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(54) Title: COMPOUNDS AND METHODS FOR MODULATING SCN1A EXPRESSION

(57) Abstract: Provided are compounds, methods, and pharmaceutical compositions for modulating SCN1A RNA and/or protein in a cell or subject. Such compounds, methods, and pharmaceutical compositions are useful to ameliorate at least one symptom of a developmental or epileptic encephalopathic disease, such as Dravet Syndrome. Such symptoms include seizures, sudden unexpected death in epilepsy, status epilepticus, behavioral and developmental delays, movement and balance dysfunctions, orthopedic conditions, motor and cognitive dysfunctions, delayed language and speech issues, visual motor integration dysfunctions, visual perception dysfunctions, executive dysfunctions, growth and nutrition issues, sleeping difficulties, chronic infections, sensory integration disorders, and dysautonomia.



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COMPOUNDS AND METHODS FOR MODULATING SCN1A EXPRESSION**Sequence Listing**

5 The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL0381WOSEQ_ST25.txt, created on February 24, 2021, which is 624 KB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

10 Field

 Provided are compounds, methods, and pharmaceutical compositions for modulating SCN1A RNA and/or protein in a cell or subject. Such compounds, methods, and pharmaceutical compositions are useful to ameliorate at least one symptom of a developmental or epileptic encephalopathic disease, such as, for example, Dravet Syndrome. Such symptoms include seizures, sudden unexpected death in epilepsy, status
15 epilepticus, behavioral and developmental delays, movement and balance dysfunctions, orthopedic conditions, motor and cognitive dysfunctions, delayed language and speech issues, visual motor integration dysfunctions, visual perception dysfunctions, executive dysfunctions, growth and nutrition issues, sleeping difficulties, chronic infections, sensory integration disorders, and dysautonomia.

20 Background

 The human gene *SCN1A* encodes human SCN1A protein, the alpha-1 subunit of the voltage-gated sodium channel NaV1.1. Mutations in *SCN1A* lead to developmental and epileptic encephalopathies (DEEs), including Dravet Syndrome (previously known as Severe Myoclonic Epilepsy of Infancy (SMEI)), one of the most severe childhood forms of epilepsy; other epileptic disorders, including, for example, Genetic Epilepsy
25 with Febrile Seizures Plus (GEFS+) and other febrile seizures, Idiopathic/Generic Generalized Epilepsies (IGE/GGE), Temporal Lobe Epilepsy, Myoclonic Astatic Epilepsy (MAE), Lennox-Gastaut Syndrome, and Migrating Partial Epilepsy of Infancy (MMPSI); and familial hemiplegic migraines, with or without epilepsy (Harkin, L.A., et al., 2007, *Brain* 130, 843-852; Escayg, A., et al., 2010, *Epilepsia* 51, 1650-1658; Miller I.O, et al., 2007 Nov 29 [Updated 2019 Apr 18]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors.
30 GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1318/>).

 DEEs are associated with SCN1A haploinsufficiency (Parihar, R., et al., 2013, *J. Human Genetics*, 58, 573-580). Symptoms associated with DEEs, including Dravet Syndrome, include prolonged seizures (often lasting longer than 10 minutes), frequent seizures (for example, convulsive, myoclonic, absence, focal,
35 obtundation status, and tonic seizures), sudden unexpected death in epilepsy, status epilepticus, behavioral and developmental delays, movement and balance dysfunctions, orthopedic conditions, motor and cognitive

dysfunctions (for example, ataxia, tremors, dysarthria, pyramidal, and extrapyramidal signs), delayed language and speech issues, visual motor integration dysfunctions, visual perception dysfunctions, executive dysfunctions, growth and nutrition issues, sleeping difficulties, chronic infections, sensory integration disorders, and dysautonomia. Dravet Syndrome patients experience additional neurodevelopmental delays, leading to severe neurological disability (Guzzetta, F., 2011, *Epilepsia* 52:S2, 35-38; Anwar et al., 2019, *Cureus* 11, e5006).

Alternative splicing of SCN1A leads to multiple SCN1A transcript variants (Parihar, R., et al., 2013). Certain transcript variants include a nonsense-mediated decay-inducing exon (NIE) (Steward, C.A., et al., 2019, *npj Genom. Med.* 4, 31; Carvill et al., 2018, *American J. Human Genetics*, 103, 1022-1029). One such NIE (NIE-1), which is 64 nucleobases in length and located in SCN1A intron 20, causes degradation of the SCN1A transcript (Carvill et al., 2018).

Currently there remains a need for therapies to treat Dravet Syndrome, GEFS+, and other DEEs. It is therefore an object herein to provide compounds, methods, and pharmaceutical compositions for the treatment of such diseases.

Summary of the Invention

Provided herein are compounds, methods, and pharmaceutical compositions for modulating splicing of SCN1A RNA and/or protein in a cell or a subject. In certain embodiments, the amount of SCN1A RNA and/or SCN1A protein is increased. In certain embodiments, the amount of full-length SCN1A RNA and/or full-length SCN1A protein is increased. In certain embodiments, the amount of SCN1A RNA including an NIE is reduced. In certain embodiments, the amount of SCN1A RNA excluding an NIE is increased. In certain embodiments, the NIE is NIE-1. In certain embodiments, the subject has a developmental or epileptic encephalopathy (DEE). In certain embodiments, the DEE is caused by SCN1A haploinsufficiency. In certain embodiments, the DEE is treated by increasing the amount of full-length SCN1A RNA and/or full-length SCN1A protein in a subject, or cell thereof, with compounds capable of excluding an NIE from an SCN1A RNA. In certain embodiments, exclusion of an NIE from an SCN1A RNA increases full-length SCN1A RNA and/or full-length SCN1A protein wherein removal of the NIE prevents degradation of the SCN1A transcript via the NMD pathway. In certain embodiments, the subject has Dravet Syndrome. In certain embodiments, compounds useful for modulating splicing of SCN1A RNA are oligomeric compounds. In certain embodiments, the oligomeric compound comprises or consists of a modified oligonucleotide.

Also provided are methods useful for ameliorating at least one symptom of a DEE. In certain embodiments, the DEE is Dravet Syndrome. In certain embodiments, symptoms include prolonged seizures (often lasting longer than 10 minutes), frequent seizures (for example, convulsive, myoclonic, absence, focal, obtundation status, and tonic seizures), sudden unexpected death in epilepsy, status epilepticus, behavioral and developmental delays, movement and balance dysfunctions, orthopedic conditions, motor and cognitive dysfunctions (for example, ataxia, tremors, dysarthria, pyramidal, and extrapyramidal signs), delayed

language and speech issues, visual motor integration dysfunctions, visual perception dysfunctions, executive dysfunctions, growth and nutrition issues, sleeping difficulties, chronic infections, sensory integration disorders, and dysautonomia. In certain embodiments, provided herein are modified oligonucleotides for treating Dravet Syndrome.

5

Detailed Description of the Invention

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive. Herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the use of “or” means “and/or” unless
10 stated otherwise. Furthermore, the use of the term “including” as well as other forms, such as “includes” and “included”, is not limiting. Also, terms such as “element” or “component” encompass both elements and components comprising one unit and elements and components that comprise more than one subunit, unless specifically stated otherwise.

The section headings used herein are for organizational purposes only and are not to be construed as
15 limiting the subject matter described. All documents, or portions of documents, cited in this application, including, but not limited to, patents, patent applications, articles, books, and treatises, and GenBank and NCBI reference sequence records are hereby expressly incorporated-by-reference for the portions of the document discussed herein, as well as in their entirety.

20 DEFINITIONS

Unless specific definitions are provided, the nomenclature used in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Where permitted, all patents, applications, published applications and other publications and other data referred to
25 throughout in the disclosure are incorporated by reference herein in their entirety.

Unless otherwise indicated, the following terms have the following meanings:

As used herein, “2’-deoxyribonucleoside” means a nucleoside comprising a 2’-H(H) deoxyribosyl sugar moiety. In certain embodiments, a 2’-deoxyribonucleoside is a 2’-β-D deoxyribonucleoside and comprises a 2’-β-D-deoxyribosyl sugar moiety, which has the β-D configuration as found in naturally
30 occurring deoxyribonucleic acids (DNA). In certain embodiments, a 2’-deoxyribonucleoside may comprise a modified nucleobase or may comprise an RNA nucleobase (uracil).

As used herein, “2’-MOE” means a 2’-OCH₂CH₂OCH₃ group in place of the 2’-OH group of a ribosyl sugar moiety. A “2’-MOE sugar moiety” is a sugar moiety with a 2’-OCH₂CH₂OCH₃ group in place of the 2’-OH group of a ribosyl sugar moiety. Unless otherwise indicated, a 2’-MOE sugar moiety is in the
35 β-D configuration. “MOE” means O-methoxyethyl.

As used herein, “2’-MOE nucleoside” means a nucleoside comprising a 2’-MOE sugar moiety.

As used herein, “2’-NMA” means a $-O-CH_2-C(=O)-NH-CH_3$ group in place of the 2’-OH group of a ribosyl sugar moiety. A “2’-NMA sugar moiety” is a sugar moiety with a $2'-O-CH_2-C(=O)-NH-CH_3$ group in place of the 2’-OH group of a ribosyl sugar moiety. Unless otherwise indicated, a 2’-NMA sugar moiety is in the β -D configuration. “NMA” means O-N-methyl acetamide.

5 As used herein, “2’-NMA nucleoside” means a nucleoside comprising a 2’-NMA sugar moiety.

As used herein, “2’-OMe” means a $2'-OCH_3$ group in place of the 2’-OH group of a ribosyl sugar moiety. A “2’-OMe sugar moiety” is a sugar moiety with a $2'-OCH_3$ group in place of the 2’-OH group of a ribosyl sugar moiety. Unless otherwise indicated, a 2’-OMe sugar moiety is in the β -D configuration. “OMe” means O-methyl.

10 As used herein, “2’-OMe nucleoside” means a nucleoside comprising a 2’-OMe sugar moiety.

As used herein, “2’-substituted nucleoside” means a nucleoside comprising a 2’-substituted sugar moiety. As used herein, “2’-substituted” in reference to a sugar moiety means a sugar moiety comprising at least one 2'-substituent group other than H or OH.

15 As used herein, “5-methyl cytosine” means a cytosine modified with a methyl group attached to the 5 position. A 5-methyl cytosine is a modified nucleobase.

As used herein, “administering” means providing a pharmaceutical agent to a subject.

As used herein, “ameliorate” in reference to a treatment means improvement in at least one symptom relative to the same symptom in the absence of the treatment. In certain embodiments, amelioration is the reduction in the severity or frequency of a symptom, or the delayed onset or slowing of progression in the severity or frequency of a symptom. In certain embodiments, the symptom is prolonged seizures (often
20 lasting longer than 10 minutes), frequent seizures (for example, convulsive, myoclonic, absence, focal, obtundation status, and tonic seizures), sudden unexpected death in epilepsy, status epilepticus, behavioral and developmental delays, movement and balance dysfunctions, orthopedic conditions, motor and cognitive dysfunctions (for example, ataxia, tremors, dysarthria, pyramidal, and extrapyramidal signs), delayed
25 language and speech issues, visual motor integration dysfunctions, visual perception dysfunctions, executive dysfunctions, growth and nutrition issues, sleeping difficulties, chronic infections, sensory integration disorders, and dysautonomia.

As used herein, “antisense activity” means any detectable and/or measurable change attributable to the hybridization of an antisense compound to its target nucleic acid.

30 As used herein, “antisense compound” means an oligomeric compound or oligomeric duplex capable of achieving at least one antisense activity.

As used herein, “bicyclic nucleoside” or “BNA” means a nucleoside comprising a bicyclic sugar moiety.

As used herein, “bicyclic sugar” or “bicyclic sugar moiety” means a modified sugar moiety
35 comprising two rings, wherein the second ring is formed via a bridge connecting two of the atoms in the first ring thereby forming a bicyclic structure. In certain embodiments, the first ring of the bicyclic sugar moiety is

a furanosyl moiety. In certain embodiments, the furanosyl moiety is a ribosyl moiety. In certain embodiments, the bicyclic sugar moiety does not comprise a furanosyl moiety.

As used herein, "cerebrospinal fluid" or "CSF" means the fluid filling the space around the brain and spinal cord. "Artificial cerebrospinal fluid" or "aCSF" means a prepared or manufactured fluid that has certain properties of cerebrospinal fluid.

As used herein, "cEt" means a 4' to 2' bridge in place of the 2'OH-group of a ribosyl sugar moiety, wherein the bridge has the formula of 4'-CH(CH₃)-O-2', and wherein the methyl group of the bridge is in the *S* configuration. A "cEt sugar moiety" is a bicyclic sugar moiety with a 4' to 2' bridge in place of the 2'OH-group of a ribosyl sugar moiety, wherein the bridge has the formula of 4'-CH(CH₃)-O-2', and wherein the methyl group of the bridge is in the *S* configuration. "cEt" means constrained ethyl.

As used herein, "cEt nucleoside" means a nucleoside comprising a cEt sugar moiety.

As used herein, "chirally enriched population" means a plurality of molecules of identical molecular formula, wherein the number or percentage of molecules within the population that contain a particular stereochemical configuration at a particular chiral center is greater than the number or percentage of molecules expected to contain the same particular stereochemical configuration at the same particular chiral center within the population if the particular chiral center were stereorandom. Chirally enriched populations of molecules having multiple chiral centers within each molecule may contain one or more stereorandom chiral centers. In certain embodiments, the molecules are modified oligonucleotides. In certain embodiments, the molecules are compounds comprising modified oligonucleotides.

As used herein, "complementary" in reference to an oligonucleotide means that at least 70% of the nucleobases of the oligonucleotide or one or more portions thereof and the nucleobases of another nucleic acid or one or more portions thereof are capable of hydrogen bonding with one another when the nucleobase sequence of the oligonucleotide and the other nucleic acid are aligned in opposing directions. Complementary nucleobases means nucleobases that are capable of forming hydrogen bonds with one another.

Complementary nucleobase pairs include adenine (A) with thymine (T), adenine (A) with uracil (U), cytosine (C) with guanine (G), and 5-methyl cytosine (^mC) with guanine (G). Complementary oligonucleotides and/or target nucleic acids need not have nucleobase complementarity at each nucleoside. Rather, some mismatches are tolerated. As used herein, "fully complementary" or "100% complementary" in reference to an oligonucleotide, or a portion thereof, means that the oligonucleotide, or portion thereof, is complementary to another oligonucleotide or target nucleic acid at each nucleobase of the shorter of the two oligonucleotides, or at each nucleoside if the oligonucleotides are the same length.

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 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.

As used herein, “internucleoside linkage” means the covalent linkage between contiguous nucleosides in an oligonucleotide. As used herein, “modified internucleoside linkage” means any internucleoside linkage other than a phosphodiester internucleoside linkage. “Phosphorothioate internucleoside linkage” is a modified internucleoside linkage in which one of the non-bridging oxygen atoms of a phosphodiester internucleoside linkage is replaced with a sulfur atom.

As used herein, “mismatch” or “non-complementary” means a nucleobase of a first oligonucleotide that is not complementary with the corresponding nucleobase of a second oligonucleotide or target nucleic acid when the first and second oligonucleotide are aligned.

As used herein, “motif” means the pattern of unmodified and/or modified sugar moieties, nucleobases, and/or internucleoside linkages, in an oligonucleotide.

As used herein, “nonsense-mediated decay-inducing exon (NIE)” is an exon, or a pseudo-exon, that, when included in an mRNA transcript can activate the nonsense-mediated decay (NMD) pathway. “NIE-1” is a 64 nucleobase in length NIE located in intron 20 (chr2:166863579-166864271, hg19; Carvill et al., 2018), which causes degradation of the SCN1A transcript. In certain embodiments, human NIE-1 has the nucleobase sequence of SEQ ID NO: 13. In certain embodiments, mouse NIE-1 has the nucleobase sequence of SEQ ID NO: 14.

As used herein, “non-bicyclic modified sugar moiety” means a modified sugar moiety that comprises a modification, such as a substituent, that does not form a bridge between two atoms of the sugar to form a second ring.

As used herein, “nucleobase” means an unmodified nucleobase or a modified nucleobase. As used herein an “unmodified nucleobase” is adenine (A), thymine (T), cytosine (C), uracil (U), or guanine (G). As used herein, a “modified nucleobase” is a group of atoms other than unmodified A, T, C, U, or G capable of pairing with at least one unmodified nucleobase. A “5-methyl cytosine” is a modified nucleobase. A universal base is a modified nucleobase that can pair with any one of the five unmodified nucleobases. As used herein, “nucleobase sequence” means the order of contiguous nucleobases in a nucleic acid or oligonucleotide independent of any sugar or internucleoside linkage modification.

As used herein, “nucleoside” means a compound comprising a nucleobase and a sugar moiety. The nucleobase and sugar moiety are each, independently, unmodified or modified. As used herein, “modified nucleoside” means a nucleoside comprising a modified nucleobase and/or a modified sugar moiety. “Linked nucleosides” are nucleosides that are connected in a contiguous sequence (i.e., no additional nucleosides are presented between those that are linked).

As used herein, “oligomeric compound” means an oligonucleotide and optionally one or more additional features, such as a conjugate group or terminal group. An oligomeric compound may be paired with a second oligomeric compound that is complementary to the first oligomeric compound or may be

unpaired. A “singled-stranded oligomeric compound” is an unpaired oligomeric compound. The term “oligomeric duplex” means a duplex formed by two oligomeric compounds having complementary nucleobase sequences. Each oligomeric compound of an oligomeric duplex may be referred to as a “duplexed oligomeric compound.”

5 As used herein, “oligonucleotide” means a strand of linked nucleosides connected via internucleoside linkages, wherein each nucleoside and internucleoside linkage may be modified or unmodified. Unless otherwise indicated, oligonucleotides consist of 8-50 linked nucleosides. As used herein, “modified oligonucleotide” means an oligonucleotide, wherein at least one nucleoside or internucleoside linkage is modified. As used herein, “unmodified oligonucleotide” means an oligonucleotide that does not comprise any
10 nucleoside modifications or internucleoside modifications.

As used herein, “pharmaceutical composition” means a mixture of substances suitable for administering to a subject. For example, a pharmaceutical composition may comprise an oligomeric compound and a sterile aqueous solution.

15 As used herein, “pharmaceutically acceptable carrier or diluent” means any substance suitable for use in administering to a subject. Certain such carriers enable pharmaceutical compositions to be formulated as, for example, tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspension, and lozenges for the oral ingestion by a subject. In certain embodiments, a pharmaceutically acceptable carrier or diluent is sterile water, sterile saline, sterile buffer solution, or sterile artificial cerebrospinal fluid.

20 As used herein, “pharmaceutically acceptable salts” means physiologically and pharmaceutically acceptable salts of compounds. Pharmaceutically acceptable salts retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

As used herein, “RNA” means an RNA transcript and includes pre-mRNA and mature mRNA unless otherwise specified.

25 As used herein, “stereorandom chiral center” in the context of a population of molecules of identical molecular formula means a chiral center having a random stereochemical configuration. For example, in a population of molecules comprising a stereorandom chiral center, the number of molecules having the (*S*) configuration of the stereorandom chiral center may be but is not necessarily the same as the number of molecules having the (*R*) configuration of the stereorandom chiral center. The stereochemical configuration of a chiral center is considered random when it is the result of a synthetic method that is not designed to
30 control the stereochemical configuration. In certain embodiments, a stereorandom chiral center is a stereorandom phosphorothioate internucleoside linkage.

As used herein, “subject” means a human or non-human animal.

35 As used herein, “sugar moiety” means an unmodified sugar moiety or a modified sugar moiety. As used herein, “unmodified sugar moiety” means a 2'-OH(H) β -D ribosyl moiety, as found in RNA (an “unmodified RNA sugar moiety”), or a 2'-H(H) β -D deoxyribosyl moiety, as found in DNA (an “unmodified DNA sugar moiety”). Unmodified sugar moieties have one hydrogen at each of the 1', 3', and 4' positions, an

oxygen at the 3' position, and two hydrogens at the 5' position. As used herein, "modified sugar moiety" or "modified sugar" means a modified furanosyl sugar moiety or a sugar surrogate.

As used herein, "sugar surrogate" means 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. Modified nucleosides comprising sugar surrogates can be incorporated into one or more positions within an oligonucleotide and such oligonucleotides are capable of hybridizing to complementary oligomeric compounds or target nucleic acids.

As used herein, "standard *in vitro* assay" means the assay described in Example 1 and reasonable variations thereof.

As used herein, "standard *in vivo* assay" means the assay described in Example 9 and reasonable variations thereof.

As used herein, "symptom" means any physical feature or test result that indicates the existence or extent of a disease or disorder. In certain embodiments, a symptom is apparent to a subject or to a medical professional examining or testing the subject.

As used herein, "target nucleic acid" means a nucleic acid that an antisense compound is designed to affect.

As used herein, "target region" means a portion of a target nucleic acid to which an oligomeric compound is designed to hybridize.

As used herein, "terminal group" means a chemical group or group of atoms that is covalently linked to a terminus of an oligonucleotide.

As used herein, "therapeutically effective amount" means an amount of a pharmaceutical agent that provides a therapeutic benefit to a subject. For example, a therapeutically effective amount improves a symptom of a disease.

CERTAIN EMBODIMENTS

The present disclosure provides the following non-limiting numbered embodiments:

Embodiment 1. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 85% complementary to an equal length portion of a SCN1A nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

Embodiment 2. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or 18 contiguous nucleobases of any of the nucleobase sequences of SEQ

ID NOs 41-889, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

Embodiment 3. The oligomeric compound of embodiment 1 or embodiment 2, wherein the modified oligonucleotide has a nucleobase sequence that is at least 90%, 95%, or 100% complementary to the nucleobase sequence of SEQ ID NO: 1 or SEQ ID NO: 2 when measured across the entire nucleobase sequence of the modified oligonucleotide.

Embodiment 4. The oligomeric compound of any of embodiments 1-3, wherein the modified oligonucleotide has a nucleobase sequence comprising a portion of at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 18 contiguous nucleobases, wherein the portion is complementary to SEQ ID NO: 13.

Embodiment 5. The oligomeric compound of any of embodiments 1-4 wherein the modified oligonucleotide comprises at least one modified sugar moiety.

Embodiment 6. The oligomeric compound of embodiment 5, wherein the modified oligonucleotide comprises at least one bicyclic sugar moiety.

Embodiment 7. The oligomeric compound of embodiment 6, wherein the bicyclic sugar moiety has a 4'-2' bridge, wherein the 4'-2' bridge is selected from -CH₂-O-; and -CH(CH₃)-O-.

Embodiment 8. The oligomeric compound of any of embodiments 5-7, wherein the modified oligonucleotide comprises at least one non-bicyclic modified sugar moiety.

Embodiment 9. The oligomeric compound of embodiment 8, wherein the non-bicyclic modified sugar moiety is any of a 2'-MOE sugar moiety, a 2'-NMA sugar moiety, a 2'-OMe sugar moiety, or a 2'-F sugar moiety.

Embodiment 10. The oligomeric compound any of embodiments 5-9, wherein the modified oligonucleotide comprises at least one sugar surrogate.

Embodiment 11. The oligomeric compound of embodiment 10, wherein the sugar surrogate is any of morpholino, modified morpholino, PNA, THP, and F-HNA.

Embodiment 12. The oligomeric compound of embodiment 5, wherein each nucleoside of the modified oligonucleotide comprises a modified sugar moiety.

Embodiment 13. The oligomeric compound of embodiment 12, wherein each modified sugar moiety is a 2'-MOE sugar moiety.

Embodiment 14. The oligomeric compound of embodiment 12, wherein each modified sugar moiety is a 2'-NMA sugar moiety.

