGACTAAAAGTGGGGCCAGAAAGTGGC
TTACACCAGGAGTTATCCAGCACGCAGCAATCCCGCTCCTGGGGGACTTTTCTCCTTTGAGAAACTTGCA
CGTGGGGGTGTGGTATCTTCTCAAAGAATAGCATATAGCTGGGAAAAGGGGACAAACCGCAGCTGTCTGC
ATGATGTCTGCAGAGGCAGCCTGCAGGTCCTTGAGTGCCCCTGCTCATTAGCTGTTTCTGTACCCAAGTG
CATAGGCTACGCACTGTGACTGATGTGGATCTATTTGCCCCTCGCTACAAAAGGGTCTCAAGTCTTGTCC
TTCAGTGTGTGGGACCCATCGTGTTACCAATGGGGCTTGGGGACTGAGGCTCAAGACTGCTTGCTGGGAA
ATGTAACCCCTTTGTTCTGGACAGGTAGAAGGAGAGGAGAATGGTCATCCAGGCCTAATGTAAAGTTTCT
GCAACCC

(**SEQ ID NO: 9594** (SOURCE NCBI Reference Sequence NG_052872.1)).

[00354] In various embodiments, a UNC13A transcript is a pre-mRNA UNC13A transcript. In various embodiments, a UNC13A pre-mRNA transcript comprises a sequence provided as SEQ ID NO: 9595. NCBI Reference Sequence NC_000019.10 Reference GRCh38.p13 Primary Assembly is SEQ ID NO: 9595.

UNC13A Oligonucleotides Targeting Regions of the UNC13A Transcript

[00355] In various embodiments, UNC13A AON disclosed herein are complementary to specific regions of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065. In some embodiments, a UNC13A AON comprises a sequence that is complementary to a specific region of the UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 9587-9595. In some embodiments, a UNC13A AON comprises a sequence that is at least 85% complementary to a specific region of the UNC13A transcript. In some embodiments, a UNC13A AON comprises a sequence that is at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% complementary to a specific region of the UNC13A transcript. In some embodiments, a UNC13A AON comprises a sequence that is 90 to 99% complementary to a specific region of the UNC13A transcript. In some embodiments, a UNC13A AON comprises a sequence that is 90 to 95% complementary to a specific region of the UNC13A transcript. In some embodiments, a UNC13A AON comprises a sequence that is 95 to 99% complementary to a specific region of the UNC13A transcript.

[00356] In some embodiments, the UNC13A AON (e.g., UNC13A AON) has a segment that has, at most, 7 linked nucleosides. In some embodiments, the UNC13A AON has a segment that has, at most, 6, 5, 4, 3, or 2 linked nucleosides. The segments of the UNC13A AON may be separated from other segments of the UNC13A AON through a spacer. The segment of the UNC13A AON is complementary to a specific region of the UNC13A transcript (for example, a UNC13A transcript) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 9587-9593or an UNC13A pre-mRNA transcript transcribed from SEQ ID NO: 9594 or 9595.

UNC13A Oligonucleotide Variants

[00357] In various embodiments, UNC13A AONs include different variants, hereafter referred to as UNC13A AON variants. A UNC13A AON variant may be an oligonucleotide sequence of 5 to 100 nucleobases in length, for example, 10 to 40 nucleobases in length, for example, 14 to 40 nucleobases in length, 10 to 30 nucleobases in length, for example, 14 to 30 nucleobases in

length, for example, 16 to 28 nucleobases in length, for example, 19 to 23 nucleobases in length, for example, 21 to 23 nucleobases in length, for example, or 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleobases in length. A UNC13A AON variant may be an oligonucleotide sequence complementary to a portion of a UNC13A pre-mRNA sequence or a UNC13A gene sequence.

[00358] In various embodiments, a UNC13A AON variant represents a modified version of a corresponding UNC13A parent oligonucleotide that includes a nucleobase sequence selected from any one of SEQ ID NOs: 4531-5794. In some embodiments, a UNC13A AON variant includes a nucleobase sequence that represents a shortened version of a nucleobase sequence of a UNC13A AON selected from any one of SEQ ID NOs: 4531-5794. As one example, if a UNC13A parent oligonucleotide includes a 25mer (*e.g.*, 25 oligonucleotide units in length) a variant (*e.g.*, a UNC13A variant) may include a shorter version (*e.g.*, 15mer, 17mer, 19mer, 21mer, or 23mer) of the 25mer UNC13A parent oligonucleotide. In one embodiment, a nucleobase sequence of a UNC13A AON variant differs from a corresponding nucleobase sequence of a UNC13A parent oligonucleotide in that 1, 2, 3, 4, 5, or 6 oligonucleotide units are removed from one or both of the 3' and 5' ends of the nucleobase sequence of the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 23mer where two oligonucleotide units were removed from one of the 3' or 5' end of a 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 23mer where one nucleotide base is removed from each of the 3' and 5' ends of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 21mer where two oligonucleotide units are removed from each of the 3' and 5' ends of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 21mer where four oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 19mer where three oligonucleotide units are removed from each of the 3' and 5' ends of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 19mer where six oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide.

[00359] Example sequences of UNC13A AON variants are shown below in Table 10.

Table 10. Example UNC13A Oligonucleotide Variant Sequences

SEQ ID NO:	AON Sequence* (5' → 3')	SEQ ID NO:	Target Sequence (5' → 3')
7059	GGAGGGGCCGAGCAATGACCCTC	8323	GAGGGTCATTGCTCGGCCCCTCC
7060	GGGAGGGGCCGAGCAATGACCCT	8324	AGGGTCATTGCTCGGCCCCTCCC
7061	TGGGAGGGGCCGAGCAATGACCC	8325	GGGTCATTGCTCGGCCCCTCCCA
7062	ATGGGAGGGGCCGAGCAATGACC	8326	GGTCATTGCTCGGCCCCTCCCAT
7063	CATGGGAGGGGCCGAGCAATGAC	8327	GTCATTGCTCGGCCCCTCCCATG
7064	GCATGGGAGGGGCCGAGCAATGA	8328	TCATTGCTCGGCCCCTCCCATGC
7065	GGCATGGGAGGGGCCGAGCAATG	8329	CATTGCTCGGCCCCTCCCATGCC
7066	TGGCATGGGAGGGGCCGAGCAAT	8330	ATTGCTCGGCCCCTCCCATGCCA
7067	GTGGCATGGGAGGGGCCGAGCAA	8331	TTGCTCGGCCCCTCCCATGCCAC
7068	AGTGGCATGGGAGGGGCCGAGCA	8332	TGCTCGGCCCCTCCCATGCCACT
7069	AAGTGGCATGGGAGGGGCCGAGC	8333	GCTCGGCCCCTCCCATGCCACTT
7070	GAAGTGGCATGGGAGGGGCCGAG	8334	CTCGGCCCCTCCCATGCCACTTC
7071	GGAAGTGGCATGGGAGGGGCCGA	8335	TCGGCCCCTCCCATGCCACTTCC
7072	TGGAAGTGGCATGGGAGGGGCCG	8336	CGGCCCCTCCCATGCCACTTCCA
7073	GTGGAAGTGGCATGGGAGGGGCC	8337	GGCCCCTCCCATGCCACTTCCAC
7074	AGTGGAAGTGGCATGGGAGGGGC	8338	GCCCCTCCCATGCCACTTCCACT
7075	GAGTGGAAGTGGCATGGGAGGGG	8339	CCCCTCCCATGCCACTTCCACTC
7076	TGAGTGGAAGTGGCATGGGAGGG	8340	CCCTCCCATGCCACTTCCACTCA
7077	GTGAGTGGAAGTGGCATGGGAGG	8341	CCTCCCATGCCACTTCCACTCAC
7078	GGTGAGTGGAAGTGGCATGGGAG	8342	CTCCCATGCCACTTCCACTCACC
7079	TGGTGAGTGGAAGTGGCATGGGA	8343	TCCCATGCCACTTCCACTCACCA
7080	ATGGTGAGTGGAAGTGGCATGGG	8344	CCCATGCCACTTCCACTCACCAT
7081	AATGGTGAGTGGAAGTGGCATGG	8345	CCATGCCACTTCCACTCACCATT
7082	GAATGGTGAGTGGAAGTGGCATG	8346	CATGCCACTTCCACTCACCATTC
7083	GGAATGGTGAGTGGAAGTGGCAT	8347	ATGCCACTTCCACTCACCATTCC
7084	AGGAATGGTGAGTGGAAGTGGCA	8348	TGCCACTTCCACTCACCATTCCT
7085	CAGGAATGGTGAGTGGAAGTGGC	8349	GCCACTTCCACTCACCATTCCTG
7086	GCAGGAATGGTGAGTGGAAGTGG	8350	CCACTTCCACTCACCATTCCTGC
7087	GGCAGGAATGGTGAGTGGAAGTG	8351	CACTTCCACTCACCATTCCTGCC
7088	AGGCAGGAATGGTGAGTGGAAGT	8352	ACTTCCACTCACCATTCCTGCCT
7089	CAGGCAGGAATGGTGAGTGGAAG	8353	CTTCCACTCACCATTCCTGCCTG
7090	GCAGGCAGGAATGGTGAGTGGAA	8354	TTCCACTCACCATTCCTGCCTGC
7091	GGCAGGCAGGAATGGTGAGTGGA	8355	TCCACTCACCATTCCTGCCTGCC
7092	GGGCAGGCAGGAATGGTGAGTGG	8356	CCACTCACCATTCCTGCCTGCCC
7093	TGGGCAGGCAGGAATGGTGAGTG	8357	CACTCACCATTCCTGCCTGCCCA
7094	CTGGGCAGGCAGGAATGGTGAGT	8358	ACTCACCATTCCTGCCTGCCCAG
7095	GCTGGGCAGGCAGGAATGGTGAG	8359	CTCACCATTCCTGCCTGCCCAGC
7096	AGCTGGGCAGGCAGGAATGGTGA	8360	TCACCATTCCTGCCTGCCCAGCT

7097	GAGCTGGGCAGGCAGGAATGGTG	8361	CACCATTCCTGCCTGCCCAGCTC
7098	AGAGCTGGGCAGGCAGGAATGGT	8362	ACCATTCCTGCCTGCCCAGCTCT
7099	AAGAGCTGGGCAGGCAGGAATGG	8363	CCATTCCTGCCTGCCCAGCTCTT
7100	GAAGAGCTGGGCAGGCAGGAATG	8364	CATTCCTGCCTGCCCAGCTCTTC
7101	GGAAGAGCTGGGCAGGCAGGAAT	8365	ATTCCTGCCTGCCCAGCTCTTCC
7102	AGGAAGAGCTGGGCAGGCAGGAA	8366	TTCCTGCCTGCCCAGCTCTTCCT
7103	GAGGAAGAGCTGGGCAGGCAGGA	8367	TCCTGCCTGCCCAGCTCTTCCTC
7104	AGAGGAAGAGCTGGGCAGGCAGG	8368	CCTGCCTGCCCAGCTCTTCCTCT
7105	AAGAGGAAGAGCTGGGCAGGCAG	8369	CTGCCTGCCCAGCTCTTCCTCTT
7106	AAAGAGGAAGAGCTGGGCAGGCA	8370	TGCCTGCCCAGCTCTTCCTCTTT
7107	GAAAGAGGAAGAGCTGGGCAGGC	8371	GCCTGCCCAGCTCTTCCTCTTTC
7108	AGAAAGAGGAAGAGCTGGGCAGG	8372	CCTGCCCAGCTCTTCCTCTTTCT
7109	CAGAAAGAGGAAGAGCTGGGCAG	8373	CTGCCCAGCTCTTCCTCTTTCTG
7110	CCAGAAAGAGGAAGAGCTGGGCA	8374	TGCCCAGCTCTTCCTCTTTCTGG
7111	GCCAGAAAGAGGAAGAGCTGGGC	8375	GCCCAGCTCTTCCTCTTTCTGGC
7112	GGCCAGAAAGAGGAAGAGCTGGG	8376	CCCAGCTCTTCCTCTTTCTGGCC
7113	TGGCCAGAAAGAGGAAGAGCTGG	8377	CCAGCTCTTCCTCTTTCTGGCCA
7114	GTGGCCAGAAAGAGGAAGAGCTG	8378	CAGCTCTTCCTCTTTCTGGCCAC
7115	TGTGGCCAGAAAGAGGAAGAGCT	8379	AGCTCTTCCTCTTTCTGGCCACA
7116	GTGTGGCCAGAAAGAGGAAGAGC	8380	GCTCTTCCTCTTTCTGGCCACAC
7117	GGTGTGGCCAGAAAGAGGAAGAG	8381	CTCTTCCTCTTTCTGGCCACACC
7118	TGGTGTGGCCAGAAAGAGGAAGA	8382	TCTTCCTCTTTCTGGCCACACCA
7119	ATGGTGTGGCCAGAAAGAGGAAG	8383	CTTCCTCTTTCTGGCCACACCAT
7120	GATGGTGTGGCCAGAAAGAGGAA	8384	TTCCTCTTTCTGGCCACACCATC
7121	GGATGGTGTGGCCAGAAAGAGGA	8385	TCCTCTTTCTGGCCACACCATCC
7122	TGGATGGTGTGGCCAGAAAGAGG	8386	CCTCTTTCTGGCCACACCATCCA
7123	GTGGATGGTGTGGCCAGAAAGAG	8387	CTCTTTCTGGCCACACCATCCAC
7124	TGTGGATGGTGTGGCCAGAAAGA	8388	TCTTTCTGGCCACACCATCCACA
7125	GTGTGGATGGTGTGGCCAGAAAG	8389	CTTTCTGGCCACACCATCCACAC
7126	AGTGTGGATGGTGTGGCCAGAAA	8390	TTTCTGGCCACACCATCCACACT
7127	GAGTGTGGATGGTGTGGCCAGAA	8391	TTCTGGCCACACCATCCACACTC
7128	AGAGTGTGGATGGTGTGGCCAGA	8392	TCTGGCCACACCATCCACACTCT
7129	GAGAGTGTGGATGGTGTGGCCAG	8393	CTGGCCACACCATCCACACTCTC
7130	GGAGAGTGTGGATGGTGTGGCCA	8394	TGGCCACACCATCCACACTCTCC
7131	AGGAGAGTGTGGATGGTGTGGCC	8395	GGCCACACCATCCACACTCTCCT
7132	CAGGAGAGTGTGGATGGTGTGGC	8396	GCCACACCATCCACACTCTCCTG
7133	CCAGGAGAGTGTGGATGGTGTGG	8397	CCACACCATCCACACTCTCCTGG
7134	GCCAGGAGAGTGTGGATGGTGTG	8398	CACACCATCCACACTCTCCTGGC
7135	GGCCAGGAGAGTGTGGATGGTGT	8399	ACACCATCCACACTCTCCTGGCC
7136	GGGCCAGGAGAGTGTGGATGGTG	8400	CACCATCCACACTCTCCTGGCCC
7137	AGGGCCAGGAGAGTGTGGATGGT	8401	ACCATCCACACTCTCCTGGCCCT
7138	GAGGGCCAGGAGAGTGTGGATGG	8402	CCATCCACACTCTCCTGGCCCTC

7139	AGAGGGCCAGGAGAGTGTGGATG	8403	CATCCACACTCTCCTGGCCCTCT
7140	CAGAGGGCCAGGAGAGTGTGGAT	8404	ATCCACACTCTCCTGGCCCTCTG
7141	TCAGAGGGCCAGGAGAGTGTGGA	8405	TCCACACTCTCCTGGCCCTCTGA
7142	CTCAGAGGGCCAGGAGAGTGTGG	8406	CCACACTCTCCTGGCCCTCTGAG
7143	TCTCAGAGGGCCAGGAGAGTGTG	8407	CACACTCTCCTGGCCCTCTGAGA
7144	GTCTCAGAGGGCCAGGAGAGTGT	8408	ACACTCTCCTGGCCCTCTGAGAC
7145	AGTCTCAGAGGGCCAGGAGAGTG	8409	CACTCTCCTGGCCCTCTGAGACT
7146	CAGTCTCAGAGGGCCAGGAGAGT	8410	ACTCTCCTGGCCCTCTGAGACTG
7147	GCAGTCTCAGAGGGCCAGGAGAG	8411	CTCTCCTGGCCCTCTGAGACTGC
7148	GGCAGTCTCAGAGGGCCAGGAGA	8412	TCTCCTGGCCCTCTGAGACTGCC
7149	GGGCAGTCTCAGAGGGCCAGGAG	8413	CTCCTGGCCCTCTGAGACTGCCC
7150	CGGGCAGTCTCAGAGGGCCAGGA	8414	TCCTGGCCCTCTGAGACTGCCCG
7151	GCGGGCAGTCTCAGAGGGCCAGG	8415	CCTGGCCCTCTGAGACTGCCCGC
7152	GGCGGGCAGTCTCAGAGGGCCAG	8416	CTGGCCCTCTGAGACTGCCCGCC
7153	TGGCGGGCAGTCTCAGAGGGCCA	8417	TGGCCCTCTGAGACTGCCCGCCA
7154	ATGGCGGGCAGTCTCAGAGGGCC	8418	GGCCCTCTGAGACTGCCCGCCAT
7155	CATGGCGGGCAGTCTCAGAGGGC	8419	GCCCTCTGAGACTGCCCGCCATG
7156	GCATGGCGGGCAGTCTCAGAGGG	8420	CCCTCTGAGACTGCCCGCCATGC
7157	GGCATGGCGGGCAGTCTCAGAGG	8421	CCTCTGAGACTGCCCGCCATGCC
7158	TGGCATGGCGGGCAGTCTCAGAG	8422	CTCTGAGACTGCCCGCCATGCCA
7159	ATGGCATGGCGGGCAGTCTCAGA	8423	TCTGAGACTGCCCGCCATGCCAT
7160	AATGGCATGGCGGGCAGTCTCAG	8424	CTGAGACTGCCCGCCATGCCATT
7161	GAATGGCATGGCGGGCAGTCTCA	8425	TGAGACTGCCCGCCATGCCATTC
7162	GGAATGGCATGGCGGGCAGTCTC	8426	GAGACTGCCCGCCATGCCATTCC
7163	GGGAATGGCATGGCGGGCAGTCT	8427	AGACTGCCCGCCATGCCATTCCC
7164	AGGGAATGGCATGGCGGGCAGTC	8428	GACTGCCCGCCATGCCATTCCCT
7165	AAGGGAATGGCATGGCGGGCAGT	8429	ACTGCCCGCCATGCCATTCCCTT
7166	AAAGGGAATGGCATGGCGGGCAG	8430	CTGCCCGCCATGCCATTCCCTTT
7167	TAAAGGGAATGGCATGGCGGGCA	8431	TGCCCGCCATGCCATTCCCTTTA
7168	GTAAAGGGAATGGCATGGCGGGC	8432	GCCCGCCATGCCATTCCCTTTAC
7169	GGTAAAGGGAATGGCATGGCGGG	8433	CCCGCCATGCCATTCCCTTTACC
7170	AGGTAAAGGGAATGGCATGGCGG	8434	CCGCCATGCCATTCCCTTTACCT
7171	CAGGTAAAGGGAATGGCATGGCG	8435	CGCCATGCCATTCCCTTTACCTG
7172	CCAGGTAAAGGGAATGGCATGGC	8436	GCCATGCCATTCCCTTTACCTGG
7173	TCCAGGTAAAGGGAATGGCATGG	8437	CCATGCCATTCCCTTTACCTGGA
7174	TTCCAGGTAAAGGGAATGGCATG	8438	CATGCCATTCCCTTTACCTGGAA
7175	TTTCCAGGTAAAGGGAATGGCAT	8439	ATGCCATTCCCTTTACCTGGAAA
7176	TTTTCCAGGTAAAGGGAATGGCA	8440	TGCCATTCCCTTTACCTGGAAAA
7177	GTTTTCCAGGTAAAGGGAATGGC	8441	GCCATTCCCTTTACCTGGAAAAC
7178	AGTTTTCCAGGTAAAGGGAATGG	8442	CCATTCCCTTTACCTGGAAAACT
7179	GAGTTTTCCAGGTAAAGGGAATG	8443	CATTCCCTTTACCTGGAAAACTC
7180	GGAGTTTTCCAGGTAAAGGGAAT	8444	ATTCCCTTTACCTGGAAAACTCC

7181	AGGAGTTTTCCAGGTAAAGGGAA	8445	TTCCCTTTACCTGGAAAACTCCT
7182	GAGGAGTTTTCCAGGTAAAGGGA	8446	TCCCTTTACCTGGAAAACTCCTC
7183	GGAGGAGTTTTCCAGGTAAAGGG	8447	CCCTTTACCTGGAAAACTCCTCC
7184	GGGAGGAGTTTTCCAGGTAAAGG	8448	CCTTTACCTGGAAAACTCCTCCC
7185	AGGGAGGAGTTTTCCAGGTAAAG	8449	CTTTACCTGGAAAACTCCTCCCT
7186	TAGGGAGGAGTTTTCCAGGTAAA	8450	TTTACCTGGAAAACTCCTCCCTA
7187	ATAGGGAGGAGTTTTCCAGGTAA	8451	TTACCTGGAAAACTCCTCCCTAT
7188	GATAGGGAGGAGTTTTCCAGGTA	8452	TACCTGGAAAACTCCTCCCTATC
7189	GGATAGGGAGGAGTTTTCCAGGT	8453	ACCTGGAAAACTCCTCCCTATCC
7190	TGGATAGGGAGGAGTTTTCCAGG	8454	CCTGGAAAACTCCTCCCTATCCA
7191	ATGGATAGGGAGGAGTTTTCCAG	8455	CTGGAAAACTCCTCCCTATCCAT
7192	GATGGATAGGGAGGAGTTTTCCA	8456	TGGAAAACTCCTCCCTATCCATC
7193	TGATGGATAGGGAGGAGTTTTCC	8457	GGAAAACTCCTCCCTATCCATCA
7194	TTGATGGATAGGGAGGAGTTTTC	8458	GAAAACTCCTCCCTATCCATCAA
7195	TTTGATGGATAGGGAGGAGTTTT	8459	AAAACTCCTCCCTATCCATCAAA
7196	CTTTGATGGATAGGGAGGAGTTT	8460	AAACTCCTCCCTATCCATCAAAG
7197	ACTTTGATGGATAGGGAGGAGTT	8461	AACTCCTCCCTATCCATCAAAGT
7198	GACTTTGATGGATAGGGAGGAGT	8462	ACTCCTCCCTATCCATCAAAGTC
7199	GGACTTTGATGGATAGGGAGGAG	8463	CTCCTCCCTATCCATCAAAGTCC
7200	TGGACTTTGATGGATAGGGAGGA	8464	TCCTCCCTATCCATCAAAGTCCA
7201	CTGGACTTTGATGGATAGGGAGG	8465	CCTCCCTATCCATCAAAGTCCAG
7202	TCTGGACTTTGATGGATAGGGAG	8466	CTCCCTATCCATCAAAGTCCAGA
7203	ATCTGGACTTTGATGGATAGGGA	8467	TCCCTATCCATCAAAGTCCAGAT
7204	AATCTGGACTTTGATGGATAGGG	8468	CCCTATCCATCAAAGTCCAGATT
7205	GAATCTGGACTTTGATGGATAGG	8469	CCTATCCATCAAAGTCCAGATTC
7206	TGAATCTGGACTTTGATGGATAG	8470	CTATCCATCAAAGTCCAGATTCA
7207	CTGAATCTGGACTTTGATGGATA	8471	TATCCATCAAAGTCCAGATTCAG
7208	CCTGAATCTGGACTTTGATGGAT	8472	ATCCATCAAAGTCCAGATTCAGG
7209	CCCTGAATCTGGACTTTGATGGA	8473	TCCATCAAAGTCCAGATTCAGGG
7210	ACCCTGAATCTGGACTTTGATGG	8474	CCATCAAAGTCCAGATTCAGGGT
7211	GACCCTGAATCTGGACTTTGATG	8475	CATCAAAGTCCAGATTCAGGGTC
7212	TGACCCTGAATCTGGACTTTGAT	8476	ATCAAAGTCCAGATTCAGGGTCA
7213	GTGACCCTGAATCTGGACTTTGA	8477	TCAAAGTCCAGATTCAGGGTCAC
7214	GGTGACCCTGAATCTGGACTTTG	8478	CAAAGTCCAGATTCAGGGTCACC
7215	AGGTGACCCTGAATCTGGACTTT	8479	AAAGTCCAGATTCAGGGTCACCT
7216	GAGGTGACCCTGAATCTGGACTT	8480	AAGTCCAGATTCAGGGTCACCTC
7217	GGAGGTGACCCTGAATCTGGACT	8481	AGTCCAGATTCAGGGTCACCTCC
7218	AGGAGGTGACCCTGAATCTGGAC	8482	GTCCAGATTCAGGGTCACCTCCT
7219	GAGGAGGTGACCCTGAATCTGGA	8483	TCCAGATTCAGGGTCACCTCCTC
7220	AGAGGAGGTGACCCTGAATCTGG	8484	CCAGATTCAGGGTCACCTCCTCT
7221	CAGAGGAGGTGACCCTGAATCTG	8485	CAGATTCAGGGTCACCTCCTCTG
7222	CCAGAGGAGGTGACCCTGAATCT	8486	AGATTCAGGGTCACCTCCTCTGG

7223	CCCAGAGGAGGTGACCCTGAATC	8487	GATTCAGGGTCACCTCCTCTGGG
7224	TCCCAGAGGAGGTGACCCTGAAT	8488	ATTCAGGGTCACCTCCTCTGGGA
7225	TTCCCAGAGGAGGTGACCCTGAA	8489	TTCAGGGTCACCTCCTCTGGGAA
7226	CTTCCCAGAGGAGGTGACCCTGA	8490	TCAGGGTCACCTCCTCTGGGAAG
7227	GCTTCCCAGAGGAGGTGACCCTG	8491	CAGGGTCACCTCCTCTGGGAAGC
7228	GGCTTCCCAGAGGAGGTGACCCT	8492	AGGGTCACCTCCTCTGGGAAGCC
7229	GGGCTTCCCAGAGGAGGTGACCC	8493	GGGTCACCTCCTCTGGGAAGCCC
7230	TGGGCTTCCCAGAGGAGGTGACC	8494	GGTCACCTCCTCTGGGAAGCCCA
7231	GTGGGCTTCCCAGAGGAGGTGAC	8495	GTCACCTCCTCTGGGAAGCCCAC
7232	GGTGGGCTTCCCAGAGGAGGTGA	8496	TCACCTCCTCTGGGAAGCCCACC
7233	AGGTGGGCTTCCCAGAGGAGGTG	8497	CACCTCCTCTGGGAAGCCCACCT
7234	AAGGTGGGCTTCCCAGAGGAGGT	8498	ACCTCCTCTGGGAAGCCCACCTT
7235	CAAGGTGGGCTTCCCAGAGGAGG	8499	CCTCCTCTGGGAAGCCCACCTTG
7236	CCAAGGTGGGCTTCCCAGAGGAG	8500	CTCCTCTGGGAAGCCCACCTTGG
7237	GCCAAGGTGGGCTTCCCAGAGGA	8501	TCCTCTGGGAAGCCCACCTTGGC
7238	GGCCAAGGTGGGCTTCCCAGAGG	8502	CCTCTGGGAAGCCCACCTTGGCC
7239	AGGCCAAGGTGGGCTTCCCAGAG	8503	CTCTGGGAAGCCCACCTTGGCCT
7240	GAGGCCAAGGTGGGCTTCCCAGA	8504	TCTGGGAAGCCCACCTTGGCCTC
7241	GGAGGCCAAGGTGGGCTTCCCAG	8505	CTGGGAAGCCCACCTTGGCCTCC
7242	TGGAGGCCAAGGTGGGCTTCCCA	8506	TGGGAAGCCCACCTTGGCCTCCA
7243	CTGGAGGCCAAGGTGGGCTTCCC	8507	GGGAAGCCCACCTTGGCCTCCAG
7244	CCTGGAGGCCAAGGTGGGCTTCC	8508	GGAAGCCCACCTTGGCCTCCAGG
7245	ACCTGGAGGCCAAGGTGGGCTTC	8509	GAAGCCCACCTTGGCCTCCAGGT
7246	AACCTGGAGGCCAAGGTGGGCTT	8510	AAGCCCACCTTGGCCTCCAGGTT
7247	CAACCTGGAGGCCAAGGTGGGCT	8511	AGCCCACCTTGGCCTCCAGGTTG
7248	TCAACCTGGAGGCCAAGGTGGGC	8512	GCCCACCTTGGCCTCCAGGTTGA
7249	GTCAACCTGGAGGCCAAGGTGGG	8513	CCCACCTTGGCCTCCAGGTTGAC
7250	AGTCAACCTGGAGGCCAAGGTGG	8514	CCACCTTGGCCTCCAGGTTGACT
7251	GAGTCAACCTGGAGGCCAAGGTG	8515	CACCTTGGCCTCCAGGTTGACTC
7252	AGAGTCAACCTGGAGGCCAAGGT	8516	ACCTTGGCCTCCAGGTTGACTCT
7253	GAGAGTCAACCTGGAGGCCAAGG	8517	CCTTGGCCTCCAGGTTGACTCTC
7254	TGAGAGTCAACCTGGAGGCCAAG	8518	CTTGGCCTCCAGGTTGACTCTCA
7255	GTGAGAGTCAACCTGGAGGCCAA	8519	TTGGCCTCCAGGTTGACTCTCAC
7256	AGTGAGAGTCAACCTGGAGGCCA	8520	TGGCCTCCAGGTTGACTCTCACT
7257	TAGTGAGAGTCAACCTGGAGGCC	8521	GGCCTCCAGGTTGACTCTCACTA
7258	GTAGTGAGAGTCAACCTGGAGGC	8522	GCCTCCAGGTTGACTCTCACTAC
7259	AGTAGTGAGAGTCAACCTGGAGG	8523	CCTCCAGGTTGACTCTCACTACT
7260	GAGTAGTGAGAGTCAACCTGGAG	8524	CTCCAGGTTGACTCTCACTACTC
7261	TGAGTAGTGAGAGTCAACCTGGA	8525	TCCAGGTTGACTCTCACTACTCA
7262	ATGAGTAGTGAGAGTCAACCTGG	8526	CCAGGTTGACTCTCACTACTCAT
7263	GATGAGTAGTGAGAGTCAACCTG	8527	CAGGTTGACTCTCACTACTCATC
7264	TGATGAGTAGTGAGAGTCAACCT	8528	AGGTTGACTCTCACTACTCATCA

7265	ATGATGAGTAGTGAGAGTCAACC	8529	GGTTGACTCTCACTACTCATCAT
7266	GATGATGAGTAGTGAGAGTCAAC	8530	GTTGACTCTCACTACTCATCATC
7267	TGATGATGAGTAGTGAGAGTCAA	8531	TTGACTCTCACTACTCATCATCA
7268	CTGATGATGAGTAGTGAGAGTCA	8532	TGACTCTCACTACTCATCATCAG
7269	CCTGATGATGAGTAGTGAGAGTC	8533	GACTCTCACTACTCATCATCAGG
7270	ACCTGATGATGAGTAGTGAGAGT	8534	ACTCTCACTACTCATCATCAGGT
7271	AACCTGATGATGAGTAGTGAGAG	8535	CTCTCACTACTCATCATCAGGTT
7272	GAACCTGATGATGAGTAGTGAGA	8536	TCTCACTACTCATCATCAGGTTC
7273	AGAACCTGATGATGAGTAGTGAG	8537	CTCACTACTCATCATCAGGTTCT
7274	AAGAACCTGATGATGAGTAGTGA	8538	TCACTACTCATCATCAGGTTCTT
7275	GAAGAACCTGATGATGAGTAGTG	8539	CACTACTCATCATCAGGTTCTTC
7276	GGAAGAACCTGATGATGAGTAGT	8540	ACTACTCATCATCAGGTTCTTCC
7277	AGGAAGAACCTGATGATGAGTAG	8541	CTACTCATCATCAGGTTCTTCCT
7278	AAGGAAGAACCTGATGATGAGTA	8542	TACTCATCATCAGGTTCTTCCTT
7279	GAAGGAAGAACCTGATGATGAGT	8543	ACTCATCATCAGGTTCTTCCTTC
7280	AGAAGGAAGAACCTGATGATGAG	8544	CTCATCATCAGGTTCTTCCTTCT
7281	TAGAAGGAAGAACCTGATGATGA	8545	TCATCATCAGGTTCTTCCTTCTA
7282	ATAGAAGGAAGAACCTGATGATG	8546	CATCATCAGGTTCTTCCTTCTAT
7283	AATAGAAGGAAGAACCTGATGAT	8547	ATCATCAGGTTCTTCCTTCTATT
7284	GAATAGAAGGAAGAACCTGATGA	8548	TCATCAGGTTCTTCCTTCTATTC
7285	GGAATAGAAGGAAGAACCTGATG	8549	CATCAGGTTCTTCCTTCTATTCC
7286	TGGAATAGAAGGAAGAACCTGAT	8550	ATCAGGTTCTTCCTTCTATTCCA
7287	CTGGAATAGAAGGAAGAACCTGA	8551	TCAGGTTCTTCCTTCTATTCCAG
7288	GCTGGAATAGAAGGAAGAACCTG	8552	CAGGTTCTTCCTTCTATTCCAGC
7289	GGCTGGAATAGAAGGAAGAACCT	8553	AGGTTCTTCCTTCTATTCCAGCC
7290	GGGCTGGAATAGAAGGAAGAACC	8554	GGTTCTTCCTTCTATTCCAGCCC
7291	AGGGCTGGAATAGAAGGAAGAAC	8555	GTTCTTCCTTCTATTCCAGCCCT
7292	TAGGGCTGGAATAGAAGGAAGAA	8556	TTCTTCCTTCTATTCCAGCCCTA
7293	TTAGGGCTGGAATAGAAGGAAGA	8557	TCTTCCTTCTATTCCAGCCCTAA
7294	GTTAGGGCTGGAATAGAAGGAAG	8558	CTTCCTTCTATTCCAGCCCTAAC
7295	GGTTAGGGCTGGAATAGAAGGAA	8559	TTCCTTCTATTCCAGCCCTAACC
7296	TGGTTAGGGCTGGAATAGAAGGA	8560	TCCTTCTATTCCAGCCCTAACCA
7297	GTGGTTAGGGCTGGAATAGAAGG	8561	CCTTCTATTCCAGCCCTAACCAC
7298	AGTGGTTAGGGCTGGAATAGAAG	8562	CTTCTATTCCAGCCCTAACCACT
7299	GAGTGGTTAGGGCTGGAATAGAA	8563	TTCTATTCCAGCCCTAACCACTC
7300	TGAGTGGTTAGGGCTGGAATAGA	8564	TCTATTCCAGCCCTAACCACTCA
7301	CTGAGTGGTTAGGGCTGGAATAG	8565	CTATTCCAGCCCTAACCACTCAG
7302	CCTGAGTGGTTAGGGCTGGAATA	8566	TATTCCAGCCCTAACCACTCAGG
7303	TCCTGAGTGGTTAGGGCTGGAAT	8567	ATTCCAGCCCTAACCACTCAGGA
7304	ATCCTGAGTGGTTAGGGCTGGAA	8568	TTCCAGCCCTAACCACTCAGGAT
7305	AATCCTGAGTGGTTAGGGCTGGA	8569	TCCAGCCCTAACCACTCAGGATT
7306	CAATCCTGAGTGGTTAGGGCTGG	8570	CCAGCCCTAACCACTCAGGATTG

7307	CCAATCCTGAGTGGTTAGGGCTG	8571	CAGCCCTAACCACTCAGGATTGG
7308	CCCAATCCTGAGTGGTTAGGGCT	8572	AGCCCTAACCACTCAGGATTGGG
7309	GCCCAATCCTGAGTGGTTAGGGC	8573	GCCCTAACCACTCAGGATTGGGC
7310	GGCCCAATCCTGAGTGGTTAGGG	8574	CCCTAACCACTCAGGATTGGGCC
7311	CGGCCCAATCCTGAGTGGTTAGG	8575	CCTAACCACTCAGGATTGGGCCG
7312	ACGGCCCAATCCTGAGTGGTTAG	8576	CTAACCACTCAGGATTGGGCCGT
7313	AACGGCCCAATCCTGAGTGGTTA	8577	TAACCACTCAGGATTGGGCCGTT
7314	AAACGGCCCAATCCTGAGTGGTT	8578	AACCACTCAGGATTGGGCCGTTT
7315	CAAACGGCCCAATCCTGAGTGGT	8579	ACCACTCAGGATTGGGCCGTTTG
7316	ACAAACGGCCCAATCCTGAGTGG	8580	CCACTCAGGATTGGGCCGTTTGT
7317	CACAAACGGCCCAATCCTGAGTG	8581	CACTCAGGATTGGGCCGTTTGTG
7318	ACACAAACGGCCCAATCCTGAGT	8582	ACTCAGGATTGGGCCGTTTGTGT
7319	GACACAAACGGCCCAATCCTGAG	8583	CTCAGGATTGGGCCGTTTGTGTC
7320	AGACACAAACGGCCCAATCCTGA	8584	TCAGGATTGGGCCGTTTGTGTCT
7321	CAGACACAAACGGCCCAATCCTG	8585	CAGGATTGGGCCGTTTGTGTCTG
7322	CCAGACACAAACGGCCCAATCCT	8586	AGGATTGGGCCGTTTGTGTCTGG
7323	CCCAGACACAAACGGCCCAATCC	8587	GGATTGGGCCGTTTGTGTCTGGG
7324	ACCCAGACACAAACGGCCCAATC	8588	GATTGGGCCGTTTGTGTCTGGGT
7325	TACCCAGACACAAACGGCCCAAT	8589	ATTGGGCCGTTTGTGTCTGGGTA
7326	ATACCCAGACACAAACGGCCCAA	8590	TTGGGCCGTTTGTGTCTGGGTAT
7327	CATACCCAGACACAAACGGCCCA	8591	TGGGCCGTTTGTGTCTGGGTATG
7328	ACATACCCAGACACAAACGGCCC	8592	GGGCCGTTTGTGTCTGGGTATGT
7329	GACATACCCAGACACAAACGGCC	8593	GGCCGTTTGTGTCTGGGTATGTC
7330	AGACATACCCAGACACAAACGGC	8594	GCCGTTTGTGTCTGGGTATGTCT
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7332	AGAGACATACCCAGACACAAACG	8596	CGTTTGTGTCTGGGTATGTCTCT
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7334	GAAGAGACATACCCAGACACAAA	8598	TTTGTGTCTGGGTATGTCTCTTC
7335	GGAAGAGACATACCCAGACACAA	8599	TTGTGTCTGGGTATGTCTCTTCC
7336	TGGAAGAGACATACCCAGACACA	8600	TGTGTCTGGGTATGTCTCTTCCA
7337	CTGGAAGAGACATACCCAGACAC	8601	GTGTCTGGGTATGTCTCTTCCAG
7338	GCTGGAAGAGACATACCCAGACA	8602	TGTCTGGGTATGTCTCTTCCAGC
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7340	CAGCTGGAAGAGACATACCCAGA	8604	TCTGGGTATGTCTCTTCCAGCTG
7341	GCAGCTGGAAGAGACATACCCAG	8605	CTGGGTATGTCTCTTCCAGCTGC
7342	GGCAGCTGGAAGAGACATACCCA	8606	TGGGTATGTCTCTTCCAGCTGCC
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7344	CAGGCAGCTGGAAGAGACATACC	8608	GGTATGTCTCTTCCAGCTGCCTG
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7346	CCCAGGCAGCTGGAAGAGACATA	8610	TATGTCTCTTCCAGCTGCCTGGG
7347	ACCCAGGCAGCTGGAAGAGACAT	8611	ATGTCTCTTCCAGCTGCCTGGGT
7348	AACCCAGGCAGCTGGAAGAGACA	8612	TGTCTCTTCCAGCTGCCTGGGTT

7349	AAACCCAGGCAGCTGGAAGAGAC	8613	GTCTCTTCCAGCTGCCTGGGTTT
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7351	GGAAACCCAGGCAGCTGGAAGAG	8615	CTCTTCCAGCTGCCTGGGTTTCC
7352	AGGAAACCCAGGCAGCTGGAAGA	8616	TCTTCCAGCTGCCTGGGTTTCCT
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7354	CCAGGAAACCCAGGCAGCTGGAA	8618	TTCCAGCTGCCTGGGTTTCCTGG
7355	TCCAGGAAACCCAGGCAGCTGGA	8619	TCCAGCTGCCTGGGTTTCCTGGA
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7357	TTTCCAGGAAACCCAGGCAGCTG	8621	CAGCTGCCTGGGTTTCCTGGAAA
7358	CTTTCCAGGAAACCCAGGCAGCT	8622	AGCTGCCTGGGTTTCCTGGAAAG
7359	TCTTTCCAGGAAACCCAGGCAGC	8623	GCTGCCTGGGTTTCCTGGAAAGA
7360	TTCTTTCCAGGAAACCCAGGCAG	8624	CTGCCTGGGTTTCCTGGAAAGAA
7361	GTTCTTTCCAGGAAACCCAGGCA	8625	TGCCTGGGTTTCCTGGAAAGAAC
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7364	AGAGTTCTTTCCAGGAAACCCAG	8628	CTGGGTTTCCTGGAAAGAACTCT
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7366	TAAGAGTTCTTTCCAGGAAACCC	8630	GGGTTTCCTGGAAAGAACTCTTA
7367	ATAAGAGTTCTTTCCAGGAAACC	8631	GGTTTCCTGGAAAGAACTCTTAT
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7372	TGGGGATAAGAGTTCTTTCCAGG	8636	CCTGGAAAGAACTCTTATCCCCA
7373	CTGGGGATAAGAGTTCTTTCCAG	8637	CTGGAAAGAACTCTTATCCCCAG
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7376	TTCCTGGGGATAAGAGTTCTTTC	8640	GAAAGAACTCTTATCCCCAGGAA
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7393	TTTATTCAACAAACTAGTTCCTG	8657	CAGGAACTAGTTTGTTGAATAAA
7394	ATTTATTCAACAAACTAGTTCCT	8658	AGGAACTAGTTTGTTGAATAAAT
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7455	ATCCATCCTTTTATCTACTCATC	8719	GATGAGTAGATAAAAGGATGGAT
7456	CATCCATCCTTTTATCTACTCAT	8720	ATGAGTAGATAAAAGGATGGATG
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7458	TCCATCCATCCTTTTATCTACTC	8722	GAGTAGATAAAAGGATGGATGGA
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7462	TCTCTCCATCCATCCTTTTATCT	8726	AGATAAAAGGATGGATGGAGAGA
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7468	CACCCATCTCTCCATCCATCCTT	8732	AAGGATGGATGGAGAGATGGGTG
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7485	CTATCCATCCATGTACTCACCCA	8749	TGGGTGAGTACATGGATGGATAG
7486	TCTATCCATCCATGTACTCACCC	8750	GGGTGAGTACATGGATGGATAGA
7487	ATCTATCCATCCATGTACTCACC	8751	GGTGAGTACATGGATGGATAGAT
7488	CATCTATCCATCCATGTACTCAC	8752	GTGAGTACATGGATGGATAGATG
7489	CCATCTATCCATCCATGTACTCA	8753	TGAGTACATGGATGGATAGATGG
7490	TCCATCTATCCATCCATGTACTC	8754	GAGTACATGGATGGATAGATGGA
7491	ATCCATCTATCCATCCATGTACT	8755	AGTACATGGATGGATAGATGGAT
7492	CATCCATCTATCCATCCATGTAC	8756	GTACATGGATGGATAGATGGATG
7493	TCATCCATCTATCCATCCATGTA	8757	TACATGGATGGATAGATGGATGA
7494	CTCATCCATCTATCCATCCATGT	8758	ACATGGATGGATAGATGGATGAG
7495	ACTCATCCATCTATCCATCCATG	8759	CATGGATGGATAGATGGATGAGT
7496	AACTCATCCATCTATCCATCCAT	8760	ATGGATGGATAGATGGATGAGTT
7497	CAACTCATCCATCTATCCATCCA	8761	TGGATGGATAGATGGATGAGTTG
7498	CCAACTCATCCATCTATCCATCC	8762	GGATGGATAGATGGATGAGTTGG
7499	ACCAACTCATCCATCTATCCATC	8763	GATGGATAGATGGATGAGTTGGT
7500	CACCAACTCATCCATCTATCCAT	8764	ATGGATAGATGGATGAGTTGGTG
7501	CCACCAACTCATCCATCTATCCA	8765	TGGATAGATGGATGAGTTGGTGG
7502	CCCACCAACTCATCCATCTATCC	8766	GGATAGATGGATGAGTTGGTGGG
7503	ACCCACCAACTCATCCATCTATC	8767	GATAGATGGATGAGTTGGTGGGT
7504	TACCCACCAACTCATCCATCTAT	8768	ATAGATGGATGAGTTGGTGGGTA
7505	CTACCCACCAACTCATCCATCTA	8769	TAGATGGATGAGTTGGTGGGTAG
7506	TCTACCCACCAACTCATCCATCT	8770	AGATGGATGAGTTGGTGGGTAGA
7507	ATCTACCCACCAACTCATCCATC	8771	GATGGATGAGTTGGTGGGTAGAT
7508	AATCTACCCACCAACTCATCCAT	8772	ATGGATGAGTTGGTGGGTAGATT
7509	GAATCTACCCACCAACTCATCCA	8773	TGGATGAGTTGGTGGGTAGATTC
7510	CGAATCTACCCACCAACTCATCC	8774	GGATGAGTTGGTGGGTAGATTCG
7511	ACGAATCTACCCACCAACTCATC	8775	GATGAGTTGGTGGGTAGATTCGT
7512	CACGAATCTACCCACCAACTCAT	8776	ATGAGTTGGTGGGTAGATTCGTG
7513	CCACGAATCTACCCACCAACTCA	8777	TGAGTTGGTGGGTAGATTCGTGG
7514	GCCACGAATCTACCCACCAACTC	8778	GAGTTGGTGGGTAGATTCGTGGC
7515	AGCCACGAATCTACCCACCAACT	8779	AGTTGGTGGGTAGATTCGTGGCT
7516	TAGCCACGAATCTACCCACCAAC	8780	GTTGGTGGGTAGATTCGTGGCTA

7517	CTAGCCACGAATCTACCCACCAA	8781	TTGGTGGGTAGATTCGTGGCTAG
7518	TCTAGCCACGAATCTACCCACCA	8782	TGGTGGGTAGATTCGTGGCTAGA
7519	ATCTAGCCACGAATCTACCCACC	8783	GGTGGGTAGATTCGTGGCTAGAT
7520	CATCTAGCCACGAATCTACCCAC	8784	GTGGGTAGATTCGTGGCTAGATG
7521	CCATCTAGCCACGAATCTACCCA	8785	TGGGTAGATTCGTGGCTAGATGG
7522	TCCATCTAGCCACGAATCTACCC	8786	GGGTAGATTCGTGGCTAGATGGA
7523	ATCCATCTAGCCACGAATCTACC	8787	GGTAGATTCGTGGCTAGATGGAT
7524	CATCCATCTAGCCACGAATCTAC	8788	GTAGATTCGTGGCTAGATGGATG
7525	TCATCCATCTAGCCACGAATCTA	8789	TAGATTCGTGGCTAGATGGATGA
7526	ATCATCCATCTAGCCACGAATCT	8790	AGATTCGTGGCTAGATGGATGAT
7527	CATCATCCATCTAGCCACGAATC	8791	GATTCGTGGCTAGATGGATGATG
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7529	TCCATCATCCATCTAGCCACGAA	8793	TTCGTGGCTAGATGGATGATGGA
7530	ATCCATCATCCATCTAGCCACGA	8794	TCGTGGCTAGATGGATGATGGAT
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7533	TCCATCCATCATCCATCTAGCCA	8797	TGGCTAGATGGATGATGGATGGA
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7535	CATCCATCCATCATCCATCTAGC	8799	GCTAGATGGATGATGGATGGATG
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7540	CTGTCCATCCATCCATCATCCAT	8804	ATGGATGATGGATGGATGGACAG
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7543	CATCTGTCCATCCATCCATCATC	8807	GATGATGGATGGATGGACAGATG
7544	CCATCTGTCCATCCATCCATCAT	8808	ATGATGGATGGATGGACAGATGG
7545	TCCATCTGTCCATCCATCCATCA	8809	TGATGGATGGATGGACAGATGGA
7546	ATCCATCTGTCCATCCATCCATC	8810	GATGGATGGATGGACAGATGGAT
7547	CATCCATCTGTCCATCCATCCAT	8811	ATGGATGGATGGACAGATGGATG
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7551	TATCCATCCATCTGTCCATCCAT	8815	ATGGATGGACAGATGGATGGATA
7552	ATATCCATCCATCTGTCCATCCA	8816	TGGATGGACAGATGGATGGATAT
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7555	CATATATCCATCCATCTGTCCAT	8819	ATGGACAGATGGATGGATATATG
7556	TCATATATCCATCCATCTGTCCA	8820	TGGACAGATGGATGGATATATGA
7557	ATCATATATCCATCCATCTGTCC	8821	GGACAGATGGATGGATATATGAT
7558	AATCATATATCCATCCATCTGTC	8822	GACAGATGGATGGATATATGATT

7559	CAATCATATATCCATCCATCTGT	8823	ACAGATGGATGGATATATGATTG
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7561	TTCAATCATATATCCATCCATCT	8825	AGATGGATGGATATATGATTGAA
7562	GTTCAATCATATATCCATCCATC	8826	GATGGATGGATATATGATTGAAC
7563	AGTTCAATCATATATCCATCCAT	8827	ATGGATGGATATATGATTGAACT
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7565	ATAGTTCAATCATATATCCATCC	8829	GGATGGATATATGATTGAACTAT
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7569	TTCAATAGTTCAATCATATATCC	8833	GGATATATGATTGAACTATTGAA
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7571	CTTTCAATAGTTCAATCATATAT	8835	ATATATGATTGAACTATTGAAAG
7572	ACTTTCAATAGTTCAATCATATA	8836	TATATGATTGAACTATTGAAAGT
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7574	ATACTTTCAATAGTTCAATCATA	8838	TATGATTGAACTATTGAAAGTAT
7575	TATACTTTCAATAGTTCAATCAT	8839	ATGATTGAACTATTGAAAGTATA
7576	CTATACTTTCAATAGTTCAATCA	8840	TGATTGAACTATTGAAAGTATAG
7577	TCTATACTTTCAATAGTTCAATC	8841	GATTGAACTATTGAAAGTATAGA
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7579	CATCTATACTTTCAATAGTTCAA	8843	TTGAACTATTGAAAGTATAGATG
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7581	TACATCTATACTTTCAATAGTTC	8845	GAACTATTGAAAGTATAGATGTA
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7756	ACCACACTTCCATCCATCCCATC	9020	GATGGGATGGATGGAAGTGTGGT
7757	AACCACACTTCCATCCATCCCAT	9021	ATGGGATGGATGGAAGTGTGGTT
7758	CAACCACACTTCCATCCATCCCA	9022	TGGGATGGATGGAAGTGTGGTTG
7759	TCAACCACACTTCCATCCATCCC	9023	GGGATGGATGGAAGTGTGGTTGA
7760	CTCAACCACACTTCCATCCATCC	9024	GGATGGATGGAAGTGTGGTTGAG
7761	ACTCAACCACACTTCCATCCATC	9025	GATGGATGGAAGTGTGGTTGAGT
7762	AACTCAACCACACTTCCATCCAT	9026	ATGGATGGAAGTGTGGTTGAGTT
7763	TAACTCAACCACACTTCCATCCA	9027	TGGATGGAAGTGTGGTTGAGTTA
7764	ATAACTCAACCACACTTCCATCC	9028	GGATGGAAGTGTGGTTGAGTTAT
7765	AATAACTCAACCACACTTCCATC	9029	GATGGAAGTGTGGTTGAGTTATT
7766	TAATAACTCAACCACACTTCCAT	9030	ATGGAAGTGTGGTTGAGTTATTA
7767	CTAATAACTCAACCACACTTCCA	9031	TGGAAGTGTGGTTGAGTTATTAG
7768	TCTAATAACTCAACCACACTTCC	9032	GGAAGTGTGGTTGAGTTATTAGA

7769	TTCTAATAACTCAACCACACTTC	9033	GAAGTGTGGTTGAGTTATTAGAA
7770	CTTCTAATAACTCAACCACACTT	9034	AAGTGTGGTTGAGTTATTAGAAG
7771	CCTTCTAATAACTCAACCACACT	9035	AGTGTGGTTGAGTTATTAGAAGG
7772	TCCTTCTAATAACTCAACCACAC	9036	GTGTGGTTGAGTTATTAGAAGGA
7773	TTCCTTCTAATAACTCAACCACA	9037	TGTGGTTGAGTTATTAGAAGGAA
7774	CTTCCTTCTAATAACTCAACCAC	9038	GTGGTTGAGTTATTAGAAGGAAG
7775	TCTTCCTTCTAATAACTCAACCA	9039	TGGTTGAGTTATTAGAAGGAAGA
7776	ATCTTCCTTCTAATAACTCAACC	9040	GGTTGAGTTATTAGAAGGAAGAT
7777	AATCTTCCTTCTAATAACTCAAC	9041	GTTGAGTTATTAGAAGGAAGATT
7778	CAATCTTCCTTCTAATAACTCAA	9042	TTGAGTTATTAGAAGGAAGATTG
7779	TCAATCTTCCTTCTAATAACTCA	9043	TGAGTTATTAGAAGGAAGATTGA
7780	CTCAATCTTCCTTCTAATAACTC	9044	GAGTTATTAGAAGGAAGATTGAG
7781	ACTCAATCTTCCTTCTAATAACT	9045	AGTTATTAGAAGGAAGATTGAGT
7782	TACTCAATCTTCCTTCTAATAAC	9046	GTTATTAGAAGGAAGATTGAGTA
7783	CTACTCAATCTTCCTTCTAATAA	9047	TTATTAGAAGGAAGATTGAGTAG
7784	TCTACTCAATCTTCCTTCTAATA	9048	TATTAGAAGGAAGATTGAGTAGA
7785	ATCTACTCAATCTTCCTTCTAAT	9049	ATTAGAAGGAAGATTGAGTAGAT
7786	TATCTACTCAATCTTCCTTCTAA	9050	TTAGAAGGAAGATTGAGTAGATA
7787	CTATCTACTCAATCTTCCTTCTA	9051	TAGAAGGAAGATTGAGTAGATAG
7788	CCTATCTACTCAATCTTCCTTCT	9052	AGAAGGAAGATTGAGTAGATAGG
7789	ACCTATCTACTCAATCTTCCTTC	9053	GAAGGAAGATTGAGTAGATAGGT
7790	CACCTATCTACTCAATCTTCCTT	9054	AAGGAAGATTGAGTAGATAGGTG
7791	TCACCTATCTACTCAATCTTCCT	9055	AGGAAGATTGAGTAGATAGGTGA
7792	TTCACCTATCTACTCAATCTTCC	9056	GGAAGATTGAGTAGATAGGTGAA
7793	ATTCACCTATCTACTCAATCTTC	9057	GAAGATTGAGTAGATAGGTGAAT
7794	AATTCACCTATCTACTCAATCTT	9058	AAGATTGAGTAGATAGGTGAATT
7795	AAATTCACCTATCTACTCAATCT	9059	AGATTGAGTAGATAGGTGAATTT
7796	CAAATTCACCTATCTACTCAATC	9060	GATTGAGTAGATAGGTGAATTTG
7797	ACAAATTCACCTATCTACTCAAT	9061	ATTGAGTAGATAGGTGAATTTGT
7798	AACAAATTCACCTATCTACTCAA	9062	TTGAGTAGATAGGTGAATTTGTT
7799	CAACAAATTCACCTATCTACTCA	9063	TGAGTAGATAGGTGAATTTGTTG
7800	TCAACAAATTCACCTATCTACTC	9064	GAGTAGATAGGTGAATTTGTTGA
7801	ATCAACAAATTCACCTATCTACT	9065	AGTAGATAGGTGAATTTGTTGAT
7802	TATCAACAAATTCACCTATCTAC	9066	GTAGATAGGTGAATTTGTTGATA
7803	CTATCAACAAATTCACCTATCTA	9067	TAGATAGGTGAATTTGTTGATAG
7804	ACTATCAACAAATTCACCTATCT	9068	AGATAGGTGAATTTGTTGATAGT
7805	GACTATCAACAAATTCACCTATC	9069	GATAGGTGAATTTGTTGATAGTC
7806	TGACTATCAACAAATTCACCTAT	9070	ATAGGTGAATTTGTTGATAGTCA
7807	CTGACTATCAACAAATTCACCTA	9071	TAGGTGAATTTGTTGATAGTCAG
7808	TCTGACTATCAACAAATTCACCT	9072	AGGTGAATTTGTTGATAGTCAGA
7809	ATCTGACTATCAACAAATTCACC	9073	GGTGAATTTGTTGATAGTCAGAT
7810	CATCTGACTATCAACAAATTCAC	9074	GTGAATTTGTTGATAGTCAGATG

7811	CCATCTGACTATCAACAAATTCA	9075	TGAATTTGTTGATAGTCAGATGG
7812	CCCATCTGACTATCAACAAATTC	9076	GAATTTGTTGATAGTCAGATGGG
7813	ACCCATCTGACTATCAACAAATT	9077	AATTTGTTGATAGTCAGATGGGT
7814	TACCCATCTGACTATCAACAAAT	9078	ATTTGTTGATAGTCAGATGGGTA
7815	CTACCCATCTGACTATCAACAAA	9079	TTTGTTGATAGTCAGATGGGTAG
7816	TCTACCCATCTGACTATCAACAA	9080	TTGTTGATAGTCAGATGGGTAGA
7817	ATCTACCCATCTGACTATCAACA	9081	TGTTGATAGTCAGATGGGTAGAT
7818	TATCTACCCATCTGACTATCAAC	9082	GTTGATAGTCAGATGGGTAGATA
7819	CTATCTACCCATCTGACTATCAA	9083	TTGATAGTCAGATGGGTAGATAG
7820	CCTATCTACCCATCTGACTATCA	9084	TGATAGTCAGATGGGTAGATAGG
7821	ACCTATCTACCCATCTGACTATC	9085	GATAGTCAGATGGGTAGATAGGT
7822	TACCTATCTACCCATCTGACTAT	9086	ATAGTCAGATGGGTAGATAGGTA
7823	CTACCTATCTACCCATCTGACTA	9087	TAGTCAGATGGGTAGATAGGTAG
7824	TCTACCTATCTACCCATCTGACT	9088	AGTCAGATGGGTAGATAGGTAGA
7825	ATCTACCTATCTACCCATCTGAC	9089	GTCAGATGGGTAGATAGGTAGAT
7826	CATCTACCTATCTACCCATCTGA	9090	TCAGATGGGTAGATAGGTAGATG
7827	CCATCTACCTATCTACCCATCTG	9091	CAGATGGGTAGATAGGTAGATGG
7828	TCCATCTACCTATCTACCCATCT	9092	AGATGGGTAGATAGGTAGATGGA
7829	ATCCATCTACCTATCTACCCATC	9093	GATGGGTAGATAGGTAGATGGAT
7830	CATCCATCTACCTATCTACCCAT	9094	ATGGGTAGATAGGTAGATGGATG
7831	CCATCCATCTACCTATCTACCCA	9095	TGGGTAGATAGGTAGATGGATGG
7832	TCCATCCATCTACCTATCTACCC	9096	GGGTAGATAGGTAGATGGATGGA
7833	ATCCATCCATCTACCTATCTACC	9097	GGTAGATAGGTAGATGGATGGAT
7834	CATCCATCCATCTACCTATCTAC	9098	GTAGATAGGTAGATGGATGGATG
7835	CCATCCATCCATCTACCTATCTA	9099	TAGATAGGTAGATGGATGGATGG
7836	TCCATCCATCCATCTACCTATCT	9100	AGATAGGTAGATGGATGGATGGA
7837	ATCCATCCATCCATCTACCTATC	9101	GATAGGTAGATGGATGGATGGAT
7838	CATCCATCCATCCATCTACCTAT	9102	ATAGGTAGATGGATGGATGGATG
7839	CCATCCATCCATCCATCTACCTA	9103	TAGGTAGATGGATGGATGGATGG
7840	TCCATCCATCCATCCATCTACCT	9104	AGGTAGATGGATGGATGGATGGA
7841	ATCCATCCATCCATCCATCTACC	9105	GGTAGATGGATGGATGGATGGAT
7842	CATCCATCCATCCATCCATCTAC	9106	GTAGATGGATGGATGGATGGATG
7843	CCATCCATCCATCCATCCATCTA	9107	TAGATGGATGGATGGATGGATGG
7844	TCCATCCATCCATCCATCCATCT	9108	AGATGGATGGATGGATGGATGGA
7845	ATCCATCCATCCATCCATCCATC	9109	GATGGATGGATGGATGGATGGAT
7846	CATCCATCCATCCATCCATCCAT	9110	ATGGATGGATGGATGGATGGATG
7847	ACATCCATCCATCCATCCATCCA	9111	TGGATGGATGGATGGATGGATGT
7848	TACATCCATCCATCCATCCATCC	9112	GGATGGATGGATGGATGGATGTA
7849	ATACATCCATCCATCCATCCATC	9113	GATGGATGGATGGATGGATGTAT
7850	TATACATCCATCCATCCATCCAT	9114	ATGGATGGATGGATGGATGTATA
7851	CTATACATCCATCCATCCATCCA	9115	TGGATGGATGGATGGATGTATAG
7852	CCTATACATCCATCCATCCATCC	9116	GGATGGATGGATGGATGTATAGG

7853	GCCTATACATCCATCCATCCATC	9117	GATGGATGGATGGATGTATAGGC
7854	TGCCTATACATCCATCCATCCAT	9118	ATGGATGGATGGATGTATAGGCA
7855	CTGCCTATACATCCATCCATCCA	9119	TGGATGGATGGATGTATAGGCAG
7856	TCTGCCTATACATCCATCCATCC	9120	GGATGGATGGATGTATAGGCAGA
7857	ATCTGCCTATACATCCATCCATC	9121	GATGGATGGATGTATAGGCAGAT
7858	CATCTGCCTATACATCCATCCAT	9122	ATGGATGGATGTATAGGCAGATG
7859	CCATCTGCCTATACATCCATCCA	9123	TGGATGGATGTATAGGCAGATGG
7860	TCCATCTGCCTATACATCCATCC	9124	GGATGGATGTATAGGCAGATGGA
7861	GTCCATCTGCCTATACATCCATC	9125	GATGGATGTATAGGCAGATGGAC
7862	TGTCCATCTGCCTATACATCCAT	9126	ATGGATGTATAGGCAGATGGACA
7863	TTGTCCATCTGCCTATACATCCA	9127	TGGATGTATAGGCAGATGGACAA
7864	TTTGTCCATCTGCCTATACATCC	9128	GGATGTATAGGCAGATGGACAAA
7865	ATTTGTCCATCTGCCTATACATC	9129	GATGTATAGGCAGATGGACAAAT
7866	CATTTGTCCATCTGCCTATACAT	9130	ATGTATAGGCAGATGGACAAATG
7867	CCATTTGTCCATCTGCCTATACA	9131	TGTATAGGCAGATGGACAAATGG
7868	TCCATTTGTCCATCTGCCTATAC	9132	GTATAGGCAGATGGACAAATGGA
7869	ATCCATTTGTCCATCTGCCTATA	9133	TATAGGCAGATGGACAAATGGAT
7870	CATCCATTTGTCCATCTGCCTAT	9134	ATAGGCAGATGGACAAATGGATG
7871	TCATCCATTTGTCCATCTGCCTA	9135	TAGGCAGATGGACAAATGGATGA
7872	TTCATCCATTTGTCCATCTGCCT	9136	AGGCAGATGGACAAATGGATGAA
7873	ATTCATCCATTTGTCCATCTGCC	9137	GGCAGATGGACAAATGGATGAAT
7874	CATTCATCCATTTGTCCATCTGC	9138	GCAGATGGACAAATGGATGAATG
7875	CCATTCATCCATTTGTCCATCTG	9139	CAGATGGACAAATGGATGAATGG
7876	CCCATTCATCCATTTGTCCATCT	9140	AGATGGACAAATGGATGAATGGG
7877	ACCCATTCATCCATTTGTCCATC	9141	GATGGACAAATGGATGAATGGGT
7878	CACCCATTCATCCATTTGTCCAT	9142	ATGGACAAATGGATGAATGGGTG
7879	CCACCCATTCATCCATTTGTCCA	9143	TGGACAAATGGATGAATGGGTGG
7880	CCCACCCATTCATCCATTTGTCC	9144	GGACAAATGGATGAATGGGTGGG
7881	ACCCACCCATTCATCCATTTGTC	9145	GACAAATGGATGAATGGGTGGGT
7882	CACCCACCCATTCATCCATTTGT	9146	ACAAATGGATGAATGGGTGGGTG
7883	CCACCCACCCATTCATCCATTTG	9147	CAAATGGATGAATGGGTGGGTGG
7884	TCCACCCACCCATTCATCCATTT	9148	AAATGGATGAATGGGTGGGTGGA
7885	ATCCACCCACCCATTCATCCATT	9149	AATGGATGAATGGGTGGGTGGAT
7886	CATCCACCCACCCATTCATCCAT	9150	ATGGATGAATGGGTGGGTGGATG
7887	TCATCCACCCACCCATTCATCCA	9151	TGGATGAATGGGTGGGTGGATGA
7888	TTCATCCACCCACCCATTCATCC	9152	GGATGAATGGGTGGGTGGATGAA
7889	ATTCATCCACCCACCCATTCATC	9153	GATGAATGGGTGGGTGGATGAAT
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7891	CCATTCATCCACCCACCCATTCA	9155	TGAATGGGTGGGTGGATGAATGG
7892	TCCATTCATCCACCCACCCATTC	9156	GAATGGGTGGGTGGATGAATGGA
7893	TTCCATTCATCCACCCACCCATT	9157	AATGGGTGGGTGGATGAATGGAA
7894	CTTCCATTCATCCACCCACCCAT	9158	ATGGGTGGGTGGATGAATGGAAG

7895	CCTTCCATTCATCCACCCACCCA	9159	TGGGTGGGTGGATGAATGGAAGG
7896	TCCTTCCATTCATCCACCCACCC	9160	GGGTGGGTGGATGAATGGAAGGA
7897	ATCCTTCCATTCATCCACCCACC	9161	GGTGGGTGGATGAATGGAAGGAT
7898	CATCCTTCCATTCATCCACCCAC	9162	GTGGGTGGATGAATGGAAGGATG
7899	ACATCCTTCCATTCATCCACCCA	9163	TGGGTGGATGAATGGAAGGATGT
7900	CACATCCTTCCATTCATCCACCC	9164	GGGTGGATGAATGGAAGGATGTG
7901	ACACATCCTTCCATTCATCCACC	9165	GGTGGATGAATGGAAGGATGTGT
7902	CACACATCCTTCCATTCATCCAC	9166	GTGGATGAATGGAAGGATGTGTG
7903	CCACACATCCTTCCATTCATCCA	9167	TGGATGAATGGAAGGATGTGTGG
7904	ACCACACATCCTTCCATTCATCC	9168	GGATGAATGGAAGGATGTGTGGT
7905	AACCACACATCCTTCCATTCATC	9169	GATGAATGGAAGGATGTGTGGTT
7906	CAACCACACATCCTTCCATTCAT	9170	ATGAATGGAAGGATGTGTGGTTG
7907	TCAACCACACATCCTTCCATTCA	9171	TGAATGGAAGGATGTGTGGTTGA
7908	TTCAACCACACATCCTTCCATTC	9172	GAATGGAAGGATGTGTGGTTGAA
7909	GTTCAACCACACATCCTTCCATT	9173	AATGGAAGGATGTGTGGTTGAAC
7910	AGTTCAACCACACATCCTTCCAT	9174	ATGGAAGGATGTGTGGTTGAACT
7911	TAGTTCAACCACACATCCTTCCA	9175	TGGAAGGATGTGTGGTTGAACTA
7912	ATAGTTCAACCACACATCCTTCC	9176	GGAAGGATGTGTGGTTGAACTAT
7913	AATAGTTCAACCACACATCCTTC	9177	GAAGGATGTGTGGTTGAACTATT
7914	CAATAGTTCAACCACACATCCTT	9178	AAGGATGTGTGGTTGAACTATTG
7915	GCAATAGTTCAACCACACATCCT	9179	AGGATGTGTGGTTGAACTATTGC
7916	TGCAATAGTTCAACCACACATCC	9180	GGATGTGTGGTTGAACTATTGCA
7917	TTGCAATAGTTCAACCACACATC	9181	GATGTGTGGTTGAACTATTGCAA
7918	CTTGCAATAGTTCAACCACACAT	9182	ATGTGTGGTTGAACTATTGCAAG
7919	ACTTGCAATAGTTCAACCACACA	9183	TGTGTGGTTGAACTATTGCAAGT
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7921	ATACTTGCAATAGTTCAACCACA	9185	TGTGGTTGAACTATTGCAAGTAT
7922	AATACTTGCAATAGTTCAACCAC	9186	GTGGTTGAACTATTGCAAGTATT
7923	CAATACTTGCAATAGTTCAACCA	9187	TGGTTGAACTATTGCAAGTATTG
7924	TCAATACTTGCAATAGTTCAACC	9188	GGTTGAACTATTGCAAGTATTGA
7925	ATCAATACTTGCAATAGTTCAAC	9189	GTTGAACTATTGCAAGTATTGAT
7926	TATCAATACTTGCAATAGTTCAA	9190	TTGAACTATTGCAAGTATTGATA
7927	TTATCAATACTTGCAATAGTTCA	9191	TGAACTATTGCAAGTATTGATAA
7928	ATTATCAATACTTGCAATAGTTC	9192	GAACTATTGCAAGTATTGATAAT
7929	AATTATCAATACTTGCAATAGTT	9193	AACTATTGCAAGTATTGATAATT
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7932	CCCAATTATCAATACTTGCAATA	9196	TATTGCAAGTATTGATAATTGGG
7933	ACCCAATTATCAATACTTGCAAT	9197	ATTGCAAGTATTGATAATTGGGT
7934	AACCCAATTATCAATACTTGCAA	9198	TTGCAAGTATTGATAATTGGGTT
7935	GAACCCAATTATCAATACTTGCA	9199	TGCAAGTATTGATAATTGGGTTC
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7937	ATGAACCCAATTATCAATACTTG	9201	CAAGTATTGATAATTGGGTTCAT
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7939	TTATGAACCCAATTATCAATACT	9203	AGTATTGATAATTGGGTTCATAA
7940	ATTATGAACCCAATTATCAATAC	9204	GTATTGATAATTGGGTTCATAAT
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7952	AAATATTCAGAAATTATGAACCC	9216	GGGTTCATAATTTCTGAATATTT
7953	TAAATATTCAGAAATTATGAACC	9217	GGTTCATAATTTCTGAATATTTA
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7955	TCTAAATATTCAGAAATTATGAA	9219	TTCATAATTTCTGAATATTTAGA
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7977	ACCAGCCACTCACAACCATCCAT	9241	ATGGATGGTTGTGAGTGGCTGGT
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7979	CCACCAGCCACTCACAACCATCC	9243	GGATGGTTGTGAGTGGCTGGTGG
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7988	TTCGTCTGTCCACCAGCCACTCA	9252	TGAGTGGCTGGTGGACAGACGAA
7989	TTTCGTCTGTCCACCAGCCACTC	9253	GAGTGGCTGGTGGACAGACGAAA
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7996	ATCCATTTTTCGTCTGTCCACCA	9260	TGGTGGACAGACGAAAAATGGAT
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8008	ATTTATCCAACCATCCATTTTTC	9272	GAAAAATGGATGGTTGGATAAAT
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8010	CAATTTATCCAACCATCCATTTT	9274	AAAATGGATGGTTGGATAAATTG
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8012	ATCAATTTATCCAACCATCCATT	9276	AATGGATGGTTGGATAAATTGAT
8013	CATCAATTTATCCAACCATCCAT	9277	ATGGATGGTTGGATAAATTGATG
8014	CCATCAATTTATCCAACCATCCA	9278	TGGATGGTTGGATAAATTGATGG
8015	CCCATCAATTTATCCAACCATCC	9279	GGATGGTTGGATAAATTGATGGG
8016	ACCCATCAATTTATCCAACCATC	9280	GATGGTTGGATAAATTGATGGGT
8017	CACCCATCAATTTATCCAACCAT	9281	ATGGTTGGATAAATTGATGGGTG
8018	CCACCCATCAATTTATCCAACCA	9282	TGGTTGGATAAATTGATGGGTGG
8019	TCCACCCATCAATTTATCCAACC	9283	GGTTGGATAAATTGATGGGTGGA
8020	ATCCACCCATCAATTTATCCAAC	9284	GTTGGATAAATTGATGGGTGGAT

8021	CATCCACCCATCAATTTATCCAA	9285	TTGGATAAATTGATGGGTGGATG
8022	CCATCCACCCATCAATTTATCCA	9286	TGGATAAATTGATGGGTGGATGG
8023	TCCATCCACCCATCAATTTATCC	9287	GGATAAATTGATGGGTGGATGGA
8024	ATCCATCCACCCATCAATTTATC	9288	GATAAATTGATGGGTGGATGGAT
8025	CATCCATCCACCCATCAATTTAT	9289	ATAAATTGATGGGTGGATGGATG
8026	CCATCCATCCACCCATCAATTTA	9290	TAAATTGATGGGTGGATGGATGG
8027	ACCATCCATCCACCCATCAATTT	9291	AAATTGATGGGTGGATGGATGGT
8028	AACCATCCATCCACCCATCAATT	9292	AATTGATGGGTGGATGGATGGTT
8029	CAACCATCCATCCACCCATCAAT	9293	ATTGATGGGTGGATGGATGGTTG
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8032	AACCAACCATCCATCCACCCATC	9296	GATGGGTGGATGGATGGTTGGTT
8033	CAACCAACCATCCATCCACCCAT	9297	ATGGGTGGATGGATGGTTGGTTG
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8035	TACAACCAACCATCCATCCACCC	9299	GGGTGGATGGATGGTTGGTTGTA
8036	ATACAACCAACCATCCATCCACC	9300	GGTGGATGGATGGTTGGTTGTAT
8037	CATACAACCAACCATCCATCCAC	9301	GTGGATGGATGGTTGGTTGTATG
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8040	TTTCATACAACCAACCATCCATC	9304	GATGGATGGTTGGTTGTATGAAA
8041	CTTTCATACAACCAACCATCCAT	9305	ATGGATGGTTGGTTGTATGAAAG
8042	TCTTTCATACAACCAACCATCCA	9306	TGGATGGTTGGTTGTATGAAAGA
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8046	TCATTCTTTCATACAACCAACCA	9310	TGGTTGGTTGTATGAAAGAATGA
8047	TTCATTCTTTCATACAACCAACC	9311	GGTTGGTTGTATGAAAGAATGAA
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8049	CATTCATTCTTTCATACAACCAA	9313	TTGGTTGTATGAAAGAATGAATG
8050	TCATTCATTCTTTCATACAACCA	9314	TGGTTGTATGAAAGAATGAATGA
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8052	AATCATTCATTCTTTCATACAAC	9316	GTTGTATGAAAGAATGAATGATT
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8054	CCAATCATTCATTCTTTCATACA	9318	TGTATGAAAGAATGAATGATTGG
8055	CCCAATCATTCATTCTTTCATAC	9319	GTATGAAAGAATGAATGATTGGG
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8059	CCTACCCAATCATTCATTCTTTC	9323	GAAAGAATGAATGATTGGGTAGG
8060	ACCTACCCAATCATTCATTCTTT	9324	AAAGAATGAATGATTGGGTAGGT
8061	CACCTACCCAATCATTCATTCTT	9325	AAGAATGAATGATTGGGTAGGTG
8062	CCACCTACCCAATCATTCATTCT	9326	AGAATGAATGATTGGGTAGGTGG

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8065	AATCCACCTACCCAATCATTCAT	9329	ATGAATGATTGGGTAGGTGGATT
8066	TAATCCACCTACCCAATCATTCA	9330	TGAATGATTGGGTAGGTGGATTA
8067	TTAATCCACCTACCCAATCATTC	9331	GAATGATTGGGTAGGTGGATTAA
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8071	CAACTTAATCCACCTACCCAATC	9335	GATTGGGTAGGTGGATTAAGTTG
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8090	CATCCCATACATTGATCCGCAAC	9354	GTTGCGGATCAATGTATGGGATG
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8108	TCCATCCATCCATTCATCCATCC	9372	GGATGGATGAATGGATGGATGGA
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8135	CCTTTCAGTAATTCAACCACACA	9399	TGTGTGGTTGAATTACTGAAAGG
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8142	CTTCCAACCTTTCAGTAATTCAA	9406	TTGAATTACTGAAAGGTTGGAAG
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8144	CTCTTCCAACCTTTCAGTAATTC	9408	GAATTACTGAAAGGTTGGAAGAG
8145	ACTCTTCCAACCTTTCAGTAATT	9409	AATTACTGAAAGGTTGGAAGAGT
8146	CACTCTTCCAACCTTTCAGTAAT	9410	ATTACTGAAAGGTTGGAAGAGTG

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8163	CCCAAATTTCACCCATCCACTCT	9427	AGAGTGGATGGGTGAAATTTGGG
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8165	ACCCCAAATTTCACCCATCCACT	9429	AGTGGATGGGTGAAATTTGGGGT
8166	TACCCCAAATTTCACCCATCCAC	9430	GTGGATGGGTGAAATTTGGGGTA
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8168	ACTACCCCAAATTTCACCCATCC	9432	GGATGGGTGAAATTTGGGGTAGT
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8170	TAACTACCCCAAATTTCACCCAT	9434	ATGGGTGAAATTTGGGGTAGTTA
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8172	TCTAACTACCCCAAATTTCACCC	9436	GGGTGAAATTTGGGGTAGTTAGA
8173	ATCTAACTACCCCAAATTTCACC	9437	GGTGAAATTTGGGGTAGTTAGAT
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8198	CTTTTATCCATCCACACACCCAC	9462	GTGGGTGTGTGGATGGATAAAAG
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8201	ACTCTTTTATCCATCCACACACC	9465	GGTGTGTGGATGGATAAAAGAGT
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8229	GCCTGTTTATTCATTAATTCATT	9493	AATGAATTAATGAATAAACAGGC
8230	TGCCTGTTTATTCATTAATTCAT	9494	ATGAATTAATGAATAAACAGGCA

8231	CTGCCTGTTTATTCATTAATTCA	9495	TGAATTAATGAATAAACAGGCAG
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3757	CAAGGGGTCGCCGGGGGTCAGAG	9551	CTCTGACCCCCGGCGACCCCTTG
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3764	GAGAGTGCAAGGGGTCGCCGGGG	9558	CCCCGGCGACCCCTTGCACTCTC
3765	GGAGAGTGCAAGGGGTCGCCGGG	9559	CCCGGCGACCCCTTGCACTCTCC
3766	TGGAGAGTGCAAGGGGTCGCCGG	9560	CCGGCGACCCCTTGCACTCTCCA
3767	ATGGAGAGTGCAAGGGGTCGCCG	9561	CGGCGACCCCTTGCACTCTCCAT
3768	CATGGAGAGTGCAAGGGGTCGCC	9562	GGCGACCCCTTGCACTCTCCATG
3769	TCATGGAGAGTGCAAGGGGTCGC	9563	GCGACCCCTTGCACTCTCCATGA
3770	GTCATGGAGAGTGCAAGGGGTCG	9564	CGACCCCTTGCACTCTCCATGAC
3771	TGTCATGGAGAGTGCAAGGGGTC	9565	GACCCCTTGCACTCTCCATGACA
3772	GTGTCATGGAGAGTGCAAGGGGT	9566	ACCCCTTGCACTCTCCATGACAC
3773	AGTGTCATGGAGAGTGCAAGGGG	9567	CCCCTTGCACTCTCCATGACACT
3774	AAGTGTCATGGAGAGTGCAAGGG	9568	CCCTTGCACTCTCCATGACACTT
3775	AAAGTGTCATGGAGAGTGCAAGG	9569	CCTTGCACTCTCCATGACACTTT
3776	GAAAGTGTCATGGAGAGTGCAAG	9570	CTTGCACTCTCCATGACACTTTC
3777	AGAAAGTGTCATGGAGAGTGCAA	9571	TTGCACTCTCCATGACACTTTCT
3778	GAGAAAGTGTCATGGAGAGTGCA	9572	TGCACTCTCCATGACACTTTCTC
3779	AGAGAAAGTGTCATGGAGAGTGC	9573	GCACTCTCCATGACACTTTCTCT
3780	GAGAGAAAGTGTCATGGAGAGTG	9574	CACTCTCCATGACACTTTCTCTC
3781	GGAGAGAAAGTGTCATGGAGAGT	9575	ACTCTCCATGACACTTTCTCTCC
3782	GGGAGAGAAAGTGTCATGGAGAG	9576	CTCTCCATGACACTTTCTCTCCC
3783	TGGGAGAGAAAGTGTCATGGAGA	9577	TCTCCATGACACTTTCTCTCCCA
3784	ATGGGAGAGAAAGTGTCATGGAG	9578	CTCCATGACACTTTCTCTCCCAT

3785	CATGGGAGAGAAAGTGTCATGGA	9579	TCCATGACACTTTCTCTCCCATG
3786	CCATGGGAGAGAAAGTGTCATGG	9580	CCATGACACTTTCTCTCCCATGG
3787	ACCATGGGAGAGAAAGTGTCATG	9581	CATGACACTTTCTCTCCCATGGT
3788	CACCATGGGAGAGAAAGTGTCAT	9582	ATGACACTTTCTCTCCCATGGTG
3789	CCACCATGGGAGAGAAAGTGTCA	9583	TGACACTTTCTCTCCCATGGTGG
3790	GCCACCATGGGAGAGAAAGTGTC	9584	GACACTTTCTCTCCCATGGTGGC
3791	TGCCACCATGGGAGAGAAAGTGT	9585	ACACTTTCTCTCCCATGGTGGCA
3792	CTGCCACCATGGGAGAGAAAGTG	9586	CACTTTCTCTCCCATGGTGGCAG

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

SMN2 Oligonucleotides Complementary to SMN2 Transcript

[00360] In some embodiments, a SMN2 AON includes a sequence that is at least 85% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a SMN2 transcript (e.g., any one of SEQ ID NOs: 9698-9709). In some embodiments, a SMN2 AON includes a sequence that is between 90-95% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a SMN2 transcript (e. g., any one of SEQ ID NOs: 9698-9709). In particular embodiments, a SMN2 AON includes a sequence that is between 85% and 90% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a SMN2 transcript (e.g., any one of SEQ ID NOs: 9698-9709). In particular embodiments, a SMN2 AON includes a sequence that is between 84% to 88% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a SMN2 transcript (e.g., any one of SEQ ID NOs: 9698-9709). In particular embodiments, a SMN2 AON includes a sequence that is between 89% to 92% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%)

identity to a region of a SMN2 transcript (e.g., any one of SEQ ID NOs: 9698-9709). In particular embodiments, a SMN2 AON includes a sequence that is between 94% to 96% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a SMN2 transcript e.g., SEQ ID NOs: 9698-9709).

[00361] In various embodiments, a SMN2 AON comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 9710-10141 and SEQ ID NOs: 10574-10651. In various embodiments, a SMN2 AON comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 9710-10141 and SEQ ID NOs: 10574-10651.

[00362] In some embodiments, the SMN2 AON comprises a spacer and has a segment having at most 7 linked nucleosides. In some embodiments, the SMN2 AON comprises a spacer and has a segment having at most 6, 5, 4, 3, or 2 linked nucleosides.

[00363] SMN2 AON binding specificity can be assessed via measurement of parameters such as dissociation constant, melting temperature or other criteria such as changes in protein or RNA expression levels or other assays that measure SMN2 activity or expression.

[00364] In some embodiments, a SMN2 AON can include a non-duplexed oligonucleotide. In some embodiments, a SMN2 AON can include a duplex of two oligonucleotides where the first oligonucleotide includes a nucleobase sequence that is completely or almost completely complementary to a SMN2 pre-mRNA sequence and the second oligonucleotide includes a nucleobase sequence that is complementary to the nucleobase sequence of the first oligonucleotide.

[00365] In some embodiments, a SMN2 AON can target SMN2 mRNAs of one or more isoforms. In some embodiments, the SMN2 AON includes a nucleobase sequence that is complementary to a nucleobase sequence of a SMN2 gene or a SMN2 mRNA.

SMN2 Transcript

[00366] In various embodiments, a SMN2 transcript comprises the sequence provided as SEQ ID NO: 9698.

GCACCCGCGGGTTTGCTATGGCGATGAGCAGCGGCGGCAGTGGTGGCGGCGTCCCG
GAGCAGGAGGATTCCGTGCTGTTCCGGCGCGGCACAGGCCAGAGCGATGATTCTGA
CATTTGGGATGATACAGCACTGATAAAAGCATATGATAAAGCTGTGGCTTCATTTAA
GCATGCTCTAAAGAATGGTGACATTTGTGAAACTTCGGGTAAACCAAAAACCACACC
TAAAAGAAAACCTGCTAAGAAGAATAAAAGCCAAAAGAAGAATACTGCAGCTTCCT

TACAACAGTGGAAAGTTGGGGACAAATGTTCTGCCATTTGGTCAGAAGACGGTTGCA
TTTACCCAGCTACCATTGCTTCAATTGATTTTAAGAGAGAAACCTGTGTTGTGGTTTA
CACTGGATATGGAAATAGAGAGGAGCAAAATCTGTCCGATCTACTTTCCCCAATCTG
TGAAGTAGCTAATAATATAGAACAAAATGCTCAAGAGAATGAAAATGAAAGCCAAG
TTTCAACAGATGAAAGTGAGAACTCCAGGTCTCCTGGAAATAAATCAGATAACATCA
AGCCCAAATCTGCTCCATGGAACTCTTTTCTCCCTCCACCACCCCCCATGCCAGGGCC
AAGACTGGGACCAGGAAAGCCAGGTCTAAAATTCAATGGCCCACCACCGCCACCGC
CACCACCACCACCCCACTTACTATCATGCTGGCTGCCTCCATTTCCTTCTGGACCACC
AATAATTCCCCCACCACCTCCCATATGTCCAGATTCTCTTGATGATGCTGATGCTTTG
GGAAGTATGTTAATTTCATGGTACATGAGTGGCTATCATACTGGCTATTATATGGGTT
TTAGACAAAATCAAAAAGAAGGAAGGTGCTCACATTCCTTAAATTAAGGAGAAATG
CTGGCATAGAGCAGCACTAAATGACACCACTAAAGAAACGATCAGACAGATCTGGA
ATGTGAAGCGTTATAGAAGATAACTGGCCTCATTTCTTCAAAATATCAAGTGTTGGG
AAAGAAAAAAGGAAGTGGAATGGGTAACTCTTCTTGATTAAAAGTTATGTAATAAC
CAAATGCAATGTGAAATATTTTACTGGACTCTATTTTGAAAAACCATCTGTAAAAGA
CTGAGGTGGGGGTGGGAGGCCAGCACGGTGGTGAGGCAGTTGAGAAAATTTGAATG
TGGATTAGATTTTGAATGATATTGGATAATTATTGGTAATTTTATGAGCTGTGAAAG
GGTGTTGTAGTTTATAAAAGACTGTCTTAATTTGCATACTTAAGCATTTAGGAATGA
AGTGTTAGAGTGTCTTAAAATGTTTCAAATGGTTTAACAAAATGTATGTGAGGCGTA
TGTGGCAAAATGTTACAGAATCTAACTGGTGGACATGGCTGTTCATTGTACTGTTTTT
TTCTATCTTCTATATGTTTAAAAGTATATAATAAAAATATTTAATTTTTTTTTAAATTA

(SEQ ID NO: 9698 (SOURCE NCBI REFERENCE NO: NM_017411.4)

[00367] In various embodiments, a SMN2 mRNA transcript comprises the sequence provided as SEQ ID NO: 9699.

GCACCCGCGGGTTTGCTATGGCGATGAGCAGCGGCGGCAGTGGTGGCGGCGTCCCG
GAGCAGGAGGATTCCGTGCTGTTCCGGCGCGGCACAGGCCAGAGCGATGATTCTGA
CATTTGGGATGATACAGCACTGATAAAAGCATATGATAAAGCTGTGGCTTCATTTAA
GCATGCTCTAAAGAATGGTGACATTTGTGAAACTTCGGGTAAACCAAAAACCACACC
TAAAAGAAAACCTGCTAAGAAGAATAAAAGCCAAAAGAAGAATACTGCAGCTTCCT
TACAACAGTGGAAAGTTGGGGACAAATGTTCTGCCATTTGGTCAGAAGACGGTTGCA
TTTACCCAGCTACCATTGCTTCAATTGATTTTAAGAGAGAAACCTGTGTTGTGGTTTA
CACTGGATATGGAAATAGAGAGGAGCAAAATCTGTCCGATCTACTTTCCCCAATCTG
TGAAGTAGCTAATAATATAGAACAAAATGCTCAAGAGAATGAAAATGAAAGCCAAG
TTTCAACAGATGAAAGTGAGAACTCCAGGTCTCCTGGAAATAAATCAGATAACATCA
AGCCCAAATCTGCTCCATGGAACTCTTTTCTCCCTCCACCACCCCCCATGCCAGGGCC
AAGACTGGGACCAGGAAAGCCAGGTCTAAAATTCAATGGCCCACCACCGCCACCGC
CACCACCACCACCCCACTTACTATCATGCTGGCTGCCTCCATTTCCTTCTGGACCACC
AATAATTCCCCCACCACCTCCCATATGTCCAGATTCTCTTGATGATGCTGATGCTTTG
GGAAGTATGTTAATTTCATGGTACATGAGTGGCTATCATACTGGCTATTATATGGAA
ATGCTGGCATAGAGCAGCACTAAATGACACCACTAAAGAAACGATCAGACAGATCT
GGAATGTGAAGCGTTATAGAAGATAACTGGCCTCATTTCTTCAAAATATCAAGTGTT
GGGAAAGAAAAAAGGAAGTGGAATGGGTAACTCTTCTTGATTAAAAGTTATGTAAT
AACCAAATGCAATGTGAAATATTTTACTGGACTCTATTTTGAAAAACCATCTGTAAA
AGACTGAGGTGGGGGTGGGAGGCCAGCACGGTGGTGAGGCAGTTGAGAAAATTTGA
ATGTGGATTAGATTTTGAATGATATTGGATAATTATTGGTAATTTTATGAGCTGTGAG
AAGGGTGTTGTAGTTTATAAAAGACTGTCTTAATTTGCATACTTAAGCATTTAGGAA
TGAAGTGTTAGAGTGTCTTAAAATGTTTCAAATGGTTTAACAAAATGTATGTGAGGC
GTATGTGGCAAAATGTTACAGAATCTAACTGGTGGACATGGCTGTTCATTGTACTGT

TTTTTTCTATCTTCTATATGTTTAAAAGTATATAATAAAAATATTTAATTTTTTTTTAA
ATTA
(SEQ ID NO: 9699) (Source: NCBI Reference Sequence: NM_022875.3).

[00368] In various embodiments, a SMN2 mRNA transcript comprises the sequence provided as SEQ ID NO: 9700.

CCACAAATGTGGGAGGGCGATAACCACTCGTAGAAAGCGTGAGAAGTTACTACAAG
CGGTCCTCCCGGCCACCGTACTGTTCCGCTCCCAGAAGCCCCGGGCGGCGGAAGTCG
TCACTCTTAAGAAGGGACGGGGCCCCACGCTGCGCACCCGCGGGTTTGCTATGGCGA
TGAGCAGCGGCGGCAGTGGTGGCGGCGTCCCGGAGCAGGAGGATTCCGTGCTGTTC
CGGCGCGGCACAGGCCAGAGCGATGATTCTGACATTTGGGATGATACAGCACTGAT
AAAAGCATATGATAAAGCTGTGGCTTCATTTAAGCATGCTCTAAAGAATGGTGACAT
TTGTGAAACTTCGGGTAAACCAAAAACCACACCTAAAAGAAAACCTGCTAAGAAGA
ATAAAAGCCAAAAGAAGAATACTGCAGCTTCCTTACAACAGTGGAAAGTTGGGGAC
AAATGTTCTGCCATTTGGTCAGAAGACGGTTGCATTTACCCAGCTACCATTGCTTCAA
TTGATTTTAAGAGAGAAACCTGTGTTGTGGTTTACACTGGATATGGAAATAGAGAGG
AGCAAAATCTGTCCGATCTACTTTCCCCAATCTGTGAAGTAGCTAATAATATAGAAC
AAAATGCTCAAGAGAATGAAAATGAAAGCCAAGTTTCAACAGATGAAAGTGAGAAC
TCCAGGTCTCCTGGAAATAAATCAGATAACATCAAGCCCAAATCTGCTCCATGGAAC
TCTTTTCTCCCTCCACCACCCCCCATGCCAGGGCCAAGACTGGGACCAGGAAAGATA
ATTCCCCCACCACCTCCCATATGTCCAGATTCTCTTGATGATGCTGATGCTTTGGGAA
GTATGTTAATTTCATGGTACATGAGTGGCTATCATACTGGCTATTATATGGGTTTTAG
ACAAAATCAAAAAGAAGGAAGGTGCTCACATTCCTTAAATTAAGGAGAAATGCTGG
CATAGAGCAGCACTAAATGACACCACTAAAGAAACGATCAGACAGATCTGGAATGT
GAAGCGTTATAGAAGATAACTGGCCTCATTTCTTCAAAATATCAAGTGTTGGGAAAG
AAAAAAGGAAGTGGAATGGGTAACTCTTCTTGATTAAAAGTTATGTAATAACCAAAT
GCAATGTGAAATATTTTACTGGACTCTATTTTGAAAAACCATCTGTAAAAGACTGAG
GTGGGGGTGGGAGGCCAGCACGGTGGTGAGGCAGTTGAGAAAATTTGAATGTGGAT
TAGATTTTGAATGATATTGGATAATTATTGGTAATTTTATGAGCTGTGAGAAGGGTG
TTGTAGTTTATAAAAGACTGTCTTAATTTGCATACTTAAGCATTTAGGAATGAAGTGT
TAGAGTGTCTTAAAATGTTTCAAATGGTTTAACAAAATGTATGTGAGGCGTATGTGG
CAAAATGTTACAGAATCTAACTGGTGGACATGGCTGTTCATTGTACTGTTTTTTTCTA
TCTTCTATATGTTTAAAAGTATATAATAAAAATATTTAATTTTTTTTTAAATTAAAAA
AA
(SEQ ID NO: 9700) (Source: NCBI Reference Sequence: NM_022876.2).

[00369] In various embodiments, a SMN2 mRNA transcript comprises the sequence provided as SEQ ID NO: 9701.

CCACAAATGTGGGAGGGCGATAACCACTCGTAGAAAGCGTGAGAAGTTACTACAAG
CGGTCCTCCCGGCCACCGTACTGTTCCGCTCCCAGAAGCCCCGGGCGGCGGAAGTCG
TCACTCTTAAGAAGGGACGGGGCCCCACGCTGCGCACCCGCGGGTTTGCTATGGCGA
TGAGCAGCGGCGGCAGTGGTGGCGGCGTCCCGGAGCAGGAGGATTCCGTGCTGTTC
CGGCGCGGCACAGGCCAGAGCGATGATTCTGACATTTGGGATGATACAGCACTGAT
AAAAGCATATGATAAAGCTGTGGCTTCATTTAAGCATGCTCTAAAGAATGGTGACAT
TTGTGAAACTTCGGGTAAACCAAAAACCACACCTAAAAGAAAACCTGCTAAGAAGA
ATAAAAGCCAAAAGAAGAATACTGCAGCTTCCTTACAACAGTGGAAAGTTGGGGAC
AAATGTTCTGCCATTTGGTCAGAAGACGGTTGCATTTACCCAGCTACCATTGCTTCAA
TTGATTTTAAGAGAGAAACCTGTGTTGTGGTTTACACTGGATATGGAAATAGAGAGG

AGCAAAATCTGTCCGATCTACTTTCCCCAATCTGTGAAGTAGCTAATAATATAGAAC
AAAATGCTCAAGAGAATGAAAATGAAAGCCAAGTTTCAACAGATGAAAGTGAGAAC
TCCAGGTCTCCTGGAAATAAATCAGATAACATCAAGCCCAAATCTGCTCCATGGAAC
TCTTTTCTCCCTCCACCACCCCCCATGCCAGGGCCAAGACTGGGACCAGGAAAGATA
ATTCCCCCACCACCTCCCATATGTCCAGATTCTCTTGATGATGCTGATGCTTTGGGAA
GTATGTTAATTTCATGGTACATGAGTGGCTATCATACTGGCTATTATATGGAAATGCT
GGCATAGAGCAGCACTAAATGACACCACTAAAGAAACGATCAGACAGATCTGGAAT
GTGAAGCGTTATAGAAGATAACTGGCCTCATTTCTTCAAAATATCAAGTGTTGGGAA
AGAAAAAAGGAAGTGGAATGGGTAACTCTTCTTGATTAAAAGTTATGTAATAACCA
AATGCAATGTGAAATATTTTACTGGACTCTATTTTGAAAAACCATCTGTAAAAGACT
GAGGTGGGGGTGGGAGGCCAGCACGGTGGTGAGGCAGTTGAGAAAATTTGAATGTG
GATTAGATTTTGAATGATATTGGATAATTATTGGTAATTTTATGAGCTGTGAGAAGG
GTGTTGTAGTTTATAAAAGACTGTCTTAATTTGCATACTTAAGCATTTAGGAATGAA
GTGTTAGAGTGTCTTAAAATGTTTCAAATGGTTTAACAAAATGTATGTGAGGCGTAT
GTGGCAAAATGTTACAGAATCTAACTGGTGGACATGGCTGTTCATTGTACTGTTTTTT
TCTATCTTCTATATGTTTAAAAGTATATAATAAAAATATTTAATTTTTTTTTAAATTAA
AAAAA
(SEQ ID NO: 9701) (Source: NCBI Reference Sequence: NM_022877.2).

[00370] In various embodiments, a SMN2 mRNA transcript comprises the sequence provided as SEQ ID NO: 9702.

GGCGGAAGTCGTCACTCTTAAGAAGGGACGGGGCCCCACGCTGCGCACCCGCGGGT
TTGCTATGGCGATGAGCAGCGGCGGCAGTGGTGGCGGCGTCCCGGAGCAGGAGGAT
TCCGTGCTGTTCCGGCGCGGCACAGGCCAGAGCGATGATTCTGACATTTGGGATGAT
ACAGCACTGATAAAAGCATATGATAAAGCTGTGGCTTCATTTAAGCATGCTCTAAAG
AATGGTGACATTTGTGAAACTTCGGGTAAACCAAAAACCACACCTAAAAGAAAACC
TGCTAAGAAGAATAAAAGCCAAAAGAAGAATACTGCAGCTTCCTTACAACAGAATG
AAAATGAAAGCCAAGTTTCAACAGATGAAAGTGAGAACTCCAGGTCTCCTGGAAAT
AAATCAGATAACATCAAGCCCAAATCTGCTCCATGGAACTCTTTTCTCCCTCCACCA
CCCCCCATGCCAGGGCCAAGACTGGGACCAGGAAAGATAATTCCCCCACCACCTCC
CATATGTCCAGATTCTCTTGATGATGCTGATGCTTTGGGAAGTATGTTAATTTCATGG
TACATGAGTGGCTATCATACTGGCTATTATATGGGTTTTAGACAAAATCAAAAAGAA
GGAAGGTGCTCACATTCCTTAAATTAAGGAGAAATGCTGGCATAGAGCAGCACTAA
ATGACACCACTAAAGAAACGATCAGACAGATCTGGAATGTGAAGCGTTATAGAAGA
TAACTGGCCTCATTTCTTCAAAATATCAAGTGTTGGGAAAGAAAAAAGGAAGTGGA
ATGGGTAACTCTTCTTGATTAAAAGTTATGTAATAACCAAATGCAATGTGAAATATT
TTACTGGACTCTATTTTGAAAAACCATCTGTAAAAGACTGAGGTGGGGGTGGGAGGC
CAGCACGGTGGTGAGGCAGTTGAGAAAATTTGAATGTGGATTAGATTTTGAATGATA
TTGGATAATTATTGGTAATTTTATGAGCTGTGAGAAGGGTGTTGTAGTTTATAAAAG
ACTGTCTTAATTTGCATACTTAAGCATTTAGGAATGAAGTGTTAGAGTGTCTTAAAAT
GTTTCAAATGGTTTAACAAAATGTATGTGAGGCGTATGTGGCAAAATGTTACAGAAT
CTAACTGGTGGACATGGCTGTTCATTGTACTGTTTTTTTCTATCTTCTATATGTTTAAA
AGTATATAATAAAAATATTTAATTTTTTTTTAAATTA
(SEQ ID NO: 9702) (Source: NCBI Reference Sequence: XM_011543602.3).

[00371] In various embodiments, SMN2 mRNA transcript comprises the sequence provided as SEQ ID NO: 9703.

GGCGGAAGTCGTCACTCTTAAGAAGGGACGGGGCCCCACGCTGCGCACCCGCGGGT
TTGCTATGGCGATGAGCAGCGGCGGCAGTGGTGGCGGCGTCCCGGAGCAGGAGGAT
TCCGTGCTGTTCCGGCGCGGCACAGGCCAGAGCGATGATTCTGACATTTGGGATGAT
ACAGCACTGATAAAAGCATATGATAAAGCTGTGGCTTCATTTAAGCATGCTCTAAAG
AATGGTGACATTTGTGAAACTTCGGGTAAACCAAAAACCACACCTAAAAGAAAACC
TGCTAAGAAGAATAAAAGCCAAAAGAAGAATACTGCAGCTTCCTTACAACAGAATG
AAAATGAAAGCCAAGTTTCAACAGATGAAAGTGAGAACTCCAGGTCTCCTGGAAAT
AAATCAGATAACATCAAGCCCAAATCTGCTCCATGGAACTCTTTTCTCCCTCCACCA
CCCCCCATGCCAGGGCCAAGACTGGGACCAGGAAAGATAATTCCCCCACCACCTCC
CATATGTCCAGATTCTCTTGATGATGCTGATGCTTTGGGAAGTATGTTAATTTCATGG
TACATGAGTGGCTATCATACTGGCTATTATATGGAAATGCTGGCATAGAGCAGCACT
AAATGACACCACTAAAGAAACGATCAGACAGATCTGGAATGTGAAGCGTTATAGAA
GATAACTGGCCTCATTTCTTCAAAATATCAAGTGTTGGGAAAGAAAAAAGGAAGTG
GAATGGGTAACTCTTCTTGATTAAAAGTTATGTAATAACCAAATGCAATGTGAAATA
TTTTACTGGACTCTATTTTGAAAAACCATCTGTAAAAGACTGAGGTGGGGGTGGGAG
GCCAGCACGGTGGTGAGGCAGTTGAGAAAATTTGAATGTGGATTAGATTTTGAATGA
TATTGGATAATTATTGGTAATTTTATGAGCTGTGAGAAGGGTGTTGTAGTTTATAAA
AGACTGTCTTAATTTGCATACTTAAGCATTTAGGAATGAAGTGTTAGAGTGTCTTAA
AATGTTTCAAATGGTTTAACAAAATGTATGTGAGGCGTATGTGGCAAAATGTTACAG
AATCTAACTGGTGGACATGGCTGTTCATTGTACTGTTTTTTTCTATCTTCTATATGTTT
AAAAGTATATAATAAAAATATTTAATTTTTTTTTAAATTA
(SEQ ID NO: 9703) (Source: NCBI Reference Sequence: XM_011543603.3).

[00372] In various embodiments, a SMN2 mRNA transcript comprises the sequence provided as SEQ ID NO: 9704.

ACTCTTAAGAAGGGACGGGGCCCCACGCTGCGCACCCGCGGGTTTGCTATGGCGATG
AGCAGCGGCGGCAGTGGTGGCGGCGTCCCGGAGCAGGAGGATTCCGTGCTGTTCCG
GCGCGGCACAGGCCAGAGCGATGATTCTGACATTTGGGATGATACAGCACTGATAA
AAGCATATGATAAAGCTGTGGCTTCATTTAAGCATGCTCTAAAGAATGGTGACATTT
GTGAAACTTCGGGTAAACCAAAAACCACACCTAAAAGAAAACCTGCTAAGAAGAAT
AAAAGCCAAAAGAAGAATACTGCAGCTTCCTTACAACAGAATGAAAATGAAAGCCA
AGTTTCAACAGATGAAAGTGAGAACTCCAGGTCTCCTGGAAATAAATCAGATAACA
TCAAGCCCAAATCTGCTCCATGGAACTCTTTTCTCCCTCCACCACCCCCCATGCCAGG
GCCAAGACTGGGACCAGGAAAGCCAGGTCTAAAATTCAATGGCCCACCACCGCCAC
CGCCACCACCACCACCCCACTTACTATCATGCTGGCTGCCTCCATTTCCTTCTGGACC
ACCAATAATTCCCCCACCACCTCCCATATGTCCAGATTCTCTTGATGATGCTGATGCT
TTGGGAAGTATGTTAATTTCATGGTACATGAGTGGCTATCATACTGGCTATTATATGG
GTTTTAGACAAAATCAAAAAGAAGGAAGGTGCTCACATTCCTTAAATTAAGGAGAA
ATGCTGGCATAGAGCAGCACTAAATGACACCACTAAAGAAACGATCAGACAGATCT
GGAATGTGAAGCGTTATAGAAGATAACTGGCCTCATTTCTTCAAAATATCAAGTGTT
GGGAAAGAAAAAAGGAAGTGGAATGGGTAACTCTTCTTGATTAAAAGTTATGTAAT
AACCAAATGCAATGTGAAATATTTTACTGGACTCTATTTTGAAAAACCATCTGTAAA
AGACTGAGGTGGGGGTGGGAGGCCAGCACGGTGGTGAGGCAGTTGAGAAAATTTGA
ATGTGGATTAGATTTTGAATGATATTGGATAATTATTGGTAATTTTATGAGCTGTGAG
AAGGGTGTTGTAGTTTATAAAAGACTGTCTTAATTTGCATACTTAAGCATTTAGGAA
TGAAGTGTTAGAGTGTCTTAAAATGTTTCAAATGGTTTAACAAAATGTATGTGAGGC
GTATGTGGCAAAATGTTACAGAATCTAACTGGTGGACATGGCTGTTCATTGTACTGT

TTTTTTCTATCTTCTATATGTTTAAAAGTATATAATAAAAATATTTAATTTTTTTTTAA
ATTA
(SEQ ID NO: 9704) (Source: NCBI Reference Sequence: XM_011543600.2

[00373] In various embodiments, a SMN2 mRNA transcript comprises the sequence provided as SEQ ID NO: 9705.

ACTCTTAAGAAGGGACGGGGCCCCACGCTGCGCACCCGCGGGTTTGCTATGGCGATG
AGCAGCGGCGGCAGTGGTGGCGGCGTCCCGGAGCAGGAGGATTCCGTGCTGTTCCG
GCGCGGCACAGGCCAGAGCGATGATTCTGACATTTGGGATGATACAGCACTGATAA
AAGCATATGATAAAGCTGTGGCTTCATTTAAGCATGCTCTAAAGAATGGTGACATTT
GTGAAACTTCGGGTAAACCAAAAACCACACCTAAAAGAAAACCTGCTAAGAAGAAT
AAAAGCCAAAAGAAGAATACTGCAGCTTCCTTACAACAGAATGAAAATGAAAGCCA
AGTTTCAACAGATGAAAGTGAGAACTCCAGGTCTCCTGGAAATAAATCAGATAACA
TCAAGCCCAAATCTGCTCCATGGAACTCTTTTCTCCCTCCACCACCCCCCATGCCAGG
GCCAAGACTGGGACCAGGAAAGCCAGGTCTAAAATTCAATGGCCCACCACCGCCAC
CGCCACCACCACCACCCCACTTACTATCATGCTGGCTGCCTCCATTTCCTTCTGGACC
ACCAATAATTCCCCCACCACCTCCCATATGTCCAGATTCTCTTGATGATGCTGATGCT
TTGGGAAGTATGTTAATTTCATGGTACATGAGTGGCTATCATACTGGCTATTATATGG
AAATGCTGGCATAGAGCAGCACTAAATGACACCACTAAAGAAACGATCAGACAGAT
CTGGAATGTGAAGCGTTATAGAAGATAACTGGCCTCATTTCTTCAAAATATCAAGTG
TTGGGAAAGAAAAAAGGAAGTGGAATGGGTAACTCTTCTTGATTAAAAGTTATGTA
ATAACCAAATGCAATGTGAAATATTTTACTGGACTCTATTTTGAAAAACCATCTGTA
AAAGACTGAGGTGGGGGTGGGAGGCCAGCACGGTGGTGAGGCAGTTGAGAAAATTT
GAATGTGGATTAGATTTTGAATGATATTGGATAATTATTGGTAATTTTATGAGCTGTG
AGAAGGGTGTTGTAGTTTATAAAAGACTGTCTTAATTTGCATACTTAAGCATTTAGG
AATGAAGTGTTAGAGTGTCTTAAAATGTTTCAAATGGTTTAACAAAATGTATGTGAG
GCGTATGTGGCAAAATGTTACAGAATCTAACTGGTGGACATGGCTGTTCATTGTACT
GTTTTTTTCTATCTTCTATATGTTTAAAAGTATATAATAAAAATATTTAATTTTTTTTT
AAATTA
(SEQ ID NO: 9705) (Source: NCBI Reference Sequence: XM_011543601.1)

[00374] In various embodiments, a SMN2 mRNA transcript comprises the sequence provided as SEQ ID NO: 9706.

AAGAAGGGACGGGGCCCCACGCTGCGCACCCGCGGGTTTGCTATGGCGATGAGCAG
CGGCGGCAGTGGTGGCGGCGTCCCGGAGCAGGAGGATTCCGTGCTGTTCCGGCGCG
GCACAGGCCAGAGCGATGATTCTGACATTTGGGATGATACAGCACTGATAAAAGCA
TATGATAAAGCTGTGGCTTCATTTAAGCATGCTCTAAAGAATGGTGACATTTGTGAA
ACTTCGGGTAAACCAAAAACCACACCTAAAAGAAAACCTGCTAAGAAGAATAAAAG
CCAAAAGAAGAATACTGCAGCTTCCTTACAACAGTGGAAAGTTGGGGACAAATGTT
CTGCCATTTGGTCAGAAGACGGTTGCATTTACCCAGCTACCATTGCTTCAATTGATTT
TAAGAGAGAAACCTGTGTTGTGGTTTACACTGGATATGGAAATAGAGAGGAGCAAA
ATCTGTCCGATCTACTTTCCCCAATCTGTGAAGTAGCTAATAATATAGAACAAAATG
CTCAAGAGAATGAAAATGAAAGCCAAGTTTCAACAGATGAAAGTGAGAACTCCAGG
TCTCCTGGAAATAAATCAGATAACATCAAGCCCAAATCTGCTCCATGGAACTCTTTT
CTCCCTCCACCACCCCCCATGCCAGGGCCAAGACTGGGACCAGGAAAGCCAGGTCT
AAAATTCAATGGCCCACCACCGCCACCGCCACCACCACCACCCCACTTACTATCATG
CTGGCTGCCTCCATTTCCTTCTGGACCACCAATAATTCCCCCACCACCTCCCATATGT

CCAGATTCTCTTGATGATGCTGATGCTTTGGGAAGTATGTTAATTTCATGGTACATGA
GTGGCTATCATACTGGCTATTATATGACAGGGTTTCACTGTGTTAGCCAGGATGGTCT
CAATCTCCTGACCCCGTGATCCACCCGCCTCGGCCTTCCAAGAGAAATGAAATTTTTT
TAATGCACAAAGATCTGGGGTAATGTGTACCACATTGAACCTTGGGGAGTATGGCTT
CAAACTTGTCACTTTATACGTTAGTCTCCTACGGACATGTTCTATTGTATTTTAGTCA
GAACATTTAAAAT
(SEQ ID NO: 9706) (Source: NCBI Reference Sequence: XM_011543599.1)

[00375] In various embodiments, a SMN2 mRNA transcript comprises the sequence provided as SEQ ID NO: 9707.

AAGAAGGGACGGGGCCCCACGCTGCGCACCCGCGGGTTTGCTATGGCGATGAGCAG
CGGCGGCAGTGGTGGCGGCGTCCCGGAGCAGGAGGATTCCGTGCTGTTCCGGCGCG
GCACAGGCCAGAGCGATGATTCTGACATTTGGGATGATACAGCACTGATAAAAGCA
TATGATAAAGCTGTGGCTTCATTTAAGCATGCTCTAAAGAATGGTGACATTTGTGAA
ACTTCGGGTAAACCAAAAACCACACCTAAAAGAAAACCTGCTAAGAAGAATAAAAG
CCAAAAGAAGAATACTGCAGCTTCCTTACAACAGTGGAAAGTTGGGGACAAATGTT
CTGCCATTTGGTCAGAAGACGGTTGCATTTACCCAGCTACCATTGCTTCAATTGATTT
TAAGAGAGAAACCTGTGTTGTGGTTTACACTGGATATGGAAATAGAGAGGAGCAAA
ATCTGTCCGATCTACTTTCCCCAATCTGTGAAGTAGCTAATAATATAGAACAAAATG
CTCAAGAGAATGAAAATGAAAGCCAAGTTTCAACAGATGAAAGTGAGAACTCCAGG
TCTCCTGGAAATAAATCAGATAACATCAAGCCCAAATCTGCTCCATGGAACTCTTTT
CTCCCTCCACCACCCCCCATGCCAGGGCCAAGACTGGGACCAGGAAAGCCAGGTCT
AAAATTCAATGGCCCACCACCGCCACCGCCACCACCACCACCCCACTTACTATCATG
CTGGCTGCCTCCATTTCCTTCTGGACCACCAATAATTCCCCCACCACCTCCCATATGT
CCAGATTCTCTTGATGATGCTGATGCTTTGGGAAGTATGTTAATTTCATGGTACATGA
GTGGCTATCATACTGGCTATTATATGGGTTTCACTGTGTTAGCCAGGATGGTCTCAAT
CTCCTGACCCCGTGATCCACCCGCCTCGGCCTTCCAAGAGAAATGAAATTTTTTTAAT
GCACAAAGATCTGGGGTAATGTGTACCACATTGAACCTTGGGGAGTATGGCTTCAAA
CTTGTCACTTTATACGTTAGTCTCCTACGGACATGTTCTATTGTATTTTAGTCAGAAC
ATTTAAAAT
(SEQ ID NO: 9707) (Source: NCBI Reference Sequence: XM_017009787.1)

[00376] In various embodiments, a SMN2 transcript is a SMN2 pre-mRNA transcript. In various embodiments, a SMN2 pre-mRNA transcript comprises a sequence provided as SEQ ID NO: 9708. NCBI Reference Sequence NG_008728.1 is SEQ ID NO: 9708.

[00377] In various embodiments, a SMN2 pre-mRNA transcript comprises a sequence provided as SEQ ID NO: 9709. NCBI Reference Sequence NC_000005.10 is SEQ ID NO: 9709.

[00378] In various embodiments, the SMN2 transcript shares between 90-100% identity with any one of SEQ ID NO: 9698-9707 or shares between 90-100% identity to a SMN2 pre-mRNA transcript comprising SEQ ID NO: 9708 or SEQ ID NO: 9709. In various embodiments, the SMN2 transcript shares at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity with SEQ ID NO: 9698-9707 or shares at least 90%, 91%, 92%, 93%, 94%, 95%, 96%,

97%, 98%, or 99% identity with a SMN2 pre-mRNA transcript transcribed from SEQ ID NO: 9708 or SEQ ID NO: 9709.

SMN2 Oligonucleotides Targeting Regions of the SMN2 Transcript

[00379] In various embodiments, SMN2 AON disclosed herein are complementary to specific regions of SMN2 transcripts (for example, a SMN2 transcript) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 9698-9709. In some embodiments, a SMN2 AON comprises a sequence that is complementary to a specific region of the SMN2 transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 9698-9709. In some embodiments, a SMN2 AON comprises a sequence that is at least 85% complementary to a specific region of the SMN2 transcript. In some embodiments, a SMN2 AON comprises a sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% complementary to a specific region of the SMN2 transcript. In some embodiments, a SMN2 AON comprises a sequence that is 90 to 99% complementary to a specific region of the SMN2 transcript. In some embodiments, a SMN2 AON comprises a sequence that is 90 to 95% complementary to a specific region of the SMN2 transcript. In some embodiments, a SMN2 AON comprises a sequence that is 95 to 99% complementary to a specific region of the SMN2 transcript

[00380] In some embodiments, the SMN2 AON (e.g., SMN2 AON) has a segment that has, at most, 7 linked nucleosides. In some embodiments, the SMN2 AON has a segment that has, at most, 6, 5, 4, 3, or 2 linked nucleosides. The segments of the SMN2 AON may be separated from other segments of the SMN2 AON through a spacer. The segment of the SMN2 AON is complementary to a specific region of the SMN2 transcript (for example, a SMN2 transcript) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 9698-9709.

SMN2 Oligonucleotide Variants

[00381] In various embodiments, SMN2 AONs include different variants, hereafter referred to as SMN2 AON variants. A SMN2 AON variant may be an oligonucleotide sequence of 5 to 100 nucleobases in length, for example, 10 to 40 nucleobases in length, for example, 14 to 40 nucleobases in length, 10 to 30 nucleobases in length, for example, 14 to 30 nucleobases in length, for example, 16 to 28 nucleobases in length, for example, 19 to 23 nucleobases in length,

for example, 21 to 23 nucleobases in length, for example, or 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleobases in length. A SMN2 AON variant may be an oligonucleotide sequence complementary to a portion of a SMN2 pre-mRNA sequence or a SMN2 gene sequence. Example SMN2 AON variants include a nucleobase sequence selected from any one of SEQ ID NOs: 9710-10141.

[00382] In various embodiments, a SMN2 AON variant represents a modified version of a corresponding SMN2 parent oligonucleotide. In some embodiments, a SMN2 AON variant includes a nucleobase sequence that represents a shortened version of a nucleobase sequence of a SMN2 parent AON. As one example, if a SMN2 parent oligonucleotide includes a 25mer (*e.g.*, 25 nucleotide bases in length) a variant (*e.g.*, a SMN2 variant) may include a shorter version (*e.g.*, 15mer, 17mer, 19mer, 21mer, or 23mer) of the 25mer SMN2 parent oligonucleotide. In one embodiment, a nucleobase sequence of a SMN2 AON variant differs from a corresponding nucleobase sequence of a SMN2 parent oligonucleotide in that 1, 2, 3, 4, 5, or 6 nucleotide bases are removed from one or both of the 3' and 5' ends of the nucleobase sequence of the SMN2 parent oligonucleotide. In one embodiment, the corresponding SMN2 AON variant may include a 23mer where two nucleotide bases were removed from one of the 3' or 5' end of a 25mer included in the SMN2 parent oligonucleotide. In one embodiment, the corresponding SMN2 AON variant may include a 23mer where one nucleotide base is removed from each of the 3' and 5' ends of the 25mer included in the SMN2 parent oligonucleotide. In one embodiment, the corresponding SMN2 AON variant may include a 21mer where two nucleotide bases are removed from each of the 3' and 5' ends of the 25mer included in the SMN2 parent oligonucleotide. In one embodiment, the corresponding SMN2 AON variant may include a 21mer where four nucleotide bases are removed from either the 3' or 5' end of the 25mer included in the SMN2 parent oligonucleotide. In one embodiment, the corresponding SMN2 AON variant may include a 19mer where three nucleotide bases are removed from each of the 3' and 5' ends of the 25mer included in the SMN2 parent oligonucleotide. In one embodiment, the corresponding SMN2 AON variant may include a 19mer where six nucleotide bases are removed from either the 3' or 5' end of the 25mer included in the SMN2 parent oligonucleotide.

[00383] Example sequences of SMN2 AON variants are shown below in Table 11.