- Embodiment 15. The oligomeric compound of any of embodiments 1-14, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.
- Embodiment 16. The oligomeric compound of any of embodiments 1-14, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.
- 5 Embodiment 17. The oligomeric compound of embodiment 15 or embodiment 16, wherein at least one modified internucleoside linkage is a phosphorothioate internucleoside linkage.
- Embodiment 18. The oligomeric compound of embodiment 15 or embodiment 17 wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.
- 10 Embodiment 19. The oligomeric compound of any of embodiments 15, 17, or 18, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage and a phosphorothioate internucleoside linkage.
- Embodiment 20. The oligomeric compound of embodiment 16, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.
- Embodiment 21. The oligomeric compound of any of embodiments 1-20, wherein the modified
15 oligonucleotide comprises at least one modified nucleobase.
- Embodiment 22. The oligomeric compound of embodiment 21, wherein the modified nucleobase is a 5-methyl cytosine.
- Embodiment 23. The oligomeric compound of any of embodiments 1-22, wherein the modified oligonucleotide consists of 12-22, 12-20, 14-20, 15-25, 16-20, 18-22 or 18-20 linked nucleosides.
- 20 Embodiment 24. The oligomeric compound of any of embodiments 1-23, wherein the modified oligonucleotide consists of 16, 17, or 18 linked nucleosides.
- Embodiment 25. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $A_{ns} G_{ns} T_{ns} T_{ns} G_{ns} G_{ns} A_{ns} G_{ns} {}^mC_{ns} A_{ns} A_{ns} G_{ns} A_{ns} T_{ns} T_{ns} A_{ns} T_{ns} {}^mC_n$ (SEQ ID NO: 41), wherein,
- 25 A = an adenine nucleobase,
 ${}^mC$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 n = a 2'-NMA sugar moiety, and
 30 s = a phosphorothioate internucleoside linkage.
- Embodiment 26. An oligomeric compound comprising a modified oligonucleotide according to any one of the following chemical notations (5' to 3'):

- i) $A_{es}G_{eo}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- ii) $A_{es}G_{eo}T_{es}T_{eo}G_{es}G_{es}A_{es}G_{es}{}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- iii) $A_{es}G_{eo}T_{es}T_{es}G_{es}G_{eo}A_{es}G_{es}{}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- iv) $A_{es}G_{eo}T_{es}T_{es}G_{es}G_{es}A_{es}G_{eo}{}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- 5 v) $A_{es}G_{es}T_{es}T_{eo}G_{eo}G_{es}A_{es}G_{es}{}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- vi) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{eo}{}^mC_{eo}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- vii) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{es}A_{eo}A_{eo}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- viii) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{es}A_{es}A_{es}G_{eo}A_{eo}T_{es}T_{es}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- ix) $A_{es}G_{eo}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{es}A_{eo}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- 10 x) $A_{es}G_{eo}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{es}A_{es}A_{es}G_{eo}A_{es}T_{es}T_{es}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- xi) $A_{es}G_{eo}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{eo}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- xii) $A_{es}G_{es}T_{eo}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{eo}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- xiii) $A_{es}G_{es}T_{es}T_{es}G_{eo}G_{es}A_{es}G_{es}{}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{eo}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- xiv) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{eo}A_{eo}G_{es}{}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- 15 xv) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{eo}G_{es}{}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{eo}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- xvi) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{eo}A_{es}A_{es}G_{es}A_{es}T_{eo}T_{es}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- xvii) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{eo}A_{es}A_{es}G_{es}A_{es}T_{es}T_{eo}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- xviii) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{es}A_{es}A_{eo}G_{es}A_{es}T_{es}T_{eo}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- xix) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{es}A_{es}A_{es}G_{eo}A_{es}T_{eo}T_{es}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- 20 xx) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{es}A_{es}A_{es}G_{es}A_{eo}T_{es}T_{eo}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- xxi) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{eo}T_{eo}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 41);
- xxii) $A_{eo}A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}{}^mC_{eo}{}^mC_e$ (SEQ ID NO: 890);
- xxiii) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}{}^mC_{eo}{}^mC_e$ (SEQ ID NO: 891);
- xxiv) $A_{eo}A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}{}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}{}^mC_e$ (SEQ ID NO: 892);
- 25 xxv) $G_{ns}G_{ns}T_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}A_{ns}A_{ns}G_{ns}G_{ns}G_{ns}G_{ns}T_{ns}A_{ns}A_{ns}T_n$ (SEQ ID NO: 881);
- xxvi) $A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}A_{ns}A_{ns}G_{ns}G_{ns}G_{ns}G_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}{}^mC_{ns}A_n$ (SEQ ID NO: 885);
- xxvii) $G_{ns}{}^mC_{ns}A_{ns}A_{ns}A_{ns}A_{ns}G_{ns}G_{ns}G_{ns}G_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}{}^mC_{ns}A_{ns}G_n$ (SEQ ID NO: 888);
- xxviii) ${}^mC_{ns}A_{ns}A_{ns}A_{ns}A_{ns}G_{ns}G_{ns}G_{ns}G_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}{}^mC_{ns}A_{ns}G_{ns}T_n$ (SEQ ID NO: 882);
- xxix) $A_{ns}A_{ns}A_{ns}G_{ns}G_{ns}G_{ns}G_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}{}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}{}^mC_n$ (SEQ ID NO: 880);
- 30 xxx) $A_{ns}A_{ns}G_{ns}G_{ns}G_{ns}G_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}{}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}{}^mC_{ns}{}^mC_n$ (SEQ ID NO: 883);
- xxxi) $G_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}{}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}{}^mC_{ns}{}^mC_{ns}{}^mC_{ns}A_{ns}T_{ns}A_{ns}A_n$ (SEQ ID NO: 511);
- xxxii) $T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}{}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}{}^mC_{ns}{}^mC_{ns}{}^mC_{ns}A_{ns}T_{ns}A_{ns}A_{ns}T_n$ (SEQ ID NO: 750);
- xxxiii) $A_{ns}A_{ns}T_{ns}A_{ns}{}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}{}^mC_{ns}{}^mC_{ns}{}^mC_{ns}A_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_n$ (SEQ ID NO: 736);
- xxxiv) $A_{ns}T_{ns}A_{ns}{}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}{}^mC_{ns}{}^mC_{ns}{}^mC_{ns}A_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}A_n$ (SEQ ID NO: 642);
- 35 xxxv) $T_{ns}A_{ns}{}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}{}^mC_{ns}{}^mC_{ns}{}^mC_{ns}A_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}A_{ns}A_n$ (SEQ ID NO: 519);
- xxxvi) $A_{ns}{}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}{}^mC_{ns}{}^mC_{ns}{}^mC_{ns}A_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}A_{ns}A_{ns}G_n$ (SEQ ID NO: 741);

- xxxvii) ${}^m\text{C}_{\text{ns}}{}^m\text{C}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{ns}}{}^m\text{C}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{T}_{\text{ns}}\text{T}_{\text{ns}}\text{G}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{n}}$ (SEQ ID NO: 664);
- xxxviii) ${}^m\text{C}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{ns}}{}^m\text{C}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{T}_{\text{ns}}\text{T}_{\text{ns}}\text{G}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{n}}$ (SEQ ID NO: 645);
- xxxix) ${}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{ns}}{}^m\text{C}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{T}_{\text{ns}}\text{T}_{\text{ns}}\text{G}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{n}}$ (SEQ ID NO: 550);
- xl) $\text{A}_{\text{ns}}\text{T}_{\text{ns}}{}^m\text{C}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{T}_{\text{ns}}\text{T}_{\text{ns}}\text{G}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{n}}$ (SEQ ID NO: 814);
- 5 xli) $\text{T}_{\text{ns}}{}^m\text{C}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{T}_{\text{ns}}\text{T}_{\text{ns}}\text{G}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{n}}$ (SEQ ID NO: 692);
- xlii) ${}^m\text{C}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{T}_{\text{ns}}\text{T}_{\text{ns}}\text{G}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{ns}}\text{T}_{\text{n}}$ (SEQ ID NO: 587);
- xliii) ${}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{T}_{\text{ns}}\text{T}_{\text{ns}}\text{G}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{ns}}\text{T}_{\text{ns}}\text{A}_{\text{n}}$ (SEQ ID NO: 523);
- xliv) $\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{T}_{\text{ns}}\text{T}_{\text{ns}}\text{G}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{ns}}\text{T}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{n}}$ (SEQ ID NO: 778);
- xlv) $\text{T}_{\text{ns}}\text{T}_{\text{ns}}\text{G}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{ns}}\text{T}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{ns}}{}^m\text{C}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{T}_{\text{ns}}\text{A}_{\text{n}}$ (SEQ ID NO: 510);
- 10 xlvii) $\text{T}_{\text{ns}}\text{G}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{ns}}\text{T}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{ns}}{}^m\text{C}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{T}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{n}}$ (SEQ ID NO: 816);
- xlvi) $\text{G}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{ns}}\text{T}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{ns}}{}^m\text{C}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{T}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{n}}$ (SEQ ID NO: 696); or
- xlvi) $\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{A}_{\text{ns}}\text{A}_{\text{ns}}\text{G}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{ns}}\text{T}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{ns}}{}^m\text{C}_{\text{ns}}{}^m\text{C}_{\text{ns}}\text{T}_{\text{ns}}\text{A}_{\text{ns}}\text{T}_{\text{ns}}\text{A}_{\text{n}}$ (SEQ ID NO: 590),

wherein,

- 15 A = an adenine nucleobase,
 ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 20 n = a 2'-NMA sugar moiety.
 o = a phosphodiester internucleoside linkage, and
 s = a phosphorothioate internucleoside linkage.

Embodiment 27. The oligomeric compound of any of embodiments 1-26, wherein the oligomeric compound is a singled-stranded oligomeric compound.

25 Embodiment 28. The oligomeric compound of any of embodiments 1-27 consisting of the modified oligonucleotide.

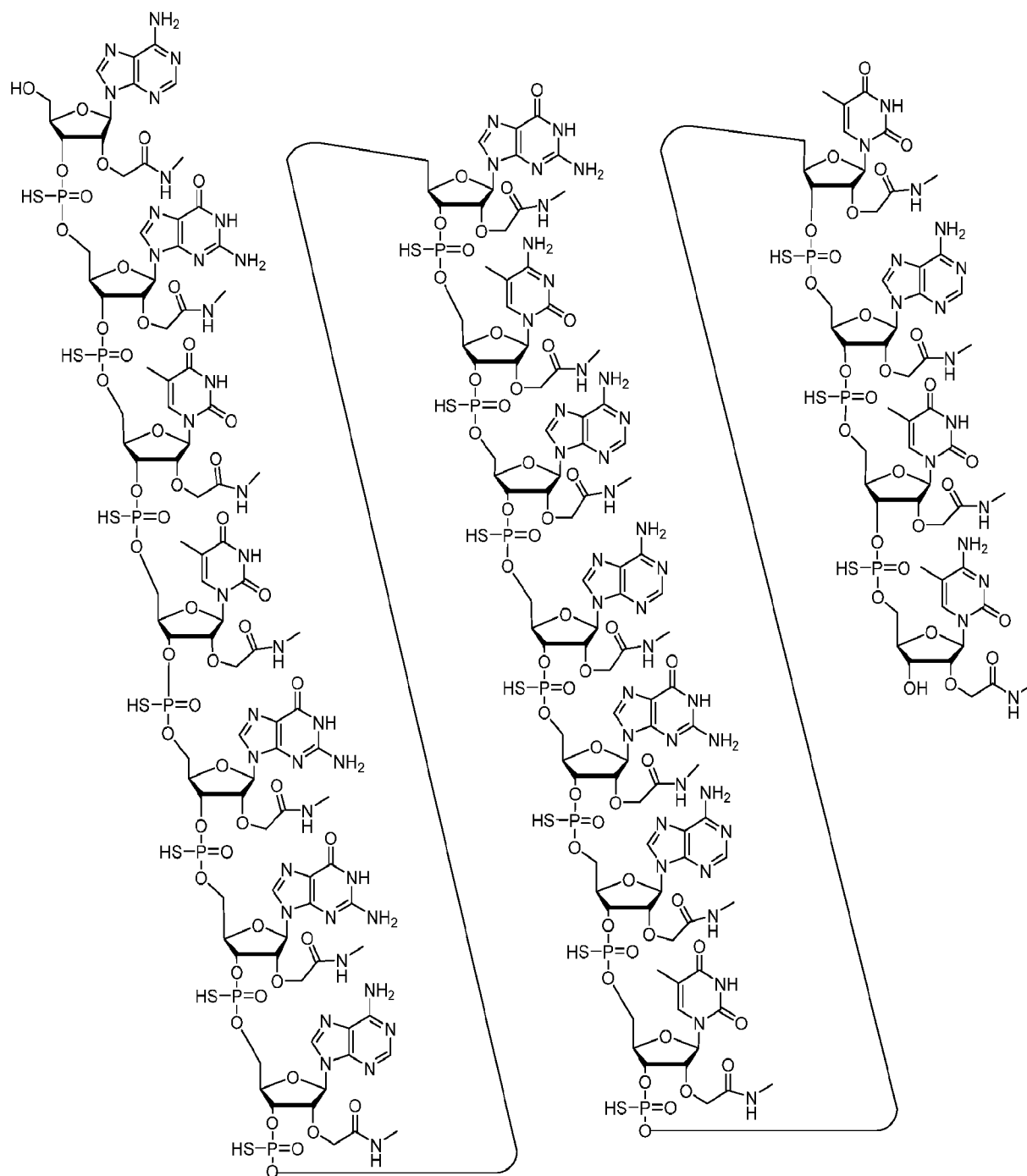
Embodiment 29. The oligomeric compound of any of embodiments 1-28 comprising a conjugate moiety comprising a conjugate group and a conjugate linker.

Embodiment 30. The oligomeric compound of embodiment 29, wherein the conjugate group
 30 comprises a GalNAc cluster comprising 1-3 GalNAc ligands.

Embodiment 31. The oligomeric compound of embodiment 29 or embodiment 30, wherein the conjugate linker consists of a single bond.

- Embodiment 32. The oligomeric compound of embodiment 29, wherein the conjugate linker is cleavable.
- Embodiment 33. The oligomeric compound of embodiment 29, wherein the conjugate linker comprises 1-3 linker-nucleosides.
- 5 Embodiment 34. The oligomeric compound of any of embodiments 29-33, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.
- Embodiment 35. The oligomeric compound of any of embodiments 29-33, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.
- Embodiment 36. The oligomeric compound of any of embodiments 1-27 or 29-35 comprising a
10 terminal group.
- Embodiment 37. The oligomeric compound of any of embodiments 1-32 or 34-35, wherein the oligomeric compound does not comprise linker-nucleosides.

Embodiment 38. A modified oligonucleotide according to the following chemical structure:

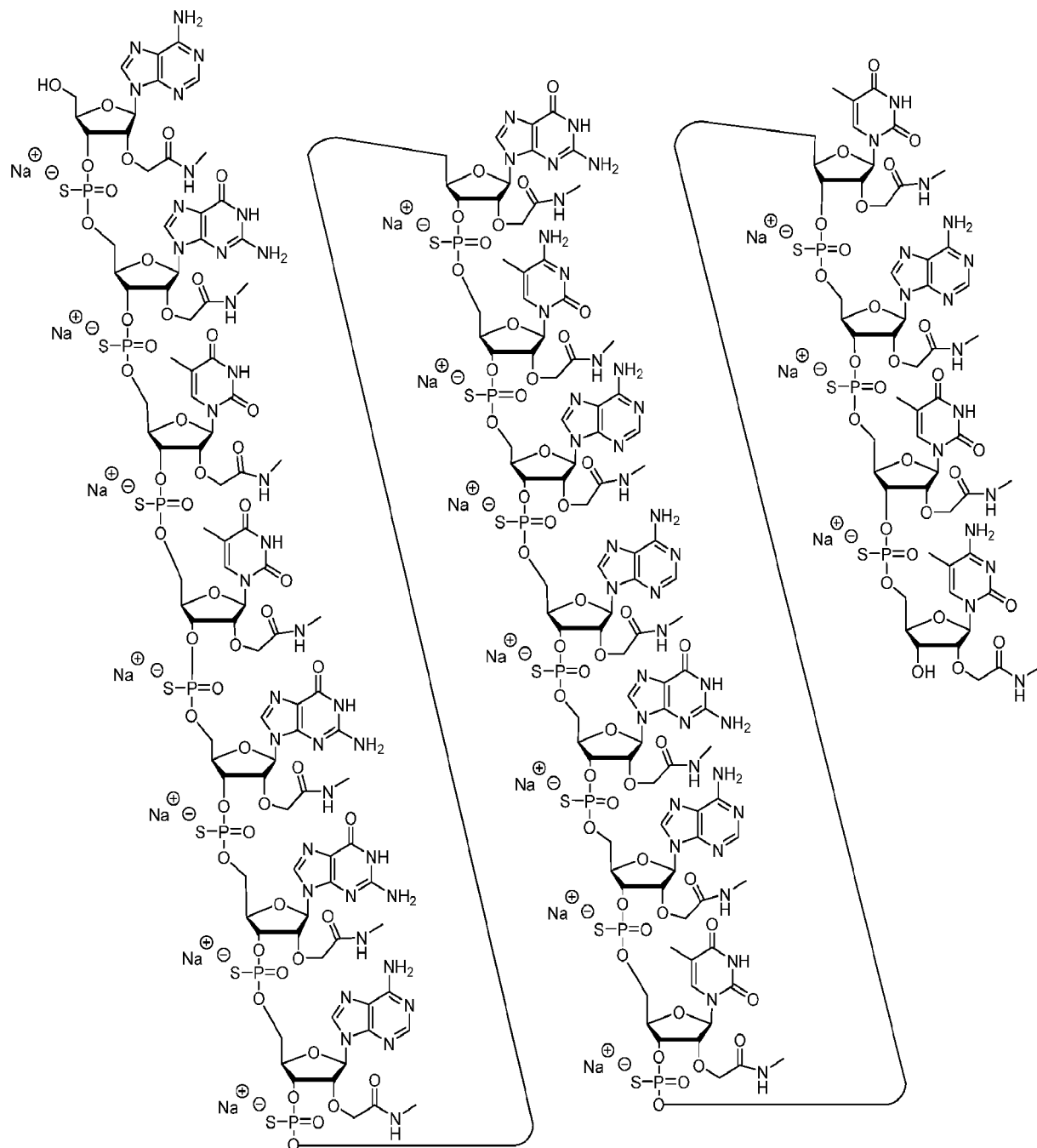


(SEQ ID NO: 41) or a salt thereof.

Embodiment 39. The modified oligonucleotide of embodiment 38, which is the sodium salt or the potassium salt.

5

Embodiment 40. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 41).

Embodiment 41. A chirally enriched population of modified oligonucleotides of any of embodiments 38-40, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

Embodiment 42. The chirally enriched population of embodiment 41, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*Sp*) configuration.

- Embodiment 43. The chirally enriched population of embodiment 41, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*Rp*) configuration.
- Embodiment 44. The chirally enriched population of embodiment 41, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.
- Embodiment 45. The chirally enriched population of embodiment 44, wherein the population is enriched for modified oligonucleotides having the (*Sp*) configuration at each phosphorothioate internucleoside linkage or for modified oligonucleotides having the (*Rp*) configuration at each phosphorothioate internucleoside linkage.
- Embodiment 46. The chirally enriched population of embodiment 44, wherein the population is enriched for modified oligonucleotides having the (*Rp*) configuration at one particular phosphorothioate internucleoside linkage and the (*Sp*) configuration at each of the remaining phosphorothioate internucleoside linkages.
- Embodiment 47. The chirally enriched population of embodiment 44, wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the *Sp*, *Sp*, and *Rp* configurations, in the 5' to 3' direction.
- Embodiment 48. A population of modified oligonucleotides of any of embodiments 38-40, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.
- Embodiment 49. A pharmaceutical composition comprising the oligomeric compound of any of embodiments 1-37, the modified oligonucleotide of any of embodiments 38-40, the chirally-enriched population of any of embodiments 41-47, or the population of modified oligonucleotides of embodiment 48, and a pharmaceutically acceptable diluent or carrier.
- Embodiment 50. The pharmaceutical composition of embodiment 49, comprising a pharmaceutically acceptable diluent and wherein the pharmaceutically acceptable diluent is artificial CSF (aCSF) or PBS.
- Embodiment 51. The pharmaceutical composition of embodiment 50, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial CSF (aCSF).
- Embodiment 52. The pharmaceutical composition of embodiment 50, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.
- Embodiment 53. A method of modulating splicing of an *SCN1A* RNA in a cell comprising contacting the cell with an oligomeric compound of any of embodiments 1-37, a modified oligonucleotide of any of embodiments 38-40, a chirally-enriched population of any of embodiments 41-47, a population of

modified oligonucleotides of embodiment 48, or a pharmaceutical composition of any of embodiments 49-52.

Embodiment 54. The method of embodiment 53, wherein the amount of SCN1A RNA that includes an NIE is reduced.

5 Embodiment 55. The method of embodiment 54, wherein the amount of SCN1A RNA that includes NIE-1 is reduced.

Embodiment 56. The method of any of embodiments 53-55, wherein the amount of SCN1A RNA that excludes an NIE is increased.

10 Embodiment 57. The method of any of embodiments 53-56, wherein the amount of SCN1A RNA that excludes NIE-1 is increased.

Embodiment 58. A method of increasing the amount of full-length SCN1A RNA in a cell, comprising contacting the cell with an oligomeric compound of any of embodiments 1-37, a modified oligonucleotide of any of embodiments 38-40, a chirally-enriched population of any of embodiments 41-47, a population of modified oligonucleotides of embodiment 48, or a pharmaceutical composition of any
15 of embodiments 49-52.

Embodiment 59. A method of increasing SCN1A RNA lacking NIE-1 in a cell, tissue, or organ, comprising contacting a cell, tissue, or organ with an oligomeric compound of any of embodiments 1-37, a modified oligonucleotide of any of embodiments 38-40, a chirally-enriched population of any of
20 embodiments 41-47, a population of modified oligonucleotides of embodiment 48, or a pharmaceutical composition of any of embodiments 49-52.

Embodiment 60. The method of any of embodiments 53-59, wherein the cell is in vitro.

Embodiment 61. The method of any of embodiments 53-59, wherein the cell is in an animal.

Embodiment 62. A method of ameliorating a disease associated with SCN1A comprising administering to a subject having or at risk for developing a disease associated with SCN1A a
25 therapeutically effective amount of a pharmaceutical composition according to any of embodiments 49-52, and thereby treating the disease associated with SCN1A.

Embodiment 63. The method of embodiment 62, comprising identifying a subject having or at risk for developing a disease associated SCN1A.

Embodiment 64. The method of embodiment 62 or embodiment 63, wherein the disease associated
30 with SCN1A is a developmental or epileptic encephalopathic disease.

Embodiment 65. The method of embodiment 64, wherein the developmental or epileptic encephalopathic disease is Dravet Syndrome.

Embodiment 66. The method of embodiment 64, wherein the developmental or epileptic encephalopathic disease is any of Genetic Epilepsy with Febrile Seizures Plus (GEFS+), febrile seizures, Idiopathic/Generic Generalized Epilepsies (IGE/GGE), Temporal Lobe Epilepsy, Myoclonic Astatic Epilepsy (MAE), Lennox-Gastaut Syndrome, or Migrating Partial Epilepsy of Infancy (MMPSEI).

5 Embodiment 67. The method of any of embodiments 64-66, wherein at least one symptom of the developmental or epileptic encephalopathic disease is ameliorated.

Embodiment 68. The method of embodiment 67, wherein the symptom is any of seizures, behavioral and developmental delays, movement and balance dysfunctions, motor and cognitive dysfunctions, delayed language and speech, visual motor integration dysfunctions, visual perception dysfunctions,
10 executive dysfunctions, growth and nutrition issues, sleeping difficulties, chronic infections, sensory integration disorders, or dysautonomia.

Embodiment 69. The method of embodiment 68, wherein the seizures are frequent or prolonged.

Embodiment 70. The method of embodiment 68 or embodiment 69, wherein the seizure is any of convulsive, myoclonic, absence, focal, obtundation status, or tonic.

15 Embodiment 71. The method of any of embodiments 62-70, wherein the pharmaceutical composition is administered to the central nervous system or systemically.

Embodiment 72. The method of embodiment 71, wherein the pharmaceutical composition is administered to the central nervous system and systemically.

Embodiment 73. The method of any of embodiments 62-71, wherein the pharmaceutical composition
20 is administered any of intrathecally, systemically, subcutaneously, or intramuscularly.

I. Certain Oligonucleotides

In certain embodiments, provided herein are oligomeric compounds comprising oligonucleotides, which consist of linked nucleosides. Oligonucleotides may be unmodified oligonucleotides (RNA or DNA) or may be modified oligonucleotides. Modified oligonucleotides comprise at least one modification relative
25 to unmodified RNA or DNA. That is, modified oligonucleotides comprise at least one modified nucleoside (comprising a modified sugar moiety and/or a modified nucleobase) and/or at least one modified internucleoside linkage.

A. Certain Modified Nucleosides

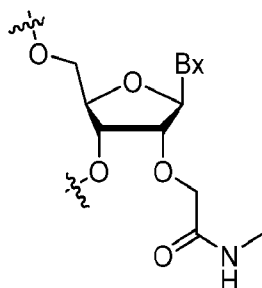
Modified nucleosides comprise a modified sugar moiety or a modified nucleobase or both a
30 modified sugar moiety and a modified nucleobase.

1. Certain Sugar Moieties

In certain embodiments, modified sugar moieties are non-bicyclic modified sugar moieties. In certain embodiments, modified sugar moieties are bicyclic or tricyclic sugar moieties. In certain

embodiments, modified sugar moieties are sugar surrogates. Such sugar surrogates may comprise one or more substitutions corresponding to those of other types of modified sugar moieties.

In certain embodiments, modified sugar moieties are non-bicyclic modified sugar moieties comprising a furanosyl ring with one or more substituent groups none of which bridges two atoms of the furanosyl ring to form a bicyclic structure. Such non bridging substituents may be at any position of the furanosyl, including but not limited to substituents at the 2', 4', and/or 5' positions. In certain embodiments one or more non-bridging substituent of non-bicyclic modified sugar moieties is branched. Examples of 2'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 2'-F, 2'-OCH₃ ("OMe" or "O-methyl"), and 2'-O(CH₂)₂OCH₃ ("MOE" or "O-methoxyethyl"), and 2'-O-N-alkyl acetamide, e.g., 2'-O-N-methyl acetamide ("NMA"), 2'-O-N-dimethyl acetamide, 2'-O-N-ethyl acetamide, or 2'-O-N-propyl acetamide. For example, see U.S. 6,147,200, Prakash et al., 2003, *Org. Lett.*, 5, 403-6. A "2'-O-N-methyl acetamide nucleoside" or "2'-NMA nucleoside" is shown below:



In certain embodiments, 2'-substituent groups are selected from among: halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, O-C₁-C₁₀ alkyl, O-C₁-C₁₀ substituted alkyl, S-alkyl, N(R_m)-alkyl, O-alkenyl, S-alkenyl, N(R_m)-alkenyl, O-alkynyl, S-alkynyl, N(R_m)-alkynyl, O-alkylenyl-O-alkyl, alkynyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, O(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n) or OCH₂C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C₁-C₁₀ alkyl, and the 2'-substituent groups described in Cook et al., U.S. 6,531,584; Cook et al., U.S. 5,859,221; and Cook et al., U.S. 6,005,087. Certain embodiments of these 2'-substituent groups can be further substituted with one or more substituent groups independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO₂), thiol, thioalkoxy, thioalkyl, halogen, alkyl, aryl, alkenyl and alkynyl. Examples of 4'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to alkoxy (e.g., methoxy), alkyl, and those described in Manoharan et al., WO 2015/106128. Examples of 5'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 5'-methyl (*R* or *S*), 5'-vinyl, and 5'-methoxy. In certain embodiments, non-bicyclic modified sugar moieties comprise more than one non-bridging sugar substituent, for example, 2'-F-5'-methyl sugar moieties and the modified sugar moieties and modified nucleosides described in Migawa et al., WO 2008/101157 and Rajeev et al., US2013/0203836.

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, NH₂, N₃, OCF₃, OCH₃,

O(CH₂)₃NH₂, CH₂CH=CH₂, OCH₂CH=CH₂, OCH₂CH₂OCH₃, O(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n), O(CH₂)₂ON(CH₃)₂, O(CH₂)₂O(CH₂)₂N(CH₃)₂, and N-substituted acetamide (OCH₂C(=O)-N(R_m)(R_n)), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C₁-C₁₀ alkyl, e.g., for example, OCH₂C(=O)-N(H)CH₃ ("NMA").

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCF₃, OCH₃, OCH₂CH₂OCH₃, O(CH₂)₂SCH₃, O(CH₂)₂ON(CH₃)₂, O(CH₂)₂O(CH₂)₂N(CH₃)₂, and OCH₂C(=O)-N(H)CH₃ ("NMA").

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCH₃, OCH₂CH₂OCH₃, and OCH₂C(=O)-N(H)CH₃.

Certain modified sugar moieties comprise a substituent that bridges two atoms of the furanosyl ring to form a second ring, resulting in a bicyclic sugar moiety. In certain such embodiments, the bicyclic sugar moiety comprises a bridge between the 4' and the 2' furanose ring atoms. Examples of such 4' to 2' bridging sugar substituents include but are not limited to: 4'-CH₂-2', 4'-(CH₂)₂-2', 4'-(CH₂)₃-2', 4'-CH₂-O-2' ("LNA"), 4'-CH₂-S-2', 4'-(CH₂)₂-O-2' ("ENA"), 4'-CH(CH₃)-O-2' (referred to as "constrained ethyl" or "cEt"), 4'-CH₂-O-CH₂-2', 4'-CH₂-N(R)-2', 4'-CH(CH₂OCH₃)-O-2' ("constrained MOE" or "cMOE") and analogs thereof (see, e.g., Seth et al., U.S. 7,399,845, Bhat et al., U.S. 7,569,686, Swayze et al., U.S. 7,741,457, and Swayze et al., U.S. 8,022,193), 4'-C(CH₃)(CH₃)-O-2' and analogs thereof (see, e.g., Seth et al., U.S. 8,278,283), 4'-CH₂-N(OCH₃)-2' and analogs thereof (see, e.g., Prakash et al., U.S. 8,278,425), 4'-CH₂-O-N(CH₃)-2' (see, e.g., Allerson et al., U.S. 7,696,345 and Allerson et al., U.S. 8,124,745), 4'-CH₂-C(H)(CH₃)-2' (see, e.g., Zhou, et al., *J. Org. Chem.*, 2009, 74, 118-134), 4'-CH₂-C(=CH₂)-2' and analogs thereof (see e.g., Seth et al., U.S. 8,278,426), 4'-C(R_aR_b)-N(R)-O-2', 4'-C(R_aR_b)-O-N(R)-2', 4'-CH₂-O-N(R)-2', and 4'-CH₂-N(R)-O-2', wherein each R, R_a, and R_b is, independently, H, a protecting group, or C₁-C₁₂ alkyl (see, e.g. Imanishi et al., U.S. 7,427,672).

In certain embodiments, such 4' to 2' bridges independently comprise from 1 to 4 linked groups independently selected from: -[C(R_a)(R_b)]_n-, -[C(R_a)(R_b)]_n-O-, -C(R_a)=C(R_b)-, -C(R_a)=N-, -C(=NR_a)-, -C(=O)-, -C(=S)-, -O-, -Si(R_a)₂-, -S(=O)_x-, and -N(R_a)-;

wherein:

x is 0, 1, or 2;

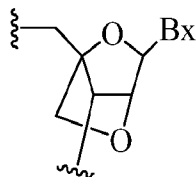
n is 1, 2, 3, or 4;

each R_a and R_b is, independently, H, a protecting group, hydroxyl, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₅-C₂₀ aryl, substituted C₅-C₂₀ aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C₅-C₇ alicyclic radical, substituted C₅-C₇ alicyclic radical, halogen, OJ₁, NJ₁J₂, SJ₁, N₃, COOJ₁, acyl (C(=O)-H), substituted acyl, CN, sulfonyl (S(=O)₂-J₁), or sulfoxyl (S(=O)-J₁); and

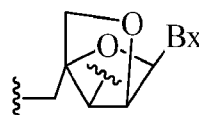
each J₁ and J₂ is, independently, H, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₅-C₂₀ aryl, substituted C₅-C₂₀ aryl, acyl (C(=O)-H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C₁-C₁₂ aminoalkyl, substituted C₁-C₁₂ aminoalkyl, or a protecting group.

Additional bicyclic sugar moieties are known in the art, see, for example: Freier et al., *Nucleic Acids Research*, 1997, 25(22), 4429-4443, Alback et al., *J. Org. Chem.*, 2006, 71, 7731-7740, Singh et al., *Chem. Commun.*, 1998, 4, 455-456; Koshkin et al., *Tetrahedron*, 1998, 54, 3607-3630; 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, 8362-8379; Wengel et al., U.S. 7,053,207; Imanishi et al., U.S. 6,268,490; Imanishi et al., U.S. 6,770,748; Imanishi et al., U.S. RE44,779; Wengel et al., U.S. 6,794,499; Wengel et al., U.S. 6,670,461; Wengel et al., U.S. 7,034,133; Wengel et al., U.S. 8,080,644; Wengel et al., U.S. 8,034,909; Wengel et al., U.S. 8,153,365; Wengel et al., U.S. 7,572,582; and Ramasamy et al., U.S. 6,525,191; Torsten et al., WO 2004/106356; Wengel et al., WO 1999/014226; Seth et al., WO 2007/134181; Seth et al., U.S. 7,547,684; Seth et al., U.S. 7,666,854; Seth et al., U.S. 8,088,746; Seth et al., U.S. 7,750,131; Seth et al., U.S. 8,030,467; Seth et al., U.S. 8,268,980; Seth et al., U.S. 8,546,556; Seth et al., U.S. 8,530,640; Migawa et al., U.S. 9,012,421; Seth et al., U.S. 8,501,805; and U.S. Patent Publication Nos. Allerson et al., US2008/0039618 and Migawa et al., US2015/0191727.

In certain embodiments, bicyclic sugar moieties and nucleosides incorporating such bicyclic sugar moieties are further defined by isomeric configuration. For example, an LNA nucleoside (described herein) may be in the α -L configuration or in the β -D configuration.



LNA (β -D-configuration)
bridge = 4'-CH₂-O-2'



α -L-LNA (α -L-configuration)
bridge = 4'-CH₂-O-2'

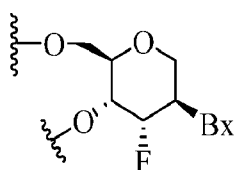
α -L-methyleneoxy (4'-CH₂-O-2') or α -L-LNA bicyclic nucleosides have been incorporated into oligonucleotides that showed antisense activity (Frieden et al., *Nucleic Acids Research*, 2003, 31, 6365-6372). Herein, general descriptions of bicyclic nucleosides include both isomeric configurations. When the positions of specific bicyclic nucleosides (e.g., LNA or cEt) are identified in exemplified embodiments herein, they are in the β -D configuration, unless otherwise specified.

In certain embodiments, modified sugar moieties comprise one or more non-bridging sugar substituent and one or more bridging sugar substituent (e.g., 5'-substituted and 4'-2' bridged sugars).

In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the sugar moiety is replaced, e.g., with a sulfur, carbon or nitrogen atom. In certain such embodiments, such modified sugar moieties also comprise bridging and/or non-bridging substituents as

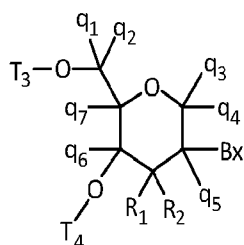
described herein. For example, certain sugar surrogates comprise a 4'-sulfur atom and a substitution at the 2'-position (*see, e.g.*, Bhat et al., U.S. 7,875,733 and Bhat et al., U.S. 7,939,677) and/or the 5' position.

In certain embodiments, sugar surrogates comprise rings having other than 5 atoms. For example, in certain embodiments, a sugar surrogate comprises a six-membered tetrahydropyran ("THP"). Such tetrahydropyrans may be further modified or substituted. Nucleosides comprising such modified tetrahydropyrans include but are not limited to hexitol nucleic acid ("HNA"), anitol nucleic acid ("ANA"), manitol nucleic acid ("MNA") (*see, e.g.*, Leumann, *CJ. Bioorg. & Med. Chem.* 2002, 10, 841-854), fluoro HNA:



F-HNA

("F-HNA", *see e.g.* Swayze et al., U.S. 8,088,904; Swayze et al., U.S. 8,440,803; Swayze et al., U.S. 8,796,437; and Swayze et al., U.S. 9,005,906; F-HNA can also be referred to as a F-THP or 3'-fluoro tetrahydropyran), and nucleosides comprising additional modified THP compounds having the formula:



wherein, independently, for each of said modified THP nucleoside:

Bx is a nucleobase moiety;

T₃ and T₄ are each, independently, an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide or one of T₃ and T₄ is an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide and the other of T₃ and T₄ is H, a hydroxyl protecting group, a linked conjugate group, or a 5' or 3'-terminal group;

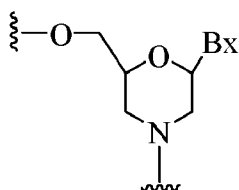
q₁, q₂, q₃, q₄, q₅, q₆ and q₇ are each, independently, H, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, C₂-C₆ alkynyl, or substituted C₂-C₆ alkynyl; and

each of R₁ and R₂ is independently selected from among: hydrogen, halogen, substituted or unsubstituted alkoxy, NJ₁J₂, SJ₁, N₃, OC(=X)J₁, OC(=X)NJ₁J₂, NJ₃C(=X)NJ₁J₂, and CN, wherein X is O, S or NJ₁, and each J₁, J₂, and J₃ is, independently, H or C₁-C₆ alkyl.

In certain embodiments, modified THP nucleosides are provided wherein q₁, q₂, q₃, q₄, q₅, q₆ and q₇ are each H. In certain embodiments, at least one of q₁, q₂, q₃, q₄, q₅, q₆ and q₇ is other than H. In certain

embodiments, at least one of q_1 , q_2 , q_3 , q_4 , q_5 , q_6 and q_7 is methyl. In certain embodiments, modified THP nucleosides are provided wherein one of R_1 and R_2 is F. In certain embodiments, R_1 is F and R_2 is H, in certain embodiments, R_1 is methoxy and R_2 is H, and in certain embodiments, R_1 is methoxyethoxy and R_2 is H.

In certain embodiments, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example, nucleosides comprising morpholino sugar moieties and their use in oligonucleotides have been reported (*see, e.g.*, Braasch et al., *Biochemistry*, 2002, 41, 4503-4510 and Summerton et al., U.S. 5,698,685; Summerton et al., U.S. 5,166,315; Summerton et al., U.S. 5,185,444; and Summerton et al., U.S. 5,034,506). As used here, the term “morpholino” means a sugar surrogate having the following structure:



In certain embodiments, morpholinos may be modified, for example by adding or altering various substituent groups from the above morpholino structure. Such sugar surrogates are referred to herein as “modified morpholinos.”

In certain embodiments, sugar surrogates comprise acyclic moieties. Examples of nucleosides and oligonucleotides comprising such acyclic sugar surrogates include but are not limited to: peptide nucleic acid (“PNA”), acyclic butyl nucleic acid (*see, e.g.*, Kumar et al., *Org. Biomol. Chem.*, 2013, 11, 5853-5865), and nucleosides and oligonucleotides described in Manoharan et al., WO2011/133876.

Many other bicyclic and tricyclic sugar and sugar surrogate ring systems are known in the art that can be used in modified nucleosides.

2. Certain Modified Nucleobases

In certain embodiments, modified oligonucleotides comprise one or more nucleosides comprising an unmodified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleosides comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleosides that does not comprise a nucleobase, referred to as an abasic nucleoside.

In certain embodiments, modified nucleobases are selected from: 5-substituted pyrimidines, 6-azapyrimidines, alkyl or alkynyl substituted pyrimidines, alkyl substituted purines, and N-2, N-6 and O-6 substituted purines. In certain embodiments, modified nucleobases are selected from: 2-aminopropyladenine, 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyl adenine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl ($-C\equiv C-CH_3$) uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo, particularly 5-bromo, 5-trifluoromethyl, 5-halouracil, and 5-halocytosine, 7-methylguanine, 7-methyladenine,

2-F-adenine, 2-aminoadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 6-N-benzoyladenine, 2-N-isobutrylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N-benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. Further modified nucleobases include tricyclic pyrimidines, such as 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one and 9-(2-aminoethoxy)-1,3-diazaphenoxazine-2-one (G-clamp). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in Merigan et al., U.S. 3,687,808, those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, Kroschwitz, J.I., Ed., John Wiley & Sons, 1990, 858-859; Englisch et al., *Angewandte Chemie*, International Edition, 1991, 30, 613; Sanghvi, Y.S., Chapter 15, *Antisense Research and Applications*, Crooke, S.T. and Lebleu, B., Eds., CRC Press, 1993, 273-288; and those disclosed in Chapters 6 and 15, *Antisense Drug Technology*, Crooke S.T., Ed., CRC Press, 2008, 163-166 and 442-443.

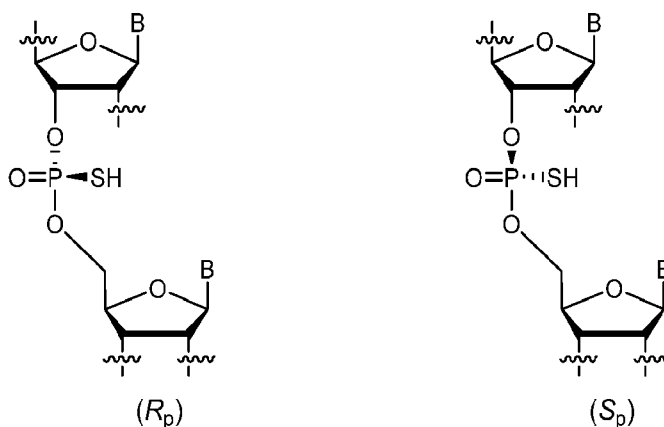
Publications that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include without limitation, Manoharan et al., US2003/0158403; Manoharan et al., US2003/0175906; Dinh et al., U.S. 4,845,205; Spielvogel et al., U.S. 5,130,302; Rogers et al., U.S. 5,134,066; Bischofberger et al., U.S. 5,175,273; Urdea et al., U.S. 5,367,066; Benner et al., U.S. 5,432,272; Matteucci et al., U.S. 5,434,257; Gmeiner et al., U.S. 5,457,187; Cook et al., U.S. 5,459,255; Froehler et al., U.S. 5,484,908; Matteucci et al., U.S. 5,502,177; Hawkins et al., U.S. 5,525,711; Haralambidis et al., U.S. 5,552,540; Cook et al., U.S. 5,587,469; Froehler et al., U.S. 5,594,121; Switzer et al., U.S. 5,596,091; Cook et al., U.S. 5,614,617; Froehler et al., U.S. 5,645,985; Cook et al., U.S. 5,681,941; Cook et al., U.S. 5,811,534; Cook et al., U.S. 5,750,692; Cook et al., U.S. 5,948,903; Cook et al., U.S. 5,587,470; Cook et al., U.S. 5,457,191; Matteucci et al., U.S. 5,763,588; Froehler et al., U.S. 5,830,653; Cook et al., U.S. 5,808,027; Cook et al., 6,166,199; and Matteucci et al., U.S. 6,005,096.

3. Certain Modified Internucleoside Linkages

In certain embodiments, nucleosides of modified oligonucleotides may be linked together using any internucleoside linkage. The two main classes of internucleoside linking groups are defined by the presence or absence of a phosphorus atom. Representative phosphorus-containing internucleoside linkages include but are not limited to phosphodiester, which contain a phosphodiester bond, $P(O_2)=O$, (also referred to as unmodified or naturally occurring linkages); phosphotriesters; methylphosphonates; methoxypropylphosphonates ("MOP"); phosphoramidates; mesyl phosphoramidates; phosphorothioates ($P(O_2)=S$); and phosphorodithioates ($HS-P=S$). Representative non-phosphorus containing internucleoside linking groups include but are not limited to methylenemethylimino ($-CH_2-N(CH_3)-O-CH_2-$); thiodiester, thionocarbamate ($-O-C(=O)(NH)-S-$); siloxane ($-O-SiH_2-O-$); and N,N'-dimethylhydrazine ($-CH_2-N(CH_3)-N(CH_3)-$). Modified internucleoside linkages, compared to naturally occurring phosphate linkages, can be used to alter, typically increase, nuclease resistance of the oligonucleotide. In certain embodiments,

internucleoside linkages having a chiral atom can be prepared as a racemic mixture, or as separate enantiomers. Methods of preparation of phosphorous-containing and non-phosphorous-containing internucleoside linkages are well known to those skilled in the art.

Representative internucleoside linkages having a chiral center include but are not limited to alkylphosphonates and phosphorothioates. Modified oligonucleotides comprising internucleoside linkages having a chiral center can be prepared as populations of modified oligonucleotides comprising stereorandom internucleoside linkages, or as populations of modified oligonucleotides comprising phosphorothioate internucleoside linkages in particular stereochemical configurations. In certain embodiments, populations of modified oligonucleotides comprise phosphorothioate internucleoside linkages wherein all of the phosphorothioate internucleoside linkages are stereorandom. Such modified oligonucleotides can be generated using synthetic methods that result in random selection of the stereochemical configuration of each phosphorothioate internucleoside linkage. Nonetheless, as is well understood by those of skill in the art, each individual phosphorothioate of each individual oligonucleotide molecule has a defined stereoconfiguration. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising one or more particular phosphorothioate internucleoside linkages in a particular, independently selected stereochemical configuration. In certain embodiments, the particular configuration of the particular phosphorothioate internucleoside linkage is present in at least 65% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate internucleoside linkage is present in at least 70% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate internucleoside linkage is present in at least 80% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate internucleoside linkage is present in at least 90% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate internucleoside linkage is present in at least 99% of the molecules in the population. Such chirally enriched populations of modified oligonucleotides can be generated using synthetic methods known in the art, *e.g.*, methods described in Oka et al., *JACS*, 2003, 125, 8307, Wan et al. *Nuc. Acid. Res.*, 2014, 42, 13456, and WO 2017/015555. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one indicated phosphorothioate in the (*Sp*) configuration. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one phosphorothioate in the (*Rp*) configuration. In certain embodiments, modified oligonucleotides comprising (*Rp*) and/or (*Sp*) phosphorothioates comprise one or more of the following formulas, respectively, wherein "B" indicates a nucleobase:



Unless otherwise indicated, chiral internucleoside linkages of modified oligonucleotides described herein can be stereorandom or in a particular stereochemical configuration.

In certain embodiments, modified oligonucleotides comprise an internucleoside motif of (5' to 3')
 5 sooooooooooooooooooooo. In certain embodiments, the particular stereochemical configuration of the modified oligonucleotides is (5' to 3') Sp-o-o-o-Sp-Sp-Sp-Rp-Sp-Sp-Rp-Sp-Sp-Sp-Sp-Sp-Sp or Sp-o-o-o-Sp-Sp-Sp-Rp-Sp-Sp-Sp-Sp-Sp-Sp-Sp-Sp-Sp; wherein each 'Sp' represents a phosphorothioate internucleoside linkage in the *S* configuration; Rp represents a phosphorothioate internucleoside linkage in the *R* configuration; and 'o' represents a phosphodiester internucleoside linkage.

10 Neutral internucleoside linkages include, without limitation, phosphotriesters, methylphosphonates, MMI (3'-CH₂-N(CH₃)-O-5'), amide-3 (3'-CH₂-C(=O)-N(H)-5'), amide-4 (3'-CH₂-N(H)-C(=O)-5'), formacetal (3'-O-CH₂-O-5'), methoxypropyl, and thioformacetal (3'-S-CH₂-O-5'). Further neutral internucleoside linkages include nonionic linkages comprising siloxane (dialkylsiloxane), carboxylate ester, carboxamide, sulfide, sulfonate ester and amides (*see e.g., Carbohydrate Modifications in Antisense Research*; Y.S.
 15 Sanghvi and P.D. Cook, Eds., ACS Symposium Series 580; Chapters 3 and 4, 40-65). Further neutral internucleoside linkages include nonionic linkages comprising mixed N, O, S and CH₂ component parts. In certain embodiments, a modified internucleoside linkage is any of those described in WO 2021/030778, incorporated by reference herein.

B. Certain Motifs

20 In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified sugar moiety. In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more modified internucleoside linkages. In such embodiments, the modified, unmodified, and differently modified sugar moieties, nucleobases, and/or internucleoside linkages
 25 of a modified oligonucleotide define a pattern or motif. In certain embodiments, the patterns of sugar moieties, nucleobases, and internucleoside linkages are each independent of one another. Thus, a modified oligonucleotide may be described by its sugar motif, nucleobase motif and/or internucleoside linkage motif

(as used herein, nucleobase motif describes the modifications to the nucleobases independent of the sequence of nucleobases).

1. Certain Sugar Motifs

In certain embodiments, oligonucleotides comprise one or more type of modified sugar and/or unmodified sugar moiety arranged along the oligonucleotide, or portion thereof, in a defined pattern or sugar motif. In certain instances, such sugar motifs include but are not limited to any of the sugar modifications discussed herein.

In certain embodiments, modified oligonucleotides have a gapmer motif, which is defined by two external regions or “wings” and a central or internal region or “gap.” The three regions of a gapmer motif (the 5'-wing, the gap, and the 3'-wing) form a contiguous sequence of nucleosides wherein at least some of the sugar moieties of the nucleosides of each of the wings differ from at least some of the sugar moieties of the nucleosides of the gap. Specifically, at least the sugar moieties of the nucleosides of each wing that are closest to the gap (the 3'-most nucleoside of the 5'-wing and the 5'-most nucleoside of the 3'-wing) differ from the sugar moiety of the neighboring gap nucleosides, thus defining the boundary between the wings and the gap (i.e., the wing/gap junction). In certain embodiments, the sugar moieties within the gap are the same as one another. In certain embodiments, the gap includes one or more nucleoside having a sugar moiety that differs from the sugar moiety of one or more other nucleosides of the gap. In certain embodiments, the sugar motifs of the two wings are the same as one another (symmetric gapmer). In certain embodiments, the sugar motif of the 5'-wing differs from the sugar motif of the 3'-wing (asymmetric gapmer).