Table 11. SMN2 Oligonucleotide Variant Sequences complementary to a sequence a SMN2 transcript

SEQ ID NO:	AON Sequence* (5' → 3')	SEQ ID NO:	Target Sequence (5' → 3')
9710	ATCCCAAAGAAAACAATTATTAG	10142	CTAATAATTGTTTTCTTTGGGAT
9711	TATCCCAAAGAAAACAATTATTA	10143	TAATAATTGTTTTCTTTGGGATA
9712	TTATCCCAAAGAAAACAATTATT	10144	AATAATTGTTTTCTTTGGGATAA
9713	GTTATCCCAAAGAAAACAATTAT	10145	ATAATTGTTTTCTTTGGGATAAC
9714	AGTTATCCCAAAGAAAACAATTA	10146	TAATTGTTTTCTTTGGGATAACT
9715	AAGTTATCCCAAAGAAAACAATT	10147	AATTGTTTTCTTTGGGATAACTT
9716	AAAGTTATCCCAAAGAAAACAAT	10148	ATTGTTTTCTTTGGGATAACTTT
9717	AAAAGTTATCCCAAAGAAAACAA	10149	TTGTTTTCTTTGGGATAACTTTT
9718	TAAAAGTTATCCCAAAGAAAACA	10150	TGTTTTCTTTGGGATAACTTTTA
9719	TTAAAAGTTATCCCAAAGAAAAC	10151	GTTTTCTTTGGGATAACTTTTAA
9720	TTTAAAAGTTATCCCAAAGAAAA	10152	TTTTCTTTGGGATAACTTTTAAA
9721	CTTTAAAAGTTATCCCAAAGAAA	10153	TTTCTTTGGGATAACTTTTAAAG
9722	ACTTTAAAAGTTATCCCAAAGAA	10154	TTCTTTGGGATAACTTTTAAAGT
9723	TACTTTAAAAGTTATCCCAAAGA	10155	TCTTTGGGATAACTTTTAAAGTA
9724	GTACTTTAAAAGTTATCCCAAAG	10156	CTTTGGGATAACTTTTAAAGTAC
9725	TGTACTTTAAAAGTTATCCCAAA	10157	TTTGGGATAACTTTTAAAGTACA
9726	ATGTACTTTAAAAGTTATCCCAA	10158	TTGGGATAACTTTTAAAGTACAT
9727	AATGTACTTTAAAAGTTATCCCA	10159	TGGGATAACTTTTAAAGTACATT
9728	TAATGTACTTTAAAAGTTATCCC	10160	GGGATAACTTTTAAAGTACATTA
9729	TTAATGTACTTTAAAAGTTATCC	10161	GGATAACTTTTAAAGTACATTAA
9730	TTTAATGTACTTTAAAAGTTATC	10162	GATAACTTTTAAAGTACATTAAA
9731	TTTTAATGTACTTTAAAAGTTAT	10163	ATAACTTTTAAAGTACATTAAAA
9732	CTTTTAATGTACTTTAAAAGTTA	10164	TAACTTTTAAAGTACATTAAAAG
9733	TCTTTTAATGTACTTTAAAAGTT	10165	AACTTTTAAAGTACATTAAAAGA
9734	GTCTTTTAATGTACTTTAAAAGT	10166	ACTTTTAAAGTACATTAAAAGAC
9735	AGTCTTTTAATGTACTTTAAAAG	10167	CTTTTAAAGTACATTAAAAGACT
9736	TAGTCTTTTAATGTACTTTAAAA	10168	TTTTAAAGTACATTAAAAGACTA
9737	ATAGTCTTTTAATGTACTTTAAA	10169	TTTAAAGTACATTAAAAGACTAT
9738	GATAGTCTTTTAATGTACTTTAA	10170	TTAAAGTACATTAAAAGACTATC
9739	TGATAGTCTTTTAATGTACTTTA	10171	TAAAGTACATTAAAAGACTATCA
9740	TTGATAGTCTTTTAATGTACTTT	10172	AAAGTACATTAAAAGACTATCAA
9741	GTTGATAGTCTTTTAATGTACTT	10173	AAGTACATTAAAAGACTATCAAC
9742	AGTTGATAGTCTTTTAATGTACT	10174	AGTACATTAAAAGACTATCAACT
9743	AAGTTGATAGTCTTTTAATGTAC	10175	GTACATTAAAAGACTATCAACTT
9744	TAAGTTGATAGTCTTTTAATGTA	10176	TACATTAAAAGACTATCAACTTA
9745	TTAAGTTGATAGTCTTTTAATGT	10177	ACATTAAAAGACTATCAACTTAA
9746	ATTAAGTTGATAGTCTTTTAATG	10178	CATTAAAAGACTATCAACTTAAT

9747	AATTAAGTTGATAGTCTTTTAAT	10179	ATTAAAAGACTATCAACTTAATT
9748	AAATTAAGTTGATAGTCTTTTAA	10180	TTAAAAGACTATCAACTTAATTT
9749	GAAATTAAGTTGATAGTCTTTTA	10181	TAAAAGACTATCAACTTAATTTC
9750	AGAAATTAAGTTGATAGTCTTTT	10182	AAAAGACTATCAACTTAATTTCT
9751	CAGAAATTAAGTTGATAGTCTTT	10183	AAAGACTATCAACTTAATTTCTG
9752	TCAGAAATTAAGTTGATAGTCTT	10184	AAGACTATCAACTTAATTTCTGA
9753	ATCAGAAATTAAGTTGATAGTCT	10185	AGACTATCAACTTAATTTCTGAT
9754	GATCAGAAATTAAGTTGATAGTC	10186	GACTATCAACTTAATTTCTGATC
9755	TGATCAGAAATTAAGTTGATAGT	10187	ACTATCAACTTAATTTCTGATCA
9756	ATGATCAGAAATTAAGTTGATAG	10188	CTATCAACTTAATTTCTGATCAT
9757	TATGATCAGAAATTAAGTTGATA	10189	TATCAACTTAATTTCTGATCATA
9758	ATATGATCAGAAATTAAGTTGAT	10190	ATCAACTTAATTTCTGATCATAT
9759	AATATGATCAGAAATTAAGTTGA	10191	TCAACTTAATTTCTGATCATATT
9760	AAATATGATCAGAAATTAAGTTG	10192	CAACTTAATTTCTGATCATATTT
9761	AAAATATGATCAGAAATTAAGTT	10193	AACTTAATTTCTGATCATATTTT
9762	CAAAATATGATCAGAAATTAAGT	10194	ACTTAATTTCTGATCATATTTTG
9763	ACAAAATATGATCAGAAATTAAG	10195	CTTAATTTCTGATCATATTTTGT
9764	AACAAAATATGATCAGAAATTAA	10196	TTAATTTCTGATCATATTTTGTT
9765	CAACAAAATATGATCAGAAATTA	10197	TAATTTCTGATCATATTTTGTTG
9766	TCAACAAAATATGATCAGAAATT	10198	AATTTCTGATCATATTTTGTTGA
9767	TTCAACAAAATATGATCAGAAAT	10199	ATTTCTGATCATATTTTGTTGAA
9768	ATTCAACAAAATATGATCAGAAA	10200	TTTCTGATCATATTTTGTTGAAT
9769	TATTCAACAAAATATGATCAGAA	10201	TTCTGATCATATTTTGTTGAATA
9770	TTATTCAACAAAATATGATCAGA	10202	TCTGATCATATTTTGTTGAATAA
9771	TTTATTCAACAAAATATGATCAG	10203	CTGATCATATTTTGTTGAATAAA
9772	TTTTATTCAACAAAATATGATCA	10204	TGATCATATTTTGTTGAATAAAA
9773	ATTTTATTCAACAAAATATGATC	10205	GATCATATTTTGTTGAATAAAAT
9774	TATTTTATTCAACAAAATATGAT	10206	ATCATATTTTGTTGAATAAAATA
9775	TTATTTTATTCAACAAAATATGA	10207	TCATATTTTGTTGAATAAAATAA
9776	CTTATTTTATTCAACAAAATATG	10208	CATATTTTGTTGAATAAAATAAG
9777	ACTTATTTTATTCAACAAAATAT	10209	ATATTTTGTTGAATAAAATAAGT
9778	TACTTATTTTATTCAACAAAATA	10210	TATTTTGTTGAATAAAATAAGTA
9779	TTACTTATTTTATTCAACAAAAT	10211	ATTTTGTTGAATAAAATAAGTAA
9780	TTTACTTATTTTATTCAACAAAA	10212	TTTTGTTGAATAAAATAAGTAAA
9781	TTTTACTTATTTTATTCAACAAA	10213	TTTGTTGAATAAAATAAGTAAAA
9782	ATTTTACTTATTTTATTCAACAA	10214	TTGTTGAATAAAATAAGTAAAAT
9783	CATTTTACTTATTTTATTCAACA	10215	TGTTGAATAAAATAAGTAAAATG
9784	ACATTTTACTTATTTTATTCAAC	10216	GTTGAATAAAATAAGTAAAATGT
9785	GACATTTTACTTATTTTATTCAA	10217	TTGAATAAAATAAGTAAAATGTC
9786	AGACATTTTACTTATTTTATTCA	10218	TGAATAAAATAAGTAAAATGTCT
9787	AAGACATTTTACTTATTTTATTC	10219	GAATAAAATAAGTAAAATGTCTT
9788	CAAGACATTTTACTTATTTTATT	10220	AATAAAATAAGTAAAATGTCTTG

9789	ACAAGACATTTTACTTATTTTAT	10221	ATAAAATAAGTAAAATGTCTTGT
9790	CACAAGACATTTTACTTATTTTA	10222	TAAAATAAGTAAAATGTCTTGTG
9791	TCACAAGACATTTTACTTATTTT	10223	AAAATAAGTAAAATGTCTTGTGA
9792	TTCACAAGACATTTTACTTATTT	10224	AAATAAGTAAAATGTCTTGTGAA
9793	TTTCACAAGACATTTTACTTATT	10225	AATAAGTAAAATGTCTTGTGAAA
9794	GTTTCACAAGACATTTTACTTAT	10226	ATAAGTAAAATGTCTTGTGAAAC
9795	TGTTTCACAAGACATTTTACTTA	10227	TAAGTAAAATGTCTTGTGAAACA
9796	TTGTTTCACAAGACATTTTACTT	10228	AAGTAAAATGTCTTGTGAAACAA
9797	TTTGTTTCACAAGACATTTTACT	10229	AGTAAAATGTCTTGTGAAACAAA
9798	TTTTGTTTCACAAGACATTTTAC	10230	GTAAAATGTCTTGTGAAACAAAA
9799	ATTTTGTTTCACAAGACATTTTA	10231	TAAAATGTCTTGTGAAACAAAAT
9800	CATTTTGTTTCACAAGACATTTT	10232	AAAATGTCTTGTGAAACAAAATG
9801	GCATTTTGTTTCACAAGACATTT	10233	AAATGTCTTGTGAAACAAAATGC
9802	AGCATTTTGTTTCACAAGACATT	10234	AATGTCTTGTGAAACAAAATGCT
9803	AAGCATTTTGTTTCACAAGACAT	10235	ATGTCTTGTGAAACAAAATGCTT
9804	AAAGCATTTTGTTTCACAAGACA	10236	TGTCTTGTGAAACAAAATGCTTT
9805	AAAAGCATTTTGTTTCACAAGAC	10237	GTCTTGTGAAACAAAATGCTTTT
9806	AAAAAGCATTTTGTTTCACAAGA	10238	TCTTGTGAAACAAAATGCTTTTT
9807	TAAAAAGCATTTTGTTTCACAAG	10239	CTTGTGAAACAAAATGCTTTTTA
9808	TTAAAAAGCATTTTGTTTCACAA	10240	TTGTGAAACAAAATGCTTTTTAA
9809	GTTAAAAAGCATTTTGTTTCACA	10241	TGTGAAACAAAATGCTTTTTAAC
9810	TGTTAAAAAGCATTTTGTTTCAC	10242	GTGAAACAAAATGCTTTTTAACA
9811	ATGTTAAAAAGCATTTTGTTTCA	10243	TGAAACAAAATGCTTTTTAACAT
9812	GATGTTAAAAAGCATTTTGTTTC	10244	GAAACAAAATGCTTTTTAACATC
9813	GGATGTTAAAAAGCATTTTGTTT	10245	AAACAAAATGCTTTTTAACATCC
9814	TGGATGTTAAAAAGCATTTTGTT	10246	AACAAAATGCTTTTTAACATCCA
9815	ATGGATGTTAAAAAGCATTTTGT	10247	ACAAAATGCTTTTTAACATCCAT
9816	TATGGATGTTAAAAAGCATTTTG	10248	CAAAATGCTTTTTAACATCCATA
9817	ATATGGATGTTAAAAAGCATTTT	10249	AAAATGCTTTTTAACATCCATAT
9818	TATATGGATGTTAAAAAGCATTT	10250	AAATGCTTTTTAACATCCATATA
9819	TTATATGGATGTTAAAAAGCATT	10251	AATGCTTTTTAACATCCATATAA
9820	TTTATATGGATGTTAAAAAGCAT	10252	ATGCTTTTTAACATCCATATAAA
9821	CTTTATATGGATGTTAAAAAGCA	10253	TGCTTTTTAACATCCATATAAAG
9822	GCTTTATATGGATGTTAAAAAGC	10254	GCTTTTTAACATCCATATAAAGC
9823	AGCTTTATATGGATGTTAAAAAG	10255	CTTTTTAACATCCATATAAAGCT
9824	TAGCTTTATATGGATGTTAAAAA	10256	TTTTTAACATCCATATAAAGCTA
9825	ATAGCTTTATATGGATGTTAAAA	10257	TTTTAACATCCATATAAAGCTAT
9826	GATAGCTTTATATGGATGTTAAA	10258	TTTAACATCCATATAAAGCTATC
9827	AGATAGCTTTATATGGATGTTAA	10259	TTAACATCCATATAAAGCTATCT
9828	TAGATAGCTTTATATGGATGTTA	10260	TAACATCCATATAAAGCTATCTA
9829	ATAGATAGCTTTATATGGATGTT	10261	AACATCCATATAAAGCTATCTAT
9830	TATAGATAGCTTTATATGGATGT	10262	ACATCCATATAAAGCTATCTATA

9831	ATATAGATAGCTTTATATGGATG	10263	CATCCATATAAAGCTATCTATAT
9832	TATATAGATAGCTTTATATGGAT	10264	ATCCATATAAAGCTATCTATATA
9833	ATATATAGATAGCTTTATATGGA	10265	TCCATATAAAGCTATCTATATAT
9834	TATATATAGATAGCTTTATATGG	10266	CCATATAAAGCTATCTATATATA
9835	CTATATATAGATAGCTTTATATG	10267	CATATAAAGCTATCTATATATAG
9836	GCTATATATAGATAGCTTTATAT	10268	ATATAAAGCTATCTATATATAGC
9837	AGCTATATATAGATAGCTTTATA	10269	TATAAAGCTATCTATATATAGCT
9838	TAGCTATATATAGATAGCTTTAT	10270	ATAAAGCTATCTATATATAGCTA
9839	ATAGCTATATATAGATAGCTTTA	10271	TAAAGCTATCTATATATAGCTAT
9840	GATAGCTATATATAGATAGCTTT	10272	AAAGCTATCTATATATAGCTATC
9841	AGATAGCTATATATAGATAGCTT	10273	AAGCTATCTATATATAGCTATCT
9842	TAGATAGCTATATATAGATAGCT	10274	AGCTATCTATATATAGCTATCTA
9843	ATAGATAGCTATATATAGATAGC	10275	GCTATCTATATATAGCTATCTAT
9844	TATAGATAGCTATATATAGATAG	10276	CTATCTATATATAGCTATCTATA
9845	ATATAGATAGCTATATATAGATA	10277	TATCTATATATAGCTATCTATAT
9846	GATATAGATAGCTATATATAGAT	10278	ATCTATATATAGCTATCTATATC
9847	AGATATAGATAGCTATATATAGA	10279	TCTATATATAGCTATCTATATCT
9848	TAGATATAGATAGCTATATATAG	10280	CTATATATAGCTATCTATATCTA
9849	ATAGATATAGATAGCTATATATA	10281	TATATATAGCTATCTATATCTAT
9850	TATAGATATAGATAGCTATATAT	10282	ATATATAGCTATCTATATCTATA
9851	ATATAGATATAGATAGCTATATA	10283	TATATAGCTATCTATATCTATAT
9852	TATATAGATATAGATAGCTATAT	10284	ATATAGCTATCTATATCTATATA
9853	CTATATAGATATAGATAGCTATA	10285	TATAGCTATCTATATCTATATAG
9854	GCTATATAGATATAGATAGCTAT	10286	ATAGCTATCTATATCTATATAGC
9855	AGCTATATAGATATAGATAGCTA	10287	TAGCTATCTATATCTATATAGCT
9856	TAGCTATATAGATATAGATAGCT	10288	AGCTATCTATATCTATATAGCTA
9857	ATAGCTATATAGATATAGATAGC	10289	GCTATCTATATCTATATAGCTAT
9858	AATAGCTATATAGATATAGATAG	10290	CTATCTATATCTATATAGCTATT
9859	AAATAGCTATATAGATATAGATA	10291	TATCTATATCTATATAGCTATTT
9860	AAAATAGCTATATAGATATAGAT	10292	ATCTATATCTATATAGCTATTTT
9861	AAAAATAGCTATATAGATATAGA	10293	TCTATATCTATATAGCTATTTTT
9862	AAAAAATAGCTATATAGATATAG	10294	CTATATCTATATAGCTATTTTTT
9863	AAAAAAATAGCTATATAGATATA	10295	TATATCTATATAGCTATTTTTTT
9864	AAAAAAAATAGCTATATAGATAT	10296	ATATCTATATAGCTATTTTTTTT
9865	TAAAAAAAATAGCTATATAGATA	10297	TATCTATATAGCTATTTTTTTTA
9866	TTAAAAAAAATAGCTATATAGAT	10298	ATCTATATAGCTATTTTTTTTAA
9867	GTTAAAAAAAAATAGCTATATAGA	10299	TCTATATAGCTATTTTTTTTAAC
9868	AGTTAAAAAAAAATAGCTATATAG	10300	CTATATAGCTATTTTTTTTAACT
9869	AAGTTAAAAAAAAATAGCTATATA	10301	TATATAGCTATTTTTTTTAACTT
9870	GAAGTTAAAAAAAAATAGCTATAT	10302	ATATAGCTATTTTTTTTAACTTC
9871	GGAAGTTAAAAAAAAATAGCTATA	10303	TATAGCTATTTTTTTTAACTTCC
9872	AGGAAGTTAAAAAAAAATAGCTAT	10304	ATAGCTATTTTTTTTAACTTCCT

9873	AAGGAAGTTAAAAAAAATAGCTA	10305	TAGCTATTTTTTTTAACTTCCTT
9874	AAAGGAAGTTAAAAAAAATAGCT	10306	AGCTATTTTTTTTAACTTCCTTT
9875	TAAAGGAAGTTAAAAAAAATAGC	10307	GCTATTTTTTTTAACTTCCTTTA
9876	ATAAAGGAAGTTAAAAAAAATAG	10308	CTATTTTTTTTAACTTCCTTTAT
9877	AATAAAGGAAGTTAAAAAAAATA	10309	TATTTTTTTTAACTTCCTTTATT
9878	AAATAAAGGAAGTTAAAAAAAAT	10310	ATTTTTTTTAACTTCCTTTATTT
9879	AAAATAAAGGAAGTTAAAAAAAA	10311	TTTTTTTTAACTTCCTTTATTTT
9880	GAAAATAAAGGAAGTTAAAAAAA	10312	TTTTTTTAACTTCCTTTATTTTC
9881	GGAAAATAAAGGAAGTTAAAAAA	10313	TTTTTTAACTTCCTTTATTTTCC
9882	AGGAAAATAAAGGAAGTTAAAAA	10314	TTTTTAACTTCCTTTATTTTCCT
9883	AAGGAAAATAAAGGAAGTTAAAA	10315	TTTTAACTTCCTTTATTTTCCTT
9884	TAAGGAAAATAAAGGAAGTTAAA	10316	TTTAACTTCCTTTATTTTCCTTA
9885	GTAAGGAAAATAAAGGAAGTTAA	10317	TTAACTTCCTTTATTTTCCTTAC
9886	TGTAAGGAAAATAAAGGAAGTTA	10318	TAACTTCCTTTATTTTCCTTACA
9887	CTGTAAGGAAAATAAAGGAAGTT	10319	AACTTCCTTTATTTTCCTTACAG
9888	CCTGTAAGGAAAATAAAGGAAGT	10320	ACTTCCTTTATTTTCCTTACAGG
9889	CCCTGTAAGGAAAATAAAGGAAG	10321	CTTCCTTTATTTTCCTTACAGGG
9890	ACCCTGTAAGGAAAATAAAGGAA	10322	TTCCTTTATTTTCCTTACAGGGT
9891	AACCCTGTAAGGAAAATAAAGGA	10323	TCCTTTATTTTCCTTACAGGGTT
9892	AAACCCTGTAAGGAAAATAAAGG	10324	CCTTTATTTTCCTTACAGGGTTT
9893	AAAACCCTGTAAGGAAAATAAAG	10325	CTTTATTTTCCTTACAGGGTTTT
9894	TAAAACCCTGTAAGGAAAATAAA	10326	TTTATTTTCCTTACAGGGTTTTA
9895	CTAAAACCCTGTAAGGAAAATAA	10327	TTATTTTCCTTACAGGGTTTTAG
9896	TCTAAAACCCTGTAAGGAAAATA	10328	TATTTTCCTTACAGGGTTTTAGA
9897	GTCTAAAACCCTGTAAGGAAAAT	10329	ATTTTCCTTACAGGGTTTTAGAC
9898	TGTCTAAAACCCTGTAAGGAAAA	10330	TTTTCCTTACAGGGTTTTAGACA
9899	TTGTCTAAAACCCTGTAAGGAAA	10331	TTTCCTTACAGGGTTTTAGACAA
9900	TTTGTCTAAAACCCTGTAAGGAA	10332	TTCCTTACAGGGTTTTAGACAAA
9901	TTTTGTCTAAAACCCTGTAAGGA	10333	TCCTTACAGGGTTTTAGACAAAA
9902	ATTTTGTCTAAAACCCTGTAAGG	10334	CCTTACAGGGTTTTAGACAAAAT
9903	GATTTTGTCTAAAACCCTGTAAG	10335	CTTACAGGGTTTTAGACAAAATC
9904	TGATTTTGTCTAAAACCCTGTAA	10336	TTACAGGGTTTTAGACAAAATCA
9905	TTGATTTTGTCTAAAACCCTGTA	10337	TACAGGGTTTTAGACAAAATCAA
9906	TTTGATTTTGTCTAAAACCCTGT	10338	ACAGGGTTTTAGACAAAATCAAA
9907	TTTTGATTTTGTCTAAAACCCTG	10339	CAGGGTTTTAGACAAAATCAAAA
9908	TTTTTGATTTTGTCTAAAACCCT	10340	AGGGTTTTAGACAAAATCAAAAA
9909	CTTTTTGATTTTGTCTAAAACCC	10341	GGGTTTTAGACAAAATCAAAAAG
9910	TCTTTTTGATTTTGTCTAAAACC	10342	GGTTTTAGACAAAATCAAAAAGA
9911	TTCTTTTTGATTTTGTCTAAAAC	10343	GTTTTAGACAAAATCAAAAAGAA
9912	CTTCTTTTTGATTTTGTCTAAAA	10344	TTTTAGACAAAATCAAAAAGAAG
9913	CCTTCTTTTTGATTTTGTCTAAA	10345	TTTAGACAAAATCAAAAAGAAGG
9914	TCCTTCTTTTTGATTTTGTCTAA	10346	TTAGACAAAATCAAAAAGAAGGA

9915	TTCCTTCTTTTTGATTTTGTCTA	10347	TAGACAAAATCAAAAAGAAGGAA
9916	CTTCCTTCTTTTTGATTTTGTCT	10348	AGACAAAATCAAAAAGAAGGAAG
9917	CCTTCCTTCTTTTTGATTTTGTC	10349	GACAAAATCAAAAAGAAGGAAGG
9918	ACCTTCCTTCTTTTTGATTTTGT	10350	ACAAAATCAAAAAGAAGGAAGGT
9919	CACCTTCCTTCTTTTTGATTTTG	10351	CAAAATCAAAAAGAAGGAAGGTG
9920	GCACCTTCCTTCTTTTTGATTTT	10352	AAAATCAAAAAGAAGGAAGGTGC
9921	AGCACCTTCCTTCTTTTTGATTT	10353	AAATCAAAAAGAAGGAAGGTGCT
9922	GAGCACCTTCCTTCTTTTTGATT	10354	AATCAAAAAGAAGGAAGGTGCTC
9923	TGAGCACCTTCCTTCTTTTTGAT	10355	ATCAAAAAGAAGGAAGGTGCTCA
9924	GTGAGCACCTTCCTTCTTTTTGA	10356	TCAAAAAGAAGGAAGGTGCTCAC
9925	TGTGAGCACCTTCCTTCTTTTTG	10357	CAAAAAGAAGGAAGGTGCTCACA
9926	ATGTGAGCACCTTCCTTCTTTTT	10358	AAAAAGAAGGAAGGTGCTCACAT
9927	AATGTGAGCACCTTCCTTCTTTT	10359	AAAAGAAGGAAGGTGCTCACATT
9928	GAATGTGAGCACCTTCCTTCTTT	10360	AAAGAAGGAAGGTGCTCACATTC
9929	GGAATGTGAGCACCTTCCTTCTT	10361	AAGAAGGAAGGTGCTCACATTCC
9930	AGGAATGTGAGCACCTTCCTTCT	10362	AGAAGGAAGGTGCTCACATTCCT
9931	AAGGAATGTGAGCACCTTCCTTC	10363	GAAGGAAGGTGCTCACATTCCTT
9932	TAAGGAATGTGAGCACCTTCCTT	10364	AAGGAAGGTGCTCACATTCCTTA
9933	TTAAGGAATGTGAGCACCTTCCT	10365	AGGAAGGTGCTCACATTCCTTAA
9934	TTTAAGGAATGTGAGCACCTTCC	10366	GGAAGGTGCTCACATTCCTTAAA
9935	ATTTAAGGAATGTGAGCACCTTC	10367	GAAGGTGCTCACATTCCTTAAAT
9936	AATTTAAGGAATGTGAGCACCTT	10368	AAGGTGCTCACATTCCTTAAATT
9937	TAATTTAAGGAATGTGAGCACCT	10369	AGGTGCTCACATTCCTTAAATTA
9938	TTAATTTAAGGAATGTGAGCACC	10370	GGTGCTCACATTCCTTAAATTAA
9939	CTTAATTTAAGGAATGTGAGCAC	10371	GTGCTCACATTCCTTAAATTAAG
9940	CCTTAATTTAAGGAATGTGAGCA	10372	TGCTCACATTCCTTAAATTAAGG
9941	TCCTTAATTTAAGGAATGTGAGC	10373	GCTCACATTCCTTAAATTAAGGA
9942	CTCCTTAATTTAAGGAATGTGAG	10374	CTCACATTCCTTAAATTAAGGAG
9943	ACTCCTTAATTTAAGGAATGTGA	10375	TCACATTCCTTAAATTAAGGAGT
9944	TACTCCTTAATTTAAGGAATGTG	10376	CACATTCCTTAAATTAAGGAGTA
9945	TTACTCCTTAATTTAAGGAATGT	10377	ACATTCCTTAAATTAAGGAGTAA
9946	CTTACTCCTTAATTTAAGGAATG	10378	CATTCCTTAAATTAAGGAGTAAG
9947	ACTTACTCCTTAATTTAAGGAAT	10379	ATTCCTTAAATTAAGGAGTAAGT
9948	GACTTACTCCTTAATTTAAGGAA	10380	TTCCTTAAATTAAGGAGTAAGTC
9949	AGACTTACTCCTTAATTTAAGGA	10381	TCCTTAAATTAAGGAGTAAGTCT
9950	CAGACTTACTCCTTAATTTAAGG	10382	CCTTAAATTAAGGAGTAAGTCTG
9951	GCAGACTTACTCCTTAATTTAAG	10383	CTTAAATTAAGGAGTAAGTCTGC
9952	GGCAGACTTACTCCTTAATTTAA	10384	TTAAATTAAGGAGTAAGTCTGCC
9953	TGGCAGACTTACTCCTTAATTTA	10385	TAAATTAAGGAGTAAGTCTGCCA
9954	CTGGCAGACTTACTCCTTAATTT	10386	AAATTAAGGAGTAAGTCTGCCAG
9955	GCTGGCAGACTTACTCCTTAATT	10387	AATTAAGGAGTAAGTCTGCCAGC
9956	TGCTGGCAGACTTACTCCTTAAT	10388	ATTAAGGAGTAAGTCTGCCAGCA

9957	ATGCTGGCAGACTTACTCCTTAA	10389	TTAAGGAGTAAGTCTGCCAGCAT
9958	AATGCTGGCAGACTTACTCCTTA	10390	TAAGGAGTAAGTCTGCCAGCATT
9959	TAATGCTGGCAGACTTACTCCTT	10391	AAGGAGTAAGTCTGCCAGCATTA
9960	ATAATGCTGGCAGACTTACTCCT	10392	AGGAGTAAGTCTGCCAGCATTAT
9961	CATAATGCTGGCAGACTTACTCC	10393	GGAGTAAGTCTGCCAGCATTATG
9962	TCATAATGCTGGCAGACTTACTC	10394	GAGTAAGTCTGCCAGCATTATGA
9963	TTCATAATGCTGGCAGACTTACT	10395	AGTAAGTCTGCCAGCATTATGAA
9964	TTTCATAATGCTGGCAGACTTAC	10396	GTAAGTCTGCCAGCATTATGAAA
9965	CTTTCATAATGCTGGCAGACTTA	10397	TAAGTCTGCCAGCATTATGAAAG
9966	ACTTTCATAATGCTGGCAGACTT	10398	AAGTCTGCCAGCATTATGAAAGT
9967	CACTTTCATAATGCTGGCAGACT	10399	AGTCTGCCAGCATTATGAAAGTG
9968	TCACTTTCATAATGCTGGCAGAC	10400	GTCTGCCAGCATTATGAAAGTGA
9969	TTCACTTTCATAATGCTGGCAGA	10401	TCTGCCAGCATTATGAAAGTGAA
9970	ATTCACTTTCATAATGCTGGCAG	10402	CTGCCAGCATTATGAAAGTGAAT
9971	GATTCACTTTCATAATGCTGGCA	10403	TGCCAGCATTATGAAAGTGAATC
9972	AGATTCACTTTCATAATGCTGGC	10404	GCCAGCATTATGAAAGTGAATCT
9973	AAGATTCACTTTCATAATGCTGG	10405	CCAGCATTATGAAAGTGAATCTT
9974	TAAGATTCACTTTCATAATGCTG	10406	CAGCATTATGAAAGTGAATCTTA
9975	GTAAGATTCACTTTCATAATGCT	10407	AGCATTATGAAAGTGAATCTTAC
9976	AGTAAGATTCACTTTCATAATGC	10408	GCATTATGAAAGTGAATCTTACT
9977	AAGTAAGATTCACTTTCATAATG	10409	CATTATGAAAGTGAATCTTACTT
9978	AAAGTAAGATTCACTTTCATAAT	10410	ATTATGAAAGTGAATCTTACTTT
9979	AAAAGTAAGATTCACTTTCATAA	10411	TTATGAAAGTGAATCTTACTTTT
9980	CAAAAGTAAGATTCACTTTCATA	10412	TATGAAAGTGAATCTTACTTTTG
9981	ACAAAAGTAAGATTCACTTTCAT	10413	ATGAAAGTGAATCTTACTTTTGT
9982	TACAAAAGTAAGATTCACTTTCA	10414	TGAAAGTGAATCTTACTTTTGTA
9983	TTACAAAAGTAAGATTCACTTTC	10415	GAAAGTGAATCTTACTTTTGTAA
9984	TTTACAAAAGTAAGATTCACTTT	10416	AAAGTGAATCTTACTTTTGTAAA
9985	TTTTACAAAAGTAAGATTCACTT	10417	AAGTGAATCTTACTTTTGTAAAA
9986	GTTTTACAAAAGTAAGATTCACT	10418	AGTGAATCTTACTTTTGTAAAAC
9987	AGTTTTACAAAAGTAAGATTCAC	10419	GTGAATCTTACTTTTGTAAAACT
9988	AAGTTTTACAAAAGTAAGATTCA	10420	TGAATCTTACTTTTGTAAAACTT
9989	AAAGTTTTACAAAAGTAAGATTC	10421	GAATCTTACTTTTGTAAAACTTT
9990	TAAAGTTTTACAAAAGTAAGATT	10422	AATCTTACTTTTGTAAAACTTTA
9991	ATAAAGTTTTACAAAAGTAAGAT	10423	ATCTTACTTTTGTAAAACTTTAT
9992	CATAAAGTTTTACAAAAGTAAGA	10424	TCTTACTTTTGTAAAACTTTATG
9993	CCATAAAGTTTTACAAAAGTAAG	10425	CTTACTTTTGTAAAACTTTATGG
9994	ACCATAAAGTTTTACAAAAGTAA	10426	TTACTTTTGTAAAACTTTATGGT
9995	AACCATAAAGTTTTACAAAAGTA	10427	TACTTTTGTAAAACTTTATGGTT
9996	AAACCATAAAGTTTTACAAAAGT	10428	ACTTTTGTAAAACTTTATGGTTT
9997	CAAACCATAAAGTTTTACAAAAG	10429	CTTTTGTAAAACTTTATGGTTTG

9998	ACAAACCATAAAGTTTTACAAAA	10430	TTTTGTAAAACTTTATGGTTTGT
9999	CACAAACCATAAAGTTTTACAAA	10431	TTTGTAAAACTTTATGGTTTGTG
10000	CCACAAACCATAAAGTTTTACAA	10432	TTGTAAAACTTTATGGTTTGTGG
10001	TCCACAAACCATAAAGTTTTACA	10433	TGTAAAACTTTATGGTTTGTGGA
10002	TTCCACAAACCATAAAGTTTTAC	10434	GTAAAACTTTATGGTTTGTGGAA
10003	TTTCCACAAACCATAAAGTTTTA	10435	TAAAACTTTATGGTTTGTGGAAA
10004	TTTTCCACAAACCATAAAGTTTT	10436	AAAACTTTATGGTTTGTGGAAAA
10005	GTTTTCCACAAACCATAAAGTTT	10437	AAACTTTATGGTTTGTGGAAAAC
10006	TGTTTTCCACAAACCATAAAGTT	10438	AACTTTATGGTTTGTGGAAAACA
10007	TTGTTTTCCACAAACCATAAAGT	10439	ACTTTATGGTTTGTGGAAAACAA
10008	TTTGTTTTCCACAAACCATAAAG	10440	CTTTATGGTTTGTGGAAAACAAA
10009	ATTTGTTTTCCACAAACCATAAA	10441	TTTATGGTTTGTGGAAAACAAAT
10010	CATTTGTTTTCCACAAACCATAA	10442	TTATGGTTTGTGGAAAACAAATG
10011	ACATTTGTTTTCCACAAACCATA	10443	TATGGTTTGTGGAAAACAAATGT
10012	AACATTTGTTTTCCACAAACCAT	10444	ATGGTTTGTGGAAAACAAATGTT
10013	AAACATTTGTTTTCCACAAACCA	10445	TGGTTTGTGGAAAACAAATGTTT
10014	AAAACATTTGTTTTCCACAAACC	10446	GGTTTGTGGAAAACAAATGTTTT
10015	AAAAACATTTGTTTTCCACAAAC	10447	GTTTGTGGAAAACAAATGTTTTT
10016	CAAAAACATTTGTTTTCCACAAA	10448	TTTGTGGAAAACAAATGTTTTTG
10017	TCAAAAACATTTGTTTTCCACAA	10449	TTGTGGAAAACAAATGTTTTTGA
10018	TTCAAAAACATTTGTTTTCCACA	10450	TGTGGAAAACAAATGTTTTTGAA
10019	GTTCAAAAACATTTGTTTTCCAC	10451	GTGGAAAACAAATGTTTTTGAAC
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10021	ATGTTCAAAAACATTTGTTTTCC	10453	GGAAAACAAATGTTTTTGAACAT
10022	AATGTTCAAAAACATTTGTTTTC	10454	GAAAACAAATGTTTTTGAACATT
10023	AAATGTTCAAAAACATTTGTTTT	10455	AAAACAAATGTTTTTGAACATTT
10024	TAAATGTTCAAAAACATTTGTTT	10456	AAACAAATGTTTTTGAACATTTA
10025	TTAAATGTTCAAAAACATTTGTT	10457	AACAAATGTTTTTGAACATTTAA
10026	TTTAAATGTTCAAAAACATTTGT	10458	ACAAATGTTTTTGAACATTTAAA
10027	TTTTAAATGTTCAAAAACATTTG	10459	CAAATGTTTTTGAACATTTAAAA
10028	TTTTTAAATGTTCAAAAACATTT	10460	AAATGTTTTTGAACATTTAAAAA
10029	CTTTTTAAATGTTCAAAAACATT	10461	AATGTTTTTGAACATTTAAAAAG
10030	ACTTTTTAAATGTTCAAAAACAT	10462	ATGTTTTTGAACATTTAAAAAGT
10031	AACTTTTTAAATGTTCAAAAACA	10463	TGTTTTTGAACATTTAAAAAGTT
10032	GAACTTTTTAAATGTTCAAAAAC	10464	GTTTTTGAACATTTAAAAAGTTC
10033	TGAACTTTTTAAATGTTCAAAAA	10465	TTTTTGAACATTTAAAAAGTTCA
10034	CTGAACTTTTTAAATGTTCAAAA	10466	TTTTGAACATTTAAAAAGTTCAG
10035	TCTGAACTTTTTAAATGTTCAAA	10467	TTTGAACATTTAAAAAGTTCAGA
10036	ATCTGAACTTTTTAAATGTTCAA	10468	TTGAACATTTAAAAAGTTCAGAT
10037	CATCTGAACTTTTTAAATGTTCA	10469	TGAACATTTAAAAAGTTCAGATG
10038	ACATCTGAACTTTTTAAATGTTC	10470	GAACATTTAAAAAGTTCAGATGT
10039	AACATCTGAACTTTTTAAATGTT	10471	AACATTTAAAAAGTTCAGATGTT

10040	TAACATCTGAACTTTTTAAATGT	10472	ACATTTAAAAAGTTCAGATGTTA
10041	CTAACATCTGAACTTTTTAAATG	10473	CATTTAAAAAGTTCAGATGTTAG
10042	TCTAACATCTGAACTTTTTAAAT	10474	ATTTAAAAAGTTCAGATGTTAGA
10043	TTCTAACATCTGAACTTTTTAAA	10475	TTTAAAAAGTTCAGATGTTAGAA
10044	TTTCTAACATCTGAACTTTTTAA	10476	TTAAAAAGTTCAGATGTTAGAAA
10045	CTTTCTAACATCTGAACTTTTTA	10477	TAAAAAGTTCAGATGTTAGAAAG
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10047	AACTTTCTAACATCTGAACTTTT	10479	AAAAGTTCAGATGTTAGAAAGTT
10048	CAACTTTCTAACATCTGAACTTT	10480	AAAGTTCAGATGTTAGAAAGTTG
10049	TCAACTTTCTAACATCTGAACTT	10481	AAGTTCAGATGTTAGAAAGTTGA
10050	TTCAACTTTCTAACATCTGAACT	10482	AGTTCAGATGTTAGAAAGTTGAA
10051	TTTCAACTTTCTAACATCTGAAC	10483	GTTCAGATGTTAGAAAGTTGAAA
10052	CTTTCAACTTTCTAACATCTGAA	10484	TTCAGATGTTAGAAAGTTGAAAG
10053	CCTTTCAACTTTCTAACATCTGA	10485	TCAGATGTTAGAAAGTTGAAAGG
10054	ACCTTTCAACTTTCTAACATCTG	10486	CAGATGTTAGAAAGTTGAAAGGT
10055	AACCTTTCAACTTTCTAACATCT	10487	AGATGTTAGAAAGTTGAAAGGTT
10056	TAACCTTTCAACTTTCTAACATC	10488	GATGTTAGAAAGTTGAAAGGTTA
10057	TTAACCTTTCAACTTTCTAACAT	10489	ATGTTAGAAAGTTGAAAGGTTAA
10058	ATTAACCTTTCAACTTTCTAACA	10490	TGTTAGAAAGTTGAAAGGTTAAT
10059	CATTAACCTTTCAACTTTCTAAC	10491	GTTAGAAAGTTGAAAGGTTAATG
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10064	TTTTACATTAACCTTTCAACTTT	10496	AAAGTTGAAAGGTTAATGTAAAA
10065	GTTTTACATTAACCTTTCAACTT	10497	AAGTTGAAAGGTTAATGTAAAAC
10066	TGTTTTACATTAACCTTTCAACT	10498	AGTTGAAAGGTTAATGTAAAACA
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10068	ATTGTTTTACATTAACCTTTCAA	10500	TTGAAAGGTTAATGTAAAACAAT
10069	GATTGTTTTACATTAACCTTTCA	10501	TGAAAGGTTAATGTAAAACAATC
10070	TGATTGTTTTACATTAACCTTTC	10502	GAAAGGTTAATGTAAAACAATCA
10071	TTGATTGTTTTACATTAACCTTT	10503	AAAGGTTAATGTAAAACAATCAA
10072	ATTGATTGTTTTACATTAACCTT	10504	AAGGTTAATGTAAAACAATCAAT
10073	TATTGATTGTTTTACATTAACCT	10505	AGGTTAATGTAAAACAATCAATA
10074	ATATTGATTGTTTTACATTAACC	10506	GGTTAATGTAAAACAATCAATAT
10075	AATATTGATTGTTTTACATTAAC	10507	GTTAATGTAAAACAATCAATATT
10076	TAATATTGATTGTTTTACATTAA	10508	TTAATGTAAAACAATCAATATTA
10077	TTAATATTGATTGTTTTACATTA	10509	TAATGTAAAACAATCAATATTAA
10078	TTTAATATTGATTGTTTTACATT	10510	AATGTAAAACAATCAATATTAAA
10079	CTTTAATATTGATTGTTTTACAT	10511	ATGTAAAACAATCAATATTAAAG
10080	TCTTTAATATTGATTGTTTTACA	10512	TGTAAAACAATCAATATTAAAGA
10081	TTCTTTAATATTGATTGTTTTAC	10513	GTAAAACAATCAATATTAAAGAA

10082	ATTCTTTAATATTGATTGTTTTA	10514	TAAAACAATCAATATTAAAGAAT
10083	AATTCTTTAATATTGATTGTTTT	10515	AAAACAATCAATATTAAAGAATT
10084	AAATTCTTTAATATTGATTGTTT	10516	AAACAATCAATATTAAAGAATTT
10085	AAAATTCTTTAATATTGATTGTT	10517	AACAATCAATATTAAAGAATTTT
10086	CAAAATTCTTTAATATTGATTGT	10518	ACAATCAATATTAAAGAATTTTG
10087	TCAAAATTCTTTAATATTGATTG	10519	CAATCAATATTAAAGAATTTTGA
10088	ATCAAAATTCTTTAATATTGATT	10520	AATCAATATTAAAGAATTTTGAT
10089	CATCAAAATTCTTTAATATTGAT	10521	ATCAATATTAAAGAATTTTGATG
10090	GCATCAAAATTCTTTAATATTGA	10522	TCAATATTAAAGAATTTTGATGC
10091	GGCATCAAAATTCTTTAATATTG	10523	CAATATTAAAGAATTTTGATGCC
10092	TGGCATCAAAATTCTTTAATATT	10524	AATATTAAAGAATTTTGATGCCA
10093	TTGGCATCAAAATTCTTTAATAT	10525	ATATTAAAGAATTTTGATGCCAA
10094	TTTGGCATCAAAATTCTTTAATA	10526	TATTAAAGAATTTTGATGCCAAA
10095	TTTTGGCATCAAAATTCTTTAAT	10527	ATTAAAGAATTTTGATGCCAAAA
10096	GTTTTGGCATCAAAATTCTTTAA	10528	TTAAAGAATTTTGATGCCAAAAC
10097	AGTTTTGGCATCAAAATTCTTTA	10529	TAAAGAATTTTGATGCCAAAACT
10098	TAGTTTTGGCATCAAAATTCTTT	10530	AAAGAATTTTGATGCCAAAACTA
10099	ATAGTTTTGGCATCAAAATTCTT	10531	AAGAATTTTGATGCCAAAACTAT
10100	AATAGTTTTGGCATCAAAATTCT	10532	AGAATTTTGATGCCAAAACTATT
10101	TAATAGTTTTGGCATCAAAATTC	10533	GAATTTTGATGCCAAAACTATTA
10102	CTAATAGTTTTGGCATCAAAATT	10534	AATTTTGATGCCAAAACTATTAG
10103	TCTAATAGTTTTGGCATCAAAAT	10535	ATTTTGATGCCAAAACTATTAGA
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10105	TATCTAATAGTTTTGGCATCAAA	10537	TTTGATGCCAAAACTATTAGATA
10106	TTATCTAATAGTTTTGGCATCAA	10538	TTGATGCCAAAACTATTAGATAA
10107	TTTATCTAATAGTTTTGGCATCA	10539	TGATGCCAAAACTATTAGATAAA
10108	TTTTATCTAATAGTTTTGGCATC	10540	GATGCCAAAACTATTAGATAAAA
10109	CTTTTATCTAATAGTTTTGGCAT	10541	ATGCCAAAACTATTAGATAAAAG
10110	CCTTTTATCTAATAGTTTTGGCA	10542	TGCCAAAACTATTAGATAAAAGG
10111	ACCTTTTATCTAATAGTTTTGGC	10543	GCCAAAACTATTAGATAAAAGGT
10112	AACCTTTTATCTAATAGTTTTGG	10544	CCAAAACTATTAGATAAAAGGTT
10113	TAACCTTTTATCTAATAGTTTTG	10545	CAAAACTATTAGATAAAAGGTTA
10114	TTAACCTTTTATCTAATAGTTTT	10546	AAAACTATTAGATAAAAGGTTAA
10115	ATTAACCTTTTATCTAATAGTTT	10547	AAACTATTAGATAAAAGGTTAAT
10116	GATTAACCTTTTATCTAATAGTT	10548	AACTATTAGATAAAAGGTTAATC
10117	AGATTAACCTTTTATCTAATAGT	10549	ACTATTAGATAAAAGGTTAATCT
10118	TAGATTAACCTTTTATCTAATAG	10550	CTATTAGATAAAAGGTTAATCTA
10119	GTAGATTAACCTTTTATCTAATA	10551	TATTAGATAAAAGGTTAATCTAC
10120	TGTAGATTAACCTTTTATCTAAT	10552	ATTAGATAAAAGGTTAATCTACA
10121	ATGTAGATTAACCTTTTATCTAA	10553	TTAGATAAAAGGTTAATCTACAT
10122	GATGTAGATTAACCTTTTATCTA	10554	TAGATAAAAGGTTAATCTACATC
10123	GGATGTAGATTAACCTTTTATCT	10555	AGATAAAAGGTTAATCTACATCC

10124	GGGATGTAGATTAACCTTTTATC	10556	GATAAAAGGTTAATCTACATCCC
10125	AGGGATGTAGATTAACCTTTTAT	10557	ATAAAAGGTTAATCTACATCCCT
10126	TAGGGATGTAGATTAACCTTTTA	10558	TAAAAGGTTAATCTACATCCCTA
10127	GTAGGGATGTAGATTAACCTTTT	10559	AAAAGGTTAATCTACATCCCTAC
10128	AGTAGGGATGTAGATTAACCTTT	10560	AAAGGTTAATCTACATCCCTACT
10129	TAGTAGGGATGTAGATTAACCTT	10561	AAGGTTAATCTACATCCCTACTA
10130	CTAGTAGGGATGTAGATTAACCT	10562	AGGTTAATCTACATCCCTACTAG
10131	TCTAGTAGGGATGTAGATTAACC	10563	GGTTAATCTACATCCCTACTAGA
10132	TTCTAGTAGGGATGTAGATTAAC	10564	GTTAATCTACATCCCTACTAGAA
10133	ATTCTAGTAGGGATGTAGATTAA	10565	TTAATCTACATCCCTACTAGAAT
10134	AATTCTAGTAGGGATGTAGATTA	10566	TAATCTACATCCCTACTAGAATT
10135	GAATTCTAGTAGGGATGTAGATT	10567	AATCTACATCCCTACTAGAATTC
10136	AGAATTCTAGTAGGGATGTAGAT	10568	ATCTACATCCCTACTAGAATTCT
10137	GAGAATTCTAGTAGGGATGTAGA	10569	TCTACATCCCTACTAGAATTCTC
10138	TGAGAATTCTAGTAGGGATGTAG	10570	CTACATCCCTACTAGAATTCTCA
10139	ATGAGAATTCTAGTAGGGATGTA	10571	TACATCCCTACTAGAATTCTCAT
10140	TATGAGAATTCTAGTAGGGATGT	10572	ACATCCCTACTAGAATTCTCATA
10141	GTATGAGAATTCTAGTAGGGATG	10573	CATCCCTACTAGAATTCTCATAC

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

Antisense Oligonucleotides with One or more Locked Nucleic Acids (LNAs)

[00384] In various embodiments, antisense oligonucleotides disclosed herein (e.g., AON parent oligonucleotides and/or AON oligonucleotide variants) comprise one or more locked nucleic acids (LNAs). In particular embodiments, an antisense oligonucleotide includes one LNA. In particular embodiments, an antisense oligonucleotide includes two LNAs. In particular embodiments, an antisense oligonucleotide includes three LNAs. Generally, a LNA refers to nucleic acid monomers having a bridge (*e.g.*, methylene, ethylene, aminooxy, or oxyimino bridge) connecting two carbon atoms between the 4' and 2' position of the nucleoside sugar unit,

thereby forming a bicyclic sugar. Generally, a LNA includes a nucleobase (e.g., one of A, C, G, or T). In various embodiments, a LNA with a cytosine nucleobase includes a modified cytosine nucleobase (e.g., a 5-methylcytosine nucleobase).

[00385] In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a LNA at a 4th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a LNA at a 7th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a LNA at a 9th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a LNA at a 12th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a LNA at a 15th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a LNA at a 17th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a LNA at a 20th position of the antisense oligonucleotide.

[00386] In various embodiments, antisense oligonucleotides disclosed herein (e.g., SMN2 parent oligonucleotides and/or SMN2 oligonucleotide variants) comprise two LNAs located at two different positions of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a first LNA at a fourth position of the antisense oligonucleotide and a second LNA at a 20th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a first LNA at a 7th position of the antisense oligonucleotide and a second LNA at a 15th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a first LNA at a 7th position of the antisense oligonucleotide and a second LNA at a 17th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a first LNA at a 9th position of the antisense oligonucleotide and a second LNA at a 17th position of the antisense oligonucleotide.

[00387] In various embodiments, antisense oligonucleotides disclosed herein (e.g., SMN2 parent oligonucleotides and/or SMN2 oligonucleotide variants) comprise three LNAs located at three different positions of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a first LNA at a 4th position

of the antisense oligonucleotide, a second LNA at a 12th position of the antisense oligonucleotide, and a third LNA at a 20th position of the antisense oligonucleotide.

Antisense Oligonucleotides with One or more Spacers

[00388] In various embodiments, antisense oligonucleotides comprise one or more spacers. In particular embodiments, an antisense oligonucleotide includes one spacer. In particular embodiments, an antisense oligonucleotide includes two spacers. In particular embodiments, an antisense oligonucleotide includes three spacers. Generally, a spacer refers to a nucleoside-replacement group lacking a nucleotide base and wherein the nucleoside sugar moiety is replaced by a non-sugar substitute group. The non-sugar substitute group is not capable of linking to a nucleobase, but is capable of linking with the 3' and 5' positions of nucleosides adjacent to the spacer through an internucleoside linking group.

[00389] In certain embodiments, an oligonucleotide with one or more spacers, such as disclosed herein, may be an oligonucleotide with 5 to 100 oligonucleotide units in length, for example, 10 to 60 oligonucleotide units in length, for example, 12 to 50 oligonucleotide units in length, 14 to 40 oligonucleotide units in length, 10 to 30 oligonucleotide units in length, for example, 14 to 30 oligonucleotide units in length, for example, 14 to 25 or 15 to 22 oligonucleotide units in length, or 18, 19, 20, 21, 22, 23, 24, or 25 oligonucleotide units in length. As used herein, an "oligonucleotide unit" refers to either a nucleoside (e.g., a nucleoside which includes a sugar and/or a nucleobase) or a nucleoside-replacement group (e.g., a spacer) of the oligonucleotide.

[00390] In particular embodiments, oligonucleotides with one or more spacers are 25 oligonucleotide units in length. In particular embodiments, the oligonucleotides with one or more spacers are 23 oligonucleotide units in length. In particular embodiments, the oligonucleotides with one or more spacers are 21 oligonucleotide units in length. In particular embodiments, the oligonucleotides with one or more spacers are 19 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 18 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 19 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 20 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 21 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 22 oligonucleotide units in length. In various embodiments, the

oligonucleotides with one or more spacers are at least 23 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 24 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 25 oligonucleotide units in length.

[00391] In various embodiments, a STMN2 AON comprises a sequence that shares at least 80% identity with an equal length portion of any one of SEQ ID NOs: 1451-1664. In various embodiments, a STMN2 AON comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1451-1664. In various embodiments, a STMN2 AON comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1451-1664. In various embodiments, a STMN2 AON comprises a sequence that shares at least 95% identity with an equal length portion of any one of SEQ ID NOs: 1451-1664. In various embodiments, a STMN2 AON comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 1451-1664.

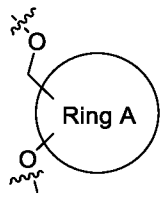
[00392] In various embodiments, a KCNQ2 AON comprises a sequence that shares at least 80% identity with an equal length portion of any one of SEQ ID NOs: 4402-4468, SEQ ID NOs: 4469-4476, and SEQ ID NOs: 4477-4530. In various embodiments, a KCNQ2 AON comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 4402-4468, SEQ ID NOs: 4469-4476, and SEQ ID NOs: 4477-4530. In various embodiments, a KCNQ2 AON comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 4402-4468, SEQ ID NOs: 4469-4476, and SEQ ID NOs: 4477-4530. In various embodiments, a KCNQ2 AON comprises a sequence that shares at least 95% identity with an equal length portion of any one of SEQ ID NOs: 4402-4468, SEQ ID NOs: 4469-4476, and SEQ ID NOs: 4477-4530. In various embodiments, a KCNQ2 AON comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 4402-4468, SEQ ID NOs: 4469-4476, and SEQ ID NOs: 4477-4530.

[00393] In various embodiments, a UNC13A AON comprises a sequence that shares at least 80% identity with an equal length portion of any one of SEQ ID NOs: 9596-9696 or SEQ ID NOs: 10670-10779. In various embodiments, a UNC13A AON comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 9596-9696 or SEQ ID NOs: 10670-10779. In various embodiments, a UNC13A AON comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 9596-9696 or SEQ ID NOs: 10670-10779. In various embodiments, a UNC13A AON comprises a sequence that shares at least 95% identity with an equal length portion of any one of SEQ ID NOs: 9596-

9696 or SEQ ID NOs: 10670-10779. In various embodiments, a UNC13A AON comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 9596-9696 or SEQ ID NOs: 10670-10779.

[00394] In various embodiments, a SMN2 AON comprises a sequence that shares at least 80% identity with an equal length portion of any one of SEQ ID NOs: 10574-10640 and SEQ ID NOs: 10644-10651. In various embodiments, a SMN2 AON comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 10574-10640 and SEQ ID NOs: 10644-10651. In various embodiments, a SMN2 AON comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 10574-10640 and SEQ ID NOs: 10644-10651. In various embodiments, a SMN2 AON comprises a sequence that shares at least 95% identity with an equal length portion of any one of SEQ ID NOs: 10574-10640 and SEQ ID NOs: 10644-10651. In various embodiments, a SMN2 AON comprises a sequence that shares at least 99% identity with an equal length portion of any one of SEQ ID NOs: 10574-10640 and SEQ ID NOs: 10644-10651. In various embodiments, a SMN2 AON comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 10574-10640 and SEQ ID NOs: 10644-10651.

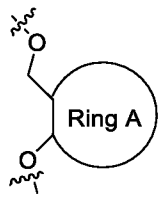
[00395] In some embodiments, the spacer is of Formula (X):



Formula (X)

wherein ring A is as defined herein.

[00396] In some embodiments, the spacer is of Formula (Xa):



Formula (Xa)

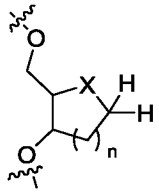
wherein ring A is as defined herein and the -CH_2-O- group is on a ring A atom adjacent to the -O- group.

[00397] As generally defined herein, ring A of formulae (X) and (Xa), is an optionally substituted 4-8 member monocyclic cycloalkyl group (*e.g.* ring A is cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl) or a 4-8 member monocyclic heterocyclyl group, wherein

the heterocyclyl group contains 1 or 2 heteroatoms selected from O, S and N (*e.g.* ring A is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepanyl). In some embodiments, ring A is tetrahydrofuranyl. In some embodiments, ring A is tetrahydropyranyl. In some embodiments, ring A is pyrrolidinyl. In some embodiments, ring A is cyclopentyl. In some embodiments, the monocyclic cycloalkyl or monocyclic heterocyclyl is not further substituted. In some embodiments, the cycloalkyl or heterocyclyl is further substituted with 0, 1, 2 or 3 substituents selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH_2)OMe, -O(CH_2)$_2$OMe and CN.

[00398] In some embodiments, tetrahydrofuranyl is substituted with 1 or 2 substituents selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH_2)OMe, -O(CH_2)$_2$OMe and CN. In some embodiments, tetrahydrofuranyl is substituted with 2 substituents selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH_2)OMe, -O(CH_2)$_2$OMe and CN. In some embodiments, tetrahydrofuranyl is substituted with 1 substituent selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH_2)OMe, -O(CH_2)$_2$OMe and CN. In some embodiments, tetrahydrofuranyl is substituted with -O(CH_2)$_2$OMe.

[00399] In some embodiments, the spacer is represented by Formula (I), wherein:

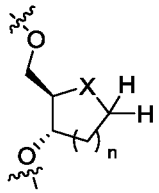


Formula (I)

X is selected from -CH_2- and -O-; and

n is 0, 1, 2 or 3.

[00400] In some embodiments, the spacer is represented by Formula (I'), wherein:

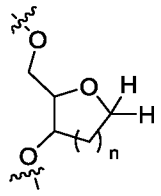


Formula (I')

X is selected from -CH_2-and -O-; and

n is 0, 1, 2 or 3.

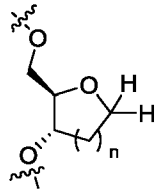
[00401] In some embodiments, the spacer is represented by Formula (Ia), wherein:



Formula (Ia)

and n is 0, 1, 2 or 3.

[00402] In some embodiments, the spacer is represented by Formula (Ia'), wherein:



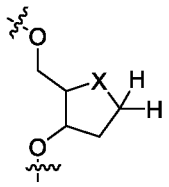
Formula (Ia')

and n is 0, 1, 2 or 3.

[00403] As generally defined herein, X is selected from -CH_2- and -O-. In some embodiments, X is -CH_2-. In other embodiments, X is -O-.

[00404] As generally defined herein, n is 0, 1, 2 or 3. In some embodiments, n is 0. In some embodiments, n is 1 or 2. In some embodiments, n is 1. In other embodiments, n is 2. In certain embodiments, n is 3.

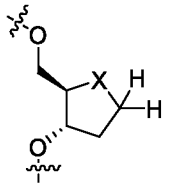
[00405] In some embodiments, the spacer is represented by Formula (II), wherein:



Formula (II)

X is selected from -CH_2- and -O-.

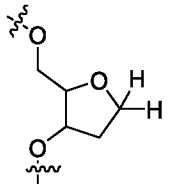
[00406] In some embodiments, the spacer is represented by Formula (II'), wherein:



Formula (II')

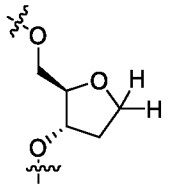
X is selected from -CH_2-and -O.

[00407] In some embodiments, the spacer is represented by Formula (Iia), wherein:



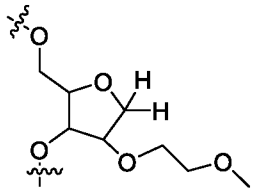
Formula (Iia).

[00408] In some embodiments, the spacer is represented by Formula (Iia'), wherein:



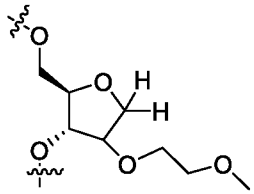
Formula (Iia').

[00409] In some embodiments, the spacer is represented by Formula (IIib), wherein:



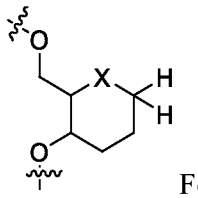
Formula (IIib).

[00410] In some embodiments, the spacer is represented by Formula (IIib'), wherein:



Formula (IIib').

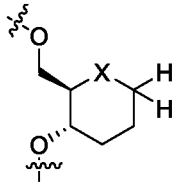
[00411] In some embodiments, the spacer is represented by Formula (III), wherein:



Formula (III)

X is selected from $-CH_2-$ and -O-.

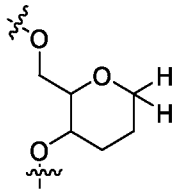
[00412] In some embodiments, the spacer is represented by Formula (III'), wherein:



Formula (III')

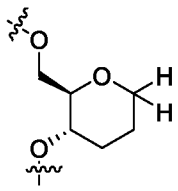
X is selected from -CH_2-and -O.

[00413] In some embodiments, the spacer is represented by Formula (IIIa), wherein:



Formula (IIIa).

[00414] In some embodiments, the spacer is represented by Formula (IIIa'), wherein:



Formula (IIIa').

[00415] In some embodiments, the open positions of Formulae (I), (I'), (Ia), (Ia'), (II), (II'), (Iia), (Iia'), (III), (III'), (IIIa) and (IIIa') (*i.e.*, the positions not specifically depicted as bearing exclusively hydrogen atoms, including the -CH_2- group of X) are further substituted with 0-3 substituents selected from halo (*e.g.*, -F, -Cl), - OMe, -OEt -O(CH_2)OMe, -O(CH_2)$_2$OMe and CN. In some embodiments, Formulae (I), (I'), (Ia), (Ia'), (II), (II'), (Iia), (Iia'), (III), (III'), (IIIa) and (IIIa') are not further substituted.

STMN2

[00416] As described further below, a STMN2 oligonucleotide with one or more spacers is described in reference to a corresponding STMN2 parent oligonucleotide. In various embodiments, a STMN2 oligonucleotide with a spacer differs from a STMN2 parent oligonucleotide in that the spacer replaces a nucleoside in the STMN2 parent oligonucleotide. As used hereafter, the "position" of the STMN2 oligonucleotide refers to a particular location as counted from the 5' end of the STMN2 oligonucleotide. In various embodiments, the spacer replaces a nucleoside at any one of positions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 of the STMN2 parent oligonucleotide. In particular

embodiments, a spacer replaces a nucleoside at one of positions 7, 8, 11, 14, 16, 19, or 22 of the STMN2 parent oligonucleotide.

[00417] In various embodiments, a STMN2 oligonucleotide includes one spacer that replaces a nucleoside in the STMN2 parent oligonucleotide (e.g., one spacer replaces one nucleoside of the STMN2 parent oligonucleotide). In particular embodiments, the spacer replaces a nucleoside between positions 9 and 15 of the STMN2 parent oligonucleotide. In particular embodiments, the spacer replaces a nucleoside between positions 9 and 12 of the STMN2 parent oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 10 of the STMN2 parent oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 11 of the STMN2 parent oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 12 of the STMN2 parent oligonucleotide. In particular embodiments, the spacer replaces a nucleoside between positions 12 and 16 of the STMN2 parent oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 15 of the STMN2 parent oligonucleotide.

[00418] In various embodiments, a STMN2 oligonucleotide including one spacer has 2 segments, where at least one of the 2 segments has at most 11 linked nucleosides. For example, the STMN2 oligonucleotide may be 23 oligonucleotide units in length, and the spacer can be located at position 12. Therefore, the STMN2 oligonucleotide has 2 segments divided by the spacer, where both of the 2 segments are 11 nucleobases in length. In various embodiments, a STMN2 oligonucleotide including one spacer has 2 segments, where at least one of the 2 segments has at most 10 linked nucleosides. For example, the STMN2 oligonucleotide may be 21 oligonucleotide units in length, and the spacer can be located at position 11. Therefore, the STMN2 oligonucleotide has 2 segments divided by the spacer, where both of the 2 segments are 10 nucleobases in length. As another example, the STMN2 oligonucleotide may be 25 oligonucleotide units in length, and the spacer can be located at position 15. Therefore, the STMN2 oligonucleotide has 2 segments divided by the spacer, where one of the 2 segments is 14 nucleobases in length and the second of the 2 segments is 10 nucleobases in length.

[00419] In various embodiments, a STMN2 oligonucleotide includes two spacers that each replace a nucleoside in the STMN2 parent oligonucleotide (e.g., two spacers replace two separate nucleosides of the STMN2 parent oligonucleotide). In various embodiments, a first spacer and a second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, at least 7 nucleobases, at least 8 nucleobases, at least 9 nucleobases, or at least 10 nucleobases in the oligonucleotide. In particular embodiments, a first spacer and a second spacer are separated by at

least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases. In particular embodiments, the first spacer and the second spacer are not adjacent to one another in the oligonucleotide.

[00420] In particular embodiments, the first spacer replaces a nucleoside between positions 7 and 11 of the STMN2 parent oligonucleotide. In various embodiments, the first spacer replaces a nucleoside between positions 8 and 11, positions 9 and 11, positions 10 and 11, positions 7 and 10, positions 7 and 9, positions 7 and 8, positions 8 and 10, positions 8 and 9, or positions 9 and 10 of the STMN2 parent oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 14 and 22 of the STMN2 parent oligonucleotide. In various embodiments, the second spacer replaces a nucleoside between positions 15 and 22, positions 16 and 22, positions 17 and 22, position 18 and 22, position 19 and 22, positions 20 and 22, positions 21 and 22, positions 15 and 21, position 16 and 21, positions 17 and 21, positions 18 and 21, positions 19 and 21, positions 20 and 21, positions 15 and 20, positions 16 and 20, positions 17 and 20, positions 18 and 20, positions 19 and 20, positions 15 and 19, positions 16 and 19, positions 17 and 19, positions 18 and 19, positions 15 and 18, position 16 and 18, position 17 and 18, positions 15 and 17, positions 16 and 17, or positions 15 and 16 of the STMN2 parent oligonucleotide.

[00421] In preferred embodiments, the first spacer replaces a nucleoside at position 7 of the STMN2 parent oligonucleotide and the second spacer replaces a nucleoside at position 14 of the STMN2 parent oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 8 of the STMN2 parent oligonucleotide and the second spacer replaces a nucleoside at position 16 of the STMN2 parent oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 11 of the STMN2 parent oligonucleotide and the second spacer replaces a nucleoside at position 22 of the STMN2 parent oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 9 of the STMN2 parent oligonucleotide and the second spacer replaces a nucleoside at position 19 of the STMN2 parent oligonucleotide.

[00422] In various embodiments, a STMN2 oligonucleotide includes three spacers that each replace a nucleoside in the STMN2 parent oligonucleotide (e.g., three spacers replace three separate nucleosides of the STMN2 parent oligonucleotide). In particular embodiments, the first spacer replaces a nucleoside between positions 7 and 11 of the STMN2 parent oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 14 and 22 of the STMN2 parent oligonucleotide. In particular embodiments, the third spacer replaces a nucleoside between positions 21 and 24 of the STMN2 parent oligonucleotide. In some

embodiments, the first spacer replaces a nucleoside between positions 2 and 5 of the STMN2 parent oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 8 and 12 of the STMN2 parent oligonucleotide. In particular embodiments, the third spacer replaces a nucleoside between positions 18 and 22 of the STMN2 parent oligonucleotide.

[00423] In various embodiments, the three spacers in a STMN2 oligonucleotide are positioned such that each of the four segments of the STMN2 oligonucleotide are at most 7 linked nucleosides in length. For example, a STMN2 oligonucleotide may have a first segment with 7 linked nucleosides connected to a first spacer, then a second segment with 7 linked nucleosides connected on one end to the first spacer and connected on another end to a second spacer, then a third segment with 6 linked nucleosides connected on one end to the second spacer and connected on another end to a third spacer, then a fourth segment with 6 linked nucleosides connected to the third spacer.

[00424] In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more adenosine or thymine nucleosides (as opposed to guanine or cytosine nucleosides). For example, the one or more spacers can replace one, two, three, four, five, six, seven, eight, or nine adenosine or thymine nucleosides in the oligonucleotide. In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more guanine or cytosine nucleosides (as opposed to adenosine or thymine nucleosides). For example, the one or more spacers can replace one, two, three, four, five, six, seven, eight, or nine guanine or cytosine nucleosides in the oligonucleotide. In various embodiments, the spacers are positioned in the oligonucleotide to replace an equal number of adenosine/thymine nucleosides and guanine/cytosine nucleosides. For example, a first spacer in the oligonucleotide may replace an adenosine/thymine nucleoside and a second spacer in the oligonucleotide may replace a guanine/cytosine nucleoside.

[00425] In various embodiments, the one or more spacers are positioned in the oligonucleotide to control the sequence content in the oligonucleotide. For example, the one or more spacers are positioned such that at least one of the spacers is located adjacent to a guanine group. In various embodiments, an oligonucleotide with spacers can include one spacer adjacent to a guanine group, two spacers adjacent to guanine groups, three spacers adjacent to guanine groups, four spacers adjacent to guanine groups, or five spacers adjacent to guanine groups. In one embodiment, if counting from the 5' end of the oligonucleotide, a spacer immediately precedes a guanine group in the sequence. Thus, in various embodiments, an oligonucleotide with spacers

can include one spacer that immediately precedes a guanine group, two spacers that each immediately precede a guanine group, three spacers that each immediately precede a guanine group, four spacers that each immediately precede a guanine group, or five spacers that each immediately precede a guanine group. In one embodiment, if counting from the 5' end of the oligonucleotide, a guanine group is immediately succeeded by a spacer. Thus, in various embodiments, an oligonucleotide with spacers can include one spacer that immediately succeeds a guanine group, two spacers that each immediately succeed a guanine group, three spacers that each immediately succeed a guanine group, four spacers that each immediately succeed a guanine group, or five spacers that each immediately succeed a guanine group. In various embodiments, the spacers in the oligonucleotide can be positioned to maximize the number of spacers adjacent to guanine groups.

[00426] In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more adenosine or thymine nucleosides such that the one or more spacers are located adjacent guanine groups. For example, two spacers can replace adenosine or thymine nucleosides in the oligonucleotide, each of the two spacers being located adjacent to a guanine group.

[00427] In various embodiments, the STMN2 oligonucleotide with one or more spacers has a particular GC content. As used herein, GC content (or guanine-cytosine content) is the percentage of nitrogenous bases in the oligonucleotide that are either guanine (G) or cytosine (C). In various embodiments, the STMN2 oligonucleotide with one or more spacers has at least 10% GC content, at least 20% GC content, at least 25% GC content, at least 30% GC content, at least 35% GC content, at least 40% GC content, at least 45% GC content, at least 50% GC content, at least 55% GC content, at least 60% GC content, at least 65% GC content, at least 75% GC content, at least 80% GC content, at least 85% GC content, at least 90% GC content, or at least 95% GC content. In particular embodiments, the STMN2 oligonucleotide with one or more spacers has at least 30% GC content. In particular embodiments, the STMN2 oligonucleotide with one or more spacers has at least 40% GC content. In various embodiments, the one or more spacers are positioned in the STMN2 oligonucleotide to maximize GC content. For example, instead of selecting a guanine or cytosine for replacement by a spacer in the STMN2 oligonucleotide, a thymine or adenine can be selected for replacement by a spacer.

[00428] In various embodiments, a STMN2 oligonucleotide with spacers is designed such that 1) each segment of the STMN2 oligonucleotide has at most 7 linked nucleosides and 2) at least two, three, or four spacers are positioned adjacent to a guanine group. In some embodiments, a

STMN2 oligonucleotide with spacers is designed such that 1) each segment of the STMN2 oligonucleotide has at most 7 linked nucleosides and 2) each of two spacers precede a guanine group.

[00429] In various embodiments, the inclusion of one or more spacers in the STMN2 oligonucleotide does not decrease the effectiveness of the STMN2 oligonucleotide with the spacers in restoring full length STMN2 protein or full length STMN2 mRNA in comparison to the effect of a corresponding STMN2 parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the STMN2 oligonucleotide increases the effectiveness of the STMN2 oligonucleotide with the spacers in restoring full length STMN2 protein or full length STMN2 mRNA in comparison to the effect of a corresponding STMN2 parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the STMN2 oligonucleotide does not decrease the effectiveness of the STMN2 oligonucleotide with the spacers in reducing quantity of STMN2 transcripts with a cryptic exon in comparison to the effect of a corresponding STMN2 parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the STMN2 oligonucleotide increases the effectiveness of the STMN2 oligonucleotide with the spacers in reducing quantity of STMN2 transcripts with a cryptic exon in comparison to the effect of a corresponding STMN2 parent oligonucleotide.

[00430] Tables 12A, 12B, 13, and 14 document example STMN2 oligonucleotides with one or more spacers and their relation to corresponding STMN2 parent oligonucleotides. Each STMN2 oligonucleotide is assigned a sequence name. As used hereafter, the nomenclature of the sequence name is expressed as "X_spA" (for a STMN2 AON with one spacer), "X_spA_spB" (for a STMN2 AON with two spacers), or "X_spA_spB_spC" (for a STMN2 AON with three spacers). Here, "X" refers to the length of the STMN2 AON, "A" refers to the position in the STMN2 AON where the first spacer is located, "B" refers to the position in the STMN2 AON where the second spacer is located, and if present, "C" refers to the position in the STMN2 AON where the third spacer is located.

[00431] In various embodiments, STMN2 oligonucleotides include one spacer. In various embodiments, the STMN2 oligonucleotides are oligonucleotide variants, such as any one of a 23mer, 21mer, or 19mer. In various embodiments, the inclusion of a spacer divides up the STMN2 oligonucleotide into two separate segments, where at least one of the segments is at most 11 linked nucleosides in length. In various embodiments, the inclusion of a spacer divides up the STMN2 oligonucleotide into two separate segments, where at least one of the segments is at most 10 linked nucleosides in length.

[00432] In various embodiments, the spacer is located between positions 10 and 15 of the oligonucleotide. In various embodiments, the spacer is located between positions 10 and 12 of the oligonucleotide. In particular embodiments, the spacer is located at position 10 of the oligonucleotide. In particular embodiments, the spacer is located at position 11 of the oligonucleotide. In particular embodiments, the spacer is located at position 12 of the oligonucleotide. In particular embodiments, the spacer is located at position 15 of the oligonucleotide.

[00433] Example STMN2 AONs with one spacer are documented below in Table 12A.

Table 12A: Identification of STMN2 AONs with one spacer. Here, each STMN2 AON has 2 segments, where at least one of the segments has at most 11 linked nucleosides.

Sequence name	**Relation to STMN2 oligonucleotide variant**	**Sequence ID Number (SEQ ID NO)**	**Sequence* (where *X* indicates a nucleoside of the STMN2 parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
STMN2 parent oligonucleotide	N/A	1522	XXXXXXXXXXXXXXXXXXXXXXXXX (25mer)
STMN2 Oligonucleotide (25mer) with Spacer at position 15 (STMN2 AON 25_sp15)	Nucleoside at position 15 of 25mer is substituted with a spacer	1523	XXXXXXXXXXXXXX$\mathbf{S_{15}}$XXXXXXXXXX
STMN2 oligonucleotide variant (23mer)	N/A	1524	XXXXXXXXXXXXXXXXXXXXXXX (23mer)
STMN2 Oligonucleotide (23mer) with Spacer at position 12 (STMN2 AON 23_sp12)	Nucleoside at position 12 of 23mer is substituted with a spacer	1525	XXXXXXXXXXX$\mathbf{S_{12}}$XXXXXXXXXX
STMN2 oligonucleotide variant (21mer)	N/A	1526	XXXXXXXXXXXXXXXXXXXXX (21mer)
STMN2 Oligonucleotide (21mer) with Spacer at position 11 (STMN2 AON 21_sp11)	Nucleoside at position 11 of 21mer is substituted with a spacer	1527	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXX
STMN2 oligonucleotide variant (19mer)	N/A	1528	XXXXXXXXXXXXXXXXXXX (19mer)
STMN2 Oligonucleotide (19mer) with Spacer at position 10 (STMN2 AON 19_sp10)	Nucleoside at position 10 of 19mer is substituted with a spacer	1529	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00434] In various embodiments, STMN2 oligonucleotides include two spacers. In various embodiments, the inclusion of a spacer divides up the STMN2 oligonucleotide into three separate segments, where at least one of the segments is at most 7 linked nucleosides in length. Example STMN2 AONs with two spacers are documented below in Table 12B.

Table 12B: Identification of STMN2 AONs with two spacers. Here, each STMN2 AON has 3 segments, where at least one of the segments has at most 7 linked nucleosides.

Sequence name	**Relation to STMN2 parent oligonucleotide**	**Sequence ID Number (SEQ ID NO)**	**Sequence* (where *X* indicates a nucleoside of the STMN2 parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
STMN2 parent oligonucleotide	N/A	1530	XXXXXXXXXXXXXXXXXXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 11 and 22 (STMN2 AON 25_sp11sp22)	Nucleosides at positions 11 and 22 are each substituted with a spacer	1531	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXXX$\mathbf{S_{22}}$XXX
STMN2 Oligonucleotide with Spacers at positions 7 and 14 (STMN2 AON 25_sp7sp14)	Nucleosides at positions 7 and 14 are each substituted with a spacer	1532	XXXXXX$\mathbf{S_7}$XXXXXX$\mathbf{S_{14}}$XXXXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 8 and 19 (STMN2 AON 25_sp8sp19)	Nucleosides at positions 8 and 19 are substituted with spacers	1533	XXXXXXX$\mathbf{S_8}$XXXXXXXXXX$\mathbf{S_{19}}$XXXXXX

STMN2 Oligonucleotide with Spacers at positions 8 and 14 (STMN2 AON 25_sp8sp14)	Nucleosides at positions 8 and 14 are substituted with spacers	1534	XXXXXXX$\mathbf{S_8}$XXXXX$\mathbf{S_{14}}$XXXXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 9 and 14 (STMN2 AON 25_sp9sp14)	Nucleosides at positions 9 and 14 are substituted with spacers	1535	XXXXXXXX$\mathbf{S_9}$XXXX$\mathbf{S_{14}}$XXXXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 10 and 14 (STMN2 AON 25_sp10sp14)	Nucleosides at positions 10 and 14 are substituted with spacers	1536	XXXXXXXXX$\mathbf{S_{10}}$XXX$\mathbf{S_{14}}$XXXXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 11 and 14 (STMN2 AON 25_sp11sp14)	Nucleosides at positions 11 and 14 are substituted with spacers	1537	XXXXXXXXXX$\mathbf{S_{11}}$XX$\mathbf{S_{14}}$XXXXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 8 and 15 (STMN2 AON 25_sp8sp15)	Nucleosides at positions 8 and 15 are substituted with spacers	1538	XXXXXXX$\mathbf{S_8}$XXXXXX$\mathbf{S_{15}}$XXXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 9 and 15 (STMN2 AON 25_sp9sp15)	Nucleosides at positions 9 and 15 are substituted with spacers	1539	XXXXXXXX$\mathbf{S_9}$XXXXX$\mathbf{S_{15}}$XXXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 10 and 15 (STMN2 AON 25_sp10sp15)	Nucleosides at positions 10 and 15 are substituted with spacers	1540	XXXXXXXXX$\mathbf{S_{10}}$XXXX$\mathbf{S_{15}}$XXXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 11 and 15 (STMN2 AON 25_sp11sp15)	Nucleosides at positions 11 and 15 are substituted with spacers	1541	XXXXXXXXXX$\mathbf{S_{11}}$XXX$\mathbf{S_{15}}$XXXXXXXXX

STMN2 Oligonucleotide with Spacers at positions 8 and 16 (STMN2 AON 25_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers	1542	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 9 and 16 (STMN2 AON 25_sp9sp16)	Nucleosides at positions 9 and 16 are substituted with spacers	1543	XXXXXXXX$\mathbf{S_9}$XXXXXX$\mathbf{S_{16}}$XXXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 10 and 16 (STMN2 AON 25_sp10sp16)	Nucleosides at positions 10 and 16 are substituted with spacers	1544	XXXXXXXXX$\mathbf{S_{10}}$XXXXX$\mathbf{S_{16}}$XXXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 11 and 16 (STMN2 AON 25_sp11sp16)	Nucleosides at positions 11 and 16 are substituted with spacers	1545	XXXXXXXXXX$\mathbf{S_{11}}$XXXX$\mathbf{S_{16}}$XXXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 8 and 17 (STMN2 AON 25_sp8sp17)	Nucleosides at positions 8 and 17 are substituted with spacers	1546	XXXXXXX$\mathbf{S_8}$XXXXXXXX$\mathbf{S_{17}}$XXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 9 and 17 (STMN2 AON 25_sp9sp17)	Nucleosides at positions 9 and 17 are substituted with spacers	1547	XXXXXXXX$\mathbf{S_9}$XXXXXXX$\mathbf{S_{17}}$XXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 10 and 17 (STMN2 AON 25_sp10sp17)	Nucleosides at positions 10 and 17 are substituted with spacers	1548	XXXXXXXXX$\mathbf{S_{10}}$XXXXXX$\mathbf{S_{17}}$XXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 11 and 17 (STMN2 AON 25_sp11sp17)	Nucleosides at positions 11 and 17 are substituted with spacers	1549	XXXXXXXXXX$\mathbf{S_{11}}$XXXXX$\mathbf{S_{17}}$XXXXXXXX

STMN2 Oligonucleotide with Spacers at positions 8 and 18 (STMN2 ATON 25_sp8sp18)	Nucleosides at positions 8 and 18 are substituted with spacers	1550	XXXXXXX$\mathbf{S_8}$XXXXXXXXX$\mathbf{S_{18}}$XXXXXXX
STMN2 Oligonucleotide with Spacers at positions 9 and 18 (STMN2 AON 25_sp9sp18)	Nucleosides at positions 9 and 18 are substituted with spacers	1551	XXXXXXXX$\mathbf{S_9}$XXXXXXXX$\mathbf{S_{18}}$XXXXXXX
STMN2 Oligonucleotide with Spacers at positions 10 and 18 (STMN2 AON 25_sp10sp18)	Nucleosides at positions 10 and 18 are substituted with spacers	1552	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX
STMN2 Oligonucleotide with Spacers at positions 11 and 18 (STMN2 AON 25_sp11sp18)	Nucleosides at positions 11 and 18 are substituted with spacers	1553	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXX$\mathbf{S_{18}}$XXXXXXX
STMN2 Oligonucleotide with Spacers at positions 9 and 19 (STMN2 AON 25_sp9sp19)	Nucleosides at positions 9 and 19 are substituted with spacers	1554	XXXXXXXX$\mathbf{S_9}$XXXXXXXXX$\mathbf{S_{19}}$XXXXXX
STMN2 Oligonucleotide with Spacers at positions 10 and 19 (STMN2 AON 25_sp10sp19)	Nucleosides at positions 10 and 19 are substituted with spacers	1555	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXX$\mathbf{S_{19}}$XXXXXX
STMN2 Oligonucleotide with Spacers at positions 11 and 19 (STMN2 AON 25_sp11sp19)	Nucleosides at positions 11 and 19 are substituted with spacers	1556	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXX$\mathbf{S_{19}}$XXXXXX
STMN2 Oligonucleotide with Spacers at positions 9 and 20 (STMN2 AON 25_sp9sp20)	Nucleosides at positions 9 and 20 are substituted with spacers	1557	XXXXXXXX$\mathbf{S_9}$XXXXXXXXXX$\mathbf{S_{20}}$XXXXX

STMN2 Oligonucleotide with Spacers at positions 10 and 20 (STMN2 AON 25_sp10sp20)	Nucleosides at positions 10 and 20 are substituted with spacers	1558	XXXXXXXXX**S$_{10}$**XXXXXXXXX**S$_{20}$**XXXXX
STMN2 Oligonucleotide with Spacers at positions 11 and 20 (STMN2 AON 25_sp11sp20)	Nucleosides at positions 11 and 20 are substituted with spacers	1559	XXXXXXXXXX**S$_{11}$**XXXXXXXX**S$_{20}$**XXXXX
STMN2 Oligonucleotide with Spacers at positions 10 and 21 (STMN2 AON 25_sp10sp21)	Nucleosides at positions 10 and 21 are substituted with spacers	1560	XXXXXXXXX**S$_{10}$**XXXXXXXXXX**S$_{21}$**XXXX
STMN2 Oligonucleotide with Spacers at positions 11 and 21 (STMN2 AON 25_sp11sp21)	Nucleosides at positions 11 and 21 are substituted with spacers	1561	XXXXXXXXXX**S$_{11}$**XXXXXXXXX**S$_{21}$**XXXX
STMN2 Oligonucleotide with Spacers at positions 4 and 15 (STMN2 AON 25_sp4sp15)	Nucleosides at positions 4 and 15 are substituted with spacers	1562	XXXS$_4$XXXXXXXXXS$_{15}$XXXXXXXXX
STMN2 Oligonucleotide with Spacers at positions 7 and 19 (STMN2 AON 25_sp7sp19)	Nucleosides at positions 7 and 19 are substituted with spacers	1563	XXXXXX**S$_7$**XXXXXXXXXX**S$_{19}$**XXXXX
STMN2 Oligonucleotide with Spacers at positions 7 and 18 (STMN2 AON 25_sp7sp18)	Nucleosides at positions 7 and 18 are substituted with spacers	1564	XXXXXX**S$_7$**XXXXXXXXXX**S$_{18}$**XXXXXX
STMN2 Oligonucleotide with Spacers at positions 9 and 21 (STMN2 AON 25_sp9sp21)	Nucleosides at positions 9 and 21 are substituted with spacers	1565	XXXXXXXX**S$_9$**XXXXXXXXXX**S$_{21}$**XXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00435] In various embodiments, STMN2 oligonucleotides include three spacers. The inclusion of three spacers divides up the STMN2 oligonucleotide into four separate segments. In various embodiments, the three spacers are located at different positions of the STMN2 oligonucleotide such that each of the segments of the STMN2 oligonucleotide are at most 7 linked nucleosides in length.

[00436] In various embodiments, STMN2 AONs with three spacers are 27 oligonucleotide units in length. For example, a STMN2 AON with three spacers can divide up a STMN2 AON into four separate segments. In various embodiments, each of the four separate segments are 6 oligonucleotide units in length. For example, the STMN2 AON may be as follows (from 5' to 3' end): a first segment of 6 linked nucleosides, a first spacer, a second segment of 6 linked nucleosides, a second spacer, a third segment of 6 linked nucleosides, a third spacer, and a fourth segment of 6 linked nucleosides.

[00437] Example STMN2 AONs with three spacers are documented below in Table 13.

Table 13: Identification of STMN2 AONs or AON variants with three spacers. Here, each STMN2 AON has 4 segments, where each segment has at most 7 linked nucleosides.

Sequence name	**Relation to STMN2 parent oligonucleotide**	**Sequence ID Number (SEQ ID NO)**	**Sequence* (where *X* indicates a nucleoside of the STMN2 parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
STMN2 Oligonucleotide with Spacers at positions 8 and 16 and 24 (STMN2	Nucleosides at positions 8 and 16 and 24 are substituted with spacers	1566	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXX$\mathbf{S_{24}}$X

AON 25_sp8sp16sp24)			
STMN2 Oligonucleotide with Spacers at positions 8 and 16 and 23 (STMN2 AON 25_sp8sp16sp23)	Nucleosides at positions 8 and 16 and 23 are substituted with spacers	1567	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXX$\mathbf{S_{23}}$XX
STMN2 Oligonucleotide with Spacers at positions 2 and 10 and 18 (STMN2 AON 25_sp8sp16sp23)	Nucleosides at positions 2 and 10 and 18 are substituted with spacers	1568	X$\mathbf{S_2}$XXXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX
STMN2 Oligonucleotide with Spacers at positions 3 and 10 and 18 (STMN2 AON 25_sp8sp16sp23)	Nucleosides at positions 3 and 10 and 18 are substituted with spacers	1569	XX$\mathbf{S_3}$XXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX
STMN2 Oligonucleotide with Spacers at positions 4 and 12 and 19 (STMN2 AON 25_sp4sp12sp19)	Nucleosides at positions 4 and 12 and 19 are substituted with spacers	1570	XXX$\mathbf{S_4}$XXXXXXX$\mathbf{S_{12}}$XXXXXX$\mathbf{S_{19}}$XXXXXX
STMN2 Oligonucleotide with Spacers at positions 8 and 13 and 18 (STMN2 AON 25_sp8sp13sp18)	Nucleosides at positions 8 and 13 and 18 are substituted with spacers	1571	XXXXXXX$\mathbf{S_8}$XXXX$\mathbf{S_{13}}$XXXX$\mathbf{S_{18}}$XXXXXXX
STMN2 Oligonucleotide with Spacers at positions 5 and 13 and 21 (STMN2 AON 25_sp5sp13sp21)	Nucleosides at positions 5 and 13 and 21 are substituted with spacers	1572	XXXX$\mathbf{S_5}$XXXXXXX$\mathbf{S_{13}}$XXXXXXX$\mathbf{S_{21}}$XXXX
STMN2 Oligonucleotide with Spacers at positions 7 and 13 and 19 (STMN2	Nucleosides at positions 7 and 13 and 19 are substituted with spacers	1573	XXXXXX$\mathbf{S_7}$XXXXX$\mathbf{S_{13}}$XXXXX$\mathbf{S_{19}}$XXXXXX

AON 25_sp7sp13sp19)			
STMN2 Oligonucleotide with Spacers at positions 6 and 13 and 20 (STMN2 AON 25_sp6sp13sp20)	Nucleosides at positions 6 and 13 and 20 are substituted with spacers	1574	XXXXX$\mathbf{S_6}$XXXXXX$\mathbf{S_{13}}$XXXXXX$\mathbf{S_{20}}$XXXXX
STMN2 Oligonucleotide with Spacers at positions 8 and 11 and 19 (STMN2 AON 25_sp8sp11sp19)	Nucleosides at positions 8 and 11 and 19 are substituted with spacers	1575	XXXXXXX$\mathbf{S_8}$XX$\mathbf{S_{11}}$XXXXXXX$\mathbf{S_{19}}$XXXXXX
STMN2 Oligonucleotide with Spacers at positions 8 and 11 and 16 (STMN2 AON 23_sp8sp11sp16)	Nucleosides at positions 8 and 11 and 16 are substituted with spacers	1576	XXXXXXX$\mathbf{S_8}$XX$\mathbf{S_{11}}$XXXX$\mathbf{S_{16}}$XXXXXX
STMN2 Oligonucleotide with Spacers at positions 7 and 14 and 22 (STMN2 AON 23_sp7sp14sp22)	Nucleosides at positions 7 and 14 and 22 are substituted with spacers	1577	XXXXXX$\mathbf{S_7}$XXXXXX$\mathbf{S_{14}}$XXXXXXX$\mathbf{S_{22}}$XXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00438] In various embodiments, STMN2 AONs with one or more spacers are reduced in length in comparison to the STMN2 AONs described above in Tables 12B and 13. For example, such

STMN2 AONs may be STMN2 oligonucleotide variants with one or more spacers. In various embodiments, the STMN2 oligonucleotide variants with one or more spacers are 23mers, 21mers, or 19mers. In various embodiments, STMN2 oligonucleotide variants include two spacers such that the STMN2 oligonucleotide variant includes three segments that are divided up by the two spacers. In various embodiments, at least one of the three segments has at most 7 linked nucleosides. In various embodiments, each of the three segments has at most 7 linked nucleosides. Example STMN2 oligonucleotide variants with one or more spacers are shown below in Table 14.

Table 14: STMN2 AONs or AON variants with three spacers. Here, each STMN2 AON variant has 3 segments, where each segment has at most 7 linked nucleosides.

Sequence name	**Relation to STMN2 oligonucleotide variant**	**Sequence ID Number (SEQ ID NO)**	**Sequence* (where *X* indicates a nucleoside of the STMN2 oligonucleotide variant and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
STMN2 oligonucleotide variant (23mer)	N/A	1578	XXXXXXXXXXXXXXXXXXXXXXX (23mer)
STMN2 Variant Oligonucleotide (23mer) with Spacers at positions 8 and 16 (STMN2 AON variant 23_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers	1579	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXX
STMN2 oligonucleotide variant (21mer)	N/A	1580	XXXXXXXXXXXXXXXXXXXXX (21mer)
STMN2 Variant Oligonucleotide (21mer) with Spacers at positions 5 and 12 (STMN2 AON variant 21_sp5sp12)	Nucleosides at positions 5 and 12 are substituted with spacers	1581	XXXX$\mathbf{S_5}$XXXXXX$\mathbf{S_{12}}$XXXXXXXXX
STMN2 Variant Oligonucleotide (21mer) with Spacers at positions 8 and 16 (STMN2	Nucleosides at positions 8 and 16 are substituted with spacers	1582	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXX

AON variant 21_sp8sp16)			
STMN2 Variant Oligonucleotide (21mer) with Spacers at positions 6 and 14 (STMN2 AON variant 21_sp6sp14)	Nucleosides at positions 6 and 14 are substituted with spacers	1583	XXXXX$\mathbf{S_6}$XXXXXXX$\mathbf{S_{14}}$XXXXXXX
STMN2 Variant Oligonucleotide (21mer) with Spacers at positions 8 and 14 (STMN2 AON variant 21_sp8sp14)	Nucleosides at positions 8 and 14 are substituted with spacers	1584	XXXXXXX$\mathbf{S_8}$XXXXX$\mathbf{S_{14}}$XXXXXXX
STMN2 Variant Oligonucleotide (21mer) with Spacers at positions 8 and 14 (STMN2 AON variant 21_sp8sp14)	Nucleosides at positions 6 and 20 are substituted with spacers	1585	XXXXX$\mathbf{S_6}$XXXXXXXXXXXXX$\mathbf{S_{20}}$X
STMN2 oligonucleotide variant (19mer)	N/A	1586	XXXXXXXXXXXXXXXXXX (19mer)
STMN2 Variant Oligonucleotide (19mer) with Spacers at positions 5 and 12 (STMN2 AON variant 19_sp5sp12)	Nucleosides at positions 5 and 12 are substituted with spacers	1587	XXXX$\mathbf{S_5}$XXXXXX$\mathbf{S_{12}}$XXXXXXX
STMN2 Variant Oligonucleotide (19mer) with Spacers at positions 8 and 15 (STMN2 AON variant 19_sp8sp15)	Nucleosides at positions 8 and 15 are substituted with spacers	1588	XXXXXXX$\mathbf{S_8}$XXXXXX$\mathbf{S_{15}}$XXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate

linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00439] In some embodiments, an antisense oligonucleotide disclosed herein (e.g., STMN2 parent oligonucleotides and/or STMN2 oligonucleotide variants) comprise one or more spacers as well as one or more locked nucleic acids (LNAs). In some embodiments, an antisense oligonucleotide disclosed herein (e.g., STMN2 parent oligonucleotides and/or STMN2 oligonucleotide variants) comprises two spacers and two LNAs. In some embodiments, an antisense oligonucleotide disclosed herein (e.g., STMN2 parent oligonucleotides and/or STMN2 oligonucleotide variants) comprises two spacers and three LNAs.

[00440] In various embodiments, a spacer and a LNA are located adjacent to one another in an antisense oligonucleotide. For example, if counting from 5' to 3', a LNA can be located at a 7th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 9th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 15th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 17th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide.

[00441] In particular embodiments, a first spacer is located adjacent to a first LNA and a second spacer is located adjacent to a second LNA in an antisense oligonucleotide. For example, if counting from 5' to 3', a first LNA can be located at a 7th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 15th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a first LNA can be located at a 7th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 17th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if

counting from 5' to 3', a first LNA can be located at a 9th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 17th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide.

[00442] In various embodiments, one or more spacers and one or more LNAs are not located adjacent to one another in an antisense oligonucleotide. For example, if counting from 5' to 3', a LNA can be located at a 4th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As example, if counting from 5' to 3', a LNA can be located at a 20th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide. In particular embodiments, if counting from 5' to 3', a first LNA can be located at a 4th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 20th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. In particular embodiments, if counting from 5' to 3', a first LNA can be located at a 4th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 12th position of the antisense oligonucleotide, a second spacer can be located at a 16th position of the antisense oligonucleotide, and a third LNA can be located at a 20th position of the antisense oligonucleotide.

KCNQ2

[00443] As described further below, a KCNQ2 oligonucleotide with one or more spacers is described in reference to a corresponding KCNQ2 parent oligonucleotide or a KCNQ2 variant oligonucleotide. In various embodiments, a KCNQ2 oligonucleotide with a spacer differs from a KCNQ2 parent oligonucleotide or a KCNQ2 variant oligonucleotide in that the spacer replaces a nucleoside in the KCNQ2 parent oligonucleotide or a KCNQ2 variant oligonucleotide. As used hereafter, the "position" of the KCNQ2 oligonucleotide refers to a particular location as counted from the 5' end of the KCNQ2 oligonucleotide. In various embodiments, the spacer replaces a nucleoside at any one of positions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 of the KCNQ2 parent oligonucleotide or a KCNQ2 variant oligonucleotide. In particular embodiments, a spacer replaces a nucleoside at one of positions 7, 8, 11, 14, 16, 19, or 22 of the KCNQ2 parent oligonucleotide or a KCNQ2 variant oligonucleotide.

[00444] In various embodiments, a KCNQ2 oligonucleotide includes one spacer that replaces a nucleoside in the KCNQ2 oligonucleotide (e.g., one spacer replaces one nucleoside of the KCNQ2 oligonucleotide). In particular embodiments, the spacer replaces a nucleoside between positions 9 and 15 of the KCNQ2 oligonucleotide. In particular embodiments, the spacer replaces a nucleoside between positions 9 and 12 of the KCNQ2 oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 10 of the KCNQ2 oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 11 of the KCNQ2 oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 12 of the KCNQ2 oligonucleotide. In particular embodiments, the spacer replaces a nucleoside between positions 12 and 16 of the KCNQ2 oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 15 of the KCNQ2 oligonucleotide.

[00445] In various embodiments, a KCNQ2 oligonucleotide including one spacer has 2 segments, where at least one of the 2 segments has at most 11 linked nucleosides. For example, the KCNQ2 oligonucleotide may be 23 oligonucleotide units in length, and the spacer can be located at position 12. Therefore, the KCNQ2 oligonucleotide has 2 segments divided by the spacer, where both of the 2 segments are 11 nucleobases in length. In various embodiments, a KCNQ2 oligonucleotide including one spacer has 2 segments, where at least one of the 2 segments has at most 10 linked nucleosides. For example, the KCNQ2 oligonucleotide may be 21 oligonucleotide units in length, and the spacer can be located at position 11. Therefore, the KCNQ2 oligonucleotide has 2 segments divided by the spacer, where both of the 2 segments are 10 nucleobases in length. As another example, the KCNQ2 oligonucleotide may be 25 oligonucleotide units in length, and the spacer can be located at position 15. Therefore, the KCNQ2 oligonucleotide has 2 segments divided by the spacer, where one of the 2 segments is 14 nucleobases in length and the second of the 2 segments is 10 nucleobases in length.

[00446] In various embodiments, a KCNQ2 oligonucleotide includes two spacers that each replace a nucleoside in the KCNQ2 oligonucleotide (e.g., two spacers replace two separate nucleosides of the KCNQ2 oligonucleotide). In various embodiments, a first spacer and a second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, at least 7 nucleobases, at least 8 nucleobases, at least 9 nucleobases, or at least 10 nucleobases in the oligonucleotide. In particular embodiments, a first spacer and a second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases. In particular embodiments, the first spacer and the second spacer are not adjacent to one another in the oligonucleotide.

[00447] In particular embodiments, the first spacer replaces a nucleoside between positions 7 and 11 of the KCNQ2 oligonucleotide. In various embodiments, the first spacer replaces a nucleoside between positions 8 and 11, positions 9 and 11, positions 10 and 11, positions 7 and 10, positions 7 and 9, positions 7 and 8, positions 8 and 10, positions 8 and 9, or positions 9 and 10 of the KCNQ2 oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 14 and 22 of the KCNQ2 oligonucleotide. In various embodiments, the second spacer replaces a nucleoside between positions 15 and 22, positions 16 and 22, positions 17 and 22, position 18 and 22, position 19 and 22, positions 20 and 22, positions 21 and 22, positions 15 and 21, position 16 and 21, positions 17 and 21, positions 18 and 21, positions 19 and 21, positions 20 and 21, positions 15 and 20, positions 16 and 20, positions 17 and 20, positions 18 and 20, positions 19 and 20, positions 15 and 19, positions 16 and 19, positions 17 and 19, positions 18 and 19, positions 15 and 18, position 16 and 18, position 17 and 18, positions 15 and 17, positions 16 and 17, or positions 15 and 16 of the KCNQ2 oligonucleotide.

[00448] In preferred embodiments, the first spacer replaces a nucleoside at position 7 of the KCNQ2 oligonucleotide and the second spacer replaces a nucleoside at position 14 of the KCNQ2 oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 7 of the KCNQ2 oligonucleotide and the second spacer replaces a nucleoside at position 19 of the KCNQ2 oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 8 of the KCNQ2 oligonucleotide and the second spacer replaces a nucleoside at position 16 of the KCNQ2 oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 8 of the KCNQ2 oligonucleotide and the second spacer replaces a nucleoside at position 15 of the KCNQ2 oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 11 of the KCNQ2 oligonucleotide and the second spacer replaces a nucleoside at position 22 of the KCNQ2 oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 9 of the KCNQ2 oligonucleotide and the second spacer replaces a nucleoside at position 19 of the KCNQ2 oligonucleotide.

[00449] In various embodiments, a KCNQ2 oligonucleotide includes three spacers that each replace a nucleoside in the KCNQ2 oligonucleotide (e.g., three spacers replace three separate nucleosides of the KCNQ2 oligonucleotide). In particular embodiments, the first spacer replaces a nucleoside between positions 7 and 11 of the KCNQ2 oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 14 and 22 of the KCNQ2 oligonucleotide. In particular embodiments, the third spacer replaces a nucleoside

between positions 21 and 24 of the KCNQ2 oligonucleotide. In some embodiments, the first spacer replaces a nucleoside between positions 2 and 5 of the KCNQ2 oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 8 and 12 of the KCNQ2 oligonucleotide. In particular embodiments, the third spacer replaces a nucleoside between positions 18 and 22 of the KCNQ2 oligonucleotide.

[00450] In various embodiments, the three spacers in a KCNQ2 oligonucleotide are positioned such that each of the four segments of the KCNQ2 oligonucleotide are at most 7 linked nucleosides in length. For example, a KCNQ2 oligonucleotide may have a first segment with 7 linked nucleosides connected to a first spacer, then a second segment with 7 linked nucleosides connected on one end to the first spacer and connected on another end to a second spacer, then a third segment with 6 linked nucleosides connected on one end to the second spacer and connected on another end to a third spacer, then a fourth segment with 6 linked nucleosides connected to the third spacer.

[00451] In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more adenosine or thymine nucleosides (as opposed to guanine or cytosine nucleosides). For example, the one or more spacers can replace one, two, three, four, five, six, seven, eight, or nine adenosine or thymine nucleosides in the oligonucleotide. In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more guanine or cytosine nucleosides (as opposed to adenosine or thymine nucleosides). For example, the one or more spacers can replace one, two, three, four, five, six, seven, eight, or nine guanine or cytosine nucleosides in the oligonucleotide. In various embodiments, the spacers are positioned in the oligonucleotide to replace an equal number of adenosine/thymine nucleosides and guanine/cytosine nucleosides. For example, a first spacer in the oligonucleotide may replace an adenosine/thymine nucleoside and a second spacer in the oligonucleotide may replace a guanine/cytosine nucleoside.

[00452] In various embodiments, the one or more spacers are positioned in the oligonucleotide to control the sequence content in the oligonucleotide. For example, the one or more spacers are positioned such that at least one of the spacers is located adjacent to a guanine group. In various embodiments, an oligonucleotide with spacers can include one spacer adjacent to a guanine group, two spacers adjacent to guanine groups, three spacers adjacent to guanine groups, four spacers adjacent to guanine groups, or five spacers adjacent to guanine groups. In one embodiment, if counting from the 5' end of the oligonucleotide, a spacer immediately precedes a guanine group in the sequence. Thus, in various embodiments, an oligonucleotide with spacers

can include one spacer that immediately precedes a guanine group, two spacers that each immediately precede a guanine group, three spacers that each immediately precede a guanine group, four spacers that each immediately precede a guanine group, or five spacers that each immediately precede a guanine group. In one embodiment, if counting from the 5' end of the oligonucleotide, a guanine group is immediately succeeded by a spacer. Thus, in various embodiments, an oligonucleotide with spacers can include one spacer that immediately succeeds a guanine group, two spacers that each immediately succeed a guanine group, three spacers that each immediately succeed a guanine group, four spacers that each immediately succeed a guanine group, or five spacers that each immediately succeed a guanine group. In various embodiments, the spacers in the oligonucleotide can be positioned to maximize the number of spacers adjacent to guanine groups.

[00453] In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more adenosine or thymine nucleosides such that the one or more spacers are located adjacent guanine groups. For example, two spacers can replace adenosine or thymine nucleosides in the oligonucleotide, each of the two spacers being located adjacent to a guanine group.

[00454] In various embodiments, the KCNQ2 oligonucleotide with one or more spacers has a particular GC content. As used herein, GC content (or guanine-cytosine content) is the percentage of nitrogenous bases in the oligonucleotide that are either guanine (G) or cytosine (C). In various embodiments, the KCNQ2 oligonucleotide with one or more spacers has at least 10% GC content, at least 20% GC content, at least 25% GC content, at least 30% GC content, at least 35% GC content, at least 40% GC content, at least 45% GC content, at least 50% GC content, at least 55% GC content, at least 60% GC content, at least 65% GC content, at least 75% GC content, at least 80% GC content, at least 85% GC content, at least 90% GC content, or at least 95% GC content. In particular embodiments, the KCNQ2 oligonucleotide with one or more spacers has at least 30% GC content. In particular embodiments, the KCNQ2 oligonucleotide with one or more spacers has at least 40% GC content. In various embodiments, the one or more spacers are positioned in the KCNQ2 oligonucleotide to maximize GC content. For example, instead of selecting a guanine or cytosine for replacement by a spacer in the KCNQ2 oligonucleotide, a thymine or adenine can be selected for replacement by a spacer.

[00455] In various embodiments, a KCNQ2 oligonucleotide with spacers is designed such that 1) each segment of the KCNQ2 oligonucleotide has at most 7 linked nucleosides and 2) at least two, three, or four spacers are positioned adjacent to a guanine group. In some embodiments, a

KCNQ2 oligonucleotide with spacers is designed such that 1) each segment of the KCNQ2 oligonucleotide has at most 7 linked nucleosides and 2) each of two spacers precede a guanine group.

[00456] In various embodiments, the inclusion of one or more spacers in the KCNQ2 oligonucleotide does not decrease the effectiveness of the KCNQ2 oligonucleotide with the spacers in restoring full length KCNQ2 protein or full length KCNQ2 mRNA in comparison to the effect of a corresponding KCNQ2 parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the KCNQ2 oligonucleotide increases the effectiveness of the KCNQ2 oligonucleotide with the spacers in restoring full length KCNQ2 protein or full length KCNQ2 mRNA in comparison to the effect of a corresponding KCNQ2 parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the KCNQ2 oligonucleotide does not decrease the effectiveness of the KCNQ2 oligonucleotide with the spacers in reducing quantity of KCNQ2 transcripts in comparison to the effect of a corresponding KCNQ2 parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the KCNQ2 oligonucleotide increases the effectiveness of the KCNQ2 oligonucleotide with the spacers in reducing quantity of KCNQ2 transcripts in comparison to the effect of a corresponding KCNQ2 parent oligonucleotide.

[00457] Tables 15A, 15B, 16, and 14 document example KCNQ2 oligonucleotides with one or more spacers and their relation to corresponding KCNQ2 parent oligonucleotides. Each KCNQ2 oligonucleotide is assigned a sequence name. As used hereafter, the nomenclature of the sequence name is expressed as "X_spA" (for a KCNQ2 AON with one spacer), "X_spA_spB" (for a KCNQ2 AON with two spacers), or "X_spA_spB_spC" (for a KCNQ2 AON with three spacers). Here, "X" refers to the length of the KCNQ2 AON, "A" refers to the position in the KCNQ2 AON where the first spacer is located, "B" refers to the position in the KCNQ2 AON where the second spacer is located, and if present, "C" refers to the position in the KCNQ2 AON where the third spacer is located.

[00458] In various embodiments, KCNQ2 oligonucleotides include one spacer. In various embodiments, the KCNQ2 oligonucleotides are oligonucleotide variants, such as any one of a 23mer, 21mer, or 19mer. In various embodiments, the inclusion of a spacer divides up the KCNQ2 oligonucleotide into two separate segments, where at least one of the segments is at most 11 linked nucleosides in length. In various embodiments, the inclusion of a spacer divides up the KCNQ2 oligonucleotide into two separate segments, where at least one of the segments is at most 10 linked nucleosides in length.

[00459] In various embodiments, the spacer is located between positions 10 and 15 of the oligonucleotide. In various embodiments, the spacer is located between positions 10 and 12 of the oligonucleotide. In particular embodiments, the spacer is located at position 10 of the oligonucleotide. In particular embodiments, the spacer is located at position 11 of the oligonucleotide. In particular embodiments, the spacer is located at position 12 of the oligonucleotide. In particular embodiments, the spacer is located at position 15 of the oligonucleotide. Example KCNQ2 AONs with one spacer are documented below in Table 15A.

Table 15A: Identification of KCNQ2 AONs with one spacer. Here, each KCNQ2 AON has 2 segments, where at least one of the segments has at most 11 linked nucleosides.

Sequence name	**Relation to KCNQ2 oligonucleotide variant**	**Sequence ID Number (SEQ ID NO)**	**Sequence* (where *X* indicates a nucleoside of the KCNQ2 parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
KCNQ2 parent oligonucleotide	N/A	4402	XXXXXXXXXXXXXXXXXXXXXXXXX (25mer)
KCNQ2 Oligonucleotide (25mer) with Spacer at position 15 (KCNQ2 AON 25_sp15)	Nucleoside at position 15 of 25mer is substituted with a spacer	4403	XXXXXXXXXXXXXX$\mathbf{S_{15}}$XXXXXXXXXX
KCNQ2 oligonucleotide variant (23mer)	N/A	444	XXXXXXXXXXXXXXXXXXXXXXX (23mer)
KCNQ2 Oligonucleotide (23mer) with Spacer at position 12 (KCNQ2 AON 23_sp12)	Nucleoside at position 12 of 23mer is substituted with a spacer	4405	XXXXXXXXXXX$\mathbf{S_{12}}$XXXXXXXXXX
KCNQ2 oligonucleotide variant (21mer)	N/A	4406	XXXXXXXXXXXXXXXXXXXXX (21mer)
KCNQ2 Oligonucleotide (21mer) with Spacer at position 11 (KCNQ2 AON 21_sp11)	Nucleoside at position 11 of 21mer is substituted with a spacer	4407	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXX
KCNQ2 oligonucleotide variant (19mer)	N/A	4408	XXXXXXXXXXXXXXXXXXX (19mer)
KCNQ2 Oligonucleotide (19mer) with Spacer at position 10 (KCNQ2 AON 19_sp10)	Nucleoside at position 10 of 19mer is substituted with a spacer	4409	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an

alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00460] In various embodiments, KCNQ2 oligonucleotides include two spacers. In various embodiments, the inclusion of a spacer divides up the KCNQ2 oligonucleotide into three separate segments, where at least one of the segments is at most 7 linked nucleosides in length. Example KCNQ2 AONs with two spacers are documented below in Table 15B.

Table 15B: Identification of KCNQ2 AONs with two spacers. Here, each KCNQ2 AON has 3 segments, where at least one of the segments has at most 7 linked nucleosides.

Sequence name	**Relation to KCNQ2 parent oligonucleotide**	**Sequence ID Number (SEQ ID NO)**	**Sequence* (where *X* indicates a nucleoside of the KCNQ2 parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
KCNQ2 parent oligonucleotide	N/A	4410	XXXXXXXXXXXXXXXXXXXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 11 and 22 (KCNQ2 AON 25_sp11sp22)	Nucleosides at positions 11 and 22 are each substituted with a spacer	4411	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXXX$\mathbf{S_{22}}$XXX
KCNQ2 Oligonucleotide with Spacers at positions 7 and 14 (KCNQ2 AON 25_sp7sp14)	Nucleosides at positions 7 and 14 are each substituted with a spacer	4412	XXXXXX$\mathbf{S_7}$XXXXXX$\mathbf{S_{14}}$XXXXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 8 and 19 (KCNQ2 AON 25_sp8sp19)	Nucleosides at positions 8 and 19 are substituted with spacers	4413	XXXXXXX$\mathbf{S_8}$XXXXXXXXXX$\mathbf{S_{19}}$XXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 8 and 14	Nucleosides at positions 8 and 14 are	4414	XXXXXXX$\mathbf{S_8}$XXXXX$\mathbf{S_{14}}$XXXXXXXXXX

(KCNQ2 AON 25_sp8sp14)	substituted with spacers		
KCNQ2 Oligonucleotide with Spacers at positions 9 and 14 (KCNQ2 AON 25_sp9sp14)	Nucleosides at positions 9 and 14 are substituted with spacers	4415	XXXXXXXX$\mathbf{S_9}$XXXX$\mathbf{S_{14}}$XXXXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 10 and 14 (KCNQ2 AON 25_sp10sp14)	Nucleosides at positions 10 and 14 are substituted with spacers	4416	XXXXXXXXX$\mathbf{S_{10}}$XXX$\mathbf{S_{14}}$XXXXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 11 and 14 (KCNQ2 AON 25_sp11sp14)	Nucleosides at positions 11 and 14 are substituted with spacers	4417	XXXXXXXXXX$\mathbf{S_{11}}$XX$\mathbf{S_{14}}$XXXXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 8 and 15 (KCNQ2 AON 25_sp8sp15)	Nucleosides at positions 8 and 15 are substituted with spacers	4418	XXXXXXX$\mathbf{S_8}$XXXXXX$\mathbf{S_{15}}$XXXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 9 and 15 (KCNQ2 AON 25_sp9sp15)	Nucleosides at positions 9 and 15 are substituted with spacers	4419	XXXXXXXX$\mathbf{S_9}$XXXXX$\mathbf{S_{15}}$XXXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 10 and 15 (KCNQ2 AON 25_sp10sp15)	Nucleosides at positions 10 and 15 are substituted with spacers	4420	XXXXXXXXX$\mathbf{S_{10}}$XXXX$\mathbf{S_{15}}$XXXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 11 and 15 (KCNQ2 AON 25_sp11sp15)	Nucleosides at positions 11 and 15 are substituted with spacers	4421	XXXXXXXXXX$\mathbf{S_{11}}$XXX$\mathbf{S_{15}}$XXXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 8 and 16	Nucleosides at positions 8 and 16 are substituted with spacers	4422	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXXXX

(KCNQ2 AON 25_sp8sp16)			
KCNQ2 Oligonucleotide with Spacers at positions 9 and 16 (KCNQ2 AON 25_sp9sp16)	Nucleosides at positions 9 and 16 are substituted with spacers	4423	XXXXXXXX$\mathbf{S_9}$XXXXXX$\mathbf{S_{16}}$XXXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 10 and 16 (KCNQ2 AON 25_sp10sp16)	Nucleosides at positions 10 and 16 are substituted with spacers	4424	XXXXXXXXX$\mathbf{S_{10}}$XXXXX$\mathbf{S_{16}}$XXXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 11 and 16 (KCNQ2 AON 25_sp11sp16)	Nucleosides at positions 11 and 16 are substituted with spacers	4425	XXXXXXXXXX$\mathbf{S_{11}}$XXXX$\mathbf{S_{16}}$XXXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 8 and 17 (KCNQ2 AON 25_sp8sp17)	Nucleosides at positions 8 and 17 are substituted with spacers	4426	XXXXXXX$\mathbf{S_8}$XXXXXXXX$\mathbf{S_{17}}$XXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 9 and 17 (KCNQ2 AON 25_sp9sp17)	Nucleosides at positions 9 and 17 are substituted with spacers	4427	XXXXXXXX$\mathbf{S_9}$XXXXXXX$\mathbf{S_{17}}$XXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 10 and 17 (KCNQ2 AON 25_sp10sp17)	Nucleosides at positions 10 and 17 are substituted with spacers	4428	XXXXXXXXX$\mathbf{S_{10}}$XXXXXX$\mathbf{S_{17}}$XXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 11 and 17 (KCNQ2 AON 25_sp11sp17)	Nucleosides at positions 11 and 17 are substituted with spacers	4429	XXXXXXXXXX$\mathbf{S_{11}}$XXXXX$\mathbf{S_{17}}$XXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 8 and 18	Nucleosides at positions 8 and 18 are substituted with spacers	4430	XXXXXXX$\mathbf{S_8}$XXXXXXXXX$\mathbf{S_{18}}$XXXXXXX

(KCNQ2 ATON 25_sp8sp18)			
KCNQ2 Oligonucleotide with Spacers at positions 9 and 18 (KCNQ2 AON 25_sp9sp18)	Nucleosides at positions 9 and 18 are substituted with spacers	4431	XXXXXXXX$\mathbf{S_9}$XXXXXXXX$\mathbf{S_{18}}$XXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 10 and 18 (KCNQ2 AON 25_sp10sp18)	Nucleosides at positions 10 and 18 are substituted with spacers	4432	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 11 and 18 (KCNQ2 AON 25_sp11sp18)	Nucleosides at positions 11 and 18 are substituted with spacers	4433	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXX$\mathbf{S_{18}}$XXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 9 and 19 (KCNQ2 AON 25_sp9sp19)	Nucleosides at positions 9 and 19 are substituted with spacers	4434	XXXXXXXX$\mathbf{S_9}$XXXXXXXXX$\mathbf{S_{19}}$XXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 10 and 19 (KCNQ2 AON 25_sp10sp19)	Nucleosides at positions 10 and 19 are substituted with spacers	4435	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXX$\mathbf{S_{19}}$XXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 11 and 19 (KCNQ2 AON 25_sp11sp19)	Nucleosides at positions 11 and 19 are substituted with spacers	4436	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXX$\mathbf{S_{19}}$XXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 9 and 20 (KCNQ2 AON 25_sp9sp20)	Nucleosides at positions 9 and 20 are substituted with spacers	4437	XXXXXXXX$\mathbf{S_9}$XXXXXXXXXX$\mathbf{S_{20}}$XXXXX
KCNQ2 Oligonucleotide with Spacers at positions 10 and 20	Nucleosides at positions 10 and 20 are substituted with spacers	4438	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXXX$\mathbf{S_{20}}$XXXXX

(KCNQ2 AON 25_sp10sp20)			
KCNQ2 Oligonucleotide with Spacers at positions 11 and 20 (KCNQ2 AON 25_sp11sp20)	Nucleosides at positions 11 and 20 are substituted with spacers	4439	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXX$\mathbf{S}_{20}$XXXXX
KCNQ2 Oligonucleotide with Spacers at positions 10 and 21 (KCNQ2 AON 25_sp10sp21)	Nucleosides at positions 10 and 21 are substituted with spacers	4440	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXXXX$\mathbf{S_{21}}$XXXX
KCNQ2 Oligonucleotide with Spacers at positions 11 and 21 (KCNQ2 AON 25_sp11sp21)	Nucleosides at positions 11 and 21 are substituted with spacers	4441	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXX$\mathbf{S_{21}}$XXXX
KCNQ2 Oligonucleotide with Spacers at positions 4 and 15 (KCNQ2 AON 25_sp4sp15)	Nucleosides at positions 4 and 15 are substituted with spacers	4442	XXX$\mathbf{S_4}$XXXXXXXXXX$\mathbf{S_{15}}$XXXXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 7 and 19 (KCNQ2 AON 25_sp7sp19)	Nucleosides at positions 7 and 19 are substituted with spacers	4443	XXXXXX$\mathbf{S_7}$XXXXXXXXXX$\mathbf{S_{19}}$XXXXX
KCNQ2 Oligonucleotide with Spacers at positions 7 and 18 (KCNQ2 AON 25_sp7sp18)	Nucleosides at positions 7 and 18 are substituted with spacers	4444	XXXXXX$\mathbf{S_7}$XXXXXXXXXX$\mathbf{S_{18}}$XXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 9 and 21 (KCNQ2 AON 25_sp9sp21)	Nucleosides at positions 9 and 21 are substituted with spacers	4445	XXXXXXXX$\mathbf{S_9}$XXXXXXXXXX$\mathbf{S_{21}}$XXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate

linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00461] In various embodiments, KCNQ2 oligonucleotides include three spacers. The inclusion of three spacers divides up the KCNQ2 oligonucleotide into four separate segments. In various embodiments, the three spacers are located at different positions of the KCNQ2 oligonucleotide such that each of the segments of the KCNQ2 oligonucleotide are at most 7 linked nucleosides in length. Example KCNQ2 AONs with three spacers are documented below in Table 16.

Table 16: Identification of KCNQ2 AONs or AON variants with three spacers. Here, each KCNQ2 AON has 4 segments, where each segment has at most 7 linked nucleosides.

Sequence name	**Relation to KCNQ2 parent oligonucleotide**	**Sequence ID Number (SEQ ID NO)**	**Sequence* (where *X* indicates a nucleoside of the KCNQ2 parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
KCNQ2 Oligonucleotide with Spacers at positions 8 and 16 and 24 (KCNQ2 AON 25_sp8sp16sp24)	Nucleosides at positions 8 and 16 and 24 are substituted with spacers	4446	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXX$\mathbf{S_{24}}$X
KCNQ2 Oligonucleotide with Spacers at positions 8 and 16 and 23 (KCNQ2 AON 25_sp8sp16sp23)	Nucleosides at positions 8 and 16 and 23 are substituted with spacers	4447	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXX$\mathbf{S_{23}}$XX
KCNQ2 Oligonucleotide with Spacers at positions 2 and 10 and 18 (KCNQ2 AON 25_sp8sp16sp23)	Nucleosides at positions 2 and 10 and 18 are substituted with spacers	4448	X$\mathbf{S_2}$XXXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 3 and 10	Nucleosides at positions 3 and 10 and 18	4449	XX$\mathbf{S_3}$XXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX

and 18 (KCNQ2 AON 25_sp8sp16sp23)	are substituted with spacers		
KCNQ2 Oligonucleotide with Spacers at positions 4 and 12 and 19 (KCNQ2 AON 25_sp4sp12sp19)	Nucleosides at positions 4 and 12 and 19 are substituted with spacers	4450	XXX$\mathbf{S_4}$XXXXXXX$\mathbf{S_{12}}$XXXXXX$\mathbf{S_{19}}$XXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 8 and 13 and 18 (KCNQ2 AON 25_sp8sp13sp18)	Nucleosides at positions 8 and 13 and 18 are substituted with spacers	4451	XXXXXXX$\mathbf{S_8}$XXXX$\mathbf{S_{13}}$XXXX$\mathbf{S_{18}}$XXXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 5 and 13 and 21 (KCNQ2 AON 25_sp5sp13sp21)	Nucleosides at positions 5 and 13 and 21 are substituted with spacers	4452	XXXX$\mathbf{S_5}$XXXXXXX$\mathbf{S_{13}}$XXXXXXX$\mathbf{S_{21}}$XXXX
KCNQ2 Oligonucleotide with Spacers at positions 7 and 13 and 19 (KCNQ2 AON 25_sp7sp13sp19)	Nucleosides at positions 7 and 13 and 19 are substituted with spacers	4453	XXXXXX$\mathbf{S_7}$XXXXX$\mathbf{S_{13}}$XXXXX$\mathbf{S_{19}}$XXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 6 and 13 and 20 (KCNQ2 AON 25_sp6sp13sp20)	Nucleosides at positions 6 and 13 and 20 are substituted with spacers	4454	XXXXX$\mathbf{S_6}$XXXXXX$\mathbf{S_{13}}$XXXXXX$\mathbf{S_{20}}$XXXXX
KCNQ2 Oligonucleotide with Spacers at positions 8 and 11 and 19 (KCNQ2 AON 25_sp8sp11sp19)	Nucleosides at positions 8 and 11 and 19 are substituted with spacers	4455	XXXXXXX$\mathbf{S_8}$XX$\mathbf{S_{11}}$XXXXXXX$\mathbf{S_{19}}$XXXXXX
KCNQ2 Oligonucleotide with Spacers at positions 8 and 11	Nucleosides at positions 8 and 11 and 16	4456	XXXXXXX$\mathbf{S_8}$XX$\mathbf{S_{11}}$XXXX$\mathbf{S_{16}}$XXXXXXX

and 16 (KCNQ2 AON 23_sp8sp11sp16)	are substituted with spacers		
KCNQ2 Oligonucleotide with Spacers at positions 7 and 14 and 22 (KCNQ2 AON 23_sp7sp14sp22)	Nucleosides at positions 7 and 14 and 22 are substituted with spacers	4457	XXXXXX$\mathbf{S_7}$XXXXXX$\mathbf{S_{14}}$XXXXXXX$\mathbf{S_{22}}$XXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00462] In various embodiments, KCNQ2 AONs with one or more spacers are reduced in length in comparison to the KCNQ2 AONs described above in Tables 15B and 16. For example, such KCNQ2 AONs may be KCNQ2 oligonucleotide variants with one or more spacers. In various embodiments, the KCNQ2 oligonucleotide variants with one or more spacers are 23mers, 21mers, or 19mers. In various embodiments, KCNQ2 oligonucleotide variants include two spacers such that the KCNQ2 oligonucleotide variant includes three segments that are divided up by the two spacers. In various embodiments, at least one of the three segments has at most 7 linked nucleosides. In various embodiments, each of the three segments has at most 7 linked nucleosides. Example KCNQ2 oligonucleotide variants with one or more spacers are shown below in Table 17.

Table 17: KCNQ2 AON variants with two spacers. Here, each KCNQ2 AON variant has 3 segments, where each segment has at most 7 linked nucleosides.

Sequence name	**Relation to KCNQ2 oligonucleotide variant**	**Sequence ID Number (SEQ ID NO)**	**Sequence* (where *X* indicates a nucleoside of the KCNQ2 oligonucleotide variant and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')

KCNQ2 oligonucleotide variant (23mer)	N/A	4458	XXXXXXXXXXXXXXXXXXXXXXX (23mer)
KCNQ2 Variant Oligonucleotide (23mer) with Spacers at positions 8 and 16 (KCNQ2 AON variant 23_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers	4459	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXX
KCNQ2 oligonucleotide variant (21mer)	N/A	4460	XXXXXXXXXXXXXXXXXXXXX (21mer)
KCNQ2 Variant Oligonucleotide (21mer) with Spacers at positions 5 and 12 (KCNQ2 AON variant 21_sp5sp12)	Nucleosides at positions 5 and 12 are substituted with spacers	4461	XXXX$\mathbf{S_5}$XXXXXX$\mathbf{S_{12}}$XXXXXXXXX
KCNQ2 Variant Oligonucleotide (21mer) with Spacers at positions 8 and 16 (KCNQ2 AON variant 21_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers	4462	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXX
KCNQ2 Variant Oligonucleotide (21mer) with Spacers at positions 6 and 14 (KCNQ2 AON variant 21_sp6sp14)	Nucleosides at positions 6 and 14 are substituted with spacers	4463	XXXXX$\mathbf{S_6}$XXXXXXX$\mathbf{S_{14}}$XXXXXXX
KCNQ2 Variant Oligonucleotide (21mer) with Spacers at positions 8 and 14 (KCNQ2 AON variant 21_sp8sp14)	Nucleosides at positions 8 and 14 are substituted with spacers	4464	XXXXXXX$\mathbf{S_8}$XXXXX$\mathbf{S_{14}}$XXXXXXX
KCNQ2 Variant Oligonucleotide (21mer) with	Nucleosides at positions 6 and 20 are	4465	XXXXX$\mathbf{S_6}$XXXXXXXXXXXX$\mathbf{S_{20}}$X

Spacers at positions 8 and 14 (KCNQ2 AON variant 21_sp8sp14)	substituted with spacers		
KCNQ2 oligonucleotide variant (19mer)	N/A	4466	XXXXXXXXXXXXXXXXXXX (19mer)
KCNQ2 Variant Oligonucleotide (19mer) with Spacers at positions 5 and 12 (KCNQ2 AON variant 19_sp5sp12)	Nucleosides at positions 5 and 12 are substituted with spacers	4467	XXXX$\mathbf{S_5}$XXXXXX$\mathbf{S_{12}}$XXXXXXX
KCNQ2 Variant Oligonucleotide (19mer) with Spacers at positions 8 and 15 (KCNQ2 AON variant 19_sp8sp15)	Nucleosides at positions 8 and 15 are substituted with spacers	4468	XXXXXXX$\mathbf{S_8}$XXXXXX$\mathbf{S_{15}}$XXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00463] In some embodiments, an antisense oligonucleotide disclosed herein (e.g., KCNQ2 parent oligonucleotides and/or KCNQ2 oligonucleotide variants) comprise one or more spacers as well as one or more locked nucleic acids (LNAs). In some embodiments, an antisense oligonucleotide disclosed herein (e.g., KCNQ2 parent oligonucleotides and/or KCNQ2 oligonucleotide variants) comprises two spacers and two LNAs. In some embodiments, an antisense oligonucleotide disclosed herein (e.g., KCNQ2 parent oligonucleotides and/or KCNQ2 oligonucleotide variants) comprises two spacers and three LNAs.

[00464] In various embodiments, a spacer and a LNA are located adjacent to one another in an antisense oligonucleotide. For example, if counting from 5' to 3', a LNA can be located at a 7th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 9th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 15th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 17th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide.

[00465] In particular embodiments, a first spacer is located adjacent to a first LNA and a second spacer is located adjacent to a second LNA in an antisense oligonucleotide. For example, if counting from 5' to 3', a first LNA can be located at a 7th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 15th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a first LNA can be located at a 7th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 17th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a first LNA can be located at a 9th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 17th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide.

[00466] In various embodiments, one or more spacers and one or more LNAs are not located adjacent to one another in an antisense oligonucleotide. For example, if counting from 5' to 3', a LNA can be located at a 4th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As example, if counting from 5' to 3', a LNA can be located at a 20th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide. In particular embodiments, if counting from 5' to 3', a first LNA can be located at a 4th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 20th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of

the antisense oligonucleotide. In particular embodiments, if counting from 5' to 3', a first LNA can be located at a 4th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 12th position of the antisense oligonucleotide, a second spacer can be located at a 16th position of the antisense oligonucleotide, and a third LNA can be located at a 20th position of the antisense oligonucleotide.

UNC13A

[00467] As described further below, a UNC13A oligonucleotide with one or more spacers is described in reference to a corresponding UNC13A parent oligonucleotide or a corresponding UNC13A variant oligonucleotide. In various embodiments, a UNC13A oligonucleotide with a spacer differs from a UNC13A parent oligonucleotide or an UNC13A variant oligonucleotide in that the spacer replaces a nucleoside in the UNC13A parent oligonucleotide or an UNC13A variant oligonucleotide. As used hereafter, the "position" of the UNC13A oligonucleotide refers to a particular location as counted from the 5' end of the UNC13A oligonucleotide. In various embodiments, the spacer replaces a nucleoside at any one of positions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 of the UNC13A parent oligonucleotide or an UNC13A variant oligonucleotide. In particular embodiments, a spacer replaces a nucleoside at one of positions 7, 8, 11, 14, 16, 19, or 22 of the UNC13A parent oligonucleotide or an UNC13A variant oligonucleotide.

[00468] In various embodiments, a UNC13A oligonucleotide includes one spacer that replaces a nucleoside in the UNC13A oligonucleotide (e.g., one spacer replaces one nucleoside of the UNC13A oligonucleotide). In particular embodiments, the spacer replaces a nucleoside between positions 9 and 15 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside between positions 9 and 12 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 10 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 11 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 12 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside between positions 12 and 16 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 15 of the UNC13A oligonucleotide.

[00469] In various embodiments, a UNC13A oligonucleotide including one spacer has 2 segments, where at least one of the 2 segments has at most 11 linked nucleosides. For example,

the UNC13A oligonucleotide may be 23 oligonucleotide units in length, and the spacer can be located at position 12. Therefore, the UNC13A oligonucleotide has 2 segments divided by the spacer, where both of the 2 segments are 11 nucleobases in length. In various embodiments, a UNC13A oligonucleotide including one spacer has 2 segments, where at least one of the 2 segments has at most 10 linked nucleosides. For example, the UNC13A oligonucleotide may be 21 oligonucleotide units in length, and the spacer can be located at position 11. Therefore, the UNC13A oligonucleotide has 2 segments divided by the spacer, where both of the 2 segments are 10 nucleobases in length. As another example, the UNC13A oligonucleotide may be 25 oligonucleotide units in length, and the spacer can be located at position 15. Therefore, the UNC13A oligonucleotide has 2 segments divided by the spacer, where one of the 2 segments is 14 nucleobases in length and the second of the 2 segments is 10 nucleobases in length.

[00470] In various embodiments, a UNC13A oligonucleotide includes two spacers that each replace a nucleoside in the UNC13A oligonucleotide (e.g., two spacers replace two separate nucleosides of the UNC13A oligonucleotide). In various embodiments, a first spacer and a second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, at least 7 nucleobases, at least 8 nucleobases, at least 9 nucleobases, or at least 10 nucleobases in the oligonucleotide. In particular embodiments, a first spacer and a second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases. In particular embodiments, the first spacer and the second spacer are not adjacent to one another in the oligonucleotide.

[00471] In particular embodiments, the first spacer replaces a nucleoside between positions 7 and 11 of the UNC13A oligonucleotide. In various embodiments, the first spacer replaces a nucleoside between positions 8 and 11, positions 9 and 11, positions 10 and 11, positions 7 and 10, positions 7 and 9, positions 7 and 8, positions 8 and 10, positions 8 and 9, or positions 9 and 10 of the UNC13A oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 14 and 22 of the UNC13A oligonucleotide. In various embodiments, the second spacer replaces a nucleoside between positions 15 and 22, positions 16 and 22, positions 17 and 22, position 18 and 22, position 19 and 22, positions 20 and 22, positions 21 and 22, positions 15 and 21, position 16 and 21, positions 17 and 21, positions 18 and 21, positions 19 and 21, positions 20 and 21, positions 15 and 20, positions 16 and 20, positions 17 and 20, positions 18 and 20, positions 19 and 20, positions 15 and 19, positions 16 and 19, positions 17 and 19, positions 18 and 19, positions 15 and 18, position 16 and 18, position 17 and 18, positions 15 and 17, positions 16 and 17, or positions 15 and 16 of the UNC13A oligonucleotide.