In certain embodiments, the wings of a gapmer comprise 1-6 nucleosides. In certain embodiments, each nucleoside of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least one, at least two, at least three, at least four, at least five, or at least six nucleosides of each wing of a gapmer comprises a modified sugar moiety.

In certain embodiments, the gap of a gapmer comprises 7-12 nucleosides. In certain embodiments, each nucleoside of the gap of a gapmer comprises a 2'-deoxyribosyl sugar moiety. In certain embodiments, at least one nucleoside of the gap of a gapmer comprises a modified sugar moiety and each remaining nucleoside comprises a 2'-deoxyribosyl sugar moiety.

Herein, the lengths (number of nucleosides) of the three regions of a gapmer may be provided using the notation [# of nucleosides in the 5'-wing] – [# of nucleosides in the gap] – [# of nucleosides in the 3'-wing]. Thus, a 5-10-5 gapmer consists of 5 linked nucleosides in each wing and 10 linked nucleosides in the gap. Where such nomenclature is followed by a specific modification, that modification is the modification in each sugar moiety of each wing and the gap nucleosides comprise a 2'-deoxyribosyl sugar moiety. Thus, a 5-10-5 MOE gapmer consists of 5 linked 2'-MOE nucleosides in the 5'-wing, 10 linked 2'-deoxyribonucleosides in the gap, and 5 linked 2'-MOE nucleosides in the 3'-wing.

In certain embodiments, each nucleoside of a modified oligonucleotide, or portion thereof, comprises a 2'-substituted sugar moiety, a bicyclic sugar moiety, a sugar surrogate, or a 2'-deoxyribosyl sugar moiety.

In certain embodiments, the 2'-substituted sugar moiety is selected from a 2'-MOE sugar moiety, a 2'-NMA sugar moiety, a 2'-OMe sugar moiety, and a 2'-F sugar moiety. In certain embodiments, the bicyclic sugar moiety is selected from a cEt sugar moiety and an LNA sugar moiety. In certain embodiments, the sugar surrogate is selected from morpholino, modified morpholino, PNA, THP, and F-HNA.

5 In certain embodiments, modified oligonucleotides comprise at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 nucleosides comprising a modified sugar moiety. In certain embodiments, the modified sugar moiety is selected independently from a 2'-substituted sugar moiety, a bicyclic sugar moiety, or a sugar surrogate. In certain embodiments, the 2'-substituted sugar moiety is selected from a 2'-MOE sugar moiety, a 2'-NMA sugar moiety, a 2'-OMe sugar moiety, and a 2'-F
10 sugar moiety. In certain embodiments, the bicyclic sugar moiety is selected from a cEt sugar moiety and an LNA sugar moiety. In certain embodiments, the sugar surrogate is selected from morpholino, modified morpholino, THP, and F-HNA.

In certain embodiments, each nucleoside of a modified oligonucleotide comprises a modified sugar moiety ("fully modified oligonucleotide"). In certain embodiments, each nucleoside of a fully modified
15 oligonucleotide comprises a 2'-substituted sugar moiety, a bicyclic sugar moiety, or a sugar surrogate. In certain embodiments, the 2'-substituted sugar moiety is selected from a 2'-MOE sugar moiety, a 2'-NMA sugar moiety, a 2'-OMe sugar moiety, and a 2'-F sugar moiety. In certain embodiments, the bicyclic sugar moiety is selected from a cEt sugar moiety and an LNA sugar moiety. In certain embodiments, the sugar surrogate is selected from morpholino, modified morpholino, THP, and F-HNA. In certain embodiments,
20 each nucleoside of a fully modified oligonucleotide comprises the same modified sugar moiety ("uniformly modified sugar motif"). In certain embodiments, the uniformly modified sugar motif is 7 to 20 nucleosides in length. In certain embodiments, each nucleoside of the uniformly modified sugar motif comprises a 2'-substituted sugar moiety, a bicyclic sugar moiety, or a sugar surrogate. In certain embodiments, the 2'-substituted sugar moiety is selected from a 2'-MOE sugar moiety, a 2'-NMA sugar moiety, a 2'-OMe sugar
25 moiety, and a 2'-F sugar moiety. In certain embodiments, the bicyclic sugar moiety is selected from a cEt sugar moiety and an LNA sugar moiety. In certain embodiments, the sugar surrogate is selected from morpholino, modified morpholino, THP, and F-HNA. In certain embodiments, modified oligonucleotides having at least one fully modified sugar motif may also comprise at least 1, at least 2, at least 3, or at least 4
2'-deoxyribonucleosides.

30 **2. Certain Nucleobase Motifs**

In certain embodiments, oligonucleotides comprise modified and/or unmodified nucleobases arranged along the oligonucleotide, or portion thereof, in a defined pattern or motif. In certain embodiments, each nucleobase is modified. In certain embodiments, none of the nucleobases are modified. In certain
35 embodiments, each purine or each pyrimidine is modified. In certain embodiments, each adenine is modified. In certain embodiments, each guanine is modified. In certain embodiments, each thymine is modified. In certain embodiments, each uracil is modified. In certain embodiments, each cytosine is modified. In certain

embodiments, some or all of the cytosine nucleobases in a modified oligonucleotide are 5-methyl cytosines. In certain embodiments, all of the cytosine nucleobases are 5-methyl cytosines and all of the other nucleobases of the modified oligonucleotide are unmodified nucleobases.

In certain embodiments, modified oligonucleotides comprise a block of modified nucleobases. In certain such embodiments, the block is at the 3'-end of the oligonucleotide. In certain embodiments the block is within 3 nucleosides of the 3'-end of the oligonucleotide. In certain embodiments, the block is at the 5'-end of the oligonucleotide. In certain embodiments the block is within 3 nucleosides of the 5'-end of the oligonucleotide.

In certain embodiments, oligonucleotides having a gapmer motif comprise a nucleoside comprising a modified nucleobase. In certain such embodiments, one nucleoside comprising a modified nucleobase is in the central gap of an oligonucleotide having a gapmer motif. In certain such embodiments, the sugar moiety of the nucleoside is a 2'-deoxyribosyl sugar moiety. In certain embodiments, the modified nucleobase is selected from: a 2-thiopyrimidine and a 5-propynepyrimidine.

3. Certain Internucleoside Linkage Motifs

In certain embodiments, oligonucleotides comprise modified and/or unmodified internucleoside linkages arranged along the oligonucleotide, or portion thereof, in a defined pattern or motif. In certain embodiments, each internucleoside linking group is a phosphodiester internucleoside linkage. In certain embodiments, each internucleoside linking group of a modified oligonucleotide is a phosphorothioate internucleoside linkage. In certain embodiments, each internucleoside linkage of a modified oligonucleotide is independently selected from a phosphorothioate internucleoside linkage and phosphodiester internucleoside linkage. In certain embodiments, each phosphorothioate internucleoside linkage is independently selected from a stereorandom phosphorothioate, a (Sp) phosphorothioate, and a (Rp) phosphorothioate. In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer and the internucleoside linkages within the gap are all modified. In certain such embodiments, some or all of the internucleoside linkages in the wings are unmodified phosphodiester internucleoside linkages. In certain embodiments, the terminal internucleoside linkages are modified. In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer, and the internucleoside linkage motif comprises at least one phosphodiester internucleoside linkage in at least one wing, wherein the at least one phosphodiester internucleoside linkage is not a terminal internucleoside linkage, and the remaining internucleoside linkages are phosphorothioate internucleoside linkages. In certain such embodiments, all of the phosphorothioate internucleoside linkages are stereorandom. In certain embodiments, all of the phosphorothioate internucleoside linkages in the wings are (Sp) phosphorothioates, and the gap comprises at least one Sp, Sp, Rp motif. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising such internucleoside linkage motifs.

In certain embodiments, modified oligonucleotides comprise at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at

least 15, at least 16, at least 17, at least 18, or at least 19 phosphodiester internucleoside linkages. In certain embodiments, modified oligonucleotides comprise at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, or at least 19 phosphorothioate internucleoside linkages. In certain embodiments, modified oligonucleotides comprise at least 1, at least 2, at least 3, at least 4, or at least 5 phosphodiester internucleoside linkages and the remainder of the internucleoside linkages are phosphorothioate internucleoside linkages.

C. Certain Lengths

It is possible to increase or decrease the length of an oligonucleotide without eliminating activity.

For example, in Woolf et al., *Proc. Natl. Acad. Sci. USA*, 1992, 89, 7305-7309, 1992), a series of oligonucleotides 13-25 nucleobases in length were tested for their ability to induce cleavage of a target nucleic acid in an oocyte injection model. Oligonucleotides 25 nucleobases in length with 8 or 11 mismatch bases near the ends of the oligonucleotides were able to direct specific cleavage of the target nucleic acid, albeit to a lesser extent than the oligonucleotides that contained no mismatches. Similarly, target specific cleavage was achieved using 13 nucleobase oligonucleotides, including those with 1 or 3 mismatches.

In certain embodiments, oligonucleotides (including modified oligonucleotides) can have any of a variety of ranges of lengths. In certain embodiments, oligonucleotides consist of X to Y linked nucleosides, where X represents the fewest number of nucleosides in the range and Y represents the largest number nucleosides in the range. In certain such embodiments, X and Y are each independently selected from 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, and 50; provided that $X \leq Y$. For example, in certain embodiments, oligonucleotides consist of 12 to 13, 12 to 14, 12 to 15, 12 to 16, 12 to 17, 12 to 18, 12 to 19, 12 to 20, 12 to 21, 12 to 22, 12 to 23, 12 to 24, 12 to 25, 12 to 26, 12 to 27, 12 to 28, 12 to 29, 12 to 30, 13 to 14, 13 to 15, 13 to 16, 13 to 17, 13 to 18, 13 to 19, 13 to 20, 13 to 21, 13 to 22, 13 to 23, 13 to 24, 13 to 25, 13 to 26, 13 to 27, 13 to 28, 13 to 29, 13 to 30, 14 to 15, 14 to 16, 14 to 17, 14 to 18, 14 to 19, 14 to 20, 14 to 21, 14 to 22, 14 to 23, 14 to 24, 14 to 25, 14 to 26, 14 to 27, 14 to 28, 14 to 29, 14 to 30, 15 to 16, 15 to 17, 15 to 18, 15 to 19, 15 to 20, 15 to 21, 15 to 22, 15 to 23, 15 to 24, 15 to 25, 15 to 26, 15 to 27, 15 to 28, 15 to 29, 15 to 30, 16 to 17, 16 to 18, 16 to 19, 16 to 20, 16 to 21, 16 to 22, 16 to 23, 16 to 24, 16 to 25, 16 to 26, 16 to 27, 16 to 28, 16 to 29, 16 to 30, 17 to 18, 17 to 19, 17 to 20, 17 to 21, 17 to 22, 17 to 23, 17 to 24, 17 to 25, 17 to 26, 17 to 27, 17 to 28, 17 to 29, 17 to 30, 18 to 19, 18 to 20, 18 to 21, 18 to 22, 18 to 23, 18 to 24, 18 to 25, 18 to 26, 18 to 27, 18 to 28, 18 to 29, 18 to 30, 19 to 20, 19 to 21, 19 to 22, 19 to 23, 19 to 24, 19 to 25, 19 to 26, 19 to 27, 19 to 28, 19 to 29, 19 to 30, 20 to 21, 20 to 22, 20 to 23, 20 to 24, 20 to 25, 20 to 26, 20 to 27, 20 to 28, 20 to 29, 20 to 30, 21 to 22, 21 to 23, 21 to 24, 21 to 25, 21 to 26, 21 to 27, 21 to 28, 21 to 29, 21 to 30, 22 to 23, 22 to 24, 22 to 25, 22 to 26, 22 to 27, 22 to 28, 22 to 29, 22 to 30, 23 to 24, 23 to 25, 23 to 26, 23 to 27, 23 to 28, 23 to 29, 23 to 30, 24 to 25, 24 to 26, 24 to 27, 24 to 28, 24 to 29, 24 to 30, 25 to 26, 25 to 27, 25 to 28, 25 to 29, 25 to 30, 26 to 27, 26 to 28, 26 to 29, 26 to 30, 27 to 28, 27 to 29, 27 to 30, 28 to 29, 28 to

30, or 29 to 30 linked nucleosides.

In certain embodiments, oligonucleotides consist of 16 linked nucleosides. In certain embodiments, oligonucleotides consist of 17 linked nucleosides. In certain embodiments, oligonucleotides consist of 18 linked nucleosides. In certain embodiments, oligonucleotides consist of 19 linked nucleosides. In certain
5 embodiments, oligonucleotides consist of 20 linked nucleosides.

D. Certain Modified Oligonucleotides

In certain embodiments, the above modifications (sugar, nucleobase, internucleoside linkage) are incorporated into a modified oligonucleotide. In certain embodiments, modified oligonucleotides are characterized by their modification motifs and overall lengths. In certain embodiments, such parameters are
10 each independent of one another. Thus, unless otherwise indicated, each internucleoside linkage of an oligonucleotide having a gapmer sugar motif may be modified or unmodified and may or may not follow the gapmer modification pattern of the sugar modifications. For example, the internucleoside linkages within the wing regions of a sugar gapmer may be the same or different from one another and may be the same or different from the internucleoside linkages of the gap region of the sugar motif. Likewise, such sugar gapmer
15 oligonucleotides may comprise one or more modified nucleobase independent of the gapmer pattern of the sugar modifications. Unless otherwise indicated, all modifications are independent of nucleobase sequence.

E. Certain Populations of Modified Oligonucleotides

Populations of modified oligonucleotides in which all of the modified oligonucleotides of the population have the same molecular formula can be stereorandom populations or chirally enriched populations. All of
20 the chiral centers of all of the modified oligonucleotides are stereorandom in a stereorandom population. In a chirally enriched population, at least one particular chiral center is not stereorandom in the modified oligonucleotides of the population. In certain embodiments, the modified oligonucleotides of a chirally enriched population are enriched for β -D ribosyl sugar moieties, and all of the phosphorothioate internucleoside linkages are stereorandom. In certain embodiments, the modified oligonucleotides of a
25 chirally enriched population are enriched for both β -D ribosyl sugar moieties and at least one, particular phosphorothioate internucleoside linkage in a particular stereochemical configuration.

F. Nucleobase Sequence

In certain embodiments, oligonucleotides (unmodified or modified oligonucleotides) are further described by their nucleobase sequence. In certain embodiments oligonucleotides have a nucleobase
30 sequence that is complementary to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain such embodiments, a portion of an oligonucleotide has a nucleobase sequence that is complementary to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain embodiments, the nucleobase sequence of a portion or entire length of an oligonucleotide is at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least
35 95%, or 100% complementary to the second oligonucleotide or nucleic acid, such as a target nucleic acid.

II. Certain Oligomeric Compounds

In certain embodiments, provided herein are oligomeric compounds, which consist of an oligonucleotide (modified or unmodified) and optionally one or more conjugate groups and/or terminal groups. Conjugate groups consist of 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.

Examples of terminal groups include but are not limited to conjugate groups, capping groups, phosphate moieties, protecting groups, abasic nucleosides, modified or unmodified nucleosides, and two or more nucleosides that are independently modified or unmodified.

A. Certain Conjugate Groups

In certain embodiments, oligonucleotides are 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 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. N.Y. 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 1,2-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).

1. Conjugate Moieties

Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides, peptides, carbohydrates, vitamin moieties, polyethylene glycols, thioethers, polyethers, 5 cholesterol, thiocholesterols, cholic acid moieties, folate, lipids, lipophilic groups, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins, fluorophores, and dyes.

In certain embodiments, a conjugate moiety comprises an active drug substance, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fen-bufen, ketoprofen, (*S*)-(+)-pranoprofen, carprofen, 10 dansylsarcosine, 2,3,5-triodobenzoic acid, fingolimod, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indo-methicin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial, or an antibiotic.

2. Conjugate Linkers

Conjugate moieties are attached to oligonucleotides through conjugate linkers. In certain oligomeric 15 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 oligomeric compounds, a conjugate moiety is attached to an oligonucleotide via a more complex conjugate linker comprising one or more conjugate linker moieties, which are sub-units making up a conjugate linker. In certain embodiments, the conjugate linker comprises a chain structure, such as a hydrocarbyl chain, or an oligomer of repeating units such as ethylene glycol, 20 nucleosides, or amino acid units.

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 25 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.

In certain embodiments, conjugate linkers, including the conjugate linkers described above, are 30 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 35 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.

Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) and 6-aminohexanoic acid (AHEx or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl or substituted or unsubstituted C₂-C₁₀ 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.

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 exactly 3 linker-nucleosides. In certain embodiments, conjugate linkers comprise the TCA motif. 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.

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. For example, an oligomeric compound may comprise (1) a modified oligonucleotide consisting of 8-30 nucleosides and (2) a conjugate group comprising 1-10 linker-nucleosides that are contiguous with the nucleosides of the modified oligonucleotide. The total number of contiguous linked nucleosides in such an oligomeric compound is more than 30. Alternatively, an oligomeric compound may comprise a modified oligonucleotide consisting of 8-30 nucleosides and no conjugate group. The total number of contiguous linked nucleosides in such an oligomeric compound is no more than 30. Unless otherwise indicated conjugate linkers comprise no more than 10 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 5 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 3 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 2 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 1 linker-nucleoside.

In certain embodiments, it is desirable for a conjugate group to be cleaved from the oligonucleotide. 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.

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.

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'-deoxyribonucleoside 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 internucleoside linkage. In certain such embodiments, the cleavable moiety is 2'-deoxyadenosine.

B. Certain Terminal Groups

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'-phosphanates, 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.

C. Oligomeric Duplexes

In certain embodiments, oligomeric compounds described herein comprise an oligonucleotide, having a nucleobase sequence complementary to that of a target nucleic acid. In certain embodiments, an oligomeric compound is paired with a second oligomeric compound to form an oligomeric duplex. Such oligomeric duplexes comprise a first oligomeric compound having a portion complementary to a target nucleic acid and a second oligomeric compound having a portion complementary to the first oligomeric

compound. In certain embodiments, the first oligomeric compound of an oligomeric duplex comprises or consists of (1) a modified or unmodified oligonucleotide and optionally a conjugate group and (2) a second modified or unmodified oligonucleotide and optionally a conjugate group. Either or both oligomeric compounds of an oligomeric duplex may comprise a conjugate group. The oligonucleotides of each oligomeric compound of an oligomeric duplex may include non-complementary overhanging nucleosides.

D. Antisense Activity

In certain embodiments, oligomeric compounds and oligomeric duplexes are capable of hybridizing to a target nucleic acid, resulting in at least one antisense activity; such oligomeric compounds and oligomeric duplexes are antisense compounds. In certain embodiments, antisense compounds have antisense activity when they reduce, modulate, or increase the amount or activity of a target nucleic acid by 25% or more in the standard cell assay. In certain embodiments, antisense compounds selectively affect one or more target nucleic acid. Such antisense compounds comprise a nucleobase sequence that hybridizes to one or more target nucleic acid, resulting in one or more desired antisense activity and does not hybridize to one or more non-target nucleic acid or does not hybridize to one or more non-target nucleic acid in such a way that results in significant undesired antisense activity.

In certain antisense activities, hybridization of an antisense compound to a target nucleic acid results in recruitment of a protein that cleaves the target nucleic acid. For example, certain antisense compounds result in RNase H mediated cleavage of the target nucleic acid. RNase H is a cellular endonuclease that cleaves the RNA strand of an RNA:DNA duplex. The DNA in such an RNA:DNA duplex need not be unmodified DNA. In certain embodiments, provided herein are antisense compounds that are sufficiently “DNA-like” to elicit RNase H activity. In certain embodiments, one or more non-DNA-like nucleoside in the gap of a gapmer is tolerated.

In certain antisense activities, an antisense compound or a portion of an antisense compound is loaded into an RNA-induced silencing complex (RISC), ultimately resulting in cleavage of the target nucleic acid. For example, certain antisense compounds result in cleavage of the target nucleic acid by Argonaute. Antisense compounds that are loaded into RISC are RNAi compounds. RNAi compounds may be double-stranded (siRNA) or single-stranded (ssRNA).

In certain embodiments, hybridization of an antisense compound to a target nucleic acid does not result in recruitment of a protein that cleaves that target nucleic acid. In certain embodiments, hybridization of the antisense compound to the target nucleic acid results in alteration of splicing of the target nucleic acid. In certain embodiments, hybridization of an antisense compound to a target nucleic acid results in inhibition of a binding interaction between the target nucleic acid and a protein or other nucleic acid. In certain embodiments, hybridization of an antisense compound to a target nucleic acid results in alteration of translation of the target nucleic acid. In certain embodiments, hybridization of an antisense compound to a target nucleic acid results in a reduced amount or level of RNA that includes an NIE. In certain embodiments, hybridization of an antisense compound to a target nucleic acid results in exon inclusion. In

certain embodiments, hybridization of an antisense compound to a target nucleic acid results in an increase in the amount or activity of a target nucleic acid. In certain embodiments, hybridization of an antisense compound complementary to a target nucleic acid results in alteration of splicing, leading to the inclusion of an exon in the mRNA.

5 Antisense activities may be observed directly or indirectly. In certain embodiments, observation or detection of an antisense activity involves observation or detection of a change in an amount of a target nucleic acid or protein encoded by such target nucleic acid, a change in the ratio of splice variants of a nucleic acid or protein and/or a phenotypic change in a cell or subject.

III. Certain Target Nucleic Acids

10 In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a portion that is complementary to a target nucleic acid. In certain embodiments, the target nucleic acid is an endogenous RNA molecule. In certain embodiments, the target nucleic acid encodes a protein. In certain such embodiments, the target nucleic acid is selected from: a mature mRNA and a pre-mRNA, including intronic, exonic and untranslated regions. In certain embodiments, the target nucleic acid is a mature mRNA.

15 In certain embodiments, the target nucleic acid is a pre-mRNA. In certain embodiments, the target region is entirely within an intron. In certain embodiments, the target region spans an intron/exon junction. In certain embodiments, the target region is at least 50% within an intron.

A. Complementarity/Mismatches to the Target Nucleic Acid

It is possible to introduce mismatch bases without eliminating activity. For example, Gautschi et al (J. Natl. Cancer Inst. 93:463-471, March 2001) demonstrated the ability of an oligonucleotide having 100% complementarity to the bcl-2 mRNA and having 3 mismatches to the bcl-xL mRNA to reduce the expression of both bcl-2 and bcl-xL *in vitro* and *in vivo*. Furthermore, this oligonucleotide demonstrated potent anti-tumor activity *in vivo*. Maher and Dolnick (Nuc. Acid. Res. 16:3341-3358, 1988) tested a series of tandem 14 nucleobase oligonucleotides, and a 28 and 42 nucleobase oligonucleotides comprised of the sequence of

25 two or three of the tandem oligonucleotides, respectively, for their ability to arrest translation of human DHFR in a rabbit reticulocyte assay. Each of the three 14 nucleobase oligonucleotides alone was able to inhibit translation, albeit at a more modest level than the 28 or 42 nucleobase oligonucleotides.

In certain embodiments, oligonucleotides are complementary to the target nucleic acid over the entire length of the oligonucleotide. In certain embodiments, oligonucleotides are 99%, 95%, 90%, 85%, or 80% complementary to the target nucleic acid. In certain embodiments, oligonucleotides are at least 80% complementary to the target nucleic acid over the entire length of the oligonucleotide and comprise a portion that is 100% or fully complementary to a target nucleic acid. In certain embodiments, the portion of full complementarity is 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleobases in length.

30

In certain embodiments, oligonucleotides comprise one or more mismatched nucleobases relative to the target nucleic acid. In certain embodiments, the mismatch is at position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 from the 5'-end of the oligonucleotide.

35

B. SCN1A

In certain embodiments, oligomeric compounds comprise or consist of a modified oligonucleotide that is complementary to a target nucleic acid encoding SCN1A, or a portion thereof. In certain embodiments, the SCN1A target nucleic acid has the nucleobase sequence set forth in SEQ ID NO: 1 (the complement of GENBANK Accession No. NC_000002.12 truncated from nucleotides 165982001 to 166152000). In certain embodiments, the SCN1A target nucleic acid has the nucleobase sequence set forth in SEQ ID NO: 2 (GENBANK Accession No. NM_001165963.2).

In certain embodiments, contacting a cell or subject with an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 modulates splicing of SCN1A RNA in a cell or a subject. In certain embodiments, contacting a cell or a subject with an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 increases the amount of SCN1A RNA and/or protein. In certain embodiments, contacting a cell or a subject with an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 reduces the amount of SCN1A RNA including a NIE. In certain embodiments, contacting a cell or a subject with an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 increases the amount of SCN1A RNA excluding a NIE. In certain embodiments, the NIE is NIE-1. In certain embodiments, the oligomeric compound comprises or consists of a modified oligonucleotide.

In certain embodiments, contacting a cell in a subject with an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 ameliorates one or more symptom of encephalopathy. In certain embodiments, the encephalopathy is Dravet Syndrome. In certain embodiments, the symptom is any of prolonged or frequent seizures, sudden unexpected death in epilepsy, status epilepticus, behavioral and developmental delays, movement and balance dysfunctions, orthopedic conditions, motor and cognitive dysfunctions, delayed language and speech issues, visual motor integration dysfunctions, visual perception dysfunctions, executive dysfunctions, growth and nutrition issues, sleeping difficulties, chronic infections, sensory integration disorders, and dysautonomia.

C. Certain Target Nucleic Acids in Certain Tissues

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a portion that is complementary to a target nucleic acid, wherein the target nucleic acid is expressed in a pharmacologically relevant tissue. In certain embodiments, the pharmacologically relevant tissues are the cells and tissues that comprise the central nervous system (CNS). Such tissues include brain tissues, such as, cerebral cortex.

IV. Certain Pharmaceutical Compositions

In certain embodiments, described herein are pharmaceutical compositions comprising one or more oligomeric compounds. In certain embodiments, the one or more oligomeric compounds each consists of a

modified oligonucleotide. In certain embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable diluent or carrier. In certain embodiments, a pharmaceutical composition comprises or consists of a sterile saline solution and one or more oligomeric compound. In certain embodiments, the sterile saline is pharmaceutical grade saline. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and sterile water. In certain embodiments, the sterile water is pharmaceutical grade water. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and phosphate-buffered saline (PBS). In certain embodiments, the sterile PBS is pharmaceutical grade PBS. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and artificial cerebrospinal fluid ("artificial CSF" or "aCSF"). In certain embodiments, the artificial cerebrospinal fluid is pharmaceutical grade.

In certain embodiments, a pharmaceutical composition comprises a modified oligonucleotide and artificial cerebrospinal fluid. In certain embodiments, a pharmaceutical composition consists of a modified oligonucleotide and artificial cerebrospinal fluid. In certain embodiments, a pharmaceutical composition consists essentially of a modified oligonucleotide and artificial cerebrospinal fluid. In certain embodiments, the artificial cerebrospinal fluid is pharmaceutical grade.

In certain embodiments, pharmaceutical compositions comprise one or more oligomeric compound and one or more excipients. In certain embodiments, excipients are selected from water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose and polyvinylpyrrolidone.

In certain embodiments, oligomeric compounds may be admixed with pharmaceutically acceptable active and/or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions depend on a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

In certain embodiments, pharmaceutical compositions comprising an oligomeric compound encompass any pharmaceutically acceptable salts of the oligomeric compound, esters of the oligomeric compound, or salts of such esters. In certain embodiments, pharmaceutical compositions comprising oligomeric compounds comprising one or more oligonucleotide, upon administration to a subject, including a human, are capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of oligomeric compounds, prodrugs, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts. In certain embodiments, prodrugs comprise one or more conjugate group attached to an oligonucleotide, wherein the conjugate group is cleaved by endogenous nucleases within the body. In certain embodiments, prodrugs comprise one or more conjugate group attached to an oligonucleotide, wherein the conjugate group is cleaved by endogenous nucleases within the body.

Lipid moieties have been used in nucleic acid therapies in a variety of methods. In certain such methods, the nucleic acid, such as an oligomeric compound, is introduced into preformed liposomes or lipoplexes made of mixtures of cationic lipids and neutral lipids. In certain methods, DNA complexes with mono- or poly-cationic lipids are formed without the presence of a neutral lipid. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to a particular cell or tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to fat tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to muscle tissue.

In certain embodiments, pharmaceutical compositions comprise a delivery system. Examples of delivery systems include, but are not limited to, liposomes and emulsions. Certain delivery systems are useful for preparing certain pharmaceutical compositions including those comprising hydrophobic compounds. In certain embodiments, certain organic solvents such as dimethylsulfoxide are used.

In certain embodiments, pharmaceutical compositions comprise one or more tissue-specific delivery molecules designed to deliver the one or more pharmaceutical agents comprising an oligomeric compound provided herein to specific tissues or cell types. For example, in certain embodiments, pharmaceutical compositions include liposomes coated with a tissue-specific antibody.

In certain embodiments, pharmaceutical compositions comprise a co-solvent system. Certain of such co-solvent systems comprise, for example, benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. In certain embodiments, such co-solvent systems are used for hydrophobic compounds. A non-limiting example of such a co-solvent system is the VPD co-solvent system, which is a solution of absolute ethanol comprising 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™ and 65% w/v polyethylene glycol 300. The proportions of such co-solvent systems may be varied considerably without significantly altering their solubility and toxicity characteristics. Furthermore, the identity of co-solvent components may be varied: for example, other surfactants may be used instead of Polysorbate 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

In certain embodiments, pharmaceutical compositions are prepared for oral administration. In certain embodiments, pharmaceutical compositions are prepared for buccal administration. In certain embodiments, a pharmaceutical composition is prepared for administration by injection (e.g., intravenous, subcutaneous, intramuscular, intrathecal (IT), intracerebroventricular (ICV), etc.). In certain of such embodiments, a pharmaceutical composition comprises a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (e.g., ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid carriers, suspending agents and the like. Certain pharmaceutical compositions for injection are presented in unit

dosage form, e.g., in ampoules or in multi-dose containers. Certain pharmaceutical compositions for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in pharmaceutical compositions for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes.

Under certain conditions, certain compounds disclosed herein act as acids. Although such compounds may be drawn or described in protonated (free acid) form, or ionized and in association with a cation (salt) form, aqueous solutions of such compounds exist in equilibrium among such forms. For example, a phosphate linkage of an oligonucleotide in aqueous solution exists in equilibrium among free acid, anion and salt forms. Unless otherwise indicated, compounds described herein are intended to include all such forms. Moreover, certain oligonucleotides have several such linkages, each of which is in equilibrium. Thus, oligonucleotides in solution exist in an ensemble of forms at multiple positions all at equilibrium. The term "oligonucleotide" is intended to include all such forms. Drawn structures necessarily depict a single form. Nevertheless, unless otherwise indicated, such drawings are likewise intended to include corresponding forms. Herein, a structure depicting the free acid of a compound followed by the term "or a salt thereof" expressly includes all such forms that may be fully or partially protonated/de-protonated/in association with a cation. In certain instances, one or more specific cation is identified.

In certain embodiments, modified oligonucleotides or oligomeric compounds are in aqueous solution with sodium. In certain embodiments, modified oligonucleotides or oligomeric compounds are in aqueous solution with potassium. In certain embodiments, modified oligonucleotides or oligomeric compounds are in PBS. In certain embodiments, modified oligonucleotides or oligomeric compounds are in water. In certain such embodiments, the pH of the solution is adjusted with NaOH and/or HCl to achieve a desired pH.

Herein, certain specific doses are described. A dose may be in the form of a dosage unit. For clarity, a dose (or dosage unit) of a modified oligonucleotide or an oligomeric compound in milligrams indicates the mass of the free acid form of the modified oligonucleotide or oligomeric compound. As described above, in aqueous solution, the free acid is in equilibrium with anionic and salt forms. However, for the purpose of calculating dose, it is assumed that the modified oligonucleotide or oligomeric compound exists as a solvent-free, sodium-acetate free, anhydrous, free acid. For example, where a modified oligonucleotide or an oligomeric compound is in solution comprising sodium (e.g., saline), the modified oligonucleotide or oligomeric compound may be partially or fully de-protonated and in association with Na⁺ ions. However, the mass of the protons are nevertheless counted toward the weight of the dose, and the mass of the Na⁺ ions are not counted toward the weight of the dose. Thus, for example, a dose, or dosage unit, of 10 mg of Compound No. 1429226, equals the number of fully protonated molecules that weighs 10 mg. This would be equivalent to 10.5 mg of solvent-free, sodium acetate-free, anhydrous sodiated Compound No. 1429226. When an oligomeric compound comprises a conjugate group, the mass of the conjugate group is included in

calculating the dose of such oligomeric compound. If the conjugate group also has an acid, the conjugate group is likewise assumed to be fully protonated for the purpose of calculating dose.

V. Certain Compositions

5 1. Compound No: 1429226

In certain embodiments, Compound No. 1429226 is characterized as a modified oligonucleotide having a sequence of (from 5' to 3') AGTTGGAGCAAGATTATC (SEQ ID NO: 41), wherein each nucleoside comprises a 2'-NMA sugar moiety, each internucleoside linkage is a phosphorothioate internucleoside linkage, and each cytosine is a 5-methyl cytosine.

10 In certain embodiments, Compound No. 1429226 is represented by the following chemical notation (5' to 3'): $A_{ns} G_{ns} T_{ns} T_{ns} G_{ns} G_{ns} A_{ns} G_{ns} {}^mC_{ns} A_{ns} A_{ns} G_{ns} A_{ns} T_{ns} T_{ns} A_{ns} T_{ns} {}^mC_n$ (SEQ ID NO: 41);

wherein,

A = an adenine nucleobase,

${}^mC$ = a 5-methyl cytosine nucleobase,

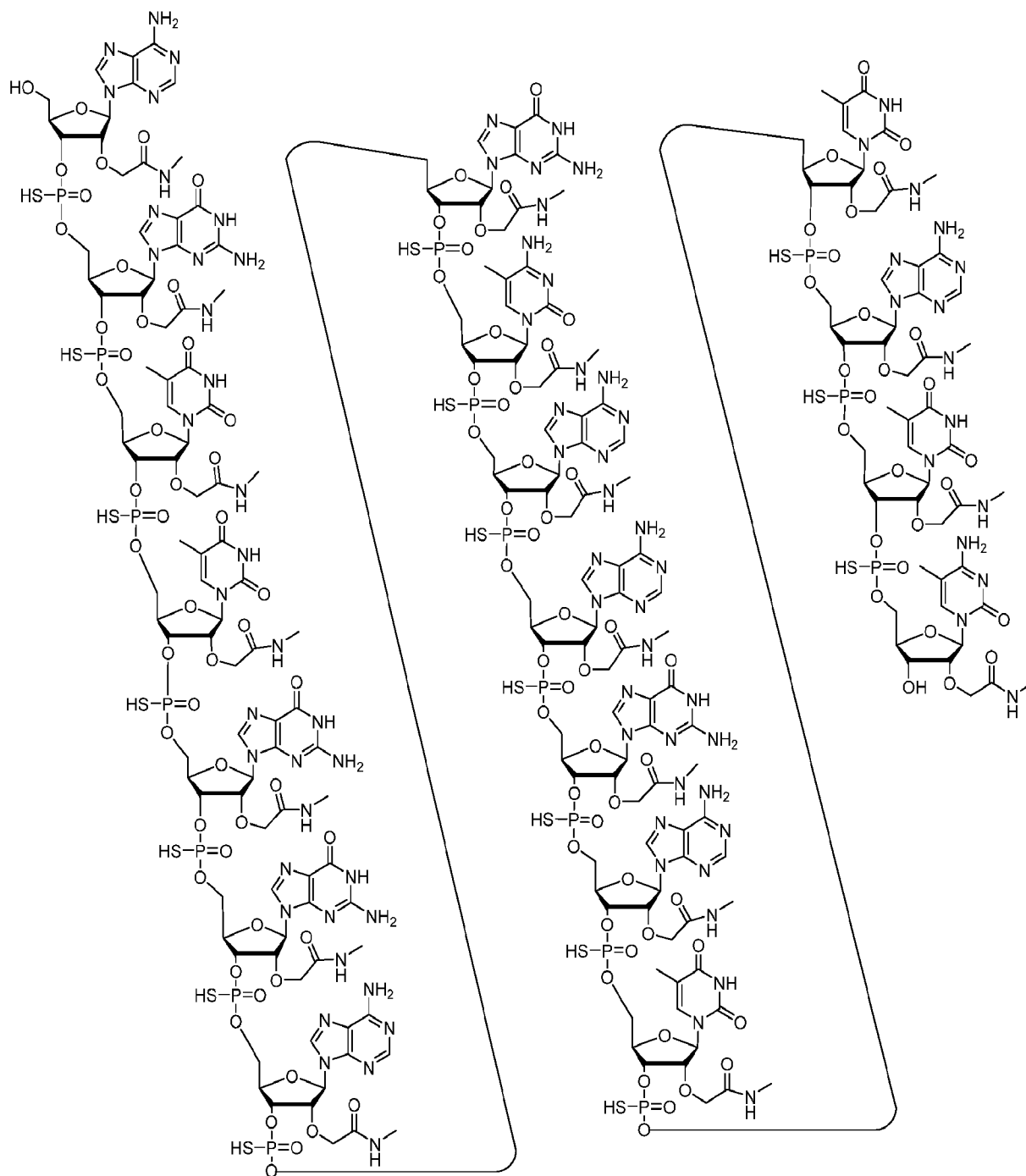
15 G = a guanine nucleobase,

T = a thymine nucleobase,

n = a 2'-NMA sugar moiety, and

s = a phosphorothioate internucleoside linkage.

In certain embodiments, Compound No. 1429226 is represented by the following chemical structure:



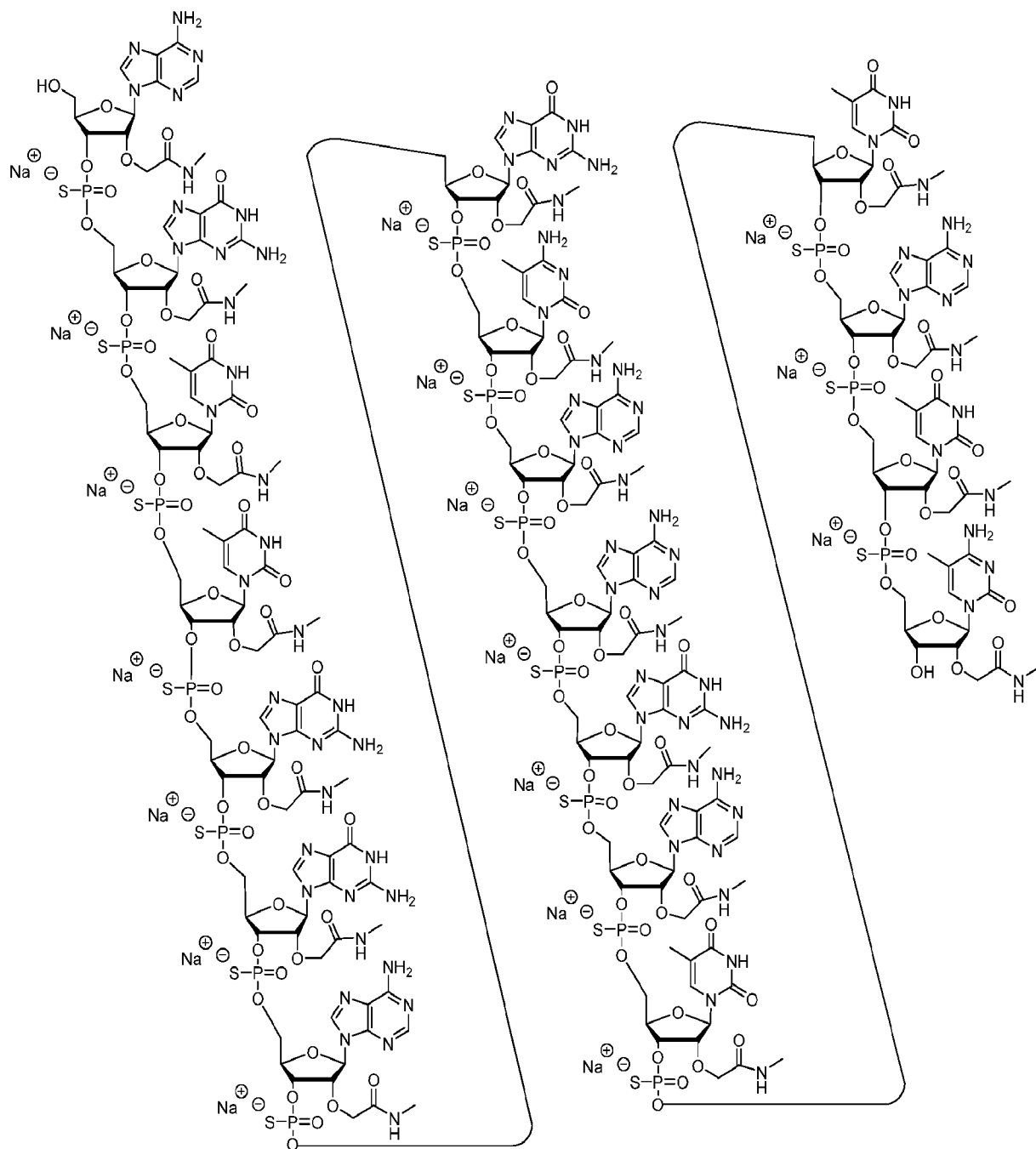
(SEQ ID NO: 41).

5 Structure 1. Compound No. 1429226

In certain embodiments, the sodium salt of Compound No. 1429226 is represented by the following

chemical

structure:



(SEQ ID NO: 41).

5 Structure 2. The sodium salt of Compound No. 1429226

Nonlimiting disclosure and incorporation by reference

Each of the literature and patent publications listed herein is incorporated by reference in its entirety. While certain compounds, compositions and methods described herein have been described with specificity

10 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.

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
5 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 moiety (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
10 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
15 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^mCGAUCG,” wherein ^mC indicates a cytosine base comprising a methyl group at the 5-position.

Certain compounds described herein (e.g., modified oligonucleotides) have one or more asymmetric
20 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 are drawn or described with undefined stereochemistry include all such possible isomers, including their
25 stereorandom and optically pure forms, unless specified otherwise. Likewise, all cis- and trans-isomers and tautomeric forms of the compounds herein are also included unless otherwise indicated. Oligomeric compounds described herein include chirally pure or enriched mixtures as well as racemic mixtures. For example, oligomeric compounds having a plurality of phosphorothioate internucleoside linkages include such compounds in which chirality of the phosphorothioate internucleoside linkages is controlled or is random.
30 Unless otherwise indicated, compounds described herein are intended to include corresponding salt forms.

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 ¹H hydrogen atoms. Isotopic substitutions encompassed by the compounds herein include but are not limited to: ²H or ³H in place
35 of ¹H, ¹³C or ¹⁴C in place of ¹²C, ¹⁵N in place of ¹⁴N, ¹⁷O or ¹⁸O in place of ¹⁶O, and ³³S, ³⁴S, ³⁵S, or ³⁶S in place of ³²S. 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. In certain embodiments, radioactive isotopic substitutions may make the compound suitable for research or diagnostic purposes such as imaging.

5 EXAMPLES

The following examples illustrate certain embodiments of the present disclosure and are not limiting. Moreover, where specific embodiments are provided, the inventors have contemplated generic application of those specific embodiments.

10 **Example 1: Activity of modified oligonucleotides targeting human SCN1A in HepG2 cells, single dose, *in vitro***

Modified oligonucleotides complementary to a human SCN1A nucleic acid were synthesized and tested for their effect on SCN1A RNA levels *in vitro*. The modified oligonucleotides were tested in a series of experiments using the same culture conditions.

15 The modified oligonucleotides in the tables below are 18 nucleosides in length. Each nucleoside comprises a 2'-MOE sugar moiety. The internucleoside linkages throughout each modified oligonucleotide are phosphorothioate internucleoside linkages. All cytosine nucleobases throughout each modified oligonucleotide are 5-methylcytosines.

Each modified oligonucleotide listed in the tables below is 100% complementary to either the human
20 SCN1A genomic sequence, designated herein as SEQ ID NO: 1 (the complement of GENBANK Accession No. NC_000002.12 truncated from nucleotides 165982001 to 166152000) or to the human SCN1A mRNA, designated herein as SEQ ID NO: 2 (GENBANK Accession No. NM_001165963.2) or to both. 'N/A' indicates that the modified oligonucleotide is not complementary to that particular target sequence with 100% complementarity. "Start site" indicates the 5'-most nucleoside of the target sequence to which the modified
25 oligonucleotide is complementary. "Stop site" indicates the 3'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary.

Cultured HepG2 cells at a density of 20,000 cells per well were transfected using electroporation with 4000 nM of modified oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and SCN1A RNA levels were measured by quantitative real-time RTPCR. Human
30 primer probe set RTS40976 (forward sequence CCAAGAAGGCTGGAATATCTTTG, designated herein as SEQ ID NO: 15; reverse sequence GCCAACTTGAAAACCTCGCA, designated herein as SEQ ID NO: 16; probe sequence ACCAGGCTAAGCGTCACAATAAAACCG, designated herein as SEQ ID NO: 17) was used to measure SCN1A RNA levels. SCN1A RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. SCN1A RNA is presented as % of the average of untreated control (%UTC).
35 As shown in the tables below, certain modified oligonucleotides complementary to SCN1A RNA increased

the amount of human SCN1A RNA compared to untreated control. Each of Tables 1-6 represents a different experiment.