[00472] In preferred embodiments, the first spacer replaces a nucleoside at position 7 of the UNC13A oligonucleotide and the second spacer replaces a nucleoside at position 14 of the UNC13A oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 7 of the UNC13A oligonucleotide and the second spacer replaces a nucleoside at position 19 of the UNC13A oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 8 of the UNC13A parent oligonucleotide and the second spacer replaces a nucleoside at position 16 of the UNC13A parent oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 8 of the UNC13A oligonucleotide and the second spacer replaces a nucleoside at position 15 of the UNC13A oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 11 of the UNC13A oligonucleotide and the second spacer replaces a nucleoside at position 22 of the UNC13A oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 9 of the UNC13A oligonucleotide and the second spacer replaces a nucleoside at position 19 of the UNC13A oligonucleotide.

[00473] In various embodiments, a UNC13A oligonucleotide includes three spacers that each replace a nucleoside in the UNC13A oligonucleotide (e.g., three spacers replace three separate nucleosides of the UNC13A oligonucleotide). In particular embodiments, the first spacer replaces a nucleoside between positions 7 and 11 of the UNC13A oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 14 and 22 of the UNC13A oligonucleotide. In particular embodiments, the third spacer replaces a nucleoside between positions 21 and 24 of the UNC13A oligonucleotide. In some embodiments, the first spacer replaces a nucleoside between positions 2 and 5 of the UNC13A oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 8 and 12 of the UNC13A oligonucleotide. In particular embodiments, the third spacer replaces a nucleoside between positions 18 and 22 of the UNC13A oligonucleotide.

[00474] In various embodiments, the three spacers in a UNC13A oligonucleotide are positioned such that each of the four segments of the UNC13A oligonucleotide are at most 7 linked nucleosides in length. For example, a UNC13A oligonucleotide may have a first segment with 7 linked nucleosides connected to a first spacer, then a second segment with 7 linked nucleosides connected on one end to the first spacer and connected on another end to a second spacer, then a third segment with 6 linked nucleosides connected on one end to the second spacer and connected on another end to a third spacer, then a fourth segment with 6 linked nucleosides connected to the third spacer.

[00475] In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more adenosine or thymine nucleosides (as opposed to guanine or cytosine nucleosides). For example, the one or more spacers can replace one, two, three, four, five, six, seven, eight, or nine adenosine or thymine nucleosides in the oligonucleotide. In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more guanine or cytosine nucleosides (as opposed to adenosine or thymine nucleosides). For example, the one or more spacers can replace one, two, three, four, five, six, seven, eight, or nine guanine or cytosine nucleosides in the oligonucleotide. In various embodiments, the spacers are positioned in the oligonucleotide to replace an equal number of adenosine/thymine nucleosides and guanine/cytosine nucleosides. For example, a first spacer in the oligonucleotide may replace an adenosine/thymine nucleoside and a second spacer in the oligonucleotide may replace a guanine/cytosine nucleoside.

[00476] In various embodiments, the one or more spacers are positioned in the oligonucleotide to control the sequence content in the oligonucleotide. For example, the one or more spacers are positioned such that at least one of the spacers is located adjacent to a guanine group. In various embodiments, an oligonucleotide with spacers can include one spacer adjacent to a guanine group, two spacers adjacent to guanine groups, three spacers adjacent to guanine groups, four spacers adjacent to guanine groups, or five spacers adjacent to guanine groups. In one embodiment, if counting from the 5' end of the oligonucleotide, a spacer immediately precedes a guanine group in the sequence. Thus, in various embodiments, an oligonucleotide with spacers can include one spacer that immediately precedes a guanine group, two spacers that each immediately precede a guanine group, three spacers that each immediately precede a guanine group, four spacers that each immediately precede a guanine group, or five spacers that each immediately precede a guanine group. In one embodiment, if counting from the 5' end of the oligonucleotide, a guanine group is immediately succeeded by a spacer. Thus, in various embodiments, an oligonucleotide with spacers can include one spacer that immediately succeeds a guanine group, two spacers that each immediately succeed a guanine group, three spacers that each immediately succeed a guanine group, four spacers that each immediately succeed a guanine group, or five spacers that each immediately succeed a guanine group. In various embodiments, the spacers in the oligonucleotide can be positioned to maximize the number of spacers adjacent to guanine groups.

[00477] In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more adenosine or thymine nucleosides such that the one or more spacers are

located adjacent guanine groups. For example, two spacers can replace adenosine or thymine nucleosides in the oligonucleotide, each of the two spacers being located adjacent to a guanine group.

[00478] In various embodiments, the UNC13A oligonucleotide with one or more spacers has a particular GC content. As used herein, GC content (or guanine-cytosine content) is the percentage of nitrogenous bases in the oligonucleotide that are either guanine (G) or cytosine (C). In various embodiments, the UNC13A oligonucleotide with one or more spacers has at least 10% GC content, at least 20% GC content, at least 25% GC content, at least 30% GC content, at least 35% GC content, at least 40% GC content, at least 45% GC content, at least 50% GC content, at least 55% GC content, at least 60% GC content, at least 65% GC content, at least 75% GC content, at least 80% GC content, at least 85% GC content, at least 90% GC content, or at least 95% GC content. In particular embodiments, the UNC13A oligonucleotide with one or more spacers has at least 30% GC content. In particular embodiments, the UNC13A oligonucleotide with one or more spacers has at least 40% GC content. In various embodiments, the one or more spacers are positioned in the UNC13A oligonucleotide to maximize GC content. For example, instead of selecting a guanine or cytosine for replacement by a spacer in the UNC13A oligonucleotide, a thymine or adenine can be selected for replacement by a spacer.

[00479] In various embodiments, a UNC13A oligonucleotide with spacers is designed such that 1) each segment of the UNC13A oligonucleotide has at most 7 linked nucleosides and 2) at least two, three, or four spacers are positioned adjacent to a guanine group. In some embodiments, a UNC13A oligonucleotide with spacers is designed such that 1) each segment of the UNC13A oligonucleotide has at most 7 linked nucleosides and 2) each of two spacers precede a guanine group.

[00480] In various embodiments, the inclusion of one or more spacers in the UNC13A oligonucleotide does not decrease the effectiveness of the UNC13A oligonucleotide with the spacers in restoring full length UNC13A protein or full length UNC13A mRNA in comparison to the effect of a corresponding UNC13A parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the UNC13A oligonucleotide increases the effectiveness of the UNC13A oligonucleotide with the spacers in restoring full length UNC13A protein or full length UNC13A mRNA in comparison to the effect of a corresponding UNC13A parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the UNC13A oligonucleotide does not decrease the effectiveness of the UNC13A oligonucleotide with the spacers in reducing quantity of UNC13A transcripts in comparison to the effect of a

corresponding UNC13A parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the UNC13A oligonucleotide increases the effectiveness of the UNC13A oligonucleotide with the spacers in reducing quantity of UNC13A transcripts in comparison to the effect of a corresponding UNC13A parent oligonucleotide.

[00481] Tables 18A, 18B, 19, and 20 document example UNC13A oligonucleotides with one or more spacers and their relation to corresponding UNC13A parent oligonucleotides. Each UNC13A oligonucleotide is assigned a sequence name. As used hereafter, the nomenclature of the sequence name is expressed as "X_spA" (for a UNC13A AON with one spacer), "X_spA_spB" (for a UNC13A AON with two spacers), or "X_spA_spB_spC" (for a UNC13A AON with three spacers). Here, "X" refers to the length of the UNC13A AON, "A" refers to the position in the UNC13A AON where the first spacer is located, "B" refers to the position in the UNC13A AON where the second spacer is located, and if present, "C" refers to the position in the UNC13A AON where the third spacer is located.

[00482] In various embodiments, UNC13A oligonucleotides include one spacer. In various embodiments, the UNC13A oligonucleotides are oligonucleotide variants, such as any one of a 23mer, 21mer, or 19mer. In various embodiments, the inclusion of a spacer divides up the UNC13A oligonucleotide into two separate segments, where at least one of the segments is at most 11 linked nucleosides in length. In various embodiments, the inclusion of a spacer divides up the UNC13A oligonucleotide into two separate segments, where at least one of the segments is at most 10 linked nucleosides in length.

[00483] In various embodiments, the spacer is located between positions 10 and 15 of the oligonucleotide. In various embodiments, the spacer is located between positions 10 and 12 of the oligonucleotide. In particular embodiments, the spacer is located at position 10 of the oligonucleotide. In particular embodiments, the spacer is located at position 11 of the oligonucleotide. In particular embodiments, the spacer is located at position 12 of the oligonucleotide. In particular embodiments, the spacer is located at position 15 of the oligonucleotide. Example UNC13A AONs with one spacer are documented below in Table 18A.

Table 18A: Identification of UNC13A AONs with one spacer. Here, each UNC13A AON has 2 segments, where at least one of the segments has at most 11 linked nucleosides.

Sequence name	Relation to UNC13A oligonucleotide variant	Sequence ID Number	Sequence* (where *X* indicates a nucleoside of the UNC13A parent oligonucleotide and S_y indicates

		(SEQ ID NO)	presence of a Spacer where *y* denotes the position) (5' → 3')
UNC13A parent oligonucleotide	N/A	9596	XXXXXXXXXXXXXXXXXXXXXXXXX (25mer)
UNC13A Oligonucleotide (25mer) with Spacer at position 15 (UNC13A AON 25_sp15)	Nucleoside at position 15 of 25mer is substituted with a spacer	9597	XXXXXXXXXXXXXX$\mathbf{S_{15}}$XXXXXXXXXX
UNC13A oligonucleotide variant (23mer)	N/A	9598	XXXXXXXXXXXXXXXXXXXXXXX (23mer)
UNC13A Oligonucleotide (23mer) with Spacer at position 12 (UNC13A AON 23_sp12)	Nucleoside at position 12 of 23mer is substituted with a spacer	9599	XXXXXXXXXXX$\mathbf{S_{12}}$XXXXXXXXXX
UNC13A oligonucleotide variant (21mer)	N/A	9600	XXXXXXXXXXXXXXXXXXXXX (21mer)
UNC13A Oligonucleotide (21mer) with Spacer at position 11 (UNC13A AON 21_sp11)	Nucleoside at position 11 of 21mer is substituted with a spacer	9601	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXX
UNC13A oligonucleotide variant (19mer)	N/A	9602	XXXXXXXXXXXXXXXXXXX (19mer)
UNC13A Oligonucleotide (19mer) with Spacer at position 10 (UNC13A AON 19_sp10)	Nucleoside at position 10 of 19mer is substituted with a spacer	9603	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00484] In various embodiments, UNC13A oligonucleotides include two spacers. In various embodiments, the inclusion of a spacer divides up the UNC13A oligonucleotide into three separate segments, where at least one of the segments is at most 7 linked nucleosides in length. Example UNC13A AONs with two spacers are documented below in Table 18B.

Table 18B: Identification of UNC13A AONs with two spacers. Here, each UNC13A AON has 3 segments, where at least one of the segments has at most 7 linked nucleosides.

Sequence name	**Relation to UNC13A parent oligonucleotide**	**Sequence ID Number (SEQ ID NO)**	**Sequence* (where *X* indicates a nucleoside of the UNC13A parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
UNC13A parent oligonucleotide	N/A	9604	XXXXXXXXXXXXXXXXXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 22 (UNC13A AON 25_sp11sp22)	Nucleosides at positions 11 and 22 are each substituted with a spacer	9605	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXXX$\mathbf{S_{22}}$XXX
UNC13A Oligonucleotide with Spacers at positions 7 and 14 (UNC13A AON 25_sp7sp14)	Nucleosides at positions 7 and 14 are each substituted with a spacer	9606	XXXXXX$\mathbf{S_7}$XXXXXX$\mathbf{S_{14}}$XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 19 (UNC13A AON 25_sp8sp19)	Nucleosides at positions 8 and 19 are substituted with spacers	9607	XXXXXXX$\mathbf{S_8}$XXXXXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 14 (UNC13A AON 25_sp8sp14)	Nucleosides at positions 8 and 14 are substituted with spacers	9608	XXXXXXX$\mathbf{S_8}$XXXXX$\mathbf{S_{14}}$XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 14 (UNC13A AON 25_sp9sp14)	Nucleosides at positions 9 and 14 are substituted with spacers	9609	XXXXXXXX$\mathbf{S_9}$XXXX$\mathbf{S_{14}}$XXXXXXXXXX

UNC13A Oligonucleotide with Spacers at positions 10 and 14 (UNC13A AON 25_sp10sp14)	Nucleosides at positions 10 and 14 are substituted with spacers	9610	XXXXXXXXX$\mathbf{S_{10}}$XXX$\mathbf{S_{14}}$XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 14 (UNC13A AON 25_sp11sp14)	Nucleosides at positions 11 and 14 are substituted with spacers	9611	XXXXXXXXXX$\mathbf{S_{11}}$XX$\mathbf{S_{14}}$XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 15 (UNC13A AON 25_sp8sp15)	Nucleosides at positions 8 and 15 are substituted with spacers	9612	XXXXXXX$\mathbf{S_{8}}$XXXXXX$\mathbf{S_{15}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 15 (UNC13A AON 25_sp9sp15)	Nucleosides at positions 9 and 15 are substituted with spacers	9613	XXXXXXXX$\mathbf{S_{9}}$XXXXX$\mathbf{S_{15}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 15 (UNC13A AON 25_sp10sp15)	Nucleosides at positions 10 and 15 are substituted with spacers	9614	XXXXXXXXX$\mathbf{S_{10}}$XXXX$\mathbf{S_{15}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 15 (UNC13A AON 25_sp11sp15)	Nucleosides at positions 11 and 15 are substituted with spacers	9615	XXXXXXXXXX$\mathbf{S_{11}}$XXX$\mathbf{S_{15}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 16 (UNC13A AON 25_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers	9616	XXXXXXX$\mathbf{S_{8}}$XXXXXXX$\mathbf{S_{16}}$XXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 16 (UNC13A AON 25_sp9sp16)	Nucleosides at positions 9 and 16 are substituted with spacers	9617	XXXXXXXX$\mathbf{S_{9}}$XXXXXX$\mathbf{S_{16}}$XXXXXXXX

UNC13A Oligonucleotide with Spacers at positions 10 and 16 (UNC13A AON 25_sp10sp16)	Nucleosides at positions 10 and 16 are substituted with spacers	9618	XXXXXXXXX$\mathbf{S_{10}}$XXXXX$\mathbf{S_{16}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 16 (UNC13A AON 25_sp11sp16)	Nucleosides at positions 11 and 16 are substituted with spacers	9619	XXXXXXXXXX$\mathbf{S_{11}}$XXXX$\mathbf{S_{16}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 17 (UNC13A AON 25_sp8sp17)	Nucleosides at positions 8 and 17 are substituted with spacers	9620	XXXXXXX$\mathbf{S_{8}}$XXXXXXXX$\mathbf{S_{17}}$XXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 17 (UNC13A AON 25_sp9sp17)	Nucleosides at positions 9 and 17 are substituted with spacers	9621	XXXXXXXX$\mathbf{S_{9}}$XXXXXXX$\mathbf{S_{17}}$XXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 17 (UNC13A AON 25_sp10sp17)	Nucleosides at positions 10 and 17 are substituted with spacers	9622	XXXXXXXXX$\mathbf{S_{10}}$XXXXXX$\mathbf{S_{17}}$XXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 17 (UNC13A AON 25_sp11sp17)	Nucleosides at positions 11 and 17 are substituted with spacers	9623	XXXXXXXXXX$\mathbf{S_{11}}$XXXXX$\mathbf{S_{17}}$XXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 18 (UNC13A ATON 25_sp8sp18)	Nucleosides at positions 8 and 18 are substituted with spacers	9624	XXXXXXX$\mathbf{S_{8}}$XXXXXXXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 18 (UNC13A AON 25_sp9sp18)	Nucleosides at positions 9 and 18 are substituted with spacers	9625	XXXXXXXX$\mathbf{S_{9}}$XXXXXXXX$\mathbf{S_{18}}$XXXXXXX

UNC13A Oligonucleotide with Spacers at positions 10 and 18 (UNC13A AON 25_sp10sp18)	Nucleosides at positions 10 and 18 are substituted with spacers	9626	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 18 (UNC13A AON 25_sp11sp18)	Nucleosides at positions 11 and 18 are substituted with spacers	9627	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 19 (UNC13A AON 25_sp9sp19)	Nucleosides at positions 9 and 19 are substituted with spacers	9628	XXXXXXXX$\mathbf{S_{9}}$XXXXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 19 (UNC13A AON 25_sp10sp19)	Nucleosides at positions 10 and 19 are substituted with spacers	9629	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 19 (UNC13A AON 25_sp11sp19)	Nucleosides at positions 11 and 19 are substituted with spacers	9630	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 20 (UNC13A AON 25_sp9sp20)	Nucleosides at positions 9 and 20 are substituted with spacers	9631	XXXXXXXX$\mathbf{S_{9}}$XXXXXXXXXX$\mathbf{S_{20}}$XXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 20 (UNC13A AON 25_sp10sp20)	Nucleosides at positions 10 and 20 are substituted with spacers	9632	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXXX$\mathbf{S_{20}}$XXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 20 (UNC13A AON 25_sp11sp20)	Nucleosides at positions 11 and 20 are substituted with spacers	9633	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXX$\mathbf{S_{20}}$XXXXX

UNC13A Oligonucleotide with Spacers at positions 10 and 21 (UNC13A AON 25_sp10sp21)	Nucleosides at positions 10 and 21 are substituted with spacers	9634	XXXXXXXXX**S$_{10}$**XXXXXXXXXX**S$_{21}$**XXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 21 (UNC13A AON 25_sp11sp21)	Nucleosides at positions 11 and 21 are substituted with spacers	9635	XXXXXXXXXX**S$_{11}$**XXXXXXXXX**S$_{21}$**XXXX
UNC13A Oligonucleotide with Spacers at positions 4 and 15 (UNC13A AON 25_sp4sp15)	Nucleosides at positions 4 and 15 are substituted with spacers	9636	XXXS$_4$XXXXXXXXXXS$_{15}$XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 7 and 19 (UNC13A AON 25_sp7sp19)	Nucleosides at positions 7 and 19 are substituted with spacers	9637	XXXXXX**S$_7$**XXXXXXXXXXX**S$_{19}$**XXXXXX
UNC13A Oligonucleotide with Spacers at positions 7 and 18 (UNC13A AON 25_sp7sp18)	Nucleosides at positions 7 and 18 are substituted with spacers	9638	XXXXXX**S$_7$**XXXXXXXXXX**S$_{18}$**XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 21 (UNC13A AON 25_sp9sp21)	Nucleosides at positions 9 and 21 are substituted with spacers	9639	XXXXXXXX**S$_9$**XXXXXXXXXX**S$_{21}$**XXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00485] In various embodiments, UNC13A oligonucleotides include three spacers. The inclusion of three spacers divides up the UNC13A oligonucleotide into four separate segments. In various embodiments, the three spacers are located at different positions of the UNC13A oligonucleotide such that each of the segments of the UNC13A oligonucleotide are at most 7 linked nucleosides in length. Example UNC13A AONs with three spacers are documented below in Table 19.

Table 19: Identification of UNC13A AONs or AON variants with three spacers. Here, each UNC13A AON has 4 segments, where each segment has at most 7 linked nucleosides.

Sequence name	**Relation to UNC13A parent oligonucleotide**	**Sequence ID Number (SEQ ID NO)**	**Sequence* (where *X* indicates a nucleoside of the UNC13A parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
UNC13A Oligonucleotide with Spacers at positions 8 and 16 and 24 (UNC13A AON 25_sp8sp16sp24)	Nucleosides at positions 8 and 16 and 24 are substituted with spacers	9640	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXX$\mathbf{S_{24}}$X
UNC13A Oligonucleotide with Spacers at positions 8 and 16 and 23 (UNC13A AON 25_sp8sp16sp23)	Nucleosides at positions 8 and 16 and 23 are substituted with spacers	9641	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXX$\mathbf{S_{23}}$XX
UNC13A Oligonucleotide with Spacers at positions 2 and 10 and 18 (UNC13A AON 25_sp8sp16sp23)	Nucleosides at positions 2 and 10 and 18 are substituted with spacers	9642	X$\mathbf{S_2}$XXXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 3 and 10 and 18 (UNC13A AON 25_sp8sp16sp23)	Nucleosides at positions 3 and 10 and 18 are substituted with spacers	9643	XX$\mathbf{S_3}$XXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 4 and 12	Nucleosides at positions 4 and 12 and 19	9644	XXX$\mathbf{S_4}$XXXXXXX$\mathbf{S_{12}}$XXXXXX$\mathbf{S_{19}}$XXXXXX

and 19 (UNC13A AON 25_sp4sp12sp19)	are substituted with spacers		
UNC13A Oligonucleotide with Spacers at positions 8 and 13 and 18 (UNC13A AON 25_sp8sp13sp18)	Nucleosides at positions 8 and 13 and 18 are substituted with spacers	9645	XXXXXXX$\mathbf{S_8}$XXXX$\mathbf{S_{13}}$XXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 5 and 13 and 21 (UNC13A AON 25_sp5sp13sp21)	Nucleosides at positions 5 and 13 and 21 are substituted with spacers	9646	XXXX$\mathbf{S_5}$XXXXXXX$\mathbf{S_{13}}$XXXXXXX$\mathbf{S_{21}}$XXXX
UNC13A Oligonucleotide with Spacers at positions 7 and 13 and 19 (UNC13A AON 25_sp7sp13sp19)	Nucleosides at positions 7 and 13 and 19 are substituted with spacers	9647	XXXXXX$\mathbf{S_7}$XXXXX$\mathbf{S_{13}}$XXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 6 and 13 and 20 (UNC13A AON 25_sp6sp13sp20)	Nucleosides at positions 6 and 13 and 20 are substituted with spacers	9648	XXXXX$\mathbf{S_6}$XXXXXX$\mathbf{S_{13}}$XXXXXX$\mathbf{S_{20}}$XXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 11 and 19 (UNC13A AON 25_sp8sp11sp19)	Nucleosides at positions 8 and 11 and 19 are substituted with spacers	9649	XXXXXXX$\mathbf{S_8}$XX$\mathbf{S_{11}}$XXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 11 and 16 (UNC13A AON 23_sp8sp11sp16)	Nucleosides at positions 8 and 11 and 16 are substituted with spacers	9650	XXXXXXX$\mathbf{S_8}$XX$\mathbf{S_{11}}$XXXX$\mathbf{S_{16}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 7 and 14	Nucleosides at positions 7 and 14 and 22	9651	XXXXXX$\mathbf{S_7}$XXXXXX$\mathbf{S_{14}}$XXXXXXX$\mathbf{S_{22}}$XXX

and 22 (UNC13A AON 23_sp7sp14sp22)	are substituted with spacers		

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00486] In various embodiments, UNC13A AONs with one or more spacers are reduced in length in comparison to the UNC13A AONs described above in Tables 18B and 19. For example, such UNC13A AONs may be UNC13A oligonucleotide variants with one or more spacers. In various embodiments, the UNC13A oligonucleotide variants with one or more spacers are 23mers, 21mers, or 19mers. In various embodiments, UNC13A oligonucleotide variants include two spacers such that the UNC13A oligonucleotide variant includes three segments that are divided up by the two spacers. In various embodiments, at least one of the three segments has at most 7 linked nucleosides. In various embodiments, each of the three segments has at most 7 linked nucleosides. Example UNC13A oligonucleotide variants with one or more spacers are shown below in Table 20.

Table 20: Example UNC13A AON variants with two spacers. Here, each UNC13A AON variant has 3 segments, where at least one segment has at most 7 linked nucleosides.

Sequence name	**Relation to UNC13A oligonucleotide variant**	**Sequence ID Number (SEQ ID NO)**	**Sequence* (where *X* indicates a nucleoside of the UNC13A oligonucleotide variant and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
UNC13A oligonucleotide variant (23mer)	N/A	9652	XXXXXXXXXXXXXXXXXXXXXXX (23mer)
UNC13A Variant Oligonucleotide (23mer) with	Nucleosides at positions 8 and 16 are	9653	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXX

Spacers at positions 8 and 16 (UNC13A AON variant 23_sp8sp16)	substituted with spacers		
UNC13A oligonucleotide variant (21mer)	N/A	9654	XXXXXXXXXXXXXXXXXXXXX (21mer)
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 5 and 12 (UNC13A AON variant 21_sp5sp12)	Nucleosides at positions 5 and 12 are substituted with spacers	9655	XXXX$\mathbf{S_5}$XXXXXX$\mathbf{S_{12}}$XXXXXXXXX
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 8 and 16 (UNC13A AON variant 21_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers	9656	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXX
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 6 and 14 (UNC13A AON variant 21_sp6sp14)	Nucleosides at positions 6 and 14 are substituted with spacers	9657	XXXXX$\mathbf{S_6}$XXXXXXX$\mathbf{S_{14}}$XXXXXXX
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 8 and 14 (UNC13A AON variant 21_sp8sp14)	Nucleosides at positions 8 and 14 are substituted with spacers	9658	XXXXXXX$\mathbf{S_8}$XXXXX$\mathbf{S_{14}}$XXXXXXX
UNC13A Variant Oligonucleotide (21mer) with Spacers at	Nucleosides at positions 6 and 20 are substituted with spacers	9659	XXXXX$\mathbf{S_6}$XXXXXXXXXXXXX$\mathbf{S_{20}}$X

positions 8 and 14 (UNC13A AON variant 21_sp8sp14)			
UNC13A oligonucleotide variant (19mer)	N/A	9660	XXXXXXXXXXXXXXXXXXX (19mer)
UNC13A Variant Oligonucleotide (19mer) with Spacers at positions 5 and 12 (UNC13A AON variant 19_sp5sp12)	Nucleosides at positions 5 and 12 are substituted with spacers	9661	XXXX$\mathbf{S_5}$XXXXXX$\mathbf{S_{12}}$XXXXXXX
UNC13A Variant Oligonucleotide (19mer) with Spacers at positions 8 and 15 (UNC13A AON variant 19_sp8sp15)	Nucleosides at positions 8 and 15 are substituted with spacers	9662	XXXXXXX$\mathbf{S_8}$XXXXXX$\mathbf{S_{15}}$XXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00487] In some embodiments, an antisense oligonucleotide disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprise one or more spacers as well as one or more locked nucleic acids (LNAs). In some embodiments, an antisense oligonucleotide disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprises two spacers and two LNAs. In some embodiments, an antisense oligonucleotide disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprises two spacers and three LNAs.

[00488] In various embodiments, a spacer and a LNA are located adjacent to one another in an antisense oligonucleotide. For example, if counting from 5' to 3', a LNA can be located at a 7th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 9th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 15th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 17th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide.

[00489] In particular embodiments, a first spacer is located adjacent to a first LNA and a second spacer is located adjacent to a second LNA in an antisense oligonucleotide. For example, if counting from 5' to 3', a first LNA can be located at a 7th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 15th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a first LNA can be located at a 7th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 17th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a first LNA can be located at a 9th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 17th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide.

[00490] In various embodiments, one or more spacers and one or more LNAs are not located adjacent to one another in an antisense oligonucleotide. For example, if counting from 5' to 3', a LNA can be located at a 4th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As example, if counting from 5' to 3', a LNA can be located at a 20th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide. In particular embodiments, if counting from 5' to 3', a first LNA can be located at a 4th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 20th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of

the antisense oligonucleotide. In particular embodiments, if counting from 5' to 3', a first LNA can be located at a 4th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 12th position of the antisense oligonucleotide, a second spacer can be located at a 16th position of the antisense oligonucleotide, and a third LNA can be located at a 20th position of the antisense oligonucleotide.

SMN2

[00491] As described further below, a SMN2 oligonucleotide with one or more spacers is described in reference to a corresponding SMN2 parent oligonucleotide. In various embodiments, a SMN2 oligonucleotide with a spacer differs from a SMN2 parent oligonucleotide in that the spacer replaces a nucleoside in the SMN2 parent oligonucleotide. As used hereafter, the "position" of the SMN2 oligonucleotide refers to a particular location as counted from the 5' end of the SMN2 oligonucleotide. In various embodiments, the spacer replaces a nucleoside at any one of positions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 of the SMN2 parent oligonucleotide. In particular embodiments, a spacer replaces a nucleoside at one of positions 7, 8, 11, 14, 16, 19, or 22 of the SMN2 parent oligonucleotide.

[00492] In various embodiments, a SMN2 oligonucleotide includes one spacer that replaces a nucleoside in the SMN2 parent oligonucleotide (e.g., one spacer replaces one nucleoside of the SMN2 parent oligonucleotide). In particular embodiments, the spacer replaces a nucleoside between positions 9 and 15 of the SMN2 parent oligonucleotide. In particular embodiments, the spacer replaces a nucleoside between positions 9 and 12 of the SMN2 parent oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 10 of the SMN2 parent oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 11 of the SMN2 parent oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 12 of the SMN2 parent oligonucleotide. In particular embodiments, the spacer replaces a nucleoside between positions 12 and 16 of the SMN2 parent oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 15 of the SMN2 parent oligonucleotide.

[00493] In various embodiments, a SMN2 oligonucleotide including one spacer has 2 segments, where at least one of the 2 segments has at most 11 linked nucleosides. For example, the SMN2 oligonucleotide may be 23 oligonucleotide units in length, and the spacer can be located at

position 12. Therefore, the SMN2 oligonucleotide has 2 segments divided by the spacer, where both of the 2 segments are 11 nucleobases in length. In various embodiments, a SMN2 oligonucleotide including one spacer has 2 segments, where at least one of the 2 segments has at most 10 linked nucleosides. For example, the SMN2 oligonucleotide may be 21 oligonucleotide units in length, and the spacer can be located at position 11. Therefore, the SMN2 oligonucleotide has 2 segments divided by the spacer, where both of the 2 segments are 10 nucleobases in length. As another example, the SMN2 oligonucleotide may be 25 oligonucleotide units in length, and the spacer can be located at position 15. Therefore, the SMN2 oligonucleotide has 2 segments divided by the spacer, where one of the 2 segments is 14 nucleobases in length and the second of the 2 segments is 10 nucleobases in length.

[00494] In various embodiments, a SMN2 oligonucleotide includes two spacers that each replace a nucleoside in the SMN2 parent oligonucleotide (e.g., two spacers replace two separate nucleosides of the SMN2 parent oligonucleotide). In various embodiments, a first spacer and a second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, at least 7 nucleobases, at least 8 nucleobases, at least 9 nucleobases, or at least 10 nucleobases in the oligonucleotide. In particular embodiments, a first spacer and a second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases. In particular embodiments, the first spacer and the second spacer are not adjacent to one another in the oligonucleotide.

[00495] In particular embodiments, the first spacer replaces a nucleoside between positions 7 and 11 of the SMN2 parent oligonucleotide. In various embodiments, the first spacer replaces a nucleoside between positions 8 and 11, positions 9 and 11, positions 10 and 11, positions 7 and 10, positions 7 and 9, positions 7 and 8, positions 8 and 10, positions 8 and 9, or positions 9 and 10 of the SMN2 parent oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 14 and 22 of the SMN2 parent oligonucleotide. In various embodiments, the second spacer replaces a nucleoside between positions 15 and 22, positions 16 and 22, positions 17 and 22, position 18 and 22, position 19 and 22, positions 20 and 22, positions 21 and 22, positions 15 and 21, position 16 and 21, positions 17 and 21, positions 18 and 21, positions 19 and 21, positions 20 and 21, positions 15 and 20, positions 16 and 20, positions 17 and 20, positions 18 and 20, positions 19 and 20, positions 15 and 19, positions 16 and 19, positions 17 and 19, positions 18 and 19, positions 15 and 18, position 16 and 18, position 17 and 18, positions 15 and 17, positions 16 and 17, or positions 15 and 16 of the SMN2 parent oligonucleotide.

[00496] In preferred embodiments, the first spacer replaces a nucleoside at position 7 of the SMN2 parent oligonucleotide and the second spacer replaces a nucleoside at position 14 of the SMN2 parent oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 7 of the SMN2 parent oligonucleotide and the second spacer replaces a nucleoside at position 19 of the SMN2 parent oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 8 of the SMN2 parent oligonucleotide and the second spacer replaces a nucleoside at position 16 of the SMN2 parent oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 11 of the SMN2 parent oligonucleotide and the second spacer replaces a nucleoside at position 22 of the SMN2 parent oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 9 of the SMN2 parent oligonucleotide and the second spacer replaces a nucleoside at position 19 of the SMN2 parent oligonucleotide.

[00497] In various embodiments, a SMN2 oligonucleotide includes three spacers that each replace a nucleoside in the SMN2 parent oligonucleotide (e.g., three spacers replace three separate nucleosides of the SMN2 parent oligonucleotide). In particular embodiments, the first spacer replaces a nucleoside between positions 7 and 11 of the SMN2 parent oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 14 and 22 of the SMN2 parent oligonucleotide. In particular embodiments, the third spacer replaces a nucleoside between positions 21 and 24 of the SMN2 parent oligonucleotide. In some embodiments, the first spacer replaces a nucleoside between positions 2 and 5 of the SMN2 parent oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 8 and 12 of the SMN2 parent oligonucleotide. In particular embodiments, the third spacer replaces a nucleoside between positions 18 and 22 of the SMN2 parent oligonucleotide.

[00498] In various embodiments, the three spacers in a SMN2 oligonucleotide are positioned such that each of the four segments of the SMN2 oligonucleotide are at most 7 linked nucleosides in length. For example, a SMN2 oligonucleotide may have a first segment with 7 linked nucleosides connected to a first spacer, then a second segment with 7 linked nucleosides connected on one end to the first spacer and connected on another end to a second spacer, then a third segment with 6 linked nucleosides connected on one end to the second spacer and connected on another end to a third spacer, then a fourth segment with 6 linked nucleosides connected to the third spacer.

[00499] In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more adenosine or thymine nucleosides (as opposed to guanine or cytosine nucleosides). For example, the one or more spacers can replace one, two, three, four, five, six, seven, eight, or nine adenosine or thymine nucleosides in the oligonucleotide. In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more guanine or cytosine nucleosides (as opposed to adenosine or thymine nucleosides). For example, the one or more spacers can replace one, two, three, four, five, six, seven, eight, or nine guanine or cytosine nucleosides in the oligonucleotide. In various embodiments, the spacers are positioned in the oligonucleotide to replace an equal number of adenosine/thymine nucleosides and guanine/cytosine nucleosides. For example, a first spacer in the oligonucleotide may replace an adenosine/thymine nucleoside and a second spacer in the oligonucleotide may replace a guanine/cytosine nucleoside.

[00500] In various embodiments, the one or more spacers are positioned in the oligonucleotide to control the sequence content in the oligonucleotide. For example, the one or more spacers are positioned such that at least one of the spacers is located adjacent to a guanine group. In various embodiments, an oligonucleotide with spacers can include one spacer adjacent to a guanine group, two spacers adjacent to guanine groups, three spacers adjacent to guanine groups, four spacers adjacent to guanine groups, or five spacers adjacent to guanine groups. In one embodiment, if counting from the 5' end of the oligonucleotide, a spacer immediately precedes a guanine group in the sequence. Thus, in various embodiments, an oligonucleotide with spacers can include one spacer that immediately precedes a guanine group, two spacers that each immediately precede a guanine group, three spacers that each immediately precede a guanine group, four spacers that each immediately precede a guanine group, or five spacers that each immediately precede a guanine group. In one embodiment, if counting from the 5' end of the oligonucleotide, a guanine group is immediately succeeded by a spacer. Thus, in various embodiments, an oligonucleotide with spacers can include one spacer that immediately succeeds a guanine group, two spacers that each immediately succeed a guanine group, three spacers that each immediately succeed a guanine group, four spacers that each immediately succeed a guanine group, or five spacers that each immediately succeed a guanine group. In various embodiments, the spacers in the oligonucleotide can be positioned to maximize the number of spacers adjacent to guanine groups.

[00501] In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more adenosine or thymine nucleosides such that the one or more spacers are

located adjacent guanine groups. For example, two spacers can replace adenosine or thymine nucleosides in the oligonucleotide, each of the two spacers being located adjacent to a guanine group.

[00502] In various embodiments, the SMN2 oligonucleotide with one or more spacers has a particular GC content. As used herein, GC content (or guanine-cytosine content) is the percentage of nitrogenous bases in the oligonucleotide that are either guanine (G) or cytosine (C). In various embodiments, the SMN2 oligonucleotide with one or more spacers has at least 10% GC content, at least 20% GC content, at least 25% GC content, at least 30% GC content, at least 35% GC content, at least 40% GC content, at least 45% GC content, at least 50% GC content, at least 55% GC content, at least 60% GC content, at least 65% GC content, at least 75% GC content, at least 80% GC content, at least 85% GC content, at least 90% GC content, or at least 95% GC content. In particular embodiments, the SMN2 oligonucleotide with one or more spacers has at least 30% GC content. In particular embodiments, the SMN2 oligonucleotide with one or more spacers has at least 40% GC content. In various embodiments, the one or more spacers are positioned in the SMN2 oligonucleotide to maximize GC content. For example, instead of selecting a guanine or cytosine for replacement by a spacer in the SMN2 oligonucleotide, a thymine or adenine can be selected for replacement by a spacer.

[00503] In various embodiments, a SMN2 oligonucleotide with spacers is designed such that 1) each segment of the SMN2 oligonucleotide has at most 7 linked nucleosides and 2) at least two, three, or four spacers are positioned adjacent to a guanine group. In some embodiments, a SMN2 oligonucleotide with spacers is designed such that 1) each segment of the SMN2 oligonucleotide has at most 7 linked nucleosides and 2) each of two spacers precede a guanine group.

[00504] In various embodiments, the inclusion of one or more spacers in the SMN2 oligonucleotide does not decrease the effectiveness of the SMN2 oligonucleotide with the spacers in restoring full length SMN2 protein or full length SMN2 mRNA in comparison to the effect of a corresponding SMN2 parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the SMN2 oligonucleotide increases the effectiveness of the SMN2 oligonucleotide with the spacers in restoring full length SMN2 protein or full length SMN2 mRNA in comparison to the effect of a corresponding SMN2 parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the SMN2 oligonucleotide does not decrease the effectiveness of the SMN2 oligonucleotide with the spacers in reducing quantity of SMN2 transcripts in comparison to the effect of a corresponding SMN2 parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the SMN2 oligonucleotide

increases the effectiveness of the SMN2 oligonucleotide with the spacers in reducing quantity of SMN2 transcripts in comparison to the effect of a corresponding SMN2 parent oligonucleotide.

[00505] Tables 21A, 21B, 22, and 23 document example SMN2 oligonucleotides with one or more spacers and their relation to corresponding SMN2 parent oligonucleotides. Each SMN2 oligonucleotide is assigned a sequence name. As used hereafter, the nomenclature of the sequence name is expressed as "X_spA" (for a SMN2 AON with one spacer), "X_spA_spB" (for a SMN2 AON with two spacers), or "X_spA_spB_spC" (for a SMN2 AON with three spacers). Here, "X" refers to the length of the SMN2 AON, "A" refers to the position in the SMN2 AON where the first spacer is located, "B" refers to the position in the SMN2 AON where the second spacer is located, and if present, "C" refers to the position in the SMN2 AON where the third spacer is located.

[00506] In various embodiments, SMN2 oligonucleotides include one spacer. In various embodiments, the SMN2 oligonucleotides are oligonucleotide variants, such as any one of a 23mer, 21mer, or 19mer. In various embodiments, the inclusion of a spacer divides up the SMN2 oligonucleotide into two separate segments, where at least one of the segments is at most 11 linked nucleosides in length. In various embodiments, the inclusion of a spacer divides up the SMN2 oligonucleotide into two separate segments, where at least one of the segments is at most 10 linked nucleosides in length.

[00507] In various embodiments, the spacer is located between positions 10 and 15 of the oligonucleotide. In various embodiments, the spacer is located between positions 10 and 12 of the oligonucleotide. In particular embodiments, the spacer is located at position 10 of the oligonucleotide. In particular embodiments, the spacer is located at position 11 of the oligonucleotide. In particular embodiments, the spacer is located at position 12 of the oligonucleotide. In particular embodiments, the spacer is located at position 15 of the oligonucleotide. Example SMN2 AONs with one spacer are documented below in Table 21A.

Table 21A: Identification of SMN2 AONs with one spacer. Here, each SMN2 AON has 2 segments, where at least one of the segments has at most 11 linked nucleosides.

Sequence name	**Relation to SMN2 oligonucleotide variant**	**Sequence ID Number (SEQ ID NO)**	**Sequence* (where *X* indicates a nucleoside of the SMN2 parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
SMN2 parent oligonucleotide	N/A	10574	XXXXXXXXXXXXXXXXXXXXXXXXX (25mer)

SMN2 Oligonucleotide (25mer) with Spacer at position 15 (SMN2 AON 25_sp15)	Nucleoside at position 15 of 25mer is substituted with a spacer	10575	XXXXXXXXXXXXXX$\mathbf{S_{15}}$XXXXXXXXXX
SMN2 oligonucleotide variant (23mer)	N/A	10576	XXXXXXXXXXXXXXXXXXXXXXX (23mer)
SMN2 Oligonucleotide (23mer) with Spacer at position 12 (SMN2 AON 23_sp12)	Nucleoside at position 12 of 23mer is substituted with a spacer	10577	XXXXXXXXXXX$\mathbf{S_{12}}$XXXXXXXXXXX
SMN2 oligonucleotide variant (21mer)	N/A	10578	XXXXXXXXXXXXXXXXXXXXX (21mer)
SMN2 Oligonucleotide (21mer) with Spacer at position 11 (SMN2 AON 21_sp11)	Nucleoside at position 11 of 21mer is substituted with a spacer	10579	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXXX
SMN2 oligonucleotide variant (19mer)	N/A	10580	XXXXXXXXXXXXXXXXXXX (19mer)
SMN2 Oligonucleotide (19mer) with Spacer at position 10 (SMN2 AON 19_sp10)	Nucleoside at position 10 of 19mer is substituted with a spacer	10581	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00508] In various embodiments, SMN2 oligonucleotides include two spacers. In various embodiments, the inclusion of a spacer divides up the SMN2 oligonucleotide into three separate segments, where at least one of the segments is at most 7 linked nucleosides in length. Example SMN2 AONs with two spacers are documented below in Table 22B.

Table 22B: Identification of SMN2 AONs with two spacers. Here, each SMN2 AON has 3 segments, where at least one of the segments has at most 7 linked nucleosides.

Sequence name	**Relation to SMN2 parent oligonucleotide**	**Sequence ID Number (SEQ ID NO)**	**Sequence* (where *X* indicates a nucleoside of the SMN2 parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
SMN2 parent oligonucleotide	N/A	10582	XXXXXXXXXXXXXXXXXXXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 11 and 22 (SMN2 AON 25_sp11sp22)	Nucleosides at positions 11 and 22 are each substituted with a spacer	10583	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXXX$\mathbf{S_{22}}$XXX
SMN2 Oligonucleotide with Spacers at positions 7 and 14 (SMN2 AON 25_sp7sp14)	Nucleosides at positions 7 and 14 are each substituted with a spacer	10584	XXXXXX$\mathbf{S_7}$XXXXXX$\mathbf{S_{14}}$XXXXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 8 and 19 (SMN2 AON 25_sp8sp19)	Nucleosides at positions 8 and 19 are substituted with spacers	10585	XXXXXXX$\mathbf{S_8}$XXXXXXXXXX$\mathbf{S_{19}}$XXXXXX
SMN2 Oligonucleotide with Spacers at positions 8 and 14 (SMN2 AON 25_sp8sp14)	Nucleosides at positions 8 and 14 are substituted with spacers	10586	XXXXXXX$\mathbf{S_8}$XXXXX$\mathbf{S_{14}}$XXXXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 9 and 14 (SMN2 AON 25_sp9sp14)	Nucleosides at positions 9 and 14 are substituted with spacers	10587	XXXXXXXX$\mathbf{S_9}$XXXX$\mathbf{S_{14}}$XXXXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 10 and 14 (SMN2 AON 25_sp10sp14)	Nucleosides at positions 10 and 14 are substituted with spacers	10588	XXXXXXXXX$\mathbf{S_{10}}$XXX$\mathbf{S_{14}}$XXXXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 11 and 14 (SMN2 AON 25_sp11sp14)	Nucleosides at positions 11 and 14 are substituted with spacers	10589	XXXXXXXXXX$\mathbf{S_{11}}$XX$\mathbf{S_{14}}$XXXXXXXXXX

SMN2 Oligonucleotide with Spacers at positions 8 and 15 (SMN2 AON 25_sp8sp15)	Nucleosides at positions 8 and 15 are substituted with spacers	10590	XXXXXXX$\mathbf{S_8}$XXXXXX$\mathbf{S_{15}}$XXXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 9 and 15 (SMN2 AON 25_sp9sp15)	Nucleosides at positions 9 and 15 are substituted with spacers	10591	XXXXXXXX$\mathbf{S_9}$XXXXX$\mathbf{S_{15}}$XXXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 10 and 15 (SMN2 AON 25_sp10sp15)	Nucleosides at positions 10 and 15 are substituted with spacers	10592	XXXXXXXXX$\mathbf{S_{10}}$XXXX$\mathbf{S_{15}}$XXXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 11 and 15 (SMN2 AON 25_sp11sp15)	Nucleosides at positions 11 and 15 are substituted with spacers	10593	XXXXXXXXXX$\mathbf{S_{11}}$XXX$\mathbf{S_{15}}$XXXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 8 and 16 (SMN2 AON 25_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers	10594	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 9 and 16 (SMN2 AON 25_sp9sp16)	Nucleosides at positions 9 and 16 are substituted with spacers	10595	XXXXXXXX$\mathbf{S_9}$XXXXXX$\mathbf{S_{16}}$XXXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 10 and 16 (SMN2 AON 25_sp10sp16)	Nucleosides at positions 10 and 16 are substituted with spacers	10596	XXXXXXXXX$\mathbf{S_{10}}$XXXXX$\mathbf{S_{16}}$XXXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 11 and 16 (SMN2 AON 25_sp11sp16)	Nucleosides at positions 11 and 16 are substituted with spacers	10597	XXXXXXXXXX$\mathbf{S_{11}}$XXXX$\mathbf{S_{16}}$XXXXXXXXX

SMN2 Oligonucleotide with Spacers at positions 8 and 17 (SMN2 AON 25_sp8sp17)	Nucleosides at positions 8 and 17 are substituted with spacers	10598	XXXXXXX$\mathbf{S_8}$XXXXXXXX$\mathbf{S_{17}}$XXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 9 and 17 (SMN2 AON 25_sp9sp17)	Nucleosides at positions 9 and 17 are substituted with spacers	10599	XXXXXXXX$\mathbf{S_9}$XXXXXXX$\mathbf{S_{17}}$XXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 10 and 17 (SMN2 AON 25_sp10sp17)	Nucleosides at positions 10 and 17 are substituted with spacers	10600	XXXXXXXXX$\mathbf{S_{10}}$XXXXXX$\mathbf{S_{17}}$XXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 11 and 17 (SMN2 AON 25_sp11sp17)	Nucleosides at positions 11 and 17 are substituted with spacers	10601	XXXXXXXXXX$\mathbf{S_{11}}$XXXXX$\mathbf{S_{17}}$XXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 8 and 18 (SMN2 ATON 25_sp8sp18)	Nucleosides at positions 8 and 18 are substituted with spacers	10602	XXXXXXX$\mathbf{S_8}$XXXXXXXXX$\mathbf{S_{18}}$XXXXXXX
SMN2 Oligonucleotide with Spacers at positions 9 and 18 (SMN2 AON 25_sp9sp18)	Nucleosides at positions 9 and 18 are substituted with spacers	10603	XXXXXXXX$\mathbf{S_9}$XXXXXXXX$\mathbf{S_{18}}$XXXXXXX
SMN2 Oligonucleotide with Spacers at positions 10 and 18 (SMN2 AON 25_sp10sp18)	Nucleosides at positions 10 and 18 are substituted with spacers	10604	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX
SMN2 Oligonucleotide with Spacers at positions 11 and 18 (SMN2 AON 25_sp11sp18)	Nucleosides at positions 11 and 18 are substituted with spacers	10605	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXX$\mathbf{S_{18}}$XXXXXXX

SMN2 Oligonucleotide with Spacers at positions 9 and 19 (SMN2 AON 25_sp9sp19)	Nucleosides at positions 9 and 19 are substituted with spacers	10606	XXXXXXXX$\mathbf{S_9}$XXXXXXXXX$\mathbf{S_{19}}$XXXXXX
SMN2 Oligonucleotide with Spacers at positions 10 and 19 (SMN2 AON 25_sp10sp19)	Nucleosides at positions 10 and 19 are substituted with spacers	10607	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXX$\mathbf{S_{19}}$XXXXXX
SMN2 Oligonucleotide with Spacers at positions 11 and 19 (SMN2 AON 25_sp11sp19)	Nucleosides at positions 11 and 19 are substituted with spacers	10608	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXX$\mathbf{S_{19}}$XXXXXX
SMN2 Oligonucleotide with Spacers at positions 9 and 20 (SMN2 AON 25_sp9sp20)	Nucleosides at positions 9 and 20 are substituted with spacers	10609	XXXXXXXX$\mathbf{S_9}$XXXXXXXXXX$\mathbf{S_{20}}$XXXXX
SMN2 Oligonucleotide with Spacers at positions 10 and 20 (SMN2 AON 25_sp10sp20)	Nucleosides at positions 10 and 20 are substituted with spacers	10610	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXXX$\mathbf{S_{20}}$XXXXX
SMN2 Oligonucleotide with Spacers at positions 11 and 20 (SMN2 AON 25_sp11sp20)	Nucleosides at positions 11 and 20 are substituted with spacers	10611	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXX$\mathbf{S_{20}}$XXXXX
SMN2 Oligonucleotide with Spacers at positions 10 and 21 (SMN2 AON 25_sp10sp21)	Nucleosides at positions 10 and 21 are substituted with spacers	10612	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXXXX$\mathbf{S_{21}}$XXXX
SMN2 Oligonucleotide with Spacers at positions 11 and 21 (SMN2 AON 25_sp11sp21)	Nucleosides at positions 11 and 21 are substituted with spacers	10613	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXX$\mathbf{S_{21}}$XXXX

SMN2 Oligonucleotide with Spacers at positions 4 and 15 (SMN2 AON 25_sp4sp15)	Nucleosides at positions 4 and 15 are substituted with spacers	10614	XXX$\mathbf{S_4}$XXXXXXXXXX$\mathbf{S_{15}}$XXXXXXXXX
SMN2 Oligonucleotide with Spacers at positions 7 and 19 (SMN2 AON 25_sp7sp19)	Nucleosides at positions 7 and 19 are substituted with spacers	10615	XXXXXX$\mathbf{S_7}$XXXXXXXXXX$\mathbf{S_{19}}$XXXXX
SMN2 Oligonucleotide with Spacers at positions 7 and 18 (SMN2 AON 25_sp7sp18)	Nucleosides at positions 7 and 18 are substituted with spacers	10616	XXXXXX$\mathbf{S_7}$XXXXXXXXXX$\mathbf{S_{18}}$XXXXXX
SMN2 Oligonucleotide with Spacers at positions 9 and 21 (SMN2 AON 25_sp9sp21)	Nucleosides at positions 9 and 21 are substituted with spacers	10617	XXXXXXXX$\mathbf{S_9}$XXXXXXXXXX$\mathbf{S_{21}}$XXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00509] In various embodiments, SMN2 oligonucleotides include three spacers. The inclusion of three spacers divides up the SMN2 oligonucleotide into four separate segments. In various embodiments, the three spacers are located at different positions of the SMN2 oligonucleotide such that each of the segments of the SMN2 oligonucleotide are at most 7 linked nucleosides in length. Example SMN2 AONs with three spacers are documented below in Table 23.

Table 23: Identification of SMN2 AONs or AON variants with three spacers. Here, each SMN2 AON has 4 segments, where each segment has at most 7 linked nucleosides.

Sequence name	Relation to SMN2 parent oligonucleotide	Sequence ID Number (SEQ ID NO)	Sequence* (where *X* indicates a nucleoside of the SMN2 parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position) (5' → 3')
SMN2 Oligonucleotide with Spacers at positions 8 and 16 and 24 (SMN2 AON 25_sp8sp16sp24)	Nucleosides at positions 8 and 16 and 24 are substituted with spacers	10618	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXX$\mathbf{S_{24}}$X
SMN2 Oligonucleotide with Spacers at positions 8 and 16 and 23 (SMN2 AON 25_sp8sp16sp23)	Nucleosides at positions 8 and 16 and 23 are substituted with spacers	10619	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXX$\mathbf{S_{23}}$XX
SMN2 Oligonucleotide with Spacers at positions 2 and 10 and 18 (SMN2 AON 25_sp8sp16sp23)	Nucleosides at positions 2 and 10 and 18 are substituted with spacers	10620	X$\mathbf{S_2}$XXXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX
SMN2 Oligonucleotide with Spacers at positions 3 and 10 and 18 (SMN2 AON 25_sp8sp16sp23)	Nucleosides at positions 3 and 10 and 18 are substituted with spacers	10621	XX$\mathbf{S_3}$XXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX
SMN2 Oligonucleotide with Spacers at positions 4 and 12 and 19 (SMN2 AON 25_sp4sp12sp19)	Nucleosides at positions 4 and 12 and 19 are substituted with spacers	10622	XXX$\mathbf{S_4}$XXXXXXX$\mathbf{S_{12}}$XXXXXX$\mathbf{S_{19}}$XXXXXX
SMN2 Oligonucleotide with Spacers at positions 8 and 13 and 18 (SMN2 AON 25_sp8sp13sp18)	Nucleosides at positions 8 and 13 and 18 are substituted with spacers	10623	XXXXXXX$\mathbf{S_8}$XXXX$\mathbf{S_{13}}$XXXX$\mathbf{S_{18}}$XXXXXXX
SMN2 Oligonucleotide	Nucleosides at positions 5	10624	XXXX$\mathbf{S_5}$XXXXXXX$\mathbf{S_{13}}$XXXXXXX$\mathbf{S_{21}}$XXXX

with Spacers at positions 5 and 13 and 21 (SMN2 AON 25_sp5sp13sp21)	and 13 and 21 are substituted with spacers		
SMN2 Oligonucleotide with Spacers at positions 7 and 13 and 19 (SMN2 AON 25_sp7sp13sp19)	Nucleosides at positions 7 and 13 and 19 are substituted with spacers	10625	XXXXXX$\mathbf{S_7}$XXXXX$\mathbf{S_{13}}$XXXXX$\mathbf{S_{19}}$XXXXXX
SMN2 Oligonucleotide with Spacers at positions 6 and 13 and 20 (SMN2 AON 25_sp6sp13sp20)	Nucleosides at positions 6 and 13 and 20 are substituted with spacers	10626	XXXXX$\mathbf{S_6}$XXXXXX$\mathbf{S_{13}}$XXXXXX$\mathbf{S_{20}}$XXXXX
SMN2 Oligonucleotide with Spacers at positions 8 and 11 and 19 (SMN2 AON 25_sp8sp11sp19)	Nucleosides at positions 8 and 11 and 19 are substituted with spacers	10627	XXXXXXX$\mathbf{S_8}$XX$\mathbf{S_{11}}$XXXXXXX$\mathbf{S_{19}}$XXXXXX
SMN2 Oligonucleotide with Spacers at positions 8 and 11 and 16 (SMN2 AON 23_sp8sp11sp16)	Nucleosides at positions 8 and 11 and 16 are substituted with spacers	10628	XXXXXXX$\mathbf{S_8}$XX$\mathbf{S_{11}}$XXXX$\mathbf{S_{16}}$XXXXXXX
SMN2 Oligonucleotide with Spacers at positions 7 and 14 and 22 (SMN2 AON 23_sp7sp14sp22)	Nucleosides at positions 7 and 14 and 22 are substituted with spacers	10629	XXXXXX$\mathbf{S_7}$XXXXXX$\mathbf{S_{14}}$XXXXXXX$\mathbf{S_{22}}$XXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose)

linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00510] In various embodiments, SMN2 AONs with one or more spacers are reduced in length in comparison to the SMN2 AONs described above in Tables 22B and 23. For example, such SMN2 AONs may be SMN2 oligonucleotide variants with one or more spacers. In various embodiments, the SMN2 oligonucleotide variants with one or more spacers are 23mers, 21mers, or 19mers. In various embodiments, SMN2 oligonucleotide variants include two spacers such that the SMN2 oligonucleotide variant includes three segments that are divided up by the two spacers. In various embodiments, at least one of the three segments has at most 7 linked nucleosides. In various embodiments, each of the three segments has at most 7 linked nucleosides. Example SMN2 oligonucleotide variants with one or more spacers are shown below in Table 24.

Table 24: SMN2 AON variants with two spacers. Here, each SMN2 AON variant has 3 segments.

Sequence name	**Relation to SMN2 oligonucleotide variant**	**Sequence ID Number (SEQ ID NO)**	**Sequence* (where *X* indicates a nucleoside of the SMN2 oligonucleotide variant and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
SMN2 oligonucleotide variant (23mer)	N/A	10630	XXXXXXXXXXXXXXXXXXXXXXX (23mer)
SMN2 Variant Oligonucleotide (23mer) with Spacers at positions 8 and 16 (SMN2 AON variant 23_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers	10631	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXX
SMN2 oligonucleotide variant (21mer)	N/A	10632	XXXXXXXXXXXXXXXXXXXXX (21mer)
SMN2 Variant Oligonucleotide (21mer) with Spacers at positions 5 and 12 (SMN2	Nucleosides at positions 5 and 12 are substituted with spacers	10633	XXXX$\mathbf{S_5}$XXXXXX$\mathbf{S_{12}}$XXXXXXXXX

AON variant 21_sp5sp12)			
SMN2 Variant Oligonucleotide (21mer) with Spacers at positions 8 and 16 (SMN2 AON variant 21_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers	10634	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXX
SMN2 Variant Oligonucleotide (21mer) with Spacers at positions 6 and 14 (SMN2 AON variant 21_sp6sp14)	Nucleosides at positions 6 and 14 are substituted with spacers	10635	XXXXX$\mathbf{S_6}$XXXXXXX$\mathbf{S_{14}}$XXXXXXX
SMN2 Variant Oligonucleotide (21mer) with Spacers at positions 8 and 14 (SMN2 AON variant 21_sp8sp14)	Nucleosides at positions 8 and 14 are substituted with spacers	10636	XXXXXXX$\mathbf{S_8}$XXXXX$\mathbf{S_{14}}$XXXXXXX
SMN2 Variant Oligonucleotide (21mer) with Spacers at positions 8 and 14 (SMN2 AON variant 21_sp8sp14)	Nucleosides at positions 6 and 20 are substituted with spacers	10637	XXXXX$\mathbf{S_6}$XXXXXXXXXXXXX$\mathbf{S_{20}}$X
SMN2 oligonucleotide variant (19mer)	N/A	10638	XXXXXXXXXXXXXXXXXXX (19mer)
SMN2 Variant Oligonucleotide (19mer) with Spacers at positions 5 and 12 (SMN2 AON variant 19_sp5sp12)	Nucleosides at positions 5 and 12 are substituted with spacers	10639	XXXX$\mathbf{S_5}$XXXXXX$\mathbf{S_{12}}$XXXXXXX
SMN2 Variant Oligonucleotide (19mer) with Spacers at	Nucleosides at positions 8 and 15 are	10640	XXXXXXX$\mathbf{S_8}$XXXXXX$\mathbf{S_{15}}$XXXX

positions 8 and 15 (SMN2 AON variant 19_sp8sp15)	substituted with spacers		

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00511] In some embodiments, an antisense oligonucleotide disclosed herein (e.g., SMN2 parent oligonucleotides and/or SMN2 oligonucleotide variants) comprise one or more spacers as well as one or more locked nucleic acids (LNAs). In some embodiments, an antisense oligonucleotide disclosed herein (e.g., SMN2 parent oligonucleotides and/or SMN2 oligonucleotide variants) comprises two spacers and two LNAs. In some embodiments, an antisense oligonucleotide disclosed herein (e.g., SMN2 parent oligonucleotides and/or SMN2 oligonucleotide variants) comprises two spacers and three LNAs.

[00512] In various embodiments, a spacer and a LNA are located adjacent to one another in an antisense oligonucleotide. For example, if counting from 5' to 3', a LNA can be located at a 7^{th} position of the antisense oligonucleotide and a spacer can be located at a 8^{th} position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 9^{th} position of the antisense oligonucleotide and a spacer can be located at a 8^{th} position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 15^{th} position of the antisense oligonucleotide and a spacer can be located at a 16^{th} position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 17^{th} position of the antisense oligonucleotide and a spacer can be located at a 16^{th} position of the antisense oligonucleotide.

[00513] In particular embodiments, a first spacer is located adjacent to a first LNA and a second spacer is located adjacent to a second LNA in an antisense oligonucleotide. For example, if counting from 5' to 3', a first LNA can be located at a 7^{th} position of the antisense oligonucleotide, a first spacer can be located at a 8^{th} position of the antisense oligonucleotide, a second LNA can be located at a 15^{th} position of the antisense oligonucleotide, and a second spacer can be located at a 16^{th} position of the antisense oligonucleotide. As another example, if

counting from 5' to 3', a first LNA can be located at a 7th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 17th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a first LNA can be located at a 9th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 17th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide.

[00514] In various embodiments, one or more spacers and one or more LNAs are not located adjacent to one another in an antisense oligonucleotide. For example, if counting from 5' to 3', a LNA can be located at a 4th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As example, if counting from 5' to 3', a LNA can be located at a 20th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide. In particular embodiments, if counting from 5' to 3', a first LNA can be located at a 4th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 20th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. In particular embodiments, if counting from 5' to 3', a first LNA can be located at a 4th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 12th position of the antisense oligonucleotide, a second spacer can be located at a 16th position of the antisense oligonucleotide, and a third LNA can be located at a 20th position of the antisense oligonucleotide.

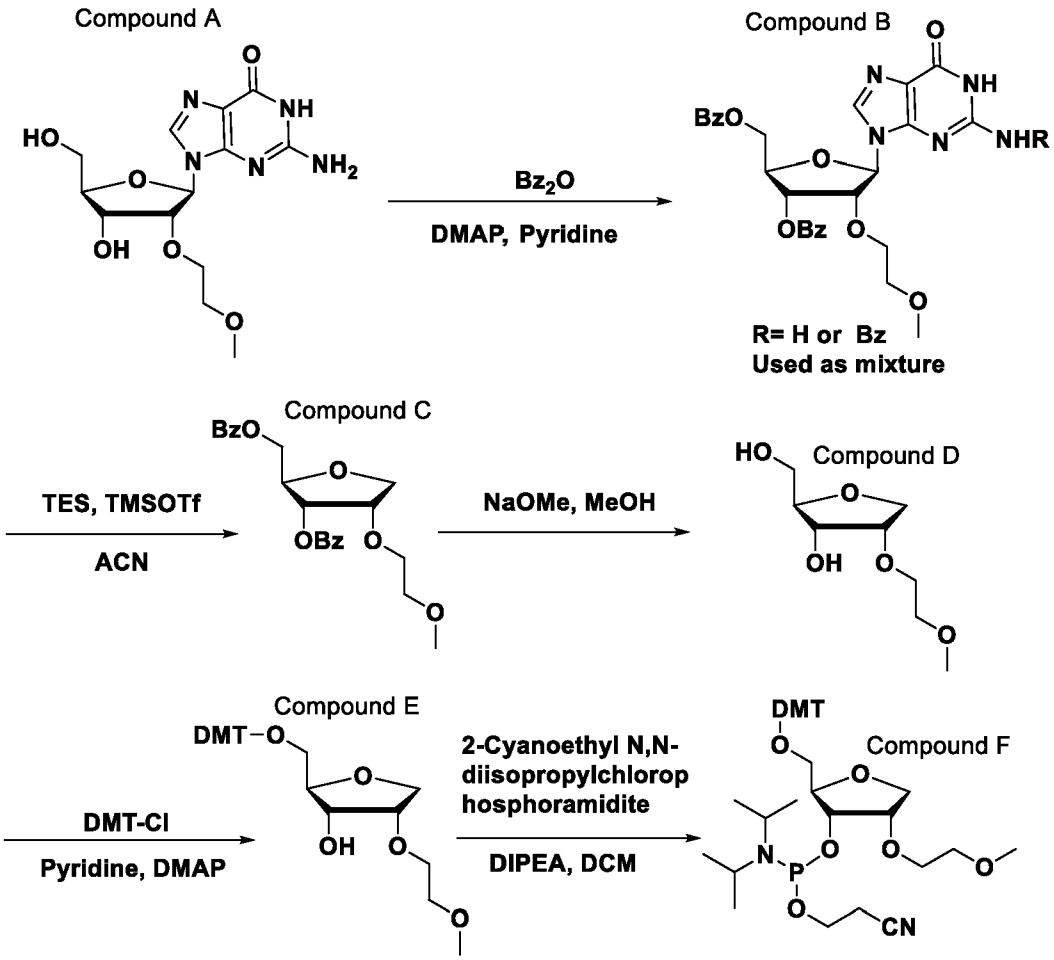
Example Synthesis of Spacer Building Blocks for Spacers

[00515] Additionally disclosed herein are compositions and methods for synthesizing a spacer, such as a spacer of any of Formulae (I), (I'), (Ia), (Ia'), (II), (II'), (Iia), (Iia'), (IIi), (IIi'), (IIib), (IIib'), (III), (III'), (IIIa) and (IIIa'). In particular embodiments, compositions and methods disclosed herein are useful for synthesizing an AON including a spacer of Formulae (IIib) or (IIib').

[00516] In various embodiments, the methods for synthesizing a spacer of Formulae (IIib) or (IIib') uses a 5 step synthesis protocol to generate a spacer building block. An example 5 step synthesis protocol is shown below. In particular the 5 step synthesis protocol starts with a Compound A, the generation of intermediate compounds (e.g., Compound B, Compound C,

Compound D, and compound E), and finally resulting in Compound F. Here, compound F represents a spacer building block for synthesizing an AON including a spacer of Formulae (IIib) or (IIib').

[00517] In various embodiments, step 1 involves a benzoyl protection step. In various embodiments, step 2 involves a reductive nucleobase cleavage step. In various embodiments, step 3 involves a saponification step. In various embodiments, step 4 involves a DMT protection step. In various embodiments, step 5 involves a phosphoramidite installation step.



Performance of STMN2 Oligonucleotides

[00518] Generally, STMN2 oligonucleotides and/or STMN2 parent oligonucleotides (*e.g.*, STMN2 oligonucleotides with sequences of any of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669) target STMN2 transcripts (for example, a STMN2 pre-mRNA comprising a cryptic exon) comprising a

sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 1339 or SEQ ID NO: 1341 in order to increase, restore, rescue, or stabilize levels of expression of STMN2 mRNA that is capable of translation to produce a functional STMN2 protein (*e.g.*, full length STMN2). In various embodiments, STMN2 AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length STMN2 protein. In various embodiments, STMN2 AONs can exhibit at least a 100%, 200%, 300%, or 400% increase of full length STMN2 protein. In some embodiments, the percent increase of the full length STMN2 protein is an increase in comparison to a reduced level of full length STMN2 protein achieved using a TDP43 antisense oligonucleotide. For example, a TDP43 antisense oligonucleotide can be used to deplete full length STMN2 protein followed by increase of the full length STMN2 protein using a STMN2 AON.

[00519] In some embodiments, STMN2 AONs can exhibit at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length STMN2 protein. In some embodiments, the percent rescue of full length STMN2 refers to the % of full length STMN2 following depletion using a TDP43 antisense oligonucleotide and a treatment using STMN2 AONs in comparison to a negative control (*e.g.*, cells that did not undergo depletion or treatment or cells that were treated with a vehicle solution).

Performance of KCNQ2 Oligonucleotides

[00520] Generally, KCNQ2 oligonucleotides and/or KCNQ2 parent oligonucleotides (*e.g.*, KCNQ2 oligonucleotides with sequences of any of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530) target KCNQ2 transcripts (for example, a KCNQ2 mRNA comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 3032-3043 in order to increase, restore, rescue, or stabilize levels of expression of KCNQ2 mRNA that is capable of translation to produce a functional KCNQ2 protein (*e.g.*, full length KCNQ2). In various embodiments, KCNQ2 AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length KCNQ2 mRNA. In various embodiments, KCNQ2 AONs can exhibit at least a 100%, 200%, 300%, or 400% increase of full length KCNQ2 mRNA. In various embodiments, KCNQ2 AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% reduction of mis-spliced KCNQ2 mRNA. In various embodiments, KCNQ2 AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length KCNQ2 protein. In various embodiments, KCNQ2 AONs can exhibit at least a 100%, 200%, 300%, or 400% increase of full length KCNQ2 protein. In

some embodiments, the percent increase of the full length KCNQ2 protein is an increase in comparison to a reduced level of full length KCNQ2 protein achieved using a KCNQ2 antisense oligonucleotide. For example, a KCNQ2 antisense oligonucleotide can be used to deplete full length KCNQ2 protein followed by increase of the full length KCNQ2 protein using a KCNQ2 AON.

[00521] In some embodiments, KCNQ2 AONs can exhibit at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length KCNQ2 protein. In some embodiments, the percent rescue of full length KCNQ2 refers to the % of full length KCNQ2 following depletion using a TDP43 antisense oligonucleotide and a treatment using KCNQ2 AONs in comparison to a negative control (*e.g.*, cells that did not undergo depletion or treatment or cells that were treated with a vehicle solution).

Performance of UNC13A Oligonucleotides

[00522] Generally, UNC13A oligonucleotides and/or UNC13A parent oligonucleotides (*e.g.*, UNC13A oligonucleotides with sequences of any of SEQ ID NOs: 4531-5794, SEQ ID NO: 7059-8322, SEQ ID NOs: 9596-9696, or SEQ ID NOs: 10670-10779) target UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 9587-9595 in order to increase, restore, rescue, or stabilize levels of expression of UNC13A mRNA that is capable of translation to produce a functional UNC13A protein (*e.g.*, full length UNC13A). In various embodiments, UNC13A AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A mRNA. In various embodiments, UNC13A AONs can exhibit at least a 100%, 200%, 300%, or 400% increase of full length UNC13A mRNA. In various embodiments, UNC13A AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% reduction of mis-spliced UNC13A mRNA. In various embodiments, UNC13A AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A protein. In various embodiments, UNC13A AONs can exhibit at least a 100%, 200%, 300%, or 400% increase of full length UNC13A protein. In some embodiments, the percent increase of the full length UNC13A protein is an increase in comparison to a reduced level of full length UNC13A protein achieved using a TDP43 antisense oligonucleotide. For example, a TDP43 antisense oligonucleotide can be used to deplete full length UNC13A protein followed by increase of the full length UNC13A protein using a UNC13A AON.

[00523] In some embodiments, UNC13A AONs can exhibit at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length UNC13A protein. In some

embodiments, the percent rescue of full length UNC13A refers to the % of full length UNC13A following depletion using a TDP43 antisense oligonucleotide and a treatment using UNC13A AONs in comparison to a negative control (*e.g.*, cells that did not undergo depletion or treatment or cells that were treated with a vehicle solution).

Performance of SMN2 Oligonucleotides

[00524] Generally, SMN2 oligonucleotides and/or SMN2 parent oligonucleotides (*e.g.*, SMN2 oligonucleotides with sequences of any of SEQ ID NOs: 9710-10141 and SEQ ID NOs: 10574-10581) target SMN2 transcripts (for example, a SMN2 mRNA comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 9698-9707 in order to increase, restore, rescue, or stabilize levels of expression of SMN2 mRNA that is capable of translation to produce a functional SMN2 protein (*e.g.*, full length SMN2). In various embodiments, SMN2 AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length SMN2 protein. In various embodiments, SMN2 AONs can exhibit at least a 100%, 200%, 300%, or 400% increase of full length SMN2 protein. In some embodiments, the percent increase of the full length SMN2 protein is an increase in comparison to a reduced level of full length SMN2 protein achieved using a SMN2 antisense oligonucleotide. For example, a SMN2 antisense oligonucleotide can be used to deplete full length SMN2 protein followed by increase of the full length SMN2 protein using a SMN2 AON.

[00525] In some embodiments, SMN2 AONs can exhibit at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length SMN2 protein. In some embodiments, the percent rescue of full length SMN2 refers to the % of full length SMN2 following depletion using a TDP43 antisense oligonucleotide and a treatment using SMN2 AONs in comparison to a negative control (*e.g.*, cells that did not undergo depletion or treatment or cells that were treated with a vehicle solution).

Modifications

[00526] A nucleoside is a base-sugar combination. The nucleobase (also known as base) portion of the nucleoside is normally a heterocyclic base moiety. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those nucleosides that include a pentofuranosyl sugar, the phosphate group can be linked to the 2', 3' or 5' hydroxyl moiety of the sugar. Oligonucleotides are formed through the covalent linkage of adjacent nucleosides to one another, to form a linear polymeric oligonucleotide. Within the

oligonucleotide structure, the phosphate groups are commonly referred to as forming the internucleoside linkages of the oligonucleotide.

[00527] Modifications to antisense compounds encompass substitutions or changes to internucleoside linkages, sugar moieties, or nucleobases. Modified antisense compounds are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases, or increased activity.

[00528] Chemically modified nucleosides may also be employed to increase the binding affinity of a shortened or truncated antisense oligonucleotide for its target nucleic acid. Consequently, comparable results can often be obtained with shorter antisense compounds that have such chemically modified nucleosides.

Modified Internucleoside Linkages

[00529] The naturally occurring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. Antisense compounds having one or more modified, i.e. non-naturally occurring, internucleoside linkages are often selected over antisense compounds having naturally occurring internucleoside linkages because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for target nucleic acids, and increased stability in the presence of nucleases.

[00530] Oligonucleotides having modified internucleoside linkages include internucleoside linkages that retain a phosphorus atom as well as internucleoside linkages that do not have a phosphorus atom. Representative phosphorus containing internucleoside linkages include, but are not limited to, phosphodiesters, phosphotriesters, methylphosphonates, phosphoramidate, and phosphorothioates. Methods of preparation of phosphorous-containing and non-phosphorous-containing linkages are well known.

[00531] In certain embodiments, antisense compounds targeted to a STMN2 nucleic acid comprise one or more modified internucleoside linkages. In certain embodiments, antisense compounds targeted to a KCNQ2 nucleic acid comprise one or more modified internucleoside linkages. In certain embodiments, antisense compounds targeted to a UNC13A nucleic acid comprise one or more modified internucleoside linkages. In certain embodiments, antisense compounds targeted to a SMN2 nucleic acid comprise one or more modified internucleoside linkages. In certain embodiments, the modified internucleoside linkages are interspersed throughout the antisense compound. In certain embodiments, the modified internucleoside linkages are phosphorothioate linkages. In certain embodiments, each internucleoside linkage of

an antisense compound is a phosphorothioate internucleoside linkage. In certain embodiments, the antisense compounds targeted to a STMN2 nucleic acid comprise at least one phosphodiester linkage and at least one phosphorothioate linkage. In certain embodiments, the antisense compounds targeted to a KCNQ2 nucleic acid comprise at least one phosphodiester linkage and at least one phosphorothioate linkage. In certain embodiments, the antisense compounds targeted to a UNC13A nucleic acid comprise at least one phosphodiester linkage and at least one phosphorothioate linkage. In certain embodiments, the antisense compounds targeted to a SMN2 nucleic acid comprise at least one phosphodiester linkage and at least one phosphorothioate linkage.

Modified Sugar Moieties

[00532] Antisense compounds can optionally contain one or more nucleosides wherein the sugar group has been modified. Such sugar modified nucleosides may impart enhanced nuclease stability, increased binding affinity, or some other beneficial biological property to the antisense compounds. In certain embodiments, nucleosides comprise chemically modified ribofuranose ring moieties. Examples of chemically modified ribofuranose rings include without limitation, addition of substituent groups (including 5' and 2' substituent groups, bridging of non-geminal ring atoms to form bicyclic nucleic acids (BNA), replacement of the ribosyl ring oxygen atom with S, N(R) or $C(R_1)(R_2)$ (R, R_1 and R_2 are each independently H, C_1-C_{12} alkyl or a protecting group) and combinations thereof. Examples of chemically modified sugars include 2'-F-5'-methyl substituted nucleoside (*see* PCT International Application WO 2008/101157 Published on Aug. 21, 2008 for other disclosed 5',2'-bis substituted nucleosides) or replacement of the ribosyl ring oxygen atom with S with further substitution at the 2'-position (*see* published U.S. Patent Application US2005-0130923, published on Jun. 16, 2005) or alternatively 5'-substitution of a BNA (*see* PCT International Application WO 2007/134181 Published on Nov. 22, 2007 wherein LNA is substituted with for example a 5'-methyl or a 5'-vinyl group).

[00533] Examples of nucleosides having modified sugar moieties include without limitation nucleosides comprising 5'-vinyl, 5'-methyl (R or 5), 4'-S, 2'-F, 2'-OCH_3, 2'-OCH_2CH_3, 2'-O CH_2 CH_2F and 2'-$O(CH_2)_2OCH_3$ substituent groups. The substituent at the 2' position can also be selected from allyl, amino, azido, thio, O-allyl, O—C_1-C_{10} alkyl, OCF_3, OCH_2F, $O(CH_2)_2S$ CH_3, $O(CH_2)_2$—O—$N(R_m)(R_n)$, O—CH_2—C(=O)—$N(R_m)(R_n)$, and O—CH_2—C(=O)—$N(R_1)$—($CH_2)_2$—$N(R_m)(R_n)$- , where each R_1, R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl.

[00534] Additional examples of modified sugar moieties include a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'-MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

[00535] As used herein, "bicyclic nucleosides" refer to modified nucleosides comprising a bicyclic sugar moiety. Examples of bicyclic nucleosides include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In certain embodiments, antisense compounds provided herein include one or more bicyclic nucleosides comprising a 4' to 2' bridge. Examples of such 4' to 2' bridged bicyclic nucleosides, include but are not limited to one of the formulae: 4'-(CH_2)—O-2' (LNA); 4'-(CH_2)—S-2'; 4'-(CH_2)$_2$—O-2' (ENA); 4'-$CH(CH_3)$—O-2' and 4'-$CH(CH_2OCH_3)$—O-2' (and analogs thereof see U.S. Pat. No. 7,399,845, issued on Jul. 15, 2008); 4'-$C(CH_3)(CH_3)$—O-2' (and analogs thereof see published International Application WO/2009/006478, published Jan. 8, 2009); 4'-CH_2—$N(OCH_3)$-2' (and analogs thereof see published International Application WO/2008/150729, published Dec. 11, 2008); 4'-CH_2—O—$N(CH_3)$-2' (see published U.S. Patent Application US2004-0171570, published Sep. 2, 2004); 4'- CH_2—N(R)—O-2', wherein R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008); 4'-CH_2—$C(H)(CH_3)$-2' (see Chattopadhyaya et al., J. Org. Chem., 2009, 74, 118-134); and 4'-CH_2—C—($=CH_2$)-2' (and analogs thereof see published International Application WO 2008/154401, published on Dec. 8, 2008).

[00536] Further reports related to bicyclic nucleosides can also be found in published literature (*see* for example: Singh et al., Chem. Commun., 1998, 4, 455-456; Koshkin et al., Tetrahedron, 1998, 54, 3607-3630; Wahlestedt et al., Proc. Natl. Acad. Sci. U.S.A., 2000, 97, 5633-5638; Kumar et al., Bioorg. Med. Chem. Lett., 1998, 8, 2219-2222; Singh et al., J. Org. Chem., 1998, 63, 10035-10039; Srivastava et al., J. Am. Chem. Soc., 2007, 129(26) 8362-8379; Elayadi et al., Curr. Opinion Invest. Drugs, 2001, 2, 558-561; Braasch et al., Chem. Biol., 2001, 8, 1-7; and Orum et al., Curr. Opinion Mol. Ther., 2001, 3, 239-243; U.S. Pat. Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 7,034,133; 7,053,207; 7,399,845; 7,547,684; and 7,696,345; U.S. Patent Publication No. US2008-0039618; US2009-0012281; U.S. Patent Ser. No. 60/989,574; 61/026,995; 61/026,998; 61/056,564; 61/086,231; 61/097,787; and 61/099,844; Published PCT International applications WO 1994/014226; WO 2004/106356; WO 2005/021570; WO 2007/134181; WO 2008/150729; WO 2008/154401; and WO 2009/006478. Each of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical

sugar configurations including for example α-L-ribofuranose and β-D-ribofuranose (see PCT international application PCT/DK98/00393, published on Mar. 25, 1999 as WO 99/14226).

[00537] In certain embodiments, bicyclic sugar moieties of BNA nucleosides include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the pentofuranosyl sugar moiety wherein such bridges independently comprises 1 or from 2 to 4 linked groups independently selected from —$[C(R_a)(R_b)]_n$—, —$C(R_a)=C(R_b)$—, —$C(R_a)=N$—, —C(=O)—, —$C(=NR_a)$—, —C(=S) —, —O—, —$Si(R_a)_2$—, —$S(=O)_x$—, and —$N(R_a)$—; wherein:

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O)—H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl (S(=O)-J_1); and

each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(=O)—H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1-C_{12} aminoalkyl, substituted C_1-C_{12} aminoalkyl or a protecting group.

[00538] In certain embodiments, the bridge of a bicyclic sugar moiety is —$[C(R_a)(R_b)]_n$—, —[—$[C(R_a)(R_b)]_n$—O—, —$C(R_aR_b)$—N(R)—O— or —$C(R_aR_b)$—O—N(R)—. In certain embodiments, the bridge is 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2—O-2', 4'-$(CH_2)_2$—O-2', 4'-CH_2—O—N(R)-2' and 4'-CH_2—N(R)—O-2'- wherein each R is, independently, H, a protecting group or C_1-C_{12} alkyl, each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O)—H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl (S(=O)-J_1); each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(=O)—H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1-C_{12}

aminoalkyl, substituted C_1-C_{12} aminoalkyl or a protecting group; and R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008).

[00539] In certain embodiments, bicyclic nucleosides are further defined by isomeric configuration. For example, a nucleoside comprising a 4'-2' methylene-oxy bridge, may be in the α-L configuration or in the β-D configuration. Previously, α-L-methyleneoxy (4'-CH_2—O-2') BNA's have been incorporated into antisense oligonucleotides that showed antisense activity (Frieden et al., Nucleic Acids Research, 2003, 21, 6365-6372).

[00540] In certain embodiments, bicyclic nucleosides include, but are not limited to, α-L-methyleneoxy (4'-CH_2—O-2') BNA, β-D-methyleneoxy (4'-CH_2—O-2') BNA, ethyleneoxy (4'-$(CH_2)_2$—O-2) BNA, aminooxy (4'-CH_2—O—N(R)-2') BNA, oxyamino (4'-CH_2—N(R)—O-2') BNA, methyl(methyleneoxy) (4'-$CH(CH_3)$—O-2') BNA, methylene-thio (4'-CH_2—S-2') BNA, methylene-amino (4'-CH_2—N(R)-2') BNA, methyl carbocyclic (4'-CH_2—$CH(CH_3)$-2') BNA, and propylene carbocyclic (4'-$(CH_2)_3$-2') BNA; wherein R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008).

[00541] The present disclosure provides, in some embodiments, methods for treating, ameliorating, or preventing a neurological disease and/or a neuropathy further include methods of administering, to a patient, a pharmaceutically acceptable composition, for example, a pharmaceutically acceptable formulation that includes one or more STMN2 oligonucleotides, KCNQ2 oligonucleotides, UNC13A oligonucleotides, and/or SMN2 oligonucleotides. STMN2 oligonucleotides can increase, restore, or stabilize STMN2 activity, for example, STMN2 activity, and/or levels of STMN2 expression, for example, STMN2 mRNA and/or protein expression. KCNQ2 oligonucleotides can increase, restore, or stabilize KCNQ2 activity, for example, KCNQ2 activity, and/or levels of KCNQ2 expression, for example, KCNQ2 mRNA and/or protein expression. UNC13A oligonucleotides can increase, restore, or stabilize UNC13A activity, for example, UNC13A activity, and/or levels of UNC13A expression, for example, UNC13A mRNA and/or protein expression. SMN2 oligonucleotides can increase, restore, or stabilize SMN2 activity, for example, SMN2 activity, and/or levels of SMN2 expression, for example, SMN2 mRNA and/or protein expression.

[00542] The present disclosure also provides pharmaceutical compositions comprising a STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide formulated together with one or more pharmaceutically or cosmetically acceptable excipients. These formulations include those suitable for oral, sublingual,

intratracheal, intranasal, transdermal, pulmonary, intrathecal, intrathalamic, intracisternal, intracerebroventricular, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, intraduodenal, or intravenous) administration, transmucosal (*e.g.*, buccal, vaginal, and rectal), or for topical use, *e.g.*, as part of a composition suitable for applying topically to skin and/or mucous membrane, for example, a composition in the form of a gel, a paste, a wax, a cream, a spray, a liquid, a foam, a lotion, an ointment, a topical solution, a transdermal patch, a powder, a vapor, or a tincture. Although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide being used.

[00543] The present disclosure also provides a pharmaceutical composition comprising a STMN2 oligonucleotide or a pharmaceutically acceptable salt thereof (for example, a STMN2 AON that includes a sequence of any of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669). The present disclosure also provides a pharmaceutical composition comprising a KCNQ2 oligonucleotide or a pharmaceutically acceptable salt thereof (for example, a KCNQ2 AON that includes a sequence of any of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs4402-4530). The present disclosure also provides a pharmaceutical composition comprising a UNC13A oligonucleotide or a pharmaceutically acceptable salt thereof (for example, a UNC13A AON that includes a sequence of any of SEQ ID NOs: 4531-5794, SEQ ID NO: 7059-8322, SEQ ID NOs: 9596-9696, or SEQ ID NOs: 10670-10779). The present disclosure also provides a pharmaceutical composition comprising a SMN2 oligonucleotide or a pharmaceutically acceptable salt thereof (for example, a SMN2 AON that includes a sequence of any of SEQ ID NOs: 9710-10141 and SEQ ID NOs: 10574-10581).

[00544] The present disclosure also provides methods that include the use of pharmaceutical compositions comprising a STMN2 AON, KCNQ2 AON, UNC13A AON, and/or SMN2 AON is formulated together with one or more pharmaceutically acceptable excipients. Exemplary compositions provided herein include compositions comprising a STMN2 AON, KCNQ2 AON, UNC13A AON, and/or SMN2 AON, and one or more pharmaceutically acceptable excipients. Formulations include those suitable for oral, sublingual, intratracheal, intranasal, transdermal, pulmonary, intrathecal, intrathalamic, intracisternal, intracerebroventricular, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, intraduodenal, or intravenous) administration, transmucosal (*e.g.*, buccal, vaginal, and rectal), or for topical use. The most suitable form of

administration in any given case will depend on the clinical symptoms, complications, or biochemical indicia of the state, disorder, disease, or condition that one is trying to prevent in a subject; the state, disorder, disease, or condition one is trying to prevent in a subject; and/or on the nature of the particular compound and/or the composition being used.

Additional Chemically Modified Oligonucleotides

[00545] STMN2 AONs, KCNQ2 AONs, UNC13A AONs, and/or SMN2 AONs described herein, can include chemically modified nucleosides, including modified ribonucleosides and modified deoxyribonucleosides. Chemically modified nucleosides include, but are not limited to, uracine, uridine, 2'-O-(2-methoxyethyl) modifications, for example, 2'-O-(2-methoxyethyl)guanosine, 2'-O-(2-methoxyethyl)adenosine, 2'-O-(2-methoxyethyl)cytosine, and 2'-O-(2-methoxyethyl)thymidine. In certain embodiments, mixed modalities, *e.g.*, a combination of a STMN2 peptide nucleic acid (PNA) and a STMN2 locked nucleic acid (LNA), a combination of a KCNQ2 peptide nucleic acid (PNA) and a KCNQ2 locked nucleic acid (LNA), a combination of a UNC13A peptide nucleic acid (PNA) and a UNC13A locked nucleic acid (LNA), and/or a combination of a SMN2 peptide nucleic acid (PNA) and a SMN2 locked nucleic acid (LNA). Chemically modified nucleosides also include, but are not limited to, locked nucleic acids (LNAs), 2'-O-methyl, 2'-fluoro, and 2'-fluoro-β-D-arabinonucleotide (FANA), and Fluoro Cyclohexenyl nucleic acid (F-CeNA) modifications. Chemically modified nucleosides that can be included in STMN2 AONs described herein are described in Johannes and Lucchino, (2018) "Current Challenges in Delivery and Cytosolic Translocation of Therapeutic RNAs" *Nucleic Acid Ther.* 28(3): 178–93; Rettig and Behlke, (2012) "Progress toward in vivo use of siRNAs-II" *Mol Ther* 20:483–512; and Khvorova and Watts, (2017) "The chemical evolution of oligonucleotide therapies of clinical utility" *Nat Biotechnol.*, 35(3):238-48, the contents of each of which are incorporated by reference herein.

[00546] STMN2 AONs, KCNQ2 AONs, UNC13A AONs, and/or SMN2 AONs described herein can include chemical modifications that promote stabilization of an oligonucleotide's terminal 5'-phosphate and phosphatase-resistant analogs of 5′-phosphate. Chemical modifications that promote oligonucleotide terminal 5'-phosphate stabilization or which are phosphatase-resistant analogs of 5′-phosphate include, but are not limited to, 5′-methyl phosphonate, 5′-methylenephosphonate, 5′-methylenephosphonate analogs, 5′-*E*-vinyl phosphonate (5′-*E*-VP), 5′-phosphorothioate, and 5′-*C*-methyl analogs. Chemical modifications that promote AON terminal 5'-phosphate stabilization and phosphatase-resistant analogues of 5′-phosphate are described in

Khvorova and Watts, (2017) "The chemical evolution of oligonucleotide therapies of clinical utility" *Nat Biotechnol.*, 35(3):238-48, the contents of which are incorporated by reference herein.

[00547] In some embodiments described herein, STMN2 AONs, KCNQ2 AONs, UNC13A AONs, and/or SMN2 AONs described herein can include chemically modified nucleosides, for example, 2' O-methyl ribonucleosides, for example, 2' O-methyl cytidine, 2' O-methyl guanosine, 2' O-methyl uridine, and/or 2' O-methyl adenosine. STMN2 AONs, KCNQ2 AONs, UNC13A AONs, and/or SMN2 AONs described herein can include one or more chemically modified bases, including a 5-methylpyrimidine, for example, 5-methylcytosine, and/or a 5-methylpurine, for example, 5-methylguanine. Chemically modified nucleosides can further include pseudo-uridine or 5'methoxyuridine. STMN2 AONs, KCNQ2 AONs, UNC13A AONs, and/or SMN2 AONs described herein can include any of the following chemically modified nucleosides: 5-methyl-2'-O-methylcytidine, 5-methyl-2'-O-methylthymidine, 5-methylcytidine, 5-methyluridine, and/or 5-methyl 2'-deoxycytidine.

[00548] STMN2 AONs, KCNQ2 AONs, UNC13A AONs, and/or SMN2 AONs described herein can include a phosphate backbone where one or more of the oligonucleoside linkages is a phosphate linkage. STMN2 AONs, KCNQ2 AONs, UNC13A AONs, and/or SMN2 AONs described herein may include a modified oligonucleotide backbone, where one or more of the nucleoside linkages of the sequence is selected from the group consisting of a phosphorothioate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage. In some embodiments of STMN2 AONs, KCNQ2 AONs, UNC13A AONs, and/or SMN2 AONs described herein, at least one (*i.e.*, one or more) internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. For example, in some embodiments of STMN2 AONs, KCNQ2 AONs, UNC13A AONs, and/or SMN2 AONs described herein, one, two, three, or more internucleoside linkages of the oligonucleotide is a phosphorothioate linkage. In preferred embodiments of STMN2 AONs, KCNQ2 AONs,

UNC13A AONs, and/or SMN2 AONs described herein, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

STMN2

[00549] In some embodiments, all of the nucleotide linkages of a STMN2 AON of any of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669 are phosphorothioate linkages. In some embodiments, one or more of the nucleotide linkages of a STMN2 AON of any of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669 are phosphorothioate linkages.

[00550] In various embodiments, nucleotide linkages of STMN2 AON described herein such as any of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669 include a mix of phosphodiester and phosphorothioate linkages.

[00551] In some embodiments, nucleoside linkages linking a base at position 3 of a STMN2 AON described herein are phosphodiester bonds. For example, the base at position 3 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer STMN2 AON with phosphodiester bonds linking the base at position 3 can be denoted as:

XXoDoXXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00552] In some embodiments, one of the nucleoside linkages linking a base at position 3 of a STMN2 AON described herein is a phosphodiester bond. For example, the base at position 3 may be linked to either the preceding base or the succeeding base through a phosphodiester bond. An example 25mer STMN2 AON with a phosphodiester bond linking the base at position 3 to a preceding base can be denoted as:

XXoDXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00553] An example 25mer STMN2 AON with a phosphodiester bond linking the base at position 3 to a succeeding base can be denoted as:

XXDoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00554] In various embodiments, in addition to one of the nucleoside linkages linking a base at position 3 of a STMN2 AON described herein being a phosphodiester bond, the STMN2 AON further includes two spacers. The two spacers can be positioned in the STMN2 AON such that the STMN2 AON includes a segment with at most 7 linked nucleosides. An example 25mer STMN2 AON with two spacers and with a phosphodiester bond linking the base at position 3 to a preceding base can be denoted as:

XxoD$\mathbf{S_1}$XXXXXXXXX$\mathbf{S_2}$XXXXXXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00555] An example 25mer STMN2 AON with two spacers and with a phosphodiester bond linking the base at position 3 to a succeeding base can be denoted as:

XXDoXXXXXXX$\mathbf{S_1}$XXXXXXXXX$\mathbf{S_2}$XXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00556] In some embodiments, nucleoside linkages linking a base at position 4 of a STMN2 AON described herein are phosphodiester bonds. For example, the base at position 4 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer STMN2 AON with phosphodiester bonds linking the base at position 4 can be denoted as:

XXXoDoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00557] In some embodiments, one of the nucleoside linkages linking a base at position 4 of a STMN2 AON described herein is a phosphodiester bond. For example, the base at position 4 may be linked to either the preceding base or the succeeding base through a phosphodiester bond. An example 25mer STMN2 AON with a phosphodiester bond linking the base at position 4 to a preceding base can be denoted as:

XXXoDXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00558] An example 25mer STMN2 AON with a phosphodiester bond linking the base at position 4 to a succeeding base can be denoted as:

XXXDoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00559] In some embodiments, nucleoside linkages linking both bases at position 3 and position 4 of a STMN2 AON described herein are phosphodiester bonds. For example, the base at position 3 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond, and the base at position 4 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer STMN2 AON with phosphodiester bonds linking the bases at positions 3 and 4 can be denoted as:

XXoDoEoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond, "D" represents the base at position 3, and "E" represents the base at position 4. In various embodiments, all other bases of the STMN2 AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00560] In various embodiments, STMN2 AON described herein include one or more spacers and phosphodiester bonds are located relative to the one or more spacers. In some embodiments, the Y number of bases immediately preceding a spacer are linked through phosphodiester bonds. In various embodiments, Y is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. In particular embodiments, Y is two bases. For example, if the spacer is located at position 15, the bases at positions 13 and 14 of the STMN2 AON are each linked to their respective adjacent bases through phosphodiester bonds. As described herein, the spacer can be located at various positions in the STMN2 AON and therefore, the 2 bases immediately preceding the spacer can vary within the STMN2 AON depending on where the spacer is situated.

[00561] In various embodiments, the STMN2 AON may include more than one spacer. In some embodiments, only one of the spacers has Y number of bases immediately preceding the spacer that are linked through phosphodiester bonds. In such embodiments, the other spacers are linked to respective preceding bases through phosphorothioate bonds. In various embodiments, two of

the spacers have Y number of bases immediately preceding the spacers that are linked through phosphodiester bonds. In various embodiments, each of the spacers in the STMN2 AON have Y number of bases immediately preceding the spacers that are linked through phosphodiester bonds. In various embodiments, all other bases of the STMN2 AON are linked through phosphorothioate bonds.

[00562] In some embodiments, Y number of bases immediately preceding a spacer and Z number of bases immediately succeeding a spacer are linked through phosphodiester bonds. In various embodiments, Y is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. In various embodiments, Z is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. Y and Z can be independent of each other. In particular embodiments, Y is one base and Z is one base. For example, if the spacer is located at position 15, the bases at positions 14 and 16 of the STMN2 AON are each linked to their respective adjacent bases through phosphodiester bonds. To provide an example, such a STMN2 AON (e.g., 25mer) can be denoted as:

XXXXXXXXXXXXXoDo**S**oEoXXXXXXXXX

where "S" represents a spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00563] As described herein, the spacer can be located at various positions in the STMN2 AON and therefore, the bases immediately preceding or immediately succeeding the spacer can vary within the STMN2 AON depending on where the spacer is situated.

[00564] In various embodiments, the STMN2 AON may include more than one spacer. In some embodiments, only one of the spacers has Y number of bases immediately preceding the spacer and Z number of bases immediately succeeding the spacer that are linked through phosphodiester bonds. In such embodiments, the other spacers of the STMN2 AON are linked to respective preceding and succeeding bases through phosphorothioate bonds. To provide an example, such a STMN2 AON (e.g., 25mer) can be denoted as:

XXXXoDo$\mathbf{S_1}$oEoXXXXXXXXXXX$\mathbf{S_2}$XXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00565] As another example, such a STMN2 AON (e.g., 25mer) can be denoted as:

XXXXX**S**$_1$XXXXXXXXXXXoDo**S**$_2$oDoXXXXX

where "S1" represents a first spacer, "S2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00566] In some embodiments, one of the spacers is linked to the immediately preceding base through a phosphodiester bond. For example, a STMN2 AON includes a first spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXo**S**$_1$XXXXXXXXXXX**S**$_2$XXXXXX

where "S1" represents a first spacer, "S2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00567] As another example, a STMN2 AON includes a second spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXX**S**$_1$XXXXXXXXXXXo**S**$_2$XXXXXX

where "S1" represents a first spacer, "S2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00568] In various embodiments, the STMN2 AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately preceding base through a phosphodiester bond. For example, the STMN2 AON may be a 21mer with a first spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXXo**S**$_1$XXXXX**S**$_2$XXXXXXX

where "S1" represents a first spacer, "S2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00569] As another example, the STMN2 AON may be a 21mer with a second spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXX**S**$_1$XXXXXo**S**$_2$XXXXXXX

where "S1" represents a first spacer, "S2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00570] In some embodiments, the STMN2 AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately preceding base through a

phosphodiester bond and the immediately preceding base is further linked to the preceding base through a phosphodiester bond. An example 21mer STMN2 AON can be denoted as:

XXXEoDo**S**$_1$XXXXXX**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_1 and "E" represents the base immediately preceding "D." Any nucleobase in the AON can be a nucleobase analog.

[00571] As another example, a 21mer STMN2 AON can be denoted as:

XXXXX**S**$_1$XXXXEoDo**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_2 and "E" represents the base immediately preceding "D." Any nucleobase in the AON can be a nucleobase analog.

[00572] In some embodiments, the STMN2 AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where a base that immediately precedes a first spacer is linked to another base through a phosphodiester bond. The base that immediately precedes the first spacer may be linked to the first spacer through a non-phosphodiester bond, such as a phosphorothioate bond. Additionally a second spacer is linked to an immediately preceding base through a phosphodiester bond. An example of a 21mer STMN2 AON can be denoted as:

XXXEoD**S**$_1$XXXXXXo**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_1 and "E" represents the base immediately preceding "D." Here, the base "D" is linked to the first spacer S_1 through a non-phosphodiester bond (e.g., phosphorothioate bond). Additionally, the base "D" is linked to base "E" through a phosphodiester bond. The second spacer S_2 is linked to an immediately preceding base through a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00573] Another example of such a 21mer STMN2 AON can be denoted as:

XXXXXo**S**$_1$XXXXEoD**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_2 and "E" represents the base immediately preceding "D." Here, the base "D" is linked to the second spacer S_2 through a non-phosphodiester bond (e.g., phosphorothioate bond). Additionally, the base "D" is linked to base "E" through a phosphodiester bond. The first spacer S_1 is linked to an immediately

preceding base through a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00574] In some embodiments, one of the spacers is linked to the immediately succeeding base through a phosphodiester bond. For example, a STMN2 AON includes a first spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXX\mathbf{S}_1oXXXXXXXXXXX\mathbf{S}_2XXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00575] As another example, a STMN2 AON includes a second spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXX\mathbf{S}_1XXXXXXXXXXX\mathbf{S}_2oXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00576] In various embodiments, the STMN2 AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately succeeding base through a phosphodiester bond. For example, the STMN2 AON may be a 21mer with a first spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXXX\mathbf{S}_1oXXXXX\mathbf{S}_2XXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00577] As another example, the STMN2 AON may be a 21mer with a second spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXXX\mathbf{S}_1XXXXX\mathbf{S}_2oXXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00578] In various embodiments, two of the spacers have Y number of bases immediately preceding the spacers and Z number of bases immediately succeeding the spacers that are linked through phosphodiester bonds. In various embodiments, each of the spacers in the STMN2 AON have Y number of bases immediately preceding the spacers and Z number of bases immediately

succeeding the spacers that are linked through phosphodiester bonds. An example of such a STMN2 AON (e.g., 25mer) can be denoted as:

XXXXoDo**S$_1$**oEoXXXXXXXXXXoFo**S$_2$**oHoXXXXX

where "S1" represents a first spacer, "S2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the first spacer, "E" represents the base immediately succeeding the first spacer, "F" represents a base immediately preceding the second spacer, and "H" represents the base immediately succeeding the second spacer. In various embodiments, all other bases of the STMN2 AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00579] In various STMN2 AON includes two or more spacers and a range of bases located between the two spacers are linked through phosphodiester bonds. In various embodiments, the range of bases include two, three, four, five, six, or seven bases linked through phosphodiester bonds. In particular embodiments, the range of bases include two bases linked through phosphodiester bonds. In particular embodiments, the range of bases include four bases linked through phosphodiester bonds. In various embodiments, all other bases of the STMN2 AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00580] In various embodiments, the range of bases linked through phosphodiester bonds are positioned Y number of bases succeeding the first spacer and Z number of preceding the second spacer. In various embodiments, Y is one, two, three, four, five, six, or seven bases. In various embodiments, Z is one, two, three, four, five, six, or seven bases. Y and Z can be independent on each other. Any nucleobase in the AON can be a nucleobase analog.

[00581] In particular embodiments, Y is five bases and Z is four bases. To provide an example, such a STMN2 AON (e.g., 25mer) can be denoted as:

XXXXXXXX**S$_1$**XXXXoDoEoFoHoXXX**S$_2$**XXXX

where "S1" represents a first spacer, "S2" represents a second spacer, and "o" represents a phosphodiester bond. The bases "D," "E," "F," and "H" represent the range of bases that are linked through phosphodiester bonds. In this example, the range of bases is located five bases after the first spacer (e.g., D is positioned five bases after the first spacer) and the range of bases is located four bases preceding the second spacer (e.g., H is positioned four bases before the second spacer). Any nucleobase in the AON can be a nucleobase analog.

[00582] In particular embodiments, Y is four bases and Z is three bases. To provide an example, such a STMN2 AON (e.g., 23mer) can be denoted as:

XXXXXXX**S$_1$**XXXoDoEoXX**S$_2$**XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, and "o" represents a phosphodiester bond. The bases "D" and "E" represent the range of bases that are linked through phosphodiester bonds. In this example, the range of bases is located four bases after the first spacer (e.g., D is positioned four bases after the first spacer) and the range of bases is located three bases preceding the second spacer (e.g., E is positioned three bases before the second spacer). In various embodiments, the positions of the two spacers differ than shown above and therefore, the range of bases linked through phosphodiester bonds are differently positioned. In various embodiments, all other bases of the STMN2 AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00583] Table 25 below further depicts examples of STMN2 AON with a mix of phosphodiester and phosphorothioate linkages. In particular, Table 25 depicts examples of STMN2 AONs including spacers and a mix of phosphodiester and phosphorothioate linkages. Any nucleobase in the AON can be a nucleobase analog.

Table 25: Example STMN2 AONs with a mixture of phosphodiester and phosphorothioate bonds.

SEQ ID NO:	AON Sequence* (5' → 3'), where "o" represents a phosphodiester bond, and where "S" indicates a spacer. All other linkages are phosphorothioate bonds.	Bases linked with phosphodiester bonds
173	GAGTCCTGCAATATGAATATAATTT	N/A
1451	GAoGoSoCCTGCAATATSAATATAATTT	Bases at positions 3 and 4
1452	GAoGoToCCTGCASTATGAATATSATTT	Bases at positions 3 and 4
1453	GAoGoToCCSGCAATATGAATSTAATTT	Bases at positions 3 and 4
1454	GAoGoToCCSGCAATATGAASATAATTT	Bases at positions 3 and 4
1455	GToCoCoTGCSATATGAASATAAT	Bases at positions 3 and 4
1456	GToCoCoTSCAATATGSATATAAT	Bases at positions 3 and 4
1457	GToCoCoTGCSATATGSATATAAT	Bases at positions 3 and 4
1458	GAGSCCTGCAAToAoToSAATATAATTT	2 bases preceding a spacer
1459	GAGTCCTGCASTATGAAToAoToSATTT	2 bases preceding a spacer
1460	GAGTCCSGCAATATGAoAoToSTAATTT	2 bases preceding a spacer
1461	GAGTCCSGCAATATGoAoAoSATAATTT	2 bases preceding a spacer
1462	GTCCTGCSATATGoAoAoSATAAT	2 bases preceding a spacer

1463	GTCCTSCAATAoToGoSATATAAT	2 bases preceding a spacer
1464	GTCCTGCSATAoToGoSATATAAT	2 bases preceding a spacer
1465	GAoGoSoCoCTGCAATATSAATATAATTT	1 base preceding and 1 base after a spacer
1466	GAGTCCTGCoAoSoToATGAATATSATTT	1 base preceding and 1 base after a spacer
1467	GAGTCoCoSoGoCAATATGAATSTAATTT	1 base preceding and 1 base after a spacer
1468	GAGTCoCoSoGoCAATATGAASATAATTT	1 base preceding and 1 base after a spacer
1469	GTCCTGoCoSoAoTATGAASATAAT	1 base preceding and 1 base after a spacer
1470	GTCCoToSoCoAATATGSATATAAT	1 base preceding and 1 base after a spacer
1471	GTCCTGoCoSoAoTATGSATATAAT	1 base preceding and 1 base after a spacer
1472	GAGSCCTGCAATAoToSoAoATATAATTT	1 base preceding and 1 base after a spacer
1473	GAGTCCTGCASTATGAATAoToSoAoTTT	1 base preceding and 1 base after a spacer
1474	GAGTCCSGCAATATGAAoToSoToAATTT	1 base preceding and 1 base after a spacer
1475	GAGTCCSGCAATATGAoAoSoAoTAATTT	1 base preceding and 1 base after a spacer
1476	GTCCTGCSATATGAoAoSoAoTAAT	1 base preceding and 1 base after a spacer
1477	GTCCTSCAATAToGoSoAoTATAAT	1 base preceding and 1 base after a spacer
1478	GTCCTGCSATAToGoSoAoTATAAT	1 base preceding and 1 base after a spacer
1479	GAoGoSoCoCTGCAATAoToSoAoATATAATTT	1 base preceding AND 1 base after EACH spacer

1480	GAGTCCTGCoAoSoToATGAATAoToSoAoTTT	1 base preceding AND 1 base after EACH spacer
1481	GAGTCoCoSoGoCAATATGAAoToSoToAATTT	1 base preceding AND 1 base after EACH spacer
1482	GAGTCoCoSoGoCAATATGAoAoSoAoTAATTT	1 base preceding AND 1 base after EACH spacer
1483	GTCCTGoCoSoAoTATGAoAoSoAoTAAT	1 base preceding AND 1 base after EACH spacer
1484	GTCCoToSoCoAATAToGoSoAoTATAAT	1 base preceding AND 1 base after EACH spacer
1485	GTCCTGoCoSoAoTAToGoSoAoTATAAT	1 base preceding AND 1 base after EACH spacer
197	CCTTTCTCTCGAAGGTCTTCTGCCG	N/A
1430	CCTTTCTCTCGAAGGTCTTCTGC	N/A
1431	CTTTCTCTCGAAGGTCTTCTGCC	N/A
1486	CCoToToTCTCTCGAAGGTCTTCTGCCG	Bases at positions 3 and 4
1487	CCoToToTCTCSCGAAGGTCTTCSGCCG	Bases at positions 3 and 4
1488	CToToToCTCSCGAAGGTSTTCTGCC	Bases at positions 3 and 4
1489	TToToCoTCTSGAAGGTCSTCTGCCG	Bases at positions 3 and 4
1490	TToToCoTCTCGAAGGTCTTCTGCCG	Bases at positions 3 and 4
1491	CCoToToTCTCTCGAAGGTCTTCTGC	Bases at positions 3 and 4
1492	CCTTTCoToCoSCGAAGGTCTTCSGCCG	2 bases preceding a spacer
1493	CTTTCoToCoSCGAAGGTSTTCTGCC	2 bases preceding a spacer
1494	TTTCToCoToSGAAGGTCSTCTGCCG	2 bases preceding a spacer
1495	CCTTTCTCSCGAAGGTCToToCoSGCCG	2 bases preceding a spacer
1496	CTTTCTCSCGAAGoGoToSTTCTGCC	2 bases preceding a spacer
1497	TTTCTCTSGAAGGoToCoSTCTGCCG	2 bases preceding a spacer
1498	CCTTTCToCoSoCoGAAGGTCTTCSGCCG	1 base preceding and 1 base after a spacer
1499	CTTTCToCoSoCoGAAGGTSTTCTGCC	1 base preceding and 1 base after a spacer

1500	TTTCTCoToSoGoAAGGTCSTCTGCCG	1 base preceding and 1 base after a spacer
1501	CCTTTCTCSCGAAGGTCTToCoSoGoCCG	1 base preceding and 1 base after a spacer
1502	CTTTCTCSCGAAGGoToSoToTCTGCC	1 base preceding and 1 base after a spacer
1503	TTTCTCTSGAAGGToCoSoToCTGCCG	1 base preceding and 1 base after a spacer
1504	CCTTTCToCoSoCoGAAGGTCTToCoSoGoCCG	1 base preceding AND 1 base after EACH spacer
1505	CTTTCToCoSoCoGAAGGoToSoToTCTGCC	1 base preceding AND 1 base after EACH spacer
1506	TTTCTCoToSoGoAAGGToCoSoToCTGCCG	1 base preceding AND 1 base after EACH spacer
1507	CCTTTCTCSCGAAoGoGoToCoTTCSGCCG	Range of 4 bases between two spacers
1508	CTTTCTCSCGAoAoGoGTSTTCTGCC	Range of 2 bases between two spacers
1509	TTTCTCTSGAAoGoGoTCSTCTGCCG	Range of 2 bases between two spacers
1510	GAoGSCCTGCAATATSAATATAATTT	Base 3 linked to preceding base through phosphodiester linkage
1511	GAGoTCCTGCASTATGAATATSATTT	Base 3 linked to preceding base through phosphodiester linkage
1512	GAGTCCoSGCAATATGAATSTAATTT	First spacer linked to preceding base through phosphodiester linkage
1513	GAGTCCSoGCAATATGAASATAATTT	First spacer linked to succeeding base through phosphodiester linkage

1514	GTCCTGCSoATATGAASATAAT	First spacer linked to succeeding base through phosphodiester linkage
1515	GTCCTGCoSATATGSATATAAT	First spacer linked to preceding base through phosphodiester linkage
1516	GTCCoToSCAATATGSATATAAT	1 base preceding a first spacer linked through phosphodiester linkage
1517	GAGTCCSGCAATATGAAToSTAATTT	Second spacer linked to preceding base through phosphodiester linkage
1518	GAGTCCSGCAATATGAASoATAATTT	Second spacer linked to succeeding base through phosphodiester linkage
1519	GTCCTGCSATATGAAoSATAAT	Second spacer linked to preceding base through phosphodiester linkage
1520	GTCCTGCSATATGSoATATAAT	First spacer linked to succeeding base through phosphodiester linkage
1521	GTCCoTSCAATATGoSATATAAT	1 base preceding a first spacer linked through phosphodiester linkage and second spacer linked to preceding base through phosphodiester linkage

[00584] In some embodiments, a disclosed STMN2 AON may have at least one modified nucleobase, *e.g.*, 5-methylcytosine, and/or at least one methylphosphonate nucleotide, which is placed, for example, either at only one of the 5′ or 3′ ends or at both 5′ and 3′ ends or along the oligonucleotide sequence.

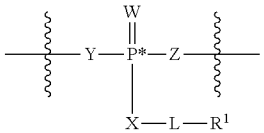
[00585] STMN2 AONs may include at least one modified sugar. For example, the sugar moiety of at least one nucleotide constituting the oligonucleotide is a ribose in which the 2′-OH group may be replaced by any one selected from the group consisting of OR, R, R′OR, SH, SR, NH_2, NR_2, N_3, CN, F, Cl, Br, and I (wherein R is an alkyl or aryl and R′ is an alkylene). Examples of a modified sugar moiety include a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'-MOE or MOE), 2'-O-(N-methylacetamide), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

[00586] In some embodiments, STMN2 AONs comprise 2'OMe (*e.g.*, a STMN2 AON comprising one or more 2'OMe modified sugar), 2'-MOE or MOE (*e.g.*, a STMN2 AON comprising one or more 2'-MOE modified sugar), PNA (*e.g.*, a STMN2 AON comprising one or more *N*-(2-aminoethyl)-glycine units linked by amide bonds or carbonyl methylene linkage as repeating units in place of a sugar-phosphate backbone), LNA (*e.g.*, a STMN2 AON comprising one or more locked ribose, and can be a mixture of 2'-deoxy nucleotides or 2'Ome nucleotides), c-ET (*e.g.*, a STMN2 AON comprising one or more cET sugar), cMOE (*e.g.*, a STMN2 AON comprising one or more cMOE sugar), morpholino oligomer (*e.g.*, a STMN2 AON comprising a backbone comprising one or more PMO), deoxy-2'-fluoro nucleoside (*e.g.*, a STMN2 AON comprising one or more 2'-fluoro-β-D-arabinonucleoside), tcDNA (*e.g.*, a STMN2 AON comprising one or more tcDNA modified sugar), ENA (*e.g.*, a STMN2 AON comprising one or more ENA modified sugar), or HNA (*e.g.*, a STMN2 AON comprising one or more HNA modified sugar). In some embodiments, a STMN2 AON comprises one or more phosphorothioate linkage, phosphodiester linkage, phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, morpholino linkage, PNA linkage, or any combination of phosphorothioate linkage, phosphodiester linkage, a phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, morpholino linkage, and PNA linkage. In some embodiments, a STMN2 AON comprises one or more phosphorothioate linkage, phosphodiester linkage, or a combination of phosphorothioate and phosphodiester linkages.

[00587] In some embodiments, STMN2 AONs with a sequence of any one of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669 is a chirally controlled oligonucleotide, such as a chirally controlled oligonucleotide described in any of US Patent No. 9,982,257, US Patent No. 10,590,413, US

10,724,035, US 10,450,568, and PCT Publication No. WO2019200185, each of which is hereby incorporated by reference in its entirety.

[00588] For example, a STMN2 AON with a sequence of any one of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669 is a chirally controlled oligonucleotide comprising a plurality of oligonucleotides of at least one type, wherein each type is defined by: 1) base sequence; 2) pattern of backbone linkages; 3) pattern of backbone chiral centers; and 4) pattern of backbone X-moieties (—X-L-R^1); wherein: the oligonucleotides of the at least one type comprise one or more phosphorothioate triester internucleotidic linkages and one or more phosphate diester linkage; the oligonucleotides of the at least one type comprise at least two consecutive modified internucleotidic linkages; and oligonucleotides of the at least one oligonucleotide type comprise one or more modified internucleotidic linkages independently having the structure of:



wherein: P* is an asymmetric phosphorus atom and is either Rp or Sp;

W is O, S or Se; each of X, Y and Z is independently —O—, —S—, —N(-L-R^1)—, or L; L is a covalent bond or an optionally substituted, linear or branched C_1-C_{50} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1-C_6 alkylene, C_1-C_6 alkenylene, —C≡C—, —C(R′)$_2$—, -Cy-, —O—, —S—, —S—S—, —N(R′)—, —C(O)—, —C(S)—, —C(NR′)—, —C(O)N(R′)—, —N(R′)C(O)N(R′)—, —N(R′)C(O)—, —N(R′)C(O)O—, —OC(O)N(R′)—, —S(O)—, —S(O)$_2$—, —S(O)$_2$N(R′)—, —N(R′)S(O)$_2$—, —SC(O)—, —C(O)S—, —OC(O)—, or —C(O)O—; R^1 is halogen, R, or an optionally substituted C_1-C_{10} aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1-C_6 alkylene, C_1-C_6 alkenylene, —C≡C—, —C(R′)$_2$—, -Cy-, —O—, —S—, —S—S—, —N(R′)—, —C(O)—, —C(S)—, —C(NR′)—, —C(O)N(R′)—, —N(R′)C(O)N(R′)—, —N(R′)C(O)—, —N(R′)C(O)O—, —OC(O)N(R′)—, —S(O)—, —S(O)$_2$—, —S(O)$_2$N(R′)—, —N(R′)S(O)$_2$—, —SC(O)—, —C(O)S—, —OC(O)—, or —C(O)O—; each R′ is independently —R, —C(O)R, —CO$_2$R, or —SO$_2$R, or: two R′ on the same nitrogen are taken together with their intervening atoms to form an optionally substituted heterocyclic or heteroaryl ring, or two R′ on the same carbon are taken together with their intervening atoms to form an optionally substituted aryl, carbocyclic, heterocyclic, or heteroaryl ring; -Cy- is an optionally substituted bivalent ring selected from phenylene, carbocyclylene,

arylene, heteroarylene, or heterocyclylene; each R is independently hydrogen, or an optionally substituted group selected from C_1-C_6 aliphatic, phenyl, carbocyclyl, aryl, heteroaryl, or heterocyclyl; and each independently represents a connection to a nucleoside. In some embodiments, a STMN2 AON with a sequence of any one of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669 is a chirally controlled oligonucleotide comprising certain chemical modifications (e.g., 2'F (2' Fluoro, which contains a fluorine molecule at the 2' ribose position (instead of 2'-hydroxyl group in an RNA monomer)), 2'-OMe, phosphorothioate linkages, lipid conjugation, etc.), as described in U.S. Patent No. 10,450,568.

KCNQ2

[00589] In some embodiments, all of the nucleotide linkages of a KCNQ2 AON of any of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, or SEQ ID NOs: 4402-4409are phosphorothioate linkages. In some embodiments, one or more of the nucleotide linkages of a KCNQ2 AON of any of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, or SEQ ID NOs: 4402-4409 are phosphorothioate linkages.

[00590] In various embodiments, nucleotide linkages of KCNQ2 AON described herein such as any of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, or SEQ ID NOs: 4402-4409 include a mix of phosphodiester and phosphorothioate linkages.

[00591] In some embodiments, nucleoside linkages linking a base at position 3 of a KCNQ2 AON described herein are phosphodiester bonds. For example, the base at position 3 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer KCNQ2 AON with phosphodiester bonds linking the base at position 3 can be denoted as:

XXoDoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00592] In some embodiments, one of the nucleoside linkages linking a base at position 3 of a KCNQ2 AON described herein is a phosphodiester bond. For example, the base at position 3 may be linked to either the preceding base or the succeeding base through a phosphodiester bond.

An example 25mer KCNQ2 AON with a phosphodiester bond linking the base at position 3 to a preceding base can be denoted as:

XXoDXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00593] An example 25mer KCNQ2 AON with a phosphodiester bond linking the base at position 3 to a succeeding base can be denoted as:

XXDoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00594] In various embodiments, in addition to one of the nucleoside linkages linking a base at position 3 of a KCNQ2 AON described herein being a phosphodiester bond, the KCNQ2 AON further includes two spacers. The two spacers can be positioned in the KCNQ2 AON such that the KCNQ2 AON includes a segment with at most 7 linked nucleosides. An example 25mer KCNQ2 AON with two spacers and with a phosphodiester bond linking the base at position 3 to a preceding base can be denoted as:

XXoD$\mathbf{S_1}$XXXXXXXXX$\mathbf{S_2}$XXXXXXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00595] An example 25mer KCNQ2 AON with two spacers and with a phosphodiester bond linking the base at position 3 to a succeeding base can be denoted as:

XXDoXXXXXXX$\mathbf{S_1}$XXXXXXXXX$\mathbf{S_2}$XXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00596] In some embodiments, nucleoside linkages linking a base at position 4 of a KCNQ2 AON described herein are phosphodiester bonds. For example, the base at position 4 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer KCNQ2 AON with phosphodiester bonds linking the base at position 4 can be denoted as:

XXXoDoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00597] In some embodiments, one of the nucleoside linkages linking a base at position 4 of a KCNQ2 AON described herein is a phosphodiester bond. For example, the base at position 4 may be linked to either the preceding base or the succeeding base through a phosphodiester bond. An example 25mer KCNQ2 AON with a phosphodiester bond linking the base at position 4 to a preceding base can be denoted as:

XXXoDXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00598] An example 25mer KCNQ2 AON with a phosphodiester bond linking the base at position 4 to a succeeding base can be denoted as:

XXXDoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00599] In some embodiments, nucleoside linkages linking both bases at position 3 and position 4 of a KCNQ2 AON described herein are phosphodiester bonds. For example, the base at position 3 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond, and the base at position 4 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer KCNQ2 AON with phosphodiester bonds linking the bases at positions 3 and 4 can be denoted as:

XXoDoEoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond, "D" represents the base at position 3, and "E" represents the base at position 4. In various embodiments, all other bases of the KCNQ2 AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00600] In various embodiments, KCNQ2 AON described herein include one or more spacers and phosphodiester bonds are located relative to the one or more spacers. In some embodiments, the Y number of bases immediately preceding a spacer are linked through phosphodiester bonds. In various embodiments, Y is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. In particular embodiments, Y is two bases. For example, if the spacer is located at position 15, the bases at positions 13 and 14 of the KCNQ2 AON are each linked to their

respective adjacent bases through phosphodiester bonds. As described herein, the spacer can be located at various positions in the KCNQ2 AON and therefore, the 2 bases immediately preceding the spacer can vary within the KCNQ2 AON depending on where the spacer is situated.

[00601] In various embodiments, the KCNQ2 AON may include more than one spacer. In some embodiments, only one of the spacers has Y number of bases immediately preceding the spacer that are linked through phosphodiester bonds. In such embodiments, the other spacers are linked to respective preceding bases through phosphorothioate bonds. In various embodiments, two of the spacers have Y number of bases immediately preceding the spacers that are linked through phosphodiester bonds. In various embodiments, each of the spacers in the KCNQ2 AON have Y number of bases immediately preceding the spacers that are linked through phosphodiester bonds. In various embodiments, all other bases of the KCNQ2 AON are linked through phosphorothioate bonds.

[00602] In some embodiments, Y number of bases immediately preceding a spacer and Z number of bases immediately succeeding a spacer are linked through phosphodiester bonds. In various embodiments, Y is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. In various embodiments, Z is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. Y and Z can be independent of each other. In particular embodiments, Y is one base and Z is one base. For example, if the spacer is located at position 15, the bases at positions 14 and 16 of the KCNQ2 AON are each linked to their respective adjacent bases through phosphodiester bonds. To provide an example, such a KCNQ2 AON (e.g., 25mer) can be denoted as:

XXXXXXXXXXXXXoDo**S**oEoXXXXXXXXX

where "S" represents a spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00603] As described herein, the spacer can be located at various positions in the KCNQ2 AON and therefore, the bases immediately preceding or immediately succeeding the spacer can vary within the KCNQ2 AON depending on where the spacer is situated.

[00604] In various embodiments, the KCNQ2 AON may include more than one spacer. In some embodiments, only one of the spacers has Y number of bases immediately preceding the spacer and Z number of bases immediately succeeding the spacer that are linked through phosphodiester bonds. In such embodiments, the other spacers of the KCNQ2 AON are linked to respective

preceding and succeeding bases through phosphorothioate bonds. To provide an example, such a KCNQ2 AON (e.g., 25mer) can be denoted as:

$$XXXXoDo\mathbf{S_1}oEoXXXXXXXXXXXX\mathbf{S_2}XXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00605] As another example, such a KCNQ2 AON (e.g., 25mer) can be denoted as:

$$XXXXX\mathbf{S_1}XXXXXXXXXXXoDo\mathbf{S_2}oDoXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00606] In some embodiments, one of the spacers is linked to the immediately preceding base through a phosphodiester bond. For example, a KCNQ2 AON includes a first spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

$$XXXXXXo\mathbf{S_1}XXXXXXXXXXX\mathbf{S_2}XXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00607] As another example, a KCNQ2 AON includes a second spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

$$XXXXXX\mathbf{S_1}XXXXXXXXXXXo\mathbf{S_2}XXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00608] In various embodiments, the KCNQ2 AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately preceding base through a phosphodiester bond. For example, the KCNQ2 AON may be a 21mer with a first spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

$$XXXXXXXo\mathbf{S_1}XXXXX\mathbf{S_2}XXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00609] As another example, the KCNQ2 AON may be a 21mer with a second spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXX**S**$_1$XXXXXo**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00610] In some embodiments, the KCNQ2 AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately preceding base through a phosphodiester bond and the immediately preceding base is further linked to the preceding base through a phosphodiester bond. An example 21mer KCNQ2 AON can be denoted as:

XXXEoDo**S**$_1$XXXXXX**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_1 and "E" represents the base immediately preceding "D." Any nucleobase in the AON can be a nucleobase analog.

[00611] As another example, a 21mer KCNQ2 AON can be denoted as:

XXXXX**S**$_1$XXXXEoDo**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_2 and "E" represents the base immediately preceding "D." Any nucleobase in the AON can be a nucleobase analog.