Table 1

Effect of modified oligonucleotides on amount of human SCN1A RNA in HepG2 cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN1A (% UTC)	SEQ ID No.
1262739	2869	2886	N/A	N/A	AACAGTTCCATGAGTTTC	57	42
1262745	2875	2892	N/A	N/A	TGGAGGAACAGTTCCATG	90	43
1262751	2881	2898	N/A	N/A	TTAATCTGGAGGAACAGT	130	44
1262757	2887	2904	N/A	N/A	GAAGTGTTAATCTGGAGG	129	45
1262763	2893	2910	N/A	N/A	ACCCCTGAAGTGTTAATC	93	46
1262769	2899	2916	N/A	N/A	TCCATAACCCCTGAAGTG	89	47
1262775	2905	2922	N/A	N/A	CCAGCTTCCATAACCCCT	87	48
1262781	2912	2929	N/A	N/A	GCTTCCTCCAGCTTCCAT	54	49
1262787	2925	2942	N/A	N/A	TAGTAAAAGCTCAGCTTC	75	50
1262793	2931	2948	N/A	N/A	AAGATGTAGTAAAAGCTC	108	51
1262799	78339	78356	457	474	TACCATTTATTCTGCATA	79	52
1262805	78359	78376	477	494	GTCATCCTGCACATTTTA	84	53
1262811	160818	160835	6589	6606	AGGAGTCCTGTTGATAAA	102	54
1262817	160825	160842	6596	6613	CTCCTAAAGGAGTCCTGT	66	55
1262823	160839	160856	6610	6627	AGTTTGGCATTGACCTCC	54	56
1262829	160874	160891	6645	6662	GCACTGACCTTAAGGAGA	126	57
1262835	160884	160901	6655	6672	CTTATTGTAGGCACTGAC	69	58
1262841	160927	160944	6698	6715	CCCCTTTACACAGAGTCA	61	59
1262847	160954	160971	6725	6742	AACAGTAACCTCCTGTCA	85	60
1262853	160966	160983	6737	6754	GCTGGTAGTGAGAACAGT	93	61
1262859	160974	160991	6745	6762	CAGTGTGAGCTGGTAGTG	84	62
1262865	161002	161019	6773	6790	GACTAGCCATTGTGCATC	113	63
1262871	161008	161025	6779	6796	CAGTCTGACTAGCCATTG	74	64
1262877	161014	161031	6785	6802	TCCCTACAGTCTGACTAG	72	65
1262883	161020	161037	6791	6808	AAGTGGTCCCTACAGTCT	73	66
1262889	161031	161048	6802	6819	GCACCCCTTGAAACTGGT	114	67
1262895	161037	161054	6808	6825	AGGTTTGCACCCCTTGAA	85	68
1262901	161087	161104	6858	6875	GATACAATTACTACACTA	81	69
1262907	161150	161167	6921	6938	GATGAATCCACTAACAGA	32	70
1262913	161231	161248	7002	7019	TAGAGGTCCTTAGCCTAT	75	71
1262919	161241	161258	7012	7029	ATACCTGTTATAGAGGTC	74	72
1262925	161247	161264	7018	7035	GGTGGCATACCTGTTATA	62	73
1262931	161258	161275	7029	7046	CATACCCCCCAGGTGGCA	70	74
1262937	161264	161281	7035	7052	GGTTGCCATACCCCCCAG	40	75

1262943	161270	161287	7041	7058	CCATGTGGTTGCCATACC	72	76
1262949	161293	161310	7064	7081	ACGACTTTGTGTAGCTGG	90	77
1262955	161299	161316	7070	7087	CAAACCACGACTTTGTGT	57	78
1262961	161305	161322	7076	7093	CTCATGCAAACCACGACT	61	79
1262967	161313	161330	7084	7101	AGCATGCCCTCATGCAAA	53	80
1262973	161319	161336	7090	7107	AAGTGCAGCATGCCCTCA	135	81
1262979	161326	161343	7097	7114	GATCTCTAAGTGCAGCAT	76	82
1262985	161400	161417	7171	7188	ATCACCCAATTACCCCTC	56	83
1262991	161406	161423	7177	7194	CCACTTATCACCCAATTA	27	84
1262997	161412	161429	7183	7200	GCACCTCCACTTATCACC	83	85
1263003	161439	161456	7210	7227	TGGATTTCGCAAAACAAG	57	86
1263009	161461	161478	7232	7249	ATAATCTACTTGGTCTAG	81	87
1263015	161477	161494	7248	7265	ACTGGCCTACCCACAAAT	67	88
1263021	161483	161500	7254	7271	AGATTTACTGGCCTACCC	104	89
1263027	161495	161512	7266	7283	TTGCACCTGCTAAGATTT	101	90
1263033	161501	161518	7272	7289	TGAAGTTTGCACCTGCTA	115	91
1263039	161601	161618	7372	7389	GTCTTCTGGCGGTGGAGG	83	92
1263045	161607	161624	7378	7395	AATTCAGTCTTCTGGCGG	65	93
1263051	161667	161684	7438	7455	CCGAAGATGGCTAAACAA	51	94
1263057	161673	161690	7444	7461	TGAGAGCCGAAGATGGCT	64	95
1263063	161680	161697	7451	7468	ACCTTGCTGAGAGCCGAA	66	96
1263069	161690	161707	7461	7478	TACAGTGTCAACCTTGCT	113	97
1263075	161743	161760	7514	7531	GCACCACAGGGTAAAATG	58	98
1263081	161779	161796	7550	7567	TACTGTGCTTAGGTCATT	83	99
1263087	161828	161845	7599	7616	GTAAAGCTTGCACTCTAC	87	100
1263093	161836	161853	7607	7624	TTACCTGTGTAAAGCTTG	40	101
1263099	161879	161896	7650	7667	GATAGCATCCAAACTATC	89	102
1263105	161887	161904	7658	7675	CATGCATTGATAGCATCC	87	103
1263111	161965	161982	7736	7753	TACCACTGACATATGGTT	71	104
1263117	162030	162047	7801	7818	AAGTGCTGCAAACCTATTG	97	105
1263123	162092	162109	7863	7880	ACAGTCTGGCTATATACC	109	106
1263129	162098	162115	7869	7886	GTCTGTACAGTCTGGCTA	75	107
1263135	162129	162146	7900	7917	AATAGGTTAAGCAGTGTG	66	108
1263141	162249	162266	8020	8037	ATTGTGATATCAACCTGA	65	109
1263147	162337	162354	8108	8125	AATCTACAACCTACCCAGT	82	110
1263153	162482	162499	8253	8270	TAGTGCAGGTACTACCAG	75	111
1263159	162488	162505	8259	8276	TTCAGTTAGTGCAGGTAC	84	112
1263165	162501	162518	8272	8289	GCACTACCTTCAATTCAG	88	113
1263171	162578	162595	8349	8366	AACAATCTAGAGCAGCAT	105	114
1263177	162638	162655	8409	8426	TATAAGTTGACTACTCTG	71	115
1263183	162656	162673	8427	8444	TCCTGATGTAATTGACTA	54	116
1263189	162696	162713	8467	8484	AGAGGAGCCTATGGTTTG	76	117
1263195	162735	162752	8506	8523	AGTTCACGAATACAGTTT	51	118

1263201	162741	162758	8512	8529	GCATGCAGTTCACGAATA	87	119
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Table 2

Effect of modified oligonucleotides on amount of human SCN1A RNA in HepG2 cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN1A (% UTC)	SEQ ID No.
1262740	2870	2887	N/A	N/A	GAACAGTTCATGAGTTT	62	120
1262746	2876	2893	N/A	N/A	CTGGAGGAACAGTTCAT	82	121
1262752	2882	2899	N/A	N/A	GTTAATCTGGAGGAACAG	92	122
1262758	2888	2905	N/A	N/A	TGAAGTGTTAATCTGGAG	71	123
1262764	2894	2911	N/A	N/A	AACCCCTGAAGTGTTAAT	83	124
1262770	2900	2917	N/A	N/A	TTCCATAACCCCTGAAGT	112	125
1262776	2906	2923	N/A	N/A	TCCAGCTTCCATAACCCC	82	126
1262782	2919	2936	N/A	N/A	AAGCTCAGCTTCCTCCAG	70	127
1262788	2926	2943	N/A	N/A	GTAGTAAAAGCTCAGCTT	82	128
1262794	2932	2949	N/A	N/A	AAAGATGTAGTAAAAGCT	75	129
1262800	78342	78359	460	477	AATTACCATTTATTCTGC	37	130
1262806	78360	78377	478	495	TGTCATCCTGCACATTTT	124	131
1262812	160819	160836	6590	6607	AAGGAGTCCTGTTGATAA	58	132
1262818	160828	160845	6599	6616	GACCTCCTAAAGGAGTCC	66	133
1262824	160840	160857	6611	6628	CAGTTTGGCATTGACCTC	54	134
1262830	160879	160896	6650	6667	TGTAGGCACTGACCTTAA	72	135
1262836	160885	160902	6656	6673	TCTTATTGTAGGCACTGA	63	136
1262842	160949	160966	6720	6737	TAACCTCCTGTCAAGGTC	88	137
1262848	160955	160972	6726	6743	GAACAGTAACCTCCTGTC	55	138
1262854	160969	160986	6740	6757	TCAGCTGGTAGTGAGAAC	113	139
1262860	160991	161008	6762	6779	GTGCATCTTATCTTCAGC	109	140
1262866	161003	161020	6774	6791	TGACTAGCCATTGTGCAT	54	141
1262872	161009	161026	6780	6797	ACAGTCTGACTAGCCATT	92	142
1262878	161015	161032	6786	6803	GTCCCTACAGTCTGACTA	129	143
1262884	161021	161038	6792	6809	AAACTGGTCCCTACAGTC	87	144
1262890	161032	161049	6803	6820	TGCACCCCTTGAACTGG	92	145
1262896	161038	161055	6809	6826	CAGGTTTGCACCCCTTGA	65	146
1262902	161088	161105	6859	6876	GGATACAATTACTACACT	79	147
1262908	161151	161168	6922	6939	AGATGAATCCACTAACAG	44	148
1262914	161232	161249	7003	7020	ATAGAGGTCCTTAGCCTA	54	149
1262920	161242	161259	7013	7030	CATACCTGTTATAGAGGT	106	150
1262926	161248	161265	7019	7036	AGGTGGCATACCTGTTAT	78	151
1262932	161259	161276	7030	7047	CCATACCCCCCAGGTGGC	88	152

1262938	161265	161282	7036	7053	TGGTTGCCATACCCCCCA	41	153
1262944	161271	161288	7042	7059	GCCATGTGGTTGCCATAC	73	154
1262950	161294	161311	7065	7082	CACGACTTTGTGTAGCTG	63	155
1262956	161300	161317	7071	7088	GCAAACCACGACTTTGTG	48	156
1262962	161306	161323	7077	7094	CCTCATGCAAACCACGAC	68	157
1262968	161314	161331	7085	7102	CAGCATGCCCTCATGCAA	77	158
1262974	161320	161337	7091	7108	TAAGTGCAGCATGCCCTC	80	159
1262980	161328	161345	7099	7116	ATGATCTCTAAGTGCAGC	114	160
1262986	161401	161418	7172	7189	TATCACCCAATTACCCCT	59	161
1262992	161407	161424	7178	7195	TCCACTTATCACCCAATT	65	162
1262998	161413	161430	7184	7201	AGCACCTCCACTTATCAC	139	163
1263004	161441	161458	7212	7229	GCTGGATTTCGCAAAACA	84	164
1263010	161462	161479	7233	7250	AATAATCTACTTGGTCTA	83	165
1263016	161478	161495	7249	7266	TACTGGCCTACCCACAAA	47	166
1263022	161484	161501	7255	7272	AAGATTTACTGGCCTACC	63	167
1263028	161496	161513	7267	7284	TTTGCACCTGCTAAGATT	68	168
1263034	161502	161519	7273	7290	ATGAAGTTTGCACCTGCT	75	169
1263040	161602	161619	7373	7390	AGTCTTCTGGCGGTGGAG	61	170
1263046	161608	161625	7379	7396	CAATTCAGTCTTCTGGCG	73	171
1263052	161668	161685	7439	7456	GCCGAAGATGGCTAAACA	102	172
1263058	161674	161691	7445	7462	CTGAGAGCCGAAGATGGC	83	173
1263064	161681	161698	7452	7469	AACCTTGCTGAGAGCCGA	109	174
1263070	161691	161708	7462	7479	ATACAGTGTCAACCTTGC	93	175
1263076	161744	161761	7515	7532	TGCACCACAGGGTAAAT	53	176
1263082	161780	161797	7551	7568	ATACTGTGCTTAGGTCAT	52	177
1263088	161829	161846	7600	7617	TGTAAAGCTTGCACTCTA	48	178
1263094	161867	161884	7638	7655	ACTATCTATAAATGGTAC	135	179
1263100	161880	161897	7651	7668	TGATAGCATCCAACTAT	56	180
1263106	161888	161905	7659	7676	ACATGCATTGATAGCATC	29	181
1263112	161966	161983	7737	7754	TTACCACTGACATATGGT	42	182
1263118	162039	162056	7810	7827	AAGCTGTAAAGTGCTGC	53	183
1263124	162093	162110	7864	7881	TACAGTCTGGCTATATAC	118	184
1263130	162099	162116	7870	7887	TGTCTGTACAGTCTGGCT	34	185
1263136	162130	162147	7901	7918	TAATAGGTAAAGCAGTGT	129	186
1263142	162250	162267	8021	8038	GATTGTGATATCAACCTG	53	187
1263148	162405	162422	8176	8193	GTGAACCTATTTTGCTCC	57	188
1263154	162483	162500	8254	8271	TTAGTGCAGGTACTACCA	72	189
1263160	162489	162506	8260	8277	ATTGAGTTAGTGCAGGTA	130	190
1263166	162510	162527	8281	8298	ATAACATAAGCACTACCT	75	191
1263172	162579	162596	8350	8367	GAACAATCTAGAGCAGCA	76	192
1263178	162641	162658	8412	8429	CTATATAAGTTGACTACT	81	193
1263184	162657	162674	8428	8445	GTCCTGATGTAATTGACT	78	194
1263190	162729	162746	8500	8517	CGAATACAGTTTATCTAA	122	195

1263196	162736	162753	8507	8524	CAGTTCACGAATACAGTT	103	196
1263202	162742	162759	8513	8530	AGCATGCAGTTCACGAAT	98	197

Table 3

Effect of modified oligonucleotides on amount of human SCN1A RNA in HepG2 cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN1A (% UTC)	SEQ ID No.
1262741	2871	2888	N/A	N/A	GGAACAGTTCCATGAGTT	99	198
1262747	2877	2894	N/A	N/A	TCTGGAGGAACAGTTCCA	28	199
1262753	2883	2900	N/A	N/A	TGTTAATCTGGAGGAACA	60	200
1262759	2889	2906	N/A	N/A	CTGAAGTGTTAATCTGGA	78	201
1262765	2895	2912	N/A	N/A	TAACCCCTGAAGTGTTAA	119	202
1262771	2901	2918	N/A	N/A	CTCCATAACCCCTGAAG	61	203
1262777	2907	2924	N/A	N/A	CTCCAGCTTCCATAACCC	147	204
1262783	2920	2937	N/A	N/A	AAAGCTCAGCTTCCTCCA	56	205
1262789	2927	2944	N/A	N/A	TGTAGTAAAAGCTCAGCT	125	206
1262795	2936	2953	N/A	N/A	CCCAAAAGATGTAGTAAA	56	207
1262801	78351	78368	469	486	GCACATTTTAATTACCAT	83	208
1262807	78361	78378	479	496	TTGTCATCCTGCACATTT	92	209
1262813	160820	160837	6591	6608	AAAGGAGTCCTGTTGATA	76	210
1262819	160829	160846	6600	6617	TGACCTCCTAAAGGAGTC	115	211
1262825	160841	160858	6612	6629	TCAGTTTGGCATTGACCT	60	212
1262831	160880	160897	6651	6668	TTGTAGGCACTGACCTTA	45	213
1262837	160886	160903	6657	6674	GTCTTATTGTAGGCACTG	62	214
1262843	160950	160967	6721	6738	GTAACCTCCTGTCAAGGT	60	215
1262849	160957	160974	6728	6745	GAGAACAGTAACCTCCTG	61	216
1262855	160970	160987	6741	6758	GTCAGCTGGTAGTGAGAA	104	217
1262861	160996	161013	6767	6784	CCATTGTGCATCTTATCT	66	218
1262867	161004	161021	6775	6792	CTGACTAGCCATTGTGCA	48	219
1262873	161010	161027	6781	6798	TACAGTCTGACTAGCCAT	57	220
1262879	161016	161033	6787	6804	GGTCCCTACAGTCTGACT	92	221
1262885	161022	161039	6793	6810	GAAACTGGTCCCTACAGT	64	222
1262891	161033	161050	6804	6821	TTGCACCCCTTGAACTG	108	223
1262897	161039	161056	6810	6827	ACAGGTTTGCACCCCTTG	74	224
1262903	161089	161106	6860	6877	TGGATACAATTACTACAC	58	225
1262909	161227	161244	6998	7015	GGTCCTTAGCCTATTCT	59	226
1262915	161233	161250	7004	7021	TATAGAGGTCCTTAGCCT	32	227
1262921	161243	161260	7014	7031	GCATACCTGTTATAGAGG	107	228
1262927	161254	161271	7025	7042	CCCCCAGGTGGCATACC	46	229

1262933	161260	161277	7031	7048	GCCATACCCCCAGGTGG	66	230
1262939	161266	161283	7037	7054	GTGGTTGCCATACCCCC	65	231
1262945	161272	161289	7043	7060	GGCCATGTGGTTGCCATA	53	232
1262951	161295	161312	7066	7083	CCACGACTTTGTGTAGCT	88	233
1262957	161301	161318	7072	7089	TGCAAACCACGACTTTGT	57	234
1262963	161307	161324	7078	7095	CCCTCATGCAAACCACGA	61	235
1262969	161315	161332	7086	7103	GCAGCATGCCCTCATGCA	80	236
1262975	161321	161338	7092	7109	CTAAGTGCAGCATGCCCT	54	237
1262981	161333	161350	7104	7121	CATGCATGATCTCTAAGT	45	238
1262987	161402	161419	7173	7190	TTATCACCCAATTACCCC	75	239
1262993	161408	161425	7179	7196	CTCCACTTATCACCCAAT	107	240
1262999	161415	161432	7186	7203	AAAGCACCTCCACTTATC	113	241
1263005	161442	161459	7213	7230	GGCTGGATTTCGCAAAAC	96	242
1263011	161473	161490	7244	7261	GCCTACCCACAAATAATC	114	243
1263017	161479	161496	7250	7267	TTACTGGCCTACCCACAA	72	244
1263023	161485	161502	7256	7273	TAAGATTTACTGGCCTAC	53	245
1263029	161497	161514	7268	7285	GTTTGCACCTGCTAAGAT	46	246
1263035	161503	161520	7274	7291	AATGAAGTTTGCACCTGC	55	247
1263041	161603	161620	7374	7391	CAGTCTTCTGGCGGTGGA	58	248
1263047	161611	161628	7382	7399	GGTCAATTCAGTCTTCTG	76	249
1263053	161669	161686	7440	7457	AGCCGAAGATGGCTAAAC	35	250
1263059	161675	161692	7446	7463	GCTGAGAGCCGAAGATGG	56	251
1263065	161682	161699	7453	7470	CAACCTTGCTGAGAGCCG	36	252
1263071	161692	161709	7463	7480	TATACAGTGTCAACCTTG	44	253
1263077	161745	161762	7516	7533	GTGCACCACAGGGTAAAA	69	254
1263083	161781	161798	7552	7569	AATACTGTGCTTAGGTCA	79	255
1263089	161830	161847	7601	7618	GTGTAAAGCTTGCCTCT	63	256
1263095	161875	161892	7646	7663	GCATCCAACTATCTATA	84	257
1263101	161881	161898	7652	7669	TTGATAGCATCCAACTA	51	258
1263107	161891	161908	7662	7679	TAAACATGCATTGATAGC	68	259
1263113	161968	161985	7739	7756	CTTTACCACTGACATATG	162	260
1263119	162079	162096	7850	7867	ATACCATATGTTATCCAC	93	261
1263125	162094	162111	7865	7882	GTACAGTCTGGCTATATA	74	262
1263131	162101	162118	7872	7889	CATGTCTGTACAGTCTGG	76	263
1263137	162131	162148	7902	7919	TTAATAGGTTAAGCAGTG	115	264
1263143	162251	162268	8022	8039	TGATTGTGATATCAACCT	54	265
1263149	162406	162423	8177	8194	CGTGAACCTATTTTGCTC	62	266
1263155	162484	162501	8255	8272	GTTAGTGCAGGTACTACC	48	267
1263161	162490	162507	8261	8278	AATTCAGTTAGTGCAGGT	51	268
1263167	162541	162558	8312	8329	CATAAACCGAAGTCAGAA	63	269
1263173	162583	162600	8354	8371	TTAGAACAACTCTAGAGC	76	270
1263179	162642	162659	8413	8430	ACTATATAAGTTGACTAC	47	271
1263185	162692	162709	8463	8480	GAGCCTATGGTTTGCTTC	83	272

1263191	162730	162747	8501	8518	ACGAATACAGTTTATCTA	124	273
1263197	162737	162754	8508	8525	GCAGTTCACGAATACAGT	83	274
1263203	162743	162760	8514	8531	CAGCATGCAGTTCACGAA	79	275

Table 4

Effect of modified oligonucleotides on amount of human SCN1A RNA in HepG2 cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN1A (% UTC)	SEQ ID No.
1262742	2872	2889	N/A	N/A	AGGAACAGTTCCATGAGT	38	276
1262748	2878	2895	N/A	N/A	ATCTGGAGGAACAGTTCC	48	277
1262754	2884	2901	N/A	N/A	GTGTTAATCTGGAGGAAC	69	278
1262760	2890	2907	N/A	N/A	CCTGAAGTGTTAATCTGG	37	279
1262766	2896	2913	N/A	N/A	ATAACCCCTGAAGTGTTA	63	280
1262772	2902	2919	N/A	N/A	GCTTCCATAACCCCTGAA	58	281
1262778	2908	2925	N/A	N/A	CCTCCAGCTTCCATAACC	68	282
1262784	2921	2938	N/A	N/A	AAAAGCTCAGCTTCCTCC	55	283
1262790	2928	2945	N/A	N/A	ATGTAGTAAAAGCTCAGC	75	284
1262796	2937	2954	N/A	N/A	CCCCAAAAGATGTAGTAA	76	285
1262802	78353	78370	471	488	CTGCACATTTTAATTACC	80	286
1262808	78362	78379	480	497	CTTGTCATCCTGCACATT	48	287
1262814	160821	160838	6592	6609	TAAAGGAGTCCTGTTGAT	56	288
1262820	160836	160853	6607	6624	TTGGCATTGACCTCCTAA	79	289
1262826	160842	160859	6613	6630	GTCAGTTTGGCATTGACC	54	290
1262832	160881	160898	6652	6669	ATTGTAGGCACTGACCTT	43	291
1262838	160887	160904	6658	6675	TGTCCTATTGTAGGCACT	69	292
1262844	160951	160968	6722	6739	AGTAACCTCCTGTCAAGG	70	293
1262850	160959	160976	6730	6747	GTGAGAACAGTAACCTCC	72	294
1262856	160971	160988	6742	6759	TGTCAGCTGGTAGTGAGA	71	295
1262862	160997	161014	6768	6785	GCCATTGTGCATCTTATC	40	296
1262868	161005	161022	6776	6793	TCTGACTAGCCATTGTGC	54	297
1262874	161011	161028	6782	6799	CTACAGTCTGACTAGCCA	72	298
1262880	161017	161034	6788	6805	TGGTCCCTACAGTCTGAC	66	299
1262886	161028	161045	6799	6816	CCCCTTGAAACTGGTCCC	52	300
1262892	161034	161051	6805	6822	TTTGCACCCCTTGAAACT	75	301
1262898	161040	161057	6811	6828	CACAGGTTTGCACCCCTT	57	302
1262904	161090	161107	6861	6878	GTGGATACAATTACTACA	42	303
1262910	161228	161245	6999	7016	AGGTCCTTAGCCTATTTT	44	304
1262916	161238	161255	7009	7026	CCTGTTATAGAGGTCCTT	41	305
1262922	161244	161261	7015	7032	GGCATACCTGTTATAGAG	86	306

1262928	161255	161272	7026	7043	ACCCCCCAGGTGGCATAC	56	307
1262934	161261	161278	7032	7049	TGCCATACCCCCCAGGTG	45	308
1262940	161267	161284	7038	7055	TGTGGTTGCCATACCCCC	66	309
1262946	161275	161292	7046	7063	GAGGGCCATGTGGTTGCC	55	310
1262952	161296	161313	7067	7084	ACCACGACTTTGTGTAGC	40	311
1262958	161302	161319	7073	7090	ATGCAAACCACGACTTTG	67	312
1262964	161308	161325	7079	7096	GCCCTCATGCAAACCACG	63	313
1262970	161316	161333	7087	7104	TGCAGCATGCCCTCATGC	46	314
1262976	161322	161339	7093	7110	TCTAAGTGCAGCATGCC	83	315
1262982	161334	161351	7105	7122	TCATGCATGATCTCTAAG	63	316
1262988	161403	161420	7174	7191	CTTATCACCCAATTACCC	61	317
1262994	161409	161426	7180	7197	CCTCCACTTATCACCCAA	57	318
1263000	161435	161452	7206	7223	TTTCGCAAAACAAGATCA	48	319
1263006	161443	161460	7214	7231	GGGCTGGATTTTCGCAAAA	87	320
1263012	161474	161491	7245	7262	GGCCTACCCACAAATAAT	66	321
1263018	161480	161497	7251	7268	TTTACTGGCCTACCCACA	44	322
1263024	161488	161505	7259	7276	TGCTAAGATTTACTGGCC	67	323
1263030	161498	161515	7269	7286	AGTTTGCACCTGCTAAGA	55	324
1263036	161504	161521	7275	7292	GAATGAAGTTTGCACCTG	77	325
1263042	161604	161621	7375	7392	TCAGTCTTCTGGCGGTGG	81	326
1263048	161659	161676	7430	7447	GGCTAAACAAAGTGCAGG	57	327
1263054	161670	161687	7441	7458	GAGCCGAAGATGGCTAAA	56	328
1263060	161677	161694	7448	7465	TTGCTGAGAGCCGAAGAT	66	329
1263066	161684	161701	7455	7472	GTCAACCTTGCTGAGAGC	59	330
1263072	161693	161710	7464	7481	ATATACAGTGTCAACCTT	77	331
1263078	161746	161763	7517	7534	CGTGCACCACAGGGTAAA	89	332
1263084	161782	161799	7553	7570	AAATACTGTGCTTAGGTC	50	333
1263090	161833	161850	7604	7621	CCTGTGTAAAGCTTGCAC	60	334
1263096	161876	161893	7647	7664	AGCATCCAAACTATCTAT	78	335
1263102	161883	161900	7654	7671	CATTGATAGCATCCAAAC	38	336
1263108	161907	161924	7678	7695	CAGCAGCATGGTAATATA	59	337
1263114	162026	162043	7797	7814	GCTGCAAACTATTGCTTA	49	338
1263120	162089	162106	7860	7877	GTCTGGCTATATAACCATA	71	339
1263126	162095	162112	7866	7883	TGTACAGTCTGGCTATAT	64	340
1263132	162102	162119	7873	7890	ACATGTCTGTACAGTCTG	98	341
1263138	162244	162261	8015	8032	GATATCAACCTGAAGATA	52	342
1263144	162252	162269	8023	8040	GTGATTGTGATATCAACC	87	343
1263150	162478	162495	8249	8266	GCAGGTACTACCAGAAAT	91	344
1263156	162485	162502	8256	8273	AGTTAGTGCAGGTACTAC	47	345
1263162	162491	162508	8262	8279	CAATTCAGTTAGTGCAGG	43	346
1263168	162542	162559	8313	8330	ACATAAACCGAAGTCAGA	65	347
1263174	162596	162613	8367	8384	AGCCCACATTCTATTTAG	53	348
1263180	162643	162660	8414	8431	GACTATATAAGTTGACTA	35	349

1263186	162693	162710	8464	8481	GGAGCCTATGGTTTGCTT	67	350
1263192	162731	162748	8502	8519	CACGAATACAGTTTATCT	56	351
1263198	162738	162755	8509	8526	TGCAGTTCACGAATACAG	45	352
1263204	162744	162761	8515	8532	CCAGCATGCAGTTCACGA	61	353

Table 5

Effect of modified oligonucleotides on amount of human SCN1A RNA in HepG2 cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN1A (% UTC)	SEQ ID No.
1262743	2873	2890	N/A	N/A	GAGGAACAGTTCATGAG	65	354
1262749	2879	2896	N/A	N/A	AATCTGGAGGAACAGTTC	58	355
1262755	2885	2902	N/A	N/A	AGTGTTAATCTGGAGGAA	47	356
1262761	2891	2908	N/A	N/A	CCCTGAAGTGTTAATCTG	68	357
1262767	2897	2914	N/A	N/A	CATAACCCCTGAAGTGTT	88	358
1262773	2903	2920	N/A	N/A	AGCTTCCATAACCCCTGA	36	359
1262779	2909	2926	N/A	N/A	TCCTCCAGCTTCCATAAC	52	360
1262785	2923	2940	N/A	N/A	GTAAAAGCTCAGCTTCCT	117	361
1262791	2929	2946	N/A	N/A	GATGTAGTAAAAGCTCAG	84	362
1262797	78337	78354	455	472	CCATTTATTCTGCATATG	111	363
1262803	78354	78371	472	489	CCTGCACATTTTAATTAC	84	364
1262809	160783	160800	6554	6571	GGCTGTAAACAATTTGTC	106	365
1262815	160822	160839	6593	6610	CTAAAGGAGTCCTGTTGA	122	366
1262821	160837	160854	6608	6625	TTTGGCATTGACCTCCTA	85	367
1262827	160843	160860	6614	6631	AGTCAGTTTGGCATTGAC	88	368
1262833	160882	160899	6653	6670	TATTGTAGGCACTGACCT	67	369
1262839	160888	160905	6659	6676	CTGTCTTATTGTAGGCAC	45	370
1262845	160952	160969	6723	6740	CAGTAACCTCCTGTCAAG	80	371
1262851	160960	160977	6731	6748	AGTGAGAACAGTAACCTC	47	372
1262857	160972	160989	6743	6760	GTGTCAGCTGGTAGTGAG	69	373
1262863	160998	161015	6769	6786	AGCCATTGTGCATCTTAT	127	374
1262869	161006	161023	6777	6794	GTCTGACTAGCCATTGTG	63	375
1262875	161012	161029	6783	6800	CCTACAGTCTGACTAGCC	104	376
1262881	161018	161035	6789	6806	CTGGTCCCTACAGTCTGA	97	377
1262887	161029	161046	6800	6817	ACCCCTTGAACTGGTCC	72	378
1262893	161035	161052	6806	6823	GTTTGCACCCCTTGAAAC	63	379
1262899	161041	161058	6812	6829	TCACAGGTTTGCACCCCT	56	380
1262905	161091	161108	6862	6879	AGTGGATACAATTACTAC	67	381
1262911	161229	161246	7000	7017	GAGGTCCTTAGCCTATTT	78	382
1262917	161239	161256	7010	7027	ACCTGTTATAGAGGTCCT	69	383

1262923	161245	161262	7016	7033	TGGCATACCTGTTATAGA	75	384
1262929	161256	161273	7027	7044	TACCCCCCAGGTGGCATA	94	385
1262935	161262	161279	7033	7050	TTGCCATACCCCCCAGGT	105	386
1262941	161268	161285	7039	7056	ATGTGGTTGCCATACCCC	64	387
1262947	161289	161306	7060	7077	CTTTGTGTAGCTGGGAGG	61	388
1262953	161297	161314	7068	7085	AACCACGACTTTGTGTAG	79	389
1262959	161303	161320	7074	7091	CATGCAAACCACGACTTT	99	390
1262965	161310	161327	7081	7098	ATGCCCTCATGCAAACCA	61	391
1262971	161317	161334	7088	7105	GTGCAGCATGCCCTCATG	63	392
1262977	161323	161340	7094	7111	CTCTAAGTGCAGCATGCC	69	393
1262983	161335	161352	7106	7123	CTCATGCATGATCTCTAA	70	394
1262989	161404	161421	7175	7192	ACTTATCACCCAATTACC	70	395
1262995	161410	161427	7181	7198	ACCTCCACTTATCACCCA	63	396
1263001	161437	161454	7208	7225	GATTTTCGCAAAACAAGAT	63	397
1263007	161459	161476	7230	7247	AATCTACTTGGTCTAGGG	87	398
1263013	161475	161492	7246	7263	TGGCCTACCCACAAATAA	58	399
1263019	161481	161498	7252	7269	ATTTACTGGCCTACCCAC	139	400
1263025	161493	161510	7264	7281	GCACCTGCTAAGATTAC	84	401
1263031	161499	161516	7270	7287	AAGTTTGCACCTGCTAAG	82	402
1263037	161530	161547	7301	7318	CATAACATTTATGACTCC	78	403
1263043	161605	161622	7376	7393	TTCAGTCTTCTGGCGGTG	58	404
1263049	161662	161679	7433	7450	GATGGCTAAACAAAGTGC	67	405
1263055	161671	161688	7442	7459	AGAGCCGAAGATGGCTAA	68	406
1263061	161678	161695	7449	7466	CTTGCTGAGAGCCGAAGA	87	407
1263067	161687	161704	7458	7475	AGTGTCAACCTTGCTGAG	58	408
1263073	161694	161711	7465	7482	CATATACAGTGTCAACCT	73	409
1263079	161777	161794	7548	7565	CTGTGCTTAGGTCATTAT	76	410
1263085	161825	161842	7596	7613	AAGCTTGCACTCTACATT	78	411
1263091	161834	161851	7605	7622	ACCTGTGTAAAGCTTGCA	97	412
1263097	161877	161894	7648	7665	TAGCATCCAAACTATCTA	72	413
1263103	161884	161901	7655	7672	GCATTGATAGCATCCAAA	50	414
1263109	161911	161928	7682	7699	GATACAGCAGCATGGTAA	64	415
1263115	162028	162045	7799	7816	GTGCTGCAAACCTATTGCT	68	416
1263121	162090	162107	7861	7878	AGTCTGGCTATATACCAT	100	417
1263127	162096	162113	7867	7884	CTGTACAGTCTGGCTATA	67	418
1263133	162103	162120	7874	7891	AACATGTCTGTACAGTCT	98	419
1263139	162246	162263	8017	8034	GTGATATCAACCTGAAGA	107	420
1263145	162253	162270	8024	8041	AGTGATTGTGATATCAAC	92	421
1263151	162480	162497	8251	8268	GTGCAGGTACTACCAGAA	67	422
1263157	162486	162503	8257	8274	CAGTTAGTGCAGGTACTA	88	423
1263163	162492	162509	8263	8280	TCAATTCAAGTTAGTGCAG	42	424
1263169	162543	162560	8314	8331	AACATAAACCGAAGTCAG	60	425
1263175	162636	162653	8407	8424	TAAGTTGACTACTCTGTT	66	426

1263181	162645	162662	8416	8433	TTGACTATATAAGTTGAC	102	427
1263187	162694	162711	8465	8482	AGGAGCCTATGGTTTGCT	102	428
1263193	162732	162749	8503	8520	TCACGAATACAGTTTATC	74	429
1263199	162739	162756	8510	8527	ATGCAGTTCACGAATACA	44	430
1263205	162745	162762	8516	8533	TCCAGCATGCAGTTCACG	61	431

Table 6

Effect of modified oligonucleotides on amount of human SCN1A RNA in HepG2 cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN1A (% UTC)	SEQ ID No.
1262744	2874	2891	N/A	N/A	GGAGGAACAGTTCCATGA	33	432
1262750	2880	2897	N/A	N/A	TAATCTGGAGGAACAGTT	56	433
1262756	2886	2903	N/A	N/A	AAGTGTTAATCTGGAGGA	57	434
1262762	2892	2909	N/A	N/A	CCCCTGAAGTGTTAATCT	34	435
1262768	2898	2915	N/A	N/A	CCATAACCCCTGAAGTGT	57	436
1262774	2904	2921	N/A	N/A	CAGCTTCCATAACCCCTG	52	437
1262780	2910	2927	N/A	N/A	TTCCTCCAGCTTCCATAA	109	438
1262786	2924	2941	N/A	N/A	AGTAAAAGCTCAGCTTCC	53	439
1262792	2930	2947	N/A	N/A	AGATGTAGTAAAAGCTCA	57	440
1262798	78338	78355	456	473	ACCATTTATTCTGCATAT	43	441
1262804	78358	78375	476	493	TCATCCTGCACATTTTAA	77	442
1262810	160817	160834	6588	6605	GGAGTCCTGTTGATAAAA	111	443
1262816	160823	160840	6594	6611	CCTAAAGGAGTCCTGTTG	30	444
1262822	160838	160855	6609	6626	GTTTGGCATTGACCTCCT	62	445
1262828	160869	160886	6640	6657	GACCTTAAGGAGATTGT	66	446
1262834	160883	160900	6654	6671	TTATTGTAGGCACTGACC	52	447
1262840	160889	160906	6660	6677	ACTGTCTTATTGTAGGCA	51	448
1262846	160953	160970	6724	6741	ACAGTAACCTCCTGTCAA	49	449
1262852	160961	160978	6732	6749	TAGTGAGAACAGTAACCT	97	450
1262858	160973	160990	6744	6761	AGTGTCAGCTGGTAGTGA	102	451
1262864	160999	161016	6770	6787	TAGCCATTGTGCATCTTA	79	452
1262870	161007	161024	6778	6795	AGTCTGACTAGCCATTGT	41	453
1262876	161013	161030	6784	6801	CCCTACAGTCTGACTAGC	170	454
1262882	161019	161036	6790	6807	ACTGGTCCCTACAGTCTG	40	455
1262888	161030	161047	6801	6818	CACCCCTTGAACTGGTC	66	456
1262894	161036	161053	6807	6824	GGTTTGCACCCCTTGAAA	115	457
1262900	161043	161060	6814	6831	AATCACAGGTTTGCACCC	70	458
1262906	161146	161163	6917	6934	AATCCACTAACAGATTCC	123	459
1262912	161230	161247	7001	7018	AGAGGTCCTTAGCCTATT	44	460
1262918	161240	161257	7011	7028	TACCTGTTATAGAGGTCC	56	461

1262924	161246	161263	7017	7034	GTGGCATACTGTTATAG	88	462
1262930	161257	161274	7028	7045	ATACCCCCCAGGTGGCAT	98	463
1262936	161263	161280	7034	7051	GTTGCCATACCCCCCAGG	54	464
1262942	161269	161286	7040	7057	CATGTGGTTGCCATACCC	45	465
1262948	161292	161309	7063	7080	CGACTTTGTGTAGCTGGG	35	466
1262954	161298	161315	7069	7086	AAACCACGACTTTGTGTA	93	467
1262960	161304	161321	7075	7092	TCATGCAAACCACGACTT	73	468
1262966	161312	161329	7083	7100	GCATGCCCTCATGCAAAC	43	469
1262972	161318	161335	7089	7106	AGTGCAGCATGCCCTCAT	76	470
1262978	161324	161341	7095	7112	TCTCTAAGTGCAGCATGC	110	471
1262984	161399	161416	7170	7187	TCACCCAATTACCCCTCC	66	472
1262990	161405	161422	7176	7193	CACTTATCACCCAATTAC	59	473
1262996	161411	161428	7182	7199	CACCTCCACTTATCACCC	69	474
1263002	161438	161455	7209	7226	GGATTTTCGCAAAACAAGA	58	475
1263008	161460	161477	7231	7248	TAATCTACTTGGTCTAGG	42	476
1263014	161476	161493	7247	7264	CTGGCCTACCCACAAATA	104	477
1263020	161482	161499	7253	7270	GATTTACTGGCCTACCCA	35	478
1263026	161494	161511	7265	7282	TGCACCTGCTAAGATTTA	30	479
1263032	161500	161517	7271	7288	GAAGTTTGCACCTGCTAA	18	480
1263038	161599	161616	7370	7387	CTTCTGGCGGTGGAGGGT	97	481
1263044	161606	161623	7377	7394	ATTCAGTCTTCTGGCGGT	82	482
1263050	161666	161683	7437	7454	CGAAGATGGCTAAACAAA	66	483
1263056	161672	161689	7443	7460	GAGAGCCGAAGATGGCTA	58	484
1263062	161679	161696	7450	7467	CCTTGCTGAGAGCCGAAG	101	485
1263068	161689	161706	7460	7477	ACAGTGTCAACCTTGCTG	67	486
1263074	161695	161712	7466	7483	ACATATACAGTGTCAACC	76	487
1263080	161778	161795	7549	7566	ACTGTGCTTAGGTCATTA	75	488
1263086	161827	161844	7598	7615	TAAAGCTTGCACTCTACA	39	489
1263092	161835	161852	7606	7623	TACCTGTGTAAAGCTTGC	136	490
1263098	161878	161895	7649	7666	ATAGCATCCAAACTATCT	125	491
1263104	161885	161902	7656	7673	TGCATTGATAGCATCCAA	42	492
1263110	161912	161929	7683	7700	AGATACAGCAGCATGGTA	32	493
1263116	162029	162046	7800	7817	AGTGCTGCAAACTATTGC	67	494
1263122	162091	162108	7862	7879	CAGTCTGGCTATATACCA	55	495
1263128	162097	162114	7868	7885	TCTGTACAGTCTGGCTAT	128	496
1263134	162128	162145	7899	7916	ATAGGTTAAGCAGTGTGT	44	497
1263140	162247	162264	8018	8035	TGTGATATCAACCTGAAG	74	498
1263146	162336	162353	8107	8124	ATCTACAACCTACCCAGTC	64	499
1263152	162481	162498	8252	8269	AGTGCAGGTACTACCAGA	76	500
1263158	162487	162504	8258	8275	TCAGTTAGTGCAGGTACT	60	501
1263164	162497	162514	8268	8285	TACCTTCAATTCAGTTAG	48	502
1263170	162572	162589	8343	8360	CTAGAGCAGCATTACTCC	42	503
1263176	162637	162654	8408	8425	ATAAGTTGACTACTCTGT	69	504

1263182	162655	162672	8426	8443	CCTGATGTAATTGACTAT	55	505
1263188	162695	162712	8466	8483	GAGGAGCCTATGGTTTGC	84	506
1263194	162734	162751	8505	8522	GTTCACGAATACAGTTTA	51	507
1263200	162740	162757	8511	8528	CATGCAGTTCACGAATAC	78	508
1263206	162767	162784	8538	8555	ATTTAGCATAATAGTAGC	78	509

Example 2: Activity of modified oligonucleotides targeting human SCN1A in HepG2 cells, single dose, *in vitro*

Modified oligonucleotides complementary to an SCN1A nucleic acid were synthesized and tested for their effect on SCN1A RNA levels *in vitro*. The modified oligonucleotides were tested in a series of experiments using the same culture conditions.

The modified oligonucleotides in the tables below are 18 nucleosides in length. Each nucleoside comprises a 2'-MOE sugar moiety. The internucleoside linkages throughout each modified oligonucleotide are phosphorothioate internucleoside linkages. All cytosine nucleobases throughout each modified oligonucleotide are 5-methylcytosines.

"Start site" indicates the 5'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. "Stop site" indicates the 3'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. As shown in the tables below, the modified oligonucleotides are complementary to either the human SCN1A genomic sequence, designated herein as SEQ ID NO: 1 (described herein above) or to the human SCN1A mRNA, designated herein as SEQ ID NO: 2 (described herein above) or to both. 'N/A' indicates that the modified oligonucleotide is not complementary to that particular target sequence with 100% complementarity.

Cultured HepG2 cells at a density of 20,000 cells per well were transfected using electroporation with 15,000 nM of modified oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and SCN1A RNA levels were measured by quantitative real-time RT-PCR. Human primer probe set RTS48189 (forward sequence CTATACCTCGACCAGGAAACAAA, designated herein as SEQ ID NO: 18; reverse sequence TGACCATGTTAAGACAGATGAGAA, designated herein as SEQ ID NO: 19; probe sequence TGTCTGGTTACGAAGTCAAAGACCATTC, designated herein as SEQ ID NO: 20) was used to measure full-length SCN1A RNA levels. SCN1A RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. SCN1A RNA is presented as % of the average of untreated control (%UTC). As shown in the tables below, certain modified oligonucleotides complementary to SCN1A RNA increased the amount of human SCN1A RNA compared to untreated control. Each of Tables 7-11 represents a different experiment.

Table 7

Effect of modified oligonucleotides on amount of human SCN1A RNA in HepG2 cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN1A (% UTC)	SEQ ID No.
1342105	144706	144723	N/A	N/A	TTGGAGCAAGATTATCCT	111	510
1342107	144766	144783	N/A	N/A	GTAATACAGTACCCATAA	61	511
1342109	144753	144770	N/A	N/A	CATAATAAAGGGCTCAGG	112	512
1342118	144686	144703	N/A	N/A	ACAAAATAGAAATATATA	173	513
1366952	95466	95483	N/A	N/A	AACACACAAAAGAAAATC	136	514
1366958	144722	144739	N/A	N/A	CTCCACCCCATCCAAGTT	114	515
1366964	152881	152898	N/A	N/A	GAGCCTGAAAGAGGCTGA	59	516
1366966	91106	91123	N/A	N/A	GAAAAAGAAATATTAGGG	89	517
1366970	91360	91377	N/A	N/A	AAAGTGGGCACATCACCT	57	518
1366971	144762	144779	N/A	N/A	TACAGTACCCATAATAAA	91	519
1366976	152950	152967	N/A	N/A	AAAATACTACATCTTACA	57	520
1366978	91136	91153	N/A	N/A	TGATGAGAGCAAACTCC	76	521
1366981	110791	110808	N/A	N/A	TTTGAAGACTAAACACAT	82	522
1366982	144710	144727	N/A	N/A	CAAGTTGGAGCAAGATTA	138	523
1366983	110807	110824	N/A	N/A	TTTTTCAAGCAGAAAATT	66	524
1366988	152876	152893	N/A	N/A	TGAAAGAGGCTGAAATCA	73	525
1366991	152924	152941	N/A	N/A	AAGAGCAAAGTTGGAATG	118	526
1367000	110787	110804	N/A	N/A	AAGACTAAACACATTTAC	83	527
1367003	95470	95487	N/A	N/A	AAGGAACACACAAAAGAA	54	528
1367004	144682	144699	N/A	N/A	AATAGAAATATATAGTTT	85	529
1367005	95434	95451	N/A	N/A	ATATTACAAAAAGCTAAC	55	530
1367011	110827	110844	N/A	N/A	ACACAATTAAATGTAAAC	167	531
1367016	110823	110840	N/A	N/A	AATTAAATGTAAACAGTT	85	532
1367021	95450	95467	N/A	N/A	TCAAAATCCAAGTGTTAT	67	533
1367022	152955	152972	N/A	N/A	GATAGAAAATACTACATC	83	534
1367024	152941	152958	N/A	N/A	CATCTTACAAAGTTTTGA	53	535
1367035	152937	152954	N/A	N/A	TTACAAAGTTTTGAAGAG	66	536
1367038	152911	152928	N/A	N/A	GAATGAGCATGAATTTCA	68	537
1367045	95458	95475	N/A	N/A	AAAGAAAATCAAAATCCA	108	538
1367047	144758	144775	N/A	N/A	GTACCCATAATAAAGGGC	61	539
1367048	152885	152902	N/A	N/A	CTTGGAGCCTGAAAGAGG	74	540
1367049	110799	110816	N/A	N/A	GCAGAAAATTTGAAGACT	83	541
1367053	110819	110836	N/A	N/A	AAATGTAAACAGTTTTTC	89	542
1367066	152907	152924	N/A	N/A	GAGCATGAATTTTCAGTTT	78	543
1367068	152959	152976	N/A	N/A	GGTTGATAGAAAATACTA	88	544
1367073	95454	95471	N/A	N/A	AAAATCAAAATCCAAGTG	113	545
1367084	144698	144715	N/A	N/A	AGATTATCCTATACAAAA	71	546

1367088	95446	95463	N/A	N/A	AATCCAAGTGTATATTA	80	547
1367090	95462	95479	N/A	N/A	CACAAAAGAAAATCAAAA	69	548
1367097	95422	95439	N/A	N/A	GCTAACATTGAAAAGCCC	55	549
1367098	144714	144731	N/A	N/A	CATCCAAGTTGGAGCAAG	147	550
1367102	152895	152912	N/A	N/A	CAGTTTAGGTCTTGGAGC	76	551
1367103	110795	110812	N/A	N/A	AAAATTTGAAGACTAAAC	44	552
1367108	152903	152920	N/A	N/A	ATGAATTCAGTTTAGGT	77	553
1367109	152899	152916	N/A	N/A	ATTTCAGTTTAGGTCTTG	69	554
1367113	152946	152963	N/A	N/A	TACTACATCTTACAAAGT	106	555
1367116	95438	95455	N/A	N/A	TGTTATATTACAAAAGC	77	556
1367123	110803	110820	N/A	N/A	TCAAGCAGAAAATTTGAA	95	557
1367124	152928	152945	N/A	N/A	TTTGAAGAGCAAAGTTGG	75	558
1367127	91140	91157	N/A	N/A	TGGGTGATGAGAGCAAAA	111	559
1367140	110771	110788	N/A	N/A	ACCTTCCAATATGCTTAC	77	560
1367141	144690	144707	N/A	N/A	CTATACAAAATAGAAATA	94	561
1367145	91144	91161	N/A	N/A	AGCCTGGGTGATGAGAGC	69	562
1367146	152932	152949	N/A	N/A	AAGTTTTGAAGAGCAAAG	75	563
1367147	95478	95495	N/A	N/A	TTATTGTAAAGGAACACA	121	564
1367150	144694	144711	N/A	N/A	TATCCTATACAAAATAGA	57	565
1367151	110775	110792	N/A	N/A	ATTACCTTCCAATATGC	77	566
1367153	152867	152884	N/A	N/A	CTGAAATCAAATAAAATA	104	567
1367162	95426	95443	N/A	N/A	AAAAGCTAACATTGAAAA	63	568
1367163	144702	144719	N/A	N/A	AGCAAGATTATCCTATAC	139	569
1367165	110783	110800	N/A	N/A	CTAAACACATTTACCTTC	117	570
1367166	110811	110828	N/A	N/A	ACAGTTTTTCAAGCAGAA	118	571
1367171	91216	91233	N/A	N/A	AGGAGAACAGGAGAATCG	83	572
1367185	95442	95459	N/A	N/A	CAAGTGTATATTACAAA	85	573
1367187	95474	95491	N/A	N/A	TGTTAAGGAACACACAAA	50	574
1367189	144718	144735	N/A	N/A	ACCCCATCCAAGTTGGAG	82	575
1367192	152872	152889	N/A	N/A	AGAGGCTGAAATCAAATA	90	576
1367193	152919	152936	N/A	N/A	CAAAGTTGGAATGAGCAT	84	577
1367195	91220	91237	N/A	N/A	AGGCAGGAGAACAGGAGA	83	578
1367196	152890	152907	N/A	N/A	TAGGTCTTGGAGCCTGAA	69	579
1367200	152915	152932	N/A	N/A	GTTGGAATGAGCATGAAT	88	580
1367203	110815	110832	N/A	N/A	GTAAACAGTTTTTCAAGC	63	581
1367205	144678	144695	N/A	N/A	GAAATATATAGTTTGTTA	63	582
1367215	152856	152873	N/A	N/A	TAAAATAGGTTTATATTT	71	583
1367229	110779	110796	N/A	N/A	ACACATTTACCTTCCAAT	72	584
1367231	95430	95447	N/A	N/A	TACAAAAAGCTAACATTG	121	585
1367240	152861	152878	N/A	N/A	TCAAATAAAATAGGTTTA	123	586