[00612] In some embodiments, the KCNQ2 AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where a base that immediately precedes a first spacer is linked to another base through a phosphodiester bond. The base that immediately precedes the first spacer may be linked to the first spacer through a non-phosphodiester bond, such as a phosphorothioate bond. Additionally a second spacer is linked to an immediately preceding base through a phosphodiester bond. An example of a 21mer KCNQ2 AON can be denoted as:

XXXEoD**S**$_1$XXXXXXo**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_1 and "E" represents the base immediately preceding "D." Here, the base "D" is linked to the first spacer S_1 through a non-phosphodiester bond (e.g., phosphorothioate bond). Additionally, the base "D" is linked to base "E" through a phosphodiester bond. The second spacer S_2 is linked to an immediately preceding base through a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00613] Another example of such a 21mer KCNQ2 AON can be denoted as:

$$XXXXXo\mathbf{S}_1XXXXEoD\mathbf{S}_2XXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_2 and "E" represents the base immediately preceding "D." Here, the base "D" is linked to the second spacer S_2 through a non-phosphodiester bond (e.g., phosphorothioate bond). Additionally, the base "D" is linked to base "E" through a phosphodiester bond. The first spacer S_1 is linked to an immediately preceding base through a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00614] In some embodiments, one of the spacers is linked to the immediately succeeding base through a phosphodiester bond. For example, a KCNQ2 AON includes a first spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXX\mathbf{S}_1oXXXXXXXXXXX\mathbf{S}_2XXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00615] As another example, a KCNQ2 AON includes a second spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXX\mathbf{S}_1XXXXXXXXXX\mathbf{S}_2oXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00616] In various embodiments, the KCNQ2 AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately succeeding base through a phosphodiester bond. For example, the KCNQ2 AON may be a 21mer with a first spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXXX\mathbf{S}_1oXXXXX\mathbf{S}_2XXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00617] As another example, the KCNQ2 AON may be a 21mer with a second spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXXX\mathbf{S}_1XXXXX\mathbf{S}_2oXXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00618] In various embodiments, two of the spacers have Y number of bases immediately preceding the spacers and Z number of bases immediately succeeding the spacers that are linked through phosphodiester bonds. In various embodiments, each of the spacers in the KCNQ2 AON have Y number of bases immediately preceding the spacers and Z number of bases immediately succeeding the spacers that are linked through phosphodiester bonds. An example of such a KCNQ2 AON (e.g., 25mer) can be denoted as:

XXXXoDo**S_1**oEoXXXXXXXXXXoFo**S_2**oHoXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the first spacer, "E" represents the base immediately succeeding the first spacer, "F" represents a base immediately preceding the second spacer, and "H" represents the base immediately succeeding the second spacer. In various embodiments, all other bases of the KCNQ2 AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00619] In various KCNQ2 AON includes two or more spacers and a range of bases located between the two spacers are linked through phosphodiester bonds. In various embodiments, the range of bases include two, three, four, five, six, or seven bases linked through phosphodiester bonds. In particular embodiments, the range of bases include two bases linked through phosphodiester bonds. In particular embodiments, the range of bases include four bases linked through phosphodiester bonds. In various embodiments, all other bases of the KCNQ2 AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00620] In various embodiments, the range of bases linked through phosphodiester bonds are positioned Y number of bases succeeding the first spacer and Z number of preceding the second spacer. In various embodiments, Y is one, two, three, four, five, six, or seven bases. In various embodiments, Z is one, two, three, four, five, six, or seven bases. Y and Z can be independent on each other. Any nucleobase in the AON can be a nucleobase analog.

[00621] In particular embodiments, Y is five bases and Z is four bases. To provide an example, such a KCNQ2 AON (e.g., 25mer) can be denoted as:

XXXXXXXX**S_1**XXXXoDoEoFoHoXXX**S_2**XXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, and "o" represents a phosphodiester bond. The bases "D," "E," "F," and "H" represent the range of bases that are linked through phosphodiester bonds. In this example, the range of bases is located five bases

after the first spacer (e.g., D is positioned five bases after the first spacer) and the range of bases is located four bases preceding the second spacer (e.g., H is positioned four bases before the second spacer). Any nucleobase in the AON can be a nucleobase analog.

[00622] In particular embodiments, Y is four bases and Z is three bases. To provide an example, such a KCNQ2 AON (e.g., 23mer) can be denoted as:

XXXXXXX**S**$_1$XXXoDoEoXX**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, and "o" represents a phosphodiester bond. The bases "D" and "E" represent the range of bases that are linked through phosphodiester bonds. In this example, the range of bases is located four bases after the first spacer (e.g., D is positioned four bases after the first spacer) and the range of bases is located three bases preceding the second spacer (e.g., E is positioned three bases before the second spacer). In various embodiments, the positions of the two spacers differ than shown above and therefore, the range of bases linked through phosphodiester bonds are differently positioned. In various embodiments, all other bases of the KCNQ2 AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00623] In some embodiments, a disclosed KCNQ2 AON may have at least one modified nucleobase, *e.g.*, 5-methylcytosine, and/or at least one methylphosphonate nucleotide, which is placed, for example, either at only one of the 5′ or 3′ ends or at both 5′ and 3′ ends or along the oligonucleotide sequence.

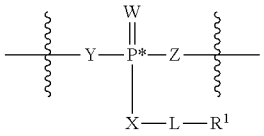
[00624] KCNQ2 AONs may include at least one modified sugar. For example, the sugar moiety of at least one nucleotide constituting the oligonucleotide is a ribose in which the 2′-OH group may be replaced by any one selected from the group consisting of OR, R, R′OR, SH, SR, NH_2, NR_2, N_3, CN, F, Cl, Br, and I (wherein R is an alkyl or aryl and R′ is an alkylene). Examples of a modified sugar moiety include a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'-MOE or MOE), 2'-O-(N-methylacetamide), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

[00625] In some embodiments, KCNQ2 AONs comprise 2'OMe (*e.g.*, a KCNQ2 AON comprising one or more 2'OMe modified sugar), 2'-MOE or MOE (*e.g.*, a KCNQ2 AON comprising one or more 2'-MOE modified sugar), PNA (*e.g.*, a KCNQ2 AON comprising one or more *N*-(2-aminoethyl)-glycine units linked by amide bonds or carbonyl methylene linkage as repeating units in place of a sugar-phosphate backbone), LNA (*e.g.*, a KCNQ2 AON comprising

one or more locked ribose, and can be a mixture of 2'-deoxy nucleotides or 2'OMe nucleotides), c-ET (*e.g.*, a KCNQ2 AON comprising one or more cET sugar), cMOE (*e.g.*, a KCNQ2 AON comprising one or more cMOE sugar), morpholino oligomer (*e.g.*, a KCNQ2 AON comprising a backbone comprising one or more PMO), deoxy-2'-fluoro nucleoside (*e.g.*, a KCNQ2 AON comprising one or more 2'-fluoro-β-D-arabinonucleoside), tcDNA (*e.g.*, a KCNQ2 AON comprising one or more tcDNA modified sugar), ENA (*e.g.*, a KCNQ2 AON comprising one or more ENA modified sugar), or HNA (*e.g.*, a KCNQ2 AON comprising one or more HNA modified sugar). In some embodiments, a KCNQ2 AON comprises one or more phosphorothioate linkage, phosphodiester linkage, phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, morpholino linkage, PNA linkage, or any combination of phosphorothioate linkage, phosphodiester linkage, a phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, morpholino linkage, and PNA linkage. In some embodiments, a KCNQ2 AON comprises one or more phosphorothioate linkage, phosphodiester linkage, or a combination of phosphorothioate and phosphodiester linkages.

[00626] In some embodiments, KCNQ2 AONs with a sequence of any one of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, or SEQ ID NOs: 4402-4409is a chirally controlled oligonucleotide, such as a chirally controlled oligonucleotide described in any of US Patent No. 9,982,257, US Patent No. 10,590,413, US 10,724,035, US 10,450,568, and PCT Publication No. WO2019200185, each of which is hereby incorporated by reference in its entirety.

[00627] For example, a KCNQ2 AON with a sequence of any one of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, or SEQ ID NOs: 4402-4409 is a chirally controlled oligonucleotide comprising a plurality of oligonucleotides of at least one type, wherein each type is defined by: 1) base sequence; 2) pattern of backbone linkages; 3) pattern of backbone chiral centers; and 4) pattern of backbone X-moieties (—X-L-R^1); wherein: the oligonucleotides of at least one type comprise one or more phosphorothioate triester internucleotidic linkages and one or more phosphate diester linkage; the oligonucleotides of at least one type comprise at least two consecutive modified internucleotidic linkages; and oligonucleotides of at least one oligonucleotide type comprise one or more modified internucleotidic linkages independently having the structure of:



wherein: P* is an asymmetric phosphorus atom and is either Rp or Sp;

W is O, S or Se; each of X, Y and Z is independently ----O----, ----S----, ----N(-L-R^1)----, or L; L is a covalent bond or an optionally substituted, linear or branched C_1-C_{50} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1-C_6 alkylene, C_1-C_6 alkenylene, ----C≡C----, ----C(R′)$_2$----, -Cy-, ----O----, ----S----, ----S----S----, ----N(R′)----, ----C(O)----, ----C(S)----, ----C(NR′)----, ----C(O)N(R′)----, ----N(R′)C(O)N(R′)----, ----N(R′)C(O)----, ----N(R′)C(O)O----, ----OC(O)N(R′)----, ----S(O)----, ----S(O)$_2$----, ----S(O)$_2$N(R′)----, ----N(R′)S(O)$_2$----, ----SC(O)----, ----C(O)S----, ----OC(O)----, or ----C(O)O----; R^1 is halogen, R, or an optionally substituted C_1-C_{10} aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1-C_6 alkylene, C_1-C_6 alkenylene, ----C≡C----, ----C(R′)$_2$----, -Cy-, ----O----, ----S----, ----S----S----, ----N(R′)----, ----C(O)----, ----C(S)----, ----C(NR′)----, ----C(O)N(R′)----, ----N(R′)C(O)N(R′)----, ----N(R′)C(O)----, ----N(R′)C(O)O----, ----OC(O)N(R′)----, ----S(O)----, ----S(O)$_2$----, ----S(O)$_2$N(R′)----, ----N(R′)S(O)$_2$----, ----SC(O)----, ----C(O)S----, ----OC(O)----, or ----C(O)O----; each R′ is independently ----R, ----C(O)R, ----CO_2R, or ----SO_2R, or: two R′ on the same nitrogen are taken together with their intervening atoms to form an optionally substituted heterocyclic or heteroaryl ring, or two R′ on the same carbon are taken together with their intervening atoms to form an optionally substituted aryl, carbocyclic, heterocyclic, or heteroaryl ring; -Cy- is an optionally substituted bivalent ring selected from phenylene, carbocyclylene, arylene, heteroarylene, or heterocyclylene; each R is independently hydrogen, or an optionally substituted group selected from C_1-C_6 aliphatic, phenyl, carbocyclyl, aryl, heteroaryl, or heterocyclyl; and each independently represents a connection to a nucleoside. In some embodiments, a KCNQ2 AON with a sequence of any one of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, or SEQ ID NOs: 4402-4409is a chirally controlled oligonucleotide comprising certain chemical modifications (e.g., 2'F (2' Fluoro, which contains a fluorine molecule at the 2' ribose position (instead of 2'-hydroxyl group in an RNA monomer)), 2'-OMe, phosphorothioate linkages, lipid conjugation, etc.), as described in U.S. Patent No. 10,450,568.

UNC13A

[00628] In some embodiments, all of the nucleotide linkages of a UNC13A AON of any of SEQ ID NOs: 4531-5794, SEQ ID NO: 7059-8322, SEQ ID NOs: 9596-9696, or SEQ ID NOs: 10670-10779 are phosphorothioate linkages. In some embodiments, one or more of the nucleotide linkages of a UNC13A AON of any of SEQ ID NOs: 4531-5794, SEQ ID NO: 7059-8322, SEQ ID NOs: 9596-9696, or SEQ ID NOs: 10670-10779 are phosphorothioate linkages.

[00629] In various embodiments, nucleotide linkages of UNC13A AON described herein such as any of SEQ ID NOs: 4531-5794, SEQ ID NO: 7059-8322, SEQ ID NOs: 9596-9696, or SEQ ID NOs: 10670-10779 include a mix of phosphodiester and phosphorothioate linkages.

[00630] In some embodiments, nucleoside linkages linking a base at position 3 of a UNC13A AON described herein are phosphodiester bonds. For example, the base at position 3 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer UNC13A AON with phosphodiester bonds linking the base at position 3 can be denoted as:

XXoDoXXXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00631] In some embodiments, one of the nucleoside linkages linking a base at position 3 of a UNC13A AON described herein is a phosphodiester bond. For example, the base at position 3 may be linked to either the preceding base or the succeeding base through a phosphodiester bond. An example 25mer UNC13A AON with a phosphodiester bond linking the base at position 3 to a preceding base can be denoted as:

XXoDXXXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00632] An example 25mer UNC13A AON with a phosphodiester bond linking the base at position 3 to a succeeding base can be denoted as:

XXDoXXXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00633] In various embodiments, in addition to one of the nucleoside linkages linking a base at position 3 of a UNC13A AON described herein being a phosphodiester bond, the UNC13A AON further includes two spacers. The two spacers can be positioned in the UNC13A AON such that the UNC13A AON includes a segment with at most 7 linked nucleosides. An example 25mer

UNC13A AON with two spacers and with a phosphodiester bond linking the base at position 3 to a preceding base can be denoted as:

XxoD$\mathbf{S_1}$XXXXXXXXX$\mathbf{S_2}$XXXXXXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00634] An example 25mer UNC13A AON with two spacers and with a phosphodiester bond linking the base at position 3 to a succeeding base can be denoted as:

XXDoXXXXXXX$\mathbf{S_1}$XXXXXXXXX$\mathbf{S_2}$XXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00635] In some embodiments, nucleoside linkages linking a base at position 4 of a UNC13A AON described herein are phosphodiester bonds. For example, the base at position 4 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer UNC13A AON with phosphodiester bonds linking the base at position 4 can be denoted as:

XXXoDoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00636] In some embodiments, one of the nucleoside linkages linking a base at position 4 of a UNC13A AON described herein is a phosphodiester bond. For example, the base at position 4 may be linked to either the preceding base or the succeeding base through a phosphodiester bond. An example 25mer UNC13A AON with a phosphodiester bond linking the base at position 4 to a preceding base can be denoted as:

XXXoDXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00637] An example 25mer UNC13A AON with a phosphodiester bond linking the base at position 4 to a succeeding base can be denoted as:

XXXDoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00638] In some embodiments, nucleoside linkages linking both bases at position 3 and position 4 of a UNC13A AON described herein are phosphodiester bonds. For example, the base at position 3 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond, and the base at position 4 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer UNC13A AON with phosphodiester bonds linking the bases at positions 3 and 4 can be denoted as:

XXoDoEoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond, "D" represents the base at position 3, and "E" represents the base at position 4. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00639] In various embodiments, UNC13A AON described herein include one or more spacers and phosphodiester bonds are located relative to the one or more spacers. In some embodiments, the Y number of bases immediately preceding a spacer are linked through phosphodiester bonds. In various embodiments, Y is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. In particular embodiments, Y is two bases. For example, if the spacer is located at position 15, the bases at positions 13 and 14 of the UNC13A AON are each linked to their respective adjacent bases through phosphodiester bonds. As described herein, the spacer can be located at various positions in the UNC13A AON and therefore, the 2 bases immediately preceding the spacer can vary within the UNC13A AON depending on where the spacer is situated.

[00640] In various embodiments, the UNC13A AON may include more than one spacer. In some embodiments, only one of the spacers has Y number of bases immediately preceding the spacer that are linked through phosphodiester bonds. In such embodiments, the other spacers are linked to respective preceding bases through phosphorothioate bonds. In various embodiments, two of the spacers have Y number of bases immediately preceding the spacers that are linked through phosphodiester bonds. In various embodiments, each of the spacers in the UNC13A AON have Y number of bases immediately preceding the spacers that are linked through phosphodiester bonds. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds.

[00641] In some embodiments, Y number of bases immediately preceding a spacer and Z number of bases immediately succeeding a spacer are linked through phosphodiester bonds. In various

embodiments, Y is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. In various embodiments, Z is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. Y and Z can be independent of each other. In particular embodiments, Y is one base and Z is one base. For example, if the spacer is located at position 15, the bases at positions 14 and 16 of the UNC13A AON are each linked to their respective adjacent bases through phosphodiester bonds. To provide an example, such a UNC13A AON (e.g., 25mer) can be denoted as:

XXXXXXXXXXXXXoDo**S**oEoXXXXXXXXX

where "S" represents a spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00642] As described herein, the spacer can be located at various positions in the UNC13A AON and therefore, the bases immediately preceding or immediately succeeding the spacer can vary within the UNC13A AON depending on where the spacer is situated.

[00643] In various embodiments, the UNC13A AON may include more than one spacer. In some embodiments, only one of the spacers has Y number of bases immediately preceding the spacer and Z number of bases immediately succeeding the spacer that are linked through phosphodiester bonds. In such embodiments, the other spacers of the UNC13A AON are linked to respective preceding and succeeding bases through phosphorothioate bonds. To provide an example, such a UNC13A AON (e.g., 25mer) can be denoted as:

XXXXoDo$\mathbf{S_1}$oEoXXXXXXXXXXX$\mathbf{S_2}$XXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00644] As another example, such a UNC13A AON (e.g., 25mer) can be denoted as:

XXXXX$\mathbf{S_1}$XXXXXXXXXXXoDo$\mathbf{S_2}$oDoXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00645] In some embodiments, one of the spacers is linked to the immediately preceding base through a phosphodiester bond. For example, a UNC13A AON includes a first spacer that is

linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXo**S**$_1$XXXXXXXXXXX**S**$_2$XXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00646] As another example, a UNC13A AON includes a second spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXX**S**$_1$XXXXXXXXXXXo**S**$_2$XXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00647] In various embodiments, the UNC13A AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately preceding base through a phosphodiester bond. For example, the UNC13A AON may be a 21mer with a first spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXXo**S**$_1$XXXXX**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00648] As another example, the UNC13A AON may be a 21mer with a second spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXX**S**$_1$XXXXXo**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00649] In some embodiments, the UNC13A AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately preceding base through a phosphodiester bond and the immediately preceding base is further linked to the preceding base through a phosphodiester bond. An example 21mer UNC13A AON can be denoted as:

XXXEoDo**S**$_1$XXXXXX**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_1 and "E" represents the base immediately preceding "D." Any nucleobase in the AON can be a nucleobase analog.

[00650] As another example, a 21mer UNC13A AON can be denoted as:

XXXXX**S**$_1$XXXXEoDo**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_2 and "E" represents the base immediately preceding "D." Any nucleobase in the AON can be a nucleobase analog.

[00651] In some embodiments, the UNC13A AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where a base that immediately precedes a first spacer is linked to another base through a phosphodiester bond. The base that immediately precedes the first spacer may be linked to the first spacer through a non-phosphodiester bond, such as a phosphorothioate bond. Additionally a second spacer is linked to an immediately preceding base through a phosphodiester bond. An example of a 21mer UNC13A AON can be denoted as:

XXXEoD**S**$_1$XXXXXXoS$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_1 and "E" represents the base immediately preceding "D." Here, the base "D" is linked to the first spacer S_1 through a non-phosphodiester bond (e.g., phosphorothioate bond). Additionally, the base "D" is linked to base "E" through a phosphodiester bond. The second spacer S_2 is linked to an immediately preceding base through a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00652] Another example of such a 21mer UNC13A AON can be denoted as:

XXXXXo**S**$_1$XXXXEoD**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_2 and "E" represents the base immediately preceding "D." Here, the base "D" is linked to the second spacer S_2 through a non-phosphodiester bond (e.g., phosphorothioate bond). Additionally, the base "D" is linked to base "E" through a phosphodiester bond. The first spacer S_1 is linked to an immediately preceding base through a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00653] In some embodiments, one of the spacers is linked to the immediately succeeding base through a phosphodiester bond. For example, a UNC13A AON includes a first spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

XXXXXX**S**$_1$oXXXXXXXXXXX**S**$_2$XXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00654] As another example, a UNC13A AON includes a second spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXX\mathbf{S}_1XXXXXXXXXXX\mathbf{S}_2oXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00655] In various embodiments, the UNC13A AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately succeeding base through a phosphodiester bond. For example, the UNC13A AON may be a 21mer with a first spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXXX\mathbf{S}_1oXXXXX\mathbf{S}_2XXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00656] As another example, the UNC13A AON may be a 21mer with a second spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXXX\mathbf{S}_1XXXXX\mathbf{S}_2oXXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00657] In various embodiments, two of the spacers have Y number of bases immediately preceding the spacers and Z number of bases immediately succeeding the spacers that are linked through phosphodiester bonds. In various embodiments, each of the spacers in the UNC13A AON have Y number of bases immediately preceding the spacers and Z number of bases immediately succeeding the spacers that are linked through phosphodiester bonds. An example of such a UNC13A AON (e.g., 25mer) can be denoted as:

$$XXXXoDo\mathbf{S}_1oEoXXXXXXXXXXoFo\mathbf{S}_2oHoXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the first spacer, "E" represents the base immediately succeeding the first spacer, "F" represents a base immediately preceding the second spacer, and "H" represents the base immediately succeeding the second

spacer. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00658] In various UNC13A AON includes two or more spacers and a range of bases located between the two spacers are linked through phosphodiester bonds. In various embodiments, the range of bases include two, three, four, five, six, or seven bases linked through phosphodiester bonds. In particular embodiments, the range of bases include two bases linked through phosphodiester bonds. In particular embodiments, the range of bases include four bases linked through phosphodiester bonds. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00659] In various embodiments, the range of bases linked through phosphodiester bonds are positioned Y number of bases succeeding the first spacer and Z number of preceding the second spacer. In various embodiments, Y is one, two, three, four, five, six, or seven bases. In various embodiments, Z is one, two, three, four, five, six, or seven bases. Y and Z can be independent on each other. Any nucleobase in the AON can be a nucleobase analog.

[00660] In particular embodiments, Y is five bases and Z is four bases. To provide an example, such a UNC13A AON (e.g., 25mer) can be denoted as:

$$XXXXXXXX\mathbf{S}_1XXXXoDoEoFoHoXXX\mathbf{S}_2XXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, and "o" represents a phosphodiester bond. The bases "D," "E," "F," and "H" represent the range of bases that are linked through phosphodiester bonds. In this example, the range of bases is located five bases after the first spacer (e.g., D is positioned five bases after the first spacer) and the range of bases is located four bases preceding the second spacer (e.g., H is positioned four bases before the second spacer). Any nucleobase in the AON can be a nucleobase analog.

[00661] In particular embodiments, Y is four bases and Z is three bases. To provide an example, such a UNC13A AON (e.g., 23mer) can be denoted as:

$$XXXXXXX\mathbf{S}_1XXXoDoEoXX\mathbf{S}_2XXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, and "o" represents a phosphodiester bond. The bases "D" and "E" represent the range of bases that are linked through phosphodiester bonds. In this example, the range of bases is located four bases after the first spacer (e.g., D is positioned four bases after the first spacer) and the range of bases is located three bases preceding the second spacer (e.g., E is positioned three bases before the second spacer). In various embodiments, the positions of the two spacers differ than shown above and

therefore, the range of bases linked through phosphodiester bonds are differently positioned. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00662] In some embodiments, a disclosed UNC13A AON may have at least one modified nucleobase, *e.g.*, 5-methylcytosine, and/or at least one methylphosphonate nucleotide, which is placed, for example, either at only one of the 5′ or 3′ ends or at both 5′ and 3′ ends or along the oligonucleotide sequence.

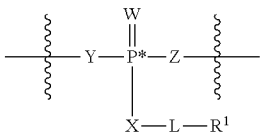
[00663] UNC13A AONs may include at least one modified sugar. For example, the sugar moiety of at least one nucleotide constituting the oligonucleotide is a ribose in which the 2′-OH group may be replaced by any one selected from the group consisting of OR, R, R′OR, SH, SR, NH_2, NR_2, N_3, CN, F, Cl, Br, and I (wherein R is an alkyl or aryl and R′ is an alkylene). Examples of a modified sugar moiety include a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'-MOE or MOE), 2'-O-(N-methylacetamide), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

[00664] In some embodiments, UNC13A AONs comprise 2'OMe (*e.g.*, a UNC13A AON comprising one or more 2'OMe modified sugar), 2'-MOE or MOE (*e.g.*, a UNC13A AON comprising one or more 2'-MOE modified sugar), PNA (*e.g.*, a UNC13A AON comprising one or more *N*-(2-aminoethyl)-glycine units linked by amide bonds or carbonyl methylene linkage as repeating units in place of a sugar-phosphate backbone), LNA (*e.g.*, a UNC13A AON comprising one or more locked ribose, and can be a mixture of 2'-deoxy nucleotides or 2'OMe nucleotides), c-ET (*e.g.*, a UNC13A AON comprising one or more cET sugar), cMOE (*e.g.*, a UNC13A AON comprising one or more cMOE sugar), morpholino oligomer (*e.g.*, a UNC13A AON comprising a backbone comprising one or more PMO), deoxy-2'-fluoro nucleoside (*e.g.*, a UNC13A AON comprising one or more 2'-fluoro-β-D-arabinonucleoside), tcDNA (*e.g.*, a UNC13A AON comprising one or more tcDNA modified sugar), ENA (*e.g.*, a UNC13A AON comprising one or more ENA modified sugar), or HNA (*e.g.*, a UNC13A AON comprising one or more HNA modified sugar). In some embodiments, a UNC13A AON comprises one or more phosphorothioate linkage, phosphodiester linkage, phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, morpholino linkage, PNA linkage, or any combination of phosphorothioate linkage, phosphodiester linkage, a phosphotriester linkage, methylphosphonate linkage, phosphoramidate

linkage, morpholino linkage, and PNA linkage. In some embodiments, a UNC13A AON comprises one or more phosphorothioate linkage, phosphodiester linkage, or a combination of phosphorothioate and phosphodiester linkages.

[00665] In some embodiments, UNC13A AONs with a sequence of any one of SEQ ID NOs: 4531-5794, SEQ ID NO: 7059-8322, SEQ ID NOs: 9596-9696, or SEQ ID NOs: 10670-10779 is a chirally controlled oligonucleotide, such as a chirally controlled oligonucleotide described in any of US Patent No. 9,982,257, US Patent No. 10,590,413, US 10,724,035, US 10,450,568, and PCT Publication No. WO2019200185, each of which is hereby incorporated by reference in its entirety.

[00666] For example, a UNC13A AON with a sequence of any one of SEQ ID NOs: 4531-5794, SEQ ID NO: 7059-8322, SEQ ID NOs: 9596-9696, or SEQ ID NOs: 10670-10779 is a chirally controlled oligonucleotide comprising a plurality of oligonucleotides of at least one type, wherein each type is defined by: 1) base sequence; 2) pattern of backbone linkages; 3) pattern of backbone chiral centers; and 4) pattern of backbone X-moieties (—X-L-R^1); wherein: the oligonucleotides of the at least one type comprise one or more phosphorothioate triester internucleotidic linkages and one or more phosphate diester linkage; the oligonucleotides of the at least one type comprise at least two consecutive modified internucleotidic linkages; and oligonucleotides of the at least one oligonucleotide type comprise one or more modified internucleotidic linkages independently having the structure of:



wherein: P* is an asymmetric phosphorus atom and is either Rp or Sp;

W is O, S or Se; each of X, Y and Z is independently —O—, —S—, —N(-L-R^1)—, or L; L is a covalent bond or an optionally substituted, linear or branched C_1-C_{50} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1-C_6 alkylene, C_1-C_6 alkenylene, —C≡C—, —C(R′)$_2$—, -Cy-, —O—, —S—, —S—S—, —N(R′)—, —C(O)—, —C(S)—, —C(NR′)—, —C(O)N(R′)—, —N(R′)C(O)N(R′)—, —N(R′)C(O)—, —N(R′)C(O)O—, —OC(O)N(R′)—, —S(O)—, —S(O)$_2$—, —S(O)$_2$N(R′)—, —N(R′)S(O)$_2$—, —SC(O)—, —C(O)S—, —OC(O)—, or —C(O)O—; R^1 is halogen, R, or an optionally substituted C_1-C_{10} aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1-C_6 alkylene, C_1-C_6 alkenylene, —C≡C—, —C(R′)$_2$—, -Cy-, —O—, —S—, —S—S—, —N(R′)—, —C(O)—, —C(S)—, —C(NR′)—, —

C(O)N(R′)—, —N(R′)C(O)N(R′)—, —N(R′)C(O)—, —N(R′)C(O)O—, —OC(O)N(R′)—, —S(O)—, —S(O)$_2$—, —S(O)$_2$N(R′)—, —N(R′)S(O)$_2$—, —SC(O)—, —C(O)S—, —OC(O)—, or —C(O)O—; each R′ is independently —R, —C(O)R, —CO$_2$R, or —SO$_2$R, or: two R′ on the same nitrogen are taken together with their intervening atoms to form an optionally substituted heterocyclic or heteroaryl ring, or two R′ on the same carbon are taken together with their intervening atoms to form an optionally substituted aryl, carbocyclic, heterocyclic, or heteroaryl ring; -Cy- is an optionally substituted bivalent ring selected from phenylene, carbocyclylene, arylene, heteroarylene, or heterocyclylene; each R is independently hydrogen, or an optionally substituted group selected from C$_1$-C$_6$ aliphatic, phenyl, carbocyclyl, aryl, heteroaryl, or heterocyclyl; and each independently represents a connection to a nucleoside. In some embodiments, a UNC13A AON with a sequence of any one of SEQ ID NOs: 4531-5794, SEQ ID NO: 7059-8322, SEQ ID NOs: 9596-9696, or SEQ ID NOs: 10670-10779 is a chirally controlled oligonucleotide comprising certain chemical modifications (e.g., 2'F (2' Fluoro, which contains a fluorine molecule at the 2' ribose position (instead of 2'-hydroxyl group in an RNA monomer)), 2'-OMe, phosphorothioate linkages, lipid conjugation, etc.), as described in U.S. Patent No. 10,450,568.

SMN2

[00667] In some embodiments, all of the nucleotide linkages of a SMN2 AON of any of SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, and SEQ ID NOs: 10783-10808 are phosphorothioate linkages. In some embodiments, one or more of the nucleotide linkages of a SMN2 AON of any of SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, and SEQ ID NOs: 10783-10808 are phosphorothioate linkages.

[00668] In various embodiments, nucleotide linkages of SMN2 AON described herein such as any of SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, and SEQ ID NOs: 10783-10808 include a mix of phosphodiester and phosphorothioate linkages.

[00669] In some embodiments, nucleoside linkages linking a base at position 3 of a SMN2 AON described herein are phosphodiester bonds. For example, the base at position 3 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer SMN2 AON with phosphodiester bonds linking the base at position 3 can be denoted as:

XXoDoXXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00670] In some embodiments, one of the nucleoside linkages linking a base at position 3 of a SMN2 AON described herein is a phosphodiester bond. For example, the base at position 3 may be linked to either the preceding base or the succeeding base through a phosphodiester bond. An example 25mer SMN2 AON with a phosphodiester bond linking the base at position 3 to a preceding base can be denoted as:

XXoDXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00671] An example 25mer SMN2 AON with a phosphodiester bond linking the base at position 3 to a succeeding base can be denoted as:

XXDoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00672] In various embodiments, in addition to one of the nucleoside linkages linking a base at position 3 of a SMN2 AON described herein being a phosphodiester bond, the SMN2 AON further includes two spacers. The two spacers can be positioned in the SMN2 AON such that the SMN2 AON includes a segment with at most 7 linked nucleosides. An example 25mer SMN2 AON with two spacers and with a phosphodiester bond linking the base at position 3 to a preceding base can be denoted as:

XxoD$\mathbf{S}_1$XXXXXXXXX$\mathbf{S}_2$XXXXXXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00673] An example 25mer SMN2 AON with two spacers and with a phosphodiester bond linking the base at position 3 to a succeeding base can be denoted as:

XXDoXXXXXXX$\mathbf{S}_1$XXXXXXXXX$\mathbf{S}_2$XXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00674] In some embodiments, nucleoside linkages linking a base at position 4 of a SMN2 AON described herein are phosphodiester bonds. For example, the base at position 4 may be linked to

each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer SMN2 AON with phosphodiester bonds linking the base at position 4 can be denoted as:

XXXoDoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00675] In some embodiments, one of the nucleoside linkages linking a base at position 4 of a SMN2 AON described herein is a phosphodiester bond. For example, the base at position 4 may be linked to either the preceding base or the succeeding base through a phosphodiester bond. An example 25mer SMN2 AON with a phosphodiester bond linking the base at position 4 to a preceding base can be denoted as:

XXXoDXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00676] An example 25mer SMN2 AON with a phosphodiester bond linking the base at position 4 to a succeeding base can be denoted as:

XXXDoXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00677] In some embodiments, nucleoside linkages linking both bases at position 3 and position 4 of a SMN2 AON described herein are phosphodiester bonds. For example, the base at position 3 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond, and the base at position 4 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer SMN2 AON with phosphodiester bonds linking the bases at positions 3 and 4 can be denoted as:

XXoDoEoXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond, "D" represents the base at position 3, and "E" represents the base at position 4. In various embodiments, all other bases of the SMN2 AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00678] In various embodiments, SMN2 AON described herein include one or more spacers and phosphodiester bonds are located relative to the one or more spacers. In some embodiments, the Y number of bases immediately preceding a spacer are linked through phosphodiester bonds. In various embodiments, Y is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or

twelve bases. In particular embodiments, Y is two bases. For example, if the spacer is located at position 15, the bases at positions 13 and 14 of the SMN2 AON are each linked to their respective adjacent bases through phosphodiester bonds. As described herein, the spacer can be located at various positions in the SMN2 AON and therefore, the 2 bases immediately preceding the spacer can vary within the SMN2 AON depending on where the spacer is situated.

[00679] In various embodiments, the SMN2 AON may include more than one spacer. In some embodiments, only one of the spacers has Y number of bases immediately preceding the spacer that are linked through phosphodiester bonds. In such embodiments, the other spacers are linked to respective preceding bases through phosphorothioate bonds. In various embodiments, two of the spacers have Y number of bases immediately preceding the spacers that are linked through phosphodiester bonds. In various embodiments, each of the spacers in the SMN2 AON have Y number of bases immediately preceding the spacers that are linked through phosphodiester bonds. In various embodiments, all other bases of the SMN2 AON are linked through phosphorothioate bonds.

[00680] In some embodiments, Y number of bases immediately preceding a spacer and Z number of bases immediately succeeding a spacer are linked through phosphodiester bonds. In various embodiments, Y is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. In various embodiments, Z is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. Y and Z can be independent of each other. In particular embodiments, Y is one base and Z is one base. For example, if the spacer is located at position 15, the bases at positions 14 and 16 of the SMN2 AON are each linked to their respective adjacent bases through phosphodiester bonds. To provide an example, such a SMN2 AON (e.g., 25mer) can be denoted as:

XXXXXXXXXXXXXoDo**S**oEoXXXXXXXXX

where "S" represents a spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00681] As described herein, the spacer can be located at various positions in the SMN2 AON and therefore, the bases immediately preceding or immediately succeeding the spacer can vary within the SMN2 AON depending on where the spacer is situated.

[00682] In various embodiments, the SMN2 AON may include more than one spacer. In some embodiments, only one of the spacers has Y number of bases immediately preceding the spacer and Z number of bases immediately succeeding the spacer that are linked through phosphodiester

bonds. In such embodiments, the other spacers of the SMN2 AON are linked to respective preceding and succeeding bases through phosphorothioate bonds. To provide an example, such a SMN2 AON (e.g., 25mer) can be denoted as:

XXXXoDo**S$_1$**oEoXXXXXXXXXXXX**S$_2$**XXXXXX

where "S1" represents a first spacer, "S2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00683] As another example, such a SMN2 AON (e.g., 25mer) can be denoted as:

XXXXX**S$_1$**XXXXXXXXXXXoDo**S$_2$**oDoXXXXX

where "S1" represents a first spacer, "S2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00684] In some embodiments, one of the spacers is linked to the immediately preceding base through a phosphodiester bond. For example, a SMN2 AON includes a first spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXo**S$_1$**XXXXXXXXXXX**S$_2$**XXXXXX

where "S1" represents a first spacer, "S2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00685] As another example, a SMN2 AON includes a second spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXX**S$_1$**XXXXXXXXXXXo**S$_2$**XXXXXX

where "S1" represents a first spacer, "S2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00686] In various embodiments, the SMN2 AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately preceding base through a phosphodiester bond. For example, the SMN2 AON may be a 21mer with a first spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXXo**S$_1$**XXXXX**S$_2$**XXXXXXX

where "S1" represents a first spacer, "S2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00687] As another example, the SMN2 AON may be a 21mer with a second spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXX**S**$_1$XXXXXo**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00688] In some embodiments, the SMN2 AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately preceding base through a phosphodiester bond and the immediately preceding base is further linked to the preceding base through a phosphodiester bond. An example 21mer SMN2 AON can be denoted as:

XXXEoDo**S**$_1$XXXXXX**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_1 and "E" represents the base immediately preceding "D." Any nucleobase in the AON can be a nucleobase analog.

[00689] As another example, a 21mer SMN2 AON can be denoted as:

XXXXX**S**$_1$XXXXEoDo**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_2 and "E" represents the base immediately preceding "D." Any nucleobase in the AON can be a nucleobase analog.

[00690] In some embodiments, the SMN2 AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where a base that immediately precedes a first spacer is linked to another base through a phosphodiester bond. The base that immediately precedes the first spacer may be linked to the first spacer through a non-phosphodiester bond, such as a phosphorothioate bond. Additionally a second spacer is linked to an immediately preceding base through a phosphodiester bond. An example of a 21mer SMN2 AON can be denoted as:

XXXEoD**S**$_1$XXXXXXo**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_1 and "E" represents the base immediately preceding "D." Here, the base "D" is linked to the first spacer S_1 through a non-phosphodiester bond (e.g., phosphorothioate bond). Additionally, the base "D" is linked to base "E" through a phosphodiester bond. The second spacer S_2 is linked to an immediately preceding base through a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00691] Another example of such a 21mer SMN2 AON can be denoted as:

$$XXXXXo\mathbf{S}_1XXXXEoD\mathbf{S}_2XXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_2 and "E" represents the base immediately preceding "D." Here, the base "D" is linked to the second spacer S_2 through a non-phosphodiester bond (e.g., phosphorothioate bond). Additionally, the base "D" is linked to base "E" through a phosphodiester bond. The first spacer S_1 is linked to an immediately preceding base through a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00692] In some embodiments, one of the spacers is linked to the immediately succeeding base through a phosphodiester bond. For example, a SMN2 AON includes a first spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXX\mathbf{S}_1oXXXXXXXXXXX\mathbf{S}_2XXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00693] As another example, a SMN2 AON includes a second spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXX\mathbf{S}_1XXXXXXXXXX\mathbf{S}_2oXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00694] In various embodiments, the SMN2 AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately succeeding base through a phosphodiester bond. For example, the SMN2 AON may be a 21mer with a first spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXXX\mathbf{S}_1oXXXXX\mathbf{S}_2XXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00695] As another example, the SMN2 AON may be a 21mer with a second spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXXX\mathbf{S}_1XXXXX\mathbf{S}_2oXXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00696] In various embodiments, two of the spacers have Y number of bases immediately preceding the spacers and Z number of bases immediately succeeding the spacers that are linked through phosphodiester bonds. In various embodiments, each of the spacers in the SMN2 AON have Y number of bases immediately preceding the spacers and Z number of bases immediately succeeding the spacers that are linked through phosphodiester bonds. An example of such a SMN2 AON (e.g., 25mer) can be denoted as:

XXXXoDo**S$_1$**oEoXXXXXXXXXXoFo**S$_2$**oHoXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the first spacer, "E" represents the base immediately succeeding the first spacer, "F" represents a base immediately preceding the second spacer, and "H" represents the base immediately succeeding the second spacer. In various embodiments, all other bases of the SMN2 AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00697] In various SMN2 AON includes two or more spacers and a range of bases located between the two spacers are linked through phosphodiester bonds. In various embodiments, the range of bases include two, three, four, five, six, or seven bases linked through phosphodiester bonds. In particular embodiments, the range of bases include two bases linked through phosphodiester bonds. In particular embodiments, the range of bases include four bases linked through phosphodiester bonds. In various embodiments, all other bases of the SMN2 AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00698] In various embodiments, the range of bases linked through phosphodiester bonds are positioned Y number of bases succeeding the first spacer and Z number of preceding the second spacer. In various embodiments, Y is one, two, three, four, five, six, or seven bases. In various embodiments, Z is one, two, three, four, five, six, or seven bases. Y and Z can be independent on each other. Any nucleobase in the AON can be a nucleobase analog.

[00699] In particular embodiments, Y is five bases and Z is four bases. To provide an example, such a SMN2 AON (e.g., 25mer) can be denoted as:

XXXXXXXX**S$_1$**XXXXoDoEoFoHoXXX**S$_2$**XXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, and "o" represents a phosphodiester bond. The bases "D," "E," "F," and "H" represent the range of bases that are linked through phosphodiester bonds. In this example, the range of bases is located five bases after the first spacer (e.g., D is positioned five bases after the first spacer) and the range of bases

is located four bases preceding the second spacer (e.g., H is positioned four bases before the second spacer). Any nucleobase in the AON can be a nucleobase analog.

[00700] In particular embodiments, Y is four bases and Z is three bases. To provide an example, such a SMN2 AON (e.g., 23mer) can be denoted as:

XXXXXXX**S**$_1$XXXoDoEoXX**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, and "o" represents a phosphodiester bond. The bases "D" and "E" represent the range of bases that are linked through phosphodiester bonds. In this example, the range of bases is located four bases after the first spacer (e.g., D is positioned four bases after the first spacer) and the range of bases is located three bases preceding the second spacer (e.g., E is positioned three bases before the second spacer). In various embodiments, the positions of the two spacers differ than shown above and therefore, the range of bases linked through phosphodiester bonds are differently positioned. In various embodiments, all other bases of the SMN2 AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00701] In some embodiments, a disclosed SMN2 AON may have at least one modified nucleobase, *e.g.*, 5-methylcytosine, and/or at least one methylphosphonate nucleotide, which is placed, for example, either at only one of the 5′ or 3′ ends or at both 5′ and 3′ ends or along the oligonucleotide sequence.

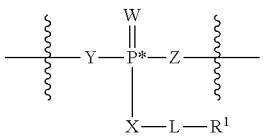
[00702] SMN2 AONs may include at least one modified sugar. For example, the sugar moiety of at least one nucleotide constituting the oligonucleotide is a ribose in which the 2′-OH group may be replaced by any one selected from the group consisting of OR, R, R′OR, SH, SR, NH_2, NR_2, N_3, CN, F, Cl, Br, and I (wherein R is an alkyl or aryl and R′ is an alkylene). Examples of a modified sugar moiety include a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'-MOE or MOE), 2'-O-(N-methylacetamide), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

[00703] In some embodiments, SMN2 AONs comprise 2'OMe (*e.g.*, a SMN2 AON comprising one or more 2'OMe modified sugar), 2'-MOE or MOE (*e.g.*, a SMN2 AON comprising one or more 2'-MOE modified sugar), PNA (*e.g.*, a SMN2 AON comprising one or more *N*-(2-aminoethyl)-glycine units linked by amide bonds or carbonyl methylene linkage as repeating units in place of a sugar-phosphate backbone), LNA (*e.g.*, a SMN2 AON comprising one or more locked ribose, and can be a mixture of 2'-deoxy nucleotides or 2'OMe nucleotides), c-ET (*e.g.*, a

SMN2 AON comprising one or more cET sugar), cMOE (*e.g.*, a SMN2 AON comprising one or more cMOE sugar), morpholino oligomer (*e.g.*, a SMN2 AON comprising a backbone comprising one or more PMO), deoxy-2'-fluoro nucleoside (*e.g.*, a SMN2 AON comprising one or more 2'-fluoro-β-D-arabinonucleoside), tcDNA (*e.g.*, a SMN2 AON comprising one or more tcDNA modified sugar), ENA (*e.g.*, a SMN2 AON comprising one or more ENA modified sugar), or HNA (*e.g.*, a SMN2 AON comprising one or more HNA modified sugar). In some embodiments, a SMN2 AON comprises one or more phosphorothioate linkage, phosphodiester linkage, phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, morpholino linkage, PNA linkage, or any combination of phosphorothioate linkage, phosphodiester linkage, a phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, morpholino linkage, and PNA linkage. In some embodiments, a SMN2 AON comprises one or more phosphorothioate linkage, phosphodiester linkage, or a combination of phosphorothioate and phosphodiester linkages.

[00704] In some embodiments, SMN2 AONs with a sequence of any one of SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, and SEQ ID NOs: 10783-10808 is a chirally controlled oligonucleotide, such as a chirally controlled oligonucleotide described in any of US Patent No. 9,982,257, US Patent No. 10,590,413, US 10,724,035, US 10,450,568, and PCT Publication No. WO2019200185, each of which is hereby incorporated by reference in its entirety.

[00705] For example, a SMN2 AON with a sequence of any one of SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, and SEQ ID NOs: 10783-10808 is a chirally controlled oligonucleotide comprising a plurality of oligonucleotides of at least one type, wherein each type is defined by: 1) base sequence; 2) pattern of backbone linkages; 3) pattern of backbone chiral centers; and 4) pattern of backbone X-moieties (—X-L-R^1); wherein: the oligonucleotides of at least one type comprise one or more phosphorothioate triester internucleotidic linkages and one or more phosphate diester linkage; the oligonucleotides of at least one type comprise at least two consecutive modified internucleotidic linkages; and oligonucleotides of at least one oligonucleotide type comprise one or more modified internucleotidic linkages independently having the structure of:



wherein: P* is an asymmetric phosphorus atom and is either Rp or Sp;

W is O, S or Se; each of X, Y and Z is independently —O—, —S—, —N(-L-R^1)—, or L; L is a covalent bond or an optionally substituted, linear or branched C_1-C_{50} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1-C_6 alkylene, C_1-C_6 alkenylene, —C≡C—, —C(R′)$_2$—, -Cy-, —O—, —S—, —S—S—, —N(R′)—, —C(O)—, —C(S)—, —C(NR′)—, —C(O)N(R′)—, —N(R′)C(O)N(R′)—, —N(R′)C(O)—, —N(R′)C(O)O—, —OC(O)N(R′)—, —S(O)—, —S(O)$_2$—, —S(O)$_2$N(R′)—, —N(R′)S(O)$_2$—, —SC(O)—, —C(O)S—, —OC(O)—, or —C(O)O—; R^1 is halogen, R, or an optionally substituted C_1-C_{10} aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1-C_6 alkylene, C_1-C_6 alkenylene, —C≡C—, —C(R′)$_2$—, -Cy-, —O—, —S—, —S—S—, —N(R′)—, —C(O)—, —C(S)—, —C(NR′)—, —C(O)N(R′)—, —N(R′)C(O)N(R′)—, —N(R′)C(O)—, —N(R′)C(O)O—, —OC(O)N(R′)—, —S(O)—, —S(O)$_2$—, —S(O)$_2$N(R′)—, —N(R′)S(O)$_2$—, —SC(O)—, —C(O)S—, —OC(O)—, or —C(O)O—; each R′ is independently —R, —C(O)R, —CO_2R, or —SO_2R, or: two R′ on the same nitrogen are taken together with their intervening atoms to form an optionally substituted heterocyclic or heteroaryl ring, or two R′ on the same carbon are taken together with their intervening atoms to form an optionally substituted aryl, carbocyclic, heterocyclic, or heteroaryl ring; -Cy- is an optionally substituted bivalent ring selected from phenylene, carbocyclylene, arylene, heteroarylene, or heterocyclylene; each R is independently hydrogen, or an optionally substituted group selected from C_1-C_6 aliphatic, phenyl, carbocyclyl, aryl, heteroaryl, or heterocyclyl; and each independently represents a connection to a nucleoside. In some embodiments, a SMN2 AON with a sequence of any one of SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, and SEQ ID NOs: 10783-10808 is a chirally controlled oligonucleotide comprising certain chemical modifications (e.g., 2'F (2' Fluoro, which contains a fluorine molecule at the 2' ribose position (instead of 2'-hydroxyl group in an RNA monomer)), 2'-OMe, phosphorothioate linkages, lipid conjugation, etc.), as described in U.S. Patent No. 10,450,568.

Motor Neuron Diseases

[00706] Motor neuron diseases are a group of diseases characterized by loss of function of motor neurons that coordinate voluntary movement of muscles by the brain. Motor neuron diseases may affect upper and/or lower motor neurons, and may have sporadic or familial origins. Motor neuron diseases include amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), progressive

bulbar palsy, pseudobulbar palsy, progressive muscular atrophy, primary lateral sclerosis, spinal muscular atrophy, post-polio syndrome, and ALS with frontotemporal dementia.

[00707] Symptoms of motor neuron diseases include muscle decay or weakening, muscle pain, spasms, slurred speech, difficulty swallowing, loss of muscle control, joint pain, stiff limbs, difficulty breathing, drooling, and complete loss of muscle control, including over basic functions such as breathing, swallowing, eating, speaking, and limb movement. These symptoms are also sometimes accompanied by depression, loss of memory, difficulty with planning, language deficits, altered behavior, and difficulty assessing spatial relationships and/or changes in personality.

[00708] Motor neuron diseases can be assessed and diagnosed by a clinician of skill, for example, a neurologist, using various tools and tests. For example, the presence or risk of developing a motor neuron disease can be assessed or diagnosed using blood and urine tests (for example, tests that assay for the presence of creatinine kinase), magnetic resonance imaging (MRI), electromyography (EMG), nerve conduction study (NCS), spinal tap, lumbar puncture, and/or muscle biopsy. Motor neuron diseases can be diagnosed with the aid of a physical exam and/or a neurological exam to assess motor and sensory skills, nerve function, hearing and speech, vision, coordination and balance, mental status, and changes in mood or behavior.

Amyotrophic Lateral Sclerosis

[00709] ALS is a progressive motor neuron disease that disrupts signals to all voluntary muscles. ALS results in atrophy of both upper and lower motor neurons. Symptoms of ALS include weakening and wasting of the bulbar muscles, general and bilateral loss of strength, spasticity, muscle spasms, muscle cramps, fasciculations, slurred speech, and difficulty breathing or loss of ability to breathe. Some individuals with ALS also suffer from cognitive decline. At the molecular level, ALS is characterized by protein and RNA aggregates in the cytoplasm of motor neurons, including aggregates of the RNA-binding protein TDP43.

[00710] ALS is most common in males above 40 years of age, although it can also occur in women and children. Risk of ALS is also heightened in individuals who smoke, are exposed to chemicals such as lead, or who have served in the military. Most instances of ALS are sporadic, while only about 10% of cases are familial. Causes of ALS include sporadic or inherited genetic mutations, high levels of glutamate, protein mishandling. Genetic mutations associated with ALS include mutations in the genes SOD1, C9orf72, TARDBP, FUS, ANG, ATXN2, CHCHD10, CHMP2B, DCTN1, ErbB4, FIG4, HNRPA1, MATR3, NEFH, OPTN, PFN1,

PRPH, SETX, SIGMAR1, SMN1, SPG11, SQSTM1, TBK1, TRPM7, TUBA4A, UBQLN2, VAPB, and VCP.

Frontotemporal Dementia

[00711] Frontotemporal dementia (FTD) is a form of dementia that affects the frontal and temporal lobes of the brain. FTD includes frontotemporal lobar degeneration (FTLD). It has an earlier average age of onset than Alzheimer's disease – 40 years of age. Symptoms of FTD include extreme changes in behavior and personality, speech and language problems, and movement-related symptoms such as tremor, rigidity, muscle spasm, weakness, and difficulty swallowing. Subtypes of FTD include behavior variant frontotemporal dementia (bvFTD), characterized by changes in personality and behavior, and primary progressive aphasia (PPA), which affects language skills, speaking, writing and comprehension. FTD is associated with tau protein accumulation (Pick bodies) and altered TDP43 function. About 30% of cases of FTD are familial, and no other risk factors other than family history of the disease are known. Genetic mutations associated with FTD include mutations in the genes C9orf72, Progranulin (GRN), microtubule-associated protein tau (MAPT), UBQLN2, VPC, CHMP2B, TARDBP, FUS, ITM2B, CHCHD10, SQSTM1, PSEN1, PSEN2, CTSF, CYP27A1, TBK1 and TBP.

Amyotrophic lateral sclerosis with frontotemporal dementia

[00712] Amyotrophic lateral sclerosis with frontotemporal dementia (ALS with FTD) is a clinical syndrome in which FTD and ALS occur in the same individual. Interestingly, mutations in C9orf72 are the most common cause of familial forms of ALS and FTD. Additionally, mutations in TBK1, VCP, SQSTM1, UBQLN2 and CHMP2B are also associated with ALS with FTD. Symptoms of ALS with FTD include dramatic changes in personality, as well as muscle weakness, muscle atrophy, fasciculations, spasticity, dysarthria, dysphagia, and degeneration of the spinal cord, motor neurons, and frontal and temporal lobes of the brain. At the molecular level, ALS with FTD is characterized by the accumulation of TDP-43 and/or FUS proteins. TBK1 mutations are associated with ALS, FTD, and ALS with FTD.

Limbic-predominant age-related TDP-43 encephalopathy (LATE)

[00713] Limbic-predominant age-related TDP-43 encephalopathy (LATE) is characterized by accumulation of misfolded TDP-43 protein in the brain, specifically in the limbic system. LATE is a neurological disorder that typically manifests in older patients (e.g., greater than 80 years

old). LATE can be a diagnosis for dementia and LATE often mimics the symptoms of Alzheimer's Disease including memory loss, confusion, and mood changes.

Spinal Muscular Atrophy

[00714] Spinal muscular atrophy (SMA) is a group of genetic neuromuscular disorders that affect the nerve cells that control voluntary muscles (motor neurons). The loss of motor neurons causes progressive muscle weakness and loss of movement due to muscle wasting (atrophy). The severity of the symptoms, the age at which symptoms begin, and genetic cause varies by type. Many types of SMA mainly affect the muscles involved in walking, sitting, arm movement, and head control. Breathing and swallowing may also become difficult as the disease progresses in many types of SMA. In some types of SMA, the loss of motor neurons makes it hard to control movement of the hands and feet.

In individuals affected by SMA, the SMN1 gene is mutated in such a way that it is unable to correctly code the SMN protein – due to either a deletion occurring at exon 7 or to other point mutations. There is no complete cure for SMA. Treatment consists of managing the symptoms and preventing complications. There are three approved therapies for treating SMA: of nusinersen (spinraza), onasemnogene abeparvovec-xioi (zolgensma), and risdiplam (evrysdi).

Methods of Treatment – STMN2

[00715] The disclosure contemplates, in part, treating neurological diseases including any of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), and Limbic-predominant age-related TDP-43 encephalopathy (LATE) in a patient in need thereof comprising administering a STMN2 AON. In some embodiments, provided herein are methods for treatment of a neurological disease in a patient in need thereof, comprising administering a disclosed STMN2 AON. In some embodiments of the disclosure, an effective amount of a disclosed STMN2 oligonucleotide may be administered to a patient in need thereof to treat a neurological disease, and/or to increase, restore, or stabilize expression of STMN2 mRNA that is capable of translation to produce a functional STMN2 protein, thereby increase, restore, or stabilize STMN2 activity and/or function.

[00716] In some embodiments, treating a neurological disease comprises at least ameliorating or reducing one symptom associated with the neurological disease (for example, reducing muscle weakness in a patient with ALS). Methods of treating a neurological disease (for example, ALS,

FTD, or ALS with FTD) in a patient suffering therefrom are provided, that include administering a disclosed STMN2 AON. In some embodiments, methods of slowing the progression of a neurological disease, for example, a motor neuron disease, are provided.

[00717] Provided herein are methods of treating, reducing the risk of developing, or delaying the onset of a neurological disease in a subject in need thereof comprising administering a disclosed STMN2 AON. The methods include for example, treating a subject at risk of developing a neurological disease; *e.g.*, administering to the subject an effective amount of a disclosed STMN2 AON. Neurological diseases that can be treated in this manner include motor neuron diseases, ALS, FTD, ALS with FTD, progressive bulbar palsy, pseudobulbar palsy, progressive muscular atrophy, primary lateral sclerosis, spinal muscular atrophy, and post-polio syndrome.

[00718] Methods of preventing or treating neurological diseases (for example, PD, ALS, FTD, and ALS with FTD) form part of this disclosure. Such methods may comprise administering to a patient in need thereof or a patient at risk, a pharmaceutical preparation comprising a STMN2 AON disclosed herein. For example, a method of preventing or treating a neurological disease is provided comprising administering to a patient in need thereof a STMN2 AON disclosed herein.

[00719] Patients treated using an above method may experience an increase, restoration of, or stabilization of STMN2 mRNA expression, which is capable of translation to produce a functional STMN2 protein, of at least about 5%, 10%, 20%, 30%, 40% or even 50%, thereby increase, restore, or stabilize STMN2 activity and/or function in a target cell (for example, a motor neuron) after administering a STMN2 oligonucleotide *e.g.* after 1 day, 2 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 1 month, 2 months, 3, months, 4 months, 5, months, or 6 months or more. In some embodiments, administering such a STMN2 oligonucleotide may be on, *e.g.*, at least a daily basis. The STMN2 oligonucleotide may be administered orally. In some embodiments, the STMN2 oligonucleotide is administered intrathecally, intrathalamically, intracerebroventricularly, or intracisternally. For example, in an embodiment described herein, a STMN2 oligonucleotide is administered intrathecally, intrathalamically or intracisternally about every 3 months. The delay or amelioration of clinical manifestation of a neurological disease in a patient as a consequence of administering a STMN2 oligonucleotide disclosed here may be at least *e.g.*, 6 months, 1 year, 18 months or even 2 years or more as compared to a patient who is not administered a STMN2 oligonucleotide, such as one disclosed herein.

[00720] STMN2 oligonucleotides can be used alone or in combination with each other whereby at least two STMN2 oligonucleotides are used together in a single composition or as part of a

treatment regimen. STMN2 oligonucleotides may also be used in combination with other drugs or AON for treating neurological diseases or conditions.

[00721] In various embodiments, disclosed herein is a method for treating amyotrophic lateral sclerosis (ALS) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

[00722] In various embodiments, disclosed herein is a method for treating frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an

aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

[00723] In various embodiments, disclosed herein is a method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

Methods of Treatment – KCNQ2

[00724] The disclosure contemplates, in part, treating neurological diseases including any of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), and Limbic-predominant age-related TDP-43 encephalopathy (LATE) in a patient in need thereof comprising administering a KCNQ2 AON. In some embodiments, provided herein are methods for treatment of a neurological disease in a patient in need thereof, comprising administering a disclosed KCNQ2 AON. In some embodiments of the disclosure, an effective amount of a disclosed KCNQ2 oligonucleotide may be administered to a patient in need thereof to treat a neurological disease, and/or to increase, restore, or stabilize expression of KCNQ2 mRNA that is capable of translation to produce a functional KCNQ2 protein, thereby increase, restore, or stabilize KCNQ2 activity and/or function.

[00725] In some embodiments, treating a neurological disease comprises at least ameliorating or reducing one symptom associated with the neurological disease (for example, reducing muscle weakness in a patient with ALS). Methods of treating a neurological disease (for example, ALS, FTD, or ALS with FTD) in a patient suffering therefrom are provided, that include administering a disclosed KCNQ2 AON. In some embodiments, methods of slowing the progression of a neurological disease, for example, a motor neuron disease, are provided.

[00726] Provided herein are methods of treating, reducing the risk of developing, or delaying the onset of a neurological disease in a subject in need thereof comprising administering a disclosed KCNQ2 AON. The methods include for example, treating a subject at risk of developing a neurological disease; *e.g.*, administering to the subject an effective amount of a disclosed KCNQ2 AON. Neurological diseases that can be treated in this manner include motor neuron diseases, ALS, FTD, ALS with FTD, progressive bulbar palsy, pseudobulbar palsy, progressive muscular atrophy, primary lateral sclerosis, spinal muscular atrophy, and post-polio syndrome.

[00727] Methods of preventing or treating neurological diseases (for example, PD, ALS, FTD, and ALS with FTD) form part of this disclosure. Such methods may comprise administering to a patient in need thereof or a patient at risk, a pharmaceutical preparation comprising a KCNQ2 AON disclosed herein. For example, a method of preventing or treating a neurological disease is provided comprising administering to a patient in need thereof a KCNQ2 AON disclosed herein.

[00728] Patients treated using an above method may experience an increase, restoration of, or stabilization of KCNQ2 mRNA expression, which is capable of translation to produce a

functional KCNQ2 protein, of at least about 5%, 10%, 20%, 30%, 40% or even 50%, thereby increase, restore, or stabilize KCNQ2 activity and/or function in a target cell (for example, a motor neuron) after administering a KCNQ2 oligonucleotide *e.g.* after 1 day, 2 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 1 month, 2 months, 3, months, 4 months, 5, months, or 6 months or more. In some embodiments, administering such a KCNQ2 oligonucleotide may be on, *e.g.*, at least a daily basis. The KCNQ2 oligonucleotide may be administered orally. In some embodiments, the KCNQ2 oligonucleotide is administered intrathecally, intrathalamically, or intracisternally. For example, in an embodiment described herein, a KCNQ2 oligonucleotide is administered intrathecally, intrathalamically or intracisternally about every 3 months. The delay or amelioration of clinical manifestation of a neurological disease in a patient as a consequence of administering a KCNQ2 oligonucleotide disclosed here may be at least *e.g.*, 6 months, 1 year, 18 months or even 2 years or more as compared to a patient who is not administered a KCNQ2 oligonucleotide, such as one disclosed herein.

[00729] KCNQ2 oligonucleotides can be used alone or in combination with each other whereby at least two KCNQ2 oligonucleotides are used together in a single composition or as part of a treatment regimen. KCNQ2 oligonucleotides may also be used in combination with other drugs or AON for treating neurological diseases or conditions.

[00730] In various embodiments, disclosed herein is a method for treating amyotrophic lateral sclerosis (ALS) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, or SEQ ID NOs: 4402-4409, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one

(*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

[00731] In various embodiments, disclosed herein is a method for treating frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, or SEQ ID NOs: 4402-4409, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

[00732] In various embodiments, disclosed herein is a method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, or SEQ ID NOs: 4402-4409, or a pharmaceutically acceptable salt thereof; wherein at least

one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

Methods of Treatment - UNC13A

[00733] The disclosure contemplates, in part, treating neurological diseases including any of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), Limbic-predominant age-related TDP-43 encephalopathy (LATE), Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, and synaptic diseases like autism) in a patient in need thereof comprising administering a UNC13A AON. In some embodiments, provided herein are methods for treatment of a neurological disease in a patient in need thereof, comprising administering a disclosed UNC13A AON. In some embodiments of the disclosure, an effective amount of a disclosed UNC13A oligonucleotide may be administered to a patient in need thereof to treat a neurological disease, and/or to increase, restore, or stabilize expression of UNC13A mRNA that is capable of translation to produce a functional UNC13A protein, thereby increase, restore, or stabilize UNC13A activity and/or function.

[00734] In some embodiments, treating a neurological disease comprises at least ameliorating or reducing one symptom associated with the neurological disease (for example, reducing muscle weakness in a patient with ALS). Methods of treating a neurological disease (for example, ALS,

FTD, or ALS with FTD) in a patient suffering therefrom are provided, that include administering a disclosed UNC13A AON. In some embodiments, methods of slowing the progression of a neurological disease, for example, a motor neuron disease, are provided.

[00735] Provided herein are methods of treating, reducing the risk of developing, or delaying the onset of a neurological disease in a subject in need thereof comprising administering a disclosed UNC13A AON. The methods include for example, treating a subject at risk of developing a neurological disease; *e.g.*, administering to the subject an effective amount of a disclosed UNC13A AON. Neurological diseases that can be treated in this manner include motor neuron diseases, ALS, FTD, ALS with FTD, progressive bulbar palsy, pseudobulbar palsy, progressive muscular atrophy, primary lateral sclerosis, spinal muscular atrophy, and post-polio syndrome.

[00736] Methods of preventing or treating neurological diseases (for example, PD, ALS, FTD, and ALS with FTD) form part of this disclosure. Such methods may comprise administering to a patient in need thereof or a patient at risk, a pharmaceutical preparation comprising a UNC13A AON disclosed herein. For example, a method of preventing or treating a neurological disease is provided comprising administering to a patient in need thereof a UNC13A AON disclosed herein.

[00737] Patients treated using an above method may experience an increase, restoration of, or stabilization of UNC13A mRNA expression, which is capable of translation to produce a functional UNC13A protein, of at least about 5%, 10%, 20%, 30%, 40% or even 50%, thereby increase, restore, or stabilize UNC13A activity and/or function in a target cell (for example, a motor neuron) after administering a UNC13A oligonucleotide *e.g.* after 1 day, 2 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 1 month, 2 months, 3, months, 4 months, 5, months, or 6 months or more. In some embodiments, administering such a UNC13A oligonucleotide may be on, *e.g.*, at least a daily basis. The UNC13A oligonucleotide may be administered orally. In some embodiments, the UNC13A oligonucleotide is administered intrathecally, intrathalamically, intracerebroventricularly, or intracisternally. For example, in an embodiment described herein, a UNC13A oligonucleotide is administered intrathecally, intrathalamically or intracisternally about every 3 months. The delay or amelioration of clinical manifestation of a neurological disease in a patient as a consequence of administering a UNC13A oligonucleotide disclosed here may be at least *e.g.*, 6 months, 1 year, 18 months or even 2 years or more as compared to a patient who is not administered a UNC13A oligonucleotide, such as one disclosed herein.

[00738] UNC13A oligonucleotides can be used alone or in combination with each other whereby at least two UNC13A oligonucleotides are used together in a single composition or as part of a treatment regimen. UNC13A oligonucleotides may also be used in combination with other drugs or AON for treating neurological diseases or conditions.

[00739] In various embodiments, disclosed herein is a method for treating amyotrophic lateral sclerosis (ALS) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 4531-5794, SEQ ID NO: 7059-8322, SEQ ID NOs: 9596-9696, or SEQ ID NOs: 10670-10779, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

[00740] In various embodiments, disclosed herein is a method for treating frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 4531-5794, SEQ ID NO: 7059-8322, SEQ ID NOs: 9596-9696, or SEQ ID NOs: 10670-10779, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a

methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

[00741] In various embodiments, disclosed herein is a method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 4531-5794, SEQ ID NO: 7059-8322, SEQ ID NOs: 9596-9696, or SEQ ID NOs: 10670-10779, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

Methods of Treatment – SMN2

[00742] The disclosure contemplates, in part, treating neurological diseases including spinal muscular atrophy (SMA) in a patient in need thereof comprising administering a SMN2 AON. In some embodiments, provided herein are methods for treatment of a neurological disease in a patient in need thereof, comprising administering a disclosed SMN2 AON. In some embodiments of the disclosure, an effective amount of a disclosed SMN2 oligonucleotide may be administered to a patient in need thereof to treat a neurological disease, and/or to increase, restore, or stabilize expression of SMN2 mRNA that is capable of translation to produce a functional SMN2 protein, thereby increase, restore, or stabilize SMN2 activity and/or function.

[00743] In some embodiments, treating a neurological disease comprises at least ameliorating or reducing one symptom associated with the neurological disease (for example, reducing muscle weakness in a patient with SMA). Methods of treating a neurological disease (for example, SMA) in a patient suffering therefrom are provided, that include administering a disclosed SMN2 AON. In some embodiments, methods of slowing the progression of a neurological disease, for example, a motor neuron disease, are provided.

[00744] Provided herein are methods of treating, reducing the risk of developing, or delaying the onset of a neurological disease in a subject in need thereof comprising administering a disclosed SMN2 AON. The methods include for example, treating a subject at risk of developing a neurological disease; *e.g.*, administering to the subject an effective amount of a disclosed SMN2 AON. Neurological diseases that can be treated in this manner include spinal muscular atrophy (SMA).

[00745] Methods of preventing or treating neurological diseases (for example, SMA) form part of this disclosure. Such methods may comprise administering to a patient in need thereof or a patient at risk, a pharmaceutical preparation comprising a SMN2 AON disclosed herein. For example, a method of preventing or treating a neurological disease is provided comprising administering to a patient in need thereof a SMN2 AON disclosed herein.

[00746] Patients treated using an above method may experience an increase, restoration of, or stabilization of SMN2 mRNA expression, which is capable of translation to produce a functional SMN2 protein, of at least about 5%, 10%, 20%, 30%, 40% or even 50%, thereby increase, restore, or stabilize SMN2 activity and/or function in a target cell (for example, a motor neuron) after administering a SMN2 oligonucleotide *e.g.* after 1 day, 2 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 1 month, 2 months, 3, months, 4 months, 5, months, or 6 months or more. In some embodiments, administering such a SMN2 oligonucleotide may be

on, *e.g.*, at least a daily basis. The SMN2 oligonucleotide may be administered orally. In some embodiments, the SMN2 oligonucleotide is administered intrathecally, intrathalamically, or intracisternally. For example, in an embodiment described herein, a SMN2 oligonucleotide is administered intrathecally, intrathalamically or intracisternally about every 3 months. The delay or amelioration of clinical manifestation of a neurological disease in a patient as a consequence of administering a SMN2 oligonucleotide disclosed here may be at least *e.g.*, 6 months, 1 year, 18 months or even 2 years or more as compared to a patient who is not administered a SMN2 oligonucleotide, such as one disclosed herein.

[00747] SMN2 oligonucleotides can be used alone or in combination with each other whereby at least two SMN2 oligonucleotides are used together in a single composition or as part of a treatment regimen. SMN2 oligonucleotides may also be used in combination with other drugs or AON for treating neurological diseases or conditions.

[00748] In various embodiments, disclosed herein is a method for treating amyotrophic lateral sclerosis (ALS) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, and SEQ ID NOs: 10783-10808, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

Treatment and Evaluation

[00749] A patient, as described herein, refers to any animal at risk for, suffering from or diagnosed with a neurological disease, including, but not limited to, mammals, primates, and humans. In certain embodiments, the patient may be a non-human mammal such as, for example, a cat, a dog, or a horse. A patient may be an individual diagnosed with a high risk of developing a neurological disease, someone who has been diagnosed with a neurological disease, someone who previously suffered from a neurological disease, or an individual evaluated for symptoms or indications of a neurological disease, for example, any of the signs or symptoms associated with neurological diseases such as: amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries (e.g., brachial plexus injuries), neuropathies (e.g., chemotherapy induced neuropathy), TDP43 proteinopathies (e.g., chronic traumatic encephalopathy, Perry Syndrome, Dementia with Lewy body in association with Alzheimer's disease, Parkinson's disease with or without dementia, and Limbic-predominant age-related TDP-43 encephalopathy (LATE)), Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, synaptic diseases like autism and spinal muscular atrophy (SMA).

[00750] "A patient in need," as used herein, refers to a patient suffering from any of the symptoms or manifestations of a neurological disease, a patient who may suffer from any of the symptoms or manifestations of a neurological disease, or any patient who might benefit from a method of the disclosure for treating a neurological disease. A patient in need may include a patient who is diagnosed with a risk of developing a neurological disease, a patient who has suffered from a neurological disease in the past, or a patient who has previously been treated for a neurological disease.

[00751] "Effective amount," as used herein, refers to the amount of an agent that is sufficient to at least partially treat a condition when administered to a patient. The therapeutically effective amount will vary depending on the severity of the condition, the route of administration of the component, and the age, weight, etc. of the patient being treated. Accordingly, an effective amount of a disclosed STMN2 oligonucleotide is the amount of the STMN2 oligonucleotide necessary to treat a neurological disease in a patient such that administration of the agent prevents a neurological disease from occurring in a subject, prevents neurological disease

progression (*e.g.*, prevents the onset or increased severity of symptoms of the neurological such as muscle weakening, spasms, or fasciculation), or relieves or completely ameliorates all associated symptoms of a neurological disease, *i.e.* causes regression of the disease. Accordingly, an effective amount of a disclosed KCNQ2 oligonucleotide is the amount of the KCNQ2 oligonucleotide necessary to treat a neurological disease in a patient such that administration of the agent prevents a neurological disease from occurring in a subject, prevents neurological disease progression (*e.g.*, prevents the onset or increased severity of symptoms of the neurological such as muscle weakening, spasms, or fasciculation), or relieves or completely ameliorates all associated symptoms of a neurological disease, *i.e.* causes regression of the disease. Accordingly, an effective amount of a disclosed UNC13A oligonucleotide is the amount of the UNC13A oligonucleotide necessary to treat a neurological disease in a patient such that administration of the agent prevents a neurological disease from occurring in a subject, prevents neurological disease progression (*e.g.*, prevents the onset or increased severity of symptoms of the neurological such as muscle weakening, spasms, or fasciculation), or relieves or completely ameliorates all associated symptoms of a neurological disease, *i.e.* causes regression of the disease. Accordingly, an effective amount of a disclosed SMN2 oligonucleotide is the amount of the SMN2 oligonucleotide necessary to treat a neurological disease in a patient such that administration of the agent prevents a neurological disease from occurring in a subject, prevents neurological disease progression (*e.g.*, prevents the onset or increased severity of symptoms of the neurological such as muscle weakening, spasms, or fasciculation), or relieves or completely ameliorates all associated symptoms of a neurological disease, *i.e.* causes regression of the disease.

[00752] Efficacy of treatment may be evaluated by means of evaluation of gross symptoms associated with a neurological disease, analysis of tissue histology, biochemical assay, imaging methods such as, for example, magnetic resonance imaging, or other known methods. For instance, efficacy of treatment may be evaluated by analyzing gross symptoms of the disease such as changes in muscle strength and control or other aspects of gross pathology associated with a neurological disease following administration, to a patient suffering from a neurological disease, a disclosed STMN2 oligonucleotide. For instance, efficacy of treatment may be evaluated by analyzing gross symptoms of the disease such as changes in muscle strength and control or other aspects of gross pathology associated with a neurological disease following administration, to a patient suffering from a neurological disease, a disclosed KCNQ2 oligonucleotide. For instance, efficacy of treatment may be evaluated by analyzing gross

symptoms of the disease such as changes in muscle strength and control or other aspects of gross pathology associated with a neurological disease following administration, to a patient suffering from a neurological disease, a disclosed UNC13A oligonucleotide. For instance, efficacy of treatment may be evaluated by analyzing gross symptoms of the disease such as changes in muscle strength and control or other aspects of gross pathology associated with a neurological disease following administration, to a patient suffering from a neurological disease, a disclosed SMN2 oligonucleotide.

[00753] Efficacy of treatment may also be evaluated at the tissue or cellular level, for example, by means of obtaining a tissue biopsy (*e.g.*, a brain, spinal, muscle, motor neuron tissue biopsy, or olfactory neurosphere cell biopsy) and evaluating gross tissue or cell morphology or staining properties. Biochemical assays that examine protein or RNA expression may also be used to evaluate efficacy of treatment. For instance, one may evaluate levels of a protein or gene product indicative of a neurological disease, in dissociated cells or non-dissociated tissue via immunocytochemical, immunohistochemical, Western blotting, or Northern blotting methods, or methods useful for evaluating RNA levels such as quantitative or semi-quantitative polymerase chain (*e.g.*, digital PCR (DigitalPCR, dPCR, or ddPCR), qPCR etc.) reaction. One may also evaluate the presence or level of expression of useful biomarkers (*e.g.*, neurofilament light (NEFL), neurofilament heavy (NEFH), TDP-43 or p75 extracellular domain ($p75^{ECD}$)) found in spinal cord fluid, cerebrospinal fluid, extracellular vesicles (for example, exosome-like cerebrospinal fluid extracellular vesicles ("CSF exosomes"), such as those described in Welton *et al.*, (2017) "Cerebrospinal fluid extracellular vesicle enrichment for protein biomarker discovery in neurological disease; multiple sclerosis" *J Extracell Vesicles.*, 6(1):1-10; and Street *et al.*, (2012) "Identification and proteomic profiling of exosomes in human cerebrospinal fluid" *J Transl. Med.*, 10:5), urine, fecal matter, lymphatic fluid, blood, plasma, or serum to evaluate disease state and efficacy of treatment. One may also evaluate the presence or level of expression of useful biomarkers found in the plasma, neuronal extracellular vesicles/exosomes. Additional measurements of efficacy may include strength duration time constant (SDTC), short interval cortical inhibition (SICI), dynamometry, accurate test of limb isometric strength (ATLIS), compound muscle action potential (CMAP), and ALSFRS-R. In certain embodiments, urinary neurotrophin receptor p75 extracellular domain ($p75^{ECD}$) is a disease progression and prognostic biomarker in amyotrophic lateral sclerosis (ALS). Phosphorylated neurofilament heavy chain (pNFH) in cerebrospinal fluid (CSF) predict disease status and survival in *C9ORF72*-associated amyotrophic lateral sclerosis (c9ALS) patients. CSF pNFH as a prognostic

biomarker for clinical trials, which will increase the likelihood of successfully developing a treatment for c9ALS.

STMN2

[00754] In evaluating efficacy of treatment, suitable controls may be chosen to ensure a valid assessment. For instance, one can compare symptoms evaluated in a patient with a neurological disease following administration of a disclosed STMN2 oligonucleotide to those symptoms in the same patient prior to treatment or at an earlier point in the course of treatment or in another patient not diagnosed with the neurological disease. Alternatively, one may compare the results of biochemical or histological analysis of tissue following administration of a disclosed STMN2 oligonucleotide with those of tissue from the same patient or from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the STMN2 oligonucleotide. Additionally, one may compare blood, plasma, serum, cell, urine, lymphatic fluid, spinal cord fluid, cerebrospinal fluid, or fecal samples following administration of the STMN2 oligonucleotide with comparable samples from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the STMN2 oligonucleotide. In some embodiments one may compare extracellular vesicles (for example CSF exosomes), following administration of the STMN2 oligonucleotide with extracellular vesicles from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the STMN2 oligonucleotide.

[00755] Validation of STMN2 oligonucleotides may be determined by direct or indirect assessment of STMN2 expression levels or activity. For instance, biochemical assays that measure STMN2 protein or RNA expression may be used to evaluate overall effect on STMN2 transcripts (for example, a STMN2 pre-mRNA comprising a cryptic exon) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 1339 or SEQ ID NO: 1341. For instance, one may measure STMN2 protein levels in cells or tissue by Western blot to evaluate overall STMN2 levels. One may also measure STMN2 mRNA levels by means of Northern blot or quantitative polymerase chain reaction to determine overall effect on STMN2 transcripts (for example, a STMN2 pre-mRNA comprising a cryptic exon) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 1339 or SEQ ID NO: 1341. One may also evaluate STMN2 protein levels or levels of another protein indicative of STMN2 signaling activity in dissociated cells, non-dissociated tissue, extracellular

vesicles (for example, CSF exosomes), blood, serum, or fecal matter via immunocytochemical or immunohistochemical methods.

[00756] Modulation of expression levels of STMN2 transcripts (for example, a STMN2 pre-mRNA comprising a cryptic exon) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 1339 or SEQ ID NO: 1341 may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of useful biomarkers (*e.g.*, neurofilament light (NEFL), neurofilament heavy (NEFH), TDP-43, or $p75^{ECD}$ found in plasma, spinal cord fluid, cerebrospinal fluid, extracellular vesicles (for example, CSF exosomes), blood, urine, lymphatic fluid, fecal matter, or tissue to evaluate the modulation of expression of STMN2 transcripts (for example, a STMN2 pre-mRNA comprising a cryptic exon) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 1339 or SEQ ID NO: 1341. Modulation of expression levels of STMN2 transcripts (for example, a STMN2 pre-mRNA comprising a cryptic exon) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 1339 or SEQ ID NO: 1341 may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of physiological biomarkers such as compound muscle action potential (CMAP). Additional measurements may include strength duration time constant (SDTC), short interval cortical inhibition (SICI), pyrrolidinyl, accurate test of limb isometric strength (ATLIS), compound muscle action potential, and ALSFRS-R. In certain embodiments, urinary neurotrophin receptor p75 extracellular domain ($p75^{ECD}$) is a disease progression and prognostic biomarker in amyotrophic lateral sclerosis (ALS). Phosphorylated neurofilament heavy chain (pNFH) in cerebrospinal fluid (CSF) predict disease status and survival in c9ALS patients. CSF pNFH as a prognostic biomarker for clinical trials, which will increase the likelihood of successfully developing a treatment for c9ALS.

[00757] The disclosure also provides methods of restoring expression of full length STMN2 transcripts in cells of a patient suffering from a neurological disease. Full length STMN2 transcripts may be restored in any cell in which STMN2 expression or activity occurs, including cells of the nervous system (including the central nervous system (e.g., spinal cord or brain), the peripheral nervous system, motor neurons, glial cells, astrocytes, oligodendrocytes, microglia, the brain, the brain stem, the frontal lobes, the temporal lobes, the spinal cord), the musculoskeletal system, spinal fluid, and cerebrospinal fluid. Cells of the musculoskeletal system include skeletal

muscle cells (*e.g.*, myocytes). Motor neurons include upper motor neurons and lower motor neurons.

KCNQ2

[00758] In evaluating efficacy of treatment, suitable controls may be chosen to ensure a valid assessment. For instance, one can compare symptoms evaluated in a patient with a neurological disease following administration of a disclosed KCNQ2 oligonucleotide to those symptoms in the same patient prior to treatment or at an earlier point in the course of treatment or in another patient not diagnosed with the neurological disease. Alternatively, one may compare the results of biochemical or histological analysis of tissue following administration of a disclosed KCNQ2 oligonucleotide with those of tissue from the same patient or from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the KCNQ2 oligonucleotide. Additionally, one may compare blood, plasma, serum, cell, urine, lymphatic fluid, spinal cord fluid, cerebrospinal fluid, or fecal samples following administration of the KCNQ2 oligonucleotide with comparable samples from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the KCNQ2 oligonucleotide. In some embodiments one may compare extracellular vesicles (for example CSF exosomes), following administration of the KCNQ2 oligonucleotide with extracellular vesicles from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the KCNQ2 oligonucleotide.

[00759] Validation of KCNQ2 oligonucleotides may be determined by direct or indirect assessment of KCNQ2 expression levels or activity. For instance, biochemical assays that measure KCNQ2 protein or RNA expression may be used to evaluate overall effect on KCNQ2 transcripts) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 3032-3043. For instance, one may measure KCNQ2 protein levels in cells or tissue by Western blot to evaluate overall KCNQ2 levels. One may also measure KCNQ2 mRNA levels by means of Northern blot or quantitative polymerase chain reaction to determine overall effect on KCNQ2 transcripts (for example, a KCNQ2 pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 3032-3043. One may also evaluate KCNQ2 protein levels or levels of another protein indicative of KCNQ2 signaling activity in dissociated cells, non-dissociated tissue, extracellular vesicles (for example, CSF exosomes), blood, serum, or fecal matter via immunocytochemical or immunohistochemical methods.

[00760] Modulation of expression levels of KCNQ2 transcripts (for example, a KCNQ2 pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 3032-3043 may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of useful biomarkers (*e.g.*, neurofilament light (NEFL), neurofilament heavy (NEFH), TDP-43, or $p75^{ECD}$ found in plasma, spinal cord fluid, cerebrospinal fluid, extracellular vesicles (for example, CSF exosomes), blood, urine, lymphatic fluid, fecal matter, or tissue to evaluate the modulation of expression of KCNQ2 transcripts (for example, a KCNQ2 pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 3032-3043. Modulation of expression levels of KCNQ2 transcripts (for example, a KCNQ2 pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 3032-3043 may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of physiological biomarkers such as compound muscle action potential (CMAP). Additional measurements may include strength duration time constant (SDTC), short interval cortical inhibition (SICI), dynamometry, accurate test of limb isometric strength (ATLIS), compound muscle action potential, and ALSFRS-R. In certain embodiments, urinary neurotrophin receptor p75 extracellular domain ($p75^{ECD}$) is a disease progression and prognostic biomarker in amyotrophic lateral sclerosis (ALS). Phosphorylated neurofilament heavy chain (pNFH) in cerebrospinal fluid (CSF) predict disease status and survival in c9ALS patients. CSF pNFH as a prognostic biomarker for clinical trials, which will increase the likelihood of successfully developing a treatment for c9ALS.

[00761] The disclosure also provides methods of restoring expression of full length KCNQ2 transcripts in cells of a patient suffering from a neurological disease. Full length KCNQ2 transcripts may be restored in any cell in which KCNQ2 expression or activity occurs, including cells of the nervous system (including the central nervous system (e.g., spinal cord or brain), the peripheral nervous system, motor neurons, glial cells, astrocytes, oligodendrocytes, microglia, the brain, the brain stem, the frontal lobes, the temporal lobes, the spinal cord), the musculoskeletal system, spinal fluid, and cerebrospinal fluid. Cells of the musculoskeletal system include skeletal muscle cells (*e.g.*, myocytes). Motor neurons include upper motor neurons and lower motor neurons.

<u>UNC13A</u>

[00762] In evaluating efficacy of treatment, suitable controls may be chosen to ensure a valid assessment. For instance, one can compare symptoms evaluated in a patient with a neurological disease following administration of a disclosed UNC13A oligonucleotide to those symptoms in the same patient prior to treatment or at an earlier point in the course of treatment or in another patient not diagnosed with the neurological disease. Alternatively, one may compare the results of biochemical or histological analysis of tissue following administration of a disclosed UNC13A oligonucleotide with those of tissue from the same patient or from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the UNC13A oligonucleotide. Additionally, one may compare blood, plasma, serum, cell, urine, lymphatic fluid, spinal cord fluid, cerebrospinal fluid, or fecal samples following administration of the UNC13A oligonucleotide with comparable samples from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the UNC13A oligonucleotide. In some embodiments one may compare extracellular vesicles (for example CSF exosomes), following administration of the UNC13A oligonucleotide with extracellular vesicles from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the UNC13A oligonucleotide.

[00763] Validation of UNC13A oligonucleotides may be determined by direct or indirect assessment of UNC13A expression levels or activity. For instance, biochemical assays that measure UNC13A protein or RNA expression may be used to evaluate overall effect on UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065. For instance, one may measure UNC13A protein levels in cells or tissue by Western blot to evaluate overall UNC13A levels. One may also measure UNC13A mRNA levels by means of Northern blot or quantitative polymerase chain reaction to determine overall effect on UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065. One may also evaluate UNC13A protein levels or levels of another protein indicative of UNC13A signaling activity in dissociated cells, non-dissociated tissue, extracellular vesicles (for example, CSF exosomes), blood, serum, or fecal matter via immunocytochemical or immunohistochemical methods.

[00764] Modulation of expression levels of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%,

96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of useful biomarkers (*e.g.*, neurofilament light (NEFL), neurofilament heavy (NEFH), TDP-43, or $p75^{ECD}$ found in plasma, spinal cord fluid, cerebrospinal fluid, extracellular vesicles (for example, CSF exosomes), blood, urine, lymphatic fluid, fecal matter, or tissue to evaluate the modulation of expression of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065. Modulation of expression levels of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of physiological biomarkers such as compound muscle action potential (CMAP). Additional measurements may include strength duration time constant (SDTC), short interval cortical inhibition (SICI), dynamometry, accurate test of limb isometric strength (ATLIS), compound muscle action potential, and ALSFRS-R. In certain embodiments, urinary neurotrophin receptor p75 extracellular domain ($p75^{ECD}$) is a disease progression and prognostic biomarker in amyotrophic lateral sclerosis (ALS). Phosphorylated neurofilament heavy chain (pNFH) in cerebrospinal fluid (CSF) predict disease status and survival in c9ALS patients. CSF pNFH as a prognostic biomarker for clinical trials, which will increase the likelihood of successfully developing a treatment for c9ALS.

[00765] The disclosure also provides methods of restoring expression of full length UNC13A transcripts in cells of a patient suffering from a neurological disease. Full length UNC13A transcripts may be restored in any cell in which UNC13A expression or activity occurs, including cells of the nervous system (including the central nervous system (e.g., spinal cord or brain), the peripheral nervous system, motor neurons, glial cells, astrocytes, oligodendrocytes, microglia, the brain, the brain stem, the frontal lobes, the temporal lobes, the spinal cord), the musculoskeletal system, spinal fluid, and cerebrospinal fluid. Cells of the musculoskeletal system include skeletal muscle cells (*e.g.*, myocytes). Motor neurons include upper motor neurons and lower motor neurons.

SMN2

[00766] In evaluating efficacy of treatment, suitable controls may be chosen to ensure a valid assessment. For instance, one can compare symptoms evaluated in a patient with a neurological

disease following administration of a disclosed SMN2 oligonucleotide to those symptoms in the same patient prior to treatment or at an earlier point in the course of treatment or in another patient not diagnosed with the neurological disease. Alternatively, one may compare the results of biochemical or histological analysis of tissue following administration of a disclosed SMN2 oligonucleotide with those of tissue from the same patient or from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the SMN2 oligonucleotide. Additionally, one may compare blood, plasma, serum, cell, urine, lymphatic fluid, spinal cord fluid, cerebrospinal fluid, or fecal samples following administration of the SMN2 oligonucleotide with comparable samples from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the SMN2 oligonucleotide. In some embodiments one may compare extracellular vesicles (for example CSF exosomes), following administration of the SMN2 oligonucleotide with extracellular vesicles from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the SMN2 oligonucleotide.

[00767] Validation of SMN2 oligonucleotides may be determined by direct or indirect assessment of SMN2 expression levels or activity. For instance, biochemical assays that measure SMN2 protein or RNA expression may be used to evaluate overall effect on SMN2 transcripts) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 9698-9709. For instance, one may measure SMN2 protein levels in cells or tissue by Western blot to evaluate overall SMN2 levels. One may also measure SMN2 mRNA levels by means of Northern blot or quantitative polymerase chain reaction to determine overall effect on SMN2 transcripts (for example, a SMN2 pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 9698-9709. One may also evaluate SMN2 protein levels or levels of another protein indicative of SMN2 signaling activity in dissociated cells, non-dissociated tissue, extracellular vesicles (for example, CSF exosomes), blood, serum, or fecal matter via immunocytochemical or immunohistochemical methods.

[00768] Modulation of expression levels of SMN2 transcripts (for example, a SMN2 pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 9698-9709 may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of useful biomarkers (*e.g.*, neurofilament light (NEFL),

neurofilament heavy (NEFH), TDP-43, or $p75^{ECD}$ found in plasma, spinal cord fluid, cerebrospinal fluid, extracellular vesicles (for example, CSF exosomes), blood, urine, lymphatic fluid, fecal matter, or tissue to evaluate the modulation of expression of SMN2 transcripts (for example, a SMN2 pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 9698-9707 . Modulation of expression levels of SMN2 transcripts (for example, a SMN2 pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 9698-9707 may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of physiological biomarkers such as compound muscle action potential (CMAP). Additional measurements may include strength duration time constant (SDTC), short interval cortical inhibition (SICI), dynamometry, accurate test of limb isometric strength (ATLIS), and compound muscle action potential. In certain embodiments, urinary neurotrophin receptor p75 extracellular domain ($p75^{ECD}$) is a disease progression and prognostic biomarker in amyotrophic lateral sclerosis (ALS). Phosphorylated neurofilament heavy chain (pNFH) in cerebrospinal fluid (CSF) predict disease status and survival in c9ALS patients. CSF pNFH as a prognostic biomarker for clinical trials, which will increase the likelihood of successfully developing a treatment for c9ALS.

[00769] The disclosure also provides methods of restoring expression of full length SMN2 transcripts in cells of a patient suffering from a neurological disease. Full length SMN2 transcripts may be restored in any cell in which SMN2 expression or activity occurs, including cells of the nervous system (including the central nervous system (e.g., spinal cord or brain), the peripheral nervous system, motor neurons, glial cells, astrocytes, oligodendrocytes, microglia, the brain, the brain stem, the frontal lobes, the temporal lobes, the spinal cord), the musculoskeletal system, spinal fluid, and cerebrospinal fluid. Cells of the musculoskeletal system include skeletal muscle cells (*e.g.*, myocytes). Motor neurons include upper motor neurons and lower motor neurons.

Pharmaceutical Compositions and Routes of Administration

[00770] The present disclosure also provides methods for treating a neurological disease via administration of a pharmaceutical composition comprising a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide. In another aspect, the disclosure provides a pharmaceutical composition for use in treating a neurological disease. The pharmaceutical composition may be comprised of a disclosed STMN2

oligonucleotide, and a pharmaceutically acceptable carrier. As used herein the term "pharmaceutical composition" means, for example, a mixture containing a specified amount of a therapeutic compound, *e.g.*, a therapeutically effective amount, of a therapeutic compound in a pharmaceutically acceptable carrier to be administered to a mammal, *e.g.*, a human, in order to treat a neurological disease. In some embodiments, described herein are pharmaceutical compositions comprising a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide, and a pharmaceutically acceptable carrier. In another aspect, the disclosure provides use of a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide in the manufacture of a medicament for treating a neurological disease. "Medicament," as used herein, has essentially the same meaning as the term "pharmaceutical composition."

[00771] As used herein, "pharmaceutically acceptable carrier" means buffers, carriers, and excipients suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers include buffers, solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art. In one embodiment the pharmaceutical composition is administered orally and includes an enteric coating suitable for regulating the site of absorption of the encapsulated substances within the digestive system or gut. For example, an enteric coating can include an ethylacrylate-methacrylic acid copolymer.

[00772] In one embodiment, a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide, and any pharmaceutical composition thereof may be administered by one or several routes, including topically, intrathecally, intrathalamically, intracerebroventricularly, intracisternally, parenterally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, or intraduodenally. The term parenteral as used herein includes subcutaneous injections, intrapancreatic administration, intravenous, intracisternal, intracerebroventricular, intrathecal, intrathalamic, intramuscular, intraperitoneal, intrasternal injection or infusion techniques. For example, a disclosed STMN2 oligonucleotide , KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide may be administered subcutaneously to a subject.

In another example, a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide may be administered orally to a subject. In another example, a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide may be administered directly to the nervous system, or specific regions or cells of the nervous system (*e.g.*, the brain, brain stem, lower motor neurons, spinal cord, upper motor neurons) via parenteral administration, for example, a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide may be administered intrathecally, intrathalamically, intracerebroventricularly, or intracisternally.

[00773] In various embodiments, a STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide, for example a STMN2 AON, KCNQ2 AON, UNC13A AON, and/or SMN2 AON, can be exposed to calcium-containing buffers prior to administration. Such calcium-containing buffers can mitigate toxicity adverse effects of the STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide. Further details of exposing an example antisense oligonucleotide to calcium-containing buffers is described in Moazami, et al., Quantifying and Mitigating Motor Phenotypes Induced by Antisense Oligonucleotides in the Central Nervous System, bioRxiv 2021.02.14.431096, which is hereby incorporated by reference in its entirety.

[00774] In some embodiments, a STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide, for example a STMN2 AON, KCNQ2 AON, UNC13A AON, and/or SMN2 AON, can be encapsulated in a nanoparticle coating. It is believed that nanoparticle encapsulation prevents AON degradation and enhances cellular uptake. For example, in some embodiments a STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide is encapsulated in a coating of a cationic polymer, for example, a synthetic polymer (*e.g.*, poly-L-lysine, polyamidoamine, a poly(β-amino ester), and polyethyleneimine) or a naturally occurring polymer (*e.g.*, chitosan and a protamine). In some embodiments, a STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide is encapsulated in a lipid or lipid-like material, for example, a cationic lipid, a cationic lipid-like material, or an ionizable lipid that is positively charged only at an acidic pH. For example, in some embodiments, a STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide is encapsulated in a lipid nanoparticle that includes hydrophobic moieties, *e.g.*, cholesterol and/or a polyethylene glycol (PEG) lipid.

[00775] Pharmaceutical compositions containing a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide, such as those disclosed herein, can be presented in a dosage unit form and can be prepared by any suitable method. A pharmaceutical composition should be formulated to be compatible with its intended route of administration. Useful formulations can be prepared by methods well known in the pharmaceutical art. For example, see *Remington's Pharmaceutical Sciences*, 18th ed. (Mack Publishing Company, 1990).

[00776] Pharmaceutical formulations, in some embodiments, are sterile. Sterilization can be accomplished, for example, by filtration through sterile filtration membranes. Where the composition is lyophilized, filter sterilization can be conducted prior to or following lyophilization and reconstitution.

Parenteral Administration

[00777] The pharmaceutical compositions of the disclosure can be formulated for parenteral administration, *e.g.*, formulated for injection via the intravenous, intracisternal, intracerebroventricular, intramuscular, subcutaneous, intrathecal, intrathalamic, intralesional, or intraperitoneal routes. The preparation of an aqueous composition, such as an aqueous pharmaceutical composition containing a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide, will be known to those of skill in the art in light of the present disclosure. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for using to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified.

[00778] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including normal saline, artificial cerebrospinal fluid, sesame oil, peanut oil or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

[00779] Solutions of active compounds as free base or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this

purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables. The sterile injectable preparation may also be a sterile injectable solution, suspension, or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. In one embodiment, a disclosed STMN2 antisense oligonucleotide may be suspended in a carrier fluid comprising 1% (w/v) sodium carboxymethylcellulose and 0.1% (v/v) TWEEN™ 80. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[00780] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. Sterile injectable solutions of the disclosure may be prepared by incorporating a disclosed STMN2 antisense oligonucleotide, KCNQ2 antisense oligonucleotide, UNC13A antisense oligonucleotide, and/or SMN2 antisense oligonucleotide in the required amount of the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The injectable formulations can be sterilized, for example, by filtration through a bacteria-retaining filter.

[00781] The preparation of more, or highly concentrated solutions for intramuscular injection is also contemplated. In this regard, the use of DMSO as solvent is preferred as this will result in extremely rapid penetration, delivering high concentrations of the disclosed oligonucleotide to a small area.

[00782] Suitable preservatives for use in such a solution include benzalkonium chloride, benzethonium chloride, chlorobutanol, thimerosal and the like. Suitable buffers include boric acid, sodium and potassium bicarbonate, sodium and potassium borates, sodium and potassium carbonate, sodium acetate, sodium biphosphate and the like, in amounts sufficient to maintain the pH at between about pH 6 and pH 8, and for example, between about pH 7 and pH 7.5. Suitable tonicity agents are dextran 40, dextran 70, dextrose, glycerin, potassium chloride, propylene

glycol, sodium chloride, and the like, such that the sodium chloride equivalent of the solution is in the range 0.9 plus or minus 0.2%. Suitable antioxidants and stabilizers include sodium bisulfite, sodium metabisulfite, sodium pyrrolidinyl, thiourea and the like. Suitable wetting and clarifying agents include polysorbate 80, polysorbate 20, poloxamer 282 and tyloxapol. Suitable viscosity-increasing agents include dextran 40, dextran 70, gelatin, glycerin, hydroxyethylcellulose, hydroxymethylpropylcellulose, lanolin, methylcellulose , petrolatum, polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose and the like.

Oral Administration

[00783] In some embodiments, contemplated herein are compositions suitable for oral delivery of a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide, *e.g.*, tablets that include an enteric coating, *e.g.*, a gastro-resistant coating, such that the compositions may deliver a STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide to, *e.g.*, the gastrointestinal tract of a patient.

[00784] For example, a tablet for oral administration is provided that comprises granules (*e.g.*, is at least partially formed from granules) that include a disclosed STMN2 oligonucleotide, *e.g.*, a STMN2 oligonucleotide represented by any SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669 that targets a STMN2 transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 1339 or SEQ ID NO: 1341, and pharmaceutically acceptable excipients. Such a tablet may be coated with an enteric coating. Contemplated tablets may include pharmaceutically acceptable excipients such as fillers, binders, disintegrants, and/or lubricants, as well as coloring agents, release agents, coating agents, sweetening, flavoring such as wintergreen, orange, xylitol, sorbitol, fructose, and maltodextrin, and perfuming agents, preservatives and/or antioxidants.

[00785] In some embodiments, contemplated pharmaceutical formulations include an intra-granular phase that includes a disclosed STMN2 oligonucleotide, *e.g.*, a STMN2 oligonucleotide represented by any of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669 that targets a STMN2 transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 1339 or SEQ ID NO: 1341, and a pharmaceutically acceptable salt. In some embodiments, contemplated pharmaceutical

formulations include an intra-granular phase that includes a disclosed STMN2 oligonucleotide, *e.g.*, a STMN2 oligonucleotide represented by any of SEQ ID NOs: 1-466, SEQ ID NO: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, and SEQ ID NOs: 10655-10669 that targets a STMN2 transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 1339 or SEQ ID NO: 1341, and a pharmaceutically acceptable filler.

[00786] For example, a tablet for oral administration is provided that comprises granules (*e.g.*, is at least partially formed from granules) that include a disclosed KCNQ2 oligonucleotide, *e.g.*, a KCNQ2 oligonucleotide represented by any SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530 that targets a KCNQ2 transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 3032-3043, and pharmaceutically acceptable excipients. Such a tablet may be coated with an enteric coating. Contemplated tablets may include pharmaceutically acceptable excipients such as fillers, binders, disintegrants, and/or lubricants, as well as coloring agents, release agents, coating agents, sweetening, flavoring such as wintergreen, orange, xylitol, sorbitol, fructose, and maltodextrin, and perfuming agents, preservatives and/or antioxidants.

[00787] In some embodiments, contemplated pharmaceutical formulations include an intra-granular phase that includes a disclosed KCNQ2 oligonucleotide, *e.g.*, a KCNQ2 oligonucleotide represented by any of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530 that targets a KCNQ2 transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 3032-3043, and a pharmaceutically acceptable salt. In some embodiments, contemplated pharmaceutical formulations include an intra-granular phase that includes a disclosed KCNQ2 oligonucleotide, *e.g.*, a KCNQ2 oligonucleotide represented by any of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530 that targets a KCNQ2 transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 3032-3043, and a pharmaceutically acceptable filler.

[00788] For example, a tablet for oral administration is provided that comprises granules (*e.g.*, is at least partially formed from granules) that include a disclosed UNC13A oligonucleotide, *e.g.*, a UNC13A oligonucleotide represented by any SEQ ID NOs: 4531-5794, SEQ ID NO: 7059-8322,

SEQ ID NOs: 9596-9696, or SEQ ID NOs: 10670-10779 that targets a UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 9587-9595, and pharmaceutically acceptable excipients. Such a tablet may be coated with an enteric coating. Contemplated tablets may include pharmaceutically acceptable excipients such as fillers, binders, disintegrants, and/or lubricants, as well as coloring agents, release agents, coating agents, sweetening, flavoring such as wintergreen, orange, xylitol, sorbitol, fructose, and maltodextrin, and perfuming agents, preservatives and/or antioxidants.

[00789] In some embodiments, contemplated pharmaceutical formulations include an intra-granular phase that includes a disclosed UNC13A oligonucleotide, *e.g.*, a UNC13A oligonucleotide represented by any of SEQ ID NOs: 4531-5794, SEQ ID NO: 7059-8322, SEQ ID NOs: 9596-9696, or SEQ ID NOs: 10670-10779 that targets a UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 9587-9595, and a pharmaceutically acceptable salt. In some embodiments, contemplated pharmaceutical formulations include an intra-granular phase that includes a disclosed UNC13A oligonucleotide, *e.g.*, a UNC13A oligonucleotide represented by any of SEQ ID NOs: 4531-5794, SEQ ID NO: 7059-8322, SEQ ID NOs: 9596-9696, or SEQ ID NOs: 10670-10779 that targets a UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 9587-9595, and a pharmaceutically acceptable filler.

[00790] For example, a tablet for oral administration is provided that comprises granules (*e.g.*, is at least partially formed from granules) that include a disclosed SMN2 oligonucleotide, *e.g.*, a SMN2 oligonucleotide represented by any SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, and SEQ ID NOs: 10783-10808 that targets a SMN2 transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 9698-9709, and pharmaceutically acceptable excipients. Such a tablet may be coated with an enteric coating. Contemplated tablets may include pharmaceutically acceptable excipients such as fillers, binders, disintegrants, and/or lubricants, as well as coloring agents, release agents, coating agents, sweetening, flavoring such as wintergreen, orange, xylitol, sorbitol, fructose, and maltodextrin, and perfuming agents, preservatives and/or antioxidants.

[00791] In some embodiments, contemplated pharmaceutical formulations include an intra-granular phase that includes a disclosed SMN2 oligonucleotide, *e.g.*, a SMN2 oligonucleotide represented by any of SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, and SEQ ID NOs: 10783-10808 that targets a SMN2 transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 9698-9707, and a pharmaceutically acceptable salt. In some embodiments, contemplated pharmaceutical formulations include an intra-granular phase that includes a disclosed SMN2 oligonucleotide, *e.g.*, a SMN2 oligonucleotide represented by any of SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, and SEQ ID NOs: 10783-10808 that targets a SMN2 transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 9698-9709, and a pharmaceutically acceptable filler.

[00792] For example, a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide and a filler may be blended together, optionally, with other excipients, and formed into granules. In some embodiments, the intragranular phase may be formed using wet granulation, *e.g.*, a liquid (*e.g.*, water) is added to the blended STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide and filler, and then the combination is dried, milled and/or sieved to produce granules. One of skill in the art would understand that other processes may be used to achieve an intragranular phase.

[00793] In some embodiments, contemplated formulations include an extra-granular phase, which may include one or more pharmaceutically acceptable excipients, and which may be blended with the intragranular phase to form a disclosed formulation.

[00794] A disclosed formulation may include an intragranular phase that includes a filler. Exemplary fillers include, but are not limited to, cellulose, gelatin, calcium phosphate, lactose, sucrose, glucose, mannitol, sorbitol, microcrystalline cellulose, pectin, polyacrylates, dextrose, cellulose acetate, hydroxypropylmethyl cellulose, partially pre-gelatinized starch, calcium carbonate, and others including combinations thereof.

[00795] In some embodiments, a disclosed formulation may include an intragranular phase and/or an extragranular phase that includes a binder, which may generally function to hold the ingredients of the pharmaceutical formulation together. Exemplary binders of the disclosure may include, but are not limited to, the following: starches, sugars, cellulose or modified cellulose such as hydroxypropyl cellulose, lactose, pre-gelatinized maize starch, polyvinyl pyrrolidone,

hydroxypropyl cellulose, hydroxypropylmethyl cellulose, low substituted hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl cellulose, sugar alcohols and others including combinations thereof.

[00796] Contemplated formulations, *e.g.*, that include an intragranular phase and/or an extragranular phase, may include a disintegrant such as but not limited to, starch, cellulose, crosslinked polyvinyl pyrrolidone, sodium starch glycolate, sodium carboxymethyl cellulose, alginates, corn starch, croscarmellose sodium, crosslinked carboxymethyl cellulose, low substituted hydroxypropyl cellulose, acacia, and others including combinations thereof. For example, an intragranular phase and/or an extragranular phase may include a disintegrant.

[00797] In some embodiments, a contemplated formulation includes an intra-granular phase comprising a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide and excipients chosen from: mannitol, microcrystalline cellulose, hydroxypropylmethyl cellulose, and sodium starch glycolate or combinations thereof, and an extra-granular phase comprising one or more of: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate or mixtures thereof.

[00798] In some embodiments, a contemplated formulation may include a lubricant, *e.g.* an extra-granular phase may contain a lubricant. Lubricants include but are not limited to talc, silica, fats, stearin, magnesium stearate, calcium phosphate, silicone dioxide, calcium silicate, calcium phosphate, colloidal silicon dioxide, metallic stearates, hydrogenated vegetable oil, corn starch, sodium benzoate, polyethylene glycols, sodium acetate, calcium stearate, sodium lauryl sulfate, sodium chloride, magnesium lauryl sulfate, talc, and stearic acid.

[00799] In some embodiments, the pharmaceutical formulation comprises an enteric coating. Generally, enteric coatings create a barrier for the oral medication that controls the location at which the drug is absorbed along the digestive track. Enteric coatings may include a polymer that disintegrates at different rates according to pH. Enteric coatings may include for example, cellulose acetate phthalate, methyl acrylate-methacrylic acid copolymers, cellulose acetate succinate, hydroxylpropylmethyl cellulose phthalate, methyl methacrylate-methacrylic acid copolymers, ethylacrylate-methacrylic acid copolymers, methacrylic acid copolymer type C, polyvinyl acetate-phthalate, and cellulose acetate phthalate.

[00800] Exemplary enteric coatings include Opadry® AMB, Acryl-EZE®, Eudragit® grades. In some embodiments, an enteric coating may comprise about 5% to about 10%, about 5% to about 20%, 8% to about 15%, about 8% to about 20%, about 10% to about 20%, or about 12% to about

20%, or about 18% of a contemplated tablet by weight. For example, enteric coatings may include an ethylacrylate-methacrylic acid copolymer.

[00801] For example, in a contemplated embodiment, a tablet is provided that comprises or consists essentially of about 0.5% to about 70%, *e.g.*, about 0.5% to about 10%, or about 1% to about 20%, by weight of a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide or a pharmaceutically acceptable salt thereof. Such a tablet may include for example, about 0.5% to about 60% by weight of mannitol, *e.g.*, about 30% to about 50% by weight mannitol, *e.g.*, about 40% by weight mannitol; and/or about 20% to about 40% by weight of microcrystalline cellulose, or about 10% to about 30% by weight of microcrystalline cellulose. For example, a disclosed tablet may comprise an intragranular phase that includes about 30% to about 60%, *e.g.* about 45% to about 65% by weight, or alternatively, about 5 to about 10% by weight of a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide, about 30% to about 50%, or alternatively, about 5% to about 15% by weight mannitol, about 5% to about 15% microcrystalline cellulose, about 0% to about 4%, or about 1% to about 7% hydroxypropylmethylcellulose, and about 0% to about 4%, *e.g.*, about 2% to about 4% sodium starch glycolate by weight.

[00802] In another contemplated embodiment, a pharmaceutical tablet formulation for oral administration of a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide comprises an intra-granular phase, wherein the intra-granular phase includes a disclosed STMN2 AON, KCNQ2 AON, UNC13A AON, and/or SMN2 AON or a pharmaceutically acceptable salt thereof (such as a sodium salt), and a pharmaceutically acceptable filler, and which may also include an extra-granular phase, that may include a pharmaceutically acceptable excipient such as a disintegrant. The extra-granular phase may include components chosen from microcrystalline cellulose, magnesium stearate, and mixtures thereof. The pharmaceutical composition may also include an enteric coating of about 12% to 20% by weight of the tablet. For example, a pharmaceutically acceptable tablet for oral use may comprise about 0.5% to 10% by weight of a disclosed STMN2 AON, KCNQ2 AON, UNC13A AON, and/or SMN2 AON, *e.g.*, a disclosed STMN2 AON, KCNQ2 AON, UNC13A AON, and/or SMN2 AON or a pharmaceutically acceptable salt thereof, about 30% to 50% by weight mannitol, about 10% to 30% by weight microcrystalline cellulose, and an enteric coating comprising an ethylacrylate-methacrylic acid copolymer.

[00803] In another example, a pharmaceutically acceptable tablet for oral use may comprise an intra-granular phase, comprising about 5 to about 10% by weight of a disclosed STMN2 AON, *e.g.*, a disclosed STMN2 AON or a pharmaceutically acceptable salt thereof, about 40% by weight mannitol, about 8% by weight microcrystalline cellulose, about 5% by weight hydroxypropylmethyl cellulose, and about 2% by weight sodium starch glycolate; an extra-granular phase comprising about 17% by weight microcrystalline cellulose, about 2% by weight sodium starch glycolate, about 0.4% by weight magnesium stearate; and an enteric coating over the tablet comprising an ethylacrylate-methacrylic acid copolymer.

[00804] In some embodiments the pharmaceutical composition may contain an enteric coating comprising about 13% or about 15%, 16%, 17% or 18% by weight, *e.g.*, AcyrlEZE® (*see, e.g.*, PCT Publication No. WO 2010/054826, which is hereby incorporated by reference in its entirety).

[00805] The rate at which the coating dissolves and the active ingredient is released is its dissolution rate. In an embodiment, a contemplated tablet may have a dissolution profile, *e.g.*, when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in a phosphate buffer with a pH of 7.2, of about 50% to about 100% of the STMN2 oligonucleotide releasing after about 120 minutes to about 240 minutes, for example after 180 minutes. In another embodiment, a contemplated tablet may have a dissolution profile, *e.g.*, when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in diluted HCl with a pH of 1.0, where substantially none of the STMN2 oligonucleotide is released after 120 minutes. A contemplated tablet, in another embodiment, may have a dissolution profile, *e.g.*, when tested in USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in a phosphate buffer with a pH of 6.6, of about 10% to about 30%, or not more than about 50% of the STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide releasing after 30 minutes.

[00806] In some embodiments, methods provided herein may further include administering at least one other agent that is directed to treatment of diseases and disorders disclosed herein. In one embodiment, contemplated other agents may be co-administered (*e.g.*, sequentially or simultaneously).

Dosage and Frequency of Administration

[00807] The dosage or amounts described below refer either to the oligonucleotide or a pharmaceutically acceptable salt thereof.

[00808] In some embodiments, methods described herein include administering at least 1 μg, at least 5 μg, at least 10 μg, at least 20 μg, at least 30 μg, at least 40 μg, at least 50 μg, at least 60

μg, at least 70 μg, at least 80 μg, at least 90 μg, or at least 100 μg of a STMN2 antisense oligonucleotide, KCNQ2 antisense oligonucleotide, UNC13A antisense oligonucleotide, and/or SMN2 antisense oligonucleotide *e.g.*, a STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide. In some embodiments, methods include administering from 10 mg to 500 mg, from 1 mg to 10 mg, from 10 mg to 20 mg, from 20 mg to 30 mg, from 30 mg to 40 mg, from 40 mg to 50 mg, from 50 mg to 60 mg, from 60 mg to 70 mg, from 70 mg to 80 mg, from 80 mg to 90 mg, from 90 mg to 100 mg, from 100 mg to 150 mg, from 150 mg to 200 mg, from 200 mg to 250 mg, from 250 mg to 300 mg, from 300 mg to 350 mg, from 350 mg to 400 mg, from 400 mg to 450 mg, from 450 mg to 500 mg, from 500 mg to 600 mg, from 600 mg to 700 mg, from 700 mg to 800 mg, from 800 mg to 900 mg, from 900 mg to 1 g, from 1 mg to 50 mg, from 20 mg to 40 mg, or from 1 mg to 500 mg of a STMN2 antisense oligonucleotide.

[00809] In some embodiments, methods described herein include administering formulations that include about 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1 g, 1.5 g, 2.0 g, 2.5 g, 3.0 g, 3.5 g, 4.0 g, 4.5 g, or 5.0 g of a disclosed STMN2 oligonucleotide. In some embodiments, a formulation may include about 40 mg, 80 mg, or 160 mg of a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide e. In some embodiments, a formulation may include at least 100 μg of a disclosed STMN2 oligonucleotide. For example, formulations may include about 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg of a disclosed STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide. The amount administered will depend on variables such as the type and extent of disease or indication to be treated, the overall health and size of the patient, the *in vivo* potency of the STMN2 oligonucleotide, the pharmaceutical formulation, and the route of administration. The initial dosage can be increased beyond the upper level in order to rapidly achieve the desired blood-level or tissue level. Alternatively, the initial dosage can be smaller than the optimum, and the dosage may be progressively increased during the course of treatment. Human dosage can be optimized, *e.g.*, in a conventional Phase I dose escalation study. Dosing frequency can vary, depending on factors such as route of administration, dosage amount and the disease being treated. Exemplary dosing frequencies are once per day, once per week and once every two weeks. In some embodiments, dosing is once per day for 7 days. In some embodiments, dosing

is once every 4 weeks, once every 5 weeks, once every 6 weeks, once every 7 weeks, once every 8 weeks, once every 9 weeks, once every 10 weeks, once every 11 weeks, or once every 12 weeks. In some embodiments, dosing is once a month to every three months.

Combination Therapies

[00810] In various embodiments, a STMN2 AON, KCNQ2 AON, UNC13A AON, and/or SMN2 AON as disclosed herein can be administered in combination with one or more additional therapies. The combination therapy of the disclosed oligonucleotide and the one or more additional therapies can, in some embodiments, be synergistic in treating any of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries (e.g., brachial plexus injuries), neuropathies (e.g., chemotherapy induced neuropathy), and TDP43 proteinopathies (e.g., chronic traumatic encephalopathy, Perry Syndrome, Dementia with Lewy body in association with Parkinson's disease, Parkinson's disease with or without dementia, Limbic-predominant age-related TDP-43 encephalopathy (LATE)) Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), progressive bulbar palsy, pseudobulbar palsy, progressive muscular atrophy, primary lateral sclerosis, spinal muscular atrophy, post-polio syndrome, and synaptic diseases like autism.

[00811] Non-limiting examples of therapies for Parkinson's disease (PD) include: deep brain stimulation, levodopa and carbidopa (duopa, rytary, Sinemet, inbrija), istradefylline (nourianz), safinamide (xadago), pramipexole (Mirapex), rotigotine (neupro), ropinirole (requip), amantadine (gocovri, Symmetrel, osmolex), benztropine (Cogentin), trihexyphenidyl (artane), selegiline (eldepryl, zelapar), rasagiline, entacapone (comtan), opicapone (ongentys), tolcapone (tasmar), apomorphine (apokyn, kynmobi), exenatide, lingzhi, BIIB054, BIIB094, Caffeine, sarizotan, Nuplazid and embryonic dopamine cell implantation.

[00812] Non-limiting examples of therapies for Alzheimer's disease (AD) include aducanamab (Aduhlem), memantine (Namenda), Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (razadyne), Namzeric, Suvorexant (belsomra), and lecanemab.

[00813] A non-limiting example of a therapy for amyotrophic lateral sclerosis (ALS) is pridopidine.

[00814] Non-limiting examples of therapies for frontotemporal dementia (FTD) include olanzapine (Zyprexa), quetiapine (Seroquel), SSRIs (citalopram (Cipramil), dapoxetine (Priligy), escitalopram (Cipralex), fluoxetine (Prozac or Oxactin), fluvoxamine (Faverin), paroxetine (Seroxat), sertraline (Lustral), vortioxetine (Brintellix)), divalproex sodium (Depakote), carbamazepine (Tegretol), and medroxyprogestrone.

[00815] Example additional therapies include any of Riluzole (Rilutek), PrimeC, Edaravone (Radicava), rivastigmine, donepezil, galantamine, selective serotonin reuptake inhibitor, antipsychotic agents, cholinesterase inhibitors, memantine, benzodiazepine antianxiety drugs, AMX0035 (ELYBRIO), ZILUCOPLAN (RA101495), pridopidine, dual AON intrathecal administration (*e.g.*, BIIB067, BIIB078, and BIIB105), BIIB100, levodopa/carbidopa, dopaminergic agents (*e.g.*, ropinirole, pramipexole, rotigotine), medroxyprosterone, KCNQ2/KCNQ3 openers (e.g., retigabine, XEN1101, or QRL-101), bioactive scaffolds, anticonvulsants and psychostimulant agents. Additional therapies can further include breathing care, physical therapy, occupational therapy, speech therapy, and nutritional support. Further non-limiting examples of additional therapies include any of deep brain stimulation, levodopa and carbidopa (duopa, rytary, Sinemet, inbrija), istradefylline (nourianz), safinamide (xadago), pramipexole (Mirapex), rotigotine (neupro), ropinirole (requip), amantadine (gocovri, Symmetrel, osmolex), benztropine (Cogentin), trihexyphenidyl (artane), selegiline (eldepryl, zelapar), rasagiline, entacapone (comtan), opicapone (ongentys), tolcapone (tasmar), apomorphine (apokyn, kynmobi), exenatide, lingzhi, BIIB054, BIIB094, Caffeine, sarizotan, embryonic dopamine cell implantation, aducanamab (Aduhlem), memantine (Namenda), Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (razadyne), Namzeric, Suvorexant (belsomra), lecanemab, olanzapine (Zyprexa), quetiapine (Seroquel), SSRIs (citalopram (Cipramil), dapoxetine (Priligy), escitalopram (Cipralex), fluoxetine (Prozac or Oxactin), fluvoxamine (Faverin), paroxetine (Seroxat), sertraline (Lustral), vortioxetine (Brintellix))), divalproex sodium (Depakote), carbamazepine (Tegretol), medroxyprogestrone, Brivaracetam (briviact), cannabidiol (epidiolex), carbamazepine (carbatrol, Tegretol), cenobamate (xcopri), diazepam (valium), lorazepam (Ativan), clonazepam (klonopin), eslicarbazepine (aptiom), ethosuximide (zarontin), felbamate (felbatol), fenfluramine (fintepla), lacosamide (VIMPAT), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (oxtellar xr, Trileptal), perampanel (fycompa), phenobarbital, phenytoin (dilantin), pregabalin (lyrica), tiagabine (gabitril), topiramate (topamax), valproate (depakene, depakote), and zonisamide (zonegran). In various embodiments, an additional therapy can be a second antisense oligonucleotide. As an

example, the second antisense oligonucleotide may target a STMN2 transcript, KCNQ2 transcript, UNC13A transcript, and/or SMN2 transcript(*e.g.*, STMN2 pre-mRNA, KCNQ2 pre-mRNA, UNC13A pre-mRNA, and/or SMN2 pre-mRNA, mature STMN2 mRNA, KCNQ2 mRNA, UNC13A mRNA, and/or SMN2 mRNA) to modulate the expression levels of full length STMN2 protein, KCNQ2 protein, UNC13A protein, and/or SMN2 protein.

[00816] Non-limiting examples of therapies for spinal cord injury includes bioactive scaffolds, such as bioactive scaffolds with enhanced supramolecular motion. Further details of example bioactive scaffolds as therapies for spinal cord injury is described in Alvarez et al., "Bioactive scaffolds with enhanced supramolecular motion promote recovery from spinal cord injury." Science, 374, 848-856 (2021), which is hereby incorporated by reference in its entirety.

[00817] Example additional therapies for spinal muscular atrophy include any of nusinersen (spinraza), onasemnogene abeparvovec-xioi (zolgensma), and risdiplam (evrysdi).

[00818] In various embodiments, the disclosed oligonucleotide and the one or more additional therapies can be conjugated to one another and provided in a conjugated form. Further description regarding conjugates involving the disclosed oligonucleotide is described below. In various embodiments, the disclosed oligonucleotide and one or more additional therapies are provided concurrently. In various embodiments, the disclosed oligonucleotide and one or more additional therapies are provided simultaneously. In various embodiments, the disclosed oligonucleotide and one or more additional therapies are provided sequentially.

Conjugates

[00819] In certain embodiments, provided herein are oligomeric compounds, which comprise an oligonucleotide (*e.g.*, STMN2 oligonucleotide, KCNQ2 oligonucleotide, UNC13A oligonucleotide, and/or SMN2 oligonucleotide) and optionally one or more conjugate groups and/or terminal groups. Conjugate groups include one or more conjugate moiety and a conjugate linker which links the conjugate moiety to the oligonucleotide. Conjugate groups may be attached to either or both ends of an oligonucleotide and/or at any internal position. In certain embodiments, conjugate groups are attached to the 2'-position of a nucleoside of a modified oligonucleotide. In certain embodiments, conjugate groups that are attached to either or both ends of an oligonucleotide are terminal groups. In certain such embodiments, conjugate groups or terminal groups are attached at the 3' and/or 5'-end of oligonucleotides. In certain such embodiments, conjugate groups (or terminal groups) are attached at the 3'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 3'-end of oligonucleotides. In certain embodiments, conjugate groups (or terminal groups) are attached at

the 5'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 5'-end of oligonucleotides.

[00820] Examples of terminal groups include but are not limited to conjugate groups, capping groups, phosphate moieties, protecting groups, modified or unmodified nucleosides, and two or more nucleosides that are independently modified or unmodified.

Conjugate Groups

[00821] In certain embodiments, a STMN2 AON, KCNQ2 AON, UNC13A AON, and/or SMN2 AON is covalently attached to one or more conjugate groups. In certain embodiments, conjugate groups modify one or more properties of the attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge, and clearance. In particular embodiments, conjugate groups modify the circulation time (e.g., increase) of the oligonucleotides in the bloodstream such that increased concentrations of the oligonucleotides are delivered to the brain. In particular embodiments, conjugate groups modify the residence time (e.g., increase residence time) of the oligonucleotides in a target organ (e.g., brain) such that increased residence time of the oligonucleotides improves their performance (e.g., efficacy). In particular embodiments, conjugate groups increase the delivery of the oligonucleotide to the brain through the blood brain barrier and/or brain parenchyma (e.g., through receptor mediated transcytosis). In particular embodiments, conjugate groups enable the oligonucleotide to target a specific organ (e.g., the brain). In certain embodiments, conjugate groups impart a new property on the attached oligonucleotide, e.g., fluorophores or reporter groups that enable detection of the oligonucleotide. Certain conjugate groups and conjugate moieties have been described previously, for example: cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., Bioorg. Med. Chem. Lett., 1994, 4, 1053-1060), a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., Ann. NY. Acad. Sci., 1992, 660, 306-309; Manoharan et al., Bioorg. Med. Chem. Lett., 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533-538), an aliphatic chain, e.g., do-decan-diol or undecyl residues (Saison-Behmoaras et al., EMBO J, 1991, 10, 1111-1118; Kabanov et al., FEBS Lett., 1990, 259, 327-330; Svinarchuk et al., Biochimie, 1993, 75, 49-54), a phospholipid, e.g., di-hexadecyl-rac -glycerol or triethyl -ammonium l,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654; Shea et al., Nucl. Acids Res., 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14, 969-973), or adamantane acetic acid a palmityl moiety (Mishra et al.,

Biochim. Biophys. Acta, 1995, 1264, 229-237), an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277, 923-937), a tocopherol group (Nishina *et al.*, Molecular Therapy Nucleic Acids, 2015, 4, e220; and Nishina *et al.*, Molecular Therapy, 2008, 16, 734-740), or a GalNAc cluster (*e.g.*, WO2014/179620).

Conjugate Moieties

[00822] Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides, peptides, carbohydrates, vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterols, thiocholesterols, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins, fluorophores, dyes, bile acids, and phenylbutyric acid. In particular embodiments, conjugate moieties are selected from a peptide, a lipid, N-acetylgalactosamine (GalNAc), cholesterol, vitamin E, lipoic acid, panthothenic acid, polyethylene glycol, an antibody (*e.g.*, an antibody for crossing the blood brain barrier such as anti-transferrin receptor antibody), or a cell-penetrating peptide (*e.g.*, transactivator of transcription (TAT) and penetratine).

[00823] In certain embodiments, a conjugate moiety comprises an active drug substance, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (*S*)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, fingolimod, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indomethacin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.

Conjugate Linkers

[00824] Conjugate moieties are attached to a STMN2 AON, KCNQ2 AON, UNC13A AON, and/or SMN2 AON through conjugate linkers. In certain oligomeric compounds, the conjugate linker is a single chemical bond (i.e., the conjugate moiety is attached directly to an oligonucleotide through a single bond). In certain embodiments, the conjugate linker comprises a chain structure, such as a hydrocarbon chain, or an oligomer of repeating units such as ethylene glycol, nucleosides, or amino acid units.

[00825] In certain embodiments, a conjugate linker comprises one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether, and hydroxylamino. In certain such embodiments, the conjugate linker comprises groups selected from alkyl, amino, oxo, amide and ether groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and amide groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and ether groups. In certain embodiments, the conjugate linker

comprises at least one phosphorus moiety. In certain embodiments, the conjugate linker comprises at least one phosphate group. In certain embodiments, the conjugate linker includes at least one neutral linking group.

[00826] In certain embodiments, conjugate linkers, including the conjugate linkers described above, are bifunctional linking moieties, *e.g.*, those known in the art to be useful for attaching conjugate groups to parent compounds, such as the oligonucleotides provided herein. In general, a bifunctional linking moiety comprises at least two functional groups. One of the functional groups is selected to bind to a particular site on a parent compound and the other is selected to bind to a conjugate group. Examples of functional groups used in a bifunctional linking moiety include but are not limited to electrophiles for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In certain embodiments, bifunctional linking moieties comprise one or more groups selected from amino, hydroxyl, carboxylic acid, thiol, alkyl, alkenyl, and alkynyl.

[00827] Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane- l-carboxylate (SMCC) and 6-aminohexanoic acid (AHEX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C_1-C_{10} alkyl, substituted or unsubstituted C_2-C_{10} alkenyl or substituted or unsubstituted C_2-C_{10} alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

[00828] In certain embodiments, conjugate linkers comprise 1-10 linker-nucleosides. In certain embodiments, conjugate linkers comprise 2-5 linker-nucleosides. In certain embodiments, conjugate linkers comprise 3 linker-nucleosides.

[00829] In certain embodiments, such linker-nucleosides are modified nucleosides. In certain embodiments such linker-nucleosides comprise a modified sugar moiety. In certain embodiments, linker-nucleosides are unmodified. In certain embodiments, linker-nucleosides comprise an optionally protected heterocyclic base selected from a purine, substituted purine, pyrimidine or substituted pyrimidine. In certain embodiments, a cleavable moiety is a nucleoside selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methyl cytosine, 4-N -benzoyl-5 -methyl cytosine, adenine, 6-N-benzoyladenine, guanine and 2-N-isobutyrylguanine. It is typically desirable for linker-nucleosides to be cleaved from the oligomeric compound after it reaches a target tissue. Accordingly, linker-nucleosides are typically linked to one another and to

the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are phosphodiester bonds.

[00830] Herein, linker-nucleosides are not considered to be part of the oligonucleotide. Accordingly, in embodiments in which an oligomeric compound comprises an oligonucleotide consisting of a specified number or range of linked nucleosides and/or a specified percent complementarity to a reference nucleic acid and the oligomeric compound also comprises a conjugate group comprising a conjugate linker comprising linker-nucleosides, those linker-nucleosides are not counted toward the length of the oligonucleotide and are not used in determining the percent complementarity of the oligonucleotide for the reference nucleic acid.

[00831] In certain embodiments, it is desirable for a conjugate group to be cleaved from the AON. For example, in certain circumstances oligomeric compounds comprising a particular conjugate moiety are better taken up by a particular cell type, but once the oligomeric compound has been taken up, it is desirable that the conjugate group be cleaved to release the unconjugated or parent oligonucleotide. Thus, certain conjugate linkers may comprise one or more cleavable moieties. In certain embodiments, a cleavable moiety is a cleavable bond. In certain embodiments, a cleavable moiety is a group of atoms comprising at least one cleavable bond. In certain embodiments, a cleavable moiety comprises a group of atoms having one, two, three, four, or more than four cleavable bonds. In certain embodiments, a cleavable moiety is selectively cleaved inside a cell or subcellular compartment, such as a lysosome. In certain embodiments, a cleavable moiety is selectively cleaved by endogenous enzymes, such as nucleases.

[00832] In certain embodiments, a cleavable bond is selected from among: an amide, an ester, an ether, one or both esters of a phosphodiester, a phosphate ester, a carbamate, or a disulfide. In certain embodiments, a cleavable bond is one or both of the esters of a phosphodiester. In certain embodiments, a cleavable moiety comprises a phosphate or phosphodiester. In certain embodiments, the cleavable moiety is a phosphate linkage between an oligonucleotide and a conjugate moiety or conjugate group.

[00833] In certain embodiments, a cleavable moiety comprises or consists of one or more linker-nucleosides. In certain such embodiments, the one or more linker-nucleosides are linked to one another and/or to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are unmodified phosphodiester bonds. In certain embodiments, a cleavable moiety is 2'-deoxy nucleoside that is attached to either the 3' or 5'-terminal nucleoside of an oligonucleotide by a phosphate internucleoside linkage and covalently

attached to the remainder of the conjugate linker or conjugate moiety by a phosphate or phosphorothioate linkage. In certain such embodiments, the cleavable moiety is 2'-deoxy adenosine.

Terminal Groups

[00834] In certain embodiments, oligomeric compounds comprise one or more terminal groups. In certain such embodiments, oligomeric compounds comprise a stabilized 5'-phosphate. Stabilized 5'-phosphates include, but are not limited to 5'-phosphonates, including, but not limited to 5'-vinylphosphonates. In certain embodiments, terminal groups comprise one or more abasic nucleosides and/or inverted nucleosides. In certain embodiments, terminal groups comprise one or more 2'-linked nucleosides. In certain such embodiments, the 2'-linked nucleoside is an abasic nucleoside. In various embodiments, terminal groups comprise one or more spacers.

Diagnostic Methods – STMN2

[00835] The disclosure also provides a method of diagnosing a patient with a neurological disease that relies upon detecting levels of STMN2 expression signal in one or more biological samples of a patient. As used herein, the term "STMN2 expression signal" can refer to any indication of STMN2 gene expression, or gene or gene product activity. STMN2 gene products include RNA (*e.g.*, mRNA), peptides, and proteins. Indices of STMN2 gene expression that can be assessed include, but are not limited to, STMN2 gene or chromatin state, STMN2 gene interaction with cellular components that regulate gene expression, STMN2 gene product expression levels (*e.g.*, expression levels of STMN2 transcripts (for example, a STMN2 pre-mRNA comprising a cryptic exon) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 1339 or SEQ ID NO: 1341, or interaction of STMN2 RNA or protein with transcriptional, translational, or post-translational processing machinery.

[00836] Detection of STMN2 expression signal may be accomplished through *in vivo*, *in vitro*, or *ex vivo* methods. In a preferred embodiment, methods of the disclosure may be carried out *in vitro*. Methods of detecting may involve detection in blood, serum, fecal matter, tissue, cerebrospinal fluid, spinal fluid, extracellular vesicles (for example, CSF exosomes), or cells of a patient. Detection may be achieved by measuring expression signal of STMN2 transcripts (for example, a STMN2 pre-mRNA comprising a cryptic exon) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to

SEQ ID NO: 1339 or SEQ ID NO: 1341 in whole tissue, tissue explants, cell cultures, dissociated cells, cell extract, extracellular vesicles (for example, CSF exosomes), or body fluids, including blood, spinal fluid, cerebrospinal fluid, urine, lymphatic fluid, or serum. Methods of detection include assays that measure levels of STMN2 gene product expression such as Western blotting, FACS, ELISA, other quantitative binding assays, cell or tissue growth assays, Northern blots, quantitative or semi-quantitative polymerase chain reaction, medical imaging methods (*e.g.*, MRI), or immunostaining methods (*e.g.*, immunohistochemistry or immunocytochemistry).

Diagnostic Methods – KCNQ2

[00837] The disclosure also provides a method of diagnosing a patient with a neurological disease that relies upon detecting levels of KCNQ2 expression signal in one or more biological samples of a patient. As used herein, the term "KCNQ2 expression signal" can refer to any indication of KCNQ2 gene expression, or gene or gene product activity. KCNQ2 gene products include RNA (*e.g.*, mRNA), peptides, and proteins. Indices of KCNQ2 gene expression that can be assessed include, but are not limited to, KCNQ2 gene or chromatin state, KCNQ2 gene interaction with cellular components that regulate gene expression, KCNQ2 gene product expression levels (*e.g.*, expression levels of KCNQ2 transcripts (for example, a KCNQ2 pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 3032-3045, or interaction of KCNQ2 RNA or protein with transcriptional, translational, or post-translational processing machinery.

[00838] Detection of KCNQ2 expression signal may be accomplished through *in vivo*, *in vitro*, or *ex vivo* methods. In a preferred embodiment, methods of the disclosure may be carried out *in vitro*. Methods of detecting may involve detection in blood, serum, fecal matter, tissue, cerebrospinal fluid, spinal fluid, urine, extracellular vesicles (for example, CSF exosomes), or cells of a patient. Detection may be achieved by measuring expression signal of KCNQ2 transcripts (for example, a KCNQ2 pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 3032-3045 in whole tissue, tissue explants, cell cultures, dissociated cells, cell extract, extracellular vesicles (for example, CSF exosomes), or body fluids, including blood, spinal fluid, cerebrospinal fluid, urine, lymphatic fluid, or serum. Methods of detection include assays that measure levels of KCNQ2 gene product expression such as Western blotting, FACS, ELISA, other quantitative binding assays, cell or tissue growth assays, Northern blots,

quantitative or semi-quantitative polymerase chain reaction, medical imaging methods (*e.g.*, MRI), or immunostaining methods (*e.g.*, immunohistochemistry or immunocytochemistry).

Diagnostic Methods – UNC13A

[00839] The disclosure also provides a method of diagnosing a patient with a neurological disease that relies upon detecting levels of UNC13A expression signal in one or more biological samples of a patient. As used herein, the term "UNC13A expression signal" can refer to any indication of UNC13A gene expression, or gene or gene product activity. UNC13A gene products include RNA (*e.g.*, mRNA), peptides, and proteins. Indices of UNC13A gene expression that can be assessed include, but are not limited to, UNC13A gene or chromatin state, UNC13A gene interaction with cellular components that regulate gene expression, UNC13A gene product expression levels (*e.g.*, expression levels of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 9587-9595, or interaction of UNC13A RNA or protein with transcriptional, translational, or post-translational processing machinery.

[00840] Detection of UNC13A expression signal may be accomplished through *in vivo*, *in vitro*, or *ex vivo* methods. In a preferred embodiment, methods of the disclosure may be carried out *in vitro*. Methods of detecting may involve detection in blood, serum, fecal matter, tissue, cerebrospinal fluid, spinal fluid, urine, extracellular vesicles (for example, CSF exosomes), or cells of a patient. Detection may be achieved by measuring expression signal of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 9587-9595 in whole tissue, tissue explants, cell cultures, dissociated cells, cell extract, extracellular vesicles (for example, CSF exosomes), or body fluids, including blood, spinal fluid, cerebrospinal fluid, urine, lymphatic fluid, plasma, or serum. Methods of detection include assays that measure levels of UNC13A gene product expression such as Western blotting, FACS, ELISA, other quantitative binding assays, cell or tissue growth assays, Northern blots, quantitative or semi-quantitative polymerase chain reaction, medical imaging methods (*e.g.*, MRI), or immunostaining methods (*e.g.*, immunohistochemistry or immunocytochemistry).

Diagnostic Methods – SMN2

[00841] The disclosure also provides a method of diagnosing a patient with a neurological disease that relies upon detecting levels of SMN2 expression signal in one or more biological samples of a patient. As used herein, the term "SMN2 expression signal" can refer to any indication of SMN2 gene expression, or gene or gene product activity. SMN2 gene products include RNA (*e.g.*, mRNA), peptides, and proteins. Indices of SMN2 gene expression that can be assessed include, but are not limited to, SMN2 gene or chromatin state, SMN2 gene interaction with cellular components that regulate gene expression, SMN2 gene product expression levels (*e.g.*, expression levels of SMN2 transcripts (for example, a SMN2 pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 9698-9709, or interaction of SMN2 RNA or protein with transcriptional, translational, or post-translational processing machinery.

[00842] Detection of SMN2 expression signal may be accomplished through *in vivo*, *in vitro*, or *ex vivo* methods. In a preferred embodiment, methods of the disclosure may be carried out *in vitro*. Methods of detecting may involve detection in blood, serum, fecal matter, tissue, cerebrospinal fluid, spinal fluid, urine, extracellular vesicles (for example, CSF exosomes), or cells of a patient. Detection may be achieved by measuring expression signal of SMN2 transcripts (for example, a SMN2 pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 9698-9707 in whole tissue, tissue explants, cell cultures, dissociated cells, cell extract, extracellular vesicles (for example, CSF exosomes), or body fluids, including blood, spinal fluid, cerebrospinal fluid, urine, lymphatic fluid, or serum. Methods of detection include assays that measure levels of SMN2 gene product expression such as Western blotting, FACS, ELISA, other quantitative binding assays, cell or tissue growth assays, Northern blots, quantitative or semi-quantitative polymerase chain reaction, medical imaging methods (*e.g.*, MRI), or immunostaining methods (*e.g.*, immunohistochemistry or immunocytochemistry).

Modifications in General

[00843] While certain compounds, compositions and methods described herein have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds described herein and are not intended to limit the same. Each of

the references, GenBank accession numbers, and the like recited in the present application is incorporated herein by reference in its entirety.

[00844] Although the sequence listing accompanying this filing identifies each sequence as either "RNA" or "DNA" as required, in reality, those sequences may be modified with any combination of chemical modifications. One of skill in the art will readily appreciate that such designation as "RNA" or "DNA" to describe modified oligonucleotides is, in certain instances, arbitrary. For example, an oligonucleotide comprising a nucleoside comprising a 2'-OH sugar moiety and a thymine base could be described as a DNA having a modified sugar (2'-OH in place of one 2'-H of DNA) or as an RNA having a modified base (thymine (methylated uracil) in place of a uracil of RNA). Accordingly, nucleic acid sequences provided herein, including, but not limited to those in the sequence listing, are intended to encompass nucleic acids containing any combination of natural or modified RNA and/or DNA, including, but not limited to such nucleic acids having modified nucleobases. By way of further example and without limitation, an oligomeric compound having the nucleobase sequence "ATCGATCG" encompasses any oligomeric compounds having such nucleobase sequence, whether modified or unmodified, including, but not limited to, such compounds comprising RNA bases, such as those having sequence "AUCGAUCG" and those having some DNA bases and some RNA bases such as "AUCGATCG" and oligomeric compounds having other modified nucleobases, such as "AT^{m}CGAUCG," wherein ^{m}C indicates a cytosine base comprising a methyl group at the 5-position.

[00845] Certain compounds described herein (*e.g.*, modified oligonucleotides) have one or more asymmetric center and thus give rise to enantiomers, diastereomers, and other stereoisomeric configurations that may be defined, in terms of absolute stereochemistry, as (R) or (S), as α or β such as for sugar anomers, or as (D) or (L), such as for amino acids, etc. Compounds provided herein that are drawn or described as having certain stereoisomeric configurations include only the indicated compounds. Compounds provided herein that contain stereocenters that are drawn or described with undefined stereochemistry included all such possible isomers, including their stereorandom and optically pure forms, unless specified otherwise. Likewise, all tautomeric forms of the compounds herein are also included unless otherwise indicated. Unless otherwise indicated, compounds described herein are intended to include corresponding salt forms.

[00846] The compounds described herein include variations in which one or more atoms are replaced with a non-radioactive isotope or radioactive isotope of the indicated element. For example, compounds herein that comprise hydrogen atoms encompass all possible deuterium

substitutions for each of the ^{1}H hydrogen atoms. Isotopic substitutions encompassed by the compounds herein include but are not limited to: ^{2}H or ^{3}H in place of ^{1}H, ^{13}C or ^{14}C in place of ^{12}C, ^{15}N in place of ^{14}N, ^{17}O or ^{18}O in place of ^{16}O, and ^{33}S, ^{34}S, ^{35}S, or ^{36}S in place of ^{32}S. In certain embodiments, non-radioactive isotopic substitutions may impart new properties on the oligomeric compound that are beneficial for use as a therapeutic or research tool.

EXAMPLES

[00847] The disclosure is further illustrated by the following examples. The examples are provided for illustrative purposes only, and are not to be construed as limiting the scope or content of the disclosure in any way.

Example 1: Design and Selection of STMN2 Oligonucleotides

[00848] STMN2 AONs oligonucleotides that target a STMN2 transcript including a cryptic exon are designed and tested to identify STMN2 AONs capable of reducing quantity of STMN2 transcripts that comprise a cryptic exon. Such STMN2 AONs include STMN2 parent oligonucleotides represented by any of SEQ ID NOs: 1-446 or SEQ ID NOs: 893-1338. The STMN2 parent oligonucleotides are 25 nucleosides in length. Each of the nucleosides of the STMN2 parent oligonucleotides are modified nucleosides with 2'-MOE sugar moieties, and each "C" is replaced with a 5-MeC. Additionally, each of the internucleoside linkages between the nucleosides of the STMN2 oligonucleotides are phosphorothioate internucleoside linkages.

[00849] FIG. 1 is a depiction of portions of the STMN2 transcript and STMN2 parent oligonucleotides that are designed to target certain portions of the STMN2 transcript including a cryptic exon. Specifically, regions of the STMN2 transcript include branch points (*e.g.*, branch point 1, 2, and 3) a 3' splice acceptor region, an ESE binding region, TDP43 binding sites, and a Poly A region. STMN2 oligonucleotides, are identified according to the position of the STMN2 transcript that the STMN2 oligonucleotide corresponds to. For example, FIG. 1 depicts a STMN2 oligonucleotide that targets positions 36 to 60 of the STMN2 transcript including a cryptic exon, which includes a branch point 1. Similarly, a different STMN2 oligonucleotide targets positions 144 to 178 of the STMN2 transcript including a cryptic exon, which includes a branch point 3. Other STMN2 oligonucleotides can be designed using any of the sequences disclosed above.

[00850] Generally, the length of the STMN2 antisense oligonucleotides are 25 nucleotide bases in length. However, variants of the STMN2 antisense oligonucleotides were also designed with

varying lengths (*e.g.*, 23mers, 21mers, or 19mers). Examples of these variant STMN2 antisense oligonucleotides were designed to include the sequences of SEQ ID NOs: 1342-1366 or SEQ ID NOs: 1392-1521.

Example 2: Methods for Evaluating STMN2 Antisense Oligonucleotides

[00851] STMN2 antisense oligonucleotides were evaluated in SY5Y cells and human motor neurons (hMN). The cells were plated in 6-well or 96-well plates and cultured to 80% confluency. Antisense oligonucleotide (AON) to TDP43 was transfected with RNAiMax (Thermo Fisher Scientific, Waltham, MA, USA) to express the cryptic exon, thus preventing transcription of full-length STMN2 (STMN2-FL) product. Vehicle was treated with RNAiMax alone. Positive controls included cells that were treated with TDP43 siRNA alone ("siRNA TDP43") and/or TDP43 AON alone ("AON TDP43" or "TDP43 AON"). siRNA TDP43 was purchased as ON-TARGETplus Human TARDBP (23435) siRNA – SMARTpool (#L-012394-00-0005) from Horizon/Dharmacon. TARDBP (23435) siRNA includes four individual siRNAs that targets four separate sequences:

1) Target sequence 1: GCUCAAGCAUGGAUUCUAA (SEQ ID NO: 1665)
2) Target sequence 2: CAAUCAAGGUAGUAAUAUG (SEQ ID NO: 1666)
3) Target sequence 3: GGGCUUCGCUACAGGAAUC (SEQ ID NO: 1667)
4) Target sequence 4: CAGGGUGGAUUUGGUAAUA (SEQ ID NO: 1668)

[00852] TDP43 AON is a gapmer oligonucleotide and has the following sequence and chemistry:

5' A*A*G*G*C*T*T*C*A*T*A*T*T*G*T*A*C*T*T*T 3' (SEQ ID NO: 1669)

where * = phosphorothioate, underlined = DNA, other=2'-MOE RNA; each "C" is 5-MeC.

[00853] To evaluate STMN2 AON ability to restore STMN2-FL, antisense oligonucleotides to STMN2 were co-incubated with TDP43 AON in RNAiMax. After 96 hours, transcript levels (*e.g.*, STMN2 full length transcript, STMN2 transcript with cryptic exon, or TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher TaqMan Gene Expression Assay Hs03929097_g1. RT-qPCR was performed for detecting STMN2 transcripts with cryptic exon using the following primer sequences: 1) Forward primer: 5' – CTCAGTGCCTTATTCAGTCTTCTC – 3' (SEQ ID NO: 1670), 2) Reverse primer: 5' – TCTTCTGCCGAGTCCCATTT-3' (SEQ ID NO: 1671) and 3) Probe: 5' - /56-FAM/ TCAGCGTCTGCACATCCCTACAAT /3BHQ_1/ -3' (SEQ ID NO: 1672). RT-qPCR was performed for detecting full length STMN2 transcripts using the following primer sequences: 1) Forward primer: 5' – CCACGAACTTTAGCTTCTCCA – 3' (SEQ ID NO: 1673), 2) Reverse primer: 5' – GCCAATTGTTTCAGCACCTG – 3' (SEQ ID NO: 1674), and 3)

Probe: 5' -/56-FAM/ ACTTTCTTCTTTCCTCTGCAGCCTCC /3BHQ_1/ - 3' (SEQ ID NO: 1675).

[00854] RT-qPCR was performed on Applied Biosystems ® 7500 Real-time PCR systems. One cycle of reverse transcription was performed at a temperature of 50°C for 5 min. One cycle of RT inactivation/initial denaturation was performed at a temperature of 95°C for 20 seconds. Forty five cycles of amplification were performed at a temperature of 95°C for 1 second followed by 60°C for 20 seconds.

[00855] STMN2-FL or STMN2 cryptic signal (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (*e.g.*, % increase of STMN-FL), the normalized STMN2-FL signal was further normalized to the vehicle (treated with RNAiMax alone, deltadeltaCt). Relative quantity of transcript level was calculated using the equation $RQ=2^{-deltadeltaCt}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0).

[00856] Percent decrease of STMN2 with cryptic exon expression was calculated using the equation of:

$$100 - \left(\frac{\text{Mean relative quantity of STMN2 with cryptic exon in response to STMN2 AON}}{\text{Mean relative quantity of STMN2 with cryptic exon in response to TDP43 AON}} * 100\right)$$

The percent increase of full length STMN2 mRNA transcript was calculated using the equation of:

$$\left(\left(\frac{\text{Mean relative quantity of FL STMN2 transcript in response to STMN2 AON}}{\text{Mean relative quantity of FL STMN2 transcript in response to TDP43 AON}}\right) * 100\right) - 100$$

[00857] STMN2 antisense oligonucleotides were also evaluated in human motor neurons for potency in reducing cryptic exon and increasing STMN2 full length transcript. iCell human motor neurons (Cellular Dynamics International) were plated at 15 x 10^3 cells/well in a 96-well plate for RT-qPCR RNA quantification or 3 x 10^5 cells/well in a 6-well plate for western blot protein quantification according to manufacturer's instructions. Neurons were transfected with TDP43 AON and/or STMN2 AON using endoporter (GeneTools, LLC.) or treated with endoporter alone. Treatment conditions were tested in biological triplicate (qRT-PCR) or duplicate (western blot) wells. The same TDP43 AON described above is used here for evaluating human motor neurons. TDP43 AON is a gapmer oligonucleotide and has the following sequence and chemistry:

5' A*A*G*G*C*T*T*C*A*T*A*T*T*G*T*A*C*T*T*T 3' (SEQ ID NO: 1669)

where * = phosphorothioate, underlined = DNA, other=2'-MOE RNA.

[00858] After 72 hours, antisense oligonucleotides and endoporter were washed out and replaced with fresh media. After 72 additional hours, RNA was collected from the 96-well plates for RT-qPCR or protein collected from the 6-well plates for western blot. RNA was isolated, cDNA generated and multiplexed RT-qPCR assay performed with taqman probes for STMN2 cryptic exon, STMN2 full length transcript and reference GAPDH quantification. The same primers for detecting GAPDH, STMN2 transcript with cryptic exon, and full length STMN2, as described above in reference to SY5Y cells, were applied here for conducting RT-qPCR for human motor neurons. For protein quantification, the soluble portion of the protein collection was denatured and separated by SDS-PAGE, transferred to polyvinylidene difluoride membranes and probed with antibodies against GAPDH (Proteintech, 60004-1-1g), TDP-43 (Proteintech, 10782-2-AP), and Stathmin-2 (ThermoFisher, PA5-23049).

Example 3: STMN2 Parent Oligonucleotides and Oligonucleotide Variants Restore Full Length STMN2 and Reduce STMN2 Transcripts with a Cryptic Exon

[00859] STMN2 parent oligonucleotides and oligonucleotide variants are tested for their ability to increase or restore full-length STMN2 mRNA (*i.e.*, mRNA from which full-length STMN2 is translated) levels in TDP43 silenced cells. In some cases, STMN2 oligonucleotides are tested for their ability to reduce STMN2 transcripts with a cryptic exon. As described further below, the quantified percentage increase/restoration of STMN2-FL and/or percentage reduction of STMN2 transcripts with cryptic exon is described in reference to levels of STMN-FL and/or STMN2 transcripts with cryptic exon in a control group (*e.g.*, cells treated with 500 nM TDP43 AON).

[00860] Referring to FIG. 2, TDP43 transcript was decreased by around 52% and STMN2-FL was decreased by around 57% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent AON with SEQ ID NO: 36 increased TDP43 levels by 25% and increased STMN-FL levels by 55% (rescued to 67%). A 50 nM and a 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 177 increased STMN-FL levels by 58% (rescued to 66%) and 53% (rescued to 68%) respectively. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 203 increased TDP43 levels by 15% and STMN-FL levels by 72% (rescued to 74%). A 50 nM and a 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 395 increased STMN-FL levels by 49% (rescued to 64%) and 37% (rescued to 59%) respectively.

[00861] Referring to FIG. 3, the quantity of STMN2 transcript with cryptic exon was increased more than 20-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 reduced STMN2 transcript with cryptic exon levels

by 68%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 181 reduced STMN2 transcript with cryptic exon levels by 65%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 197 reduced STMN2 transcript with cryptic exon levels by 39%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 215 reduced STMN2 transcript with cryptic exon levels by 31%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 385 reduced STMN2 transcript with cryptic exon levels by 53%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 400 reduced STMN2 transcript with cryptic exon levels by 74%.

[00862] Referring to FIG. 4, STMN2-FL was decreased by around 59% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 increased STMN-FL levels by 66% (rescued to 68%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 197 increased STMN-FL levels by 46% (rescued to 60%).

[00863] Referring to FIG. 5A, the quantity of STMN2 transcript with cryptic exon was increased more than 36-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 185 reduced STMN2 transcript with cryptic exon levels by 58%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 87%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 380 reduced STMN2 transcript with cryptic exon levels by 70%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 390 reduced STMN2 transcript with cryptic exon levels by 58%.

[00864] Referring to FIG. 5B, STMN2-FL was decreased by 66% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 185 increased STMN-FL levels by 109% (rescued to 71%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 increased STMN-FL levels by 247% (rescued to 118%).

[00865] Referring to FIG. 6A, the quantity of STMN2 transcript with cryptic exon was increased more than 20-fold when treated with 500 nM TDP43 AON (two different syntheses). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 144 reduced STMN2 transcript with cryptic exon levels by 83 to 88%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 92 to 93%.

[00866] Referring to FIG. 6B, STMN2-FL was decreased by about 80% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 144 increased STMN-FL levels by 276% to 329% (rescued to 79% to 90%). A 500 nM

treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 increased STMN-FL levels by 390% to 438% (rescued to 103% to 113 %).

[00867] Referring to FIG. 7A, the quantity of STMN2 transcript with cryptic exon was increased more than 23-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 reduced STMN2 transcript with cryptic exon levels by 83%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 177 reduced STMN2 transcript with cryptic exon levels by 83%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 181 reduced STMN2 transcript with cryptic exon levels by 72%.

[00868] Referring to FIG. 7B, STMN2-FL was decreased by about 58% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 increased STMN-FL levels by 119% (rescued to 92%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 181 increased STMN-FL levels by 88% (rescued to 79%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 185 increased STMN-FL levels by 74% (rescued to 73%).

[00869] Referring to FIG. 8A, the quantity of STMN2 transcript with cryptic exon was increased more than 20-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 197 reduced STMN2 transcript with cryptic exon levels by 65%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 94%.

[00870] Referring to FIG. 8B, STMN2-FL was decreased by 59% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 197 increased STMN-FL levels by 85% (rescued to 76%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 increased STMN-FL levels by 127% (rescued to 93%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 380 increased STMN-FL levels by 71% (rescued to 70%).

[00871] Referring to FIG. 9A, the quantity of STMN2 transcript with cryptic exon was increased more than 50-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 144 reduced STMN2 transcript with cryptic exon levels by 92%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 reduced STMN2 transcript with cryptic exon levels by 82%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 96%.

[00872] Referring to FIG. 9B, STMN2-FL was decreased by 67% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 144 increased STMN-FL levels by 135% (rescued to 87%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 increased STMN-FL levels by 132% (rescued to 86%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 increased STMN-FL levels by 143% (rescued to 90%).

[00873] Referring to FIG. 10A, the quantity of STMN2 transcript with cryptic exon was increased more than 65-fold when treated with 500 nM TDP43 AON. A 200 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 181 reduced STMN2 transcript with cryptic exon levels by 50%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 181 reduced STMN2 transcript with cryptic exon levels by 73%. Referring to FIG. 10B, STMN2-FL was decreased by 67% when treated with 500 nM TDP43 AON. A 50 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 181 increased STMN-FL levels by 115% (rescued to 71%). A 200 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 181 increased STMN-FL levels by 97% (rescued to 65%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 181 increased STMN-FL levels by 94% (rescued to 64%).

[00874] Referring to FIG. 11A, the quantity of STMN2 transcript with cryptic exon was increased more than 26-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 185 reduced STMN2 transcript with cryptic exon levels by 47%. Referring to FIG. 11B, STMN2-FL was decreased by 74% when treated with 500 nM TDP43 AON. A 50 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 185 increased STMN-FL levels by 73% (rescued to 45%). A 200 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 185 increased STMN-FL levels by 246% (rescued to 90%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 185 increased STMN-FL levels by 165% (rescued to 69%).

[00875] Referring to FIG. 12A, the quantity of STMN2 transcript with cryptic exon was increased more than 41-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 197 reduced STMN2 transcript with cryptic exon levels by 51%. Referring to FIG. 12B, STMN2-FL was decreased by 65% when treated with 500 nM TDP43 AON. A 20 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 197 increased STMN-FL levels by 86% (rescued to 65%). A 50 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 197 increased STMN-FL levels by 131% (rescued to

81%). A 200 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 197 increased STMN-FL levels by 154% (rescued to 89%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 197 increased STMN-FL levels by 169% (rescued to 94%).

[00876] Referring to FIG. 13A, the quantity of STMN2 transcript with cryptic exon was increased more than 41-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 144 reduced STMN2 transcript with cryptic exon levels by 93%. Referring to FIG. 13B, STMN2-FL was decreased by 84% when treated with 500 nM TDP43 AON. A 50 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 144 increased STMN-FL levels by 75% (rescued to 28%). A 200 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 144 increased STMN-FL levels by 260% (rescued to 57%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 144 increased STMN-FL levels by 444% (rescued to 87%).

[00877] Referring to FIG. 14A, the quantity of STMN2 transcript with cryptic exon was increased more than 24-fold when treated with 500 nM TDP43 AON. A 200 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 reduced STMN2 transcript with cryptic exon levels by 59%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 reduced STMN2 transcript with cryptic exon levels by 70%. Referring to FIG. 14B, STMN2-FL was decreased by 62% when treated with 500 nM TDP43 AON. A 200 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 increased STMN-FL levels by 100% (rescued to 76%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 increased STMN-FL levels by 158% (rescued to 98%).

[00878] Referring to FIG. 15A, the quantity of STMN2 transcript with cryptic exon was increased more than 70-fold when treated with 500 nM TDP43 AON. A 200 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 78%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 92%. Referring to FIG. 15B, STMN2-FL was decreased by 77% when treated with 500 nM TDP43 AON. A 50 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 increased STMN-FL levels by 87% (rescued to 43%). A 200 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 increased STMN-FL levels by 135% (rescued to 54%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 increased STMN-FL levels by 209% (rescued to 71%).

[00879] Referring to FIG. 16, STMN2 protein levels were decreased by 44% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 increased STMN protein levels by 52%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 increased STMN protein levels by 34%.

[00880] Referring to FIG. 17A, the quantity of STMN2 transcript with cryptic exon was increased more than 30-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 96%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1348 reduced STMN2 transcript with cryptic exon levels by 97%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1349 reduced STMN2 transcript with cryptic exon levels by 97%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1360 reduced STMN2 transcript with cryptic exon levels by 71%.

[00881] Referring to FIG. 17B, STMN2-FL was decreased by 76% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 increased STMN-FL levels by 238% (rescued to 81%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1348 increased STMN-FL levels by 63% (rescued to 39%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1359 increased STMN-FL levels by 96% (rescued to 47%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1360 increased STMN-FL levels by 125% (rescued to 54%).

[00882] Referring to FIG. 18A, the quantity of STMN2 transcript with cryptic exon was increased more than 19-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 185 reduced STMN2 transcript with cryptic exon levels by 83%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1347 reduced STMN2 transcript with cryptic exon levels by 85%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1356 reduced STMN2 transcript with cryptic exon levels by 56%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1357 reduced STMN2 transcript with cryptic exon levels by 78%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1364 reduced STMN2 transcript with cryptic exon levels by 78%.

[00883] Referring to FIG. 18B, STMN2-FL was decreased by 82% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 185 increased STMN-FL levels by 161% (rescued to 47%). A 500 nM treatment of a STMN2

oligonucleotide variant with SEQ ID NO: 1347 increased STMN-FL levels by 144% (rescued to 44%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1356 increased STMN-FL levels by 128% (rescued to 41%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1357 increased STMN-FL levels by 144% (rescued to 44%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1364 increased STMN-FL levels by 183% (rescued to 51%).

[00884] Referring to FIG. 19A, the quantity of STMN2 transcript with cryptic exon was increased more than 23-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 reduced STMN2 transcript with cryptic exon levels by 81%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1345 reduced STMN2 transcript with cryptic exon levels by 86%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1354 reduced STMN2 transcript with cryptic exon levels by 81%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1355 reduced STMN2 transcript with cryptic exon levels by 47%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1362 reduced STMN2 transcript with cryptic exon levels by 75%.

[00885] Referring to FIG. 19B, STMN2-FL was decreased by 83 % when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 increased STMN-FL levels by 265% (rescued to 62%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1345 increased STMN-FL levels by 206% (rescued to 52%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1354 increased STMN-FL levels by 212% (rescued to 53%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1355 increased STMN-FL levels by 88% (rescued to 32%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1362 increased STMN-FL levels by 188% (rescued to 49%).

[00886] Referring to FIG. 20A, the quantity of STMN2 transcript with cryptic exon was increased more than 35-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 91%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1348 reduced STMN2 transcript with cryptic exon levels by 94%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1349 reduced STMN2 transcript with cryptic exon levels by 96%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1365 reduced STMN2 transcript with cryptic exon levels by 82%. A 500 nM treatment of a

STMN2 oligonucleotide variant with SEQ ID NO: 1366 reduced STMN2 transcript with cryptic exon levels by 38%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1358 reduced STMN2 transcript with cryptic exon levels by 33%.

[00887] Referring to FIG. 20B, STMN2-FL was decreased by 80% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 increased STMN-FL levels by 325% (rescued to 85%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1348 increased STMN-FL levels by 350% (rescued to 90%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1366 increased STMN-FL levels by 105% (rescued to 41%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1358 increased STMN-FL levels by 20% (rescued to 24%).

[00888] Referring to FIG. 21A, the quantity of STMN2 transcript with cryptic exon was increased more than 11-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 reduced STMN2 transcript with cryptic exon levels by 72%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1346 reduced STMN2 transcript with cryptic exon levels by 85%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1353 reduced STMN2 transcript with cryptic exon levels by 55%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1662 (G*A*G*TCCTGCAATATGAATATA*AT*T*T, where * indicates phosphodiester linkage) reduced STMN2 transcript with cryptic exon levels by 49%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1663 (GAGTCCTG*C*A*A*T*A*TGAATATAATTT, where * indicates phosphodiester linkage) reduced STMN2 transcript with cryptic exon levels by 57%.

[00889] Referring to FIG. 21B, STMN2-FL was decreased by 73% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 increased STMN-FL levels by 85% (rescued to 50%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1353 increased STMN-FL levels by 85% (rescued to 50%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1662 increased STMN-FL levels by 74% (rescued to 47%). A 500 nM treatment of a STMN2 oligonucleotide variant SEQ ID NO: 1663 increased STMN-FL levels by 89% (rescued to 51%).

[00890] Referring to FIG. 22A, the quantity of STMN2 transcript with cryptic exon was increased more than 13-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 144 reduced STMN2 transcript with cryptic

exon levels by 91%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1344 reduced STMN2 transcript with cryptic exon levels by 80%. A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1342 reduced STMN2 transcript with cryptic exon levels by 85%.

[00891] Referring to FIG. 22B, STMN2-FL was decreased by 65% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 144 increased STMN-FL levels by 94% (rescued to 68%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 1343 increased STMN-FL levels by 11% (rescued to 39%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 1351 increased STMN-FL levels by 9% (rescued to 38%). A 500 nM treatment of a STMN2 oligonucleotide variant with SEQ ID NO: 1344 increased STMN-FL levels by 114% (rescued to 75%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 1350 increased STMN-FL levels by 3% (rescued to 36%). A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 1361 increased STMN-FL levels by 9% (rescued to 38%).

Example 4: Neuropathy as an indication that can be targeted by a Stathmin-2 cryptic splicing modulator

[00892] Experimentally, iCell human motor neurons (Cellular Dynamics International) were plated at 19,000 cells/well in a 96-well plate according to manufacturer's instructions. Neurons were treated with SEQ ID NO: 237 and endoporter (GeneTools, LLC.) or treated with endoporter alone in triplicate wells at day 7 post-plating. After 72 hours, SEQ ID NO: 237 STMN2 parent oligonucleotide and endoporter were washed out and MG132 added. After 18 hours, RNA was isolated, cDNA generated and multiplexed QPCR assay performed for STMN2 cryptic exon and reference GAPDH quantification.

[00893] Referring to FIG. 23, it illustrates a bar graph showing reversal of cryptic exon induction using SEQ ID NO: 237 STMN2 parent oligonucleotide even in view of increasing proteasome inhibition. As a control, cells that were treated with endoporter alone (no AON) and then subsequently treated with MG132 (across all concentrations of MG132) demonstrated high levels of cryptic exon. This is indicative of TDP-43 pathology induced by proteasome inhibition in human motor neurons. Mislocalization of TDP-43 leads to STMN2 mis-splicing and increased cryptic exon expression. The addition of SEQ ID NO: 237 parent oligonucleotide reverses cryptic exon induction with high potency (IC50 <5nM). As shown in FIG. 23, increasing concentrations of SEQ ID NO: 237 (ranging from 5 nM up to 500 nM) significantly reduces the cryptic exon relative quantity.

[00894] In totality, this data establishes that the SEQ ID NO: 237 parent oligonucleotide protects against proteotoxic stress induction of cryptic exon expression. This is applicable in settings where neurons are to be protected from proteotoxic stress present in neurodegenerative disorders.

Example 5: Dose response restoration of full length STMN2 mRNA and STMN2 protein using Stathmin-2 cryptic splicing modulator

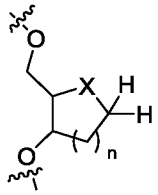
[00895] The experiment was performed as previously described in human neuroblastoma SY5Y cells. The cells were plated in 6-well or 96-well plates and cultured to 80% confluency. TDP-43 expression in cells were knocked down using an AON to TDP43 to express the cryptic exon, thus preventing transcription of full-length STMN2 (STMN2-FL) product. Cells were additionally co-transfected with a STMN2 oligonucleotide variant (specifically, SEQ ID NO: 1348) at varying doses (5nM, 50nM, 100nM, 200nM, and 500nM). RNA and protein were isolated for QPCR and western blot assays.

[00896] FIG. 24 shows the dose response curve illustrating increasing restoration of full length STMN2 transcript with increasing concentrations of STMN2 oligonucleotide variant with SEQ ID NO: 1348. Generally, increasing concentrations of the oligonucleotide increased full length STMN2 mRNA, decreased cryptic exon levels. Specifically, a 5nM treatment of the STMN2 oligonucleotide variant resulted in ~40% restoration of full length STMN2 transcript. A 500nM treatment of the STMN2 oligonucleotide variant resulted in nearly 100% restoration of full length STMN2 transcript. Additionally, the 500nM treatment of the STMN2 oligonucleotide variant resulted in the significant reduction (close to 0%) of cryptic exon.

[00897] FIG. 25A shows a protein blot assay demonstrating the qualitative increase of full length STMN2 protein in response to higher concentrations of STMN2 oligonucleotide variant with SEQ ID NO: 1348. FIG. 25B shows the quantitated levels of full length STMN2 protein normalized to GAPDH in response to different concentrations of STMN2 oligonucleotide variant. Generally, both FIG. 25A and 25B show that increasing concentrations of the STMN2 oligonucleotide variant resulted in increasing concentrations of full length STMN2 protein. Specifically, as shown in FIG. 25B, lower concentrations (5nM and 50nM) of the STMN2 oligonucleotide variant resulted in full length STMN2 protein concentrations that were ~60% of the control group (cell only). Notably, the 500nM treatment of the STMN2 oligonucleotide variant resulted in nearly 100% restoration of the full length STMN2 protein (in comparison to the cell only control group).

Example 6: STMN2 AONs with Spacer Technology Restore Full Length STMN2 and Reduces STMN2 Transcripts with a Cryptic Exon

[00898] STMN2 AONs with two or three spacers were developed. Here, a spacer is represented by Formula (I), wherein:



Formula (I)

X is -O-; and

n is 1.

[00899] STMN2 AONs (*e.g.*, STMN2 oligonucleotides each with two spacers) were tested in human motor neurons (hMN) for their ability to increase or restore full-length STMN2 mRNA (*i.e.*, mRNA from which full-length STMN2 is translated) levels in TDP43 silenced cells. In some cases, STMN2 oligonucleotides are tested for their ability to reduce STMN2 transcripts with a cryptic exon. As described further below, the quantified percentage increase/restoration of STMN2-FL and/or percentage reduction of STMN2 transcripts with cryptic exon is described in reference to levels of STMN-FL and/or STMN2 transcripts with cryptic exon in a control group (*e.g.*, cells treated with 500 nM TDP43 AON).

[00900] Three different STMN2 oligonucleotides with two spacers were generated. These three example STMN2 oligonucleotides are named 1) SEQ ID NO: 1589 (a 25mer with a first spacer at position 11 and a second spacer at position 22), 2) SEQ ID NO: 1590 (a 25mer with a first spacer at position 7 and a second spacer at position 14), and 3) SEQ ID NO: 1591 (a 25mer with a first spacer at position 8 and a second spacer at position 19). The STMN2 AONs are shown in Table 26.

Table 26: STMN2 AONs (including STMN2 parent oligonucleotides and STMN2 oligonucleotides with two spacers)

Sequence ID Number (SEQ ID NO)	Oligonucleotide Sequence* (where S indicates presence of a Spacer) (5' → 3')
144	AATCCAATTAAGAGAGAGTGATGGG

1589	AATCCAATTASGAGAGAGTGASGGG
173	GAGTCCTGCAATATGAATATAATTT
1590	GAGTCCSGCAATASGAATATAATTT
237	GCACACATGCTCACACAGAGAGCCA
1591	GCACACASGCTCACACAGSGAGCCA

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 26 are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

[00901] Referring to FIG. 26A, the quantity of STMN2 transcript with cryptic exon was increased more than 27-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 144 reduced STMN2 transcript with cryptic exon levels by 71%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 1589 reduced STMN2 transcript with cryptic exon levels by 88%. Here, SEQ ID NO: 1589 exhibited further reduction of STMN2 transcripts with cryptic exon in comparison to SEQ ID NO: 144 (without two spacers.) A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 reduced STMN2 transcript with cryptic exon levels by 77%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 1590 reduced STMN2 transcript with cryptic exon levels by 48%. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 93%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 1591 reduced STMN2 transcript with cryptic exon levels by 96%. Here, SEQ ID NO: 1591 exhibited similar reduction of STMN2 transcripts with cryptic exon in comparison to SEQ ID NO: 237 (without two spacers.)

[00902] Referring to FIG. 26B, STMN2-FL was decreased by 68% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 144 increased STMN-FL levels by 165% (rescued to 85%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 1589 increased STMN-FL levels by 256% (rescued to 114%). Here, SEQ ID NO: 1589 exhibited improved restoration of STMN2 FL mRNA in comparison to SEQ ID NO: 144 (without two spacers.) A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 173 increased STMN-FL levels by 184% (rescued to 91%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 1590 increased STMN-FL levels by 156% (rescued to 82%). Here, SEQ ID NO: 1590 exhibited similar restoration of STMN2 FL mRNA in comparison to

SEQ ID NO: 173 (without two spacers.) A 500 nM treatment of a STMN2 parent oligonucleotide with SEQ ID NO: 237 increased STMN-FL levels by 225% (rescued to 104%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 1591 increased STMN-FL levels by 225% (rescued to 104%). Here, SEQ ID NO: 1591 exhibited similar restoration of STMN2 FL mRNA in comparison to SEQ ID NO: 237 (without two spacers.).

[00903] Additional example STMN2 AONs (including STMN2 AONs described above in Table 26) are shown below in Table 27. Specifically, Table 27 includes example STMN2 AONs with two spacers and STMN2 AONs with three spacers. Furthermore, Table 27 includes example STMN2 AON variants with one or more spacers that are shorter in length (e.g., 23mer, 21mer or 19mer) in comparison to STMN2 parent oligonucleotides described above in Table 26.

Table 27: STMN2 AONs with two or three spacers and STMN2 AON variants with two spacers.

Sequence ID Number (SEQ ID NO).	Oligonucleotide Sequence* (where S indicates presence of a Spacer) (5' → 3')
144	AATCCAATTAAGAGAGAGTGATGGG
1589	AATCCAATTASGAGAGAGTGASGGG
1592	AATCCAASTAAGAGASAGTGATGSG
1593	AATCCAASTAAGAGASAGTGATSGG
1594	ASTCCAATTSAGAGAGASTGATGGG
1417	AATCCSATTASGAGAGAGSGATGGG
1595	TCCAATTSAGAGAGASTGATGGG
173	GAGTCCTGCAATATGAATATAATTT
1590	GAGTCCSGCAATASGAATATAATTT
1596	GAGTCCTSCAATATGSATATAATST
1597	GAGSCCTGCAASATGAATSTAATTT
1418	GAGTCCSGCAATASGAATATASTTT
1598	GTCCTGCSATATGAASATAAT
1599	GTCCTSCAATATGSATATAAT
1419	GTCCSGCAATASGAATATA
237	GCACACATGCTCACACAGAGAGCCA

1591	GCACACASGCTCACACAGSGAGCCA
1600	GCACACASGCTCACASAGAGAGSCA
1601	GCSCACATGSTCACACASAGAGCCA
1420	GCACACASGCTCACASAGAGSGCCA
1602	GCACACASGCTCACASAGAGAGC
1603	AATSCAATTAAGAGSGAGTGATGGG
1604	AATCCAATTASGAGAGAGTGSTGGG
1605	AATCCASTTAAGAGAGAGSGATGGG
1606	AATCCASTTAAGAGAGASTGATGGG
1607	AATCCAASTAAGSGAGASTGATGGG
1608	GAGSCCTGCAATATSAATATAATTT
1609	GAGTCCTGCASTATGAATATSATTT
1610	GAGTCCSGCAATATGAATSTAATTT
1611	GAGTCCSGCAATATGAASATAATTT
1612	GAGTCCTSCAATSTGAASATAATTT
1613	GAGTCCSGCAATSTGAATSTAATTT
1614	GAGTCSTGCAATSTGAATASAATTT
1615	GAGTSCTGCAATSTGAATATSATTT
1616	GTCCTGCSATATGSATATAAT
1617	CCTTTCTCSCGAAGGTCTTCSGCCG
1618	CTTTCTCSCGAAGGTSTTCTGCC
1619	TTTCTCTSGAAGGTCSTCTGCCG
1664	GCACACASGCSCACACAGSGAGCCA
1621	GCACACASGCTCSCACASAGAGCCA

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 27 are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer, as indicated by S, is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

[00904] Table 13 depicts the performance of STMN2 AONs, including STMN2 AONs with two or three spacers.

[00905] STMN2 AONs that included two spacers increased levels of STMN2-FL. For example, at a dose of 200nM ASO, SEQ ID NO: 1608 and SEQ ID NO: 1609 increased levels of STMN-FL to 0.65 and 0.78, respectively. Additionally, at a dose of 200nM ASO, SEQ ID NO: 1610 and SEQ ID NO: 1611 increased levels of STMN-FL to 0.95 and 1.09, respectively. Notably, a number of STMN2 AONs increased levels of STMN-FL to a lesser extent. Specifically, at a 200 nM dose of STMN2 AON, SEQ ID NO: 1612, SEQ ID NO: 1613, SEQ ID NO: 1614, and SEQ ID NO: 1615 increased levels of STMN-FL to between 0.10 and 0.20.

[00906] At a dose of 200nM AON, all STMN2 AON derived from SEQ ID NO: 197 significantly increased levels of STMN-FL. Specifically, SEQ ID NO: 1617, SEQ ID NO: 1618, and SEQ ID NO: 1619 increased levels of STMN-FL to 0.99, 0.94, and 1.00, respectively.

[00907] Altogether, these results demonstrate that different STMN2 AONs including two spacers are capable of increasing STMN-FL to levels that are close or comparable to their non-spacer counterparts (e.g., SEQ ID NO: 173 or SEQ ID NO: 197).

[00908] The differences in performance between STMN2 AONs derived from SEQ ID NO: 173, including SEQ ID NO: 1612, SEQ ID NO: 1613, SEQ ID NO: 1614, and SEQ ID NO: 1615 and STMN2 AONs derived from SEQ ID NO: 197 including SEQ ID NO: 1617, SEQ ID NO: 1618, and SEQ ID NO: 1619 may be attributable to GC content in the respective STMN2 AONs. Specifically, as shown in Table 28, STMN2 AONs derived from SEQ ID NO: 173 had below 30% GC content, which may lead to their reduced performance. In contrast, as shown in Table 28, STMN2 AONs derived from SEQ ID NO: 197 had above 40% GC content. Thus, including two or more spacers in a higher GC content AON may be preferable.

[00909] In addition to GC content, the location of spacers relative to guanine and cytosine nucleobases can also impact the performance of the STMN2 AON. For example, at a 200 nM AON dose, SEQ ID NO: 1615, SEQ ID NO: 1596, and SEQ ID NO: 1597 increased levels of STMN2-FL to 0.12, 0.26, and 0.29. Each of these STMN2 AONs have three spacers. In comparison, at a 200 nM AON dose, SEQ ID NO: 1418 increased levels of STMN2-FL to 0.73. SEQ ID NO: 1418 includes spacers that are positioned to maximize the number of spacers that are immediately preceding a guanine base. Specifically, the first and second spacers of SEQ ID NO: 1418 each respectively precede a guanine base. Thus, maximizing the number of spacers in a STMN2 AON that immediately precede a guanine base can improve the performance of the STMN2 AON.

Table 28: Performance of varying STMN2 AONs, including STMN2 AONs with two or three spacers.

Sequence ID No. (SEQ ID NO)	Oligonucleotide Sequence* (where S indicates presence of a Spacer) (5' → 3')	Relative Quantity of STMN-FL in response to 200 nM ASO Treatment	Relative Quantity of STMN-FL in response to 50 nM ASO treatment	GC content
169	CCTGCAATATGAATATAATTTTAAA	0.73	0.45	20%
1421	CCTGCAATATGAATATAATTTTA	1.19	0.48	22%
1422	TGCAATATGAATATAATTTTAAA	0.85	0.63	13%
1423	CTGCAATATGAATATAATTTTAA	0.93	0.69	17%
1424	TGCAATATGAATATAATTTTA	0.8	0.44	14%
170	TCCTGCAATATGAATATAATTTTAA	1.01	0.46	20%
1425	TCCTGCAATATGAATATAATTTT	0.83	0.49	22%
1426	CTGCAATATGAATATAATTTT	0.83	0.57	19%
171	GTCCTGCAATATGAATATAATTTTA	0.89	0.41	24%
1346	GTCCTGCAATATGAATATAATTT	1.1	1.13	26%
1355	CCTGCAATATGAATATAATTT	0.82	0.44	24%
172	AGTCCTGCAATATGAATATAATTTT	0.79	0.45	24%
1427	AGTCCTGCAATATGAATATAATT	0.89	0.52	26%
1428	TCCTGCAATATGAATATAATT	1.18	0.66	24%

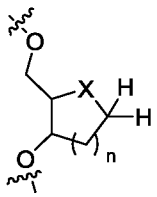
252	CTCTCTCGCACACACGCACACATGC	0.67	0.43	60%
1432	CTCTCGCACACACGCACACATGC	0.67	0.52	61%
1433	CTCTCTCGCACACACGCACACAT	0.63	0.24	57%
1434	TCTCTCGCACACACGCACACATG	0.73	0.45	57%
1435	CTCTCGCACACACGCACACAT	0.84	0.36	57%
173	GAGTCCTGCAATATGAATATAATTT	1.12	0.6	28%
1608	GAGSCCTGCAATATSAATATAATTT	0.65	0.19	24%
1609	GAGTCCTGCASTATGAATATSATTT	0.78	0.25	28%
1610	GAGTCCSGCAATATGAATSTAATTT	0.95	0.43	28%
1611	GAGTCCSGCAATATGAASATAATTT	1.09	0.32	28%
1612	GAGTCCTSCAATSTGAASATAATTT	0.15	0.08	24%
1613	GAGTCCSGCAATSTGAATSTAATTT	0.2	0.13	28%
1614	GAGTCSTGCAATSTGAATASAATTT	0.13	0.18	24%
1615	GAGTSCTGCAATSTGAATATSATTT	0.12	0.12	24%
1596	GAGTCCTSCAATATGSATATAATST	0.26	0.13	24%
1597	GAGSCCTGCAASATGAATSTAATTT	0.29	0.17	28%
1418	GAGTCCSGCAATASGAATATASTTT	0.73	0.24	28%

1598	GTCCTGCSATATGAASATAAT	0.72	0.31	29%
1599	GTCCTSCAATATGSATATAAT	0.1	0.16	24%
1616	GTCCTGCSATATGSATATAAT	0.77	0.23	29%
197	CCTTTCTCTCGAAGGTCTTCTGCCG	1.04	0.44	56%
1429	TTTCTCTCGAAGGTCTTCTGCCG	1.35	1.06	48%
1430	CCTTTCTCTCGAAGGTCTTCTGC	0.98	0.44	48%
1431	CTTTCTCTCGAAGGTCTTCTGCC	1.33	0.55	48%
1617	CCTTTCTCSCGAAGGTCTTCSGCCG	0.99	0.69	56%
1618	CTTTCTCSCGAAGGTSTTCTGCC	0.94	0.58	48%
1619	TTTCTCTSGAAGGTCSTCTGCCG	1	0.54	48%

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 28 are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

Example 7: Additional Experiments Demonstrate STMN2 AONs with Spacer Technology Restore Full Length STMN2 and Reduces STMN2 Transcripts with a Cryptic Exon

[00910] STMN2 AONs with one, two, or three spacers were developed. Generally, in this Example, except for SEQ ID NO: 1649 described below, a spacer is represented by Formula (I), wherein:

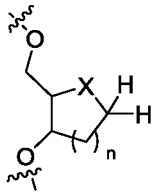


Formula (I)

X is -O-; and

n is 1.

For SEQ ID NO: 1649, each spacer included in the ASO is represented by Formula (I), wherein:



Formula (I)

X is -O-; and

n is 2.

[00911] STMN2 AONs with spacers were characterized and compared to STMN2 AON without spacer counterparts. Specifically, the melting temperature of STMN2 AON with and without spacers were determined to demonstrate the structural differences of the STMN2 AONs. Table 29 shows the different melting temperatures of STMN2 AONs across two different replicates. STMN2 AONs with two spacers exhibited a lower melting temperature (approximately 10°C lower) in comparison to STMN2 AONs without spacers.

Table 29: Melting temperatures of STMN2 AONs with and without spacers.

ASO + RNA target (25bases)	Tm (°C) Replicate 1	Tm (°C) Replicate 2	ΔTm °C Replicate 1	ΔTm °C Replicate 2	%GC

SEQ ID NO: 237 (no spacer)	86.6	86.5	11.6	11.4	56
SEQ ID NO: 1591 (2 spacers)	75.0	75.1			
SEQ ID NO: 144 (no spacer)	75.5	75.5	9.5	9.7	40
SEQ ID NO: 1589 (2 spacers)	66.0	65.8			
SEQ ID NO: 173 (no spacer)	71.2	71.1	13.5	13.5	28
SEQ ID NO: 1590 (2 spacers)	57.7	57.6			

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides identified in Table 29 are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer is not a nucleoside and is represented by Formula (Iia') as disclosed herein.

[00912] STMN2 AONs (*e.g.*, STMN2 oligonucleotides with one, two, or three spacers) were tested for their ability to increase or restore full-length STMN2 mRNA (*i.e.*, mRNA from which full-length STMN2 is translated) levels in TDP43 silenced cells. In some cases, STMN2 oligonucleotides are tested for their ability to reduce STMN2 transcripts with a cryptic exon. FIGs. 27-35 show effects of STMN2 AONs with spacers in increasing full-length STMN2 mRNA ("STMN2 FL") and/or in reducing STMN2 transcripts with a cryptic exon ("STMN2 cryptic"). Furthermore, Table 30 identifies the respective STMN2 AONs as well as their respective performances. Treatment groups are identified on the X-axis of FIGs. 27-35 and include the concentration of specific AON sequences. Here, specific AON sequences are labeled according to their corresponding SEQ ID NO.

[00913] FIG. 27A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 173, SEQ ID NO: 1608, SEQ ID NO: 1609, SEQ ID NO: 1610, SEQ ID NO: 1611, SEQ ID NO: 1612, SEQ ID NO: 1613, SEQ ID NO: 1614, SEQ ID NO: 1615, SEQ ID NO: 1596, SEQ ID NO: 1597, and SEQ ID NO: 1418. FIG. 27B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs

including SEQ ID NO: 173, SEQ ID NO: 1608, SEQ ID NO: 1609, SEQ ID NO: 1610, SEQ ID NO: 1611, SEQ ID NO: 1612, SEQ ID NO: 1613, SEQ ID NO: 1614, SEQ ID NO: 1615, SEQ ID NO: 1596, SEQ ID NO: 1597, and SEQ ID NO: 1418. Generally, FIGs. 27A and 27B demonstrate the performance of STMN2 AONs with spacers (e.g., SEQ ID NO: 1608, SEQ ID NO: 1609, SEQ ID NO: 1610, SEQ ID NO: 1611, SEQ ID NO: 1612, SEQ ID NO: 1613, SEQ ID NO: 1614, SEQ ID NO: 1615, SEQ ID NO: 1596, SEQ ID NO: 1597, and SEQ ID NO: 1418) in comparison to STMN2 AON without spacers (SEQ ID NO: 173). Here, a number of STMN2 AON with spacers perform as well, or outperform the STMN2 AON without spacers (SEQ ID NO: 173). Specifically, 200 nM of SEQ ID NO: 1609, SEQ ID NO: 1610, and SEQ ID NO: 1611 achieve comparable levels of STMN2 transcript with cryptic exon mRNA levels and STMN2 full-length mRNA levels in the presence of TDP43 in comparison to STMN2 AON without spacers (SEQ ID NO: 173).

[00914] FIG. 28A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 173, SEQ ID NO: 1632, SEQ ID NO: 1346, SEQ ID NO: 1631, SEQ ID NO: 1353, and SEQ ID NO: 1598. FIG. 28B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs including SEQ ID NO: 173, SEQ ID NO: 1632, SEQ ID NO: 1346, SEQ ID NO: 1631, SEQ ID NO: 1353, and SEQ ID NO: 1598. Generally, FIGs. 28A and 28B demonstrate the performance of STMN2 AONs with spacers (e.g., SEQ ID NO: 1632, SEQ ID NO: 1631, and SEQ ID NO: 1598) in comparison to their STMN2 AON counterparts without spacer (e.g., SEQ ID NO: 173, SEQ ID NO: 1346, and SEQ ID NO: 1353). Here, a 50nM or 200 nM dose of SEQ ID NO: 1632 achieves comparable levels of STMN2 transcript with cryptic exon mRNA levels and STMN2 full-length mRNA levels in the presence of TDP43 in comparison to a 50nM or 200nM dose of the STMN2 AON counterpart without spacers (SEQ ID NO: 173). A 200 nM dose of SEQ ID NO: 1631 achieves comparable levels of STMN2 full-length mRNA levels in the presence of TDP43 in comparison to 200 nM dose of the STMN2 AON counterpart without spacers (SEQ ID NO: 1346).

[00915] FIG. 29A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 173 and SEQ ID NO: 1610. FIG. 29B is a bar graph showing the results of RT-

qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs including SEQ ID NO: 173 and SEQ ID NO: 1610. Generally, FIGs. 29A and 29B demonstrate the performance of STMN2 AONs with spacers (e.g., SEQ ID NO: 1610) in comparison to the STMN2 AON counterpart without spacers (e.g., SEQ ID NO: 173). Across the different doses (e.g., 500 nM, 200 nM, 50 nM, 20 nM, and 5 nM), SEQ ID NO: 1610 achieves comparable levels of STMN2 transcript with cryptic exon mRNA levels and STMN2 full-length mRNA levels in the presence of TDP43 in comparison to the STMN2 AON counterpart without spacers (SEQ ID NO: 173).

[00916] FIG. 30A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 185 and SEQ ID NO: 1635. FIG. 30B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs including SEQ ID NO: 185 and SEQ ID NO: 1635. Generally, FIGs. 30A and 30B demonstrate the performance of STMN2 AONs with spacers (e.g., SEQ ID NO: 1635) in comparison to the STMN2 AON counterpart without spacers (e.g., SEQ ID NO: 185). Across the different doses (e.g., 500 nM, 200 nM, 50 nM, 20 nM, and 5 nM), SEQ ID NO: 1610 achieves comparable or reduced levels of STMN2 transcript with cryptic exon mRNA levels and comparable or increased STMN2 full-length mRNA levels in the presence of TDP43 in comparison to the STMN2 AON counterpart without spacers (SEQ ID NO: 185).

[00917] FIG. 31A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 1347, SEQ ID NO: 1633, and SEQ ID NO: 1634. FIG. 31B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs including SEQ ID NO: 1347, SEQ ID NO: 1633, and SEQ ID NO: 1634. Generally, FIGs. 31A and 31B demonstrate the performance of STMN2 AONs with spacers (e.g., SEQ ID NO: 1633 and SEQ ID NO: 1634) in comparison to the STMN2 AON counterpart without spacers (e.g., SEQ ID NO: 1347). Across the different doses (e.g., 500 nM, 200 nM, 50 nM, 20 nM, and 5 nM), SEQ ID NO: 1633 achieves comparable or reduced levels of STMN2 transcript with

cryptic exon mRNA levels and comparable or increased STMN2 full-length mRNA levels in the presence of TDP43 in comparison to the STMN2 AON counterpart without spacers (SEQ ID NO: 1347). Similarly, across the different doses (e.g., 500 nM, 200 nM, 50 nM, 20 nM, and 5 nM), SEQ ID NO: 1634 achieves comparable or reduced levels of STMN2 transcript with cryptic exon mRNA levels and comparable or increased STMN2 full-length mRNA levels in the presence of TDP43 in comparison to the STMN2 AON counterpart without spacers (SEQ ID NO: 1347).

[00918] FIG. 32A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 197, SEQ ID NO: 1617, SEQ ID NO: 1618, and SEQ ID NO: 1619. FIG. 32B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs including SEQ ID NO: 197, SEQ ID NO: 1617, SEQ ID NO: 1618, and SEQ ID NO: 1619. Generally, FIGs. 32A and 32B demonstrate the performance of STMN2 AONs with spacers (e.g., SEQ ID NO: 1617, SEQ ID NO: 1618, and SEQ ID NO: 1619) in comparison to the STMN2 AON counterpart without spacers (e.g., SEQ ID NO: 197). At a 50 nM or 200 nM dose, SEQ ID NO: 1617 achieves comparable or reduced levels of STMN2 transcript with cryptic exon mRNA levels and comparable or increased STMN2 full-length mRNA levels in the presence of TDP43 in comparison to a 50 nM or 200 nM dose of the STMN2 AON counterpart without spacers (SEQ ID NO: 197). At a 50 nM or 200 nM dose, SEQ ID NO: 1618 achieves comparable or reduced levels of STMN2 transcript with cryptic exon mRNA levels and comparable or increased STMN2 full-length mRNA levels in the presence of TDP43 in comparison to a 50 nM or 200 nM dose of the STMN2 AON counterpart without spacers (SEQ ID NO: 197). At a 50 nM or 200 nM dose, SEQ ID NO: 1619 achieves comparable or reduced levels of STMN2 transcript with cryptic exon mRNA levels and comparable or increased STMN2 full-length mRNA levels in the presence of TDP43 in comparison to a 50 nM or 200 nM dose of the STMN2 AON counterpart without spacers (SEQ ID NO: 197).

[00919] FIG. 33A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 252, SEQ ID NO: 1650, SEQ ID NO: 1434, SEQ ID NO: 1651, and SEQ ID NO: 1620. FIG. 33B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2

transcript across different dosages of STMN2 AONs including SEQ ID NO: 252, SEQ ID NO: 1650, SEQ ID NO: 1434, SEQ ID NO: 1651, and SEQ ID NO: 1620. Generally, FIGs. 33A and 33B demonstrate the performance of STMN2 AONs with spacers (e.g., SEQ ID NO: 1620) in comparison to the STMN2 AON counterpart without spacers (e.g., SEQ ID NO: 252, SEQ ID NO: 1650, SEQ ID NO: 1434, and SEQ ID NO: 1651). At a 50 nM or 200 nM dose, SEQ ID NO: 1620 achieves comparable or reduced levels of STMN2 transcript with cryptic exon mRNA levels and comparable or increased STMN2 full-length mRNA levels in the presence of TDP43 in comparison to a 50 nM or 200 nM dose of the STMN2 AON counterparts without spacers (SEQ ID NO: 252, SEQ ID NO: 1650, SEQ ID NO: 1434, and SEQ ID NO: 1651).

[00920] FIG. 34A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of STMN2 AONs including SEQ ID NO: 1434 and SEQ ID NO: 1620. FIG. 34B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of STMN2 AONs including SEQ ID NO: 1434 and SEQ ID NO: 1620. Generally, FIGs. 34A and 34B demonstrate the performance of STMN2 AONs with spacers (e.g., SEQ ID NO: 1620) in comparison to the STMN2 AON counterpart without spacers (e.g., SEQ ID NO: 1434). Across the different doses (e.g., 500 nM, 200 nM, 50 nM, 20 nM, and 5 nM), SEQ ID NO: 1620 achieves reduced levels of STMN2 transcript with cryptic exon mRNA levels and increased STMN2 full-length mRNA levels in the presence of TDP43 in comparison to the STMN2 AON counterpart without spacers (SEQ ID NO: 1434).

[00921] FIG. 35 is a bar graph showing normalized STMN2 protein levels following treatment with TDP43 antisense and restoration using 500 nM STMN2 AONs including SEQ ID NO: 144, SEQ ID NO: 1589, SEQ ID NO: 173, SEQ ID NO: 1616, SEQ ID NO: 237, and SEQ ID NO: 1591. Generally, FIG. 35 demonstrates the performance of STMN2 AONs with spacers (e.g., SEQ ID NO: 1589, SEQ ID NO: 1616, and SEQ ID NO: 1591) in comparison to their STMN2 AON counterparts without spacers (e.g., SEQ ID NO: 144, SEQ ID NO: 173, SEQ ID NO: 237). Generally, STMN2 AONs with spacers are able to achieve comparable levels of STMN2 protein levels in comparison to their STMN2 AON counterparts. Specifically, SEQ ID NO: 1589 achieves comparable levels of STMN2 protein levels in comparison to SEQ ID NO: 144. SEQ ID NO: 1616 achieves comparable levels of STMN2 protein levels in comparison to SEQ ID NO:

173. SEQ ID NO: 1591 achieves comparable levels of STMN2 protein levels in comparison to SEQ ID NO: 237.

[00922] Referring to Tables 30 and 31A-31C, they show the performance of STMN2 AONs with spacers (e.g., Table 30 and Tables 31B-31C) and performance of STMN2 AONs without spacers (e.g., Table 31A) in human motor neurons. RT-qPCR results for STMN2 full-length transcript provided in Tables 30 and 31A-31C are normalized values using the equation ((RQASO-RQTDP43)/(Rqendo-RQTDP43))*100 where RQ refers to Relative Quantity described above. RT-qPCR results for STMN2 transcript with a cryptic exon provided in Tables 30 and 31A-31C are normalized values using the equation (1-((RQASO-RQTDP43)/(RQendo-RQTDP43)))*100 where RQ refers to Relative Quantity described above. Each RT-qPCR experiment was run in triplicate wells and performed N number of independent replicate runs. Standard deviation or SD is calculated as the SD between each run. Where N=1, SD was reported as the standard deviation between the triplicate well results in the single experiment. Notably, as shown in Table 30, a 200nM dose of SEQ ID NO: 1631 (GTCCTGCSATATGAASATAATTT with two spacers) rescued full length STMN2 mRNA to 69% and reduced STMN2 transcript with cryptic exon levels to 49% (reduced by 51%).

[00923] Additionally, as shown in Table 30, a 200 nM dose of SEQ ID NO: 1633 (GTCTTCTSCCGAGTCSTGCAATA with two spacers) rescued full length STMN2 mRNA to 83% and reduced STMN2 transcript with cryptic exon levels to 10% (reduced by 90%). Comparatively, as shown in Table 31A, a 200nM dose of SEQ ID NO: 1347 (GTCTTCTGCCGAGTCCTGCAATA with no spacers) rescued full length STMN2 mRNA to 40.2% and reduced STMN2 transcript with cryptic exon levels to 20.8% (reduced by 80.2%). This indicates that the addition of spacers improves the performance of SEQ ID NO: 1633 in comparison to the STMN2 AON counterpart without spacers (e.g., SEQ ID NO: 1347).

[00924] Additionally, as shown in Table 30, a 200 nM dose of SEQ ID NO: 1618 (CTTTCTCSCGAAGGTSTTCTGCC with two spacers) rescued full length STMN2 mRNA to 82% and reduced STMN2 transcript with cryptic exon levels to 11% (reduced by 89%). A 200 nM dose of SEQ ID NO: 1619 (TTTCTCTSGAAGGTCSTCTGCCG with two spacers) rescued full length STMN2 mRNA to 80% and reduced STMN2 transcript with cryptic exon levels to 12% (reduced by 88%). Comparatively, as shown in Table 31A, a 200nM dose of SEQ ID NO: 197 (CCTTTCTCTCGAAGGTCTTCTGCCG with no spacers) rescued full length STMN2 mRNA to 79.3% and reduced STMN2 transcript with cryptic exon levels to 12.1% (reduced by 87.9%). Here, at 200 nM dose, the performance of STMN2 AONs with two spacers (e.g., SEQ

ID NO: 1618 and SEQ ID NO: 1619) is comparable to the STMN2 AON counterpart without spacers (e.g., SEQ ID NO: 197). Notably, at a 50nM dose, the performance of STMN2 AONs with two spacers (e.g., SEQ ID NO: 1618 and SEQ ID NO: 1619) is improve din comparison to the STMN2 AON counterpart without spacers (e.g., SEQ ID NO: 197). Specifically, at the 50 nM dose, SEQ ID NO: 1618 rescued full length STMN2 mRNA to 46% and SEQ ID NO: 1619 rescued full length STMN2 mRNA to 42% whereas SEQ ID NO: 197 (without spacers) rescued full length STMN2 mRNA to 26.7%.

[00925] Additionally, as shown in Table 30, a 200 nM dose of SEQ ID NO: 1620 (TCTCTCGSACACACGSACACATG with two spacers) rescued full length STMN2 mRNA to 103% and reduced STMN2 transcript with cryptic exon levels to 1% (reduced by 99%). A 50 nM dose of SEQ ID NO: 1620 rescued full length STMN2 mRNA to 74% and reduced STMN2 transcript with cryptic exon levels to 5% (reduced by 95%). Comparatively, as shown in Table 31A, a 200 nM dose and 50 nM dose of SEQ ID NO: 1434 (TCTCTCGCACACACGCACACATG with no spacers) rescued full length STMN2 mRNA to 77.5% and 16.6%, respectively and reduced STMN2 transcript with cryptic exon levels to 2.7% (reduced by 97.3%) and 18.3% (reduced by 81.7%), respectively. This indicates that the addition of spacers improves the performance of SEQ ID NO: 1620 in comparison to the STMN2 AON counterpart without spacers (e.g., SEQ ID NO: 1434).

[00926] Additional STMN2 AONs were developed with LNA modifications and evaluated for their ability to restore STMN2 FL while reducing STMN2 cryptic levels. Tables 31D and 31E below shows the results of the evaluation.

Table 30: Performance of STMN2 AONs (STMN2 oligonucleotides with one, two, or three spacers).

SEQ ID NO:	Oligonucleotide Sequence[#] (where S indicates presence of a Spacer) (5' to 3')	QPCR potency in hMN STMN2 FL		QPCR potency in hMN STMN2 cryptic	
		50 nM	200 nM	50 nM	200 nM
		Mean	Mean	Mean	Mean
1622	TGCAATASGAATATASTTTTAAA	1	47	76	340
1623	TCCTGCASTATGAATSTAATTTT	6	31	82	100
1624	CTGCAATATGSATATAATTTT	5	11	104	61
1625	CTGCAATSTGAATATSATTTTAA	2	-4	116	147
1626	CCTGCAATATSAATATAATTT	2	42	65	59
1627	TCCTGCAATASGAATATAATT	19	65	85	36
1628	GTCCTGCSATATGAASATAAT	20	65	79	45
1629	GTCCTSCAATATGSATATAAT	5	13	119	133
1630	GTCCTGCSATATGSATATAAT	16	71	97	51
1631	GTCCTGCSATATGAASATAATTT	13	69	81	49
1596	GAGTCCTSCAATATGSATATAATST	3	18	52	50
1597	GAGSCCTGCAASATGAATSTAATTT	7	20	79	82
1418	GAGTCCSGCAATASGAATATASTTT	15	69	70	48
1632	GAGTCCTGCAATATSAATATAATTT	27	75	55	24
1608	GAGSCCTGCAATATSAATATAATTT	10	60	44	30
1609	GAGTCCTGCASTATGAATATSATTT	17	70	67	42

1610	GAGTCCSGCAATATGAATSTAATTT	29	83	76	40
1611	GAGTCCSGCAATATGAASATAATTT	23	95	60	41
1612	GAGTCCTSCAATSTGAASATAATTT	-2	5	106	92
1613	GAGTCCSGCAATSTGAATSTAATTT	3	11	100	96
1614	GAGTCSTGCAATSTGAATASAATTT	8	2	94	101
1615	GAGTSCTGCAATSTGAATATSATTT	1	2	90	99
1633	GTCTTCTSCCGAGTCSTGCAATA	53	83	45	10
1634	GTCTTCTGCCGSGTCCTGCAATA	31	74	41	12
1635	AGGTCTTCSGCCGAGTCCSGCAATA	23	N/A	43	N/A
1617	CCTTTCTCSCGAAGGTCTTCSGCCG	49	89	24	9
1618	CTTTCTCSCGAAGGTSTTCTGCC	46	82	35	11
1619	TTTCTCTSGAAGGTCSTCTGCCG	42	80	40	12
1620	TCTCTCGSACACACGSACACATG	74	103	5	1
1589	AATCCAATTASGAGAGAGTGASGGG	7	32	107	47
1590	GAGTCCSGCAATASGAATATAATTT	23	63	76	47
1591	GCACACASGCTCACACAGSGAGCCA	45	86	11	2
1636	GT*C*C*TGCSATATGAASATAAT	18	53	75	74
1637	GT*C*C*TSCAATATGSATATAAT	4	2	130	105
1638	GT*C*C*TGCSATATGSATATAAT	24	41	75	68
1639	GTCTTCTSCCGAGT*C*S*T*GCAATA	26	67	60	30
1640	GT*CT*TC*TGCCGSGTCCTGCAATA	33	63	36	17

1641	GTCTTCTGCC*G*S*G*TCCTGCAATA	21	91	34	23
1642	CCTTTCTCSCGAAGGTCT*T*C*SGCCG	40	77	28	14
1643	CCTTTCTCSCGAAGGTCTT*C*S*G*CCG	40	77	21	15
1644	CTTTCTCSCGAAGG*T*S*T*TCTGCC	28	46	60	36
1645	GC*A*CA*C*ASGCTCACASAGAGAGC	30	73	22	4
1646	GCACAC*A*S*G*CTCACASAGAGAGC	12	37	29	11
1647	TC*TC*TC*GSACACACGSACACATG	40	90	15	3
1648	TCTCTCGSACACACGSA*CA*CA*TG	58	108	19	7
1649	GTCTTCTS^CCGAGTCS^TGCAATA	26	71	19	21

Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 30 are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties and each "C" is replaced with a 5-methylcytosine (5-MeC). * indicates presence of phosphodiester linkage. All other internucleoside linkages are phosphorothioate linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein. S^ represents a spacer of Formula (IIIa') as disclosed herein.

Table 31A: Performance of STMN2 AONs (STMN2 oligonucleotides without spacers).

SEQ ID NO:	Oligonucleotide Sequence# (5' to 3')	QPCR potency in hMN STMN2 FL		QPCR potency in hMN STMN2 cryptic	
		50 nM	200 nM	50 nM	200 nM
		Mean	Mean	Mean	Mean
144	AATCCAATTAAGAGAGAGTGATGGG	2	23	71	49

146	AAAATCCAATTAAGAGAGAGTGATG	11	19	45	36
150	TTTAAAAATCCAATTAAGAGAGAGT	43.7	46.7	38.7	17.7
169	CCTGCAATATGAATATAATTTTAAA	36.3	72.3	45.3	11.7
170	TCCTGCAATATGAATATAATTTTAA	28.3	86.3	69.3	25.3
171	GTCCTGCAATATGAATATAATTTTA	30.7	85.0	56.3	12.3
172	AGTCCTGCAATATGAATATAATTTT	33.0	79.3	54.7	15.7
173	GAGTCCTGCAATATGAATATAATTT	29.0	81.5	61.3	21.0
197	CCTTTCTCTCGAAGGTCTTCTGCCG	26.7	79.3	44.4	12.1
237	GCACACATGCTCACACAGAGAGCCA	46	80	7	1
252	CTCTCTCGCACACACGCACACATGC	37.6	69.6	19.0	2.3
1343	AATCCAATTAAGAGAGAGTGATG	7	15	56	33
1346	GTCCTGCAATATGAATATAATTT	67.3	98.0	49.3	10.3
1347	GTCTTCTGCCGAGTCCTGCAATA	12.5	40.2	55.7	20.8
1348	GCACACATGCTCACACAGAGAGC	45.6	89.5	11.6	0.7
1351	AATCCAATTAAGAGAGAGTGA	10.0	12.0	69.0	35.0
1353	GTCCTGCAATATGAATATAAT	48.2	100.5	47.2	18.3
1353	GT*CC*TG*CAATATGAA*TA*TA*AT	36.4	84.3	64.0	32.8
1355	CCTGCAATATGAATATAATTT	50.0	79.0	21.5	7.0
1421	CCTGCAATATGAATATAATTTTA	44.0	120.0	32.0	8.0
1422	TGCAATATGAATATAATTTTAAA	43.9	80.7	40.5	24.0
1423	CTGCAATATGAATATAATTTTAA	48.0	88.7	38.3	10.7

1424	TGCAATATGAATATAATTTTA	40.0	79.0	33.0	15.0
1425	TCCTGCAATATGAATATAATTTT	39.0	95.8	40.6	12.0
1426	CTGCAATATGAATATAATTTT	45.5	85.2	39.4	12.6
1427	AGTCCTGCAATATGAATATAATT	39.7	76.0	42.3	13.3
1428	TCCTGCAATATGAATATAATT	43.0	91.5	42.8	10.0
1429	TTTCTCTCGAAGGTCTTCTGCCG	49.5	85.5	40.9	9.5
1430	CCTTTCTCTCGAAGGTCTTCTGC	41.5	98.2	27.5	5.9
1431	CTTTCTCTCGAAGGTCTTCTGCC	32.6	83.3	40.6	12.6
1432	CTCTCGCACACACGCACACATGC	34.0	51.8	25.5	3.1
1433	CTCTCTCGCACACACGCACACAT	20.2	60.8	6.5	2.9
1434	TCTCTCGCACACACGCACACATG	43.3	77.5	18.3	2.7
1435	CTCTCGCACACACGCACACAT	33.0	83.4	22.6	3.7
1650	CT*C*TC*T*CGCACACACGCACACATGC	26.6	68.8	40.3	13.3
1651	TC*TC*TC*GCACACACGCACACATG	46.1	91.0	32.4	8.9
1652	TTTCTCTCGAAGGTCTTCTGC	26.0	75.9	49.4	8.9
1653	AAAATCCAATTAAGAGAGAGTGA	15.0	19.0	49.0	29.0
1654	AAATCCAATTAAGAGAGAGTGAT	12.0	18.0	55.0	31.0
1655	TAAAAATCCAATTAAGAGAGAGT	32.0	42.0	37.0	24.0
1656	TTTAAAAATCCAATTAAGAGAGA	25.0	32.0	37.0	29.0
1657	TTAAAAATCCAATTAAGAGAGAG	18.0	20.0	33.0	19.0
1658	TAAAAATCCAATTAAGAGAGA	21.7	52.0	60.0	42.0

1659	CC*T*T*TCTCTCGAAGGTCTTCTGCCG	40.0	99.7	35.5	13.8
1660	GCACACATGCTCACACA*GA*GA*GC	40.8	85.1	12.9	3.4
1661	GC*A*CA*C*ATGCTCACACAGAGAGC	38.2	81.0	26.0	4.4

Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 31A are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties and each "C" is replaced with a 5-methylcytosine (5-MeC). * indicates presence of phosphodiester linkage. All other internucleoside linkages are phosphorothioate linkages.

Table 31B: Performance of STMN2 AONs with one, two, or three spacers (as measured by restoration of full length (FL) STMN2).

SEQ ID NO:	Oligonucleotide Sequence* (5' to 3')	Normalized 200nM ASO-STMN2 FL	Rq 200nM ASO STMN2 FL	Normalized 500nM ASO STMN2 FL	Rq 500nM ASO STMN2 FL
10655	CTCTCTCGCACACACGCACACATGCTC	203.68	1.55	145.43	1.19
10656	CTCTCTSGCACACSCGCACASATGCTC	83.90	0.82	60.07	0.68
10657	GAGTCCTGCAATATGAATATAATTTTA	44.36	0.58	69.10	0.73
10658	GAGTCCSGCAATASGAATATSATTTTA	5.56	0.34	-0.26	0.31
1620	TCTCTCGSACACACGSACACATG	72.43	0.79	53.69	0.64
10660	TCoTCoTCGSACACACGSACACATG	69.29	0.76	52.48	0.63
10661	TCTCTCGSACACACGSAoCAoCAoTG	51.35	0.62	31.71	0.47
10662	GCoAoCAoCoASGCTCACASAGAGAGC	69.24	0.79	41.40	0.60
10663	GCACACoAoSoGoCTCACASAGAGAGC	59.60	0.72	41.43	0.60
1602	GCACACASGCTCACASAGAGAGC	71.29	0.80	42.77	0.61
1618	CTTTCTCSCGAAGGTSTTCTGCC	98.11	0.99	37.50	0.50
1619	TTTCTCTSGAAGGTCSTCTGCCG	75.63	0.81	31.19	0.45
10667	CTTTCTCSCGAAGGoToSoToTCTGCC	39.99	0.52	18.62	0.34
1633	GTCTTCTSCCGAGTCSTGCAATA	47.05	0.54	14.65	0.25
10669	GTCTTCTSCCGAGToCoSoToGCAATA	54.26	0.65	51.66	0.63

Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 31B are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties and each "C" is replaced with a 5-methylcytosine (5-MeC). "o" indicates presence of phosphodiester linkage. All other internucleoside linkages are phosphorothioate linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

Table 31C: Performance of STMN2 AONs with one, two, or three spacers (as measured by reduction of STMN2 Cryptic exon).

SEQ ID NO:	Oligonucleotide Sequence* (5' to 3')	Normalized 200nM ASO-STMN2 Cryptic	Rq 200nM ASO STMN2 Cryptic	Normalized 500nM ASO STMN2 Cryptic	Rq 500nM ASO STMN2 Cryptic
10655	CTCTCTCGCACACACGCACACATGCTC	-0.99	0.93	-1.17	0.24
10656	CTCTCTSGCACACSCGCACASATGCTC	0.39	6.32	-1.19	0.17
10657	GAGTCCTGCAATATGAATATAATTTTA	9.99	43.73	-0.08	4.47
10658	GAGTCCSGCAATASGAATATSATTTTA	23.34	95.76	12.79	54.62
1620	TCTCTCGSACACACGSACACATG	1.60	25.68	6.54	100.04
10660	TCoTCoTCGSACACACGSACACATG	1.87	29.84	7.90	120.43
10661	TCTCTCGSACACACGSAoCAoCAoTG	7.94	121.09	19.57	295.96
10662	GCoAoCAoCoASGCTCACASAGAGAGC	4.49	65.78	22.89	330.02
10663	GCACACoAoSoGoCTCACASAGAGAGC	10.69	154.87	24.42	352.10
1602	GCACACASGCTCACASAGAGAGC	2.29	34.28	9.71	140.78
1618	CTTTCTCSCGAAGGTSTTCTGCC	15.39	284.63	20.65	381.44
1619	TTTCTCTSGAAGGTCSTCTGCCG	68.67	1265.76	7.87	146.12
10667	CTTTCTCSCGAAGGoToSoToTCTGCC	33.07	610.23	41.91	772.91
1633	GTCTTCTSCCGAGTCSTGCAATA	12.61	166.34	73.59	966.16
10669	GTCTTCTSCCGAGToCoSoToGCAATA	33.65	433.07	72.06	926.00

Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 31C are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties and each "C" is replaced with a 5-methylcytosine (5-MeC). "o" indicates presence of phosphodiester linkage. All other internucleoside linkages are phosphorothioate linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

Table 31D: Performance of STMN2 AONs with LNA modifications.

		STMN2 FL			
SEQ ID NO:	**Oligonucleotide Sequence* (5' to 3')**	200nM Normalized RQ	200nM Normalized RQ STD	50nM Normalized RQ	50nM Normalized RQ STD
1620	TCTCTCGSACACACGSACACATG	72.79	6.953	44.89	3.64
10815	TCTCTC[LNA-G]S[LNA-A]CACACGSACACATG	85.67	3.037	59.83	1.924
10816	TCTCTCGSACACAC[LNA-G]S[LNA-A]CACATG	77.56	2.304	61.92	7.248
1633	GTCTTCTSCCGAGTCSTGCAATA	49.66	5.794	21.1	1.551
10817	GTCTTC[LNA-T]S[LNA-C]CGAGTCSTGCAATA	51.12	11.34	19.65	1.85
10818	GTCTTCTSCCGAGT[LNA-C]S[LNA-T]GCAATA	50.83	6.278	23.95	2.508
1618	CTTTCTCSCGAAGGTSTTCTGCC	67	22.27	31.26	17.12
10819	CTTTCT[LNA-C]S[LNA-C]GAAGGTSTTCTGCC	74.7	21.25	43.38	27.35
10820	CTTTCTCSCGAAGG[LNA-T]S[LNA-T]TCTGCC	63.52	26.61	37.99	20.32

Table 31E: Performance of STMN2 AONs with LNA modifications.

		STMN2 Cryptic			
SEQ ID NO:	**Oligonucleotide Sequence* (5' to 3')**	200nM Normalized RQ	200nM Normalized RQ STD	50nM Normalized RQ	50nM Normalized RQ STD
1620	TCTCTCGSACACACGSACACATG	4.043	1.967	26.9	6.989
10815	TCTCTC[LNA-G]S[LNA-A]CACACGSACACATG	0.8398	0.7405	16.75	10.8
10816	TCTCTCGSACACAC[LNA-G]S[LNA-A]CACATG	3.702	3.39	10.58	5.852
1633	GTCTTCTSCCGAGTCSTGCAATA	24.71	1.319	55.5	8.628

10817	GTCTTC[LNA-T]S[LNA-C]CGAGTCSTGCAATA	17.95	3.209	51.88	1.863
10818	GTCTTCTSCCGAGT[LNA-C]S[LNA-T]GCAATA	21.85	3.382	63.6	11.8
1618	CTTTCTCSCGAAGGTSTTCTGCC	24.66	9.5	72.62	11.89
10819	CTTTCT[LNA-C]S[LNA-C]GAAGGTSTTCTGCC	18.21	5.833	45.17	9.862
10820	CTTTCTCSCGAAGG[LNA-T]S[LNA-T]TCTGCC	22.84	4.195	63.19	11.64

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Tables 31D and 31E are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. Spacer as indicated by S is a nucleoside-replacement group and is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein. [LNA-X] refers to a locked nucleic acid with a corresponding base X (e.g., LNA-A refers to a locked nucleic acid with an adenine nucleobase, LNA-G refers to a locked nucleic acid with a guanine nucleobase, LNA-T refers to a locked nucleic acid with a thymine nucleobase, and LNA-C refers to a locked nucleic acid with a 5-methylcytosine nucleobase).

Example 8: Design and Selection of KCNQ2 Oligonucleotides

[00927] KCNQ2 AONs that target a KCNQ2 transcript are designed and tested to identify KCNQ2 AONs capable of reducing quantity of mis-spliced KCNQ2 transcripts. Such KCNQ2 AONs include a subset of the KCNQ2 parent oligonucleotides represented by any of SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, or SEQ ID NOs: 4402-4409. The KCNQ2 parent oligonucleotides are 25 nucleosides in length. Each of the nucleosides of the KCNQ2 parent oligonucleotides are modified nucleosides with 2'-MOE sugar moieties, and each "C" is replaced with a 5-MeC. Additionally, each of the internucleoside linkages between the nucleosides of the KCNQ2 oligonucleotides are phosphorothioate internucleoside linkages.

[00928] Generally, the length of the KCNQ2 antisense oligonucleotides are 25 oligonucleotide units in length. However, variants of the KCNQ2 antisense oligonucleotides were also designed with varying lengths (*e.g.*, 23mers). Examples of these variant KCNQ2 antisense oligonucleotides were designed to include a subset of the sequences of SEQ ID NOs: 3046-3221 and SEQ ID NOs: 3398-3899.

Table 32: KCNQ2 AONs (including KCNQ2 parent oligonucleotides and KCNQ2 oligonucleotides with two spacers)

SEQ ID No:	Oligonucleotide Sequence* (where S indicates presence of a Spacer) (5' to 3')
4469	CACCACSGACTCCATCCCSCCACCC
4470	CTCGTTSACACCTGATGGSCTCCAG
4471	AGTCACSAGAAGAAGCACSGAGAAG
4472	GCTCTTSAAGCAAACCCCSGGCAGG
4473	CACCACTGSCTCCATCCCSCCACCC
4474	CTCGTTCASACCTGATGGSCTCCAG
4475	AGTCACGASAAGAAGCACSGAGAAG
4476	GCTCTTGASGCAAACCCCSGGCAGG
3117	TCTTGAAGCAAACCCCAGGCAGG
3119	GCTCTTGAAGCAAACCCCAGGCA
3118	CTCTTGAAGCAAACCCCAGGCAG
3142	CTGACTCCATCCCTCCACCCAGG
3144	CACTGACTCCATCCCTCCACCCA
3143	ACTGACTCCATCCCTCCACCCAG
3153	GAGCCACCACTGACTCCATCCCT
3152	CAGAGCCACCACTGACTCCATCC
3177	AGAGCCACCACTGACTCCATCCC
3117	CGTTCACACCTGATGGGCTCCAG

3179	CTCGTTCACACCTGATGGGCTCC
3178	TCGTTCACACCTGATGGGCTCCA
3186	AGGGAGGCTCGTTCACACCTGAT
3188	GGAGGGAGGCTCGTTCACACCTG
3187	GAGGGAGGCTCGTTCACACCTGA
3216	TCACGAGAAGAAGCACCGAGAAG
3218	AGTCACGAGAAGAAGCACCGAGA
3217	GTCACGAGAAGAAGCACCGAGAA
4477	TCTTGAASCAAACCCSAGGCAGG
4478	GCTCTTGSAGCAAACSCCAGGCA
4479	CTCTTGASGCAAACCSCAGGCAG
4480	CTGACTCSATCCCTCSACCCAGG
4481	CACTGACSCCATCCCSCCACCCA
4482	ACTGACTSCATCCCTSCACCCAG
4483	GAGCCACSACTGACTSCATCCCT
4484	CAGAGCCSCCACTGASTCCATCC
4485	AGAGCCASCACTGACSCCATCCC
4486	CGTTCACSCCTGATGSGCTCCAG
4487	CTCGTTCSCACCTGASGGGCTCC
4488	TCGTTCASACCTGATSGGCTCCA
4489	AGGGAGGSTCGTTCASACCTGAT
4490	GGAGGGASGCTCGTTSACACCTG
4491	GAGGGAGSCTCGTTCSCACCTGA
4492	TCACGAGSAGAAGCASCGAGAAG
4493	AGTCACGSGAAGAAGSACCGAGA
4494	GTCACGASAAGAAGCSCCGAGAA
4495	TCAACASCATGACCACCASCACCAC
4496	ACCAGASGCATCACCATCSCCACCA
4497	GAGACASAGGAAGCCGATSTACCAG
4498	AAGTACSCCAGGAACGAGSCCAGGA
4499	ACAGGGSCAGGGGTGTATSAGCAGG
4500	TCGACCSCAAGCCATCATSACCACG
4501	TCAACACCSTGACCACCASCACCAC
4502	ACCAGAAGSATCACCATCSCCACCA
4503	GAGACAAASGAAGCCGATSTACCAG
4504	AAGTACACSAGGAACGAGSCCAGGA
4505	ACAGGGACSGGGGTGTATSAGCAGG
4506	TCGACCACSAGCCATCATSACCACG
3489	AACACCATGACCACCATCACCAC
3491	TCAACACCATGACCACCATCACC
3490	CAACACCATGACCACCATCACCA
3534	CAGAAGCATCACCATCACCACCA
3536	ACCAGAAGCATCACCATCACCAC
3535	CCAGAAGCATCACCATCACCACC
3563	GACGGCACCACCATCATGACCAC
3565	CAGACGGCACCACCATCATGACC
3564	AGACGGCACCACCATCATGACCA
3621	GGCCAGGATGAGACAAAGGAAGC

3623	GAGGCCAGGATGAGACAAAGGAA
3522	AGGCCAGGATGAGACAAAGGAAG
3636	GTACACCAGGAACGAGGCCAGGA
3638	AAGTACACCAGGAACGAGGCCAG
3637	AGTACACCAGGAACGAGGCCAGG
3666	AAAGTGGTCGTTCTCCCCCTTCT
3668	TCAAAGTGGTCGTTCTCCCCCTT
3667	CAAAGTGGTCGTTCTCCCCCTTC
3753	AGGGACAGGGGTGTATCAGCAGG
3755	ACAGGGACAGGGGTGTATCAGCA
3754	CAGGGACAGGGGTGTATCAGCAG
3845	GACCACAAGCCATCATGACCACG
3847	TCGACCACAAGCCATCATGACCA
3846	CGACCACAAGCCATCATGACCAC
4507	AACACCASGACCACCSTCACCAC
4508	TCAACACSATGACCASCATCACC
4509	CAACACCSTGACCACSATCACCA
4510	CAGAAGCSTCACCATSACCACCA
4511	ACCAGAASCATCACCSTCACCAC
4512	CCAGAAGSATCACCASCACCACC
4513	GACGGCASCACCATCSTGACCAC
4514	CAGACGGSACCACCASCATGACC
4515	AGACGGCSCCACCATSATGACCA
4516	GGCCAGGSTGAGACASAGGAAGC
4517	GAGGCCASGATGAGASAAAGGAA
4518	AGGCCAGSATGAGACSAAGGAAG
4519	GTACACCSGGAACGASGCCAGGA
4520	AAGTACASCAGGAACSAGGCCAG
4521	AGTACACSAGGAACGSGGCCAGG
4522	AAAGTGGSCGTTCTCSCCCTTCT
4523	TCAAAGTSGTCGTTCSCCCCTT
4524	CAAAGTGSTCGTTCTSCCCCTTC
4525	AGGGACASGGGTGTASCAGCAGG
4526	ACAGGGASAGGGGTGSATCAGCA
4527	CAGGGACSGGGGTGTSTCAGCAG
4528	GACCACASGCCATCASGACCACG
4529	TCGACCASAAGCCATSATGACCA
4530	CGACCACSAGCCATCSTGACCAC
1774	CACTGACTCCATCCCTCCACCCAGG
1777	CACCACTGACTCCATCCCTCCACCC
1780	AGCCACCACTGACTCCATCCCTCCA
1783	CAGAGCCACCACTGACTCCATCCCT
1786	AGCCAGAGCCACCACTGACTCCATC
1789	TCCAGCCAGAGCCACCACTGACTCC
1809	CTCGTTCACACCTGATGGGCTCCAG
1812	AGGCTCGTTCACACCTGATGGGCTC
1815	GGGAGGCTCGTTCACACCTGATGGG
1818	GGAGGGAGGCTCGTTCACACCTGAT

1843	CGAGAAGAAGCACCGAGAAGAAAGG
1848	AGTCACGAGAAGAAGCACCGAGAAG
1749	GCTCTTGAAGCAAACCCCAGGCAGG
3117	TCTTGAAGCAAACCCCAGGCAGG
3119	GCTCTTGAAGCAAACCCCAGGCA
3118	CTCTTGAAGCAAACCCCAGGCAG
3142	CTGACTCCATCCCTCCACCCAGG
3144	CACTGACTCCATCCCTCCACCCA
3143	ACTGACTCCATCCCTCCACCCAG
3151	GAGCCACCACTGACTCCATCCCT
3153	CAGAGCCACCACTGACTCCATCC
3152	AGAGCCACCACTGACTCCATCCC
3177	CGTTCACACCTGATGGGCTCCAG
3179	CTCGTTCACACCTGATGGGCTCC
3178	TCGTTCACACCTGATGGGCTCCA
3186	AGGGAGGCTCGTTCACACCTGAT
3188	GGAGGGAGGCTCGTTCACACCTG
3187	GAGGGAGGCTCGTTCACACCTGA
3216	TCACGAGAAGAAGCACCGAGAAG
3218	AGTCACGAGAAGAAGCACCGAGA
3217	GTCACGAGAAGAAGCACCGAGAA
2121	TCAACACCATGACCACCATCACCAC
2135	CCACCACCATCACATCAACACCATG
2166	ACCAGAAGCATCACCATCACCACCA
2177	TGACCACCATCACCAGAAGCATCAC
2195	CAGACGGCACCACCATCATGACCAC
2208	AGCTCCTGAGAGGCAGACGGCACCA
2223	TACCAGGCAGTGACCAGCTCCTGAG
2242	GAGACAAAGGAAGCCGATGTACCAG
2253	GAGGCCAGGATGAGACAAAGGAAGC
2268	AAGTACACCAGGAACGAGGCCAGGA
2283	TCCCCCTTCTCTGCCAAGTACACCA
2298	TCAAAGTGGTCGTTCTCCCCCTTCT
2307	GCGTAGGTGTCAAAGTGGTCGTTCT
2322	CACCAGAGTGCATCCGCGTAGGTGT
2342	GACCACAACTCACCAGGCCCCACCA
2385	ACAGGGACAGGGGTGTATCAGCAGG
2422	ATGGAGCAGGCTCAGCCAGTGAGAG
2434	CCAAAGAGATGTATGGAGCAGGCTC
2446	CAGCAGGTGGCCCCAAAGAGATGTA
2465	CATCATGACCACGGGCAGCCAGCAG
2477	TCGACCACAAGCCATCATGACCACG
2492	AACCACCACCCCGCCTCGACCACAA
3489	AACACCATGACCACCATCACCAC
3491	TCAACACCATGACCACCATCACC
3490	CAACACCATGACCACCATCACCA
3534	CAGAAGCATCACCATCACCACCA
3536	ACCAGAAGCATCACCATCACCAC

3535	CCAGAAGCATCACCATCACCACC
3563	GACGGCACCACCATCATGACCAC
3565	CAGACGGCACCACCATCATGACC
3564	AGACGGCACCACCATCATGACCA
3621	GGCCAGGATGAGACAAAGGAAGC
3623	GAGGCCAGGATGAGACAAAGGAA
3622	AGGCCAGGATGAGACAAAGGAAG
3636	GTACACCAGGAACGAGGCCAGGA
3638	AAGTACACCAGGAACGAGGCCAG
3637	AGTACACCAGGAACGAGGCCAGG
3666	AAAGTGGTCGTTCTCCCCCTTCT
3668	TCAAAGTGGTCGTTCTCCCCCTT
3667	CAAAGTGGTCGTTCTCCCCCTTC
3753	AGGGACAGGGGTGTATCAGCAGG
3755	ACAGGGACAGGGGTGTATCAGCA
3754	CAGGGACAGGGGTGTATCAGCAG
3845	GACCACAAGCCATCATGACCACG
3847	TCGACCACAAGCCATCATGACCA
3846	CGACCACAAGCCATCATGACCAC

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 32 are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

Example 9: Methods for Evaluating KCNQ2 Antisense Oligonucleotides

[00929] KCNQ2 antisense oligonucleotides were evaluated in iPSC derived human motor neurons (hMN). The cells were seeded in 96-well plates at a density of 50,000 cells/ well. Antisense oligonucleotide (AON) to TDP43 was transfected with Endoporter (Gene Tools, Philomath, OR, USA) to increase expression of exon 5 containing KCNQ2 transcript. Vehicle control consisted of motor neuron treatment with Endoporter alone. Positive controls included cells that were treated with TDP43 AON alone ("AON TDP43" or "TDP43 AON").

[00930] TDP43 AON is a gapmer oligonucleotide and has the following sequence and chemistry: 5' A*A*G*G*C*T*T*C*A*T*A*T*T*G*T*A*C*T*T*T 3' (SEQ ID NO: 1669) where * = phosphorothioate, underlined = DNA, other=2'-MOE RNA; each "C" is 5-MeC.

[00931] To evaluate KCNQ2 AON ability to restore Exon 5 inclusion in the presence of TDP-43 knockdown, antisense oligonucleotides to KCNQ2 were co-incubated with TDP43 AON in Endoporter in media before addition to the cells. After 72 hours, antisense oligonucleotides and Endoporter were washed out and replaced with fresh media. After 72 additional hours fresh

media was replaced, and after 72 hours RNA was collected from the 96-well plates for RT-qPCR. RNA was isolated, cDNA generated, and multiplexed RT-qPCR assay performed with TaqMan probes for KCNQ2 exon 5 inclusion in the transcript and reference GAPDH quantification.

[00932] Transcript levels (*e.g.*, KCNQ2 exon 5 containing transcript or TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher TaqMan Gene Expression Assay Hs03929097_g1. RT-qPCR was performed for detecting KCNQ2 exon 5 containing transcripts using custom Thermofisher TaqMan targeting exon junction 5/6.

Exon 5/6 Primers:

Forward: 5' GGGAGAACGACCACTTTGA 3' (SEQ ID NO: 10652)

Reverse: 3' GAAGAAGGAGACACCGATGAG 3' (SEQ ID NO: 10653)

Probe: 5' TAGCCAATGGTGGTCAGCGTGATC 3'(SEQ ID NO: 10654)

[00933] RT-qPCR was also performed for detecting KCNQ2 exon 5 containing transcripts using custom Thermofisher TaqMan targeting exon junction 4/5.

Exon 4/5 Primers:

Forward: 5' GGATGATCCGCATGGAC 3' (SEQ ID NO: 10,821)

Reverse: 3' CCTTCTCTGCCAAGTACAC 3' (SEQ ID NO: 10,822)

Probe: 5' AGGCCAGGATGAGACAAAGGAAGC 3'(SEQ ID NO: 10,823)

[00934] RT-qPCR was performed on Applied Biosystems ® 7500 Real-time PCR systems. One cycle of reverse transcription was performed at a temperature of 50°C for 5 min. One cycle of RT inactivation/initial denaturation was performed at a temperature of 95°C for 20 seconds. Forty five cycles of amplification were performed at a temperature of 95°C for 1 second followed by 60°C for 20 seconds.

[00935] KCNQ2 Exon 5 inclusion (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (*e.g.*, % increase of KCNQ2 Exon 5 inclusion), the normalized KCNQ2 Exon 5 inclusion signal was further normalized to the vehicle (treated with Endoporter alone, deltadeltaCt). Relative quantity (RQ) of transcript level was calculated using the equation $RQ=2^{-deltadeltaCt}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0).

[00936] RQ values for KCNQ2 Exon Junctions 5/6 and 4/5 were normalized using the following formula:

$$((RQAON - RQTDP43)/(RQendo - RQTDP43)) * 100$$

[00937] Tables 33A, 33B, and 34 show the RT-qPCR results of KCNQ2 AONs with spacers and performance of KCNQ2 AONs without spacers in human motor neurons. KCNQ2 AONs (*e.g.*, KCNQ2 oligonucleotides without spacers or with one or two spacers) were tested for their ability to increase or restore full-length KCNQ2 mRNA (*i.e.*, mRNA from which full-length KCNQ2 is translated which include exon 5 in the transcript) levels. In some cases, KCNQ2 AONs with spacers increased full-length KCNQ2 mRNA ("KCNQ2 FL"). In some cases, KCNQ2 AONs without spacers increased full-length KCNQ2 mRNA ("KCNQ2 FL"). Specific AON sequences are labeled according to their corresponding SEQ ID NO.

[00938] As shown in Table 33A, a 200 nM dose of SEQ ID NO: 3621 (GGCCAGGATGAGACAAAGGAAGC with no spacers) rescued full length KCNQ2 mRNA to -0.2490%. A 500 nM dose of SEQ ID NO: 3621 (GGCCAGGATGAGACAAAGGAAGC with no spacers) rescued full length KCNQ2 mRNA to 27.870%. Comparatively, 200 nM dose of SEQ ID NO: 4516 (GGCCAGGSTGAGACASAGGAAGC with two spacers) rescued full length KCNQ2 mRNA to 4.1655%. A 500 nM dose of SEQ ID NO: 4516 (GGCCAGGSTGAGACASAGGAAGC with two spacers) rescued full length KCNQ2 mRNA to 59.333%. This indicates that the addition of spacers of SEQ ID NO: 4516 improves the performance in comparison to the KCNQ2 AON counterpart without spacers (e.g., SEQ ID NO: 3621).

[00939] Additionally shown in Table 33A, a 200 nM dose of SEQ ID NO: 3564 (AGACGGCACCACCATCATGACCA with no spacers) rescued full length KCNQ2 mRNA to -3.66%. A 500 nM dose of SEQ ID NO: 3564 (AGACGGCACCACCATCATGACCA with no spacers) rescued full length KCNQ2 mRNA to 16.627%. Comparatively, a 200nM dose of SEQ ID NO: 4515 (AGACGGCSCCACCATSATGACCAT with two spacers) rescued full length KCNQ2 mRNA to 18.720%. A 500 nM dose of SEQ ID NO: 4515 (AGACGGCSCCACCATSATGACCAT with two spacers) rescued full length KCNQ2 mRNA to 26,191%. This indicates that the addition of spacers of SEQ ID NO: 4515 improves the performance in comparison to the KCNQ2 AON counterpart without spacers (e.g., SEQ ID NO: 3564).

[00940] Additionally shown in Table 33A, a 200 nM dose of SEQ ID NO: 3534 (CAGAAGCATCACCATCACCACCA with no spacers) rescued full length KCNQ2 mRNA to -4.824%. A 500 nM dose of SEQ ID NO: 3534 (CAGAAGCATCACCATCACCACCA with no spacers) rescued full length KCNQ2 mRNA to -4.822%. Comparatively, a 200nM dose of SEQ ID NO: 4510 (CAGAAGCSTCACCATSACCACCA with two spacers) rescued full length

KCNQ2 mRNA to -4.361%. A 500 nM dose of SEQ ID NO: 4510 (CAGAAGCSTCACCATSACCACCA with two spacers) rescued full length KCNQ2 mRNA to 31.426%. This indicates that the addition of spacers of SEQ ID NO: 4510 improves the performance in comparison to the KCNQ2 AON counterpart without spacers (e.g., SEQ ID NO: 3534).

[00941] Additionally shown in Table 33A, a 200 nM dose of SEQ ID NO: 3536 (ACCAGAAGCATCACCATCACCAC with no spacers) rescued full length KCNQ2 mRNA to -1.253%. A 500 nM dose of SEQ ID NO: 3536 (ACCAGAAGCATCACCATCACCAC with no spacers) rescued full length KCNQ2 mRNA to -4.846%. Comparatively, a 200nM dose of SEQ ID NO: 4511 (ACCAGAASCATCACCSTCACCAC with two spacers) rescued full length KCNQ2 mRNA to 11.898%. A 500 nM dose of SEQ ID NO: 4511 (ACCAGAASCATCACCSTCACCAC with two spacers) rescued full length KCNQ2 mRNA to 27.103%. This indicates that the addition of spacers of SEQ ID NO: 4511 improves the performance in comparison to the KCNQ2 AON counterpart without spacers (e.g., SEQ ID NO: 3536).

[00942] Additionally shown in Table 33A, a 200 nM dose of SEQ ID NO: 3535 (CCAGAAGCATCACCATCACCACC with no spacers) rescued full length KCNQ2 mRNA to 0.349%. A 500 nM dose of SEQ ID NO: 3535 (CCAGAAGCATCACCATCACCACC with no spacers) rescued full length KCNQ2 mRNA to -2.195%. Comparatively, a 200nM dose of SEQ ID NO: 4512 (CCAGAAGSATCACCASCACCACC with two spacers) rescued full length KCNQ2 mRNA to 12.326%. A 500 nM dose of SEQ ID NO: 4512 (CCAGAAGSATCACCASCACCACC with two spacers) rescued full length KCNQ2 mRNA to 18.047%. This indicates that the addition of spacers of SEQ ID NO: 4512 improves the performance in comparison to the KCNQ2 AON counterpart without spacers (e.g., SEQ ID NO: 3535).

[00943] Additionally shown in Table 33A, a 200 nM dose of SEQ ID NO: 3491 (TCAACACCATGACCACCATCACC with no spacers) rescued full length KCNQ2 mRNA to -5.7868%. A 500 nM dose of SEQ ID NO: 3491 (TCAACACCATGACCACCATCACC with no spacers) rescued full length KCNQ2 mRNA to -0.189%. Comparatively, a 200nM dose of SEQ ID NO: 4508 (TCAACACSATGACCASCATCACC with two spacers) rescued full length KCNQ2 mRNA to 9.940%. A 500 nM dose of SEQ ID NO: 4508 (TCAACACSATGACCASCATCACC with two spacers) rescued full length KCNQ2 mRNA to 13.392%. This indicates that the addition of spacers of SEQ ID NO: 4508 improves the

performance in comparison to the KCNQ2 AON counterpart without spacers (e.g., SEQ ID NO: 3491).

[00944] Additionally shown in Table 33A, a 200 nM dose of SEQ ID NO: 3490 (CAACACCATGACCACCATCACCA with no spacers) rescued full length KCNQ2 mRNA to -5.760%. A 500 nM dose of SEQ ID NO: 3490 (CAACACCATGACCACCATCACCA with no spacers) rescued full length KCNQ2 mRNA to 2.607%. Comparatively, a 200nM dose of SEQ ID NO: 4509 (CAACACCSTGACCACSATCACCA with two spacers) rescued full length KCNQ2 mRNA to -3.772%. A 500 nM dose of SEQ ID NO: 4509 (CAACACCSTGACCACSATCACCA with two spacers) rescued full length KCNQ2 mRNA to 29.909%. This indicates that the addition of spacers of SEQ ID NO: 4509 improves the performance in comparison to the KCNQ2 AON counterpart without spacers (e.g., SEQ ID NO: 3490).

[00945] Additionally shown in Table 33B, a 200 nM dose of SEQ ID NO: 3119 (GCTCTTGAAGCAAACCCCAGGCA with no spacers) rescued full length KCNQ2 mRNA to 1.091%. A 500 nM dose of SEQ ID NO: 3119 (GCTCTTGAAGCAAACCCCAGGCA with no spacers) rescued full length KCNQ2 mRNA to 0.847%. Comparatively, a 200nM dose of SEQ ID NO: 4478 (GCTCTTGSAGCAAACSCCAGGCA with two spacers) rescued full length KCNQ2 mRNA to -5.0199%. A 500 nM dose of SEQ ID NO: 4478 (GCTCTTGSAGCAAACSCCAGGCA with two spacers) rescued full length KCNQ2 mRNA to 12.505%. This indicates that the addition of spacers of SEQ ID NO: 4478 improves the performance in comparison to the KCNQ2 AON counterpart without spacers (e.g., SEQ ID NO: 3119).

[00946] Additionally shown in Table 33B, a 200 nM dose of SEQ ID NO: 3122 (CTGACTCCATCCCTCCACCCAGGwith no spacers) rescued full length KCNQ2 mRNA to -3.1968%. A 500 nM dose of SEQ ID NO: 3122 (CTGACTCCATCCCTCCACCCAGG with no spacers) rescued full length KCNQ2 mRNA to -2.600%. Comparatively, a 200nM dose of SEQ ID NO: 4480 (CTGACTCSATCCCTCSACCCAGG with two spacers) rescued full length KCNQ2 mRNA to 0.28284%. A 500 nM dose of SEQ ID NO: 4480 (CTGACTCSATCCCTCSACCCAGG with two spacers) rescued full length KCNQ2 mRNA to 10.232%. This indicates that the addition of spacers of SEQ ID NO: 4480 improves the performance in comparison to the KCNQ2 AON counterpart without spacers (e.g., SEQ ID NO: 3122).

[00947] Altogether, these results demonstrate that different KCNQ2 AONs including two spacers are capable of increasing KCNQ2-FL to levels that are close or comparable to their non-spacer counterparts.

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Table 33A. Performance of Exon 5 KCNQ2 AONs

Seq ID NO:	Oligonucleotide Sequence* (5' to 3')	200nM ASO- KCNQ2 Ex 5/6		500nM ASO KCNQ2 Ex 5/6	
		Normalized	RQ	Normalized	RQ
2121	TCAACACCATGACCACCATCACCAC	8.325616	0.150071	-5.77457	0.002139
3490	CAACACCATGACCACCATCACCA	-5.76045	0.002287	2.607233	0.090077
4509	CAACACCSTGACCACSATCACCA	-3.77247	0.023144	29.90924	0.376515
3491	TCAACACCATGACCACCATCACC	-5.78681	0.002011	-0.18977	0.060732
4508	TCAACACSATGACCASCATCACC	9.940254	0.167011	13.93271	0.208898
3489	AACACCATGACCACCATCACCAC	-2.30475	0.038543	-5.7947	0.001928
4507	AACACCASGACCACCSTCACCAC	-1.71265	0.044755	-5.74463	0.002453
4495	TCAACASCATGACCACCASCACCAC	-2.72537	0.03413	8.421964	0.151082
4501	TCAACACCSTGACCACCASCACCAC	-0.25086	0.060091	1.407007	0.077484
2135	CCACCACCATCACATCAACACCATG	-19.0639	0.071713	-28.2601	0.002939
2166	ACCAGAAGCATCACCATCACCACCA	-3.0601	0.01759	-2.36099	0.024278
3535	CCAGAAGCATCACCATCACCACC	0.349521	0.050206	-2.19539	0.025862
4512	CCAGAAGSATCACCASCACCACC	12.32676	0.164778	18.04785	0.219505
3536	ACCAGAAGCATCACCATCACCAC	-1.25378	0.034869	-4.84679	0.000499
4511	ACCAGAASCATCACCSTCACCAC	11.89858	0.160682	27.10304	0.306125
3534	CAGAAGCATCACCATCACCACCA	-4.82434	0.000714	-4.82226	0.000734
4510	CAGAAGCSTCACCATSACCACCA	-4.36192	0.005137	31.42647	0.347482
4496	ACCAGASGCATCACCATCSCCACCA	2.007292	0.066064	-1.64228	0.031153
4502	ACCAGAAGSATCACCATCSCCACCA	-1.79673	0.029676	-2.31004	0.024765
2177	TGACCACCATCACCAGAAGCATCAC	-28.2653	0.0029	-19.2815	0.070085
2195	CAGACGGCACCACCATCATGACCAC	-4.69235	0.00137	2.30004	0.072169
3564	AGACGGCACCACCATCATGACCA	-3.66478	0.011775	10.29784	0.153148

4515	AGACGGCSCCACCATSATGACCA	18.7204	0.238428	26.19085	0.314068
3565	CAGACGGCACCACCATCATGACC	11.90306	0.169402	9.477831	0.144846
4514	CAGACGGSACCACCASCATGACC	-3.8861	0.009534	10.74563	0.157682
3563	GACGGCACCACCATCATGACCAC	0.445321	0.05339	8.490921	0.134853
4513	GACGGCASCACCATCSTGACCAC	-2.49403	0.023629	14.90492	0.199796
2208	AGCTCCTGAGAGGCAGACGGCACCA	-28.4183	0.001756	-16.699	0.089398
2223	TACCAGGCAGTGACCAGCTCCTGAG	-28.4845	0.001261	-28.2576	0.002958
2242	GAGACAAAGGAAGCCGATGTACCAG	4.549223	0.046631	22.22418	0.224454
4497	GAGACASAGGAAGCCGATSTACCAG	5.349911	0.054687	9.317288	0.094601
4503	GAGACAAASGAAGCCGATSTACCAG	14.35194	0.145253	31.10439	0.313795
2253	GAGGCCAGGATGAGACAAAGGAAGC	4.805941	0.08232	12.73105	0.159425
3522	AGGCCAGGATGAGACAAAGGAAG	-1.31397	0.022778	34.54471	0.257518
4518	AGGCCAGSATGAGACSAAGGAAG	4.925139	0.08348	27.34078	0.301566
3623	GAGGCCAGGATGAGACAAAGGAA	5.710273	0.091118	14.34585	0.175136
4517	GAGGCCASGATGAGASAAAGGAA	20.78607	0.202769	24.68592	0.275736
3621	GGCCAGGATGAGACAAAGGAAGC	-0.24903	0.033139	27.87085	0.306723
4516	GGCCAGGSTGAGACASAGGAAGC	4.165559	0.121048	59.33334	0.447587
2268	AAGTACACCAGGAACGAGGCCAGGA	1.649394	0.092803	-7.87145	0.001263
3637	AGTACACCAGGAACGAGGCCAGG	5.673752	0.131496	12.60887	0.198175
4521	AGTACACSAGGAACGSGGCCAGG	-3.74555	0.040932	17.13297	0.241673
3638	AAGTACACCAGGAACGAGGCCAG	-6.43814	0.015044	-4.46211	0.034043
4520	AAGTACASCAGGAACSAGGCCAG	7.768486	0.151636	22.29004	0.291257
3636	GTACACCAGGAACGAGGCCAGGA	-7.86809	0.001295	-0.75004	0.069733
4519	GTACACCSGGAACGASGCCAGGA	0.506936	0.081819	5.158879	0.126546
4498	AAGTACSCCAGGAACGAGSCCAGGA	7.834674	0.152273	4.585338	0.121031
4504	AAGTACACSAGGAACGAGSCCAGGA	2.254296	0.098619	14.06631	0.212188

2283	TCCCCCTTCTCTGCCAAGTACACCA	-28.1841	0.003508	-27.7819	0.006516
2298	TCAAAGTGGTCGTTCTCCCCCTTCT	-6.56377	0.000837	-6.55768	0.000895
3667	CAAAGTGGTCGTTCTCCCCCTTC	-5.20966	0.013609	-1.57848	0.047857
4524	CAAAGTGSTCGTTCTSCCCCTTC	-2.76459	0.03667	-6.37846	0.002585
3668	TCAAAGTGGTCGTTCTCCCCCTT	-6.60007	0.000495	-6.59773	0.000517
4523	TCAAAGTSGTCGTTCSCCCCCTT	-2.95555	0.034869	-6.6049	0.000449
3666	AAAGTGGTCGTTCTCCCCCTTCT	-0.96274	0.053665	-6.56497	0.000826
4522	AAAGTGGSCGTTCTCSCCCTTCT	-6.63355	0.000179	-6.63443	0.000171
2307	GCGTAGGTGTCAAAGTGGTCGTTCT	-28.2064	0.003341	-28.3379	0.002357
2322	CACCAGAGTGCATCCGCGTAGGTGT	-24.562	0.030595	-26.3803	0.016997
2342	GACCACAACTCACCAGGCCCCACCA	76.19122	0.784073	57.94834	0.647645
2385	ACAGGGACAGGGGTGTATCAGCAGG	-0.593	0.048787	-1.52436	0.039978
3754	CAGGGACAGGGGTGTATCAGCAG	-2.19416	0.033643	-5.5571	0.001837
4527	CAGGGACSGGGGTGTSTCAGCAG	2.146985	0.074701	5.988388	0.111033
3755	ACAGGGACAGGGGTGTATCAGCA	-2.91064	0.026867	-5.52224	0.002167
4526	ACAGGGASAGGGGTGSATCAGCA	7.735775	0.127559	-0.90206	0.045864
3753	AGGGACAGGGGTGTATCAGCAGG	-5.48914	0.00248	-5.4487	0.002862
4525	AGGGACASGGGTGTASCAGCAGG	-2.58444	0.029952	8.499329	0.134781
4499	ACAGGGSCAGGGGTGTATSAGCAGG	0.392099	0.058104	-5.19929	0.005221
4505	ACAGGGACSGGGGTGTATSAGCAGG	3.138933	0.084083	2.89336	0.08176
2422	ATGGAGCAGGCTCAGCCAGTGAGAG	-9.66659	0.06989	19.72048	0.324655
2434	CCAAAGAGATGTATGGAGCAGGCTC	-12.4194	0.046026	2.501353	0.175377
2446	CAGCAGGTGGCCCCAAAGAGATGTA	-17.6094	0.001032	1.740016	0.168777
2465	CATCATGACCACGGGCAGCCAGCAG	-14.1249	0.031239	-10.6075	0.061733
2477	TCGACCACAAGCCATCATGACCACG	5.246421	0.065339	8.169241	0.095061
3846	CGACCACAAGCCATCATGACCAC	5.997216	0.072974	1.215942	0.024354

4530	CGACCACSAGCCATCSTGACCAC	7.441267	0.087658	-0.05528	0.011427
3847	TCGACCACAAGCCATCATGACCA	0.058253	0.012582	-0.37611	0.008165
4529	TCGACCASAAGCCATSATGACCA	9.68244	0.110448	-1.12929	0.000506
3845	GACCACAAGCCATCATGACCACG	8.700139	0.100459	5.620028	0.069138
4528	GACCACASGCCATCASGACCACG	-1.08149	0.000992	2.175398	0.03411
4500	TCGACCSCAAGCCATCATSACCACG	4.464673	0.05739	0.740754	0.019522
4506	TCGACCACSAGCCATCATSACCACG	7.790323	0.091207	6.057462	0.073586
2492	AACCACCACCCCGCCTCGACCACAA	-17.5167	0.001835	-17.6258	0.000889

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 33A are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

Table 33B. Performance of Additional KCNQ2 AONs

SEQ ID NO:	**Oligonucleotide Sequence*** (5' to 3')	**200nM ASO- KCNQ2 Ex 5/6**		**500nM ASO KCNQ2 Ex 5/6**	
		Normalized	**Rq**	**Normalized**	**Rq**
1749	GCTCTTGAAGCAAACCCCAGGCAGG	1.93649	0.068425	18.38289	0.285738
3118	CTCTTGAAGCAAACCCCAGGCAG	2.250466	0.072573	6.589694	0.129909
4479	CTCTTGASGCAAACCSCAGGCAG	-2.14824	0.014452	6.53018	0.129123
3119	GCTCTTGAAGCAAACCCCAGGCA	1.091966	0.057266	0.847707	0.054038
4478	GCTCTTGSAGCAAACSCCAGGCA	5.091992	0.11012	12.50502	0.208071
3117	TCTTGAAGCAAACCCCAGGCAGG	4.754464	0.10566	6.094406	0.123365
4477	TCTTGAASCAAACCCSAGGCAGG	0.230027	0.045877	5.753291	0.118858
4472	GCTCTTSAAGCAAACCCCSGGCAGG	9.440352	0.167576	11.28187	0.191909
4476	GCTCTTGASGCAAACCCCSGGCAGG	2.996807	0.082435	10.75228	0.184911

1774	CACTGACTCCATCCCTCCACCCAGG	3.799346	0.068647	4.098425	0.07156
3143	ACTGACTCCATCCCTCCACCCAG	-3.19909	0.000485	-1.02264	0.021683
4482	ACTGACTSCATCCCTSCACCCAG	0.596296	0.037451	-3.17927	0.000678
3144	CACTGACTCCATCCCTCCACCCA	-3.20264	0.000451	5.184762	0.082141
4481	CACTGACSCCATCCCSCCACCCA	-0.06587	0.031002	0.919638	0.0406
3142	CTGACTCCATCCCTCCACCCAGG	-3.19678	0.000508	-2.60029	0.006317
4480	CTGACTCSATCCCTCSACCCAGG	0.282843	0.034398	10.23219	0.131301
1777	CACCACTGACTCCATCCCTCCACCC	0.010805	0.000972	9.903886	0.100503
4469	CACCACSGACTCCATCCCSCCACCC	0.044825	0.001314	12.68526	0.128485
4473	CACCACTGSCTCCATCCCSCCACCC	8.672383	0.088113	2.887498	0.029913
1780	AGCCACCACTGACTCCATCCCTCCA	-14.66	0.026601	-16.5539	0.010182
1783	CAGAGCCACCACTGACTCCATCCCT	-7.04437	0.096055	10.43101	0.243866
3152	AGAGCCACCACTGACTCCATCCC	-1.35312	0.144193	1.344652	0.167012
4485	AGAGCCASCACTGACSCCATCCC	-12.0146	0.054015	2.669907	0.178221
3153	CAGAGCCACCACTGACTCCATCC	-6.40193	0.101489	-3.85	0.123074
4484	CAGAGCCSCCACTGASTCCATCC	-5.00699	0.113288	0.59525	0.160673
3151	GAGCCACCACTGACTCCATCCCT	-6.59523	0.099854	-9.62124	0.074259
4483	GAGCCACSACTGACTSCATCCCT	-7.45797	0.092557	-1.63694	0.141792
1786	AGCCAGAGCCACCACTGACTCCATC	-10.7868	0.060179	-16.1477	0.013703
1789	TCCAGCCAGAGCCACCACTGACTCC	-10.175	0.065483	-13.7112	0.034827
1809	CTCGTTCACACCTGATGGGCTCCAG	-2.239	0.024616	2.317326	0.071087
3178	TCGTTCACACCTGATGGGCTCCA	0.786719	0.055476	3.932325	0.087559
4488	TCGTTCASACCTGATSGGCTCCA	1.958548	0.067428	5.1286	0.09976
3179	CTCGTTCACACCTGATGGGCTCC	1.297235	0.060683	4.81057	0.096516
4487	CTCGTTCSCACCTGASGGGCTCC	4.292697	0.091234	-1.40928	0.033079
3177	CGTTCACACCTGATGGGCTCCAG	2.594567	0.073915	-0.18297	0.045586
4486	CGTTCACSCCTGATGSGCTCCAG	-4.46372	0.001926	4.237993	0.090676

4470	CTCGTTSACACCTGATGGSCTCCAG	-4.58767	0.000662	5.551197	0.10407
4474	CTCGTTCASACCTGATGGSCTCCAG	-4.55861	0.000958	-4.58782	0.00066
1812	AGGCTCGTTCACACCTGATGGGCTC	-0.35963	0.001218	-0.36405	0.001171
1815	GGGAGGCTCGTTCACACCTGATGGG	2.023388	0.026268	9.707654	0.107046
1818	GGAGGGAGGCTCGTTCACACCTGAT	14.31439	0.229398	23.07648	0.311912
3187	GAGGGAGGCTCGTTCACACCTGA	-6.86994	0.029903	30.5004	0.381824
4491	GAGGGAGSCTCGTTCSCACCTGA	19.74948	0.280581	5.058917	0.142238
3188	GGAGGGAGGCTCGTTCACACCTG	10.77789	0.196095	10.0375	0.189122
4490	GGAGGGASGCTCGTTSACACCTG	0.988222	0.103904	1.280966	0.106661
3186	AGGGAGGCTCGTTCACACCTGAT	9.70545	0.185995	10.49864	0.193465
4489	AGGGAGGSTCGTTCASACCTGAT	0.331036	0.097715	-3.57754	0.060908
1843	CGAGAAGAAGCACCGAGAAGAAAGG	-0.37951	0.001009	14.7896	0.160469
1848	AGTCACGAGAAGAAGCACCGAGAAG	-10.1678	0.11889	-7.62889	0.140594
3217	GTCACGAGAAGAAGCACCGAGAA	-18.752	0.045507	-13.6372	0.089231
4494	GTCACGASAAGAAGCSCCGAGAA	-20.1269	0.033753	-11.8098	0.104852
3218	AGTCACGAGAAGAAGCACCGAGA	-20.7987	0.028009	-22.4503	0.013891
4493	AGTCACGSGAAGAAGSACCGAGA	0.340654	0.208723	-11.0172	0.111628
3216	TCACGAGAAGAAGCACCGAGAAG	-14.1492	0.084854	-9.95005	0.120751
4492	TCACGAGSAGAAGCASCGAGAAG	-9.64096	0.123393	-2.37911	0.185472
4471	AGTCACSAGAAGAAGCACSGAGAAG	-21.0213	0.026107	-12.3651	0.100106
4475	AGTCACGASAAGAAGCACSGAGAAG	-16.5444	0.064379	-3.15146	0.17887

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 33B are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

Table 34. Performance of Additional KCNQ2 AONs

		Exons 4/5						Exons 5/6					
		200nM			50nM			200nM			50nM		
SEQ ID NO:	Oligonucleotide Sequence (5' to 3')	Normalized Fold Change	SD	N	Normalized Fold Change	SD	N	Normalized Fold Change	SD	N	Normalized Fold Change	SD	N
2135	CCACCACCATCACATCAACACCATG	13.23	0.96	3	7.50	4.18	3	42.41	4.38	3	15.17	6.78	3
2166	ACCAGAAGCATCACCATCACCACCA	-4.71	2.24	3	2.41	3.65	3	-0.22	4.73	3	5.06	2.84	3
3535	CCAGAAGCATCACCATCACCACC	5.68	5.11	3	9.12	4.89	3	5.24	7.00	3	14.45	4.65	3
4512	CCAGAAGSATCACCASCACCACC	5.22	1.02	3	-0.15	2.22	3	8.81	3.04	3	2.65	2.02	3
3536	ACCAGAAGCATCACCATCACCAC	3.68	1.44	3	2.79	4.61	3	9.80	1.85	3	5.25	3.72	3
4511	ACCAGAASCATCACCSTCACCAC	6.48	1.38	3	5.54	3.56	3	8.84	0.75	3	8.44	3.46	3
3534	CAGAAGCATCACCATCACCACCA	4.62	2.40	3	-0.82	3.17	3	9.74	2.87	3	-1.62	5.29	3
4510	CAGAAGCSTCACCATSACCACCA	1.65	2.63	3	2.41	3.38	3	4.99	2.68	3	3.37	2.06	3
2177	TGACCACCATCACCAGAAGCATCAC	17.59	2.99	3	32.89	5.03	3	22.71	5.33	3	40.05	9.13	3
2195	CAGACGGCACCACCATCATGACCAC	5.96	4.82	3	4.08	0.45	3	11.89	4.65	3	10.42	3.55	3
3564	AGACGGCACCACCATCATGACCA	-0.51	1.72	3	5.01	1.48	3	2.64	1.18	3	11.23	2.54	3
4515	AGACGGCSCCACCATSATGACCA	3.25	1.79	3	-1.27	1.34	3	9.39	4.89	3	2.98	3.40	3
3565	CAGACGGCACCACCATCATGACC	8.65	3.02	3	3.15	4.16	3	12.63	2.82	3	8.02	6.60	3
4514	CAGACGGSACCACCASCATGACC	-0.17	0.84	3	9.43	6.75	3	2.46	2.09	3	8.70	5.28	3
3563	GACGGCACCACCATCATGACCAC	9.17	2.02	3	3.36	3.16	3	17.48	3.76	3	8.77	3.65	3
4513	GACGGCASCACCATCSTGACCAC	9.12	3.32	3	4.82	0.84	3	18.11	2.37	3	12.82	3.80	3
2208	AGCTCCTGAGAGGCAGACGGCACCA	7.98	2.21	3	9.20	2.06	3	11.55	1.89	3	15.76	4.15	3
2223	TACCAGGCAGTGACCAGCTCCTGAG	0.76	6.67	3	-0.45	6.01	3	9.87	10.00	3	4.21	4.42	3
2253	GAGGCCAGGATGAGACAAAGGAAGC	-2.82	2.04	3	-1.31	4.02	3	6.98	1.42	3	3.60	1.24	3
3522	AGGCCAGGATGAGACAAAGGAAG	-5.75	2.12	3	-6.11	3.24	3	0.43	3.74	3	-1.44	5.54	3
4518	AGGCCAGSATGAGACSAAGGAAG	1.92	1.47	3	-1.36	4.31	3	6.38	2.89	3	1.17	3.18	3
3623	GAGGCCAGGATGAGACAAAGGAA	3.10	2.76	3	0.79	2.00	3	13.38	1.72	3	3.00	4.06	3

4517	GAGGCCASGATGAGASAAAGGAA	-0.24	2.71	3	0.94	1.49	3	3.44	1.21	3	2.71	3.62	3
3621	GGCCAGGATGAGACAAAGGAAGC	-4.64	0.31	3	-10.34	2.60	3	5.24	1.48	3	-8.00	3.49	3
4516	GGCCAGGSTGAGACASAGGAAGC	-2.99	2.86	3	-0.62	1.30	3	1.30	4.39	3	3.70	0.81	3
2268	AAGTACACCAGGAACGAGGCCAGGA	-9.39	4.33	3	-10.32	1.90	3	6.59	3.65	3	5.59	6.88	3
3637	AGTACACCAGGAACGAGGCCAGG	-13.72	4.46	3	-6.94	6.67	3	-1.11	11.33	3	5.86	9.58	3
4521	AGTACACSAGGAACGSGGCCAGG	-10.97	2.72	3	-3.35	3.85	3	-1.89	5.81	3	4.51	4.02	3
3638	AAGTACACCAGGAACGAGGCCAG	-11.25	2.10	3	-8.14	7.24	3	3.18	3.03	3	-0.08	8.78	3
4520	AAGTACASCAGGAACSAGGCCAG	-9.94	4.34	3	3.20	3.53	3	-2.53	4.63	3	11.09	2.93	3
3636	GTACACCAGGAACGAGGCCAGGA	-2.32	0.94	3	-15.34	0.39	3	16.61	1.16	3	-6.81	4.93	3
4519	GTACACCSGGAACGASGCCAGGA	-11.44	3.41	3	-12.13	1.03	3	-1.60	7.70	3	-4.08	2.37	3
2283	TCCCCCTTCTCTGCCAAGTACACCA	-8.58	0.52	3	1.38	2.41	3	-1.96	1.59	3	8.98	2.74	3
2298	TCAAAGTGGTCGTTCTCCCCCTTCT	-22.23	0.80	3	-8.71	3.31	3	-20.40	1.04	3	-7.81	3.68	3
3667	CAAAGTGGTCGTTCTCCCCCTTC	-15.09	0.64	3	-12.54	0.65	3	-15.86	0.43	3	-9.26	1.70	3
4524	CAAAGTGSTCGTTCTSCCCCTTC	-19.11	4.04	3	-26.45	1.15	3	-15.49	5.45	3	-26.40	2.00	3
3668	TCAAAGTGGTCGTTCTCCCCCTT	-9.51	1.09	3	-14.08	2.43	3	-8.55	0.42	3	-13.79	3.70	3
4523	TCAAAGTSGTCGTTCSCCCCCTT	-17.92	2.25	3	-11.73	0.79	3	-16.53	0.91	3	-9.02	2.70	3
3666	AAAGTGGTCGTTCTCCCCCTTCT	-15.05	1.82	3	-11.97	2.72	3	-11.83	1.19	3	-7.04	4.94	3
4522	AAAGTGGSCGTTCTCSCCCTTCT	-17.53	2.49	3	-7.72	2.74	3	-14.23	2.57	3	-7.18	3.43	3
2307	GCGTAGGTGTCAAAGTGGTCGTTCT	-12.37	0.72	3	-0.59	0.24	3	-17.33	1.02	3	-5.25	0.38	3
2322	CACCAGAGTGCATCCGCGTAGGTGT	-7.17	1.07	3	-2.02	3.43	3	-8.21	2.19	3	-2.94	1.99	3
2342	GACCACAACTCACCAGGCCCCACCA	-3.52	0.15	3	3.98	2.84	3	2.06	0.84	3	11.28	3.63	3
2385	ACAGGGACAGGGGTGTATCAGCAGG	-2.02	1.69	3	-6.47	0.93	3	2.29	1.79	3	-3.01	0.99	3
3754	CAGGGACAGGGGTGTATCAGCAG	-1.46	3.58	3	-7.13	1.45	3	-2.39	1.23	3	-2.78	1.35	3
4527	CAGGGACSGGGGTGTSTCAGCAG	-4.18	2.57	3	-8.72	0.65	3	0.94	5.79	3	-5.29	1.58	3
3755	ACAGGGACAGGGGTGTATCAGCA	-3.74	0.92	3	-10.27	0.71	3	-0.91	2.00	3	-7.14	2.05	3
4526	ACAGGGASAGGGGTGSATCAGCA	-11.18	0.55	3	0.67	0.61	3	-7.16	0.42	3	5.91	2.03	3
3753	AGGGACAGGGGTGTATCAGCAGG	-7.05	2.23	3	-4.52	3.05	3	-1.24	1.16	3	-2.67	3.84	3
4525	AGGGACASGGGTGTASCAGCAGG	-0.83	2.45	3	-8.90	0.60	3	1.58	2.52	3	-5.58	1.62	3
2422	ATGGAGCAGGCTCAGCCAGTGAGAG	27.64	11.01	3	22.46	4.41	3	34.84	9.98	3	31.70	4.70	3

2434	CCAAAGAGATGTATGGAGCAGGCTC	25.65	6.66	3	27.85	8.30	3	38.45	12.30	3	34.42	10.27	3
2446	CAGCAGGTGGCCCCAAAGAGATGTA	14.58	11.65	3	31.12	5.29	3	18.13	16.07	3	41.88	7.13	3
2465	CATCATGACCACGGGCAGCCAGCAG	41.69	3.91	3	28.44	2.21	3	51.84	4.79	3	38.90	4.44	3
2477	TCGACCACAAGCCATCATGACCACG	11.77	0.06	3	8.75	2.23	3	23.04	1.41	3	15.12	3.46	3
3846	CGACCACAAGCCATCATGACCAC	-9.69	2.12	3	7.70	3.00	3	-2.77	2.51	3	12.13	4.02	3
4530	CGACCACSAGCCATCSTGACCAC	3.86	2.82	3	-0.56	2.08	3	7.82	2.26	3	-0.74	2.31	3
3847	TCGACCACAAGCCATCATGACCA	-7.18	2.11	3	-10.87	5.29	3	-2.44	1.28	3	-6.74	3.63	3
4529	TCGACCASAAGCCATSATGACCA	-8.50	2.66	3	1.19	6.06	3	-6.71	2.36	3	4.36	7.98	3
3845	GACCACAAGCCATCATGACCACG	-5.69	0.39	3	7.08	3.00	3	0.12	1.32	3	9.58	5.60	3
4528	GACCACASGCCATCASGACCACG	2.37	1.29	3	-3.03	3.45	3	10.91	2.03	3	0.54	2.45	3
2492	AACCACCACCCCGCCTCGACCACAA	34.71	1.02	3	32.62	4.60	3	78.59	11.49	3	39.00	5.11	3
2121	TCAACACCATGACCACCATCACCAC	2.82	3.79	3	4.06	1.82	3	13.25	1.50	3	8.35	2.18	3
3490	CAACACCATGACCACCATCACCA	-23.86	3.03	3	-4.90	0.75	3	1.72	2.65	3	3.76	2.55	3
4509	CAACACCSTGACCACSATCACCA	-0.86	2.02	3	-7.48	1.73	3	7.51	3.61	3	-4.29	2.55	3
3491	TCAACACCATGACCACCATCACC	4.79	3.15	3	-0.23	0.59	3	15.16	0.91	3	4.09	2.15	3
4508	TCAACACSATGACCASCATCACC	-10.85	1.92	3	-10.52	3.21	3	-6.61	0.58	3	-4.52	1.51	3
3489	AACACCATGACCACCATCACCAC	0.11	1.01	3	-5.62	0.66	3	15.37	2.99	3	-1.85	2.14	3
4507	AACACCASGACCACCSTCACCAC	-8.42	1.65	3	-5.16	1.62	3	-0.51	2.49	3	-2.96	0.99	3
1780	AGCCACCACTGACTCCATCCCTCCA	18.29	7.59	3	34.42	3.34	3	42.41	7.78	3	50.15	7.27	3
1783	CAGAGCCACCACTGACTCCATCCCT	-0.42	2.35	3	1.83	2.82	3	1.16	3.66	3	7.25	0.76	3
3152	AGAGCCACCACTGACTCCATCCC	-1.67	7.55	3	8.17	1.95	3	-0.58	10.45	3	13.50	3.41	3
4485	AGAGCCASCACTGACSCCATCCC	-1.74	1.39	3	-2.22	1.69	3	6.08	2.73	3	6.46	1.34	3
3153	CAGAGCCACCACTGACTCCATCC	-7.13	0.21	3	-1.63	1.38	3	-2.53	4.15	3	3.53	1.74	3
4484	CAGAGCCSCCACTGASTCCATCC	-5.40	1.19	3	3.99	1.97	3	1.32	0.98	3	7.07	2.50	3
3151	GAGCCACCACTGACTCCATCCCT	-2.85	8.97	3	-1.39	1.80	3	5.54	9.87	3	5.03	2.03	3
4483	GAGCCACSACTGACTSCATCCCT	-12.63	1.26	3	0.34	4.74	3	-10.50	3.13	3	4.90	4.65	3
1786	AGCCAGAGCCACCACTGACTCCATC	-1.89	6.71	3	4.39	5.55	3	5.42	9.34	3	14.40	2.83	3
1789	TCCAGCCAGAGCCACCACTGACTCC	-1.21	4.35	3	1.54	5.17	3	14.28	13.50	3	8.32	6.95	3
1809	CTCGTTCACACCTGATGGGCTCCAG	-10.05	5.15	3	4.85	1.13	3	-7.21	3.62	3	9.13	3.75	3

3178	TCGTTCACACCTGATGGGCTCCA	-7.80	1.65	3	-1.68	2.26	3	-5.88	0.42	3	3.80	2.86	3
4488	TCGTTCASACCTGATSGGCTCCA	1.17	0.29	3	-5.21	4.34	3	3.95	2.65	3	-4.67	2.61	3
3179	CTCGTTCACACCTGATGGGCTCC	-6.62	5.41	3	-4.12	2.77	3	-1.32	1.64	3	-3.48	2.17	3
4487	CTCGTTCSCACCTGASGGGCTCC	-9.29	0.93	3	-18.77	5.14	3	-6.68	1.03	3	-17.26	2.99	3
3177	CGTTCACACCTGATGGGCTCCAG	-22.64	2.20	3	-26.65	3.28	3	-21.21	1.30	3	-21.96	0.95	3
4486	CGTTCACSCCTGATGSGCTCCAG	30.72	3.39	3	-2.00	3.97	3	23.60	4.03	3	-7.70	2.43	3
4470	CTCGTTSACACCTGATGGSCTCCAG	3.31	5.98	3	-8.32	4.06	3	15.59	11.34	3	-0.88	0.58	3
4474	CTCGTTCASACCTGATGGSCTCCAG	13.25	12.40	3	15.47	4.14	3	20.50	10.05	3	32.33	5.74	3
1812	AGGCTCGTTCACACCTGATGGGCTC	11.70	4.10	3	11.57	2.92	3	21.34	3.17	3	28.03	2.49	3
4496	ACCAGASGCATCACCATCSCCACCA	3.64	1.09	3	22.71	3.04	3	39.79	2.17	3	53.79	54.11	3
4502	ACCAGAAGSATCACCATCSCCACCA	9.40	2.42	3	10.68	8.44	3	18.97	7.44	3	16.09	6.87	3
1815	GGGAGGCTCGTTCACACCTGATGGG	16.74	6.47	3	5.72	1.11	3	21.02	2.36	3	10.87	2.62	3
1818	GGAGGGAGGCTCGTTCACACCTGAT	4.34	1.25	3	3.98	2.02	3	2.42	2.83	3	4.42	1.85	3
3187	GAGGGAGGCTCGTTCACACCTGA	-2.33	2.32	3	-7.92	1.78	3	5.16	5.38	3	-8.91	1.16	3
4491	GAGGGAGSCTCGTTCSCACCTGA	-0.84	5.15	3	-9.91	3.20	3	0.25	6.70	3	-5.57	3.10	3
3188	GGAGGGAGGCTCGTTCACACCTG	2.64	2.00	3	-4.17	2.78	3	-0.15	0.84	3	-2.47	5.32	3
4490	GGAGGGASGCTCGTTSACACCTG	-5.69	0.85	3	-0.56	3.57	3	-2.92	1.41	3	-1.30	2.34	3
3186	AGGGAGGCTCGTTCACACCTGAT	-3.48	2.89	3	-5.92	1.08	3	-3.05	3.85	3	-3.55	4.75	3
4489	AGGGAGGSTCGTTCASACCTGAT	-10.48	3.10	3	-16.43	1.36	3	-14.43	2.77	3	-15.99	3.76	3
1843	CGAGAAGAAGCACCGAGAAGAAAGG	1.88	1.81	3	20.60	4.70	3	5.24	9.03	3	33.13	5.11	3
1848	AGTCACGAGAAGAAGCACCGAGAAG	20.23	4.29	3	7.44	4.76	3	18.02	3.26	3	6.67	1.30	3
3217	GTCACGAGAAGAAGCACCGAGAA	13.12	0.72	3	9.52	5.98	3	10.08	0.51	3	9.58	3.28	3
4494	GTCACGASAAGAAGCSCCGAGAA	9.68	2.36	3	-0.91	6.39	3	10.12	1.61	3	-1.73	7.56	3
3218	AGTCACGAGAAGAAGCACCGAGA	16.86	1.93	3	8.85	0.49	3	14.17	4.84	3	5.65	1.53	3
4493	AGTCACGSGAAGAAGSACCGAGA	-3.49	5.85	3	14.86	1.55	3	-6.76	7.53	3	14.20	2.40	3
3216	TCACGAGAAGAAGCACCGAGAAG	3.79	1.42	3	0.36	1.80	3	2.52	1.86	3	-2.15	2.36	3
4492	TCACGAGSAGAAGCASCGAGAAG	11.30	3.09	3	0.00	0.89	3	13.30	1.65	3	0.10	3.57	3
4471	AGTCACSAGAAGAAGCACSGAGAAG	-7.58	4.89	3	-8.35	9.54	3	4.67	6.75	3	0.76	11.81	3
4475	AGTCACGASAAGAAGCACSGAGAAG	9.02	10.30	3	-17.71	8.26	3	29.48	10.29	3	-9.94	10.72	3

4498	AAGTACSCCAGGAACGAGSCCAGGA	-1.31	3.42	3	5.34	2.71	3	-2.48	2.14	3	4.78	3.59	3
4504	AAGTACACSAGGAACGAGSCCAGGA	-1.30	1.10	3	2.26	1.78	3	-0.81	2.06	3	1.16	2.09	3
1749	GCTCTTGAAGCAAACCCCAGGCAGG	-3.34	2.72	3	-10.58	0.70	3	-2.62	1.30	3	-10.08	2.61	3
3118	CTCTTGAAGCAAACCCCAGGCAG	-11.90	0.52	3	-11.40	0.41	3	-13.21	1.98	3	-11.64	1.20	3
4479	CTCTTGASGCAAACCSCAGGCAG	-7.68	3.19	3	-9.11	2.70	3	-6.38	3.39	3	-7.82	3.19	3
3119	GCTCTTGAAGCAAACCCCAGGCA	-4.09	1.67	3	-4.91	2.51	3	0.26	1.95	3	-2.87	2.17	3
4478	GCTCTTGSAGCAAACSCCAGGCA	-3.12	0.54	3	-1.01	6.66	3	-0.87	4.06	3	4.96	7.18	3
3117	TCTTGAAGCAAACCCCAGGCAGG	-10.82	0.13	3	-9.64	0.82	3	-8.40	1.21	3	-9.49	1.64	3
4477	TCTTGAASCAAACCCSAGGCAGG	-5.69	1.71	3	-5.51	4.26	3	-2.67	2.32	3	-2.79	4.41	3
1774	CACTGACTCCATCCCTCCACCCAGG	3.71	0.79	3	1.85	2.54	3	2.85	1.65	3	1.59	2.04	3
3143	ACTGACTCCATCCCTCCACCCAG	5.30	5.18	3	2.26	1.06	3	2.74	1.78	3	0.04	2.37	3
4482	ACTGACTSCATCCCTSCACCCAG	1.00	2.04	3	-1.50	1.79	3	2.36	2.04	3	-2.04	2.02	3
3144	CACTGACTCCATCCCTCCACCCA	0.91	1.61	3	-0.70	1.58	3	1.60	1.21	3	-1.03	0.32	3
4481	CACTGACSCCATCCCSCCACCCA	4.83	1.31	3	1.79	0.97	3	3.25	1.75	3	1.13	2.26	3
3142	CTGACTCCATCCCTCCACCCAGG	6.92	1.97	3	6.66	2.08	3	8.17	1.78	3	8.13	3.21	3
4480	CTGACTCSATCCCTCSACCCAGG	13.39	2.34	3	2.54	6.61	3	11.08	0.98	3	3.64	6.11	3
4499	ACAGGGSCAGGGGTGTATSAGCAGG	6.59	5.05	3	6.33	1.86	3	14.95	6.32	3	13.10	1.60	3
4505	ACAGGGACSGGGGTGTATSAGCAGG	7.47	0.68	3	7.48	1.97	3	11.20	0.98	3	13.21	3.65	3
4500	TCGACCSCAAGCCATCATSACCACG	18.23	5.32	3	14.37	5.75	3	27.23	4.59	3	21.77	2.94	3
4506	TCGACCACSAGCCATCATSACCACG	34.70	9.05	3	31.42	5.95	3	60.23	10.63	3	43.91	8.79	3
4472	GCTCTTSAAGCAAACCCCSGGCAGG	6.15	7.74	3	-0.54	0.82	3	14.16	10.84	3	9.32	4.10	3
4476	GCTCTTGASGCAAACCCCSGGCAGG	2.45	2.87	3	14.93	6.65	3	10.31	3.46	3	18.48	0.39	3
4495	TCAACASCATGACCACCASCACCAC	19.19	5.02	3	13.50	2.06	3	20.16	4.33	3	13.88	4.01	3
4501	TCAACACCSTGACCACCASCACCAC	5.52	5.25	3	18.65	3.28	3	18.45	9.19	3	22.97	5.99	3

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 34 are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

Example 10: Design and Selection of UNC13A Oligonucleotides

[00948] UNC13A AONs oligonucleotides that target a UNC13A transcript are designed and tested to identify UNC13A AONs capable of reducing quantity of UNC13A transcripts (e.g., mis-spliced UNC13A transcripts). Such UNC13A AONs include UNC13A parent oligonucleotides represented by any of SEQ ID NOs: 4531-5794 or UNC13A oligonucleotide variants represented by SEQ ID NOs: 7059-8322. The UNC13A parent oligonucleotides are 25 nucleosides in length. Each of the nucleosides of the UNC13A parent oligonucleotides are modified nucleosides with 2'-MOE sugar moieties, and each "C" is replaced with a 5-MeC. Additionally, each of the internucleoside linkages between the nucleosides of the UNC13A oligonucleotides are phosphorothioate internucleoside linkages.

[00949] Generally, the length of the UNC13A antisense oligonucleotides are 25 oligonucleotide units in length. However, variants of the UNC13A antisense oligonucleotides were also designed with varying lengths (*e.g.*, 23mers, 21mers, or 19mers). Examples of these variant UNC13A antisense oligonucleotides were designed to include a subset of the sequences of SEQ ID NOs: 7059-8322.

[00950] Table 35A: Example UNC13A AONs (including UNC13A oligonucleotides with two spacers)

SEQ ID No:	Oligonucleotide Sequence* (where S indicates presence of a Spacer) (5' → 3')	Length
9663	GGGCAGSCAGGAATGGTGSGTGGAA	25
9664	AGGGAGSAGTTTTCCAGGSAAAGGG	25
9665	GCAGCTSGAAGAGACATASCCAGAC	25
9666	TCCACCSGCCACTCACAASCATCCA	25
9667	GAAAGTSTCATGGAGAGTSCAAGGG	25
9668	GGGCAGGCSGGAATGGTGSGTGGAA	25
9669	AGGGAGGASTTTTCCAGGSAAAGGG	25
9670	GCAGCTGGSAGAGACATASCCAGAC	25
9671	TCCACCAGSCACTCACAASCATCCA	25
9672	GAAAGTGTSATGGAGAGTSCAAGGG	25
9673	GCAGGCASGAATGGTSAGTGGAA	23
9674	GGGCAGGSAGGAATGSTGAGTGG	23

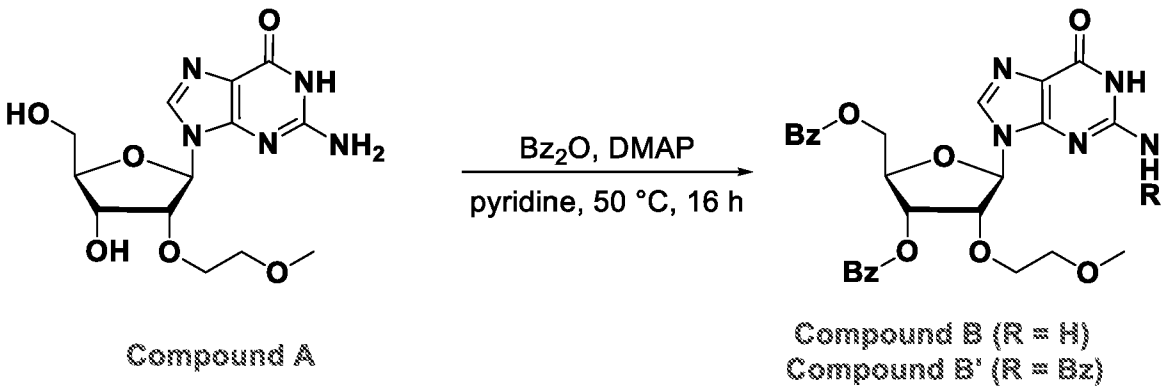
9675	GGCAGGCSGGAATGGSGAGTGGA	23
9676	GTAAAGGSAATGGCASGGCGGGC	23
9677	AGGTAAASGGAATGGSATGGCGG	23
9678	GGTAAAGSGAATGGCSTGGCGGG	23
9679	AGGAGGTSACCCTGASTCTGGAC	23
9680	AGAGGAGSTGACCCTSAATCTGG	23
9681	GAGGAGGSGACCCTGSATCTGGA	23
9682	ACAAACGSCCCAATCSTGAGTGG	23
9683	ACACAAASGGCCCAASCCTGAGT	23
9684	CACAAACSGCCCAATSCTGAGTG	23
9685	TCTTTCCSGGAAACCSAGGCAGC	23
9686	GTTCTTTSCAGGAAASCCAGGCA	23
9687	TTCTTTCSAGGAAACSCAGGCAG	23
9688	TCCGCAASTTAATCCSCCTACCC	23
9689	GATCCGCSACTTAATSCACCTAC	23
9690	ATCCGCASCTTAATCSACCTACC	23
9691	CCCACCCSTCTAACTSCCCCAAA	23
9692	CACCCACSCATCTAASTACCCCA	23
9693	ACCCACCSATCTAACSACCCCAA	23
9694	AAGTGTCSTGGAGAGSGCAAGGG	23
9695	GAAAGTGSCATGGAGSGTGCAAG	23
9696	AAAGTGTSATGGAGASTGCAAGG	23

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 35A are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

Methods for Synthesizing a Spacer building block for Spacers of Formula (IIib')

[00951] Several UNC13A AONs were synthesized with one or more spacers of Formula (IIib'), as disclosed herein. The method of generating the spacer building block involved a 5 step synthesis method, described below.

[00952] Step 1: Benzoyl protection



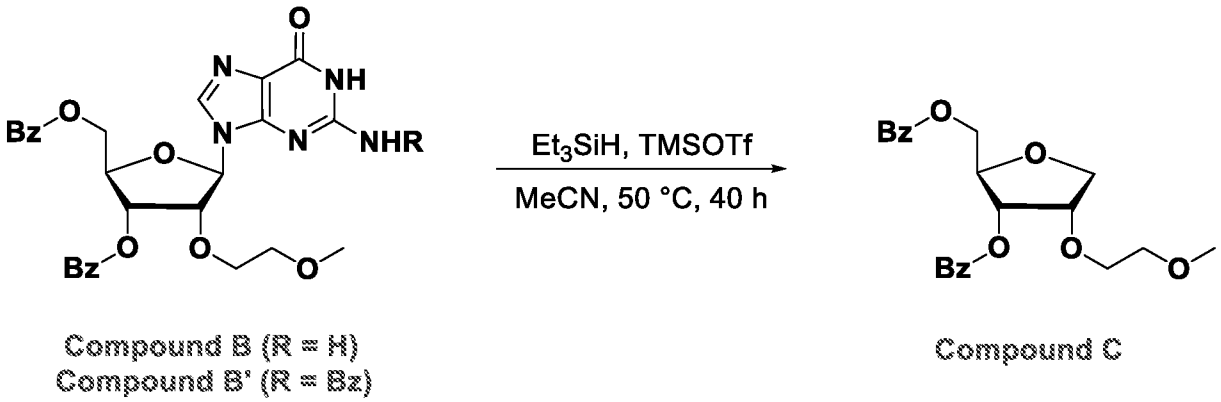
Compound A

Compound B (R = H)
Compound B' (R = Bz)

(2R,3R,4R,5R)-5-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-2-((benzoyloxy)methyl)-4-(2-methoxyethoxy)tetrahydrofuran-3-yl benzoate ***(2)*** *& (2R,3R,4R,5R)-5-(2-benzamido-6-oxo-1,6-dihydro-9H-purin-9-yl)-2-((benzoyloxy)methyl)-4-(2-methoxyethoxy) tetrahydrofuran-3-yl benzoate* ***(2')***

[00953] To a solution of 2'-O-(2-methoxyethyl)-guanosine (15.00 g, 42.6 mmol) in dry pyridine (300 mL) was added benzoic anhydride (26.2 g, 114 mmol) followed by 4-dimethylaminopyridine (1.77 g, 14.2 mmol) at rt, then the temperature was raised to 50 °C and allowed to stir for 16 h. LCMS showed complete consumption of starting material. The reaction was then diluted with water, quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate (x3). The organic layers were further washed with brine, then dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (0 – 15% methanol in dichloromethane) to give an approximate 2:1 mixture of **compound B** and **compound B'** (20.0 g) as a colorless oil. Calculated mass for **B**: $C_{27}H_{27}N_5O_8$ = 549.19; found = 550.3 $(M+H)^+$. Calculated mass for **B'**: $C_{34}H_{31}N_5O_9$ = 653.21; found 654.3 $(M+H)^+$. **LCMS:** CSH C18 AMB (3 min): compound **B**, R_T = 1.33 min, compound **B'**, R_T = 1.48 min.

[00954] Step 2: Reductive nucleobase cleavage

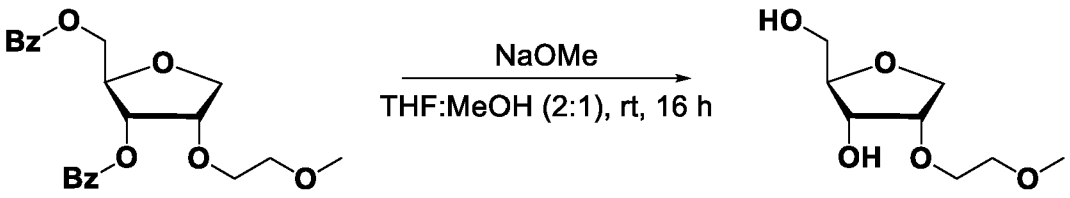


*((2R,3S,4S)-3-(benzoyloxy)-4-(2-methoxyethoxy) tetrahydrofuran-2-yl) methyl benzoate (**3**)*

[00955] To a mixture of compound B & B' (20.0 g) in acetonitrile (120 mL) was added triethylsilane (49.3 mL, 306 mmol) followed by trimethylsilyl trifluoromethanesulfonate (37.3 mL, 204 mmol) dropwise at rt then the temperature was raised to 50 °C and allowed to stir for 16 h. Additional triethylsilane (28.9 mL, 179 mmol) and trimethylsilyl trifluoromethanesulfonate (21.8 mL, 119 mmol) was added and the reaction was continued at 50 °C for an additional 24 h. LCMS showed complete consumption of starting material, therefore the reaction was quenched with saturated aqueous sodium bicarbonate then extracted with diethyl ether (x3). The organic layers were combined and further washed with brine, then dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (0 – 50% ethyl acetate in hexanes) to give compound C (5.61 g, 33% yield over 2 steps) as a colorless oil. Calculated mass for $C_{22}H_{24}O_7$ = 400.15; found = 401.3 $(M+H)^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 – 7.99 (m, 4H), 7.63 – 7.50 (m, 2H), 7.49 – 7.36 (m, 4H), 5.40 – 5.33 (m, 1H), 4.63 – 4.53 (m, 1H), 4.52 – 4.42 (m, 2H), 4.34 (q, *J* = 5.6 Hz, 1H), 4.24 (dd, *J* = 9.4, 5.7 Hz, 1H), 3.96 (dd, *J* = 9.4, 5.7 Hz, 1H), 3.69 – 3.63 (m, 2H), 3.45 – 3.39 (m, 2H), 3.23 (s, 3H). **LCMS:** CSH C18 AMB (3 min): R_T = 1.55 min

[00956] Step 3: Saponification



Compound C Compound D

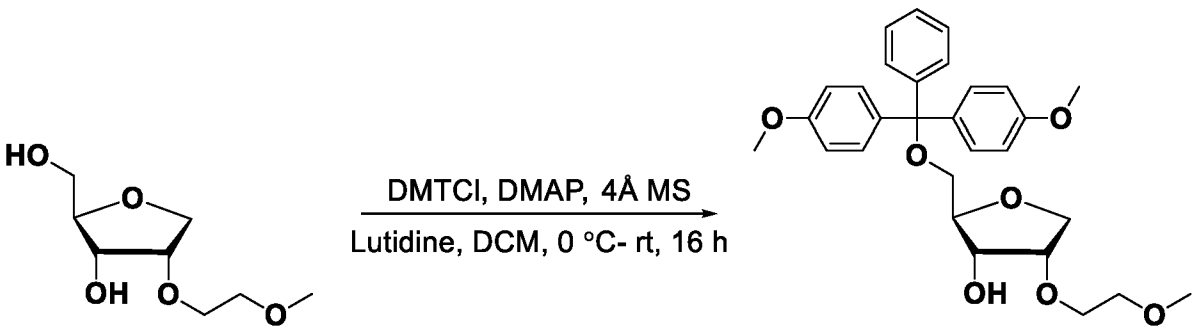
*(2R,3R,4S)-2-(hydroxymethyl)-4-(2-methoxyethoxy) tetrahydrofuran-3-ol (**4**)*

To a solution of compound C (5.00 g, 12.5 mmol) in tetrahydrofuran (60 mL) and methanol (30 mL) was added a 25% solution of sodium methoxide in methanol (14.3 mL, 214 mmol) at rt and the reaction mixture was stirred at rt for 16 h. LCMS and TLC showed complete consumption of staring material. The reaction mixture was then concentrated *in vacuo* and purified by silica gel column chromatography (0 – 10% methanol in dichloromethane) to give compound D (1.50 g, 62 % yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.08 – 4.00 (m, 2H), 3.94 (dd, *J* = 10.0, 5.1 Hz, 1H), 3.82 – 3.74 (m, 4H), 3.69 – 3.45 (m, 4H), 3.36 (s, 3H), 3.32 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 83.84, 79.60, 71.93, 71.44, 70.67, 69.87, 62.56, 59.07.

[00957] Step 4: DMT-protection



Compound D Compound E

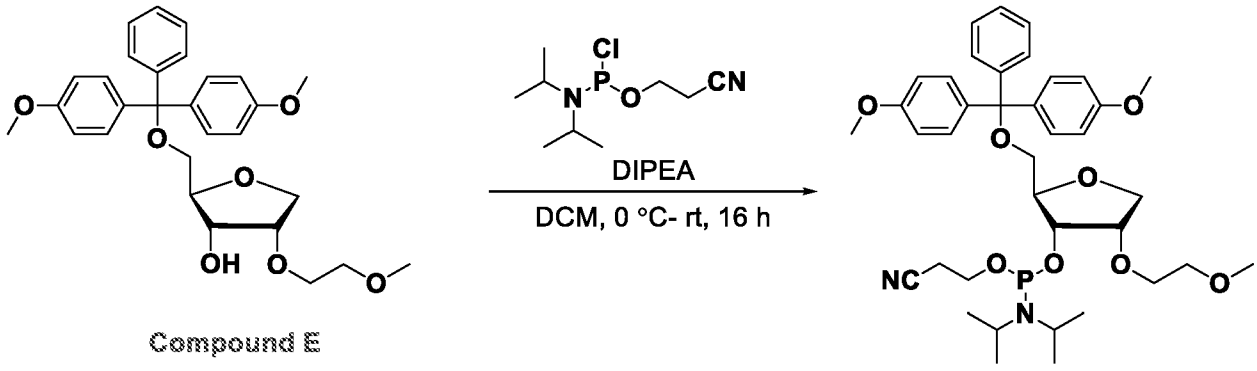
*(2R,3S,4S)-2-((bis(4-methoxyphenyl) (phenyl)methoxy) methyl)-4-(2-hydroxyethoxy) tetrahydrofuran-3-ol (**5**)*

To a suspension of compound D (1.00 g, 5.20 mmol) and 4Å molecular sieves (120 mg) in 2,6-lutidine (20.0 mL) was added 4-dimethylaminopyridine (128 mg, 1.04 mmol) followed by a solution of 4,4′-dimethoxytrityl chloride (3.60 g, 10.4 mmol) in dichloromethane (10.0 mL) at 0 °C, then slowly raised the temperature to rt and allowed to stir for 16 h. LCMS and TLC showed the reaction was complete, therefore hexanes (10 mL) and methanol (10 mL) were added and the mixture was concentrated *in vacuo*. The residue was then dissolved in ethyl acetate and washed with saturated aqueous copper sulfate (x2) followed by brine, then dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (0 – 50% ethyl acetate in hexanes) to give compound E (1.85 g, 72 % yield) as a pale-yellow oil. Calculated mass for $C_{29}H_{34}O_7$ = 494.23; found 493.5 $(M-H)^-$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.40 (m, 2H), 7.37 – 7.30 (m, 3H), 7.30 – 7.22 (m, 3H), 7.21 – 7.13 (m, 1H), 6.81 (dd, *J* = 8.8, 1.7 Hz, 4H), 4.17 – 4.11 (m, 1H), 4.11 – 4.03 (m, 2H), 4.00 – 3.93 (m, 1H), 3.86 – 3.79 (m, 2H), 3.78 – 3.74 (m, 6H), 3.70 – 3.62 (m, 1H), 3.61 – 3.47 (m, 2H), 3.40 – 3.36 (m, 3H), 3.34 – 3.27 (m, 2H), 3.12 – 3.07 (m, 1H).

LCMS: CSH C18 AMB (7 min) : R_T = 3.28 min

[00958] Step 5: Phosphoramidite installation



Compound E

Compound F

(2R,3S,4S)-2-((bis(4-methoxyphenyl) (phenyl)methoxy) methyl)-4-(2-methoxyethoxy) tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite

To a suspension of compound E (6.85 g, 13.9 mmol) in dry dichloromethane (150 mL) was added N,N-diisopropylethylamine (21.1 mL, 120 mmol) and the resulting solution was cooled to 0 °C under a nitrogen atmosphere. 2-Cyanoethyl N,N-diisopropylchlorophosphoramidite (6.18 mL, 27.7 mmol) was then added dropwise and the resulting solution was allowed to attain rt and stir for

16 h. LCMS and TLC showed the reaction was complete. The reaction mixture was then cooled to 0 °C, diluted with dichloromethane and washed with cold saturated aqueous sodium bicarbonate, followed by brine, then dried over sodium sulfate and concentrated *in vacuo*. The crude product was then purified by silica gel column chromatography (5% triethylamine in ethyl acetate and hexanes, 5 – 80%) to give, after lyophilization, Compound F (6.35 g, 66 % yield) as a colorless oil (mixture of diastereomers at P). Calculated mass for $C_{38}H_{51}N_2O_8P$ = 694.34; found = 695.6 $(M+H)^+$.

Example 11: Methods for Evaluating UNC13a Antisense Oligonucleotides

[00959] UNC13A antisense oligonucleotides were evaluated in iPSC derived human motor neurons (hMN). The cells were seeded in 96-well plates at a density of 50,000 cells / well. Antisense oligonucleotide (AON) to TDP43 was transfected with Endoporter (Gene Tools, Philomath, OR, USA) to decrease expression of the full length UNC13a transcript. Vehicle control consisted of motor neuron treatment with Endoporter alone. Positive controls included cells that were treated with TDP43 AON alone ("AON TDP43" or "TDP43 AON").

[00960] TDP43 AON is a gapmer oligonucleotide and has the following sequence and chemistry: 5' A*A*G*G*C*T*T*C*A*T*A*T*T*G*T*A*C*T*T*T 3' (SEQ ID NO: 1669) where * = phosphorothioate, underlined = DNA, other=2'-MOE RNA; each "C" is 5-MeC.

[00961] To evaluate UNC13a AON ability to restore full length UNC13A (UNC13A FL) mRNA (also referred to as correctly spliced UNC13A (UNC13A CS) mRNA), antisense oligonucleotides to UNC13A were co-incubated with TDP43 AON in Endoporter in media before addition to the cells. After 72 hours, antisense oligonucleotides and Endoporter were washed out and replaced with fresh media. After 72 additional hours, RNA was collected from the 96-well plates for RT-qPCR. RNA was isolated, cDNA generated, and multiplexed RT-qPCR assay performed with Taqman probes for UNC13A full length transcript and reference GAPDH quantification.

[00962] Transcript levels (e.g., UNC13A full length transcript or TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher® TaqMan Gene Expression Assay Hs03929097_g1. RT-qPCR was performed for detecting UNC13aFL transcripts using Thermofisher® TaqMan Gene Expression Assay Hs00392638_m1.

[00963] RT-qPCR was performed on Applied Biosystems ® 7500 Real-time PCR systems. One cycle of reverse transcription was performed at a temperature of 50°C for 5 min. One cycle of RT inactivation/initial denaturation was performed at a temperature of 95°C for 20 seconds. Forty

five cycles of amplification were performed at a temperature of 95°C for 1 second followed by 60°C for 20 seconds.

[00964] UNC13A-FL (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (e.g., % decrease of UNC13A-FL), the normalized UNC13A-FL signal was further normalized to the vehicle (treated with Endoporter alone, deltadeltaCt). Relative quantity (RQ) of transcript level was calculated using the equation $RQ=2^{-deltadeltaCt}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0). RQ values for UNC13A FL were normalized using the following formula:

$$(((RQAON - RQTDP43)/(RQendo-RQTDP43))*100$$

[00965] Table 35B shows the RT-qPCR results of UNC13A AONs with spacers and performance of UNC13A AONs without spacers in human motor neurons. UNC13A AONs (*e.g.*, UNC13A oligonucleotides without spacers or with one or two spacers) were tested for their ability to increase or restore full-length UNC13A mRNA (*i.e.*, mRNA from which full-length UNC13A protein is translated) levels. In some cases, UNC13A AONs with spacers increased full-length UNC13A mRNA ("UNC13A FL"), also referred to herein as correctly spliced UNC13A (UNC13A CS). In some cases, UNC13A AONs without spacers increased full-length UNC13A mRNA or correctly spliced UNC13A mRNA. Specific AON sequences are labeled according to their corresponding SEQ ID NO.

[00966] As shown in Table 35B, a 500 nM dose of SEQ ID NO: 9683 (ACACAAASGGCCCAASCCTGAGT with two spacers) rescued full length UNC13A mRNA to 55.690%. Comparatively, a 500 nM dose of SEQ ID NO: 7318 (ACACAAACGGCCCAATCCTGAGT with no spacers) rescued full length UNC13A mRNA to 41.869%. This indicates that the addition of spacers of SEQ ID NO: 9683 improves the performance in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 7318).

[00967] Additionally shown in Table 35B, a 200 nM dose of SEQ ID NO: 9689 (GATCCGCSACTTAATSCACCTAC with two spacers) rescued full length UNC13A mRNA to 55.876%. A 500 nM dose of SEQ ID NO: 9689 (GATCCGCSACTTAATSCACCTAC with two spacers) rescued full length UNC13A mRNA to 66.616%. Comparatively, a 200 nM dose of SEQ ID NO: 8077 (GATCCGCAACTTAATCCACCTAC with no spacers) rescued full length UNC13A mRNA to 43.878%. A 500 nM dose of SEQ ID NO: 8077 (GATCCGCAACTTAATCCACCTAC with no spacers) rescued full length UNC13A mRNA to 66.9823%. This indicates that at 200 nM and 500 nM doses, the performance of an AON with

SEQ ID NO: 9689 (with spacers) is similar to the performance of the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 8077).

[00968] Additionally shown in Table 35B, a 200 nM dose of SEQ ID NO: 9692 (CACCCACSCATCTAASTACCCCA with two spacers) rescued full length UNC13A mRNA to 47.943%. A 500 nM dose of SEQ ID NO: 9692 (CACCCACSCATCTAASTACCCCA with two spacers) rescued full length UNC13A mRNA to 83.190%. Comparatively, a 200 nM dose of SEQ ID NO: 8182 (CACCCACCCATCTAACTACCCCA with no spacers) rescued full length UNC13A mRNA to 47.681%. A 500 nM dose of SEQ ID NO: 8182 (CACCCACCCATCTAACTACCCCA with no spacers) rescued full length UNC13A mRNA to 41.1564%. This indicates that at a 200 nM dose, the performance of SEQ ID NO: 9692 (with spacers) is similar to the performance of the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 8182). However, at a 500 nM dose, the addition of spacers of SEQ ID NO: 9692 improves the performance in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 8182).

[00969] Additionally shown in Table 35B, a 500 nM dose of SEQ ID NO: 9691 (CCCACCCSTCTAACTSCCCCAAA with two spacers) rescued full length UNC13A mRNA to 43.097%. Comparatively, a 500 nM dose of SEQ ID NO: 8180 (CCCACCCATCTAACTACCCCAAA with no spacers) rescued full length UNC13A mRNA to 23.368%. This indicates that at a 500 nM dose, the addition of spacers improves the performance of an AON with SEQ ID NO: 9691 in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 8180).

[00970] Additionally shown in Table 35B, a 200 nM dose of SEQ ID NO: 9694 (AAGTGTCSTGGAGAGSGCAAGGG with two spacers) rescued full length UNC13A mRNA to 35.388%. A 500 nM dose of SEQ ID NO: 9694 (AAGTGTCSTGGAGAGSGCAAGGG with two spacers) rescued full length UNC13A mRNA to 6.602 %. Comparatively, a 200 nM dose of SEQ ID NO: 8304 (AAGTGTCATGGAGAGTGCAAGGG with no spacers) rescued full length UNC13A mRNA to 19.044%. A 500 nM dose of SEQ ID NO: 8304 (AAGTGTCATGGAGAGTGCAAGGG with no spacers) rescued full length UNC13A mRNA to -34.581%. This indicates that at 200 nM and 500 nM doses, the addition of spacers improves the performance of an AON with SEQ ID NO: 9694 in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 8304).

[00971] Additionally shown in Table 35B, a 200 nM dose of SEQ ID NO: 9672 (GAAAGTGTSATGGAGAGTSCAAGGG with two spacers) rescued full length UNC13A

mRNA to 67.769%. A 500 nM dose of SEQ ID NO: 9672 (GAAAGTGTSATGGAGAGTSCAAGGG with two spacers) rescued full length UNC13A mRNA to 84.785 %. Comparatively, a 200 nM dose of SEQ ID NO: 5778 (GAAAGTGTCATGGAGAGTGCAAGGG with no spacers) rescued full length UNC13A mRNA to 22.475%. A 500 nM dose of SEQ ID NO: 5778 (GAAAGTGTCATGGAGAGTGCAAGGG with no spacers) rescued full length UNC13A mRNA to 24.836%. This indicates that at 200 nM and 500 nM doses, the addition of spacers improves the performance of an AON with SEQ ID NO: 9672 in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 5778).

[00972] Altogether, these results demonstrate that different UNC13A AONs including two spacers are capable of increasing UNC13A-FL mRNA to levels that are comparable to or improved beyond their non-spacer counterparts.

Table 35B: Performance of UNC13A AONs (UNC13A oligonucleotides without spacers, or with one or two spacers) for restoring UNC13A FL.

SEQ ID NO:	Oligonucleotide Sequence* (where S indicates presence of a Spacer) (5' → 3')	QPCR potency		QPCR potency	
		200 nM	200 nM	500 nM	500 nM
		Normalized	RQ	Normalized	RQ
4572	GAAGAGCTGGGCAGGCAGGAATGGT	3.79367	0.480565	-63.053	0.19433
4596	TGTGGATGGTGTGGCCAGAAAGAGG	60.6986	0.724229	-23.435	0.36397
4607	GGCCAGGAGAGTGTGGATGGTGTGG	154.828	1.127288	434.631	2.32539
4631	ATGGCATGGCGGGCAGTCTCAGAGG	37.1601	0.448286	12.6634	0.41631
4638	AAAGGGAATGGCATGGCGGGCAGTC	-26.139	0.13718	22.9464	0.49028
4642	AGGTAAAGGGAATGGCATGGCGGGC	-5.3242	0.383369	-37.199	0.17903
7169	GGTAAAGGGAATGGCATGGCGGG	-29.228	0.227001	-33.566	0.20089
9678	GGTAAAGSGAATGGCSTGGCGGG	-16.331	0.304608	-29.739	0.22392
7170	AGGTAAAGGGAATGGCATGGCGG	-13.385	0.322337	-40.436	0.15956
9677	AGGTAAASGGAATGGSATGGCGG	-13.664	0.320657	-24.027	0.2583
7168	GTAAAGGGAATGGCATGGCGGGC	-29.989	0.222419	-26.677	0.24235
9676	GTAAAGGSAATGGCASGGCGGGC	25.771	0.557959	-18.428	0.29199
4645	TCCAGGTAAAGGGAATGGCATGGCG	-7.8349	0.268854	40.2877	0.61503
4657	AGGGAGGAGTTTTCCAGGTAAAGGG	-32.255	0.392785	-25.109	0.4256
9664	AGGGAGSAGTTTTCCAGGSAAAGGG	6.97605	0.572906	-3.6889	0.52394
9669	AGGGAGGASTTTTCCAGGSAAAGGG	-70.51	0.217148	-78.696	0.17957
4692	AGAGGAGGTGACCCTGAATCTGGAC	129.033	0.93262	110.34	1.0505

7219	GAGGAGGTGACCCTGAATCTGGA	169.855	1.024819	164.814	1.30762
9681	GAGGAGGSGACCCTGSATCTGGA	-72.457	0.658323	138.629	1.28191
7220	AGAGGAGGTGACCCTGAATCTGG	171.498	1.135638	3.26987	0.54512
9680	AGAGGAGSTGACCCTSAATCTGG	7.49253	0.565048	-57.946	0.25617
7218	AGGAGGTGACCCTGAATCTGGAC	44.7095	0.740715	125.001	1.1197
9679	AGGAGGTSACCCTGASTCTGGAC	-44.26	0.320771	12.8179	0.59018
4725	GAGAGTCAACCTGGAGGCCAAGGTG	32.5688	0.559505	57.0338	0.7355
4730	GTAGTGAGAGTCAACCTGGAGGCCA	70.681	0.905428	67.6819	0.88671
4733	TGAGTAGTGAGAGTCAACCTGGAGG	91.2119	1.033573	59.7857	0.83742
4774	CCTGAGTGGTTAGGGCTGGAATAGA	46.7792	0.756244	-24.332	0.3124
4778	CAATCCTGAGTGGTTAGGGCTGGAA	-8.5	0.411217	73.8646	0.9253
4784	ACGGCCCAATCCTGAGTGGTTAGGG	66.8521	0.88153	45.3726	0.74746
4790	ACACAAACGGCCCAATCCTGAGTGG	-11.42	0.462541	75.8487	0.8839
7317	CACAAACGGCCCAATCCTGAGTG	-11.128	0.463949	-41.939	0.31518
9684	CACAAACSGCCCAATSCTGAGTG	50.7872	0.762897	-14.314	0.44857
7318	ACACAAACGGCCCAATCCTGAGT	-27.43	0.385239	41.8694	0.71984
9683	ACACAAASGGCCCAASCCTGAGT	-14.732	0.44655	55.6902	0.78657
7316	ACAAACGGCCCAATCCTGAGTGG	-49.751	0.277462	-20.306	0.41964
9682	ACAAACGSCCCAATCSTGAGTGG	105.349	1.026341	47.8744	0.74883
4793	CAGACACAAACGGCCCAATCCTGAG	-40.7843	0.3272	-5.4793	0.5486
4799	CATACCCAGACACAAACGGCCCAAT	-21.2475	0.3317	14.4015	0.5542
4803	GAGACATACCCAGACACAAACGGCC	47.2141	0.7590	116.3656	1.1906

4813	GCAGCTGGAAGAGACATACCCAGAC	4.7146	0.5625	-66.6389	0.2349
9665	GCAGCTSGAAGAGACATASCCAGAC	33.7840	0.6960	-6.4957	0.5111
9670	GCAGCTGGSAGAGACATASCCAGAC	3.7461	0.5581	35.3538	0.7032
4831	TCTTTCCAGGAAACCCAGGCAGCTG	17.5514	0.5395	30.5680	0.5952
9741	GTTCTTTCCAGGAAACCCAGGCAGC	41.1141	0.5932	-27.3254	0.2666
7360	TTCTTTCCAGGAAACCCAGGCAG	-31.8396	0.2450	-7.7732	0.3599
9687	TTCTTTCSAGGAAACSCAGGCAG	-72.0800	0.0530	-37.1813	0.2196
7361	GTTCTTTCCAGGAAACCCAGGCA	-14.5643	0.3275	44.7209	0.6104
9686	GTTCTTTSCAGGAAASCCAGGCA	-38.7597	0.2120	-22.4863	0.2897
7359	TCTTTCCAGGAAACCCAGGCAGC	2.0002	0.4065	-15.1244	0.3248
9685	TCTTTCCSGGAAACCSAGGCAGC	-59.9899	0.1107	-64.5153	0.0891
4984	CACGAATCTACCCACCAACTCATCC	-39.5824	0.2948	-56.2924	0.2233
4990	TCTAGCCACGAATCTACCCACCAAC	75.4170	0.7873	-12.0685	0.4126
5457	GTCTGTCCACCAGCCACTCACAACC	121.2337	0.9834	-62.7895	0.1955
5460	TTCGTCTGTCCACCAGCCACTCACA	-18.2285	0.3863	-45.7096	0.2686
5467	TCCATTTTTCGTCTGTCCACCAGCC	-63.8195	0.2479	-54.2647	0.2917
5549	GATCCGCAACTTAATCCACCTACCC	88.0305	0.9091	44.9905	0.5436
8076	ATCCGCAACTTAATCCACCTACC	30.7027	0.4223	45.1113	0.5446
9690	ATCCGCASCTTAATCSACCTACC	38.8278	0.4913	50.8796	0.5936
8077	GATCCGCAACTTAATCCACCTAC	43.8789	0.5342	66.9823	0.7303
9689	GATCCGCSACTTAATSCACCTAC	55.8768	0.6360	66.6162	0.7272
8075	TCCGCAACTTAATCCACCTACCC	64.3790	0.7082	67.3066	0.7331

9688	TCCGCAASTTAATCCSCCTACCC	53.4236	0.6152	51.3988	0.5980
5654	CACCCACCCATCTAACTACCCCAAA	64.1844	0.6729	44.6783	0.4941
8181	ACCCACCCATCTAACTACCCCAA	41.2908	0.4631	64.1844	0.6729
9693	ACCCACCSATCTAACSACCCCAA	46.9810	0.4070	58.8250	0.6238
8182	CACCCACCCATCTAACTACCCCA	47.6810	0.5217	41.0564	0.4609
9692	CACCCACSCATCTAASTACCCCA	47.9432	0.5241	83.1895	0.8471
8180	CCCACCCATCTAACTACCCCAAA	72.0651	0.5775	23.3677	0.2988
9691	CCCACCCSTCTAACTSCCCCAAA	41.8445	0.4682	43.0965	0.4796
5778	GAAAGTGTCATGGAGAGTGCAAGGG	22.4754	0.5041	24.8358	0.5167
8305	AAAGTGTCATGGAGAGTGCAAGG	82.5919	0.8245	7.0300	0.4218
9696	AAAGTGTSATGGAGASTGCAAGG	61.0070	0.7095	-4.8799	0.3583
8306	GAAAGTGTCATGGAGAGTGCAAG	55.7844	0.6816	-19.7864	0.2789
9695	GAAAGTGSCATGGAGSGTGCAAG	40.0402	0.5977	3.6974	0.4040
8304	AAGTGTCATGGAGAGTGCAAGGG	19.0435	0.4858	-34.5807	0.2001
9694	AAGTGTCSTGGAGAGSGCAAGGG	35.3880	0.5729	6.6020	0.4195
9667	GAAAGTSTCATGGAGAGTSCAAGGG	-10.6183	0.3278	50.6900	0.6545
9672	GAAAGTGTSATGGAGAGTSCAAGGG	67.7691	0.7455	84.7852	0.8362
5790	CACCATGGGAGAGAAAGTGTCATGG	17.7544	0.4529	64.3335	0.7880

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 35B are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC) , and all internucleoside linkages are phosphorothioat linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

Example 12: Methods for Evaluating UNC13A Antisense Oligonucleotides

[00973] UNC13A antisense oligonucleotides were evaluated in iPSC derived human motor neurons (hMN). The cells were seeded in 96-well plates at a density of 40,000 cells / well. Antisense oligonucleotide (AON) to TDP43 was transfected with Endoporter (Gene Tools, Philomath, OR, USA) to decrease expression of the full length UNC13A transcript and increase expression of UNC13A cryptic exon. Vehicle control consisted of motor neuron treatment with Endoporter alone. Positive controls included cells that were treated with TDP43 AON alone ("AON TDP43" or "TDP43 AON").

[00974] TDP43 AON is a gapmer oligonucleotide and has the following sequence and chemistry: 5' A*A*G*G*C*T*T*C*A*T*A*T*T*G*T*A*C*T*T*T 3' (SEQ ID NO: 1669) where * = phosphorothioate, underlined = DNA, other=2'-MOE RNA; each "C"is 5-MeC.

[00975] To evaluate UNC13A AON ability to reduce UNC13A cryptic exon levels, antisense oligonucleotides to UNC13A were co-incubated with TDP43 AON in Endoporter in media before addition to the cells. After 72 hours, antisense oligonucleotides and Endoporter were washed out and replaced with fresh media alone. After six additional days, RNA was collected from the 96-well plates for RT-qPCR. RNA was isolated, cDNA generated and multiplexed RT-qPCR assay performed with Taqman probes for UNC13A cryptic exon, and reference GAPDH quantification.

[00976] Transcript levels (e.g., UNC13A cryptic exon, and TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher® TaqMan Gene Expression Assay Hs03929097_g1. UNC13a cryptic exon was detected using custom sequences.

UNC13a Cryptic Exon:

Forward Primer: ATTGTTCTGCACGTCGGT (SEQ ID NO: 10780)

Reverse Primer: GTCTGGGTATGTCTCTTCCAG (SEQ ID NO: 10781)

Probe Sequence: AGTTCTTTCCAGGAAACCCAGGCA (SEQ ID NO: 10782)

[00977] RT-qPCR was performed on Applied Biosystems ® 7500 Real-time PCR systems. One cycle of reverse transcription was performed at a temperature of 50°C for 5 min. One cycle of RT inactivation/initial denaturation was performed at a temperature of 95°C for 20 seconds. Forty five cycles of amplification were performed at a temperature of 95°C for 1 second followed by 60°C for 20 seconds.

[00978] UNC13A-cryptic (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (e.g., % decrease of UNC13A-cryptic), the normalized UNC13A-cryptic signal was further normalized to the vehicle (treated with Endoporter alone, deltadeltaCt). Relative quantity (RQ) of transcript level was calculated using the equation $RQ=2^{-deltadeltaCt}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0). RQ values for UNC13A cryptic were normalized using the following formula:

$$(((RQAON - RQendo)/(RQTDP43- RQendo))*100$$

[00979] Table 36 shows the RT-qPCR results of UNC13A AONs with spacers and performance of UNC13A AONs without spacers in human motor neurons.

[00980] As shown in Table 36, UNC13A AONs (*e.g.*, UNC13A oligonucleotides without spacers or with one or two spacers) were tested for their ability to reduce UNC13A transcripts with a cryptic exon. In some cases, UNC13A AONs with spacers reduced UNC13A cryptic exon levels. In some cases, UNC13A AONs without spacers reduced UNC13A cryptic exon levels. Specific AON sequences are labeled according to their corresponding SEQ ID NO.

[00981] As shown in Table 36, a 200 nM dose of SEQ ID NO: 4803 (GAGACATACCCAGACACAAACGGCC with no spacers) reduced UNC13A cryptic exon levels to 4.4%. A 50 nM dose of SEQ ID NO: 4803 (GAGACATACCCAGACACAAACGGCC with no spacers) reduced UNC13A cryptic exon levels to 20.3%.

[00982] As shown in Table 36, a 200 nM dose of SEQ ID NO: 7361 (GTTCTTTCCAGGAAACCCAGGCA with no spacers) reduced UNC13A cryptic exon levels to 5.1%. A 50 nM dose of SEQ ID NO: 7361 (GTTCTTTCCAGGAAACCCAGGCA with no spacers) reduced UNC13A cryptic exon levels to 26.0%.

[00983] As shown in Table 36, a 200 nM dose of SEQ ID NO: 9686 (GTTCTTTSCAGGAAASCCAGGCA with two spacers) reduced UNC13A cryptic exon levels to 6.6%. A 50 nM dose of SEQ ID NO: 9686 (GTTCTTTSCAGGAAASCCAGGCA with two spacers) reduced UNC13A cryptic exon levels to 41.2%.

[00984] As shown in Table 36, a 200 nM dose of SEQ ID NO: 9670 (GCAGCTGGSAGAGACATASCCAGAC with two spacers) reduced UNC13A cryptic exon levels to 8.3%. A 50 nM dose of SEQ ID NO: 9670 (GCAGCTGGSAGAGACATASCCAGAC with two spacers) reduced UNC13A cryptic exon levels to 31.0%.

[00985] As shown in Table 36, a 200 nM dose of SEQ ID NO: 4833 (GTTCTTTCCAGGAAACCCAGGCAGC with no spacers) reduced UNC13A cryptic exon levels to 8.8%. A 50 nM dose of SEQ ID NO: 4833 (GTTCTTTCCAGGAAACCCAGGCAGC with no spacers) reduced UNC13A cryptic exon levels to 35.4%.

[00986] As shown in Table 36, a 200 nM dose of SEQ ID NO: 9655 (GCAGCTSGAAGAGACATASCCAGAC with two spacers) reduced UNC13A cryptic exon levels to 11.8%. A 50 nM dose of SEQ ID NO: 9655 (GCAGCTSGAAGAGACATASCCAGAC with two spacers) reduced UNC13A cryptic exon levels to 30.6%.

[00987] As shown in Table 36, a 200 nM dose of SEQ ID NO: 4813 (GCAGCTGGAAGAGACATACCCAGAC with no spacers) reduced UNC13A cryptic exon levels to 13.8%. A 50 nM dose of SEQ ID NO: 4813 (GCAGCTGGAAGAGACATACCCAGAC with no spacers) reduced UNC13A cryptic exon levels to 66.0%.

[00988] As shown in Table 36, a 200 nM dose of SEQ ID NO: 7360 (TTCTTTCCAGGAAACCCAGGCAG with no spacers) reduced UNC13A cryptic exon levels to 15.2%. A 50 nM dose of SEQ ID NO: 7360 (TTCTTTCCAGGAAACCCAGGCAG with no spacers) reduced UNC13A cryptic exon levels to 34.4%.

[00989] As shown in Table 36, a 200 nM dose of SEQ ID NO: 8115 (ACATCCATCCATCCATCCATTCA with no spacers) reduced UNC13A cryptic exon levels to 15.8%. A 50 nM dose of SEQ ID NO: 8115 (ACATCCATCCATCCATCCATTCA with no spacers) reduced UNC13A cryptic exon levels to 45.4%.

[00990] As shown in Table 36, a 200 nM dose of SEQ ID NO: 9685 (TCTTTCCSGGAAACCSAGGCAGC with two spacers) reduced UNC13A cryptic exon levels to 18.2%. A 50 nM dose of SEQ ID NO: 9685 (TCTTTCCSGGAAACCSAGGCAGC with two spacers) reduced UNC13A cryptic exon levels to 41.9%.

[00991] As shown in Table 36, a 200 nM dose of SEQ ID NO: 9687 (TTCTTTCSAGGAAACSCAGGCAG with two spacers) reduced UNC13A cryptic exon levels to 20.1%. A 50 nM dose of SEQ ID NO: 9687 (TTCTTTCSAGGAAACSCAGGCAG with two spacers) reduced UNC13A cryptic exon levels to 42.8%.

[00992] As shown in Table 36, a 200 nM dose of SEQ ID NO: 5589 (ACACATCCATCCATCCATCCATTCA with no spacers) reduced UNC13A cryptic exon levels to 23.1%. A 50 nM dose of SEQ ID NO: 5589 (ACACATCCATCCATCCATCCATTCA with no spacers) reduced UNC13A cryptic exon levels to 50.2%.

[00993] As shown in Table 36, a 200 nM dose of SEQ ID NO: 7359 (TCTTTCCAGGAAACCCAGGCAGC with no spacers) reduced UNC13A cryptic exon levels to 25%. A 50 nM dose of SEQ ID NO: 7359 (TCTTTCCAGGAAACCCAGGCAGC with no spacers) reduced UNC13A cryptic exon levels to 40.6%.

[00994] As shown in Table 36, a 200 nM dose of SEQ ID NO: 4799 (CATACCCAGACACAAACGGCCCAAT with no spacers) reduced UNC13A cryptic exon levels to 27.2%. A 50 nM dose of SEQ ID NO: 4799 (CATACCCAGACACAAACGGCCCAAT with no spacers) reduced UNC13A cryptic exon levels to 43.4%.

[00995] As shown in Table 36, a 200 nM dose of SEQ ID NO: 5672 (CTCTTTTATCCATCCACACACCCAC with no spacers) reduced UNC13A cryptic exon levels to 34.4%. A 50 nM dose of SEQ ID NO: 5672 (CTCTTTTATCCATCCACACACCCAC with no spacers) reduced UNC13A cryptic exon levels to 64.3%.

[00996] As shown in Table 36, a 200 nM dose of SEQ ID NO: 8200 (CTCTTTTATCCATCCACACACCC with no spacers) reduced UNC13A cryptic exon levels to 40.5%. A 50 nM dose of SEQ ID NO: 8200 (CTCTTTTATCCATCCACACACCC with no spacers) reduced UNC13A cryptic exon levels to 82.2%.

[00997] As shown in Table 36, a 200 nM dose of SEQ ID NO: 4831 (TCTTTCCAGGAAACCCAGGCAGCTG with no spacers) reduced UNC13A cryptic exon levels to 41.6%. A 50 nM dose of SEQ ID NO: 4831 (TCTTTCCAGGAAACCCAGGCAGCTG with no spacers) reduced UNC13A cryptic exon levels to 54.2%.

[00998] As shown in Table 36, a 200 nM dose of SEQ ID NO: 9695 (GAAAGTGSCATGGAGSGTGCAAG with two spacers) reduced UNC13A cryptic exon levels to 42.0%. A 50 nM dose of SEQ ID NO: 9695 (GAAAGTGSCATGGAGSGTGCAAG with two spacers) reduced UNC13A cryptic exon levels to 54.0%.

[00999] As shown in Table 36, a 200 nM dose of SEQ ID NO: 10670 (ATCTACSCTTTTATCCATSCACACA with two spacers) reduced UNC13A cryptic exon levels to 44.5%. A 50 nM dose of SEQ ID NO: 10670 (ATCTACSCTTTTATCCATSCACACA with two spacers) reduced UNC13A cryptic exon levels to 45.5%.

[001000] As shown in Table 36, a 200 nM dose of SEQ ID NO: 5677 (ATCTACTCTTTTATCCATCCACACA with no spacers) reduced UNC13A cryptic exon levels to 46.4%. A 50 nM dose of SEQ ID NO: 5677 (ATCTACTCTTTTATCCATCCACACA with no spacers) reduced UNC13A cryptic exon levels to 69.7%.

[001001] As shown in Table 36, a 200 nM dose of SEQ ID NO: 8177 (ACACATCCATCCATCCATCCATT with no spacers) reduced UNC13A cryptic exon levels to 47.8%.

[001002] As shown in Table 36, a 200 nM dose of SEQ ID NO: 10671 (CTACTCTSTTATCCASCCACACA with two spacers) reduced UNC13A cryptic exon levels to 48.1%. A 50 nM dose of SEQ ID NO: 10671 (CTACTCTSTTATCCASCCACACA with two spacers) reduced UNC13A cryptic exon levels to 76.5%.

[001003] As shown in Table 36, a 200 nM dose of SEQ ID NO: 10672 (ATCTACTCSTTTATCCATSCACACA with two spacers) reduced UNC13A cryptic exon levels to 48.2%. A 50 nM dose of SEQ ID NO: 10672 (ATCTACTCSTTTATCCATSCACACA with two spacers) reduced UNC13A cryptic exon levels to 62.8%.

[001004] As shown in Table 36, a 200 nM dose of SEQ ID NO: 10673 (CTTTCAGSAATTCAASCACACAT with two spacers) reduced UNC13A cryptic exon levels to 49.6%. A 50 nM dose of SEQ ID NO: 10673 (CTTTCAGSAATTCAASCACACAT with two spacers) reduced UNC13A cryptic exon levels to 70.9%.

[001005] As shown in Table 36, a 200 nM dose of SEQ ID NO: 3774 (AAGTGTCATGGAGAGTGCAAGGG with no spacers) reduced UNC13A cryptic exon levels to 49.8%. A 50 nM dose of SEQ ID NO: 3774 (AAGTGTCATGGAGAGTGCAAGGG with no spacers) reduced UNC13A cryptic exon levels to 67.0%.

ɔle 36. Performance of Exemplary UNC13A AONs evaluated in human derived iPSC motor neurons

SEQ ID NO:	Oligonucleotide Sequence* (where S indicates presence of a Spacer) (5' → 3')	QPCR potency		QPCR potency	
		200 nM	200 nM	50 nM	50 nM
		Normalized UNC13A Cryptic Exon	SD Normalized UNC13A Cryptic Exon	Normalized UNC13A Cryptic Exon	SD Normalized UNC13A Cryptic Exon
4803	GAGACATACCCAGACACAAACGGCC	4.38	4.41	20.3	14.4
7361	GTTCTTTCCAGGAAACCCAGGCA	5.11	4.14	26	15.2
9686	GTTCTTTSCAGGAAASCCAGGCA	6.62	6.06	41.2	15.2
9670	GCAGCTGGSAGAGACATASCCAGAC	8.3	7.86	31	26.4
4833	GTTCTTTCCAGGAAACCCAGGCAGC	8.84	7.85	35.4	22.4
9655	GCAGCTSGAAGAGACATASCCAGAC	11.8	10.7	30.6	13
4813	GCAGCTGGAAGAGACATACCCAGAC	13.8	7.11	66	45.9
7360	TTCTTTCCAGGAAACCCAGGCAG	15.2	7.39	34.4	25.1
8115	ACATCCATCCATCCATCCATTCA	15.8	8.84	45.4	14
9685	TCTTTCCSGGAAACCSAGGCAGC	18.2	9.18	41.9	24.2
9687	TTCTTTCSAGGAAACSCAGGCAG	20.1	9.33	42.8	27.7
5589	ACACATCCATCCATCCATCCATTCA	23.1	15.7	50.2	21.5
7359	TCTTTCCAGGAAACCCAGGCAGC	25	11.7	40.6	22.9
4799	CATACCCAGACACAAACGGCCCAAT	27.2	20.6	43.4	28
5672	CTCTTTTATCCATCCACACACCCAC	34.4	20.1	64.3	34.7
8200	CTCTTTTATCCATCCACACACCC	40.5	15.2	82.2	45.5

4831	TCTTTCCAGGAAACCCAGGCAGCTG	41.6	30.5	54.2	20.8
9695	GAAAGTGSCATGGAGSGTGCAAG	42	38.1	54	32.5
10670	ATCTACSCTTTTATCCATSCACACA	44.5	22.4	45.5	34.4
5677	ATCTACTCTTTTATCCATCCACACA	46.4	29.9	69.7	47.6
8177	ACACATCCATCCATCCATCCATT	47.8	24.9	122	41.9
10671	CTACTCTSTTATCCASCCACACA	48.1	35.4	76.5	37.9
10672	ATCTACTCSTTTATCCATSCACACA	48.2	21.5	62.8	44.3
10673	CTTTCAGSAATTCAASCACACAT	49.6	39.2	70.9	46.3
3774	AAGTGTCATGGAGAGTGCAAGGG	49.8	39.3	67	59.7
8116	CACATCCATCCATCCATCCATTC	51.6	14.2	80.3	41.4
4778	CAATCCTGAGTGGTTAGGGCTGGAA	54.2	18.8	59.6	16.2
4793	CAGACACAAACGGCCCAATCCTGAG	54.4	19.2	73.2	43.7
8198	CTTTTATCCATCCACACACCCAC	55.4	30.5	59	34.2
8199	TCTTTTATCCATCCACACACCCA	55.7	29.2	61.1	45.6
10674	CTCTTTTSTCCATCCSCACACCC	55.9	29.8	83.8	50.9
7092	GGGCAGGCAGGAATGGTGAGTGG	56.6	41	73.6	47.2
9671	TCCACCAGSCACTCACAASCATCCA	58	17.7	86.1	36.5
5654	CACCCACCCATCTAACTACCCCAAA	58.2	42.7	91	34.4
7091	GGCAGGCAGGAATGGTGAGTGGA	59.1	43.9	57.9	41.1
10675	TCTTTTASCCATCCASACACCCA	63.1	23.5	54.3	40.7
8182	CACCCACCCATCTAACTACCCCA	63.1	44.6	74.3	51.2

9696	AAAGTGTSATGGAGASTGCAAGG	63.7	39.2	55.5	53
10676	TGCAATASTTCAACCSCACATCC	64.1	25.7	75.7	42.9
9668	GGGCAGGCSGGAATGGTGSGTGGAA	64.2	32	73	39
4564	GGGCAGGCAGGAATGGTGAGTGGAA	64.6	42.2	91.2	48.4
9675	GGCAGGCSGGAATGGSGAGTGGA	64.6	49.5	92.8	65
10677	CTCTTTSATCCATCCACASACCCAC	65.1	34.1	53	32.2
3775	AAAGTGTCATGGAGAGTGCAAGG	65.3	45.4	71.2	64.2
10678	CAGTAATSCAACCACSCATCCAT	65.5	23.7	92.7	24.1
10679	CTCTTTTASCCATCCACASACCCAC	65.6	37.8	67.8	29.5
8203	CTACTCTTTTATCCATCCACACA	67.1	32	50.5	34
5608	ACCTTTCAGTAATTCAACCACACAT	67.5	52.3	87.4	58
8306	GAAAGTGTCATGGAGAGTGCAAG	68.3	52.7	52.7	38.7
10680	CTTTTATSCATCCACSCACCCAC	68.7	58.9	59.2	33.2
10681	ACCTTTCASTAATTCAACSACACAT	69.2	35.5	115	79.8
9683	ACACAAASGGCCCAASCCTGAGT	69.3	54.9	114	67.4
9692	CACCCACSCATCTAASTACCCCA	71.4	65.7	111	77.3
10682	AGTAATTSAACCACASATCCATC	72	16	58	21.7
9694	AAGTGTCSTGGAGAGSGCAAGGG	72.1	51.9	70.7	59.6
7318	ACACAAACGGCCCAATCCTGAGT	72.4	18.3	99.8	34.6
7916	TGCAATAGTTCAACCACACATCC	74	35.8	124	53.6
8134	CTTTCAGTAATTCAACCACACAT	74.1	39.5	65.7	57.3

4790	ACACAAACGGCCCAATCCTGAGTGG	74.3	16.6	109	53.2
4774	CCTGAGTGGTTAGGGCTGGAATAGA	75.2	42.7	92.4	35.7
8135	CCTTTCAGTAATTCAACCACACA	76.2	42.9	145	138
7317	CACAAACGGCCCAATCCTGAGTG	76.8	37.3	91.2	46.8
8181	ACCCACCCATCTAACTACCCCAA	77.1	52.6	87.2	59.1
10683	TCTACTCSTTTATCCSTCCACAC	78.2	43.6	88.6	71.7
9684	CACAAACSGCCCAATSCTGAGTG	78.2	45.6	86.8	45.4
9682	ACAAACGSCCCAATCSTGAGTGG	78.3	38.8	66.1	35
9666	TCCACCSGCCACTCACAASCATCCA	78.7	73.6	120	50.9
8180	CCCACCCATCTAACTACCCCAAA	78.9	50.3	71.8	60.4
9674	GGGCAGGSAGGAATGSTGAGTGG	82.7	67.3	142	100
10684	CTTGCASTAGTTCAACCASACATCC	86	34.4	140	132
10685	ATCTACTSTTTTATCSATCCACA	86.3	55.6	117	68.8
4784	ACGGCCCAATCCTGAGTGGTTAGGG	86.9	44.1	108	78
8077	GATCCGCAACTTAATCCACCTAC	88.3	76.5	115	86.5
9667	GAAAGTSTCATGGAGAGTSCAAGGG	89.6	50.5	107	42.8
8205	ATCTACTCTTTTATCCATCCACA	91.1	60.9	89.8	70.4
7316	ACAAACGGCCCAATCCTGAGTGG	92.9	43.5	78.5	47.3
7090	GCAGGCAGGAATGGTGAGTGGAA	94	74.1	118	82.7
10686	ACCTTTCSGTAATTCSACCACAC	95.2	44.9	60.6	52.1
4642	AGGTAAAGGGAATGGCATGGCGGGC	96	49.3	115	57

8075	TCCGCAACTTAATCCACCTACCC	96	82.6	111	77.3
5778	GAAAGTGTCATGGAGAGTGCAAGGG	96.3	58.9	118	77.8
10687	CTTGCAASAGTTCAASCACACAT	98.9	42.4	90.8	40.8
7918	CTTGCAATAGTTCAACCACACAT	99.5	39	95.7	46.1
9691	CCCACCCSTCTAACTSCCCCAAA	99.7	71.7	112	82.8
10688	CAGTAATTSAACCACACASCCATCC	101	95.2	128	130
7917	TTGCAATAGTTCAACCACACATC	102	54.4	138	55.5
8136	ACCTTTCAGTAATTCAACCACAC	105	105	120	108
10689	GTAATTCSACCACACSTCCATCC	106	60.1	116	48.6
4730	GTAGTGAGAGTCAACCTGGAGGCCA	107	21.8	92.6	27.2
8204	TCTACTCTTTTATCCATCCACAC	107	71.4	83.2	56.9
5790	CACCATGGGAGAGAAAGTGTCATGG	108	103	67.4	60.1
4657	AGGGAGGAGTTTTCCAGGTAAAGGG	109	50.5	95.7	21.4
9673	GCAGGCASGAATGGTSAGTGGAA	109	74.8	150	98.2
9693	ACCCACCSATCTAACSACCCCAA	112	74.4	81.6	45.8
10690	ACACATSCATCCATCCATSCATTCA	114	36.7	135	39.5
10691	TTGCAATSGTTCAACSACACATC	115	54.7	98.6	51.2
9664	AGGGAGSAGTTTTCCAGGSAAAGGG	116	30	110	29.8
10692	ACATCCASCCATCCASCCATTCA	116	50.6	111	38
10693	ACCTTTSAGTAATTCAACSACACAT	116	81.4	101	74.7
9672	GAAAGTGTSATGGAGAGTSCAAGGG	117	40.6	115	66.2

9669	AGGGAGGASTTTTCCAGGSAAAGGG	118	30.4	111	22.7
4725	GAGAGTCAACCTGGAGGCCAAGGTG	118	43.8	96.1	17.9
7909	GTTCAACCACACATCCTTCCATT	119	70.8	186	142
5390	CTTGCAATAGTTCAACCACACATCC	120	57.3	140	70.5
5457	GTCTGTCCACCAGCCACTCACAACC	120	104	154	122
7910	AGTTCAACCACACATCCTTCCAT	121	55	161	77.7
10694	AGTTCAACSACACATCCTSCCATTC	122	71.7	129	96.7
10695	ACACATCSATCCATCSATCCATT	123	40.6	108	40.9
7908	TTCAACCACACATCCTTCCATTC	124	9.97	143	48.5
9681	GAGGAGGSGACCCTGSATCTGGA	124	33.6	117	67.2
7169	GGTAAAGGGAATGGCATGGCGGG	125	50.2	110	68.5
10696	AGTTCAASCACACATSCTTCCAT	125	81.5	142	155
10697	CACATCCSTCCATCCSTCCATTC	128	67	89.1	32
9677	AGGTAAASGGAATGGSATGGCGG	128	77.5	149	85.4
9663	GGGCAGSCAGGAATGGTGSGTGGAA	129	72.2	105	58.4
9689	GATCCGCSACTTAATSCACCTAC	136	111	152	102
8128	GTAATTCAACCACACATCCATCC	137	54	107	52.1
9680	AGAGGAGSTGACCCTSAATCTGG	139	55.6	118	48.1
10698	GTTCAACSACACATCSTTCCATT	145	80.5	138	84.8
8130	CAGTAATTCAACCACACATCCAT	146	47.3	119	22.7
9690	ATCCGCASCTTAATCSACCTACC	147	63.2	132	76.5

7170	AGGTAAAGGGAATGGCATGGCGG	147	82.1	148	92.8
9688	TCCGCAASTTAATCCSCCTACCC	148	97	180	93.3
9679	AGGAGGTSACCCTGASTCTGGAC	149	47.3	101	58.2
10699	AGTTCASCCACACATCCTSCCATTC	149	79	132	60.8
10700	CAGTAASTCAACCACACASCCATCC	149	84.3	116	53.3
5382	AGTTCAACCACACATCCTTCCATTC	151	106	137	114
9678	GGTAAAGSGAATGGCSTGGCGGG	151	111	106	63.6
5602	CAGTAATTCAACCACACATCCATCC	155	85.5	133	58.7
10701	TTCAACCSCACATCCSTCCATTC	156	159	139	80.1
10702	CTTGCAATSGTTCAACCASACATCC	157	99.7	123	77
4572	GAAGAGCTGGGCAGGCAGGAATGGT	158	99.8	160	79.5
5549	GATCCGCAACTTAATCCACCTACCC	161	73	154	72
10703	ACACATCCSTCCATCCATSCATTCA	163	45.7	163	44.5
4733	TGAGTAGTGAGAGTCAACCTGGAGG	164	54.7	108	59.6
4631	ATGGCATGGCGGGCAGTCTCAGAGG	168	99.2	166	76.5
8129	AGTAATTCAACCACACATCCATC	173	58.2	107	51.4
5452	TCCACCAGCCACTCACAACCATCCA	173	134	84.3	45.9
7218	AGGAGGTGACCCTGAATCTGGAC	176	46.2	85.1	44.1
4984	CACGAATCTACCCACCAACTCATCC	178	116	140	49.4
7219	GAGGAGGTGACCCTGAATCTGGA	182	60.1	108	36.8
10704	CCTTTCASTAATTCASCCACACA	182	192	114	61.7

4596	TGTGGATGGTGTGGCCAGAAAGAGG	185	70.1	156	70.7
8076	ATCCGCAACTTAATCCACCTACC	186	58.2	149	63.5
9676	GTAAAGGSAATGGCASGGCGGGC	193	116	161	79.1
5460	TTCGTCTGTCCACCAGCCACTCACA	193	125	119	81.2
5467	TCCATTTTTCGTCTGTCCACCAGCC	196	122	113	51.4
7220	AGAGGAGGTGACCCTGAATCTGG	197	67.6	108	41.2
4692	AGAGGAGGTGACCCTGAATCTGGAC	197	92.2	119	37.6
4607	GGCCAGGAGAGTGTGGATGGTGTGG	200	74.8	162	83.3
7168	GTAAAGGGAATGGCATGGCGGGC	205	79.8	80	52
4645	TCCAGGTAAAGGGAATGGCATGGCG	215	102	149	127
4638	AAAGGGAATGGCATGGCGGGCAGTC	226	99.9	178	113
4807	GGAAGAGACATACCCAGACACAAAC	0.02	0.00	11.43	6.56
4812	CAGCTGGAAGAGACATACCCAGACA	0.03	0.02	16.20	7.83
4806	GAAGAGACATACCCAGACACAAACG	0.94	1.59	0.61	1.01
4836	AGAGTTCTTTCCAGGAAACCCAGGC	1.47	2.28	19.61	9.44
4837	AAGAGTTCTTTCCAGGAAACCCAGG	3.01	2.16	21.95	5.43
4835	GAGTTCTTTCCAGGAAACCCAGGCA	3.49	2.07	29.80	2.76
4834	AGTTCTTTCCAGGAAACCCAGGCAG	3.62	3.79	38.61	18.71
4815	AGGCAGCTGGAAGAGACATACCCAG	4.63	5.37	32.99	2.70
4804	AGAGACATACCCAGACACAAACGGC	5.98	6.18	12.51	6.77
4809	CTGGAAGAGACATACCCAGACACAA	6.26	10.82	58.24	12.87

4805	AAGAGACATACCCAGACACAAACGG	9.32	5.24	16.02	3.73
4802	AGACATACCCAGACACAAACGGCCC	12.07	2.14	29.94	15.81
4814	GGCAGCTGGAAGAGACATACCCAGA	12.92	4.64	50.87	17.93
4816	CAGGCAGCTGGAAGAGACATACCCA	14.04	2.17	32.22	17.05
4810	GCTGGAAGAGACATACCCAGACACA	15.74	19.34	36.35	14.55
4811	AGCTGGAAGAGACATACCCAGACAC	18.82	10.27	20.31	17.71
4813	GCAGCTGGAAGAGACATACCCAGAC	18.87	22.30	55.59	34.27
4801	GACATACCCAGACACAAACGGCCCA	19.96	11.08	28.25	4.42
4803	GAGACATACCCAGACACAAACGGCC	21.01	9.29	26.91	8.72
5587	ACATCCATCCATCCATCCATTCATC	21.36	5.97	63.61	8.59
5588	CACATCCATCCATCCATCCATTCAT	23.52	1.80	108.40	54.14
4817	CCAGGCAGCTGGAAGAGACATACCC	25.02	3.34	60.96	5.29
5585	ATCCATCCATCCATCCATTCATCCA	25.59	10.98	86.98	36.11
5589	ACACATCCATCCATCCATCCATTCA	27.76	4.11	72.26	37.32
4832	TTCTTTCCAGGAAACCCAGGCAGCT	30.66	1.40	86.91	11.41
4831	TCTTTCCAGGAAACCCAGGCAGCTG	31.13	5.45	52.43	7.09
5586	CATCCATCCATCCATCCATTCATCC	35.45	4.51	75.99	10.37
5590	CACACATCCATCCATCCATCCATTC	38.25	19.28	96.63	22.67
4800	ACATACCCAGACACAAACGGCCCAA	38.57	4.68	44.89	1.89
5592	ACCACACATCCATCCATCCATCCAT	39.40	7.68	71.32	18.18
5591	CCACACATCCATCCATCCATCCATT	39.80	8.88	77.72	2.82

5593	AACCACACATCCATCCATCCATCCA	41.07	10.10	97.41	24.31
4830	CTTTCCAGGAAACCCAGGCAGCTGG	42.16	22.26	77.70	9.85
4829	TTTCCAGGAAACCCAGGCAGCTGGA	51.84	9.47	72.21	10.14
4799	CATACCCAGACACAAACGGCCCAAT	60.89	6.26	84.01	23.09

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 36 are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC) , and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

Example 13: Methods for Evaluating UNC13A Antisense Oligonucleotides

[001006] UNC13A antisense oligonucleotides were evaluated in iPSC derived human motor neurons (hMN). The cells were seeded in 96-well plates at a density of 40,000 cells / well. Antisense oligonucleotide (AON) to TDP43 was transfected with Endoporter (Gene Tools, Philomath, OR, USA) to decrease expression of the full length UNC13A transcript and increase expression of UNC13A cryptic exon. Vehicle control consisted of motor neuron treatment with Endoporter alone. Positive controls included cells that were treated with TDP43 AON alone ("AON TDP43" or "TDP43 AON").

[001007] TDP43 AON is a gapmer oligonucleotide and has the following sequence and chemistry: 5' A*A*G*G*C*T*T*C*A*T*A*T*T*G*T*A*C*T*T*T 3' (SEQ ID NO: 1669) where * = phosphorothioate, underlined = DNA, other=2'-MOE RNA;each "C"is 5-MeC.

[001008] To evaluate UNC13A AON ability to reduce UNC13A cryptic exon levels, antisense oligonucleotides to UNC13A were co-incubated with TDP43 AON in Endoporter in media before addition to the cells. After 72 hours, antisense oligonucleotides and Endoporter were washed out and replaced with fresh media alone. After six additional days, RNA was collected from the 96-well plates for RT-qPCR. RNA was isolated, cDNA generated and multiplexed RT-qPCR assay performed with Taqman probes for UNC13A cryptic exon, and reference GAPDH quantification.

[001009] Transcript levels (e.g., UNC13A cryptic exon, and TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher® TaqMan Gene Expression Assay Hs03929097_g1. UNC13a cryptic exon was detected using custom sequences.

UNC13a Cryptic Exon:

Forward Primer: ATTGTTCTGCACGTCGGT (SEQ ID NO: 10780)

Reverse Primer: GTCTGGGTATGTCTCTTCCAG (SEQ ID NO: 10781)

Probe Sequence: AGTTCTTTCCAGGAAACCCAGGCA (SEQ ID NO: 10782)

[001010] To evaluate UNC13A AON ability to reduce UNC13A correctly spliced (CS)exon junction 20/21 levels, antisense oligonucleotides to UNC13A were co-incubated with TDP43 AON in Endoporter in media before addition to the cells. After 72 hours, antisense oligonucleotides and Endoporter were washed out and replaced with fresh media alone. After six additional days, RNA was collected from the 96-well plates for RT-qPCR. RNA was isolated, cDNA generated and multiplexed RT-qPCR assay performed with Taqman probes for UNC13A CS exon 20/21 junction, and reference GAPDH quantification.

[001011] Transcript levels (e.g., UNC13A exon junction 20/21, and TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher® TaqMan Gene Expression Assay Hs03929097_g1. UNC13a exon 20/21 junction was detected using TaqMan Gene Expression Assay Hs01000584_m1.

[001012] RT-qPCR was performed on Applied Biosystems ® 7500 Real-time PCR systems. One cycle of reverse transcription was performed at a temperature of 50°C for 5 min. One cycle of RT inactivation/initial denaturation was performed at a temperature of 95°C for 20 seconds. Forty five cycles of amplification were performed at a temperature of 95°C for 1 second followed by 60°C for 20 seconds.

[001013] UNC13A-cryptic (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (e.g., % decrease of UNC13A-cryptic), the normalized UNC13A-cryptic signal was further normalized to the vehicle (treated with Endoporter alone, deltadeltaCt). Relative quantity (RQ) of transcript level was calculated using the equation $RQ=2^{-deltadeltaCt}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0). RQ values for UNC13A cryptic were normalized using the following formula:

$$(((RQAON - RQendo)/(RQTDP43- RQendo))*100$$

[001014] Table 37 shows the RT-qPCR results of UNC13A AONs with spacers and performance of UNC13A AONs without spacers in human motor neurons.

[001015] As shown in Tables 37A and 37B, UNC13A AONs (*e.g.*, UNC13A oligonucleotides without spacers or with one or two spacers) were tested for their ability to reduce UNC13A transcripts with a cryptic exon. In some cases, UNC13A AONs with spacers reduced UNC13A cryptic exon levels. In some cases, UNC13A AONs without spacers reduced UNC13A cryptic exon levels. Specific AON sequences are labeled according to their corresponding SEQ ID NO.

[001016] Correctly spliced UNC13A (Ct) was also normalized to GAPDH (deltaCt). To visualize the quantitative changes (e.g., % increase of correctly spliced UNC13A), the normalized correctly spliced UNC13A signal was further normalized to the vehicle (treated with Endoporter alone, deltadeltaCt).

[001017] Relative quantity (RQ) of transcript level was calculated using the equation RQ=2^(-deltadeltaCt) and is used to describe the treatment condition comparison to normal, healthy levels (1.0). RQ values for UNC13A corrected splicing were normalized using the following formula:

$$(((RQAON - RQTDP43)/(RQendo-RQTDP43))*100$$

Table 37A. Exemplary UNC13A AONs evaluated in human derived iPSC motor neurons

SEQ ID NO:	**Oligonucleotide Sequence*(5' to 3')**
10705	GAGACAT(S1)CCCAGAC(S1)CAAACGG
10706	GACATAC(S1)CAGACAC(S1)AACGGCC
10707	AGACATA(S1)CCAGACA(S1)AAACGGC
10708	GAGACAT(S#)CCCAGAC(S#)CAAACGG
10709	GACATAC(S#)CAGACAC(S#)AACGGCC
10710	AGACATA(S#)CCAGACA(S#)AAACGGC
10711	AGACATASCCAGACASAAACGGC
10712	GACATACSCAGACACSAACGGCC
10713	GAGACATSCCCAGACSCAAACGG
10714	GAGACATASCCAGACACASACGGCC
10715	GAGACASACCCAGACACASACGGCC
7330	AGACATACCCAGACACAAACGGC
7329	GACATACCCAGACACAAACGGCC
7331	GAGACATACCCAGACACAAACGG
10716	AAGAGACSTACCCAGSCACAAAC
10717	AGAGACASACCCAGASACAAACG
10718	GAAGAGASATACCCASACACAAA
10719	GAAGAGACSTACCCAGACSCAAACG
10720	GAAGAGSCATACCCAGACSCAAACG
7333	AAGAGACATACCCAGACACAAAC
7332	AGAGACATACCCAGACACAAACG
7334	GAAGAGACATACCCAGACACAAA
4806	GAAGAGACATACCCAGACACAAACG
10721	CAGCTGGSAGAGACASACCCAGA
10722	AGCTGGASGAGACATSCCCAGAC
10723	GCAGCTGSAAGAGACSTACCCAG
7340	CAGCTGGAAGAGACATACCCAGA
7339	AGCTGGAAGAGACATACCCAGAC
7341	GCAGCTGGAAGAGACATACCCAG
10724	GGCAGCTSGAAGAGASATACCCA
10725	AGGCAGCSGGAAGAGSCATACCC
10726	AGGCAGCTSGAAGAGACASACCCAG
10727	AGGCAGSTGGAAGAGACASACCCAG
10723	GCAGCTGSAAGAGACSTACCCAG
7342	GGCAGCTGGAAGAGACATACCCA
7343	AGGCAGCTGGAAGAGACATACCC
7341	GCAGCTGGAAGAGACATACCCAG
4815	AGGCAGCTGGAAGAGACATACCCAG
10724	TCTTTCC(S1)GGAAACC(S1)AGGCAGC
10725	GTTCTTT(S1)CAGGAAA(S1)CCAGGCA
10726	TTCTTTC(S1)AGGAAAC(S1)CAGGCAG
10727	TCTTTCC(S#)GGAAACC(S#)AGGCAGC
10728	GTTCTTT(S#)CAGGAAA(S#)CCAGGCA
10729	TTCTTTC(S#)AGGAAAC(S#)CAGGCAG
10730	GTTCTTTCSAGGAAACCCSGGCAGC

10731	GTTCTTSCCAGGAAACCCSGGCAGC
10732	TCTTTCCAGGAAACC
10733	CAGGAAACCCAGGCA
10734	TCTTTCCAGGAAACCC
10735	CCAGGAAACCCAGGCA
10736	TCTTTCCAGGAAACCCA
10737	TCCAGGAAACCCAGGCA
10738	TCTTTCCAGGAAACCCAG
10739	TTCCAGGAAACCCAGGCA
10740	TCTTTCCAGGAAACCCAGG
10741	TTTCCAGGAAACCCAGGCA
10742	TCTTTCCAGGAAACCCAGGC
10743	CTTTCCAGGAAACCCAGGCA
10744	GAGTTCTSTCCAGGASACCCAGG
10755	AGTTCTTSCCAGGAASCCCAGGC
10756	AGAGTTCSTTCCAGGSAACCCAG
10757	AGAGTTCTSTCCAGGAAASCCAGGC
10758	AGAGTTSTTTCCAGGAAASCCAGGC
7363	GAGTTCTTTCCAGGAAACCCAGG
7362	AGTTCTTTCCAGGAAACCCAGGC
7364	AGAGTTCTTTCCAGGAAACCCAG
4836	AGAGTTCTTTCCAGGAAACCCAGGC
10759	CACATCC(S1)TCCATCC(S1)TCCATTC
10760	ACACATC(S1)ATCCATC(S1)ATCCATT
10761	ACATCCA(S1)CCATCCA(S1)CCATTCA
10762	CACATCC(S#)TCCATCC(S#)TCCATTC
10763	ACACATC(S#)ATCCATC(S#)ATCCATT
10764	ACATCCA(S#)CCATCCA(S#)CCATTCA
10765	GCAGCTS[LNA-G]AAGAGACATAS[LNA-C]CAGAC
10766	GCAGC[LNA-T]SGAAGAGACATAS[LNA-C]CAGAC
10767	GCAGC[LNA-T]SGAAGAGACAT[LNA-A]SCCAGAC
10768	GCA[LNA-G]CTSGAAGA[LNA-G]ACATASCC[LNA-A]GAC
10769	GCA[LNA-G]CTSGAAGAGACATASCC[LNA-A]GAC
10770	GCAGCTGGS[LNA-A]GAGACATAS[LNA-C]CAGAC
10771	GCAGCTG[LNA-G]SAGAGACATAS[LNA-C]CAGAC
10772	GCAGCTG[LNA-G]SAGAGACAT[LNA-A]SCCAGAC
10773	GCA[LNA-G]CTGGSAGA[LNA-G]ACATASCC[LNA-A]GAC
10774	GCA[LNA-G]CTGGSAGAGACATASCC[LNA-A]GAC
10775	GTTCTTTS[LNA-C]AGGAAAS[LNA-C]CAGGCA
10776	GTTCTT[LNA-T]SCAGGAAAS[LNA-C]CAGGCA
10777	GTTCTT[LNA-T]SCAGGAA[LNA-A]SCCAGGCA
10778	GTT[LNA-C]TTTSCAG[LNA-G]AAASCCA[LNA-G]GCA
10779	GTT[LNA-C]TTTSCAGGAAASCCA[LNA-G]GCA

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 37A are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer, as indicated by any of S, S1, or S#, is not a nucleoside. S represents a spacer

of Formula (Iia') as disclosed herein. S1 represents a spacer of Formula (IIIa'); S# represents a spacer of Formula (IIib'). [LNA-X] refers to a locked nucleic acid with a corresponding base X (e.g., LNA-A refers to a locked nucleic acid with an adenine nucleobase, LNA-G refers to a locked nucleic acid with a guanine nucleobase, LNA-T refers to a locked nucleic acid with a thymine nucleobase, and LNA-C refers to a locked nucleic acid with a 5-methylcytosine nucleobase).

Table 37B. Performance of Exemplary UNC13A AONs evaluated in human derived iPSC motor neurons

		UNC13A Corrected Splicing Normalized Rq				UNC13A Cryptic Splicing Normalized Rq			
		200nM		50nM		200nM		50nM	
SEQ ID NO:	Oligonucleotide Sequence* (5' to 3')	Mean	STD	Mean	STD	Mean	STD	Mean	STD
4806	GAAGAGACATACCCAGACACAAACG	41.82	18.84	-27.56	73.08	3.16	1.03	18.87	12.38
7334	GAAGAGACATACCCAGACACAAA	8.93	7.32	-7.13	7.81	15.78	7.41	42.31	31.11
7333	AAGAGACATACCCAGACACAAAC	-28.45	72.83	-12.62	12.84	12.06	9.62	57.27	34.91
7332	AGAGACATACCCAGACACAAACG	13.03	15.19	9.48	11.41	14.78	6.73	61.44	25.31
7331	GAGACATACCCAGACACAAACGG	28.03	29.67	7.69	35.17	18.53	10.52	33.25	20.41
7330	AGACATACCCAGACACAAACGGC	24.21	33.06	23.24	30.63	29.74	33.32	50.76	39.49
7329	GACATACCCAGACACAAACGGCC	2.47	35.11	2.89	26.90	26.29	25.67	46.66	32.30
4815	AGGCAGCTGGAAGAGACATACCCAG	47.19	57.85	15.52	30.16	2.07	3.30	13.45	13.12
7343	AGGCAGCTGGAAGAGACATACCC	37.80	13.72	1.51	9.33	2.32	3.41	22.31	14.52
7342	GGCAGCTGGAAGAGACATACCCA	39.83	25.50	19.20	21.74	7.01	5.73	25.13	28.23
7341	GCAGCTGGAAGAGACATACCCAG	43.08	23.32	4.48	7.87	5.11	6.91	32.17	23.76
7340	CAGCTGGAAGAGACATACCCAGA	-21.34	16.48	-144.30	28.86	7.59	6.87	21.20	16.74
7339	AGCTGGAAGAGACATACCCAGAC	-173.70	29.80	-75.73	8.72	4.20	7.60	165.20	96.22
10723	GCAGCTGSAAGAGACSTACCCAG	64.46	20.00	-11.79	20.17	2.34	1.77	17.01	6.37
10721	CAGCTGGSAGAGACASACCCAGA	87.01	8.70	28.35	13.19	5.72	3.41	22.86	10.45
10731	GTTCTTSCCAGGAAACCCSGGCAGC	-8.32	3.39	-10.50	8.45	29.49	14.34	51.95	12.36
10730	GTTCTTTCSAGGAAACCCSGGCAGC	6.29	22.23	6.58	3.64	8.10	5.42	28.87	7.85
10756	AGAGTTCSTTCCAGGSAACCCAG	61.99	21.81	-24.46	58.00	12.82	3.63	55.05	18.66
10744	GAGTTCTSTCCAGGASACCCAGG	38.47	29.10	-14.70	48.97	17.11	11.96	80.63	36.03
10755	AGTTCTTSCCAGGAASCCCAGGC	9.90	25.86	-7.31	26.47	26.33	9.18	92.35	32.38
10758	AGAGTTSTTTCCAGGAAASCCAGGC	44.52	32.61	57.40	14.54	9.44	4.83	22.79	6.99
10757	AGAGTTCTSTCCAGGAAASCCAGGC	44.46	8.40	48.23	22.36	3.31	2.76	14.18	10.22

10713	GAGACATSCCCAGACSCAAACGG	84.50	29.82	47.59	10.35	31.74	13.09	79.61	17.53
10711	AGACATASCCAGACASAAACGGC	90.95	10.72	22.20	40.15	30.38	13.73	82.12	14.48
10712	GACATACSCAGACACSAACGGCC	73.81	41.97	36.23	29.75	22.06	9.58	70.87	9.37
5245	GAGACASACCCAGACACASACGGCC	80.40	19.16	23.13	19.81	31.05	15.73	88.26	28.47
5244	GAGACATASCCAGACACASACGGCC	126.50	25.60	88.00	43.30	17.80	10.45	77.70	25.98
5257	AGGCAGSTGGAAGAGACASACCCAG	96.50	22.07	44.00	25.12	10.88	6.15	35.95	13.92
5256	AGGCAGCTSGAAGAGACASACCCAG	103.10	12.62	66.18	15.49	4.04	2.80	27.84	10.66
5255	AGGCAGCSGGAAGAGSCATACCC	92.83	15.27	58.96	6.90	12.26	4.78	31.13	9.49
5254	GGCAGCTSGAAGAGASATACCCA	82.43	18.79	58.45	12.96	8.83	8.20	37.74	10.12
5252	AGCTGGASGAGACATSCCCAGAC	87.57	8.14	9.59	32.49	7.43	3.22	28.79	15.38
5250	GAAGAGSCATACCCAGACSCAAACG	102.70	14.83	54.28	31.30	29.53	14.04	75.86	28.78
5249	GAAGAGACSTACCCAGACSCAAACG	99.18	24.63	46.29	25.42	22.36	7.32	75.43	35.92
5248	GAAGAGASATACCCASACACAAA	49.24	20.69	21.53	23.44	89.72	39.56	135.70	43.02
5246	AAGAGACSTACCCAGSCACAAAC	28.09	21.14	22.72	15.94	52.17	11.17	112.70	38.44
5247	AGAGACASACCCAGASACAAACG	78.70	27.23	29.31	21.53	29.70	17.53	85.44	19.01
5292	GTT[LNA-C]TTTSCAGGAAASCCA[LNA-G]GCA	25.91	16.04	21.89	19.68	4.99	12.69	17.06	44.28
5291	GTT[LNA-C]TTTSCAG[LNA-G]AAASCCA[LNA-G]GCA	19.94	10.97	10.81	5.00	20.25	27.06	28.08	34.90
5290	GTTCTT[LNA-T]SCAGGAA[LNA-A]SCCAGGCA	8.93	9.25	6.86	7.65	-1.28	1.43	7.60	13.16
5289	GTTCTT[LNA-T]SCAGGAAAS[LNA-C]CAGGCA	0.18	4.96	12.23	11.77	-1.20	1.39	29.03	35.58
5288	GTTCTTTS[LNA-C]AGGAAAS[LNA-C]CAGGCA	14.39	10.91	10.40	7.95	6.29	12.97	21.83	31.86
5287	GCA[LNA-G]CTGGSAGAGACATASCC[LNA-A]GAC	-10.22	30.13	29.91	20.97	11.14	21.19	6.45	7.80
5286	GCA[LNA-G]CTGGSAGA[LNA-G]ACATASCC[LNA-A]GAC	10.40	16.54	5.17	18.78	12.36	10.45	32.23	21.90
5285	GCAGCTG[LNA-G]SAGAGACAT[LNA-A]SCCAGAC	0.57	12.49	-14.07	16.60	7.76	8.69	16.24	14.15
5284	GCAGCTG[LNA-G]SAGAGACATAS[LNA-C]CAGAC	-6.16	17.10	7.57	18.74	14.62	9.19	46.32	24.49
5283	GCAGCTGGS[LNA-A]GAGACATAS[LNA-C]CAGAC	18.14	16.98	9.28	26.20	8.90	6.17	40.24	12.47
5292	GTT[LNA-C]TTTSCAGGAAASCCA[LNA-G]GCA	4.16	16.50	4.89	11.13	15.39	21.60	19.66	21.58
5291	GTT[LNA-C]TTTSCAG[LNA-G]AAASCCA[LNA-G]GCA	-0.74	10.05	1.42	8.15	11.70	16.06	52.88	33.79
5290	GTTCTT[LNA-T]SCAGGAA[LNA-A]SCCAGGCA	-3.14	10.20	0.93	12.63	11.03	12.72	21.48	26.72
5289	GTTCTT[LNA-T]SCAGGAAAS[LNA-C]CAGGCA	0.43	5.96	0.99	9.62	6.88	15.65	39.99	36.29

5288	GTTCTTTS[LNA-C]AGGAAAS[LNA-C]CAGGCA	-6.06	6.61	-11.46	10.35	6.58	11.97	20.12	30.75
10711	AGACATASCCAGACASAAACGGC	37.10	22.45	53.64	15.42	43.13	22.30	79.66	21.62
10712	GACATACSCAGACACSAACGGCC	50.01	21.60	21.58	15.74	67.02	35.41	83.55	61.27
10713	GAGACATSCCCAGACSCAAACGG	49.95	11.51	29.51	6.61	40.47	25.79	143.30	44.64
10707	AGACATA(S1)CCAGACA(S1)AAACGGC	41.00	21.58	27.91	8.85	51.69	49.87	103.79	37.66
10706	GACATAC(S1)CAGACAC(S1)AACGGCC	46.48	5.54	20.34	11.08	9.03	14.52	72.91	57.87
10705	GAGACAT(S1)CCCAGAC(S1)CAAACGG	45.33	8.89	33.99	13.59	23.89	18.73	133.34	42.50
9687	TTCTTTCSAGGAAACSCAGGCAG	11.16	8.04	9.91	7.60	5.90	10.52	94.03	74.88
9686	GTTCTTTSCAGGAAASCCAGGCA	5.10	4.93	-8.11	6.11	12.92	15.28	25.15	25.51
9685	TCTTTCCSGGAAACCSAGGCAGC	10.06	10.19	3.12	11.72	6.96	9.36	26.97	9.87
10726	TTCTTTC(S1)AGGAAAC(S1)CAGGCAG	11.38	11.69	7.69	15.12	11.99	14.32	54.16	41.27
10725	GTTCTTT(S1)CAGGAAA(S1)CCAGGCA	1.44	7.33	-4.17	4.75	9.79	9.57	27.69	15.98
10724	TCTTTCC(S1)GGAAACC(S1)AGGCAGC	7.18	11.81	-11.24	5.27	18.13	13.56	55.71	28.06
10692	ACATCCASCCATCCASCCATTCA	-37.97	26.85	-4.07	52.32	129.74	41.79	122.30	48.42
10695	ACACATCSATCCATCSATCCATT	5.77	35.61	-11.91	27.75	96.81	38.14	111.73	35.15
10697	CACATCCSTCCATCCSTCCATTC	-14.00	37.66	1.96	30.50	159.36	43.66	164.55	47.07
10761	ACATCCA(S1)CCATCCA(S1)CCATTCA	-16.66	14.80	-5.26	26.53	165.82	42.96	151.38	29.35
10760	ACACATC(S1)ATCCATC(S1)ATCCATT	-7.44	24.85	-21.89	16.44	162.48	39.49	116.38	15.71
10759	CACATCC(S1)TCCATCC(S1)TCCATTC	-9.65	36.42	-0.61	27.96	145.25	19.25	132.10	35.74
10814	TCTTTCCAGGAAACCCAGGCA	18.29	17.99	9.91	14.01	16.42	18.29	16.34	9.91
10733	CAGGAAACCCAGGCA	2.74	3.88	2.44	1.85	16.24	2.74	14.66	2.44
10732	TCTTTCCAGGAAACC	12.94	2.00	7.34	7.10	12.75	12.94	12.29	7.34
10735	CCAGGAAACCCAGGCA	0.00	0.00	0.74	1.05	13.49	0.00	16.04	0.74
10734	TCTTTCCAGGAAACCC	17.89	25.30	17.60	2.62	18.82	17.89	15.79	17.60
10737	TCCAGGAAACCCAGGCA	0.00	0.00	1.54	2.17	14.54	0.00	15.41	1.54
10736	TCTTTCCAGGAAACCCA	6.80	9.61	2.79	1.25	12.77	6.80	15.04	2.79
10739	TTCCAGGAAACCCAGGCA	0.70	0.98	0.00	0.00	16.31	0.70	11.42	0.00
10738	TCTTTCCAGGAAACCCAG	19.21	8.43	49.84	70.94	16.89	19.21	19.14	49.84
10741	TTTCCAGGAAACCCAGGCA	0.55	0.78	3.96	5.60	13.97	0.55	12.15	3.96

10740	TCTTTCCAGGAAACCCAGG	11.47	8.56	2.24	3.17	16.52	11.47	15.47	2.24
10743	CTTTCCAGGAAACCCAGGCA	6.60	0.75	1.59	2.25	18.60	6.60	12.55	1.59
10742	TCTTTCCAGGAAACCCAGGC	15.08	15.12	11.29	4.48	15.92	15.08	12.81	11.29

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 37B are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer, as indicated by any of S, S1, or S#, is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein. S1 represents a spacer of Formula (IIIa'); S# represents a spacer of Formula (IIib'). [LNA-X] refers to a locked nucleic acid with a corresponding base X (e.g., LNA-A refers to a locked nucleic acid with an adenine nucleobase, LNA-G refers to a locked nucleic acid with a guanine nucleobase, LNA-T refers to a locked nucleic acid with a thymine nucleobase, and LNA-C refers to a locked nucleic acid with a 5-methylcytosine nucleobase).

Example 14: Design and Selection of SMN2 Oligonucleotides

[001019] SMN2 AONs oligonucleotides that target a SMN2 transcript are designed and tested to identify SMN2 AONs capable of reducing quantity of mis-spliced SMN2 transcripts. Such SMN2 AONs include a subset of the SMN2 oligonucleotide variants represented by any of SEQ ID NOs: 9710-10141. The SMN2 parent oligonucleotides are 25 nucleosides in length. Each of the nucleosides of the SMN2 parent oligonucleotides are modified nucleosides with 2'-MOE sugar moieties, and each "C" is replaced with a 5-MeC. Additionally, each of the internucleoside linkages between the nucleosides of the SMN2 oligonucleotides are phosphorothioate internucleoside linkages.

[001020] Generally, the length of the SMN2 antisense oligonucleotides are 25 oligonucleotide units in length. However, variants of the SMN2 antisense oligonucleotides were also designed with varying lengths (*e.g.*, 23mers). Examples of these variant SMN2 antisense oligonucleotides were designed to include a subset of the sequences of SEQ ID NOs: 9710-10141.

[001021] Table 38: SMN2 AONs (including SMN2 parent oligonucleotides and SMN2 oligonucleotides with two spacers)

SEQ ID No:	Oligonucleotide Sequence* (where S indicates presence of a Spacer) (5' → 3')
10641	ATTCACTTTCATAATGCTGG
10642	GTAAGATTCACTTTCATAATGCTGG
10643	ATTCACTTTCATAATGCTGGCAGAC
10644	GTAAGASTCACTTTCATASTGCTGG
10645	GTAAGATTSACTTTCATASTGCTGG
10646	ATTCACSTTCATAATGCTSGCAGAC
10647	ATTCACTTSCATAATGCTSGCAGAC
10648	AAGATTCACTTTCATAATGCTGG
10649	AAGATTCSCTTTCATSATGCTGG
10650	AGATTCACTTTCATAATGCTGGC
10651	AGATTCASTTTCATASTGCTGGC
9971	GATTCACTTTCATAATGCTGGCA
10783	GATTCACSTTCATAASGCTGGCA
9970	ATTCACTTTCATAATGCTGGCAG

10784	ATTCACTSTCATAATSCTGGCAG

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 38 are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer, as indicated by S, is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

Example 15: Methods for Evaluating SMN2 Antisense Oligonucleotides

[001022] SMN2 antisense oligonucleotides were evaluated in primary human fibroblasts from an SMA patient (NIGMS Human Genetic Cell Repository, Coriell Institute, Camden, New Jersey). The cells were seeded in 96-well plates at a density of 20,000 cells/ well. Antisense oligonucleotide (AON) to SMN2 was transfected into fibroblasts with Endoporter (Gene Tools, Philomath, OR, USA) to increase expression of the full length SMN2 transcript and reduce expression of the Delta7 variant. Vehicle control consisted of cell treatment with Endoporter alone. Positive controls included cells that were treated with AON control alone.

[001023] AON control is a splice switching oligonucleotide and has the following sequence and chemistry:

5' A*T*T*C*A*C*T*T*T*C*A*T*A*A*T*G*C*T*G*G 3' (SEQ ID NO: 9697)

where * = phosphorothioate, underlined = DNA, other=2'-MOE RNA; each "C" is 5-MeC.

[001024] To evaluate SMN2 AON ability to restore SMN2 -FL and reduce the Delta7 transcript, antisense oligonucleotides to SMN2 were co-incubated Endoporter in media before addition to the cells. After 72 hours, antisense oligonucleotides and endoporter were washed out and replaced with fresh media. After 72 additional hours, RNA was collected from the 96-well plates for RT-qPCR. RNA was isolated, cDNA generated and multiplexed RT-qPCR assay performed with taqman probes for SMN2 full length transcript, SMN2 Delta7 transcript, and reference GAPDH quantification.

[001025] Transcript levels (*e.g.*, SMN2 full length transcript or TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher TaqMan Gene Expression Assay Hs03929097_g1. RT-qPCR was performed for detecting SMN2 transcripts using custom Thermofisher TaqMan Gene Expression Assays with the following sequences:

SMN2-FL:

Forward Primer: 5' GCTCACATTCCTTAAATTAAGGAGAAA 3' (SEQ ID NO: 10810)

Reverse Primer: 5' TCCAGATCTGTCTGATCGTTTCTT 3' (SEQ ID NO: 10811)

Probe Sequence: 5' CTGGCATAGAGCAGCACTAAATGACACCAC 3' (SEQ ID NO: 10812)

SMN2 Delta7:

Forward Primer: 5' TGGCTATCATACTGGCTATTATATGGAA 3' (SEQ ID NO: 10813)

Reverse Primer: 5' TCCAGATCTGTCTGATCGTTTCTT 3' (SEQ ID NO: 10811)

Probe Sequence: 5' CTGGCATAGAGCAGCACTAAATGACACCAC 3' (SEQ ID NO: 10812)

[001026] RT-qPCR was performed on Applied Biosystems ® 7500 Real-time PCR systems. One cycle of reverse transcription was performed at a temperature of 50°C for 5 min. One cycle of RT inactivation/initial denaturation was performed at a temperature of 95°C for 20 seconds. Forty five cycles of amplification were performed at a temperature of 95°C for 1 second followed by 60°C for 20 seconds.

[001027] SMN2 -FL and SMN2 Delta7 (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (*e.g.*, % increase of SMN2 -FL, decrease of SMN2 Delta7), the normalized SMN2 -FL and SMN2 Delta7 signal was further normalized to the vehicle (treated with Endoporter alone, deltadeltaCt). Relative quantity of transcript level was calculated using the equation $RQ=2^{-deltadeltaCt}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0).

Table 39. Performance of SMN2 AONs evaluated in human derived iPSC motor neurons

SEQ ID NO:	Oligonucleotide Sequence* (5' to 3')	200nM ASO SMN2 FL Rq	500nM ASO SMN2 FL Rq	200nM ASO SMN2 Delta7 Rq	500nM ASO SMN2 Delta7 Rq
10641	ATTCACTTTCATAATGCTGG	1.9895	1.7061	0.8194	0.4527
9971	GATTCACTTTCATAATGCTGGCA	1.3173	1.2035	0.5861	0.1667
10783	GATTCACSTTCATAASGCTGGCA	1.3833	1.4217	0.5407	0.2094
9972	AGATTCACTTTCATAATGCTGGC	1.3820	1.4660	0.6529	0.0964
10651	AGATTCASTTTCATASTGCTGGC	1.3113	1.1082	0.5664	0.2429
9970	ATTCACTTTCATAATGCTGGCAG	1.2012	0.9794	0.6978	0.1799
10784	ATTCACTSTCATAATSCTGGCAG	1.3275	0.8486	0.6869	0.3260
9973	AAGATTCACTTTCATAATGCTGG	1.1847	1.3186	0.9021	0.4403
10649	AAGATTCSCTTTCATSATGCTGG	0.9119	1.1494	0.8714	0.4857
10643	ATTCACTTTCATAATGCTGGCAGAC	0.8669	0.8240	1.1727	1.6183
10646	ATTCACSTTCATAATGCTSGCAGAC	0.7046	0.5606	1.2103	1.5860

10647	ATTCACTTSCATAATGCTSGCAGAC	0.7889	0.4940	1.2433	1.2746
10642	GTAAGATTCACTTTCATAATGCTGG	1.9557	2.4185	0.9007	0.4565
10644	GTAAGASTCACTTTCATASTGCTGG	1.8845	2.2573	0.9753	0.8837
10645	GTAAGATTSACTTTCATASTGCTGG	1.2126	1.6212	0.8690	0.6738

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 39 are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC) , and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

Example 16: Methods for Evaluating SMN2 Antisense Oligonucleotides

[001028] SMN2 antisense oligonucleotides were evaluated in human derived iPSC motor neurons from an SMA patient (NIGMS Human Genetic Cell Repository, Coriell Institute, Camden, New Jersey). The cells were seeded in 96-well plates at a density of 40,000 cells/ well. Antisense oligonucleotide (AON) to SMN2 was transfected into motor neurons with Endoporter (Gene Tools, Philomath, OR, USA) to increase expression of the full length SMN2 transcript and reduce expression of the Delta7 variant. Vehicle control consisted of cell treatment with Endoporter alone. Positive controls included cells that were treated with an AON control alone.

[001029] The AON Control is a splice switching oligonucleotide and has the following sequence and chemistry:

5' T*C*A*C*T*T*T*C*A*T*A*A*T*G*C*T*G*G* 3' (SEQ ID NO: 10809)

where * = phosphorothioate, underlined = DNA, other=2'-MOE RNA; each "C" is 5-MeC.

[001030] To evaluate SMN2 AON ability to restore SMN2 -FL and reduce the Delta7 transcript, antisense oligonucleotides to SMN2 were co-incubated Endoporter in media before addition to the cells. After 72 hours, antisense oligonucleotides and endoporter were washed out and replaced with fresh media. After six additional days, RNA was collected from the 96-well plates for RT-qPCR. RNA was isolated, cDNA generated and multiplexed RT-qPCR assay performed with taqman probes for SMN2 full length transcript, SMN2 Delta7 transcript, and reference GAPDH quantification.

[001031] Transcript levels (*e.g.*, SMN2 full length transcript or SMN2 Delta7 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher TaqMan Gene Expression Assay Hs03929097_g1. RT-qPCR was performed for detecting SMN2 transcripts using custom Thermofisher TaqMan Gene Expression Assays with the following sequences:

SMN2-FL:

Forward Primer: 5' GCTCACATTCCTTAAATTAAGGAGAAA 3' (SEQ ID NO: 10810)
Reverse Primer: 5' TCCAGATCTGTCTGATCGTTTCTT 3' (SEQ ID NO: 10811)
Probe Sequence: 5' CTGGCATAGAGCAGCACTAAATGACACCAC 3' (SEQ ID NO: 10812)

SMN2 Delta7:
Forward Primer: 5' TGGCTATCATACTGGCTATTATATGGAA 3' (SEQ ID NO: 10813)
Reverse Primer: 5' TCCAGATCTGTCTGATCGTTTCTT 3' (SEQ ID NO: 10811)
Probe Sequence: 5' CTGGCATAGAGCAGCACTAAATGACACCAC 3' (SEQ ID NO: 10812)

[001032] RT-qPCR was performed on Applied Biosystems ® 7500 Real-time PCR systems. One cycle of reverse transcription was performed at a temperature of 50°C for 5 min. One cycle of RT inactivation/initial denaturation was performed at a temperature of 95°C for 20 seconds. Forty five cycles of amplification were performed at a temperature of 95°C for 1 second followed by 60°C for 20 seconds. Relative quantity (RQ) of the transcript levels are displayed in the table.

[001033] SMN2 -FL and SMN2 Delta7 (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (*e.g.*, % increase of SMN2 -FL, decrease of SMN2 Delta7), the normalized SMN2 -FL and SMN2 Delta7 signal was further normalized to the vehicle (treated with Endoporter alone, deltadeltaCt). Relative quantity of transcript level was calculated using the equation $RQ=2^{-deltadeltaCt}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0).

Table 40. Performance of SMN2 AONs evaluated in human derived iPSC motor neurons

SEQ ID NO:	**Oligonucleotide Sequence*** (5' to 3')	**200nM ASO SMN2 FL RQ**	**50nM ASO SMN2 FL RQ**	**200 nM ASO SMN2 Delta7 RQ**	**50 nM ASO SMN2 Delta7 RQ**
10641	ATTCACTTTCATAATGCTGG	2.7	2.99	0.0861	0.0285
10642	GTAAGATTCACTTTCATAATGCTGG	1.85	2.1	0.186	0.172
10643	ATTCACTTTCATAATGCTGGCAGAC	0.131	0.427	15	2.28
10644	GTAAGA**S**TCACTTTCATA**S**TGCTGG	2.28	2.36	0.247	0.139
10645	GTAAGATT**S**ACTTTCATA**S**TGCTGG	1.79	2.21	0.0916	0.157
10646	ATTCAC**S**TTCATAATGCT**S**GCAGAC	0.0894	0.132	3.25	2.77
10647	ATTCACTT**S**CATAATGCT**S**GCAGAC	0.0709	0.142	2.75	2.98
10648	AAGATTCACTTTCATAATGCTGG	0.173	0.187	2.82	2.95
10649	AAGATTC**S**CTTTCAT**S**ATGCTGG	2.41	2.2	0.0701	0.212

10650	AGATTCACTTTCATAATGCTGGC	2.34	2.79	0.0197	0.0479
10651	AGATTCA**S**TTTCATA**S**TGCTGGC	2.67	2.97	0.0413	0.11
9971	GATTCACTTTCATAATGCTGGCA	2.71	2.75	0.023	0.0892
10783	GATTCAC**S**TTCATAA**S**GCTGGCA	3.08	2.94	0.0343	0.101
9970	ATTCACTTTCATAATGCTGGCAG	1.86	1.7	0.08	0.0999
10784	ATTCACT**S**TCATAAT**S**CTGGCAG	1.88	2.03	0.224	0.416
10785	TCACTTTCATAATGCTGG	1.88	2.45	0.011	0.0206
10786	TCACTTTC**S**TAATGCTGG	1.75	2.41	0.012	0.0253
10787	TCACTTTCA**S**AATGCTGG	2.40	2.290	0.007	0.0132
10788	TCACTTTC**SS**AATGCTGG	1.82	2.23	0.0189	0.0322

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 40 are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC) , and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

Example 17: Methods for Evaluating SMN2 Antisense Oligonucleotides with Locked Nucleic Acids

[001034] SMN2 antisense oligonucleotides were evaluated in human derived iPSC motor neurons from an SMA patient (NIGMS Human Genetic Cell Repository, Coriell Institute, Camden, New Jersey). The cells were seeded in 96-well plates at a density of 40,000 cells/ well. Antisense oligonucleotide (AON) to SMN2 was transfected into motor neurons with Endoporter (Gene Tools, Philomath, OR, USA) to increase expression of the full length SMN2 transcript and reduce expression of the Delta7 variant. Vehicle control consisted of cell treatment with Endoporter alone.

[001035] To evaluate SMN2 AON ability to restore SMN2 -FL and reduce the Delta7 transcript, antisense oligonucleotides to SMN2 were co-incubated Endoporter in media before addition to the cells. After 72 hours, antisense oligonucleotides and endoporter were washed out and replaced with fresh media. After six additional days, RNA was collected from the 96-well plates for RT-qPCR. RNA was isolated, cDNA generated and multiplexed RT-qPCR assay performed with taqman probes for SMN2 full length transcript, SMN2 Delta7 transcript, and reference GAPDH quantification.

[001036] Transcript levels (*e.g.*, SMN2 full length transcript or SMN2 Delta7 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher TaqMan Gene Expression Assay Hs03929097_g1. RT-qPCR was

performed for detecting SMN2 transcripts using custom Thermofisher TaqMan Gene Expression Assays with the following sequences:

SMN2-FL:

Forward Primer: 5' GCTCACATTCCTTAAATTAAGGAGAAA 3' (SEQ ID NO: 10810)

Reverse Primer: 5' TCCAGATCTGTCTGATCGTTTCTT 3' (SEQ ID NO: 10811)

Probe Sequence: 5' CTGGCATAGAGCAGCACTAAATGACACCAC 3' (SEQ ID NO: 10812)

SMN2 Delta7:

Forward Primer: 5' TGGCTATCATACTGGCTATTATATGGAA 3' (SEQ ID NO: 10813)

Reverse Primer: 5' TCCAGATCTGTCTGATCGTTTCTT 3' (SEQ ID NO: 10811)

Probe Sequence: 5' CTGGCATAGAGCAGCACTAAATGACACCAC 3' (SEQ ID NO: 10812)

[001037] RT-qPCR was performed on Applied Biosystems ® 7500 Real-time PCR systems. One cycle of reverse transcription was performed at a temperature of 50°C for 5 min. One cycle of RT inactivation/initial denaturation was performed at a temperature of 95°C for 20 seconds. Forty five cycles of amplification were performed at a temperature of 95°C for 1 second followed by 60°C for 20 seconds.

[001038] SMN2 -FL and SMN2 Delta7 (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (*e.g.*, % increase of SMN2 -FL, decrease of SMN2 Delta7), the normalized SMN2 -FL and SMN2 Delta7 signal was further normalized to the vehicle (treated with Endoporter alone, deltadeltaCt). Relative quantity of transcript level was calculated using the equation $RQ=2^{-deltadeltaCt}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0).

Table 41. Performance of SMN2 LNA AONs evaluated in human derived iPSC motor neurons

		200nM ASO SMN2 FL RQ		50nM SMN2 FL RQ		200nM ASO SMN2 Delta7 RQ		50nM ASO SMN2 Delta7 RQ	
SEQ ID NO:	**Oligonucleotide Sequence*** (5' to 3')	AVG	STD	AVG	STD	AVG	STD	AVG	STD
10789	GAT[LNA-T]CACTTTCATAATGCT[LNA-G]GCA	1.114	0.887	1.498	0.685	0.042	0.033	0.107	0.050
10790	GAT[LNA-T]CACTTTC[LNA-A]TAATGCT[LNA-G]GCA	1.458	0.018	1.271	0.480	0.049	0.016	0.095	0.032
10791	GATTCA[LNA-C]TTTCATA[LNA-A]TGCTGGCA	1.796	0.823	1.984	0.245	0.035	0.016	0.066	0.030
10792	GATTCA[LNA-C]TTTCATAAT[LNA-G]CTGGCA	0.760	0.690	1.813	0.217	0.024	0.016	0.068	0.035
10793	GATTCACT[LNA-T]TCATAAT[LNA-G]CTGGCA	1.168	0.185	1.166	0.359	0.034	0.013	0.081	0.021
10794	GAT[LNA-T]CACSTTCATAASGCT[LNA-G]GCA	0.667	0.482	1.851	1.068	0.003	0.006	0.058	0.028
10795	GAT[LNA-T]CACSTTC[LNA-A]TAASGCT[LNA-G]GCA	1.397	0.422	1.770	0.652	0.019	0.007	0.044	0.029
10796	GATTCA[LNA-C]STTCATA[LNA-A]SGCTGGCA	1.415	1.091	2.279	0.522	0.034	0.040	0.058	0.055
10797	GATTCA[LNA-C]STTCATAAS[LNA-G]CTGGCA	0.952	0.082	1.623	1.070	0.000	0.000	0.056	0.036
10798	GATTCACS[LNA-T]TCATAAS[LNA-G]CTGGCA	1.609	0.579	1.869	0.479	0.041	0.028	0.029	0.016
10799	AGA[LNA-T]TCACTTTCATAATGC[LNA-T]GGC	1.283	0.974	1.812	1.410	0.015	0.026	0.047	0.041
10800	AGA[LNA-T]TCACTTT[LNA-C]ATAATGC[LNA-T]GGC	1.895	1.301	2.693	1.431	0.065	0.093	0.118	0.037
10801	AGATTC[LNA-A]CTTTCAT[LNA-A]ATGCTGGC	2.834	0.193	3.735	0.618	0.028	0.020	0.094	0.072
10802	AGATTC[LNA-A]CTTTCATAA[LNA-T]GCTGGC	2.554	0.870	2.924	0.509	0.043	0.025	0.139	0.061
10803	AGATTCAC[LNA-T]TTCATAA[LNA-T]GCTGGC	1.885	0.772	3.131	0.236	0.028	0.025	0.093	0.052
10804	AGA[LNA-T]TCASTTTCATASTGC[LNA-T]GGC	1.798	0.235	2.098	0.213	0.027	0.008	0.094	0.013
10805	AGA[LNA-T]TCASTTT[LNA-C]ATASTGC[LNA-T]GGC	2.242	0.068	1.519	0.814	0.030	0.016	0.036	0.009
10806	AGATTC[LNA-A]STTTCAT[LNA-A]STGCTGGC	1.802	0.212	1.678	0.163	0.011	0.002	0.053	0.019
10807	AGATTC[LNA-A]STTTCATAS[LNA-T]GCTGGC	1.437	0.298	1.190	0.425	0.000	0.000	0.039	0.023
10808	AGATTCAS[LNA-T]TTCATAS[LNA-T]GCTGGC	2.464	0.444	0.571	0.435	0.010	0.010	0.021	0.018

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown in Table 37 are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer, as indicated by **S,** is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein. [LNA-X] refers to a locked nucleic acid with a corresponding base X (e.g., LNA-A refers to a locked nucleic acid with an adenine nucleobase, LNA-G refers to a locked nucleic acid with a guanine

nucleobase, LNA-T refers to a locked nucleic acid with a thymine nucleobase, and LNA-C refers to a locked nucleic acid with a 5-methylcytosine nucleobase).

CLAIMS

WHAT IS CLAIMED IS:

1. A compound comprising a splice-switching oligonucleotide, wherein the splice-switching oligonucleotide comprises a spacer.

2. The compound of claim 1, wherein the splice-switching oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease.

3. The compound of claim 1, wherein the splice-switching oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript regulated by TDP-43, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

4. The compound of claim 1 or 2, wherein the modified oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2.

5. The compound of claim 1-2 or 4, wherein the modified oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

6. A compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

7. The compound of claim 6, wherein the modified oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ

ID NO: 9698-9707, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof.

8. A splice-switching oligonucleotide, wherein the splice-switching oligonucleotide comprises a spacer.

9. The oligonucleotide of claim 8, wherein the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease.

10. The oligonucleotide of claim 8, wherein the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript regulated by TDP-43, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

11. The oligonucleotide of claim 8 or 9, wherein the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2.

12. The oligonucleotide of claim 8-9 or 11, wherein the modified oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

13. A splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2, wherein at least one (i.e., one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

14. The oligonucleotide of claim 13, wherein the modified oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

15. An oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

16. A compound comprising a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

17. A compound comprising a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript regulated by TDP-43, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

18. The compound of claim 16, wherein the splice-switching oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

19. The compound of claim 16 or 18, wherein the modified splice-switching oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

20. A compound comprising a modified splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one of STMN2, KCNQ2, UNC13A, or SMN2, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

21. The compound of claim 20, wherein the modified oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ

ID NO: 9698-9707, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof.

22. A splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

23. A splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript regulated by TDP-43, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

24. The oligonucleotide of claim 23, wherein the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2.

25. The oligonucleotide of claim 22 or 24, wherein the modified oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

26. A splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one of STMN2, KCNQ2, UNC13A, or SMN2, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

27. The oligonucleotide of claim 26, wherein the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

28. A splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707, wherein

at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

29. The oligonucleotide of claim 28, further comprising a spacer.

30. The compound or oligonucleotide of claims 1-29, wherein the oligonucleotide comprises a segment with at most 11 linked nucleosides.

31. The compound or oligonucleotide of claims 1-29, wherein the oligonucleotide comprises a segment with at most 10, 9, or 8 linked nucleosides.

32. The compound or oligonucleotide of claims 1-29, wherein the oligonucleotide comprises a segment with at most 7 linked nucleosides.

33. The compound or oligonucleotide of claims 1-29, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides.

34. The compound or oligonucleotide of claims 1-33, wherein every segment of the oligonucleotide comprises at most 7 linked nucleosides.

35. The compound or oligonucleotide of any one of claims 30-34, wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9603, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820.

36. The compound or oligonucleotide of any one of claims 30-35, wherein the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9603, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820.

37. The compound or oligonucleotide of any one of claims 30-36, wherein the oligonucleotide comprises a sequence that shares at least 95% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs; 9596-9603, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820.

38. The compound or oligonucleotide of any one of claims 30-36, wherein the oligonucleotide comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9603, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820.

39. The compound or oligonucleotide of any one of claims 1-38, wherein the oligonucleotide comprises a segment with at most 11 linked nucleosides or at most 7 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9603, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820.

40. The compound or oligonucleotide of claim 39, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9603, SEQ ID NOs:

9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820.

41. The compound or oligonucleotide of claim 39 or 40, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9603, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820.

42. The compound or oligonucleotide of any one of claims 1-41, wherein the oligonucleotide is at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 oligonucleotide units in length.

43. The compound or oligonucleotide of claim 42, wherein the oligonucleotide is at least 19 oligonucleotide units in length.

44. The compound or oligonucleotide of any one of claims 1-43, wherein the spacer is a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base.

45. The compound or oligonucleotide of claim 44, wherein the spacer is located between positions 10 and 15 of the oligonucleotide.

46. The compound or oligonucleotide of claim 44, wherein the spacer is located between positions 7 and 11 of the oligonucleotide.

47. The compound or oligonucleotide of claim 44-46, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide.

48. The compound or oligonucleotide of claim 47, wherein the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide.

49. The compound or oligonucleotide of claim 47 or 48, wherein the spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide.

50. The compound or oligonucleotide of any one of claims 47-49, wherein the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide.

51. The compound or oligonucleotide of any one of claims 47-50, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide.

52. The compound or oligonucleotide of claim 44, wherein the spacer is located between positions 2 and 5 of the oligonucleotide.

53. The compound or oligonucleotide of claim 52, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide.

54. The compound or oligonucleotide of claim 53, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide.

55. The compound or oligonucleotide of claim 44, wherein the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides.

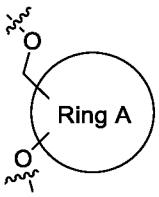
56. The compound or oligonucleotide of claim 55, wherein at least two of the three spacers are adjacent to a guanine nucleobase.

57. The compound or oligonucleotide of claim 56, wherein each of the at least two of the three spacers immediately precede a guanine nucleobase.

58. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal,

hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

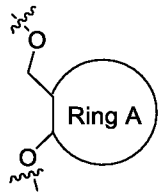
59. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula (X), wherein:



Formula (X)

Ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group or a 4-8 member monocyclic heterocyclyl group, wherein the heterocyclyl group contains 1 or 2 heteroatoms selected from O, S and N, provided that A is not capable of forming a covalent bond to a nucleobase; and the symbol represents the point of connection to an internucleoside linkage.

60. The compound or oligonucleotide of claim 59, wherein each of the first, second or third spacers is independently represented by Formula (Xa), wherein:



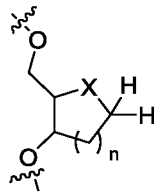
Formula (Xa).

61. The compound or nucleotide of claim 59 or 60, wherein ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

62. The compound or nucleotide of claim 61 wherein ring A is tetrahydrofuranyl.

63. The compound or nucleotide of claim 61 wherein ring A is tetrahydropyranyl.

64. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula I, wherein:

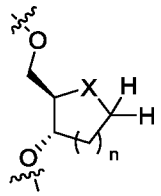


Formula (I)

X is selected from -CH_2- and -O-; and

n is 0, 1, 2 or 3.

65. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula I', wherein:

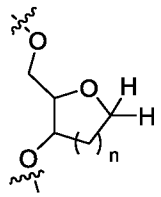


Formula (I')

X is selected from -CH_2- and -O-; and

n is 0, 1, 2 or 3.

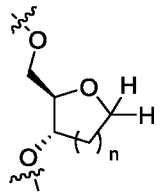
66. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

n is 0, 1, 2 or 3.

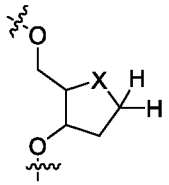
67. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia'); and

n is 0, 1, 2 or 3.

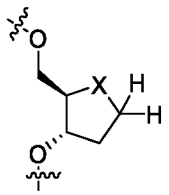
68. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

X is selected from -CH_2- and -O-.

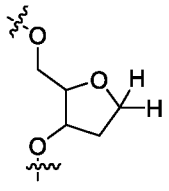
69. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

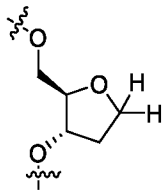
X is selected from -CH_2- and -O-.

70. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula (Iia), wherein:



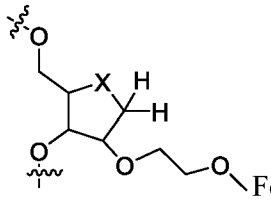
Formula (Iia).

71. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula (Iia'), wherein:



Formula (Iia').

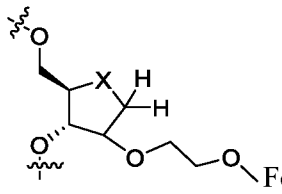
72. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula (IIi), wherein:



Formula (IIi)

X is selected from -CH_2- and -O-.

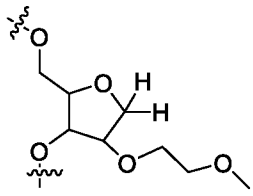
73. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula (IIi'), wherein:



Formula (IIi')

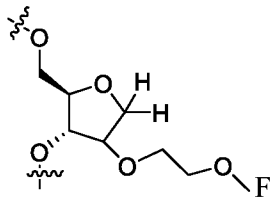
X is selected from -CH_2- and -O-.

74. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula (IIib), wherein:

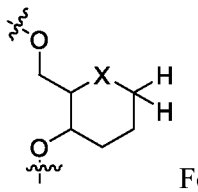


Formula (IIib).

75. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula (IIib'), wherein:

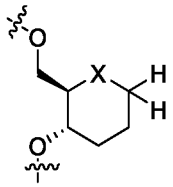

Formula (IIib').

76. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula III, wherein:


Formula (III); and

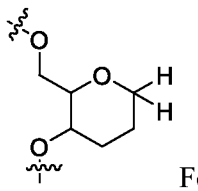
X is selected from -CH_2- and -O-.

77. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula III', wherein:

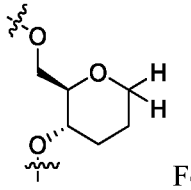

Formula (III'); and

X is selected from -CH_2- and -O-.

78. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula (IIIa), wherein:


Formula (IIIa).

79. The compound or oligonucleotide of any one of claims 44-57, wherein each of the first, second or third spacers is independently represented by Formula (IIIa'), wherein:



Formula (IIIa').

80. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide further comprises a locked nucleic acid (LNA).

81. The compound or oligonucleotide of claim 80, wherein the locked nucleic acid (LNA) is located at one of positions 4, 7, 9, 12, 15, or 20 of the oligonucleotide.

82. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 10%.

83. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 20%.

84. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 25%.

85. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 30%.

86. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 40%.

87. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 50%.

88. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide is between 12 and 40 oligonucleotide units in length.

89. The compound or oligonucleotide of any one of the above claims, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate

linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

90. The compound or oligonucleotide of any one of claims 1-89, wherein one or more nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages.

91. The compound or oligonucleotide of claim 90, wherein only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage.

92. The compound or oligonucleotide of any one of claims 1-89, wherein nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages.

93. The compound or oligonucleotide of any one of claims 1-89, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds.

94. The compound or oligonucleotide of claim 93, wherein only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

95. The compound or oligonucleotide of claim 94, wherein the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond.

96. The compound or oligonucleotide of claim 94, wherein the oligonucleotide comprises a second spacer, wherein a base immediately preceding the second spacer is linked to a further preceding base through a phosphodiester bond.

97. The compound or oligonucleotide of any one of claims 1-89, wherein one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds.

98. The compound or oligonucleotide of claim 97, wherein only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

99. The compound or oligonucleotide of claim 93, wherein two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds.

100. The compound or oligonucleotide of any one of claims 1-89, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the spacer in the oligonucleotide are linked through phosphodiester bonds.

101. The compound or oligonucleotide of claim 100, wherein one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds.

102. The compound or oligonucleotide of claim 100 or 101, wherein the oligonucleotide includes a second spacer, and wherein one or more bases immediately preceding the second spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer in the oligonucleotide are linked through phosphodiester bonds.

103. The compound or oligonucleotide of claim 102, wherein one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.

104. The compound or oligonucleotide of any one of claims 1-89, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases.

105. The compound or oligonucleotide of any one of claims 1-89, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases.

106. The compound or oligonucleotide of claim 104 or 105, wherein the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

107. The compound or oligonucleotide of any one of the above claims, wherein one or more internucleoside linkage of the oligonucleotide is a modified internucleoside linkage.

108. The compound or oligonucleotide of claim 107, wherein the modified internucleoside linkage of the oligonucleotide is a phosphorothioate linkage.

109. The compound or oligonucleotide of claim 107 or 108, wherein all internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

110. The compound or oligonucleotide of claim 108, wherein the phosphorothioate linkage is in one of a *R*p configuration or a *S*p configuration.

111. The compound or oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified sugar moiety.

112. The compound or oligonucleotide of claim 111, wherein the modified sugar moiety is one of a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'-MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

113. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length STMN2, KCNQ2, UNC13A, or SMN2 protein.

114. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 100% increase of full length protein.

115. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 200% increase of full length protein.

116. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 300% increase of full length protein.

117. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 400% increase of full length protein.

118. The compound or oligonucleotide of any one of claims 113-117, wherein increase of the full length protein is measured in comparison to a reduced level of full length protein achieved using a TDP43 antisense oligonucleotide.

119. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length protein.

120. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 50%, 60%, 70%, 80%, or 90% reduction of a mis-spliced transcript.

121. A method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to the patient a compound or an oligonucleotide of any one of claims 1-120.

122. The method of claim 121, wherein the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, tuberous sclerosis complex, Pick's Disease, tauopathies, primary age-related tauopathy, Down Syndrome, epilepsy/seizure disorder, depression, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), HIV-associated neurocognitive disorders (HAND), multisystem atrophy, amnestic mild cognitive impairment, corticobasal degeneration (CBD) and/or neuropathies such a chemotherapy induced neuropathy, Spinocerebellar ataxia (SCA), SCA type 2, Spinal Muscular Atrophy (SMA), Parkinsonism, Niemann-Pick disease type C (NPC), Charcot-Marie-Tooth Disease (CMT), Mucopolysaccharidosis type II (MPSIIA), Mucolipidosis IV, GM1 gangliosidosis, Sporadic inclusion body myositis (sIBM), Henoch-Schonlein purpura (HSP), Limbic-predominant age-related TDP-43 encephalopathy (LATE)), Cerebral Age-Related TDP-43 With Sclerosis (CARTS), Gaucher's disease, and facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, Perry disease, and synaptic diseases like autism.

123. The method of claim 122, wherein the neurological disease is ALS.

124. The method of claim 122, wherein the neurological disease is FTD.

125. The method of claim 122, wherein the neurological disease is ALS with FTD.

126. The method of claim 122, wherein the neurological disease is AD.

127. The method of claim 122, wherein the neurological disease is PD.

128. The method of claim 122, wherein the neurological disease is spinal muscular atrophy (SMA).

129. The method of claim 121, wherein the neuropathy is chemotherapy induced neuropathy.

130. A method of restoring axonal outgrowth and/or regeneration of a neuron, the method comprising exposing the neuron to a compound or an oligonucleotide of any one of claims 1-120.

131. A method of increasing, promoting, stabilizing, or maintaining any one of STMN2, KCNQ2, UNC13A, or SMN2 expression and/or function in a neuron, the method comprising exposing the cell to a compound or an oligonucleotide of any one of claims 1-120.

132. The method of claim 130 or 131, wherein the neuron is a motor neuron.

133. The method of claim 130 or 131, wherein the neuron is a spinal cord neuron.

134. The method of any one of claims 130-133, wherein the neuron is a neuron of a patient in need of treatment of a neurological disease and/or a neuropathy.

135. The method of claim 134, wherein the neuropathy is chemotherapy induced neuropathy.

136. The method of any one of claims 130-135, wherein the exposing is performed *in vivo* or *ex vivo*.

137. The method of any one of claims 130-135, wherein the exposing comprises administering the oligonucleotide to a patient in need thereof.

138. The method of any one of claims 130-137, wherein the oligonucleotide is administered topically, parenterally, intrathecally, intrathalamically, intracisternally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, intraduodenally, or intracerebroventricularly.

139. The method of claim 138, wherein the oligonucleotide is administered orally.

140. The method of any one of claims 130-138, wherein a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically, intracerebroventricularly, or intracisternally.

141. The method of any one of claims 130-140, wherein the patient is a human.

142. A pharmaceutical composition comprising the oligonucleotide of any one of claims 1-120, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

143. The pharmaceutical composition of claim 142, wherein the pharmaceutical composition is suitable for topical, intrathecal, intrathalamic, intracisternal, intracerebroventricular, parenteral, oral, pulmonary, intratracheal, intranasal, transdermal, rectal, buccal, sublingual, vaginal, or intraduodenal administration.

144. A method of treating a neurological disease or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 142 or 143.

145. The method of claim 144, wherein the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, tuberous sclerosis complex, Pick's Disease, tauopathies, primary age-related tauopathy, Down Syndrome, epilepsy/seizure disorder, depression, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), HIV-associated neurocognitive disorders (HAND), multisystem atrophy, amnestic mild cognitive impairment, corticobasal degeneration (CBD) and/or neuropathies such a chemotherapy induced neuropathy,

Spinocerebellar ataxia (SCA), SCA type 2, Spinal Muscular Atrophy (SMA), Parkinsonism, Niemann-Pick disease type C (NPC), Charcot-Marie-Tooth Disease (CMT), Mucopolysaccharidosis type II (MPSIIA), Mucolipidosis IV, GM1 gangliosidosis, Sporadic inclusion body myositis (sIBM), Henoch-Schonlein purpura (HSP), Limbic-predominant age-related TDP-43 encephalopathy (LATE)), Cerebral Age-Related TDP-43 With Sclerosis (CARTS), Gaucher's disease, and facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, Perry disease, and synaptic diseases like autism.

146. The method of claim 145, wherein the neurological disease is ALS.

147. The method of claim 145, wherein the neurological disease is FTD.

148. The method of claim 145, wherein the neurological disease is ALS with FTD.

149. The method of claim 145, wherein the neurological disease is AD.

150. The method of claim 145, wherein the neurological disease is PD.

151. The method of claim 145, wherein the neurological disease is spinal muscular atrophy (SMA).

152. The method of claim 144, wherein the neuropathy is chemotherapy induced neuropathy.

153. The method of any one of claims 144-152, wherein the pharmaceutical composition is administered topically, parenterally, orally, pulmonarily, rectally, buccally, sublingually, vaginally, intratracheally, intranasally, intracisternally, intrathecally, intrathalamically, transdermally, intraduodenally, or intracerebroventricularly.

154. The method of any one of claims 144-152, wherein the pharmaceutical composition is administered intrathecally, intrathalamically, or intracisternally.

155. The method of any one of claims 144-154, wherein a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally.

156. The method of any one of claims 144-155, wherein the patient is human.

157. A method for treating a neurological disease in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein the oligonucleotide is at least 85% complementary to an equal length portion of a sequence from a transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

158. A method for treating a neurological disease in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide is at least 85% complementary to a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a

phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

159. A method for treating a neurological disease in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9596-9603, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10574-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, and SEQ ID NOs: 10814-10820, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate

linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

160. A method for treating amyotrophic lateral sclerosis (ALS) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, or SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, or SEQ ID NOs: 9596-9603, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl

nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

161. A method for treating Alzheimer's Disease (AD) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, or SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, or SEQ ID NOs: 9596-9603, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally, wherein the oligonucleotide further comprises a spacer

162. A method for treating frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, or SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, or SEQ ID NOs: 9596-9603, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

163. A method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-

3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4402-4530, or SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, or SEQ ID NOs: 9596-9603, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

164. The method of any one of claims 157-163, wherein nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages.

165. The method of claim 164, wherein only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage.

166. The method of any one of claims 157-163, wherein nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages.

167. The method of any one of claims 157-163, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds.

168. The method of claim 167, wherein only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

169. The method of claim 168, wherein the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond.

170. The method of claim 168, wherein the oligonucleotide comprises a second spacer, wherein a base immediately preceding the second spacer is linked to a further preceding base through a phosphodiester bond.

171. The method of any one of claims 157-163, wherein one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds.

172. The method of claim 171, wherein only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

173. The method of any one of claims 157-163, wherein two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds.

174. The method of any one of claims 157-163, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the spacer in the oligonucleotide are linked through phosphodiester bonds.

175. The method of claim 174, wherein one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds.

176. The method of claim 174 or 175, wherein the oligonucleotide includes a second spacer, and wherein one or more bases immediately preceding the second spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer in the oligonucleotide are linked through phosphodiester bonds.

177. The method of claim 176, wherein one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.

178. The method of any one of claims 157-163, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases.

179. The method of any one of claims 157-163, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases.

180. The method of claim 178 or 179, wherein the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

181. The method of any of claims 164-180, wherein the oligonucleotide is any one of a 19mer, 21mer, 23mer, or 25mer.

182. The method of any one of claims 157-163, wherein at least one (*i.e.*, one or more) internucleoside linkage of the oligonucleotide is a phosphorothioate linkage.

183. The method of any one of claims 157-163, wherein all internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

184. An oligonucleotide and a pharmaceutically acceptable excipient, the oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707., a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, optionally wherein the oligonucleotide comprises a spacer and wherein the oligonucleotide is capable of increasing, restoring, or stabilizing expression of one or more of STMN2, KCNQ2, UNC13A, or SMN2 mRNA capable of translation of a functional protein in a cell or a human patient of an immune-mediated demyelinating disease, and wherein the level of increase, restoration, or stabilization of expression and/or activity and/or function is sufficient for use of the oligonucleotide as a medicament for the treatment of the immune-mediated demyelinating disease.

185. The method of any one of claims 121-141 or 144-183, the pharmaceutical composition of claim 142 or 143, or the oligonucleotide of any one of claims 1-120 or 184, wherein the oligonucleotide comprises one or more chiral centers and/or double bonds.

186. The method of any one of claims 121-141, 144-183, or 185, the pharmaceutical composition of claim 142, 143, or 185, or the oligonucleotide of any one of claims 1-120 or 184-185, wherein the oligonucleotide exist as stereoisomers selected from geometric isomers, enantiomers, and diastereomers.

187. A method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 142 or 143, in combination with a second therapeutic agent.

188. The method of claim 187, wherein the second therapeutic agent is selected from Riluzole (Rilutek), PrimeC, Edaravone (Radicava), rivastigmine, donepezil, galantamine, selective serotonin reuptake inhibitor, antipsychotic agents, cholinesterase inhibitors, memantine, benzodiazepine antianxiety drugs, AMX0035 (ELYBRIO), ZILUCOPLAN (RA101495), pridopidine, dual AON intrathecal administration (*e.g.*, BIIB067, BIIB078, and BIIB105), BIIB100, levodopa/carbidopa, dopaminergic agents (*e.g.*, ropinirole, pramipexole, rotigotine), medroxyprogesetrone, KCNQ2/KCNQ3 openers (e.g., retigabine, XEN1101, or QRL-101), bioactive scaffolds, anticonvulsants and psychostimulant agents, a therapy (*e.g.*, selected from breathing care, physical therapy, occupational therapy, speech therapy, nutritional support), deep brain stimulation, levodopa and carbidopa (duopa, rytary, Sinemet, inbrija), istradefylline (nourianz), safinamide (xadago), pramipexole (Mirapex), rotigotine (neupro), ropinirole (requip), amantadine (gocovri, Symmetrel, osmolex), benztropine (Cogentin), trihexyphenidyl (artane), selegiline (eldepryl, zelapar), rasagiline, entacapone (comtan), opicapone (ongentys), tolcapone (tasmar), apomorphine (apokyn, kynmobi), exenatide, lingzhi, BIIB054, BIIB094, Caffeine, sarizotan, embryonic dopamine cell implantation, aducanamab (Aduhlem), memantine (Namenda), Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (razadyne), Namzeric, Suvorexant (belsomra), lecanemab, olanzapine (Zyprexa), quetiapine (Seroquel), SSRIs (citalopram (Cipramil), dapoxetine (Priligy), escitalopram (Cipralex), fluoxetine (Prozac or Oxactin), fluvoxamine (Faverin), paroxetine (Seroxat), sertraline (Lustral), vortioxetine (Brintellix)), divalproex sodium (Depakote), carbamazepine (Tegretol), medroxyprogestrone, Brivaracetam (briviact), cannabidiol (epidiolex), carbamazepine (carbatrol, Tegretol), cenobamate (xcopri), diazepam (valium), lorazepam (Ativan), clonazepam (klonopin), eslicarbazepine (aptiom), ethosuximide (zarontin), felbamate (felbatol), fenfluramine (fintepla), lacosamide

(VIMPAT), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (oxtellar xr, Trileptal), perampanel (fycompa), phenobarbital, phenytoin (dilantin), pregabalin (lyrica), tiagabine (gabitril), topiramate (topamax), valproate (depakene, depakote), and/or zonisamide (zonegran), for treating said neurologic disease.

189. A method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 142 or 143, wherein at least one nucleoside linkage of the oligonucleotide is a non-natural linkage, optionally wherein the oligonucleotide comprises a spacer, and wherein the oligonucleotide further comprises a targeting or conjugate moiety selected from cholesterol, lipoic acid, panthothenic acid, polyethylene glycol, and an antibody for crossing the blood brain barrier.

190. The method of any one of claims 121-141, 144-183, or 185-189, wherein the spacer is a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base.

191. The method of claim 190, wherein the spacer is located between positions 10 and 15 of the oligonucleotide.

192. The method of claim 190, wherein the spacer is located between positions 7 and 11 of the oligonucleotide.

193. The method of claim 190 or 192, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide.

194. The method of claim 193, wherein the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide.

195. The method of claim 193 or 194, wherein the spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide.

196. The method of any one of claims 193-195, wherein the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide.

197. The method of any one of claims 193-196, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide.

198. The method of claim 190, wherein the spacer is located between positions 2 and 5 of the oligonucleotide.

199. The method of claim 198, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide.

200. The method of claim 199, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide.

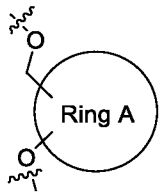
201. The method of claim 190, wherein the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides.

202. The method of claim 201, wherein at least two of the three spacers are adjacent to a guanine nucleobase.

203. The method of claim 202, wherein each of the at least two of the three spacers immediately precede a guanine nucleobase.

204. The method of any one of claims 190-203, wherein each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal, hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

205. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula (X), wherein:

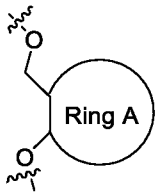


Formula (X)

Ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group or a 4-8 member monocyclic heterocyclyl group, wherein the heterocyclyl group contains 1 or 2 heteroatoms selected from O, S and N, provided that A is not capable of forming a covalent bond to a nucleobase; and

the symbol represents the point of connection to an internucleoside linkage.

206. The method of claim 205, wherein each of the first, second or third spacers is independently represented by Formula (Xa), wherein:



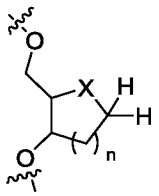
Formula (Xa).

207. The method of claim 205 or 206, wherein ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

208. The method of claim 207, wherein ring A is tetrahydrofuranyl.

209. The method of claim 207, wherein ring A is tetrahydropyranyl.

210. The method of any one of claims 190-203 wherein each of the first, second or third spacers is independently represented by Formula (I), wherein:

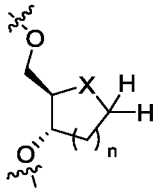


Formula (I)

X is selected from -CH_2- and -O-; and

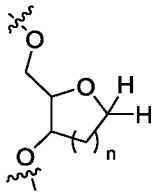
n is 0, 1, 2 or 3.

211. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula (I'), wherein:



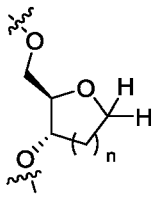
Formula (I').

212. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



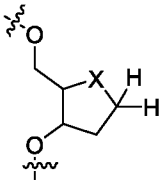
Formula (Ia).

213. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia').

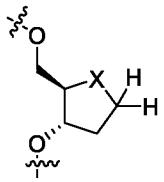
214. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

X is selected from -CH_2- and -O-.

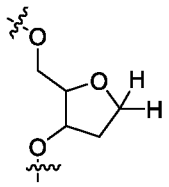
215. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

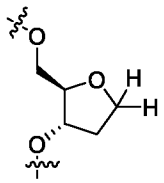
X is selected from -CH_2- and -O-.

216. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula (IIa), wherein:



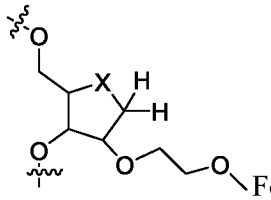
Formula (IIa).

217. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula (Iia'), wherein:



Formula (Iia').

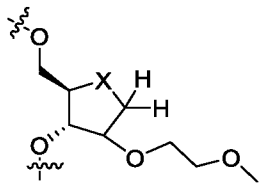
218. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula (IIi), wherein:



Formula (IIi)

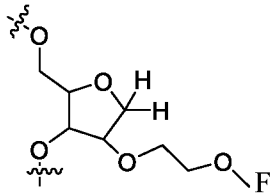
X is selected from -CH_2- and -O-.

219. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula (IIi'), wherein:

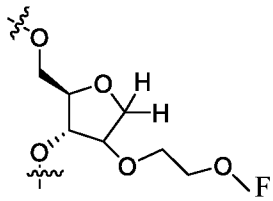

Formula (IIi')

X is selected from -CH_2- and -O-.

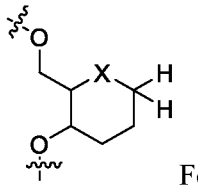
220. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula (IIib), wherein:


Formula (IIib).

221. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula (IIib'), wherein:

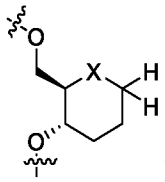

Formula (IIib').

222. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula III, wherein:


Formula (III); and

X is selected from -CH_2- and -O-.

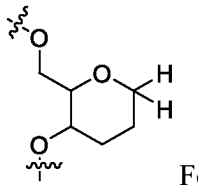
223. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

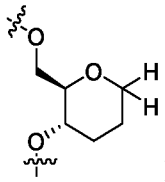
X is selected from -CH_2- and -O-.

224. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula (IIIa), wherein:



Formula (IIIa).

225. The method of any one of claims 190-203, wherein each of the first, second or third spacers is independently represented by Formula (IIIa'), wherein:



Formula (IIIa').

226. The method of any one of claims 190-225, wherein the oligonucleotide comprising the spacer has a GC content of at least 10%.

227. The method of any one of claims 190-226, wherein the oligonucleotide comprising the spacer has a GC content of at least 20%.

228. The method of any one of claims 190-227, wherein the oligonucleotide comprising the spacer has a GC content of at least 25%.

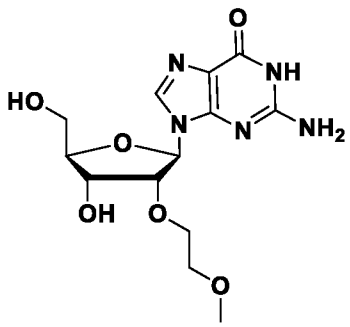
229. The method of any one of claims 190-228, wherein the oligonucleotide comprising the spacer has a GC content of at least 30%.

230. The method of any one of claims 190-229, wherein the oligonucleotide comprising the spacer has a GC content of at least 40%.

231. The method of any one of claims 190-230, wherein the oligonucleotide comprising the spacer has a GC content of at least 50%.

232. A method for synthesizing an AON with a spacer, the method comprising:

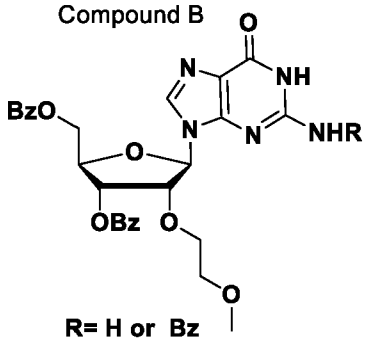
Compound A



obtaining compound A represented by the formula of ;

performing a benzoyl protection reaction of compound A to generate compound B

Compound B

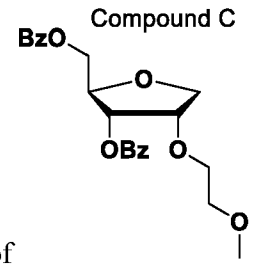


R= H or Bz
Used as mixture

represented by the formula of ;

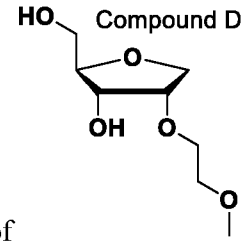
performing reductive nucleobase cleavage of compound B to generate compound C

Compound C



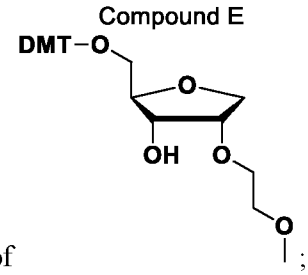
represented by the formula of ;

performing a saponification reaction of compound C to generate compound D



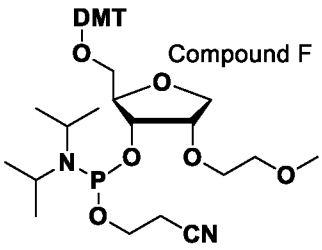
represented by the formula of ;

performing a protection reaction of compound D to generate compound E represented



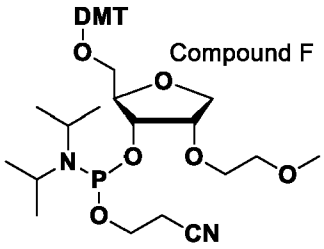
by the formula of ; and

performing a phosphoramidite installation reaction of compound E to generate



compound F represented by the formula of

233. A composition comprising:



compound F having formula .

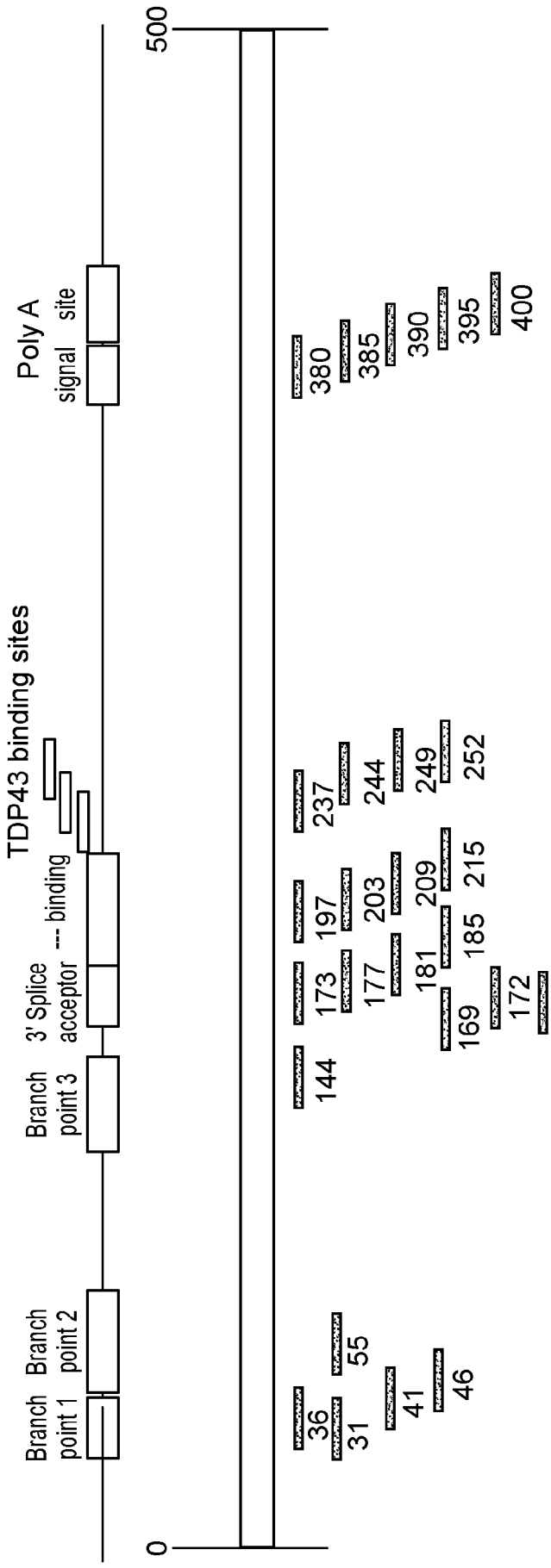

0
500
Branch point 1
Branch point 2
Branch point 3
3' Splice acceptor
--- binding
TDP43 binding sites
Poly A signal site
36
31
55
41
46
144
169
173
177
181
185
197
203
209
215
237
244
249
252
170
171
172
380
385
390
395
400

FIG. 1

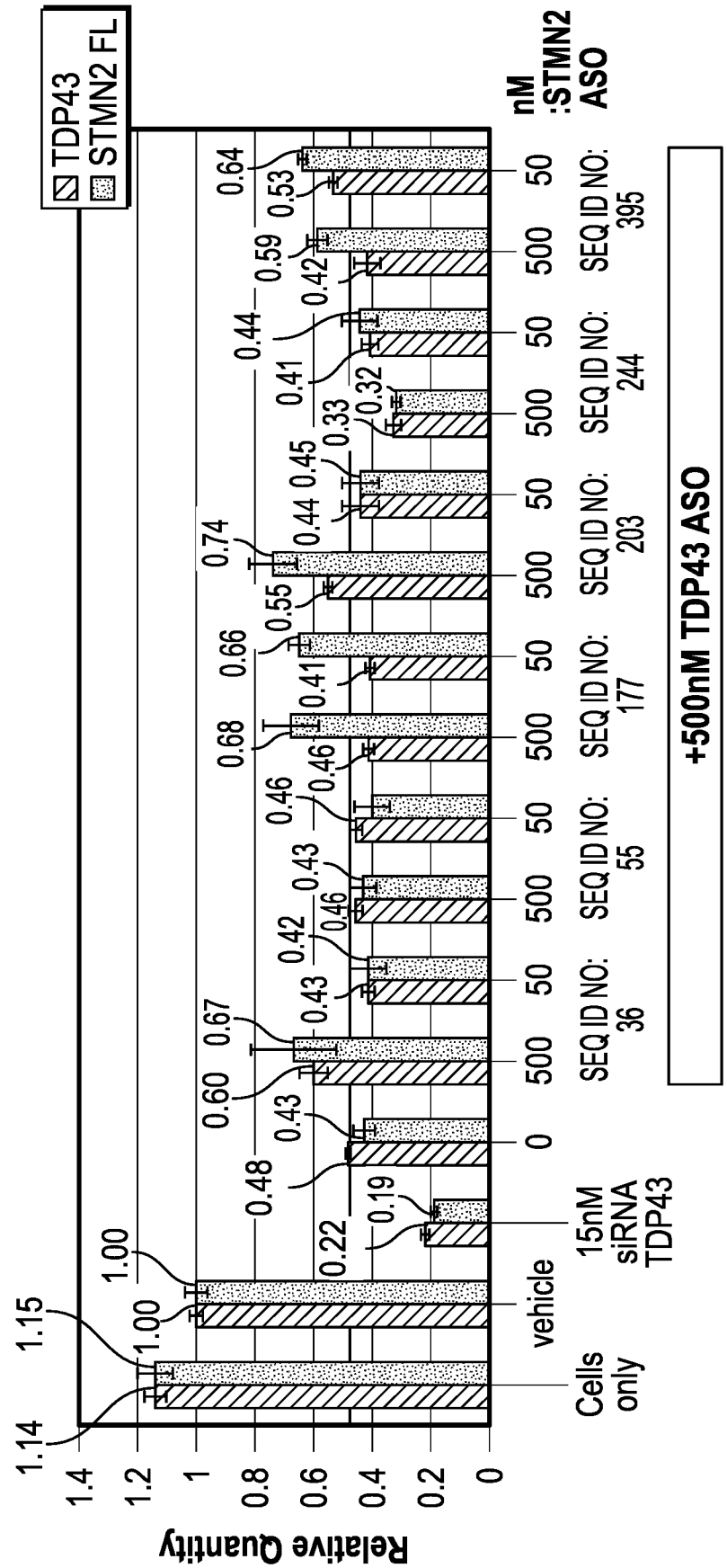

TDP43
STMN2 FL
Relative Quantity
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Cells only
vehicle
15nM siRNA TDP43
nM :STMN2 ASO
0
500
50
500
50
500
50
500
50
500
50
500
50
500
50
500
50
SEQ ID NO: 36
SEQ ID NO: 55
SEQ ID NO: 177
SEQ ID NO: 203
SEQ ID NO: 244
SEQ ID NO: 395
+500nM TDP43 ASO

FIG. 2

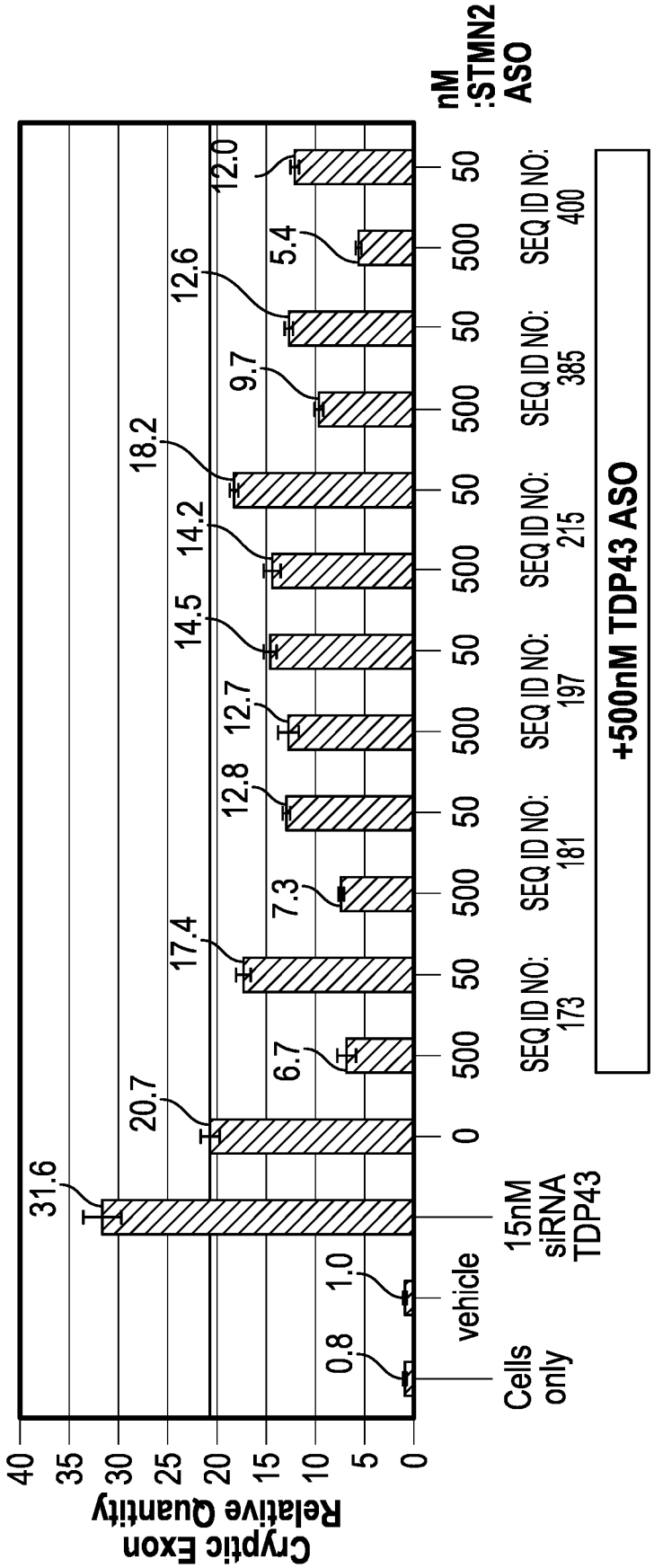

Cryptic Exon Relative Quantity
0
5
10
15
20
25
30
35
40
Cells only
vehicle
15nM siRNA TDP43
0.8
1.0
31.6
20.7
6.7
17.4
7.3
12.8
12.7
14.5
14.2
18.2
9.7
12.6
5.4
12.0
0
500
50
500
SEQ ID NO: 173
SEQ ID NO: 181
SEQ ID NO: 197
SEQ ID NO: 215
SEQ ID NO: 385
SEQ ID NO: 400
+500nM TDP43 ASO
nM :STMN2 ASO

FIG. 3

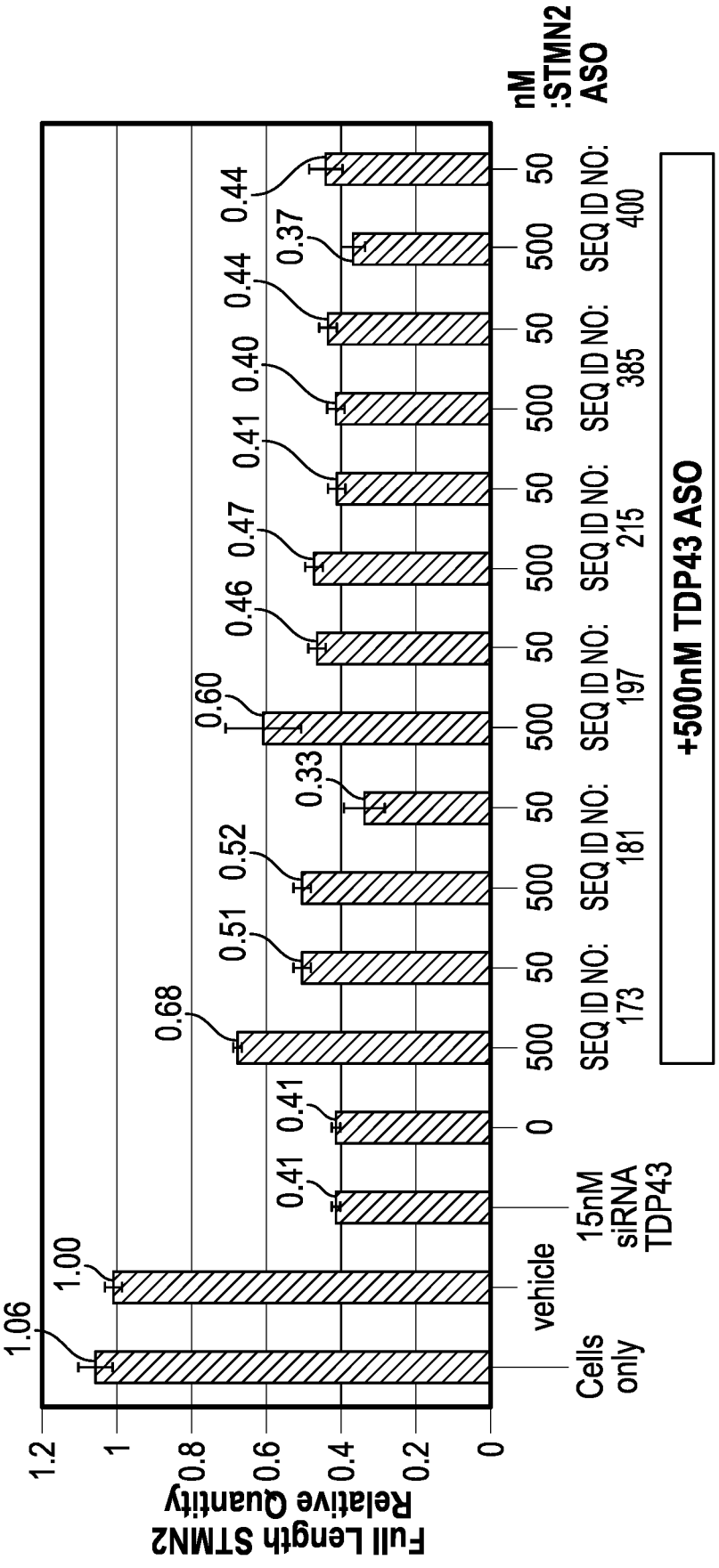

Full Length STMN2
Relative Quantity
0
0.2
0.4
0.6
0.8
1
1.2
1.06
1.00
0.41
0.41
0.68
0.51
0.52
0.33
0.60
0.46
0.47
0.41
0.40
0.44
0.37
0.44
Cells only
vehicle
15nM siRNA TDP43
0
500
50
500
50
500
50
500
50
500
50
500
50
nM :STMN2 ASO
SEQ ID NO: 173
SEQ ID NO: 181
SEQ ID NO: 197
SEQ ID NO: 215
SEQ ID NO: 385
SEQ ID NO: 400
+500nM TDP43 ASO

FIG. 4

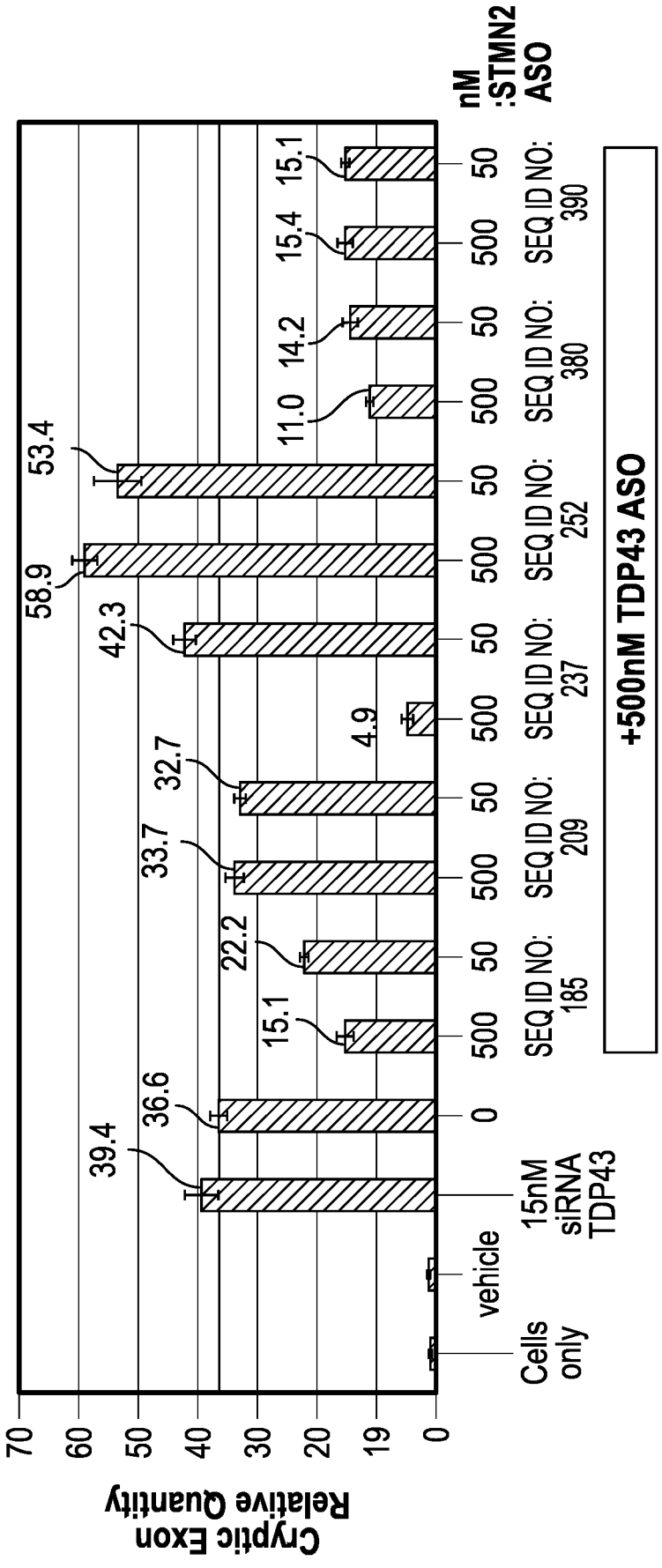

Cryptic Exon Relative Quantity
70
60
50
40
30
20
19
0
Cells only
vehicle
15nM siRNA TDP43
39.4
36.6
0
15.1
22.2
33.7
32.7
4.9
42.3
58.9
53.4
11.0
14.2
15.4
15.1
500
50
SEQ ID NO: 185
SEQ ID NO: 209
SEQ ID NO: 237
SEQ ID NO: 252
SEQ ID NO: 380
SEQ ID NO: 390
+500nM TDP43 ASO
nM :STMN2 ASO

FIG. 5A

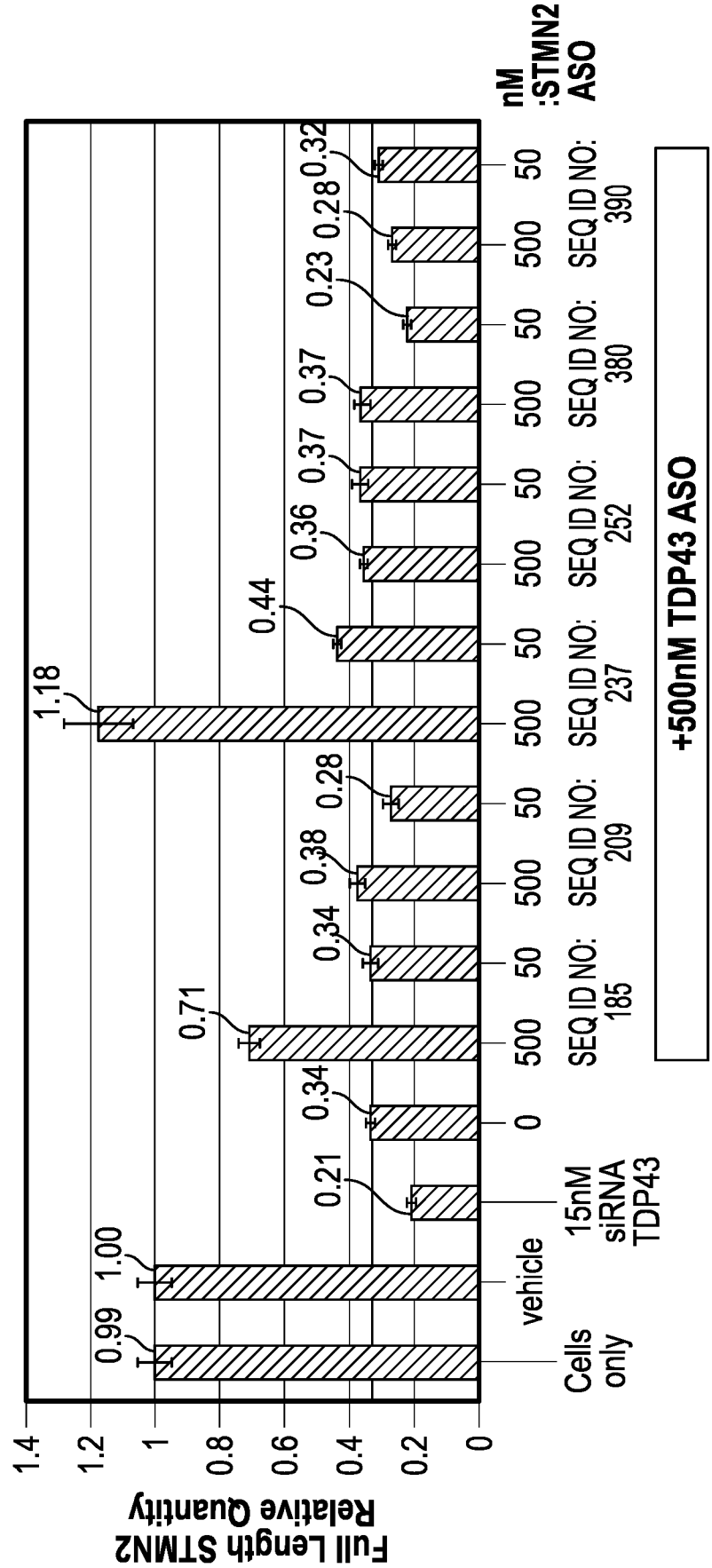

Full Length STMN2
Relative Quantity
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Cells only
vehicle
15nM siRNA TDP43
nM :STMN2 ASO
0
500
50
500
50
500
50
500
50
500
50
500
50
500
50
500
SEQ ID NO: 185
SEQ ID NO: 209
SEQ ID NO: 237
SEQ ID NO: 252
SEQ ID NO: 380
SEQ ID NO: 390
+500nM TDP43 ASO
0.99
1.00
0.21
0.34
0.71
0.34
0.38
0.28
1.18
0.44
0.36
0.37
0.37
0.23
0.28
0.32

FIG. 5B

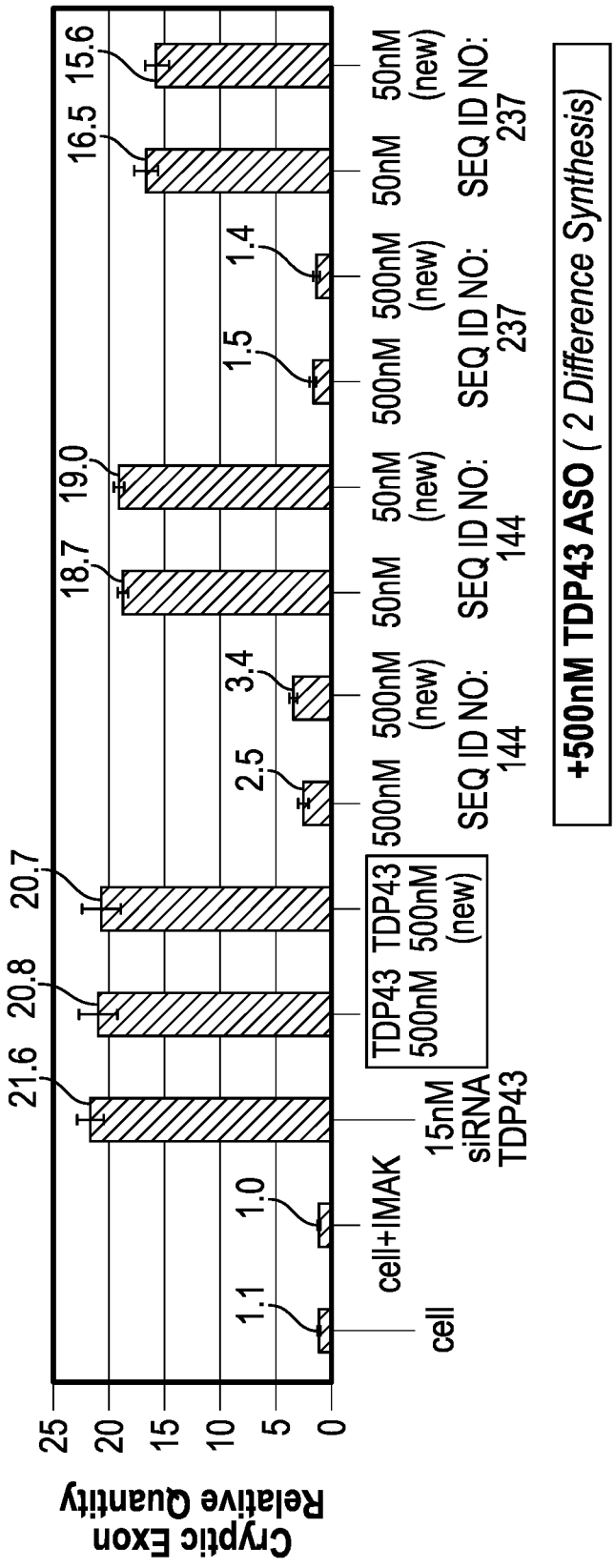

Cryptic Exon Relative Quantity
25
20
15
10
5
0
1.1
1.0
21.6
20.8
20.7
2.5
3.4
18.7
19.0
1.5
1.4
16.5
15.6
cell
cell+IMAK
15nM siRNA TDP43
TDP43 500nM
TDP43 500nM (new)
500nM SEQ ID NO: 144
500nM (new) SEQ ID NO: 144
50nM SEQ ID NO: 144
50nM (new) SEQ ID NO: 144
500nM SEQ ID NO: 237
500nM (new) SEQ ID NO: 237
50nM SEQ ID NO: 237
50nM (new) SEQ ID NO: 237
+500nM TDP43 ASO (2 Difference Synthesis)

FIG. 6A

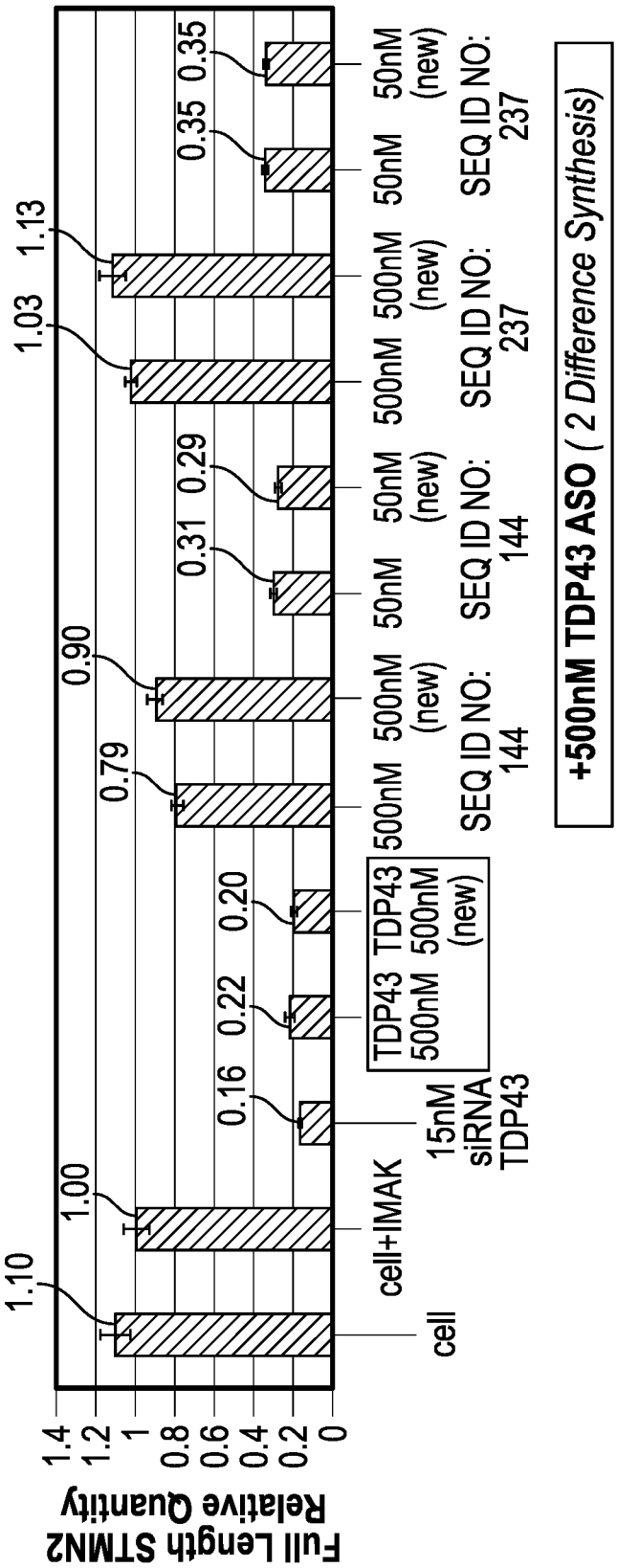

Full Length STMN2
Relative Quantity
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1.10
1.00
0.16
0.22
0.20
0.79
0.90
0.31
0.29
1.03
1.13
0.35
0.35
cell
cell+IMAK
15nM siRNA TDP43
TDP43 500nM
TDP43 500nM (new)
500nM (new)
SEQ ID NO: 144
50nM (new)
50nM
500nM (new)
SEQ ID NO: 237
50nM (new)
+500nM TDP43 ASO (2 Difference Synthesis)

FIG. 6B

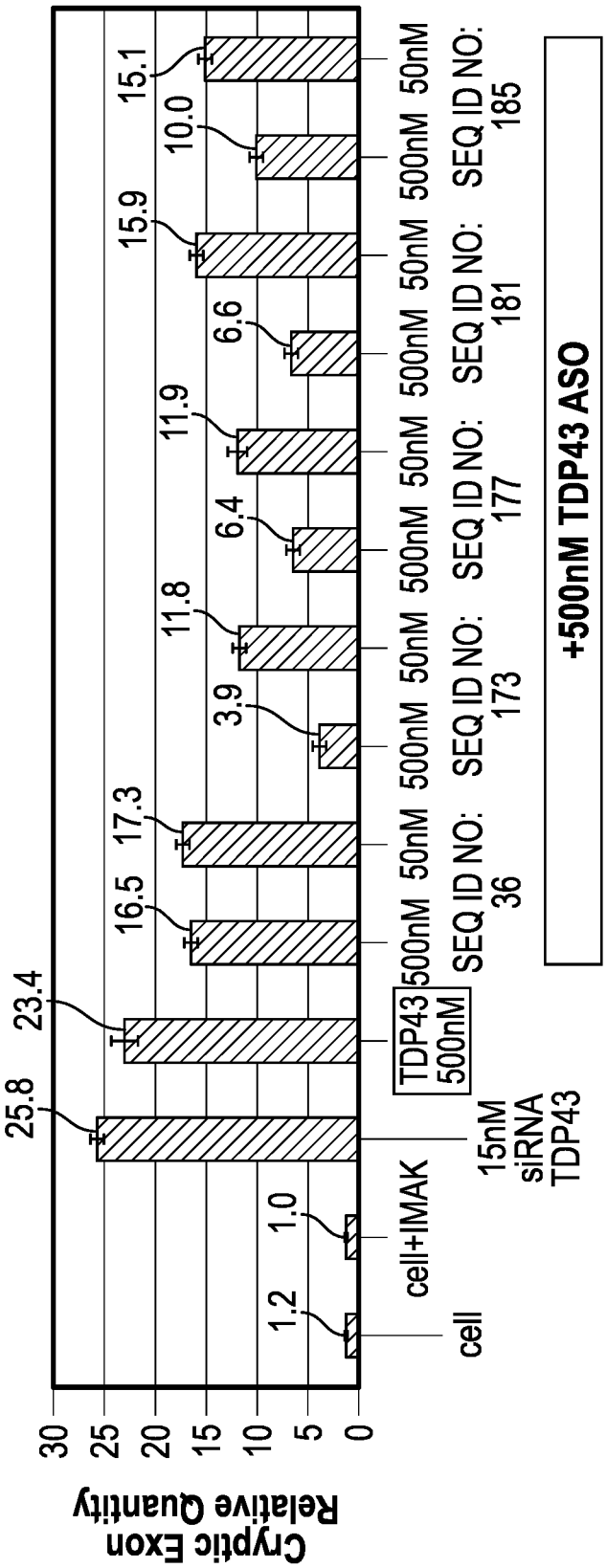

Cryptic Exon Relative Quantity
0
5
10
15
20
25
30
1.2
1.0
25.8
23.4
16.5
17.3
3.9
11.8
6.4
11.9
6.6
15.9
10.0
15.1
cell
cell+IMAK
15nM siRNA TDP43
TDP43 500nM
500nM
50nM
SEQ ID NO: 36
SEQ ID NO: 173
SEQ ID NO: 177
SEQ ID NO: 181
SEQ ID NO: 185
+500nM TDP43 ASO

FIG. 7A

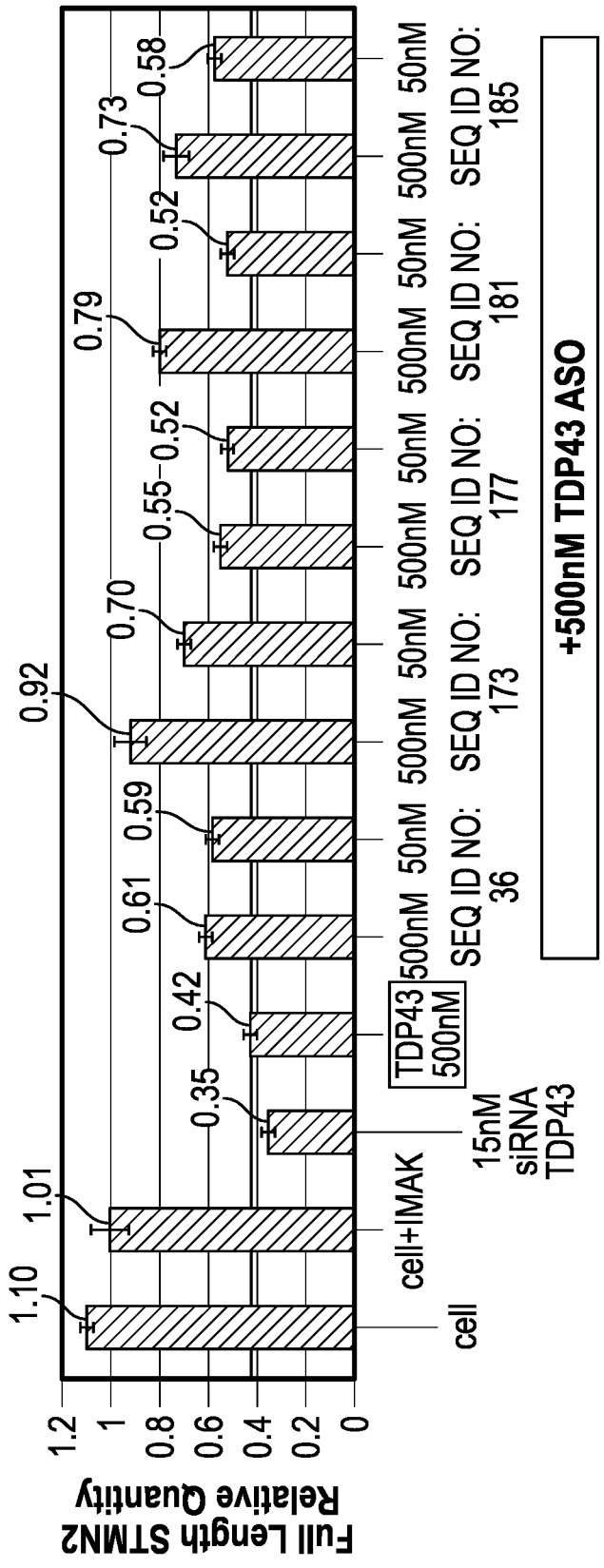

Full Length STMN2
Relative Quantity
1.2
1
0.8
0.6
0.4
0.2
0
1.10
1.01
0.35
0.42
0.61
0.59
0.92
0.70
0.55
0.52
0.79
0.52
0.73
0.58
cell
cell+IMAK
15nM siRNA TDP43
TDP43 500nM
500nM
SEQ ID NO: 36
50nM
500nM
SEQ ID NO: 173
50nM
500nM
SEQ ID NO: 177
50nM
500nM
SEQ ID NO: 181
50nM
500nM
SEQ ID NO: 185
50nM
+500nM TDP43 ASO

FIG. 7B

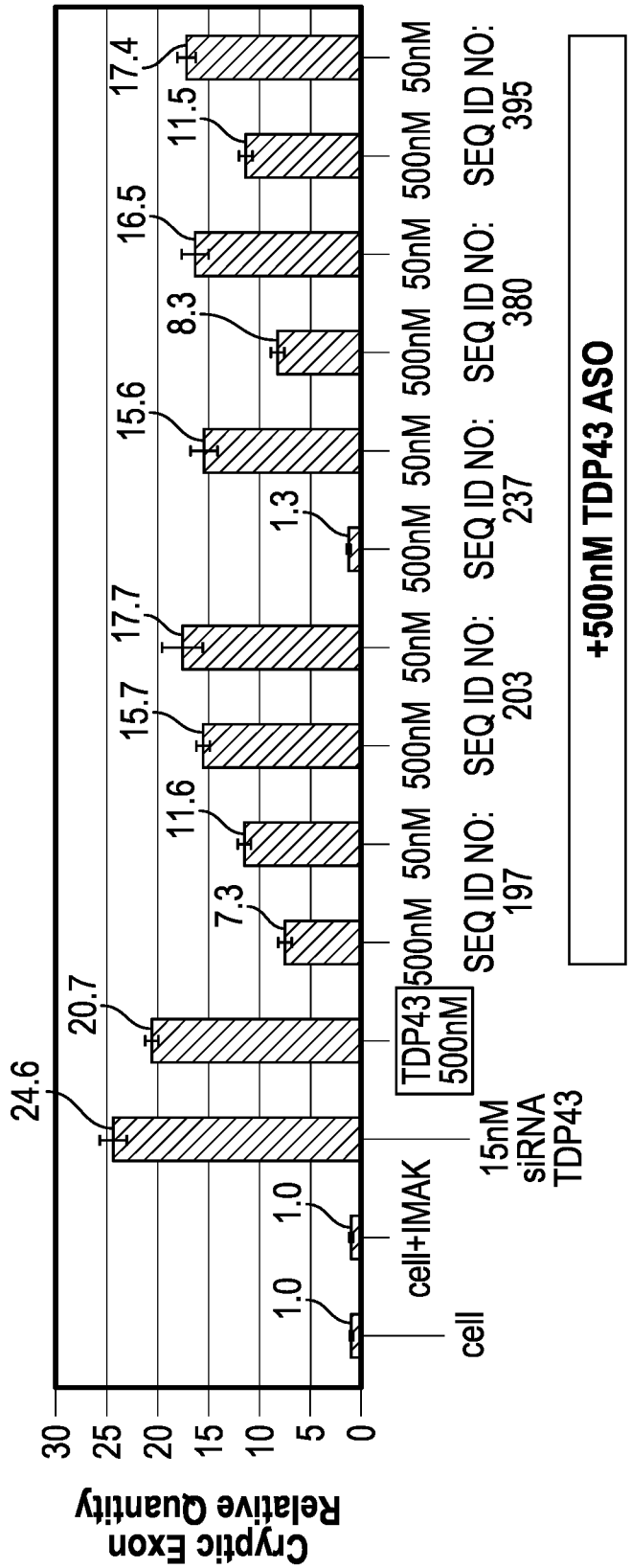

Cryptic Exon Relative Quantity
0
5
10
15
20
25
30
cell
cell+IMAK
15nM siRNA TDP43
TDP43 500nM
500nM 50nM 500nM 50nM 500nM 50nM 500nM 50nM 500nM 50nM
SEQ ID NO: 197
SEQ ID NO: 203
SEQ ID NO: 237
SEQ ID NO: 380
SEQ ID NO: 395
1.0
1.0
24.6
20.7
7.3
11.6
15.7
17.7
1.3
15.6
8.3
16.5
11.5
17.4
+500nM TDP43 ASO

FIG. 8A

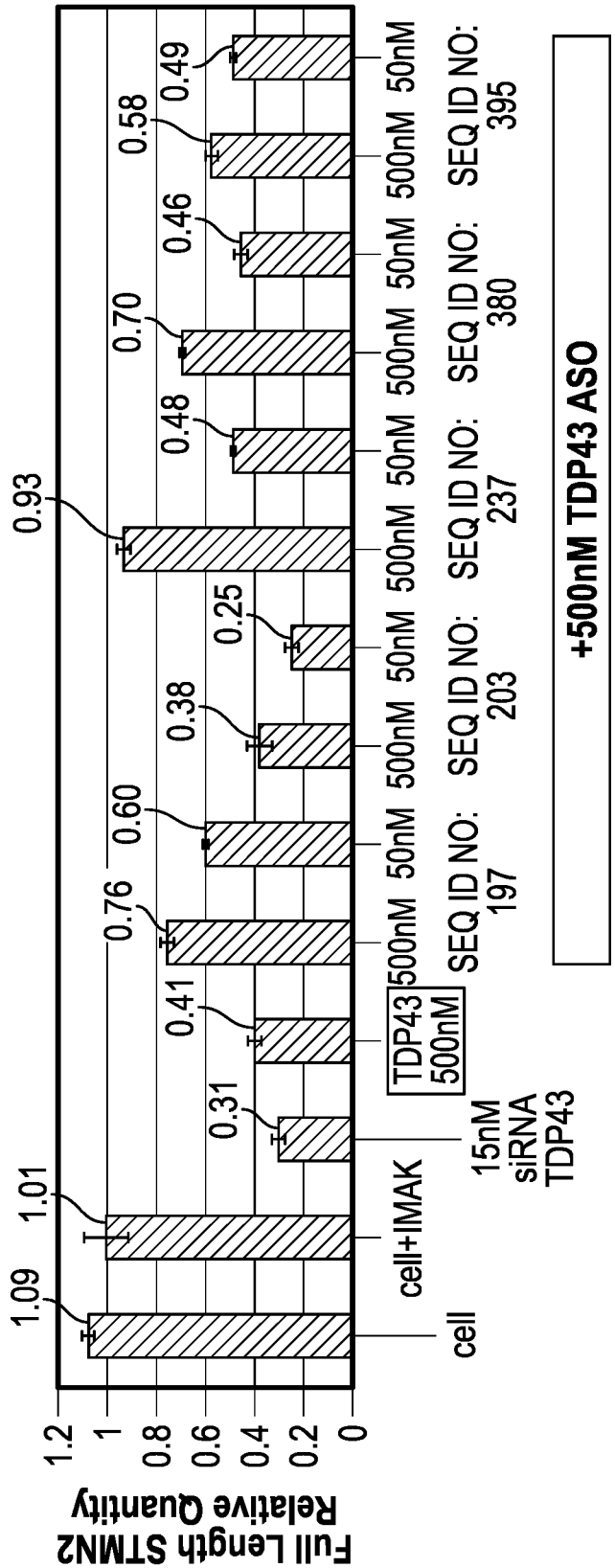

Full Length STMN2
Relative Quantity
1.2
1
0.8
0.6
0.4
0.2
0
1.09
1.01
0.93
0.76
0.60
0.38
0.25
0.41
0.31
0.70
0.48
0.58
0.49
0.46
cell
cell+IMAK
15nM siRNA TDP43
TDP43 500nM
50nM 500nM 50nM 500nM 50nM 500nM 50nM 500nM 50nM 500nM
SEQ ID NO: 197
SEQ ID NO: 203
SEQ ID NO: 237
SEQ ID NO: 380
SEQ ID NO: 395
+500nM TDP43 ASO

FIG. 8B

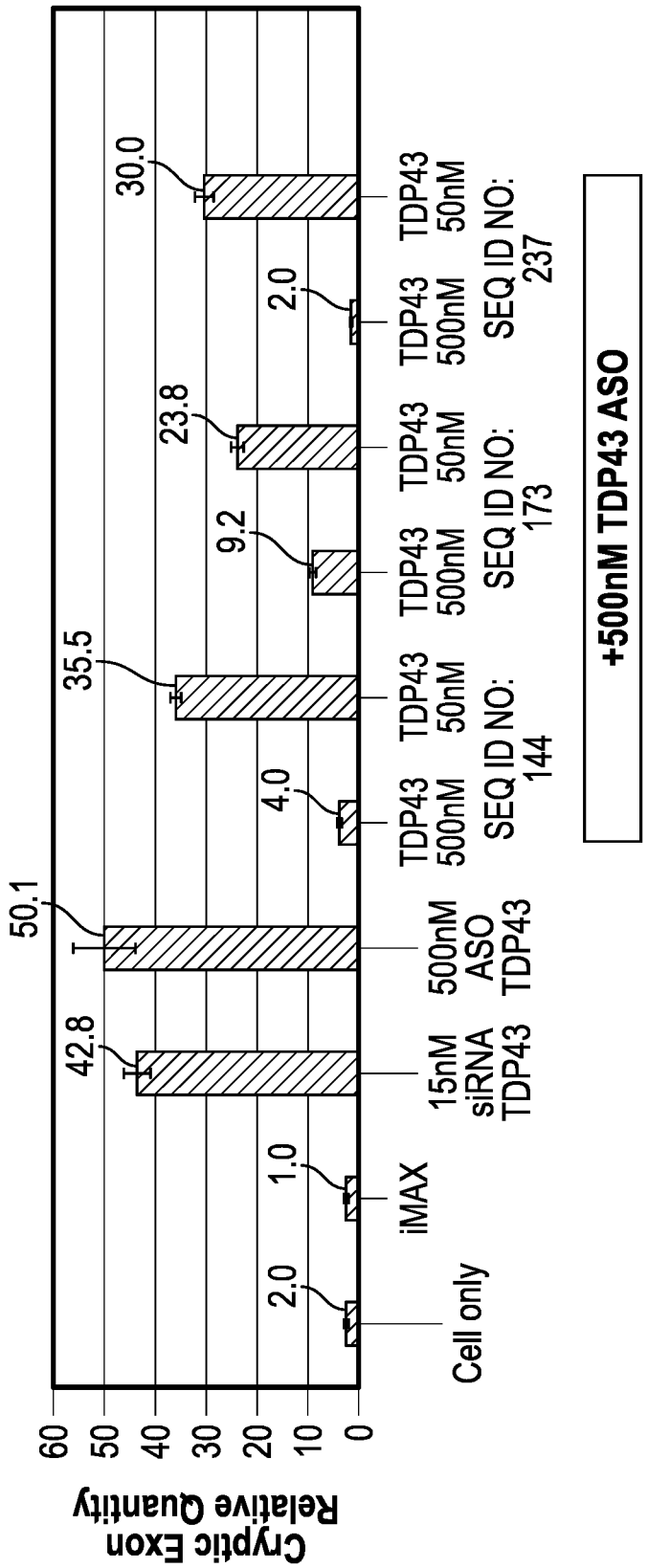

Cryptic Exon Relative Quantity
0
10
20
30
40
50
60
Cell only
iMAX
15nM siRNA TDP43
500nM ASO TDP43
TDP43 500nM
TDP43 50nM SEQ ID NO: 144
TDP43 500nM
TDP43 50nM SEQ ID NO: 173
TDP43 500nM
TDP43 50nM SEQ ID NO: 237
+500nM TDP43 ASO
2.0
1.0
42.8
50.1
4.0
35.5
9.2
23.8
2.0
30.0

FIG. 9A

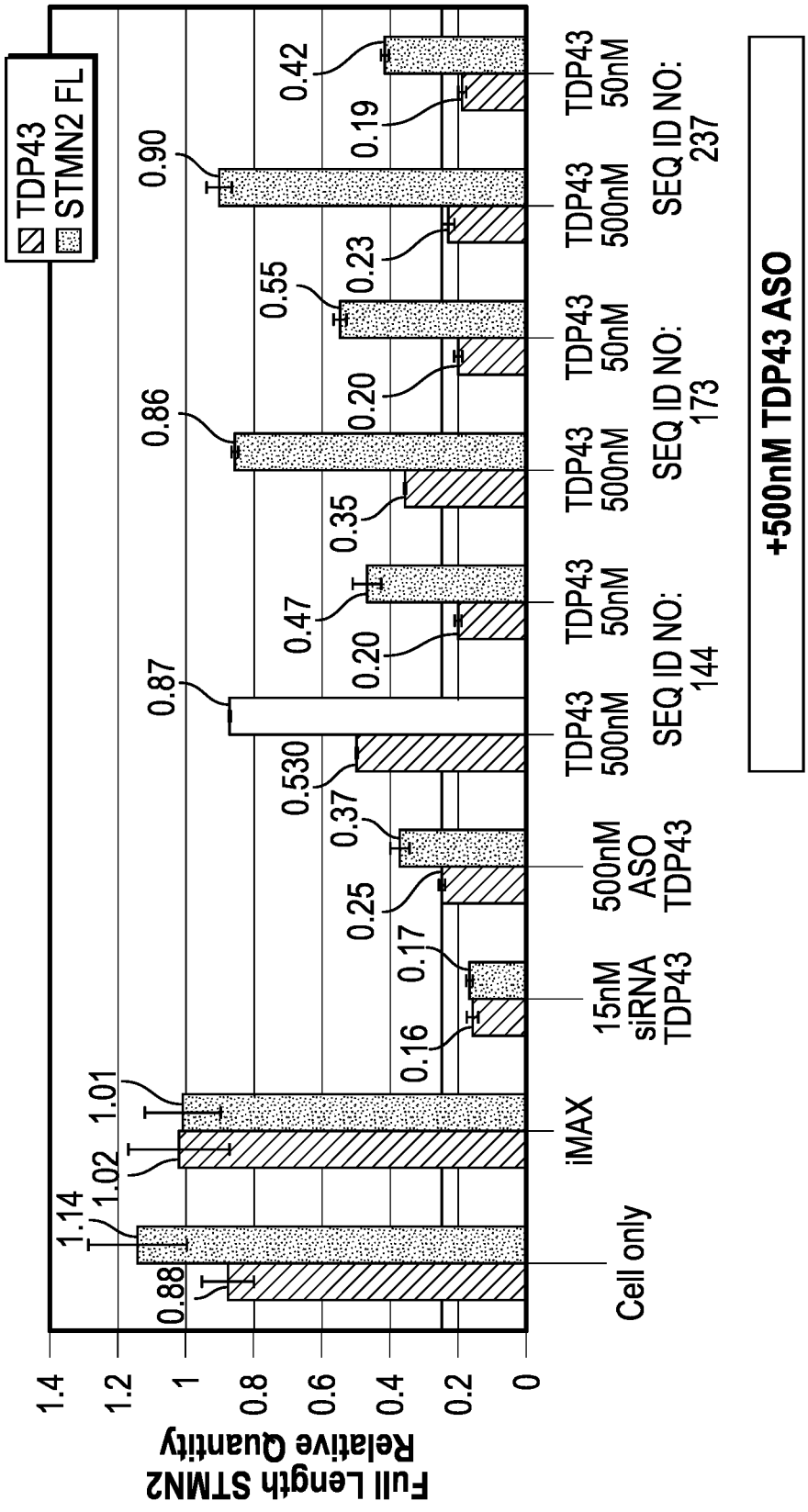

TDP43
STMN2 FL
Full Length STMN2
Relative Quantity
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1.14
1.02
1.01
0.88
0.90
0.86
0.87
0.55
0.47
0.530
0.37
0.25
0.17
0.16
0.42
0.19
0.23
0.20
0.35
0.20
Cell only
iMAX
15nM siRNA TDP43
500nM ASO TDP43
TDP43 500nM
TDP43 50nM
SEQ ID NO: 144
TDP43 500nM
TDP43 50nM
SEQ ID NO: 173
TDP43 500nM
TDP43 50nM
SEQ ID NO: 237
+500nM TDP43 ASO

FIG. 9B

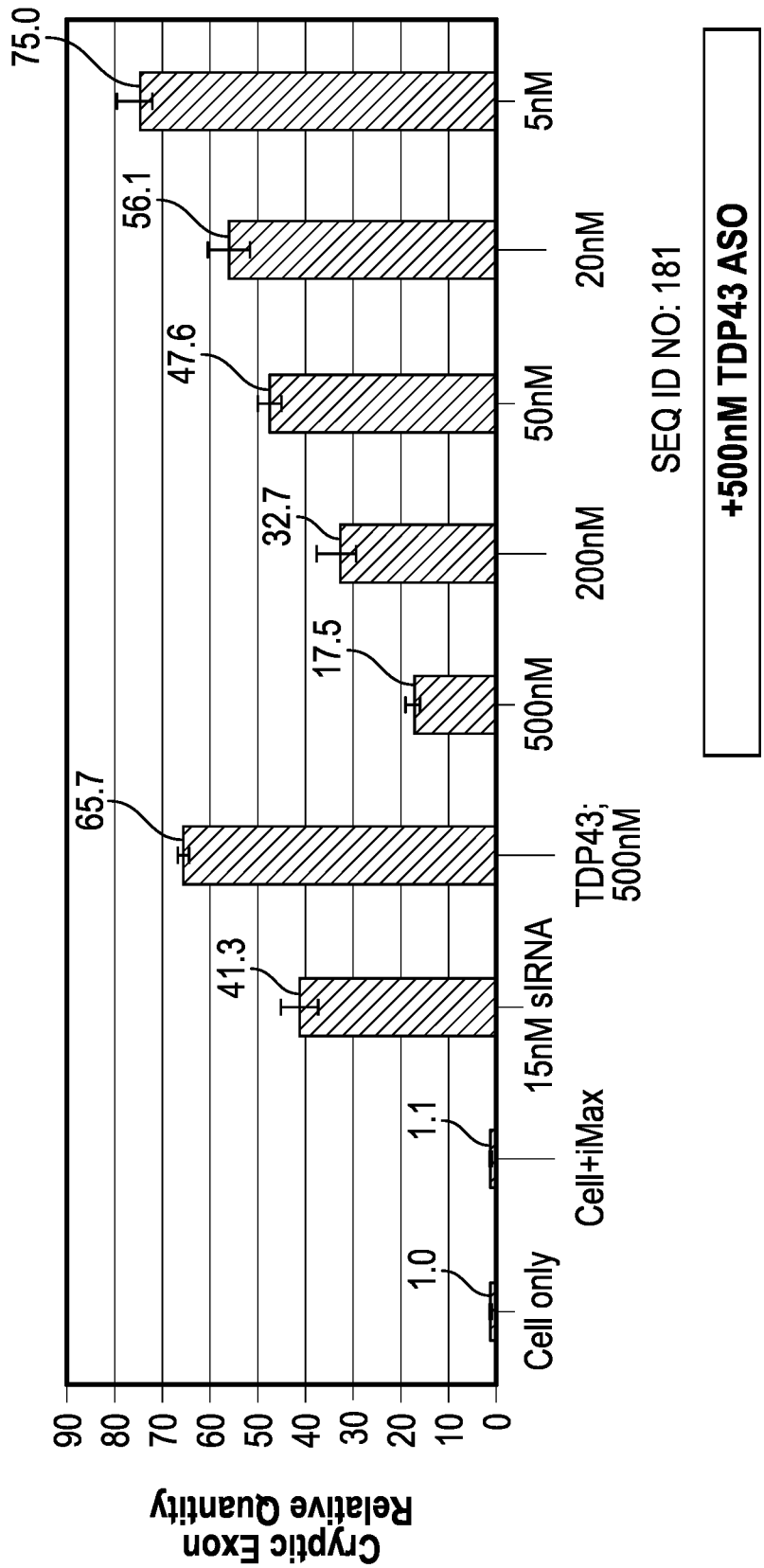

Cryptic Exon Relative Quantity
0
10
20
30
40
50
60
70
80
90
1.0
1.1
41.3
65.7
17.5
32.7
47.6
56.1
75.0
Cell only
Cell+iMax
15nM siRNA
TDP43; 500nM
500nM
200nM
50nM
20nM
5nM
SEQ ID NO: 181
+500nM TDP43 ASO

FIG. 10A

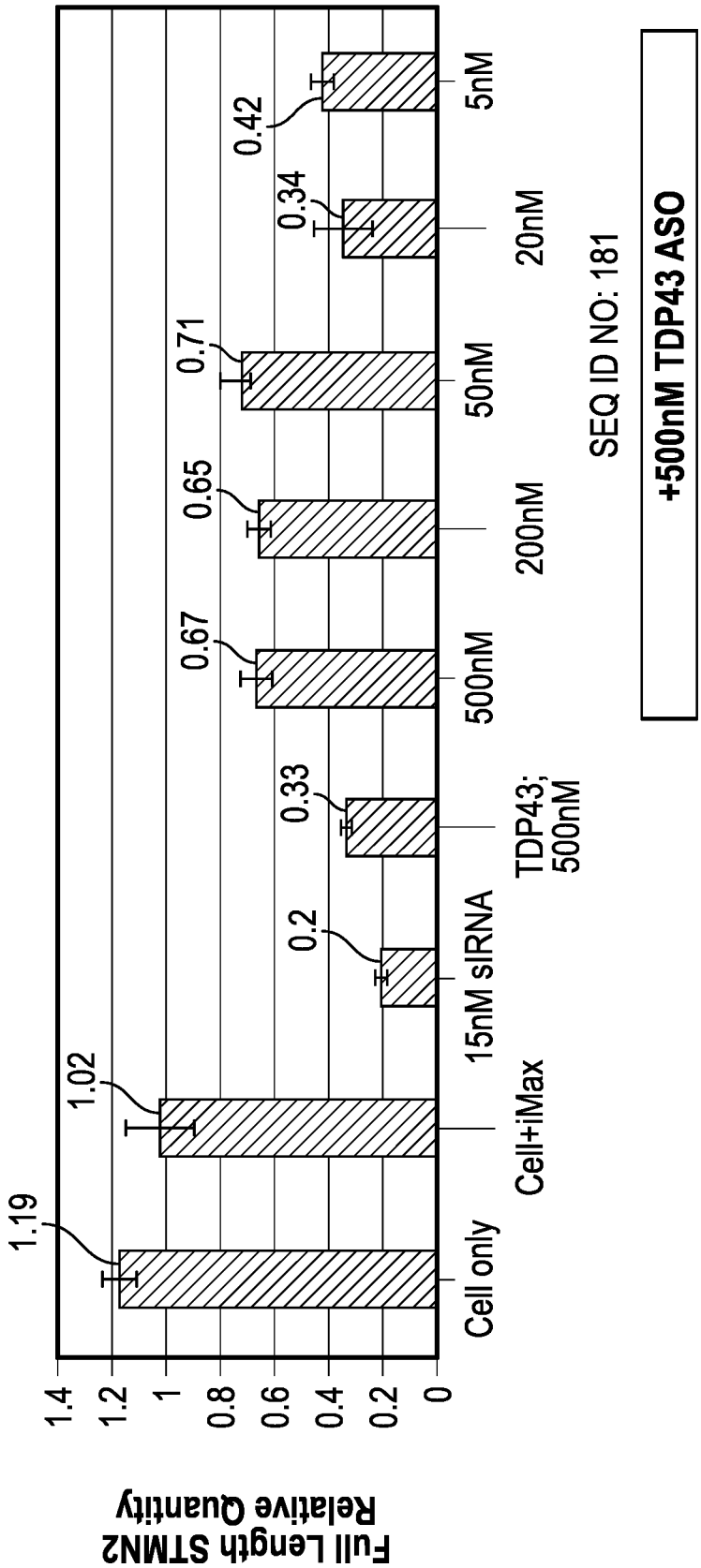

Full Length STMN2
Relative Quantity
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1.19
1.02
0.2
0.33
0.67
0.65
0.71
0.34
0.42
Cell only
Cell+iMax
15nM siRNA
TDP43; 500nM
500nM
200nM
50nM
20nM
5nM
SEQ ID NO: 181
+500nM TDP43 ASO

FIG. 10B

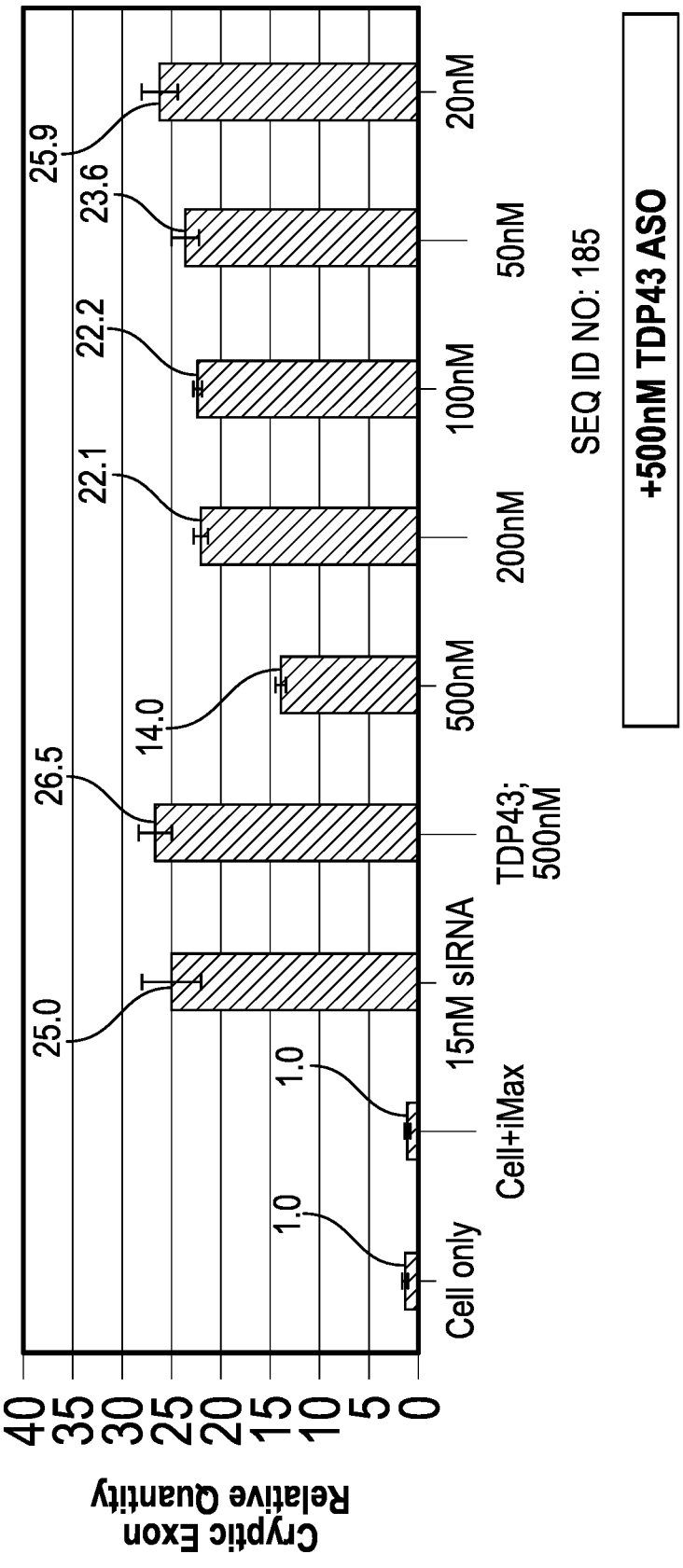

Cryptic Exon
Relative Quantity
40
35
30
25
20
15
10
5
0
Cell only
Cell+iMax
15nM siRNA
TDP43;
500nM
500nM
200nM
100nM
50nM
20nM
SEQ ID NO: 185
+500nM TDP43 ASO
25.0
1.0
1.0
26.5
14.0
22.1
22.2
23.6
25.9

FIG. 11A

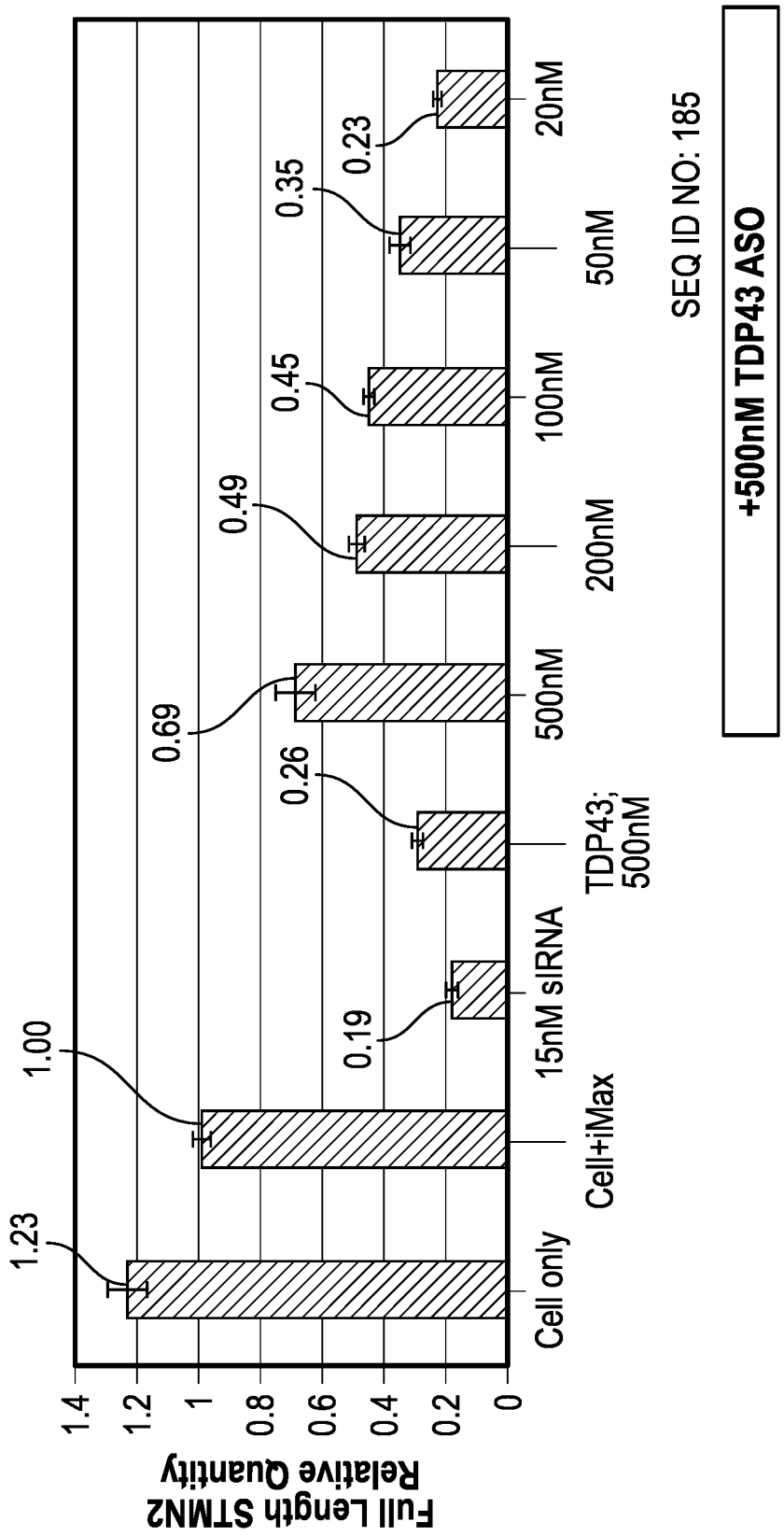

Full Length STMN2
Relative Quantity
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1.23
1.00
0.19
0.69
0.26
0.49
0.45
0.35
0.23
Cell only
Cell+iMax
15nM siRNA
TDP43; 500nM
500nM
200nM
100nM
50nM
20nM
SEQ ID NO: 185
+500nM TDP43 ASO

FIG. 11B

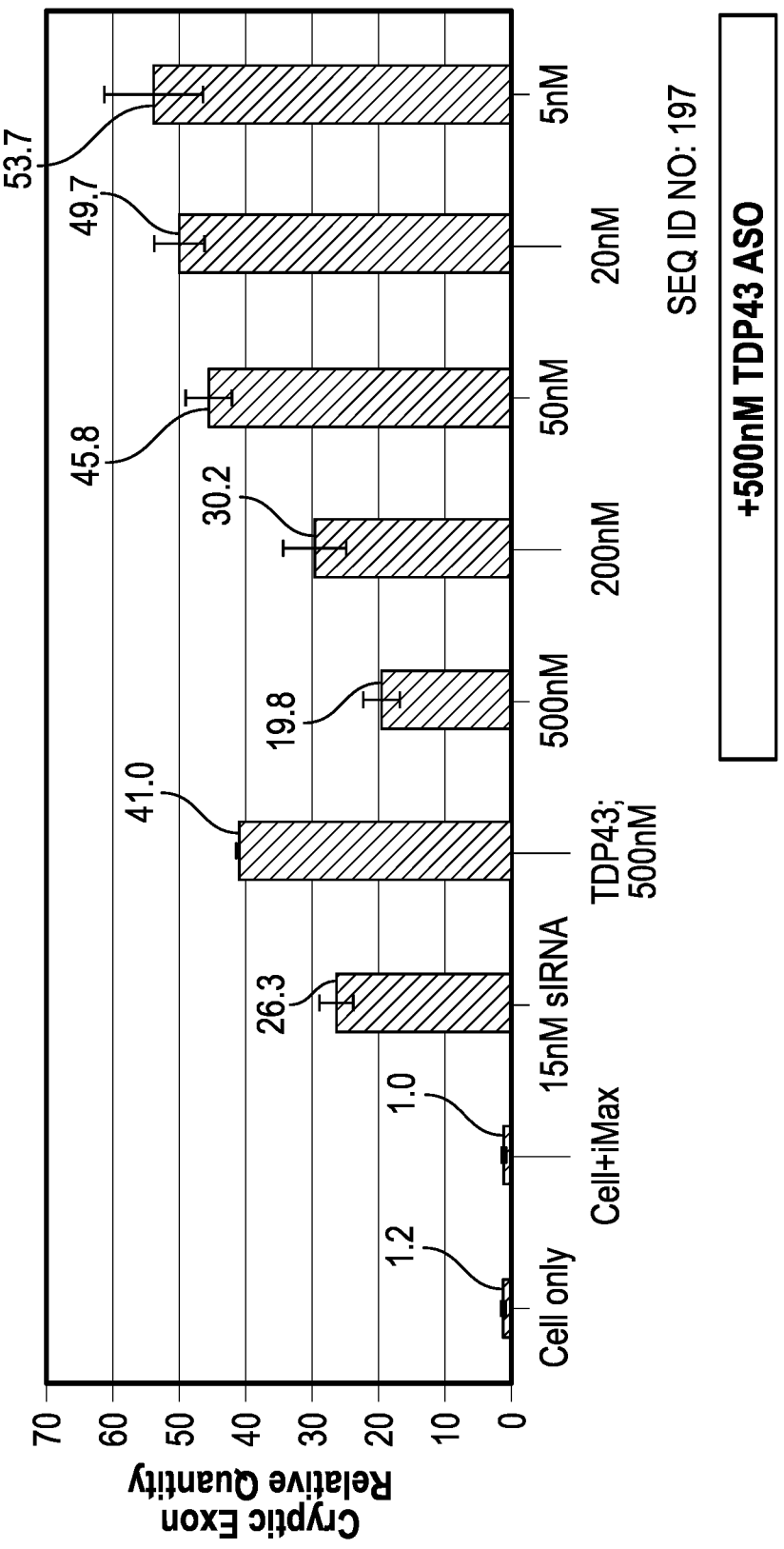

Cryptic Exon Relative Quantity
70
60
50
40
30
20
10
0
53.7
49.7
45.8
30.2
19.8
41.0
26.3
1.0
1.2
Cell only
Cell+iMax
15nM siRNA
TDP43; 500nM
500nM
200nM
50nM
20nM
5nM
SEQ ID NO: 197
+500nM TDP43 ASO

FIG. 12A

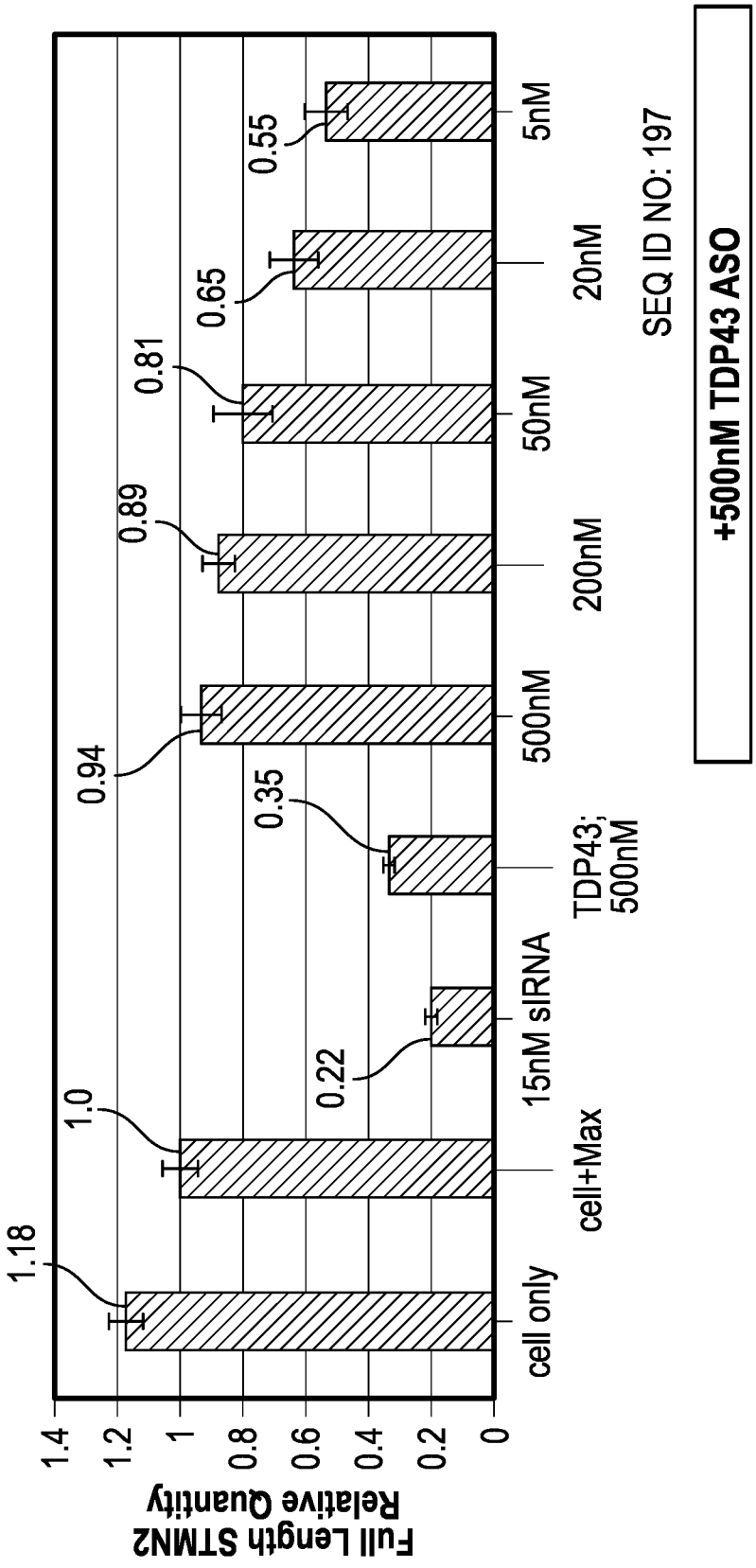

Full Length STMN2
Relative Quantity
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1.18
1.0
0.22
0.35
0.94
0.89
0.81
0.65
0.55
cell only
cell+Max
15nM siRNA
TDP43; 500nM
500nM
200nM
50nM
20nM
5nM
SEQ ID NO: 197
+500nM TDP43 ASO

FIG. 12B

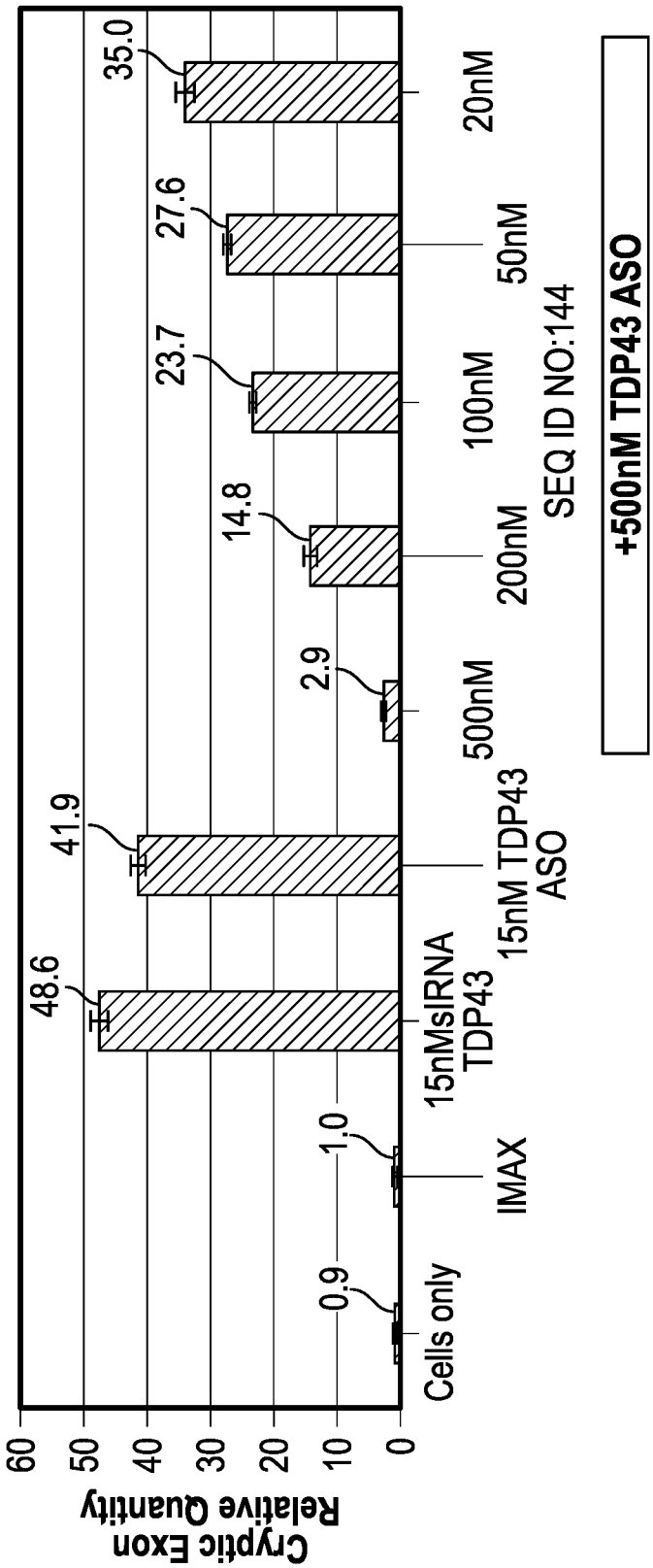

Cryptic Exon Relative Quantity
60
50
40
30
20
10
0
0.9
1.0
48.6
41.9
2.9
14.8
23.7
27.6
35.0
Cells only
IMAX
15nMsIRNA TDP43
15nM TDP43 ASO
500nM
200nM
100nM
50nM
20nM
SEQ ID NO:144
+500nM TDP43 ASO

FIG. 13A

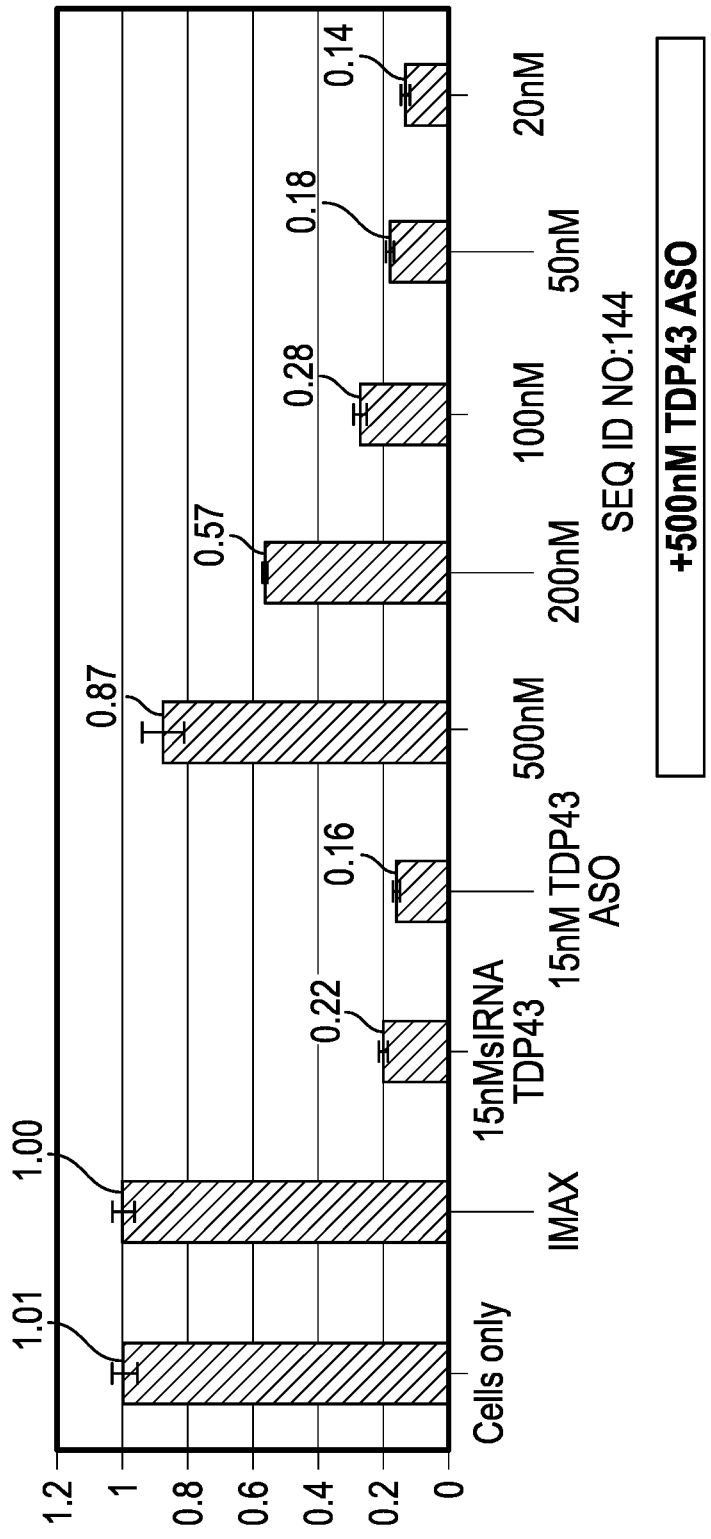

1.2
1
0.8
0.6
0.4
0.2
0
1.01
1.00
0.22
0.16
0.87
0.57
0.28
0.18
0.14
Cells only
IMAX
15nMsIRNA TDP43
15nM TDP43 ASO
500nM
200nM
100nM
50nM
20nM
SEQ ID NO:144
+500nM TDP43 ASO

FIG. 13B

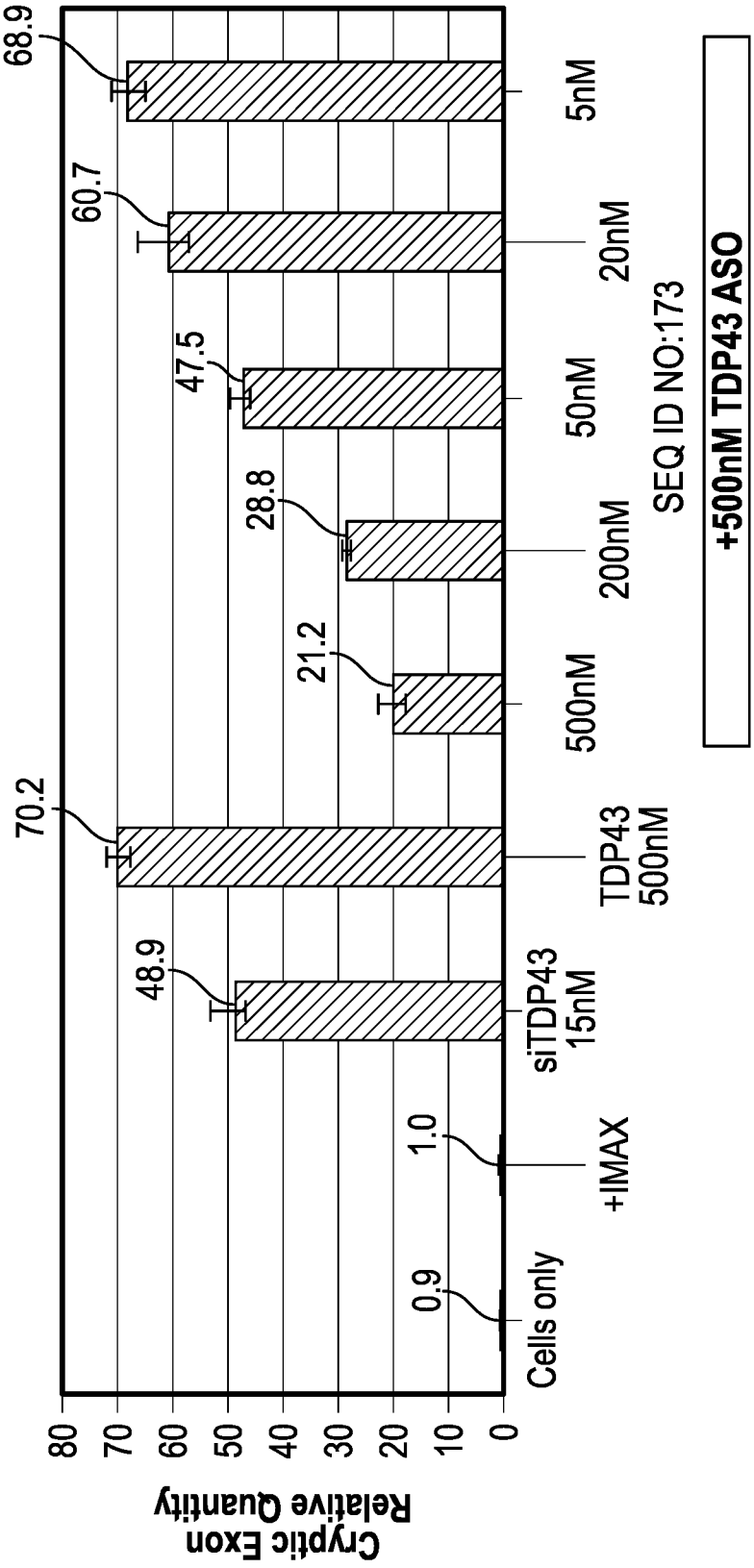

Cryptic Exon Relative Quantity
0
10
20
30
40
50
60
70
80
Cells only
0.9
+IMAX
1.0
siTDP43 15nM
48.9
TDP43 500nM
70.2
500nM
21.2
200nM
28.8
50nM
47.5
20nM
60.7
5nM
68.9
SEQ ID NO:173
+500nM TDP43 ASO

FIG. 14A

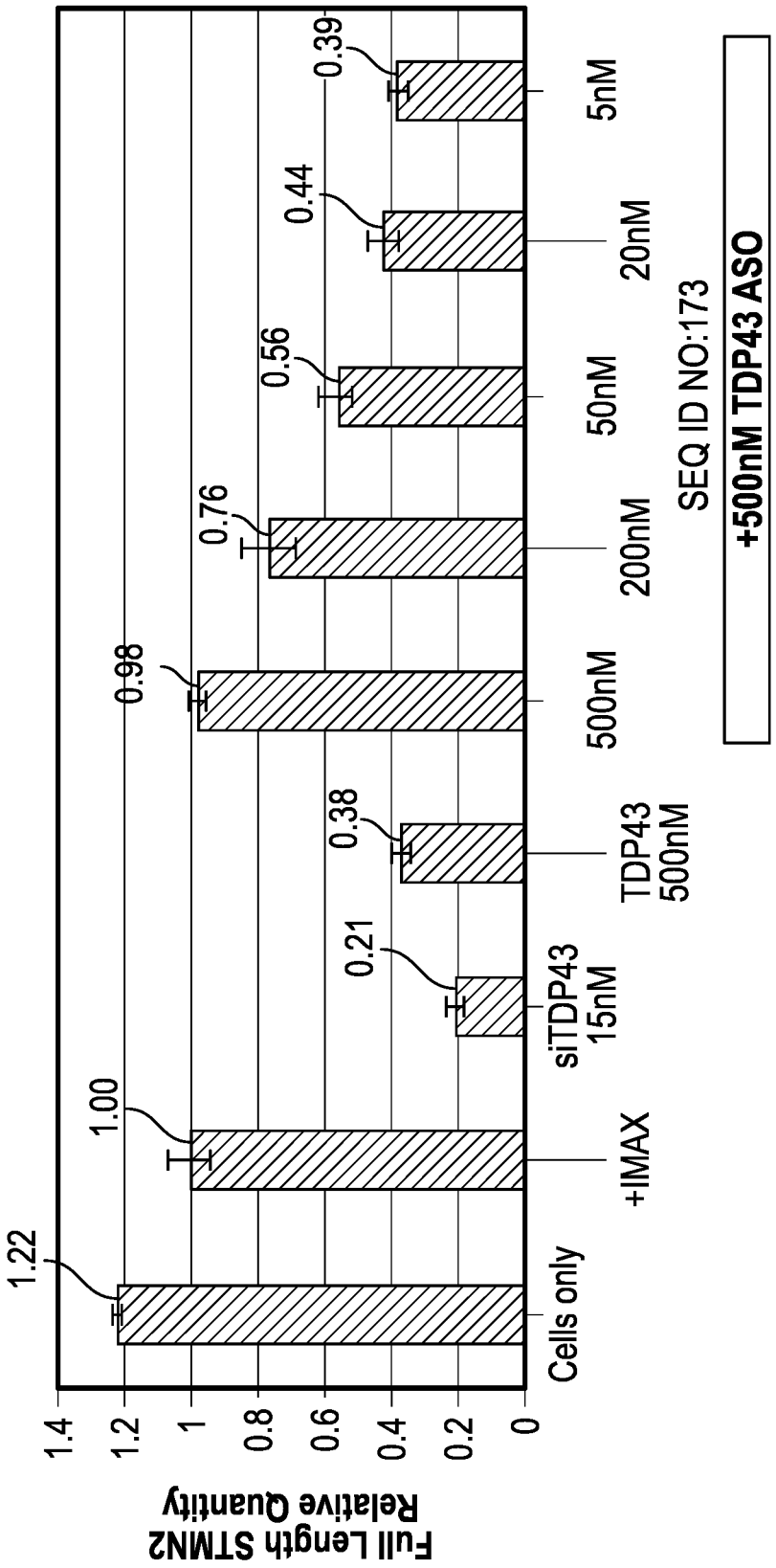

Full Length STMN2
Relative Quantity
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.22
1.00
0.21
0.38
0.98
0.76
0.56
0.44
0.39
Cells only
+IMAX
siTDP43
15nM
TDP43
500nM
500nM
200nM
50nM
20nM
5nM
SEQ ID NO:173
+500nM TDP43 ASO

FIG. 14B

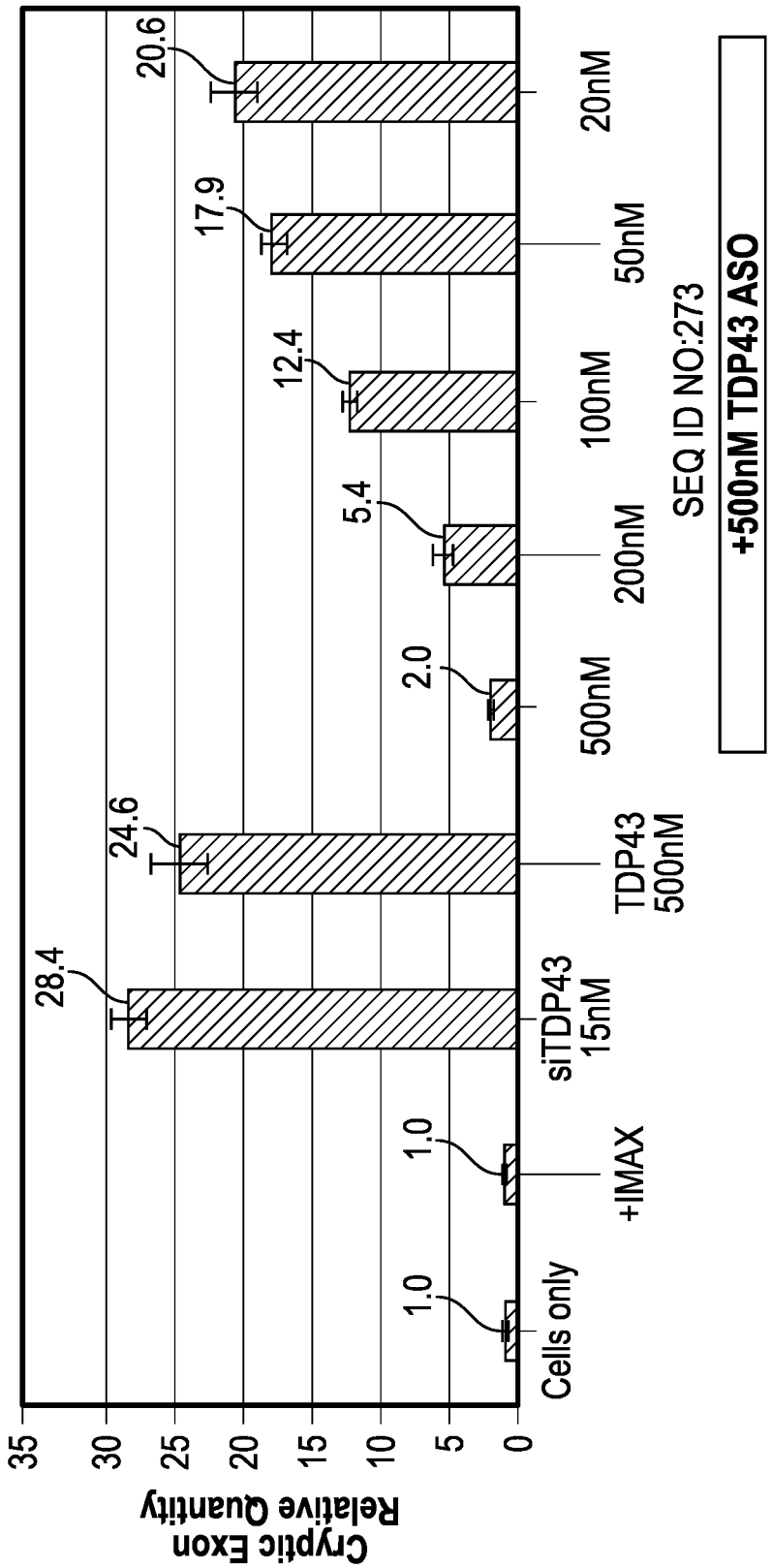

Cryptic Exon
Relative Quantity
35
30
25
20
15
10
5
0
Cells only
+IMAX
siTDP43
15nM
TDP43
500nM
500nM
200nM
100nM
50nM
20nM
SEQ ID NO:273
+500nM TDP43 ASO
1.0
1.0
28.4
24.6
2.0
5.4
12.4
17.9
20.6

FIG. 15A

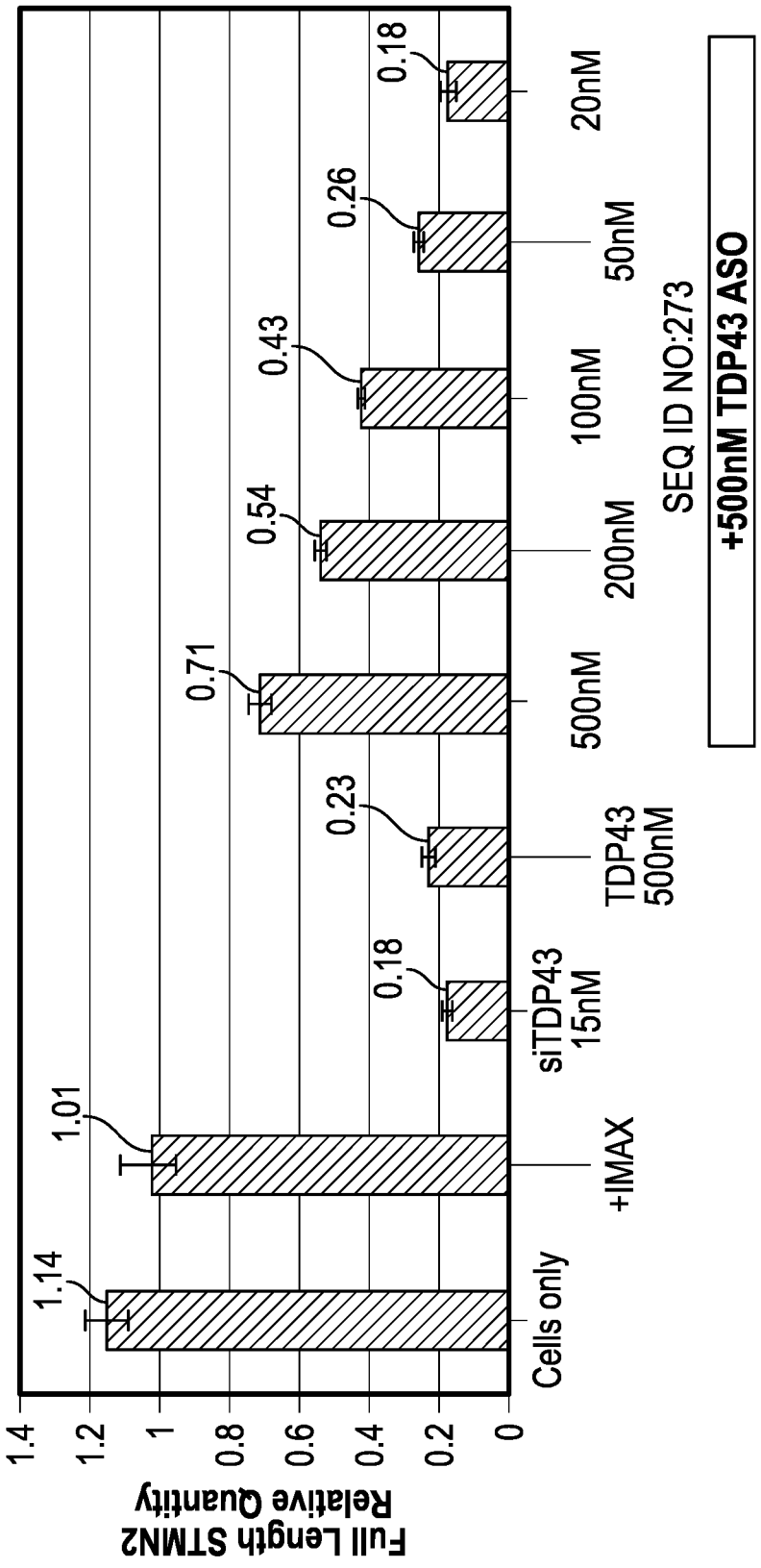

Full Length STMN2
Relative Quantity
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1.14
1.01
0.18
0.23
0.71
0.54
0.43
0.26
0.18
Cells only
+IMAX
siTDP43 15nM
TDP43 500nM
500nM
200nM
100nM
50nM
20nM
SEQ ID NO:273
+500nM TDP43 ASO

FIG. 15B

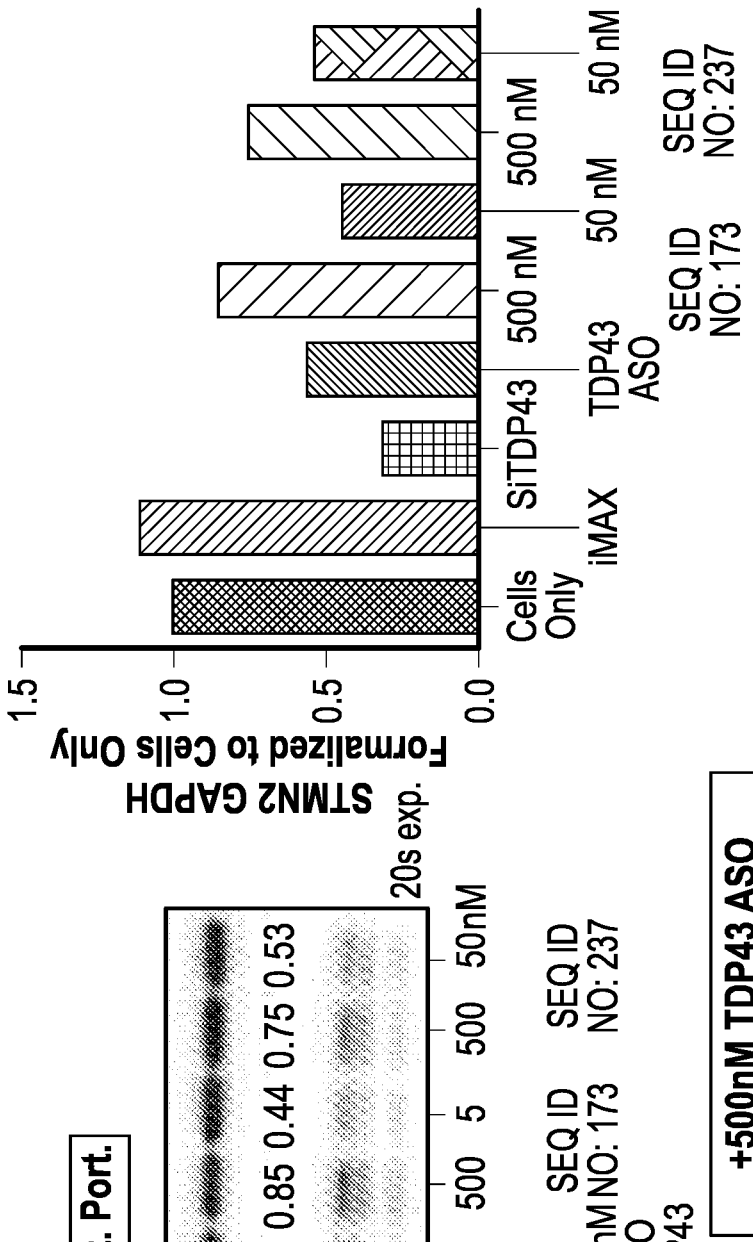

STMN2 GAPDH
Formalized to Cells Only
1.5
1.0
0.5
0.0
Cells Only
iMAX
SiTDP43
TDP43 ASO
500 nM
50 nM
SEQ ID NO: 173
SEQ ID NO: 237
10ug tot. Port.
GAPDH (1:10 000)
Relative Level STMN2 (1:20 000)
(xxx)
35
25
20
17
1.0 1.10 0.31 0.56 0.85 0.44 0.75 0.53
20s exp.
Cells only
IMAX
15nM siRNA TDP43
500nM ASO TDP43
500 5 500 50nM
SEQ ID NO: 173
SEQ ID NO: 237
+500nM TDP43 ASO

FIG. 16

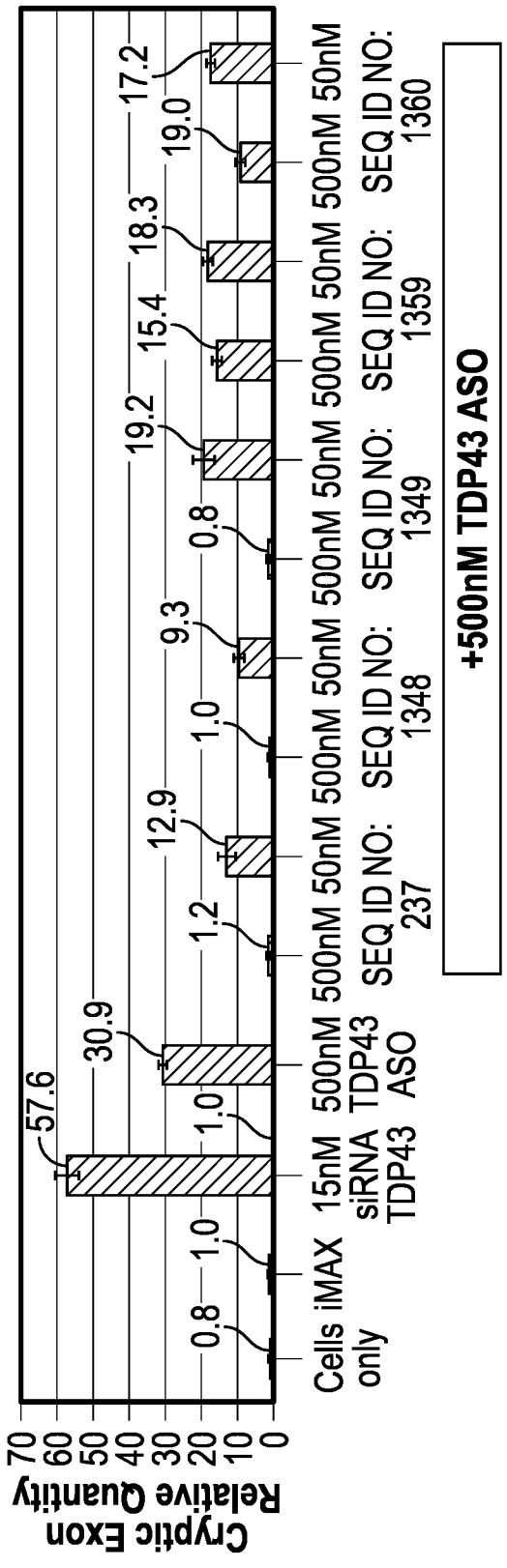


FIG. 17A

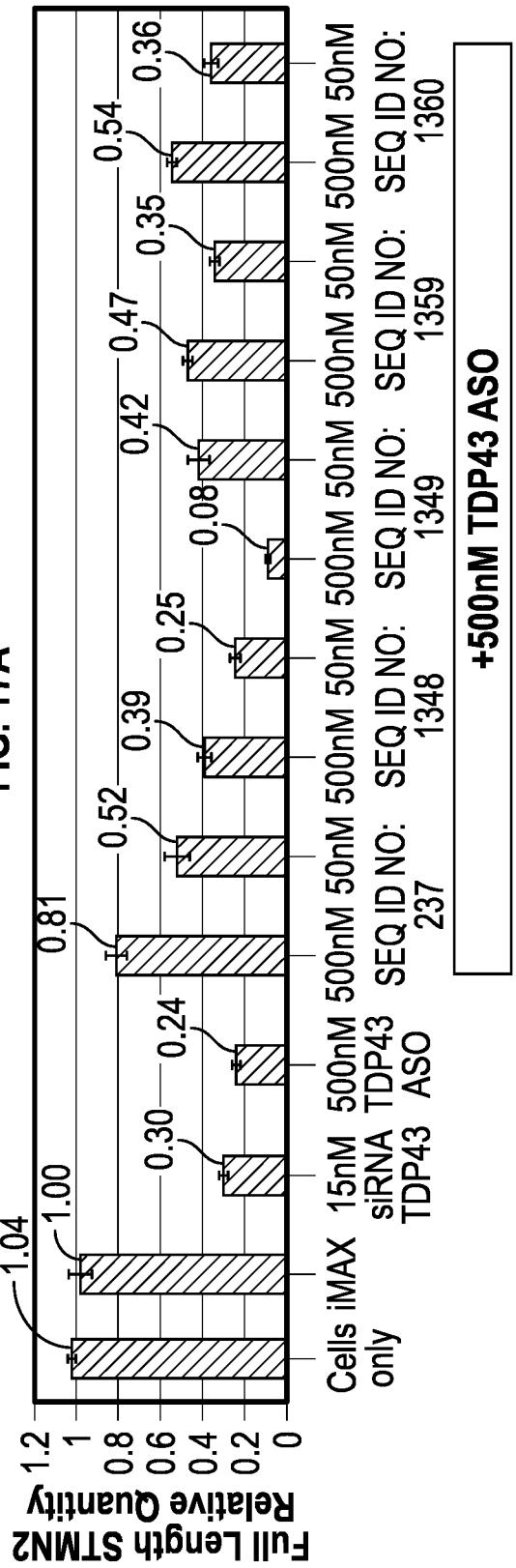
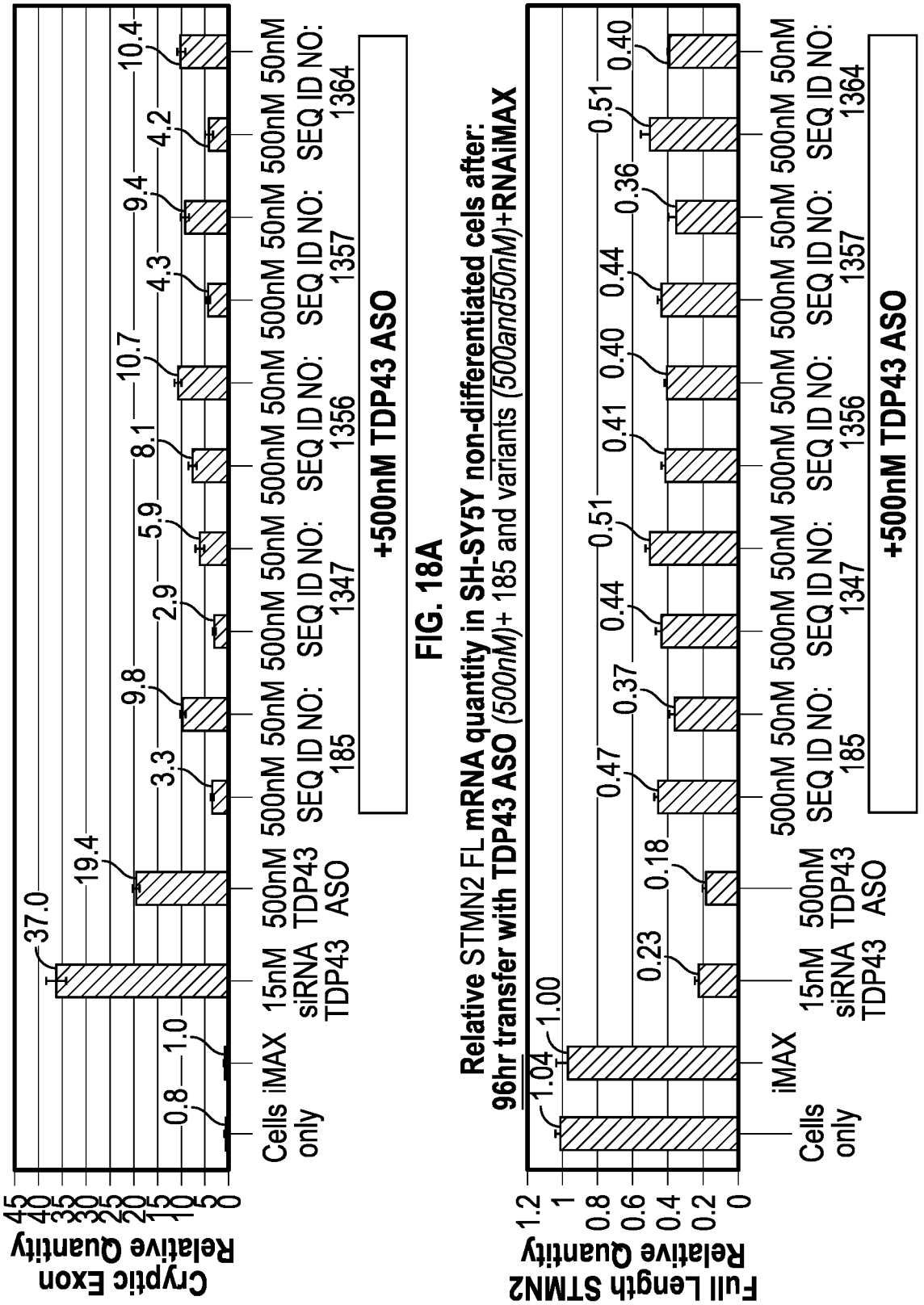


FIG. 17B

FIG. 18A



Relative STMN2 FL mRNA quantity in SH-SY5Y non-differentiated cels after: 96hr transfer with TDP43 ASO *(500nM)*+ 185 and variants *(500and50nM)*+**RNAiMAX**

FIG. 18B

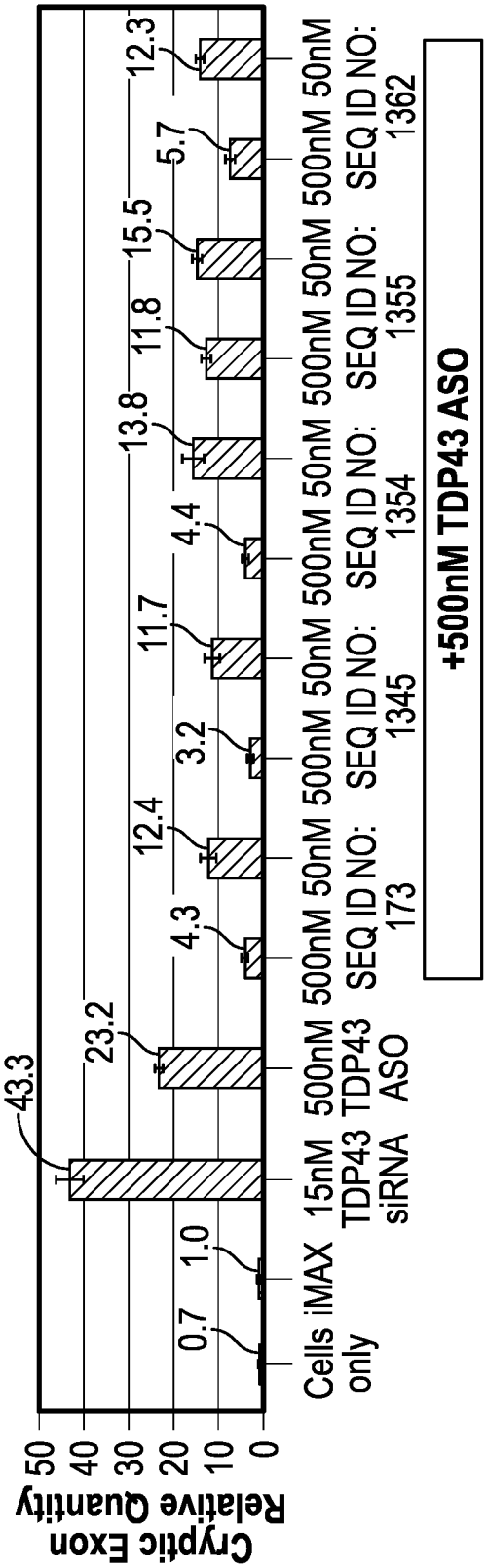


FIG. 19A

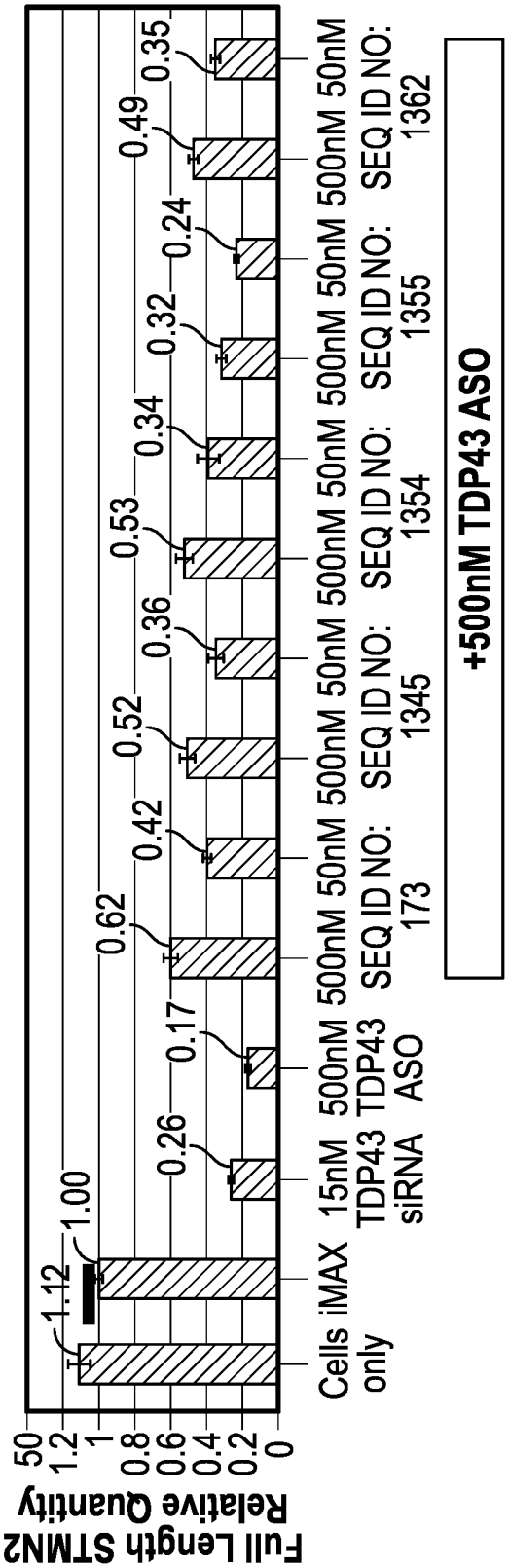


FIG. 19B

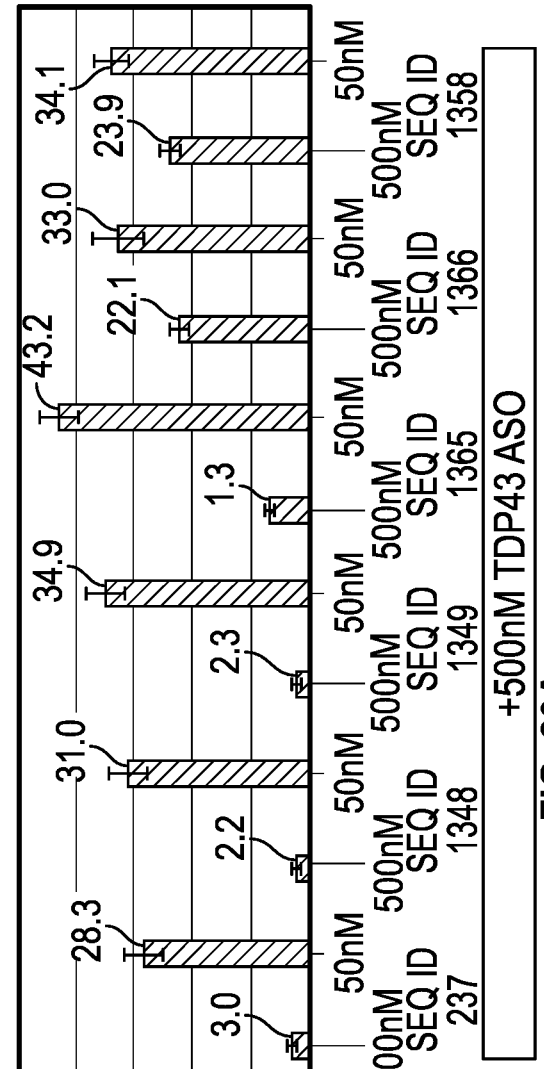


FIG. 20A

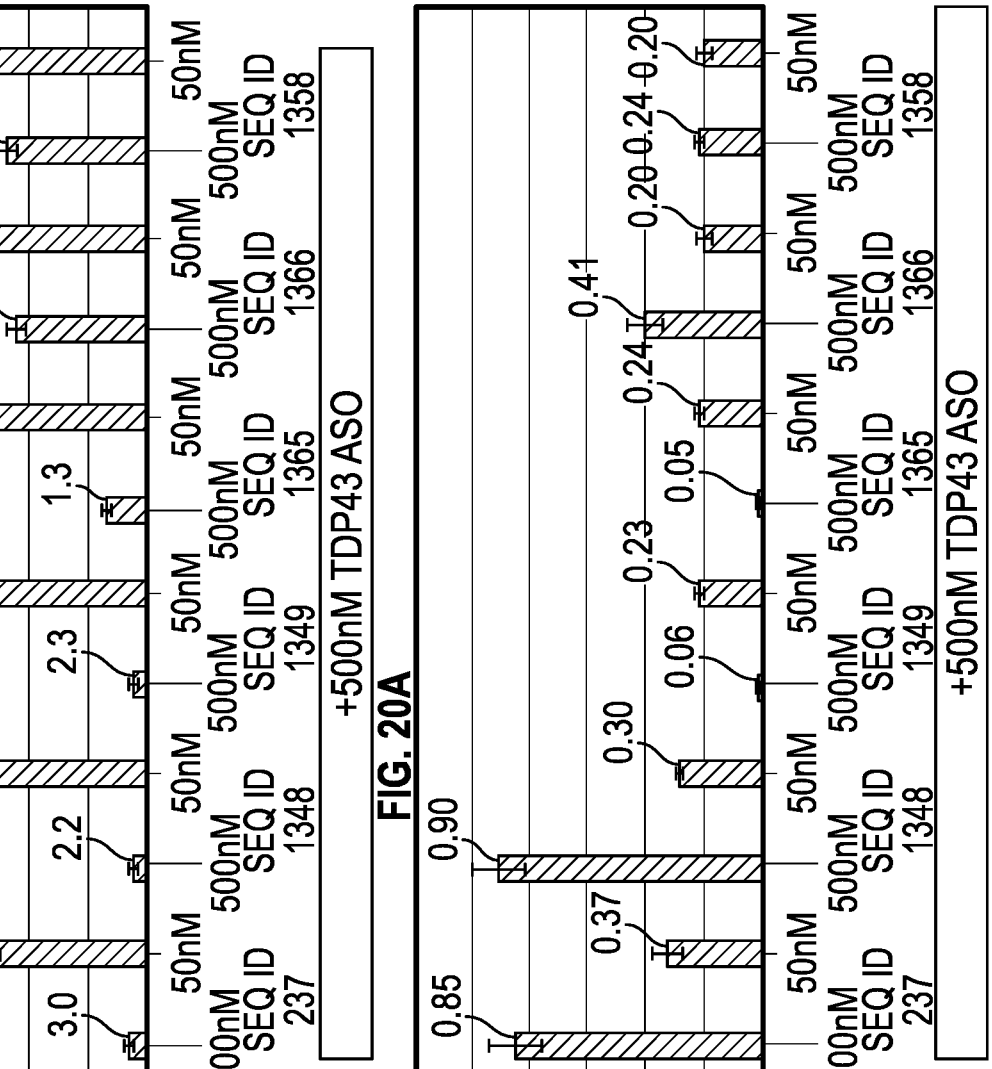


FIG. 20B

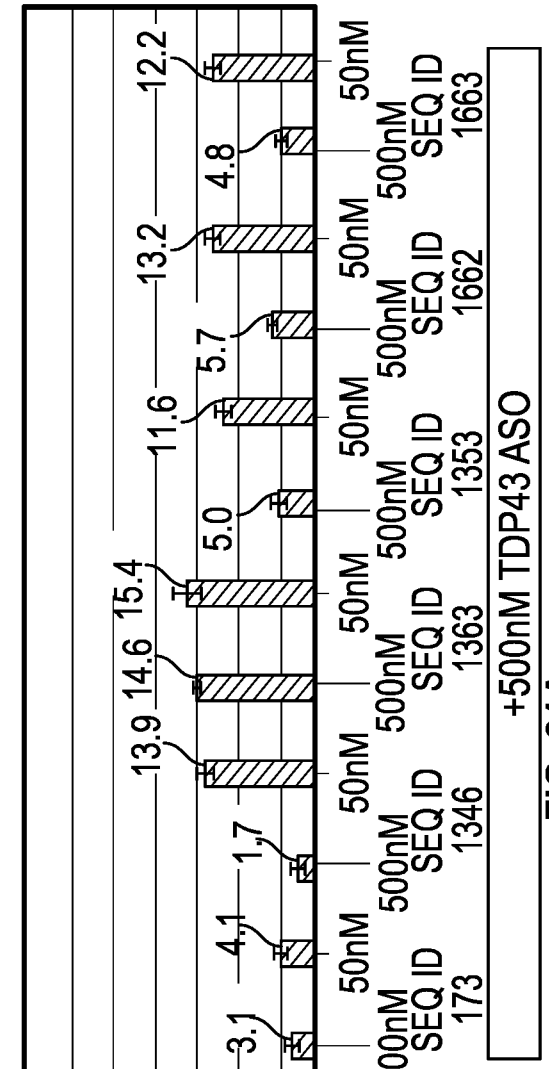


FIG. 21A

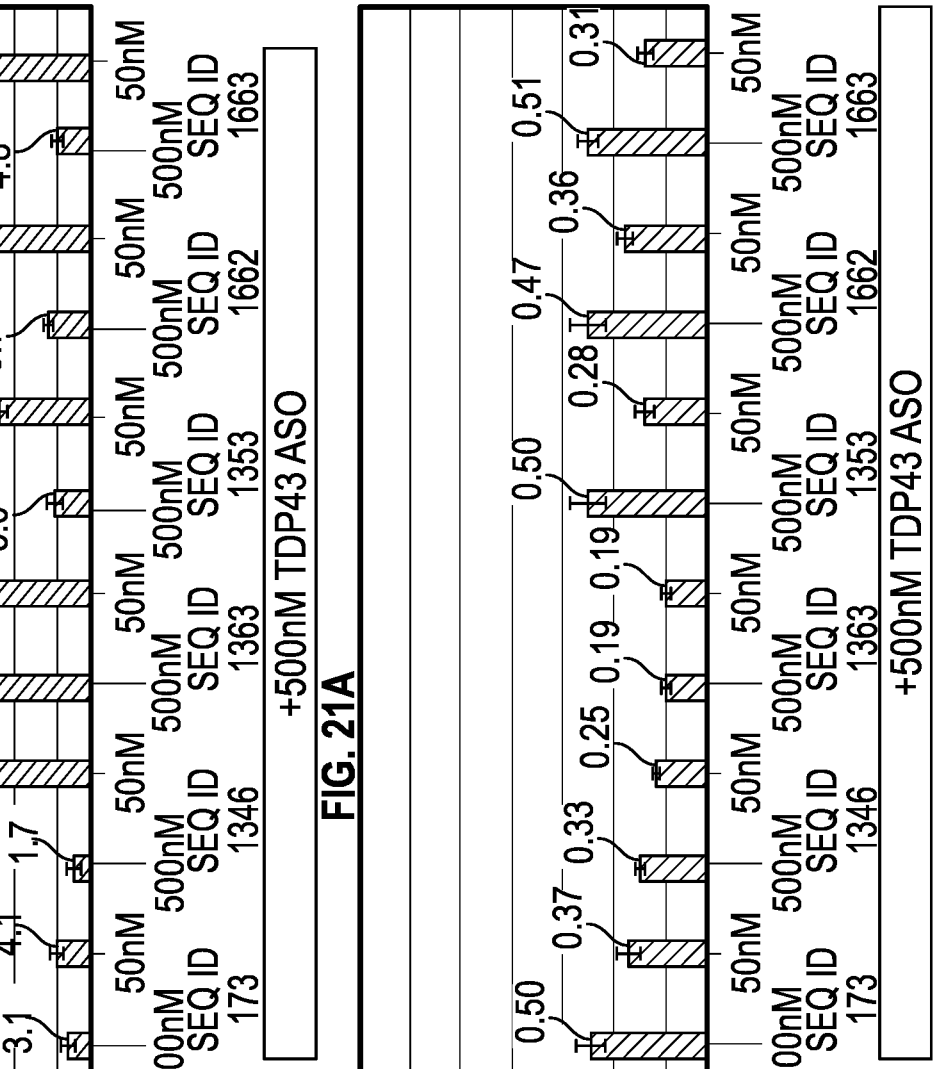


FIG. 21B

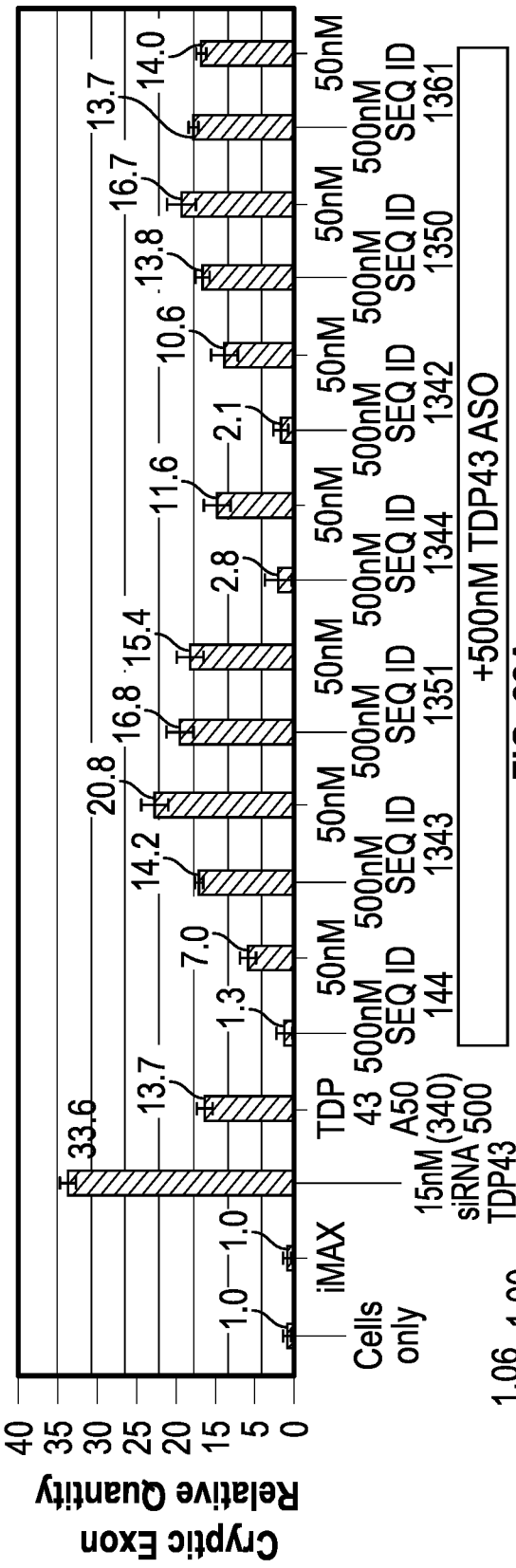


FIG. 22A

FIG. 22B

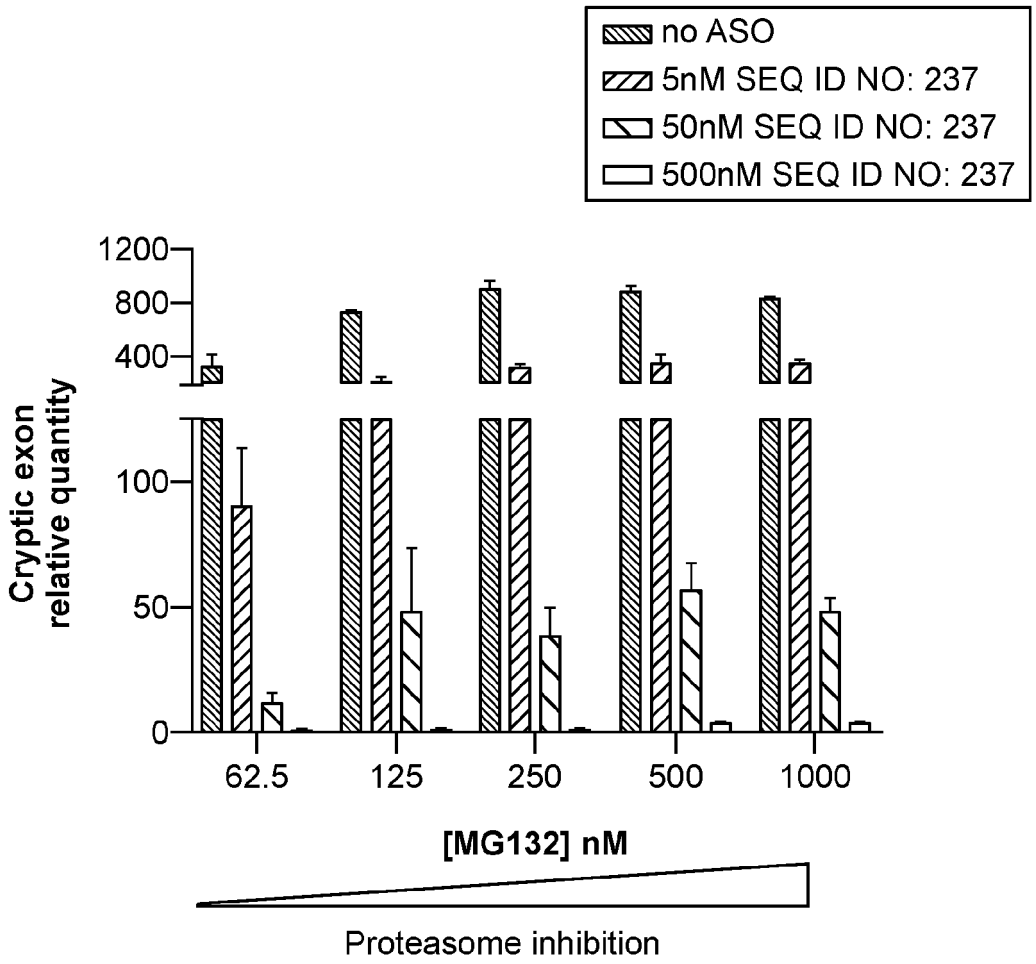

no ASO
5nM SEQ ID NO: 237
50nM SEQ ID NO: 237
500nM SEQ ID NO: 237
1200
800
400
100
50
0
Cryptic exon relative quantity
62.5
125
250
500
1000
[MG132] nM
Proteasome inhibition

FIG. 23

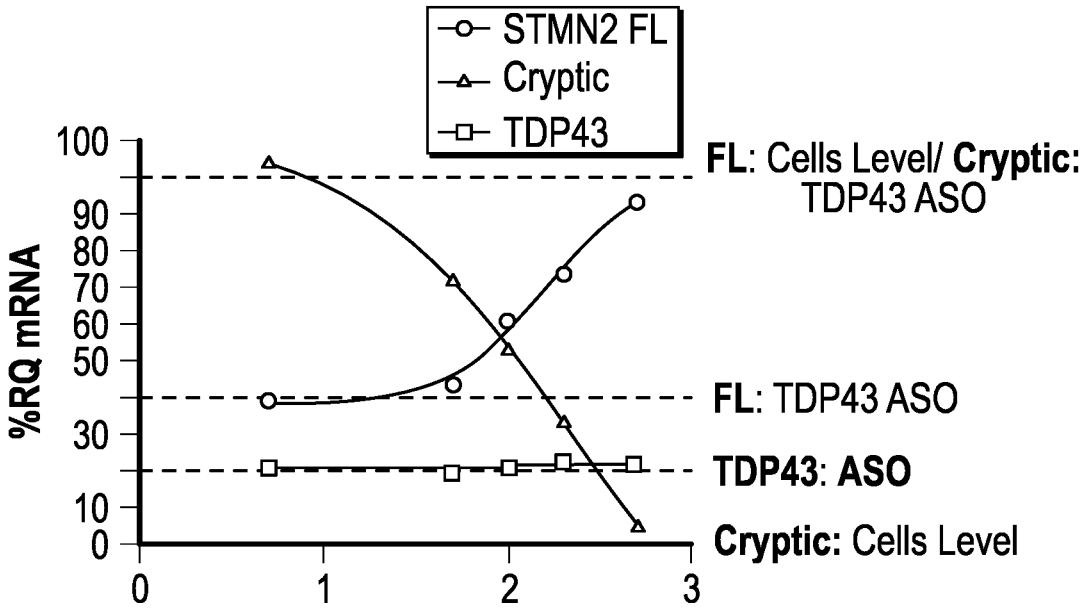


FIG. 24

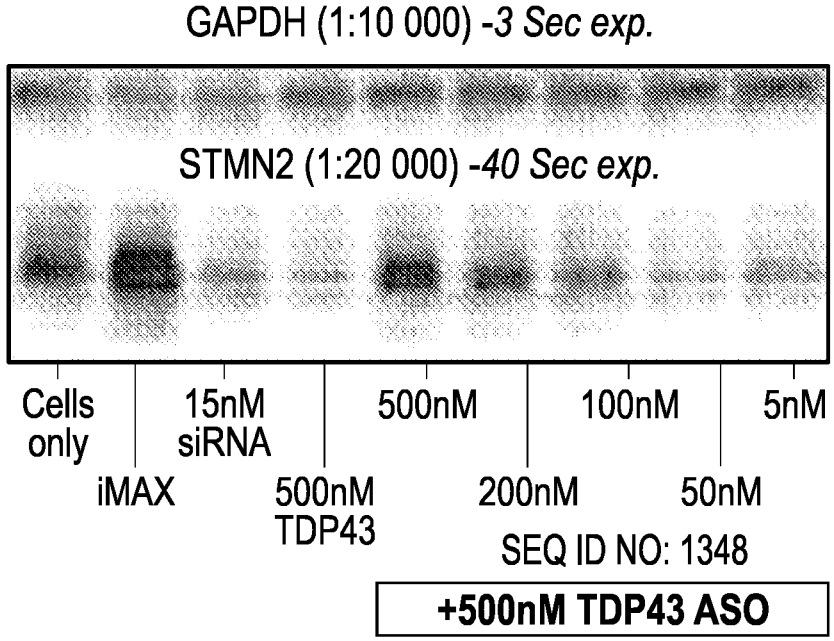


FIG. 25A

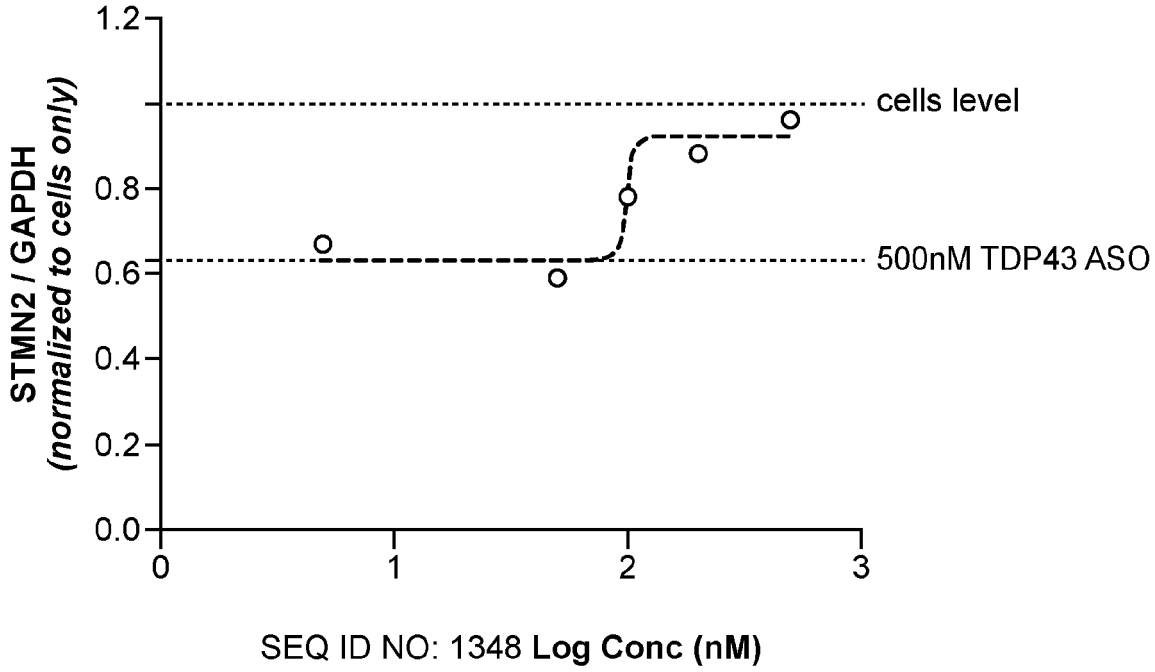

1.2
0.8
0.6
0.4
0.2
0.0
0
1
2
3
STMN2 / GAPDH
(normalized to cells only)
cells level
500nM TDP43 ASO
SEQ ID NO: 1348 Log Conc (nM)

FIG. 25B

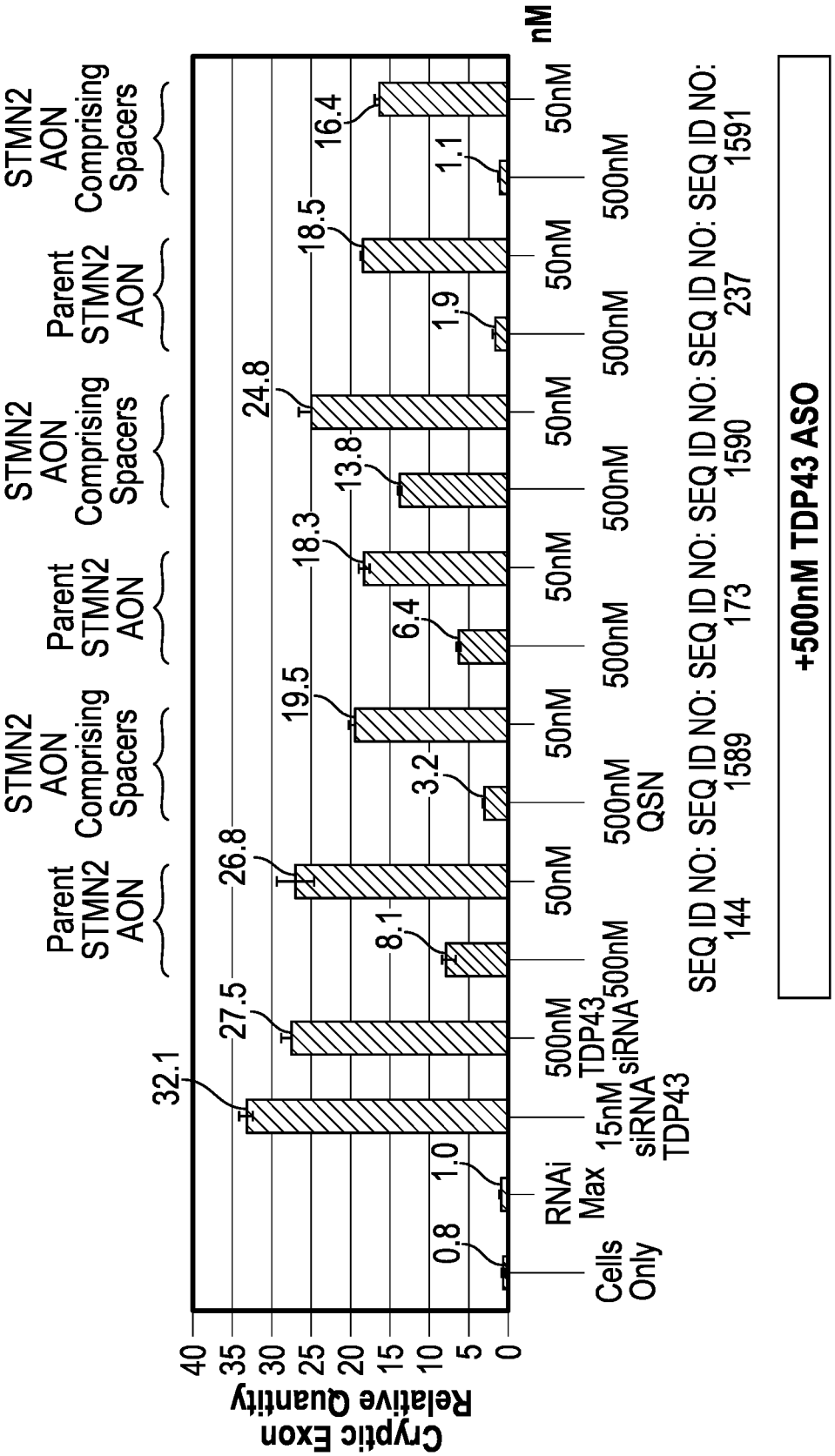

Cryptic Exon Relative Quantity
0
5
10
15
20
25
30
35
40
nM
Cells Only
RNAi Max
15nM siRNA TDP43
500nM TDP43 siRNA
500nM QSN
Parent STMN2 AON
STMN2 AON Comprising Spacers
50nM
500nM
0.8
1.0
32.1
27.5
8.1
26.8
3.2
19.5
6.4
18.3
13.8
24.8
1.9
18.5
1.1
16.4
SEQ ID NO: 144
SEQ ID NO: 1589
SEQ ID NO: 173
SEQ ID NO: 1590
SEQ ID NO: 237
SEQ ID NO: 1591
+500nM TDP43 ASO

FIG. 26A

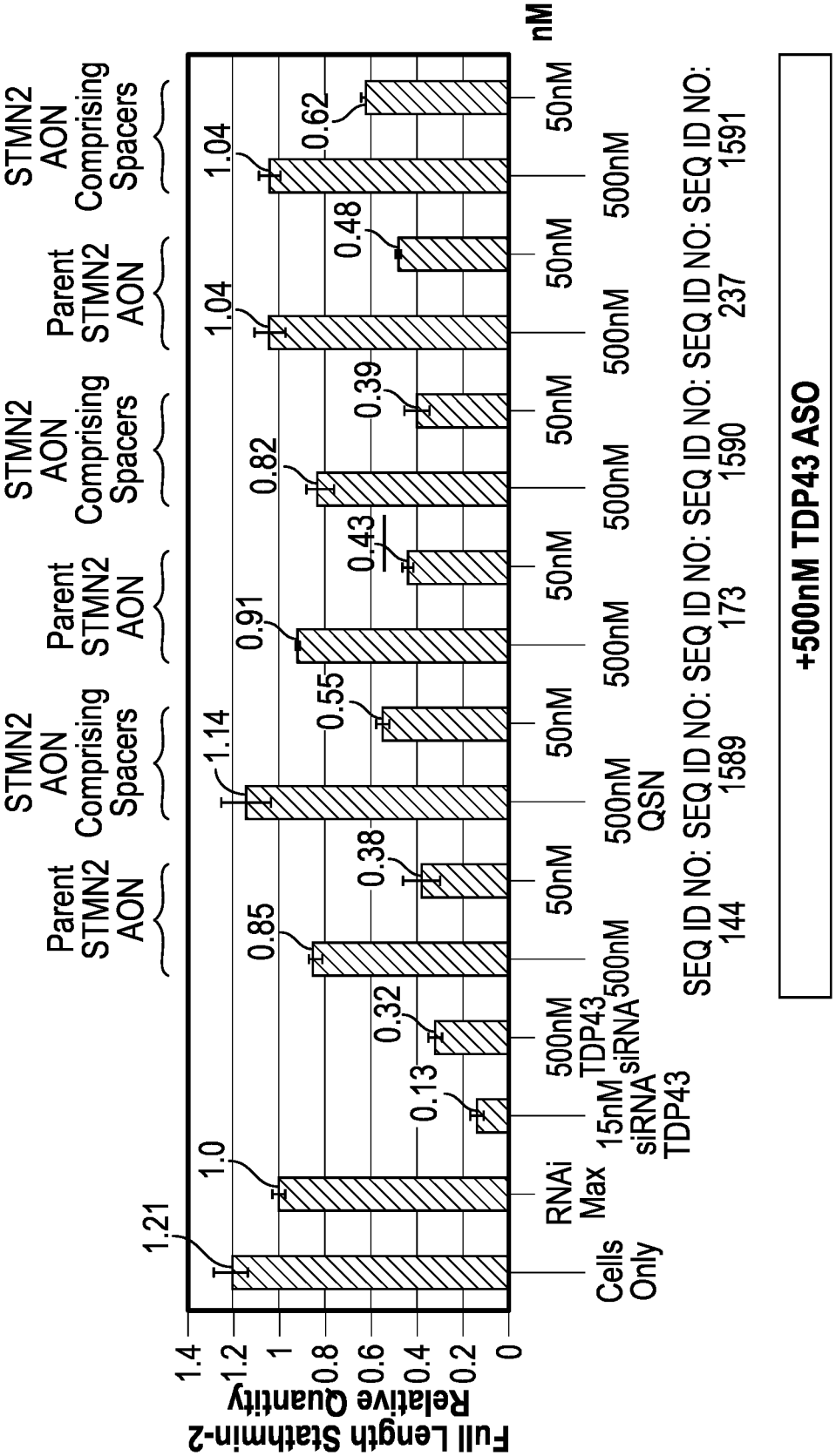

Full Length Stathmin-2 Relative Quantity
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1.21
1.0
0.13
0.32
0.85
0.38
1.14
0.55
0.91
0.43
0.82
0.39
1.04
0.48
1.04
0.62
Cells Only
RNAi Max
15nM siRNA TDP43
500nM siRNA TDP43
500nM QSN
50nM
500nM
SEQ ID NO: 144
SEQ ID NO: 1589
SEQ ID NO: 173
SEQ ID NO: 1590
SEQ ID NO: 237
SEQ ID NO: 1591
Parent STMN2 AON
STMN2 AON Comprising Spacers
+500nM TDP43 ASO

FIG. 26B

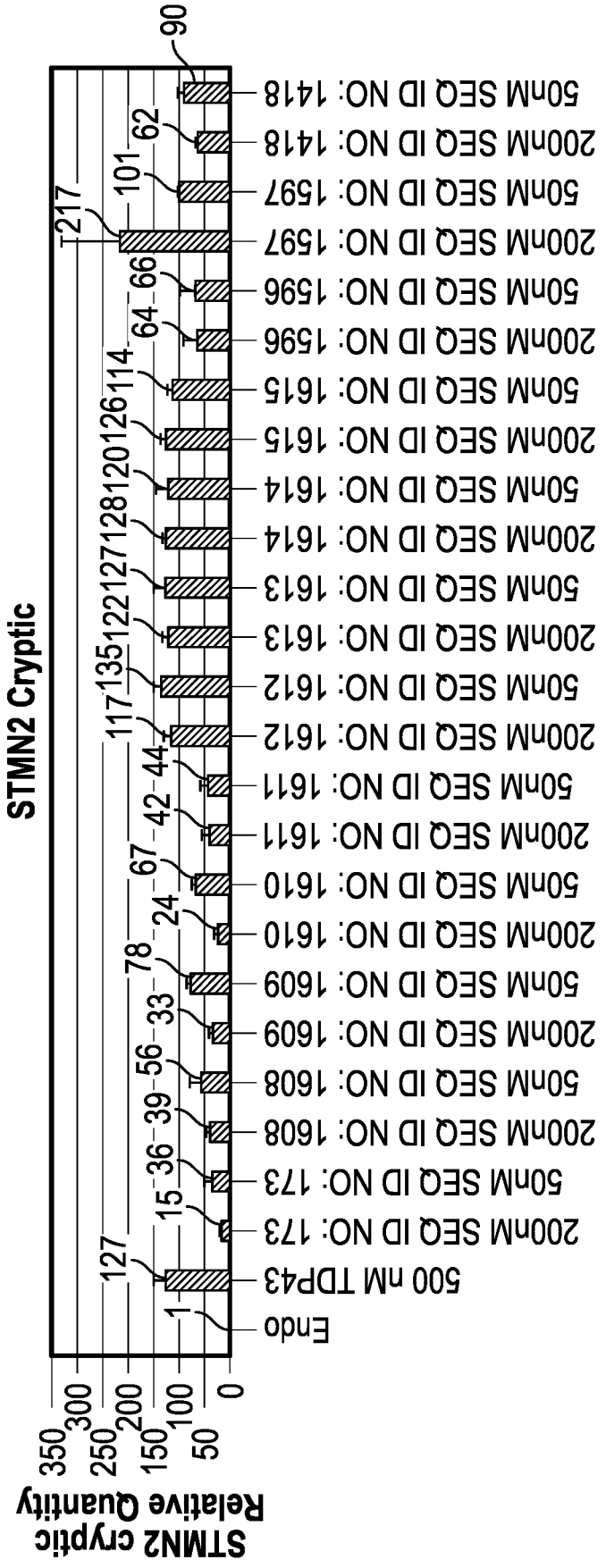

STMN2 Cryptic
STMN2 cryptic Relative Quantity
350
300
250
200
150
100
50
0
Endo
500 nM TDP43
200nM SEQ ID NO: 173
50nM SEQ ID NO: 173
200nM SEQ ID NO: 1608
50nM SEQ ID NO: 1608
200nM SEQ ID NO: 1609
50nM SEQ ID NO: 1609
200nM SEQ ID NO: 1610
50nM SEQ ID NO: 1610
200nM SEQ ID NO: 1611
50nM SEQ ID NO: 1611
200nM SEQ ID NO: 1612
50nM SEQ ID NO: 1612
200nM SEQ ID NO: 1613
50nM SEQ ID NO: 1613
200nM SEQ ID NO: 1614
50nM SEQ ID NO: 1614
200nM SEQ ID NO: 1615
50nM SEQ ID NO: 1615
200nM SEQ ID NO: 1596
50nM SEQ ID NO: 1596
200nM SEQ ID NO: 1597
50nM SEQ ID NO: 1597
200nM SEQ ID NO: 1418
50nM SEQ ID NO: 1418
1
127
3
15
36
39
56
33
78
24
67
42
44
117
135
122
127
128
120
126
114
64
66
217
101
62
90

FIG. 27A

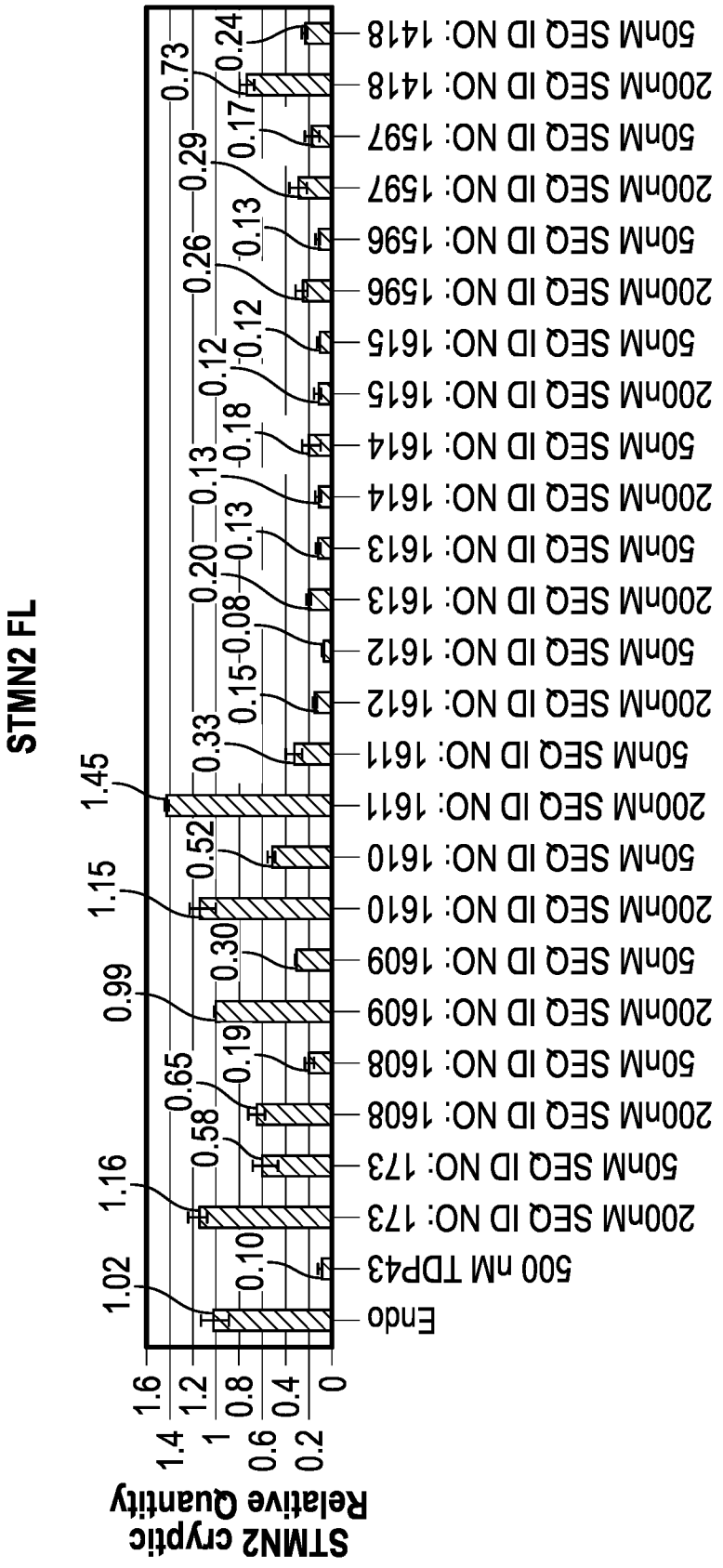

STMN2 FL
STMN2 cryptic
Relative Quantity
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
Endo
500 nM TDP43
200nM SEQ ID NO: 173
50nM SEQ ID NO: 173
200nM SEQ ID NO: 1608
50nM SEQ ID NO: 1608
200nM SEQ ID NO: 1609
50nM SEQ ID NO: 1609
200nM SEQ ID NO: 1610
50nM SEQ ID NO: 1610
200nM SEQ ID NO: 1611
50nM SEQ ID NO: 1611
200nM SEQ ID NO: 1612
50nM SEQ ID NO: 1612
200nM SEQ ID NO: 1613
50nM SEQ ID NO: 1613
200nM SEQ ID NO: 1614
50nM SEQ ID NO: 1614
200nM SEQ ID NO: 1615
50nM SEQ ID NO: 1615
200nM SEQ ID NO: 1596
50nM SEQ ID NO: 1596
200nM SEQ ID NO: 1597
50nM SEQ ID NO: 1597
200nM SEQ ID NO: 1418
50nM SEQ ID NO: 1418
1.02
0.10
1.16
0.58
0.65
0.19
0.99
0.30
1.15
0.52
1.45
0.33
0.15
0.08
0.20
0.13
0.13
0.18
0.12
0.26
0.13
0.29
0.17
0.73
0.24

FIG. 27B

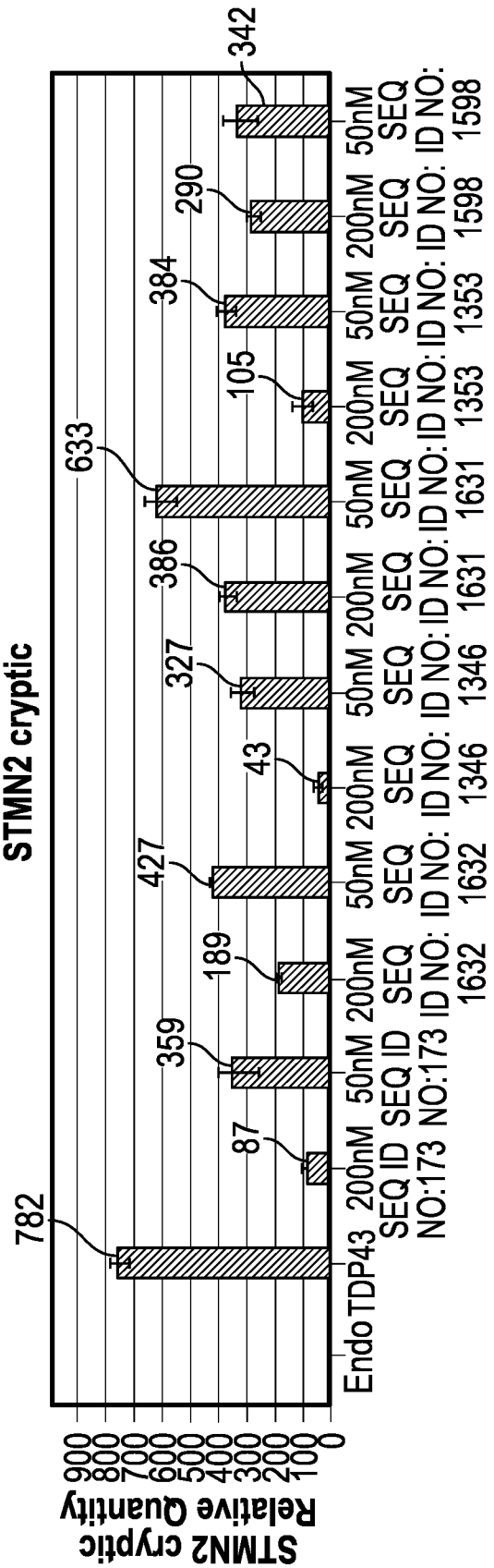

STMN2 cryptic
STMN2 cryptic Relative Quantity
900
800
700
600
500
400
300
200
100
0
782
87
359
189
427
43
327
386
633
105
384
290
342
Endo TDP43 200nM SEQ ID NO:173
50nM SEQ ID NO:173
200nM SEQ ID NO: 1632
50nM SEQ ID NO: 1632
200nM SEQ ID NO: 1346
50nM SEQ ID NO: 1346
200nM SEQ ID NO: 1631
50nM SEQ ID NO: 1631
200nM SEQ ID NO: 1353
50nM SEQ ID NO: 1353
200nM SEQ ID NO: 1598
50nM SEQ ID NO: 1598

FIG. 28A

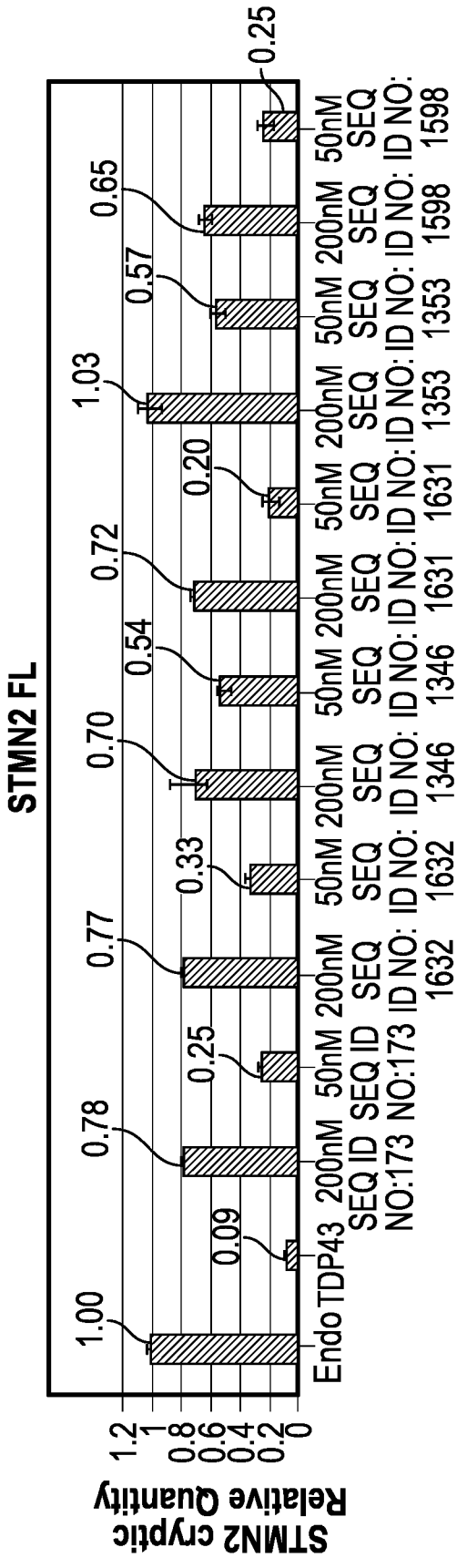

STMN2 FL
STMN2 cryptic Relative Quantity
1.2
1
0.8
0.6
0.4
0.2
0
1.00
0.78
0.09
0.25
0.77
0.33
0.70
0.72
0.54
0.20
1.03
0.57
0.65
0.25
Endo TDP43 200nM
50nM
200nM
50nM
200nM
50nM
200nM
50nM
200nM
50nM
200nM
50nM
SEQ ID NO:173
SEQ ID NO: 1632
SEQ ID NO: 1632
SEQ ID NO: 1346
SEQ ID NO: 1346
SEQ ID NO: 1631
SEQ ID NO: 1631
SEQ ID NO: 1353
SEQ ID NO: 1353
SEQ ID NO: 1598
SEQ ID NO: 1598
SEQ ID NO: 1598

FIG. 28B

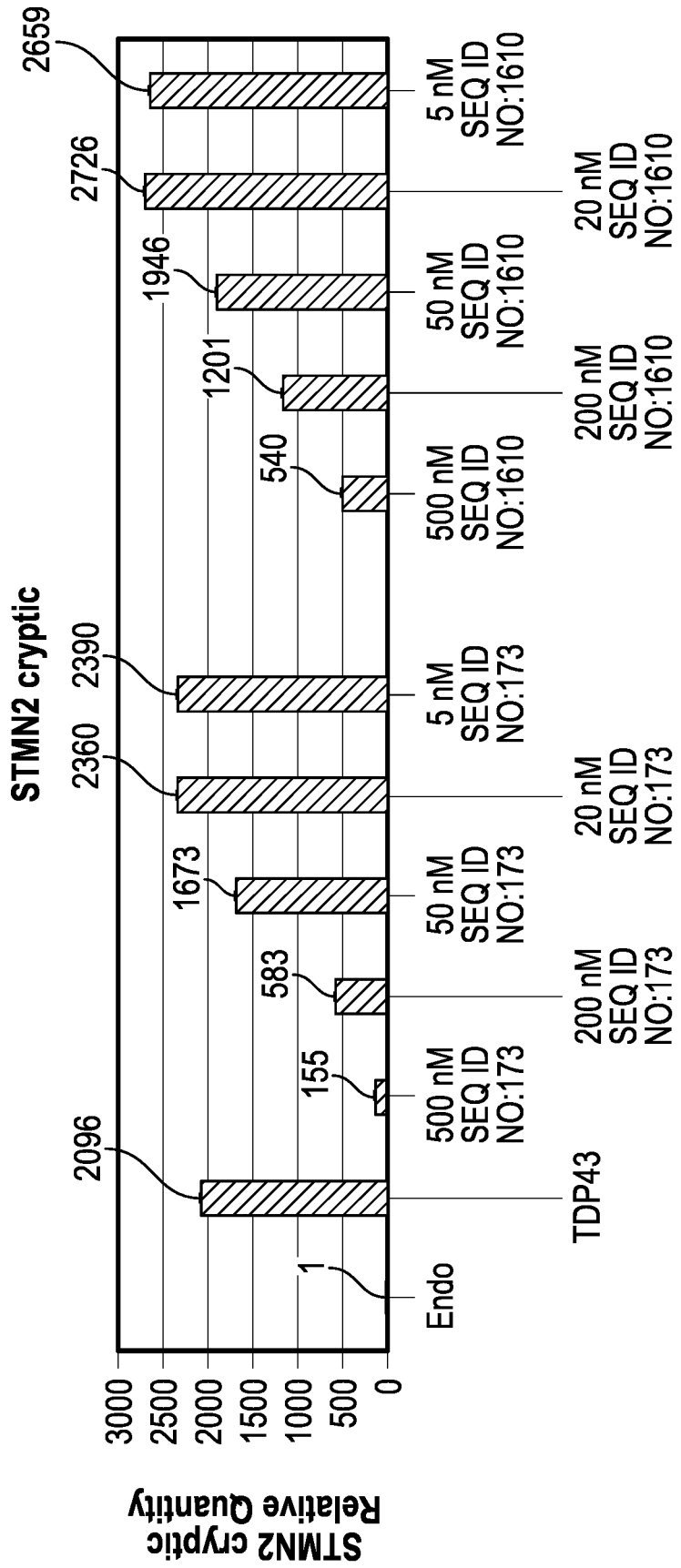

STMN2 cryptic
STMN2 cryptic Relative Quantity
3000
2500
2000
1500
1000
500
0
2659
2726
1946
1201
540
2390
2360
1673
583
155
2096
1
Endo
TDP43
5 nM SEQ ID NO:1610
20 nM SEQ ID NO:1610
50 nM SEQ ID NO:1610
200 nM SEQ ID NO:1610
500 nM SEQ ID NO:1610
5 nM SEQ ID NO:173
20 nM SEQ ID NO:173
50 nM SEQ ID NO:173
200 nM SEQ ID NO:173
500 nM SEQ ID NO:173

FIG. 29A

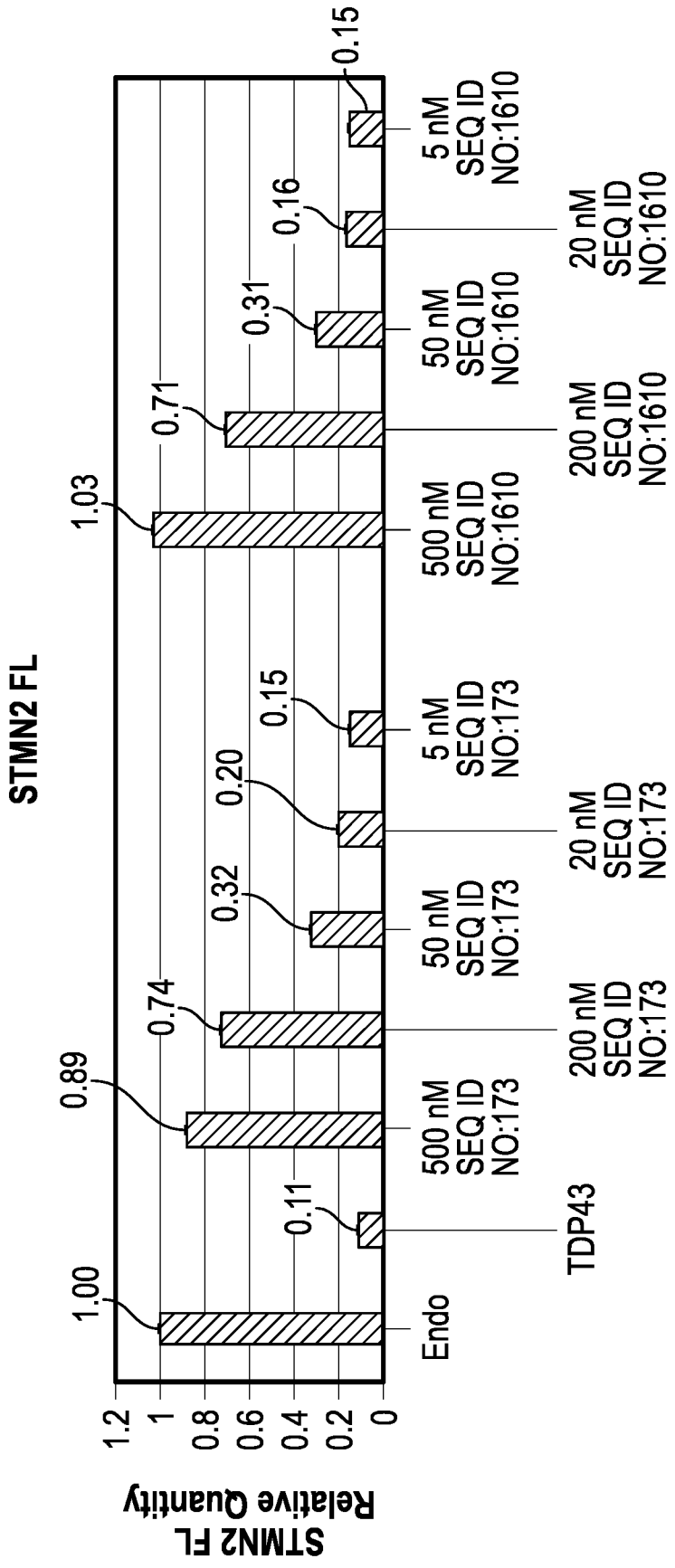

STMN2 FL
STMN2 FL Relative Quantity
1.2
1
0.8
0.6
0.4
0.2
0
Endo
1.00
TDP43
0.11
500 nM SEQ ID NO:173
0.89
200 nM SEQ ID NO:173
0.74
50 nM SEQ ID NO:173
0.32
20 nM SEQ ID NO:173
0.20
5 nM SEQ ID NO:173
0.15
500 nM SEQ ID NO:1610
1.03
200 nM SEQ ID NO:1610
0.71
50 nM SEQ ID NO:1610
0.31
20 nM SEQ ID NO:1610
0.16
5 nM SEQ ID NO:1610
0.15

FIG. 29B

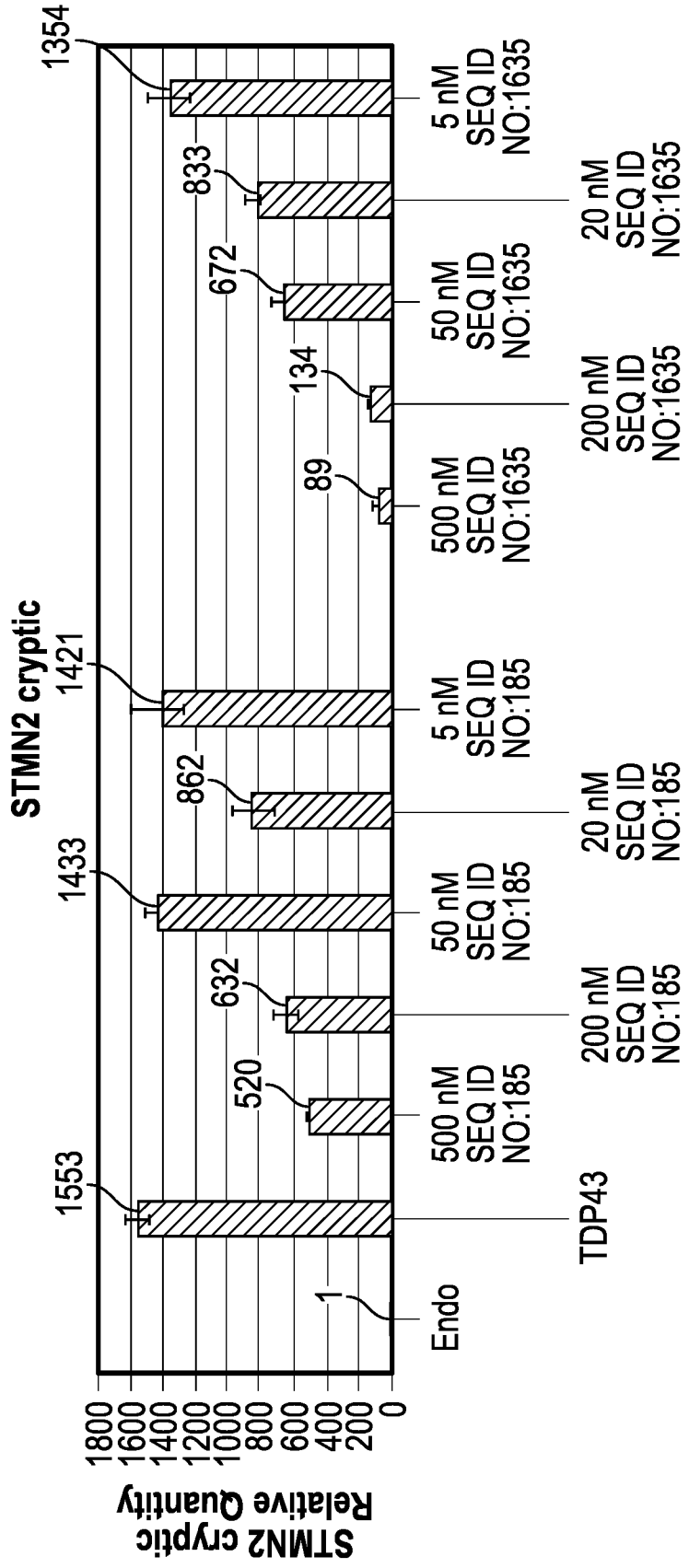

STMN2 cryptic
Relative Quantity
1800
1600
1400
1200
1000
800
600
400
200
0
1354
833
672
134
89
1421
862
1433
632
520
1553
1
Endo
TDP43
5 nM SEQ ID NO:1635
20 nM SEQ ID NO:1635
50 nM SEQ ID NO:1635
200 nM SEQ ID NO:1635
500 nM SEQ ID NO:1635
5 nM SEQ ID NO:185
20 nM SEQ ID NO:185
50 nM SEQ ID NO:185
200 nM SEQ ID NO:185
500 nM SEQ ID NO:185

FIG. 30A

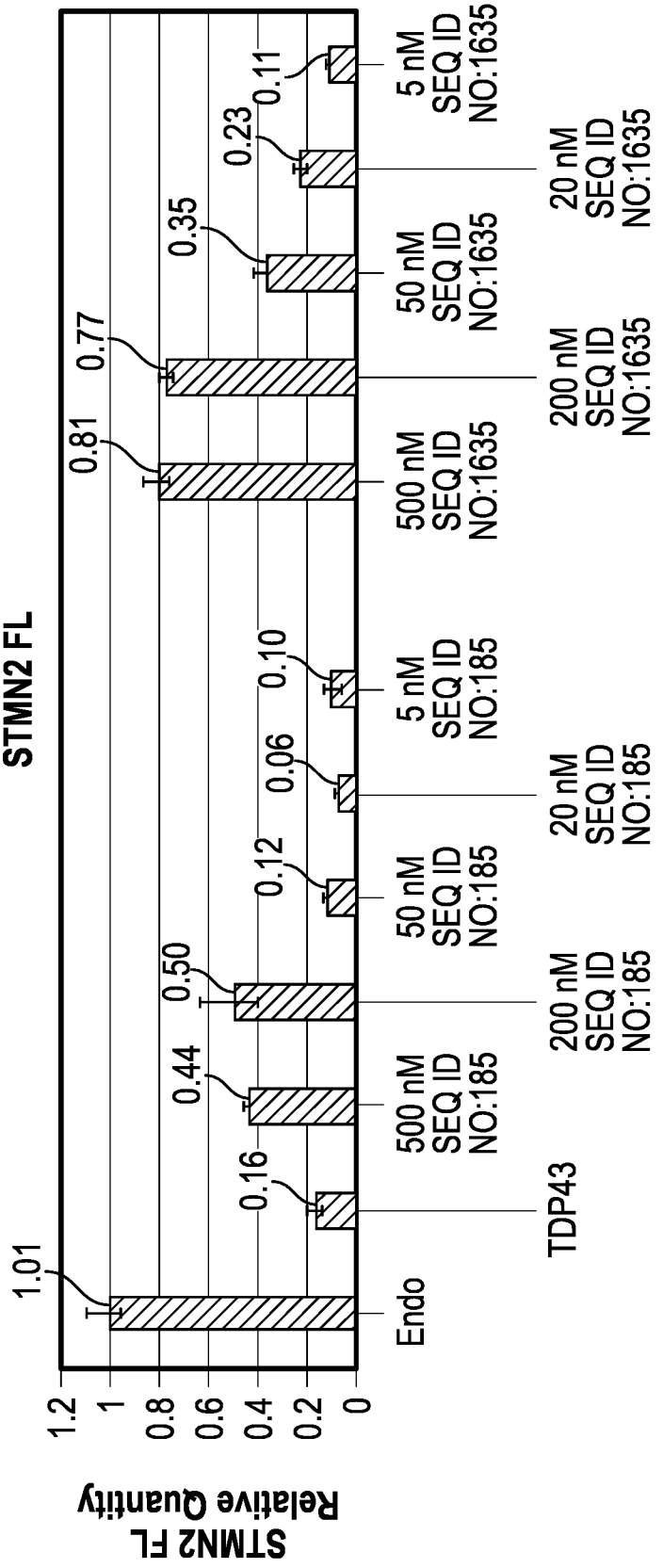

STMN2 FL
STMN2 FL Relative Quantity
1.2
1
0.8
0.6
0.4
0.2
0
1.01
0.16
0.44
0.50
0.12
0.06
0.10
0.81
0.77
0.35
0.23
0.11
Endo
TDP43
500 nM SEQ ID NO:185
200 nM SEQ ID NO:185
50 nM SEQ ID NO:185
20 nM SEQ ID NO:185
5 nM SEQ ID NO:185
500 nM SEQ ID NO:1635
200 nM SEQ ID NO:1635
50 nM SEQ ID NO:1635
20 nM SEQ ID NO:1635
5 nM SEQ ID NO:1635

FIG. 30B

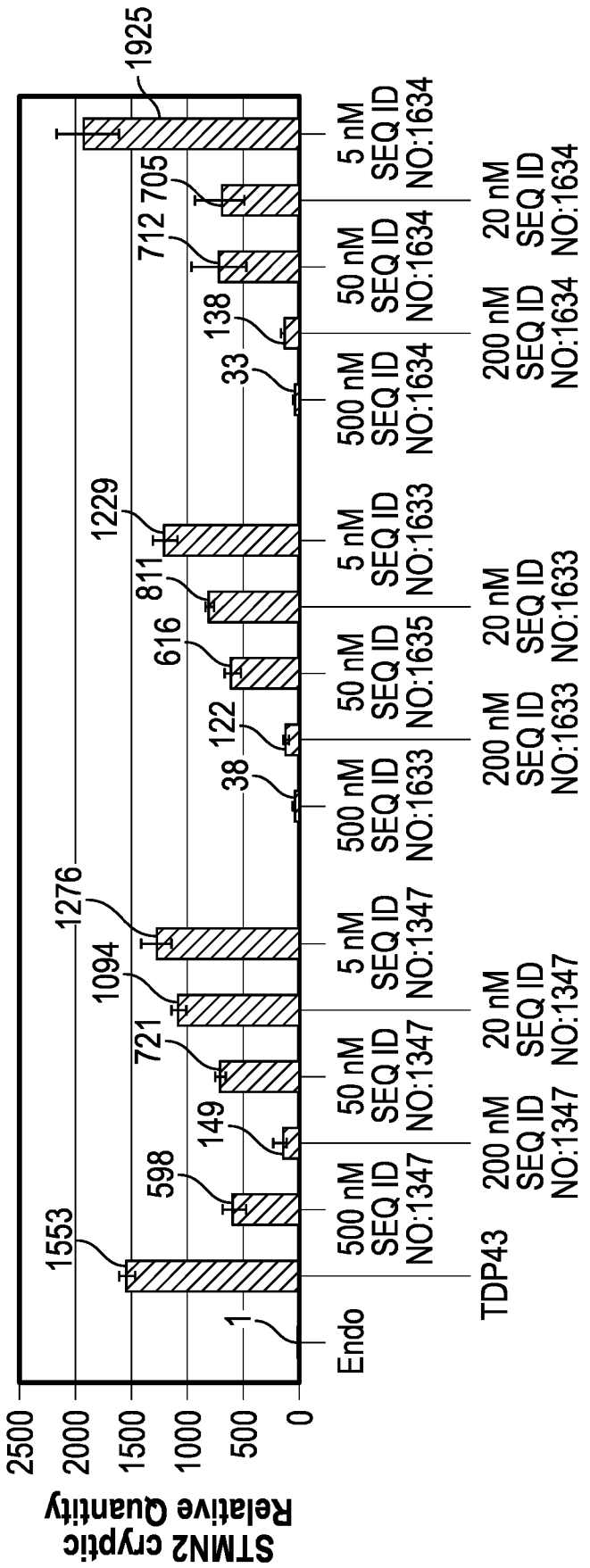

STMN2 cryptic
STMN2 cryptic Relative Quantity
2500
2000
1500
1000
500
0
1925
1553
1276
1229
1094
811
721
712
705
616
598
149
138
122
38
33
1
Endo
TDP43
500 nM SEQ ID NO:1347
200 nM SEQ ID NO:1347
50 nM SEQ ID NO:1347
20 nM SEQ ID NO:1347
5 nM SEQ ID NO:1347
500 nM SEQ ID NO:1633
200 nM SEQ ID NO:1633
50 nM SEQ ID NO:1635
20 nM SEQ ID NO:1633
5 nM SEQ ID NO:1633
500 nM SEQ ID NO:1634
200 nM SEQ ID NO:1634
50 nM SEQ ID NO:1634
20 nM SEQ ID NO:1634
5 nM SEQ ID NO:1634

FIG. 31A

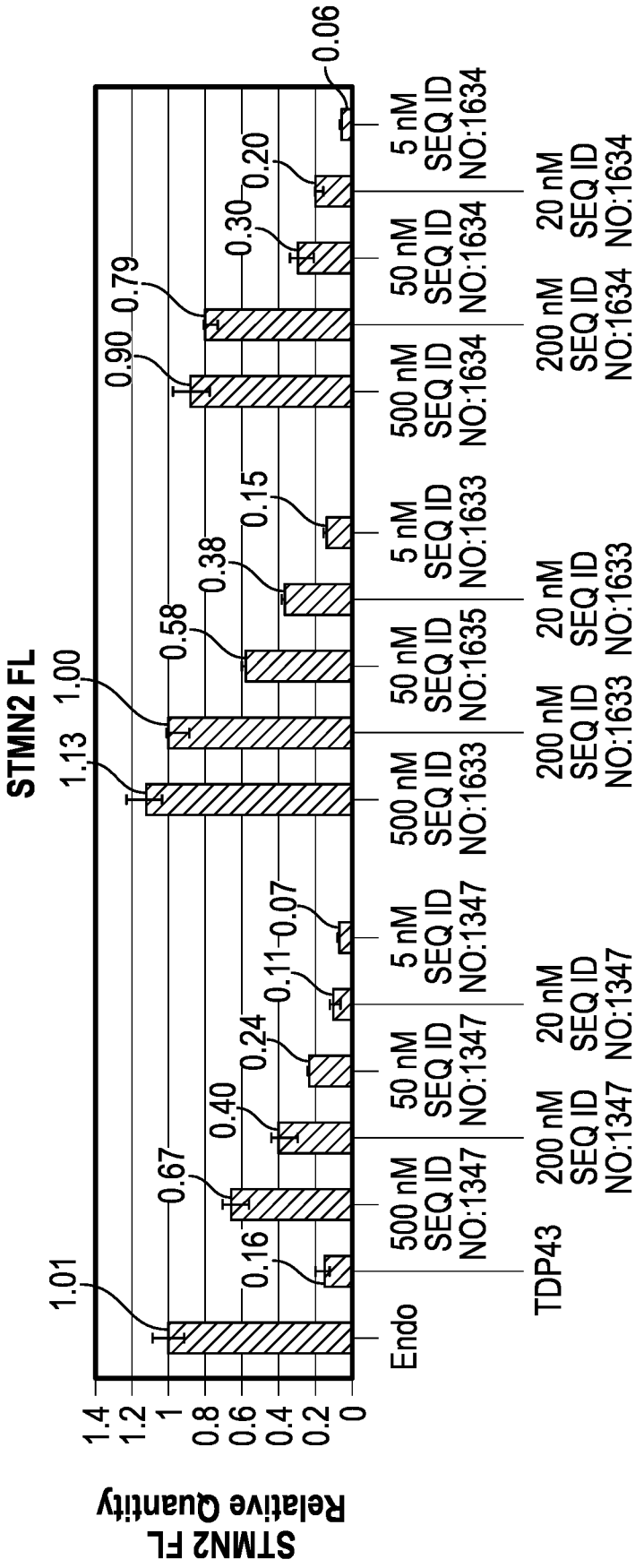

STMN2 FL
STMN2 FL Relative Quantity
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Endo
TDP43
500 nM SEQ ID NO:1347
200 nM SEQ ID NO:1347
50 nM SEQ ID NO:1347
20 nM SEQ ID NO:1347
5 nM SEQ ID NO:1347
500 nM SEQ ID NO:1633
200 nM SEQ ID NO:1633
50 nM SEQ ID NO:1635
20 nM SEQ ID NO:1633
5 nM SEQ ID NO:1633
500 nM SEQ ID NO:1634
200 nM SEQ ID NO:1634
50 nM SEQ ID NO:1634
20 nM SEQ ID NO:1634
5 nM SEQ ID NO:1634
1.01
0.67
0.16
0.40
0.24
0.11
0.07
1.13
1.00
0.58
0.38
0.15
0.90
0.79
0.30
0.20
0.06

FIG. 31B

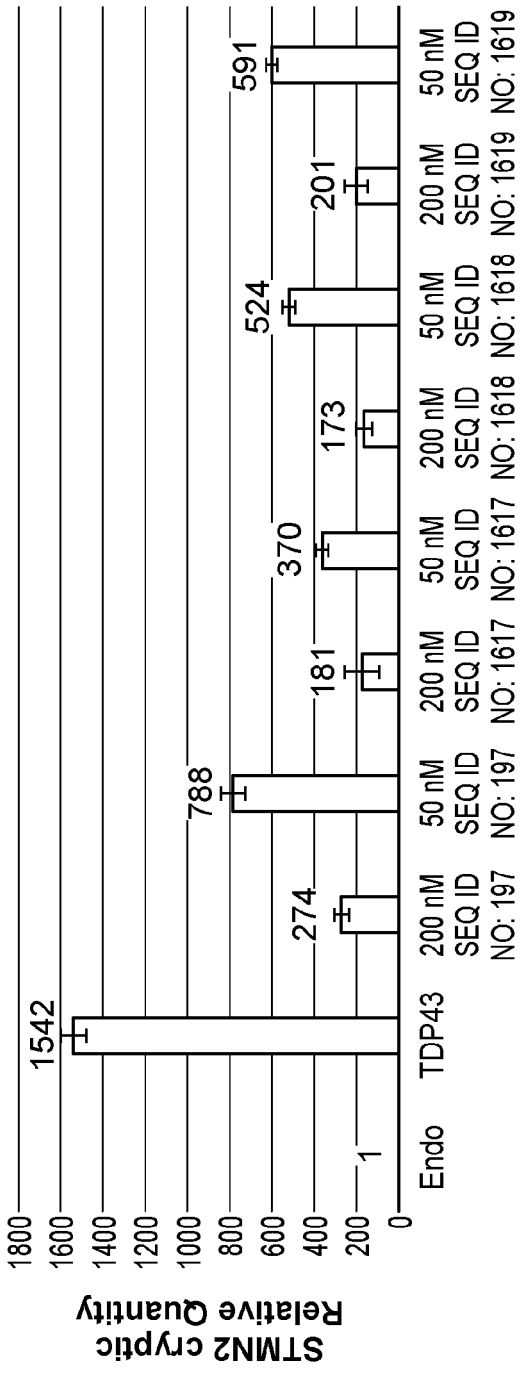


FIG. 32A

FIG. 32B

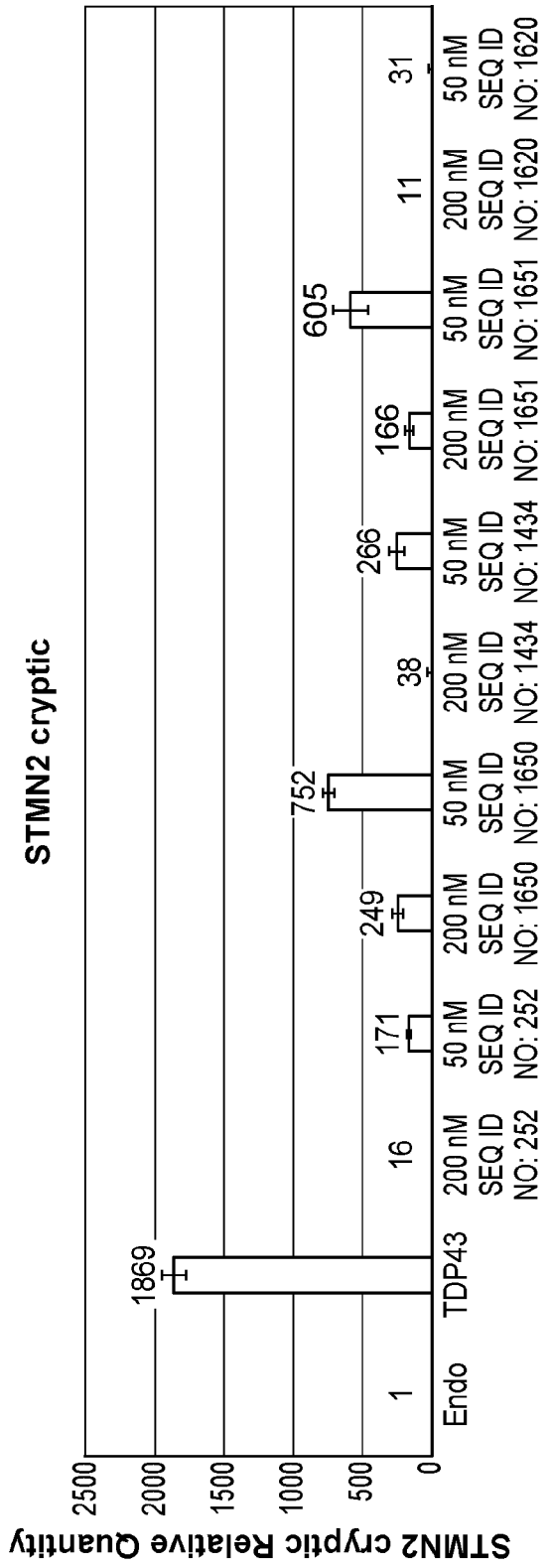


FIG. 33A

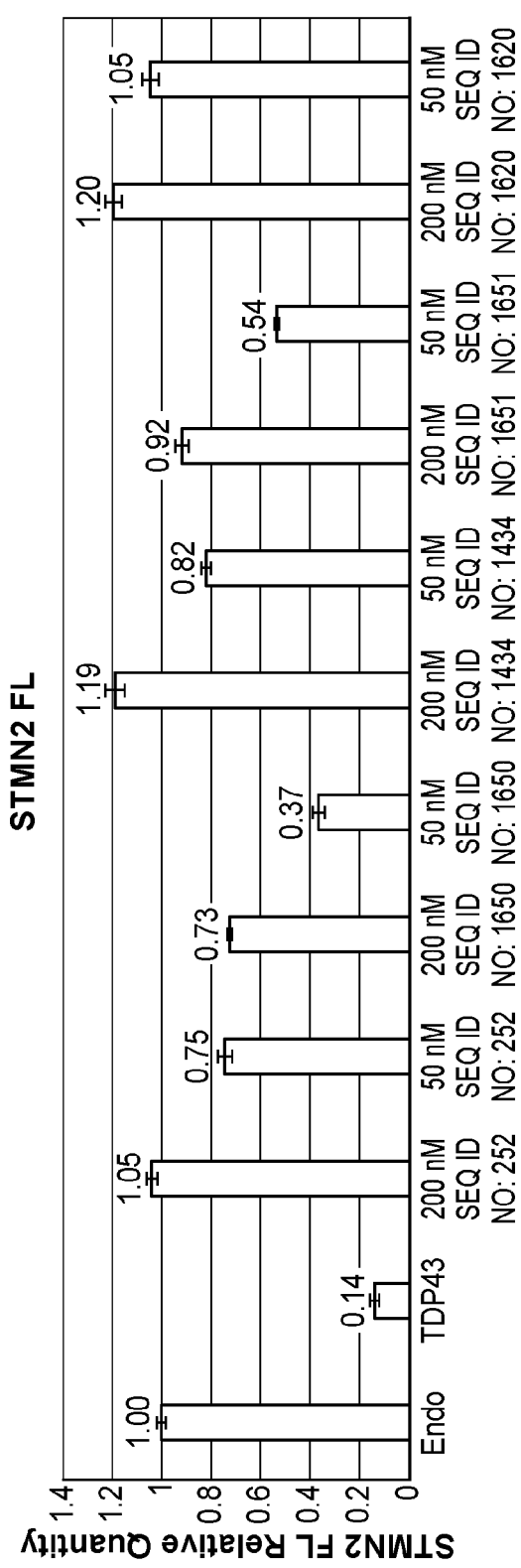


FIG. 33B

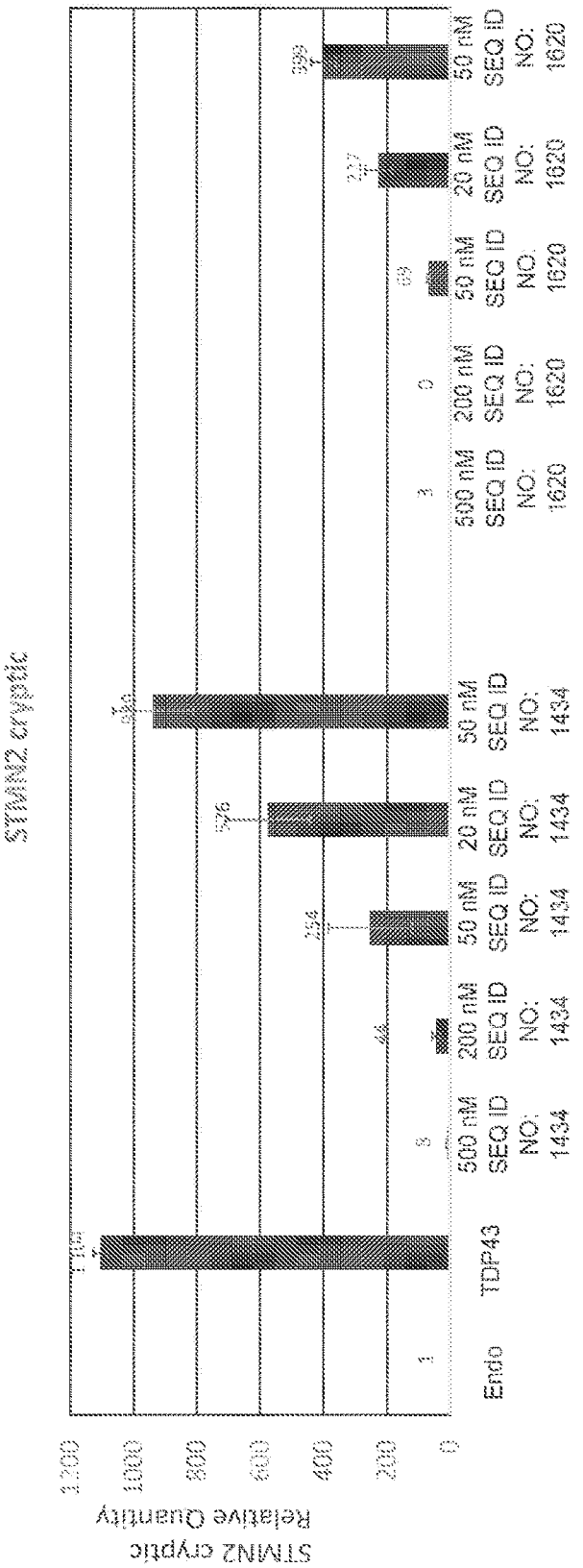

STMN2 cryptic
STMN2 cryptic
Relative Quantity
1200
1000
800
600
400
200
0
Endo
TDP43
500 nM SEQ ID NO: 1434
200 nM SEQ ID NO: 1434
50 nM SEQ ID NO: 1434
20 nM SEQ ID NO: 1434
50 nM SEQ ID NO: 1434
500 nM SEQ ID NO: 1620
200 nM SEQ ID NO: 1620
50 nM SEQ ID NO: 1620
20 nM SEQ ID NO: 1620
50 nM SEQ ID NO: 1620
1
1186
3
44
254
576
836
3
0
69
227
599

FIG. 34A

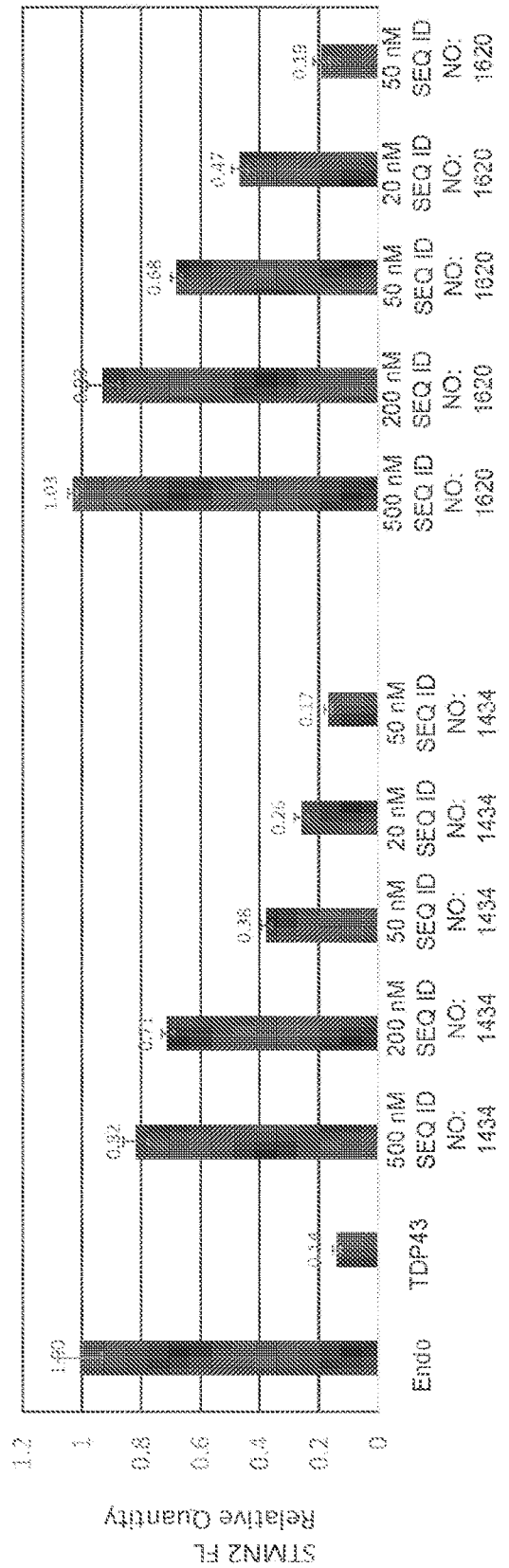

STMN2 FL
Relative Quantity
1.2
1
0.8
0.6
0.4
0.2
0
1.00
0.14
0.92
0.77
0.38
0.26
0.17
1.03
0.93
0.68
0.47
0.38
Endo
TDP43
500 nM SEQ ID NO: 1434
200 nM SEQ ID NO: 1434
50 nM SEQ ID NO: 1434
20 nM SEQ ID NO: 1434
50 nM SEQ ID NO: 1434
500 nM SEQ ID NO: 1620
200 nM SEQ ID NO: 1620
50 nM SEQ ID NO: 1620
20 nM SEQ ID NO: 1620
50 nM SEQ ID NO: 1620

FIG. 34B

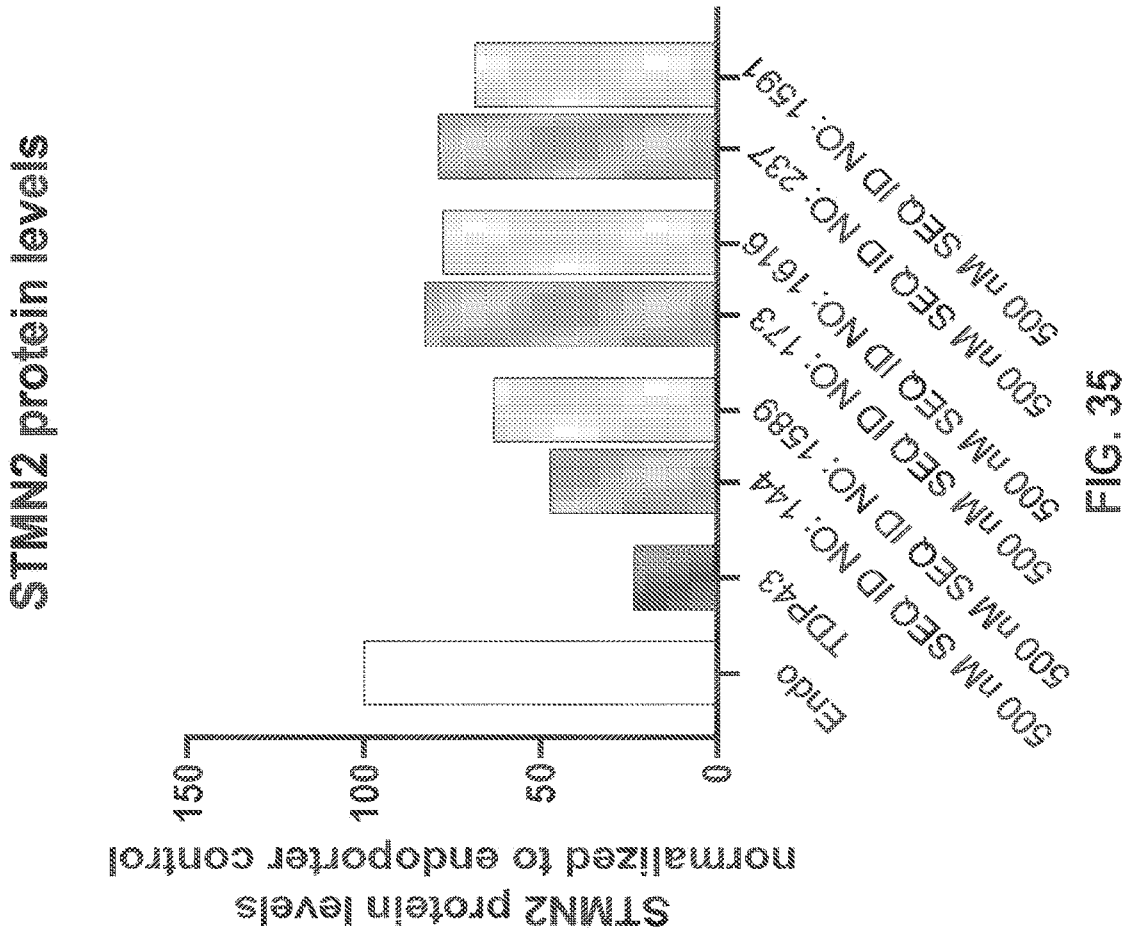

STMN2 protein levels
STMN2 protein levels normalized to endoporter control
0
50
100
150
Endo
TDP43
500 nM SEQ ID NO: 144
500 nM SEQ ID NO: 1589
500 nM SEQ ID NO: 173
500 nM SEQ ID NO: 1616
500 nM SEQ ID NO: 237
500 nM SEQ ID NO: 1591

FIG. 25

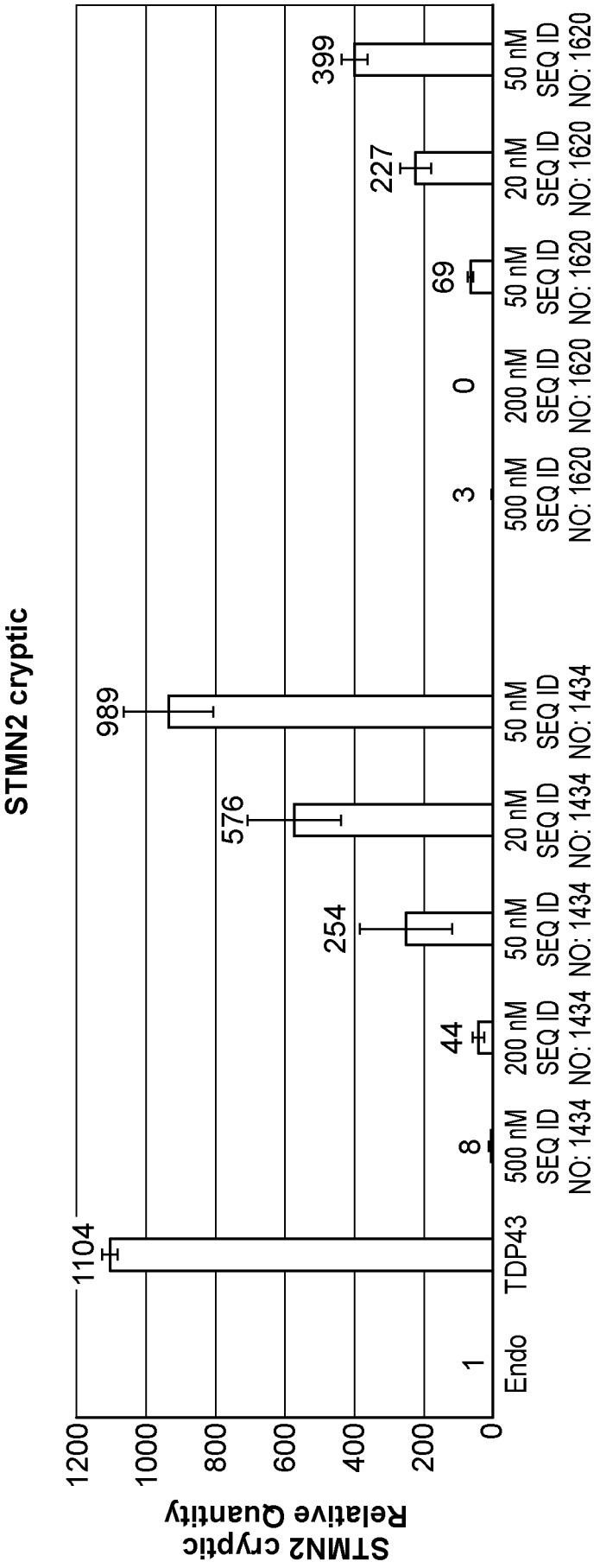

STMN2 cryptic
STMN2 cryptic Relative Quantity
1200
1000
800
600
400
200
0
1
1104
8
44
254
576
989
3
0
69
227
399
Endo
TDP43
500 nM SEQ ID NO: 1434
200 nM SEQ ID NO: 1434
50 nM SEQ ID NO: 1434
20 nM SEQ ID NO: 1434
50 nM SEQ ID NO: 1434
500 nM SEQ ID NO: 1620
200 nM SEQ ID NO: 1620
50 nM SEQ ID NO: 1620
20 nM SEQ ID NO: 1620
50 nM SEQ ID NO: 1620

FIG. 34A

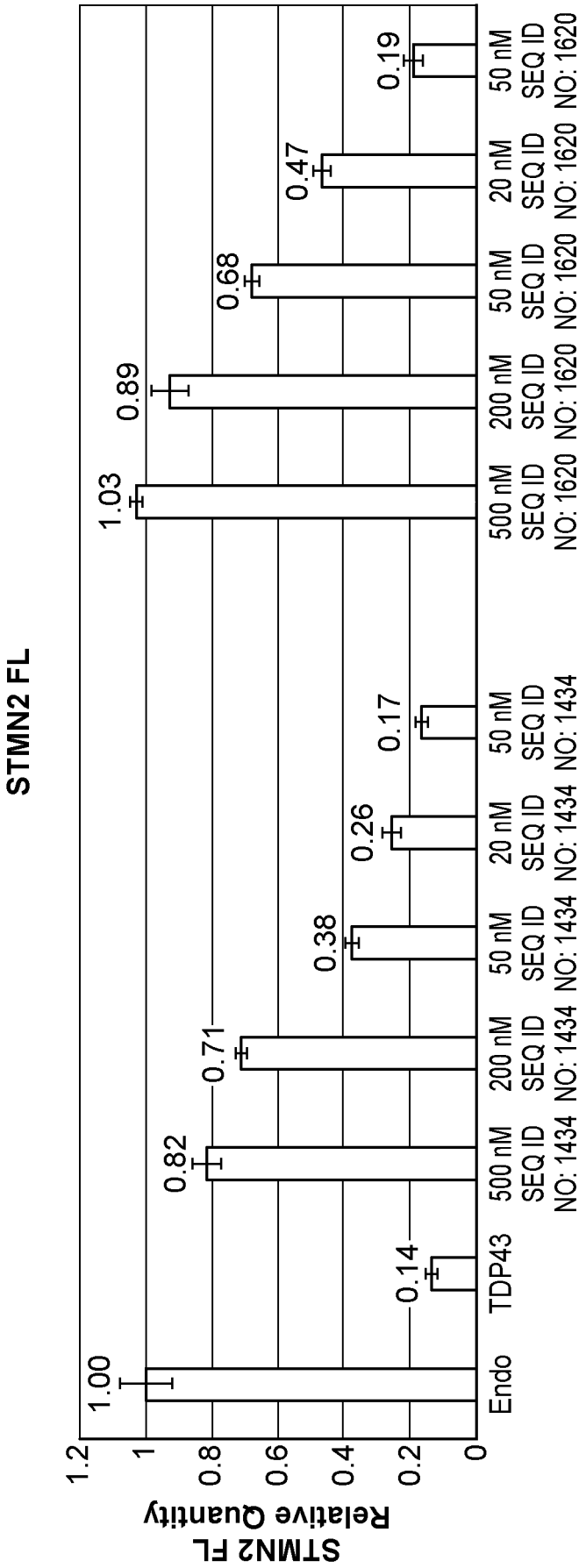

STMN2 FL
STMN2 FL
Relative Quantity
1.2
1
0.8
0.6
0.4
0.2
0
1.00
0.14
0.82
0.71
0.38
0.26
0.17
1.03
0.89
0.68
0.47
0.19
Endo
TDP43
500 nM SEQ ID NO: 1434
200 nM SEQ ID NO: 1434
50 nM SEQ ID NO: 1434
20 nM SEQ ID NO: 1434
50 nM SEQ ID NO: 1434
500 nM SEQ ID NO: 1620
200 nM SEQ ID NO: 1620
50 nM SEQ ID NO: 1620
20 nM SEQ ID NO: 1620
50 nM SEQ ID NO: 1620

FIG. 34B

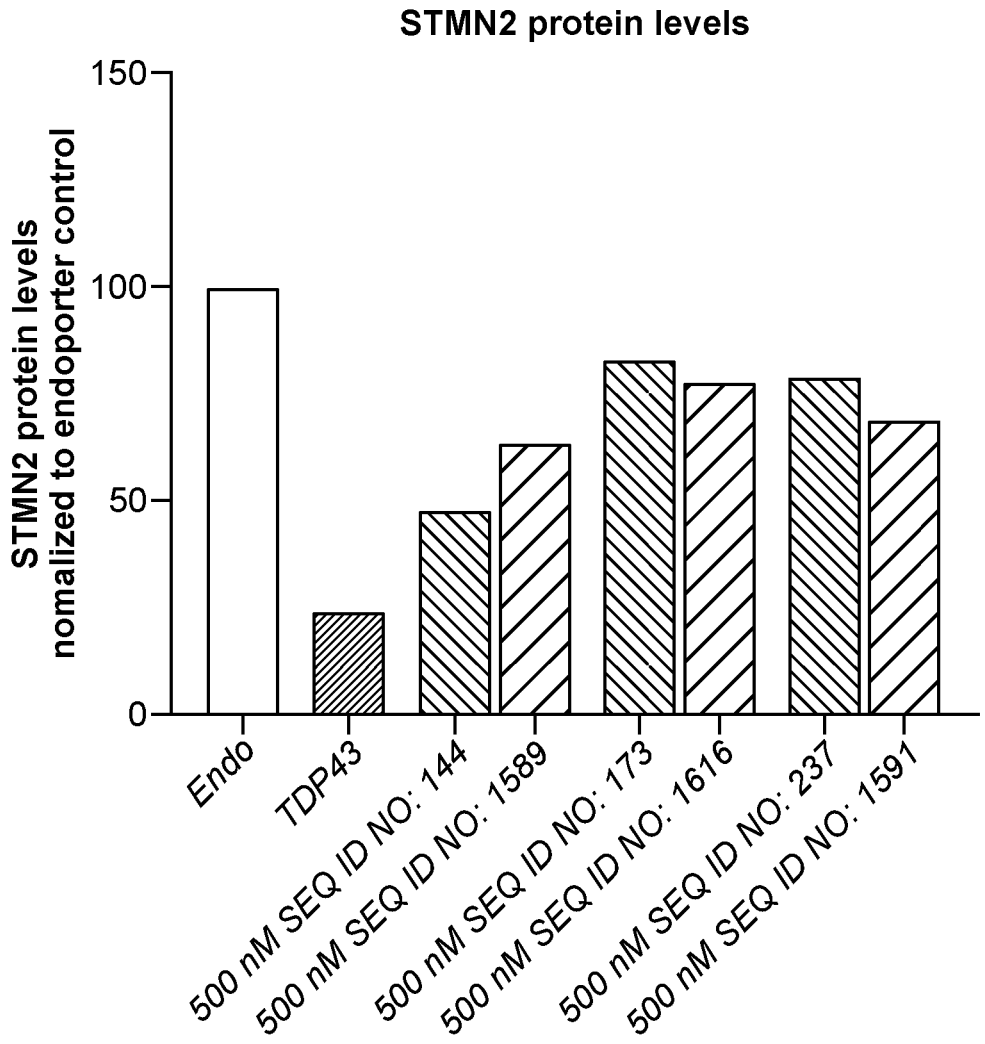

STMN2 protein levels
STMN2 protein levels nomalized to endoporter control
150
100
50
0
Endo
TDP43
500 nM SEQ ID NO: 144
500 nM SEQ ID NO: 1589
500 nM SEQ ID NO: 173
500 nM SEQ ID NO: 1616
500 nM SEQ ID NO: 237
500 nM SEQ ID NO: 1591

FIG. 35