Table 8

Effect of modified oligonucleotides on amount of human SCN1A RNA in HepG2 cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN1A (% UTC)	SEQ ID No.
1342110	144711	144728	N/A	N/A	CCAAGTTGGAGCAAGATT	67	587
1342115	144691	144708	N/A	N/A	CCTATACAAAATAGAAAT	25	588
1366953	95479	95496	N/A	N/A	GTTATTGTTAAGGAACAC	40	589
1366954	144703	144720	N/A	N/A	GAGCAAGATTATCCTATA	72	590
1366957	95447	95464	N/A	N/A	AAATCCAAGTGTTATATT	117	591
1366959	144699	144716	N/A	N/A	AAGATTATCCTATACAAA	54	592
1366967	91137	91154	N/A	N/A	GTGATGAGAGCAAACTC	50	593
1366973	95455	95472	N/A	N/A	GAAAATCAAAATCCAAGT	43	594
1366974	152929	152946	N/A	N/A	TTTTGAAGAGCAAAGTTG	81	595
1366977	110828	110845	N/A	N/A	TACACAATTAAATGTAAA	213	596
1366980	152908	152925	N/A	N/A	TGAGCATGAATTTTCAGTT	152	597
1366984	152904	152921	N/A	N/A	CATGAATTTTCAGTTTAGG	124	598
1366990	95435	95452	N/A	N/A	TATATTACAAAAAGCTAA	62	599
1366992	110788	110805	N/A	N/A	GAAGACTAAACACATTTA	57	600
1366995	152878	152895	N/A	N/A	CCTGAAAGAGGCTGAAAT	66	601
1366999	91213	91230	N/A	N/A	AGAACAGGAGAATCGCTT	60	602
1367002	91217	91234	N/A	N/A	CAGGAGAACAGGAGAATC	44	603
1367014	152938	152955	N/A	N/A	CTTACAAAGTTTTGAAGA	155	604
1367015	152868	152885	N/A	N/A	GCTGAAATCAAATAAAAT	51	605
1367017	95443	95460	N/A	N/A	CCAAGTGTTATATTACAA	25	606
1367020	152896	152913	N/A	N/A	TCAGTTTAGGTCTTGGAG	109	607
1367023	110804	110821	N/A	N/A	TTCAAGCAGAAAATTTGA	62	608
1367031	152934	152951	N/A	N/A	CAAAGTTTTGAAGAGCAA	25	609
1367034	95451	95468	N/A	N/A	ATCAAAATCCAAGTGTTA	52	610
1367036	152947	152964	N/A	N/A	ATACTACATCTTACAAAG	85	611
1367050	95475	95492	N/A	N/A	TTGTAAAGGAACACACAA	24	612
1367054	91361	91378	N/A	N/A	CAAAGTGGGCACATCACC	69	613
1367056	152956	152973	N/A	N/A	TGATAGAAAATACTACAT	69	614
1367057	95463	95480	N/A	N/A	ACACAAAAGAAAATCAAA	63	615
1367058	152951	152968	N/A	N/A	GAAAATACTACATCTTAC	73	616
1367059	152920	152937	N/A	N/A	GCAAAGTTGGAATGAGCA	107	617
1367060	95459	95476	N/A	N/A	AAAAGAAAATCAAAATCC	44	618
1367061	144679	144696	N/A	N/A	AGAAATATATAGTTTGTT	56	619
1367069	152891	152908	N/A	N/A	TTAGGTCTTGGAGCCTGA	61	620
1367075	152882	152899	N/A	N/A	GGAGCCTGAAAGAGGCTG	62	621

1367078	144687	144704	N/A	N/A	TACAAAATAGAAATATAT	34	622
1367081	95471	95488	N/A	N/A	TAAGGAACACACAAAAGA	54	623
1367099	152887	152904	N/A	N/A	GTCTTGGAGCCTGAAAGA	96	624
1367107	144695	144712	N/A	N/A	TTATCCTATACAAAATAG	101	625
1367114	110792	110809	N/A	N/A	ATTTGAAGACTAAACACA	28	626
1367117	110780	110797	N/A	N/A	AACACATTTACCTTCCAA	45	627
1367121	144719	144736	N/A	N/A	CACCCCATCCAAGTTGGA	188	628
1367122	152925	152942	N/A	N/A	GAAGAGCAAAGTTGGAAT	56	629
1367125	91107	91124	N/A	N/A	AGAAAAAGAAATATTAGG	78	630
1367128	95427	95444	N/A	N/A	AAAAAGCTAACATTGAAA	65	631
1367129	110820	110837	N/A	N/A	TAAATGTAAACAGTTTTT	55	632
1367133	152858	152875	N/A	N/A	AATAAAATAGGTTTATAT	42	633
1367135	144759	144776	N/A	N/A	AGTACCATAATAAAGGG	102	634
1367137	110816	110833	N/A	N/A	TGTAAACAGTTTTTCAAG	22	635
1367152	95423	95440	N/A	N/A	AGCTAACATTGAAAAGCC	46	636
1367155	144723	144740	N/A	N/A	GCTCCACCCCATCCAAGT	161	637
1367157	110784	110801	N/A	N/A	ACTAAACACATTTACCTT	82	638
1367161	152916	152933	N/A	N/A	AGTTGGAATGAGCATGAA	59	639
1367164	152900	152917	N/A	N/A	AATTTTCAGTTTAGGTCTT	76	640
1367172	152912	152929	N/A	N/A	GGAATGAGCATGAATTTTC	73	641
1367174	144763	144780	N/A	N/A	ATACAGTACCCATAATAA	48	642
1367177	110776	110793	N/A	N/A	CATTACCTTCCAATATG	28	643
1367179	95431	95448	N/A	N/A	TTACAAAAAGCTAACATT	69	644
1367182	144715	144732	N/A	N/A	CCATCCAAGTTGGAGCAA	129	645
1367184	144767	144784	N/A	N/A	GGTAATACAGTACCCATA	125	646
1367188	95439	95456	N/A	N/A	GTGTTATATTACAAAAAG	82	647
1367191	110772	110789	N/A	N/A	TACCTTCCAATATGCTTA	9	648
1367197	110796	110813	N/A	N/A	GAAAATTTGAAGACTAAA	38	649
1367208	152960	152977	N/A	N/A	AGGTTGATAGAAAATACT	36	650
1367210	144754	144771	N/A	N/A	CCATAATAAAGGGCTCAG	31	651
1367212	152873	152890	N/A	N/A	AAGAGGCTGAAATCAAAT	66	652
1367214	110824	110841	N/A	N/A	CAATTAAATGTAAACAGT	165	653
1367216	91141	91158	N/A	N/A	CTGGGTGATGAGAGCAAA	100	654
1367218	144707	144724	N/A	N/A	GTTGGAGCAAGATTATCC	112	655
1367221	144683	144700	N/A	N/A	AAATAGAAATATATAGTT	76	656
1367222	91221	91238	N/A	N/A	GAGGCAGGAGAACAGGAG	51	657
1367223	152862	152879	N/A	N/A	ATCAAATAAAATAGGTTT	70	658
1367228	110812	110829	N/A	N/A	AACAGTTTTTCAAGCAGA	72	659
1367232	95467	95484	N/A	N/A	GAACACACAAAAGAAAAT	141	660
1367233	110800	110817	N/A	N/A	AGCAGAAAATTTGAAGAC	52	661
1367236	110808	110825	N/A	N/A	GTTTTTCAAGCAGAAAAT	239	662
1367243	152942	152959	N/A	N/A	ACATCTTACAAAGTTTTG	41	663

Table 9

Effect of modified oligonucleotides on amount of human SCN1A RNA in HepG2 cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN1A (% UTC)	SEQ ID No.
1342108	144716	144733	N/A	N/A	CCCATCCAAGTTGGAGCA	97	664
1342111	144768	144785	N/A	N/A	GGGTAATACAGTACCCAT	50	665
1342122	144696	144713	N/A	N/A	ATTATCCTATACAAAATA	60	666
1366955	95456	95473	N/A	N/A	AGAAAATCAAAATCCAAG	41	667
1366961	152888	152905	N/A	N/A	GGTCTTGGAGCCTGAAAG	136	668
1366962	95468	95485	N/A	N/A	GGAACACACAAAAGAAA A	117	669
1366963	152952	152969	N/A	N/A	AGAAAATACTACATCTTA	55	670
1366965	152926	152943	N/A	N/A	TGAAGAGCAAAGTTGGAA	79	671
1366968	152865	152882	N/A	N/A	GAAATCAAATAAAATAGG	54	672
1366969	95452	95469	N/A	N/A	AATCAAAATCCAAGTGTT	54	673
1366972	95460	95477	N/A	N/A	CAAAAGAAAATCAAAATC	66	674
1366975	110829	110846	N/A	N/A	ATACACAATTAAATGTAA	60	675
1366985	95440	95457	N/A	N/A	AGTGTTATATTACAAAAA	52	676
1366996	152909	152926	N/A	N/A	ATGAGCATGAATTCAGT	67	677
1366997	152917	152934	N/A	N/A	AAGTTGGAATGAGCATGA	71	678
1367001	95424	95441	N/A	N/A	AAGCTAACATTGAAAAGC	93	679
1367007	152905	152922	N/A	N/A	GCATGAATTCAGTTTAG	68	680
1367008	152944	152961	N/A	N/A	CTACATCTTACAAAGTTT	104	681
1367018	152897	152914	N/A	N/A	TTCAGTTTAGGTCTTGGA	87	682
1367025	91218	91235	N/A	N/A	GCAGGAGAACAGGAGAAT	59	683
1367026	152874	152891	N/A	N/A	AAAGAGGCTGAAATCAAA	68	684
1367029	95420	95437	N/A	N/A	TAACATTGAAAAGCCCAA	78	685
1367032	91142	91159	N/A	N/A	CCTGGGTGATGAGAGCAA	98	686
1367033	144688	144705	N/A	N/A	ATACAAAATAGAAATATA	77	687
1367037	152901	152918	N/A	N/A	GAATTCAGTTTAGGTCT	95	688
1367039	144755	144772	N/A	N/A	CCCATAATAAAGGGCTCA	66	689
1367040	152961	152978	N/A	N/A	AAGGTTGATAGAAAATAC	133	690
1367042	91222	91239	N/A	N/A	TGAGGCAGGAGAACAGGA	57	691
1367043	144712	144729	N/A	N/A	TCCAAGTTGGAGCAAGAT	67	692
1367044	144700	144717	N/A	N/A	CAAGATTATCCTATACAA	57	693
1367071	144760	144777	N/A	N/A	CAGTACCCATAATAAAGG	49	694
1367072	152869	152886	N/A	N/A	GGCTGAAATCAAATAAAA	84	695
1367076	144704	144721	N/A	N/A	GGAGCAAGATTATCCTAT	113	696
1367079	95428	95445	N/A	N/A	CAAAAAGCTAACATTGAA	38	697

1367080	110789	110806	N/A	N/A	TGAAGACTAAACACATTT	29	698
1367082	152957	152974	N/A	N/A	TTGATAGAAAATACTACA	89	699
1367083	152883	152900	N/A	N/A	TGGAGCCTGAAAGAGGCT	81	700
1367085	110793	110810	N/A	N/A	AATTTGAAGACTAAACAC	46	701
1367087	152930	152947	N/A	N/A	GTTTTGAAGAGCAAAGTT	85	702
1367089	144684	144701	N/A	N/A	AAAATAGAAATATATAGT	70	703
1367091	152892	152909	N/A	N/A	TTTAGGTCTTGGAGCCTG	34	704
1367093	95432	95449	N/A	N/A	ATTACAAAAAGCTAACAT	57	705
1367096	110813	110830	N/A	N/A	AAACAGTTTTTCAAGCAG	59	706
1367100	110773	110790	N/A	N/A	TTACCTTCCAATATGCTT	24	707
1367101	110801	110818	N/A	N/A	AAGCAGAAAATTTGAAGA	102	708
1367104	110825	110842	N/A	N/A	ACAATTAAATGTAAACAG	58	709
1367105	110805	110822	N/A	N/A	TTTCAAGCAGAAAATTTG	78	710
1367110	95480	95497	N/A	N/A	GGTTATTGTTAAGGAACA	61	711
1367115	95444	95461	N/A	N/A	TCCAAGTGTTATATTACA	72	712
1367119	95436	95453	N/A	N/A	TTATATTACAAAAAGCTA	99	713
1367120	110777	110794	N/A	N/A	ACATTTACCTTCCAATAT	79	714
1367126	95472	95489	N/A	N/A	TTAAGGAACACACAAAAG	39	715
1367131	144724	144741	N/A	N/A	CGCTCCACCCCATCCAAG	167	716
1367132	95464	95481	N/A	N/A	CACACAAAAGAAAATCAA	155	717
1367136	152913	152930	N/A	N/A	TGGAATGAGCATGAATTT	55	718
1367138	152939	152956	N/A	N/A	TCTTACAAAGTTTTGAAG	36	719
1367139	152948	152965	N/A	N/A	AATACTACATCTTACAAA	66	720
1367143	152921	152938	N/A	N/A	AGCAAAGTTGGAATGAGC	97	721
1367144	144720	144737	N/A	N/A	CCACCCCATCCAAGTTGG	45	722
1367167	110781	110798	N/A	N/A	AAACACATTTACCTTCCA	46	723
1367169	110821	110838	N/A	N/A	TTAAATGTAAACAGTTTT	61	724
1367173	91138	91155	N/A	N/A	GGTGATGAGAGCAAACT	64	725
1367175	91108	91125	N/A	N/A	AAGAAAAAGAAATATTAG	32	726
1367176	110797	110814	N/A	N/A	AGAAAATTTGAAGACTAA	36	727
1367180	95476	95493	N/A	N/A	ATTGTTAAGGAACACACA	101	728
1367194	152879	152896	N/A	N/A	GCCTGAAAGAGGCTGAAA	58	729
1367198	91214	91231	N/A	N/A	GAGAACAGGAGAATCGCT	45	730
1367204	144692	144709	N/A	N/A	TCCTATACAAAATAGAAA	72	731
1367206	110817	110834	N/A	N/A	ATGTAAACAGTTTTTCAA	18	732
1367207	95448	95465	N/A	N/A	AAAATCCAAGTGTTATAT	107	733
1367209	110785	110802	N/A	N/A	GACTAAACACATTTACCT	97	734
1367211	144680	144697	N/A	N/A	TAGAAATATATAGTTTGT	157	735
1367219	144764	144781	N/A	N/A	AATACAGTACCCATAATA	49	736
1367220	110809	110826	N/A	N/A	AGTTTTTCAAGCAGAAAA	108	737
1367225	152935	152952	N/A	N/A	ACAAAGTTTTGAAGAGCA	82	738
1367227	152859	152876	N/A	N/A	AAATAAAATAGGTTTATA	92	739

Table 10

Effect of modified oligonucleotides on amount of human SCN1A RNA in HepG2 cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN1A (% UTC)	SEQ ID No.
1342103	144725	144742	N/A	N/A	GCGCTCCACCCCATCCAA	101	740
1342104	144761	144778	N/A	N/A	ACAGTACCCATAATAAAG	72	741
1342106	144721	144738	N/A	N/A	TCCACCCCATCCAAGTTG	73	742
1342112	144756	144773	N/A	N/A	ACCCATAATAAAGGGCTC	97	743
1342120	144681	144698	N/A	N/A	ATAGAAATATATAGTTTG	94	744
1342121	144701	144718	N/A	N/A	GCAAGATTATCCTATACA	77	745
1366951	152906	152923	N/A	N/A	AGCATGAATTTTCAGTTTA	78	746
1366956	95421	95438	N/A	N/A	CTAACATTGAAAAGCCCA	218	747
1366960	95461	95478	N/A	N/A	ACAAAAGAAAATCAAAAT	187	748
1366979	110774	110791	N/A	N/A	TTTACCTTCCAATATGCT	33	749
1366986	144765	144782	N/A	N/A	TAATACAGTACCCATAAT	50	750
1366987	95449	95466	N/A	N/A	CAAAATCCAAGTGTATA	73	751
1366989	110814	110831	N/A	N/A	TAAACAGTTTTTCAAGCA	71	752
1366993	152918	152935	N/A	N/A	AAAGTTGGAATGAGCATG	109	753
1366994	95441	95458	N/A	N/A	AAGTGTTATATTACAAAA	81	754
1366998	152927	152944	N/A	N/A	TTGAAGAGCAAAGTTGGA	61	755
1367006	95453	95470	N/A	N/A	AAATCAAAATCCAAGTGT	54	756
1367009	152949	152966	N/A	N/A	AAATACTACATCTTACAA	23	757
1367012	110802	110819	N/A	N/A	CAAGCAGAAAATTTGAAG	80	758
1367013	110786	110803	N/A	N/A	AGACTAAACACATTTACC	61	759
1367019	144757	144774	N/A	N/A	TACCCATAATAAAGGGCT	70	760
1367027	152910	152927	N/A	N/A	AATGAGCATGAATTTTCAG	74	761
1367028	91250	91267	N/A	N/A	TCCCTGTAATCCCAGTTG	61	762
1367030	95457	95474	N/A	N/A	AAGAAAATCAAAATCCAA	76	763
1367041	110778	110795	N/A	N/A	CACATTTACCTTCCAATA	50	764
1367046	152889	152906	N/A	N/A	AGGTCTTGAGCCTGAAA	55	765
1367051	110830	110847	N/A	N/A	TATACACAATTAAATGTA	74	766
1367052	144685	144702	N/A	N/A	CAAAATAGAAATATATAG	126	767
1367055	91219	91236	N/A	N/A	GGCAGGAGAACAGGAGAA	89	768
1367062	152940	152957	N/A	N/A	ATCTTACAAAGTTTTGAA	67	769
1367063	144689	144706	N/A	N/A	TATACAAAATAGAAATAT	78	770
1367064	110806	110823	N/A	N/A	TTTTCAAGCAGAAAATTT	65	771
1367065	95433	95450	N/A	N/A	TATTACAAAAAGCTAACA	56	772
1367067	110826	110843	N/A	N/A	CACAATTAAATGTAAACA	68	773
1367070	152914	152931	N/A	N/A	TTGGAATGAGCATGAATT	71	774

1367074	152870	152887	N/A	N/A	AGGCTGAAATCAAATAAA	70	775
1367077	152880	152897	N/A	N/A	AGCCTGAAAGAGGCTGAA	58	776
1367086	110782	110799	N/A	N/A	TAAACACATTTACCTTCC	129	777
1367092	144709	144726	N/A	N/A	AAGTTGGAGCAAGATTAT	229	778
1367094	110794	110811	N/A	N/A	AAATTTGAAGACTAAACA	54	779
1367095	152884	152901	N/A	N/A	TTGGAGCCTGAAAGAGGC	126	780
1367106	152958	152975	N/A	N/A	GTTGATAGAAAATACTAC	63	781
1367111	95477	95494	N/A	N/A	TATTGTTAAGGAACACAC	80	782
1367112	91143	91160	N/A	N/A	GCCTGGGTGATGAGAGCA	45	783
1367118	152894	152911	N/A	N/A	AGTTTAGGTCTTGGAGCC	146	784
1367130	91215	91232	N/A	N/A	GGAGAACAGGAGAATCGC	53	785
1367134	95429	95446	N/A	N/A	ACAAAAAGCTAACATTGA	357	786
1367142	95445	95462	N/A	N/A	ATCCAAGTGTTATATTAC	87	787
1367148	152962	152979	N/A	N/A	GAAGGTTGATAGAAAATA	172	788
1367149	95473	95490	N/A	N/A	GTTAAGGAACACACAAAA	48	789
1367154	152936	152953	N/A	N/A	TACAAAGTTTTGAAGAGC	37	790
1367156	152953	152970	N/A	N/A	TAGAAAATACTACATCTT	33	791
1367158	110822	110839	N/A	N/A	ATTAAATGTAAACAGTTT	54	792
1367159	95469	95486	N/A	N/A	AGGAACACACAAAAGAAA	48	793
1367160	152931	152948	N/A	N/A	AGTTTTGAAGAGCAAAGT	86	794
1367168	144693	144710	N/A	N/A	ATCCTATACAAAATAGAA	67	795
1367170	91139	91156	N/A	N/A	GGGTGATGAGAGCAAAAC	37	796
1367178	95465	95482	N/A	N/A	ACACACAAAAGAAAATCA	39	797
1367181	110810	110827	N/A	N/A	CAGTTTTTCAAGCAGAAA	72	798
1367183	152875	152892	N/A	N/A	GAAAGAGGCTGAAATCAA	49	799
1367186	144697	144714	N/A	N/A	GATTATCCTATACAAAAT	77	800
1367190	152866	152883	N/A	N/A	TGAAATCAAATAAAATAG	38	801
1367199	110818	110835	N/A	N/A	AATGTAAACAGTTTTTCA	118	802
1367201	152898	152915	N/A	N/A	TTTCAGTTTAGGTCTTGG	65	803
1367202	91135	91152	N/A	N/A	GATGAGAGCAAAACTCCA	104	804
1367213	110798	110815	N/A	N/A	CAGAAAATTTGAAGACTA	65	805
1367217	152902	152919	N/A	N/A	TGAATTTCAAGTTTAGGTC	53	806
1367224	110790	110807	N/A	N/A	TTGAAGACTAAACACATT	50	807
1367226	95481	95498	N/A	N/A	AGGTTATTGTTAAGGAAC	123	808
1367230	152922	152939	N/A	N/A	GAGCAAAGTTGGAATGAG	72	809
1367234	95437	95454	N/A	N/A	GTTATATTACAAAAGCT	80	810
1367235	95425	95442	N/A	N/A	AAAGCTAACATTGAAAAG	79	811
1367237	152945	152962	N/A	N/A	ACTACATCTTACAAAGTT	92	812
1367238	152860	152877	N/A	N/A	CAAATAAAATAGGTTTAT	105	813
1367239	144713	144730	N/A	N/A	ATCCAAGTTGGAGCAAGA	112	814
1367241	144717	144734	N/A	N/A	CCCCATCCAAGTTGGAGC	212	815
1367242	144705	144722	N/A	N/A	TGGAGCAAGATTATCCTA	147	816

Table 11

Effect of modified oligonucleotides on amount of human SCN1A RNA in HepG2 cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN1A (% UTC)	SEQ ID No.
1342083	144866	144883	N/A	N/A	GTATTTTCCCTACTGTGG	43	817
1342084	144871	144888	N/A	N/A	ATAATGTATTTTCCCTAC	261	818
1342085	144886	144903	N/A	N/A	GGGATTAGGATGTAAATA	105	819
1342086	144920	144937	N/A	N/A	TTTTTCAAATGAAATTTA	100	820
1342087	144861	144878	N/A	N/A	TTCCCTACTGTGGTGCAA	44	821
1342088	144876	144893	N/A	N/A	TGTAAATAATGTATTTTC	71	822
1342089	144911	144928	N/A	N/A	TGAAATTTAAGACAATTG	51	823
1342090	144881	144898	N/A	N/A	TAGGATGTAAATAATGTA	96	824
1342091	144902	144919	N/A	N/A	AGACAATTGAAAAGAGGG	91	825
1342092	144916	144933	N/A	N/A	TCAAATGAAATTTAAGAC	68	826
1342093	144906	144923	N/A	N/A	TTTAAGACAATTGAAAAG	94	827
1342094	144821	144838	N/A	N/A	TCCCTCACCCCACTACAC	80	828
1342095	144791	144808	N/A	N/A	GCAAGGATTAAAGGTAGC	83	829
1342096	144816	144833	N/A	N/A	CACCCCACTACACATAAG	58	830
1342097	144784	144801	N/A	N/A	TTAAAGGTAGCAAAAGGG	101	831
1342098	144796	144813	N/A	N/A	ACAGTGCAAGGATTAAAG	120	832
1342099	144801	144818	N/A	N/A	AAGTCACAGTGCAAGGAT	8	833
1342100	144806	144823	N/A	N/A	CACATAAGTCACAGTGCA	49	834
1342101	144786	144803	N/A	N/A	GATTAAAGGTAGCAAAAG	88	835
1342102	144811	144828	N/A	N/A	CACTACACATAAGTCACA	82	836
1342103	144725	144742	N/A	N/A	GCGCTCCACCCCATCCAA	107	740
1342104	144761	144778	N/A	N/A	ACAGTACCCATAATAAAG	55	741
1342105	144706	144723	N/A	N/A	TTGGAGCAAGATTATCCT	88	510
1342106	144721	144738	N/A	N/A	TCCACCCCATCCAAGTTG	71	742
1342107	144766	144783	N/A	N/A	GTAATACAGTACCCATAA	102	511
1342108	144716	144733	N/A	N/A	CCCATCCAAGTTGGAGCA	70	664
1342109	144753	144770	N/A	N/A	CATAATAAAGGGCTCAGG	89	512
1342110	144711	144728	N/A	N/A	CCAAGTTGGAGCAAGATT	97	587
1342111	144768	144785	N/A	N/A	GGGTAATACAGTACCCAT	51	665
1342112	144756	144773	N/A	N/A	ACCCATAATAAAGGGCTC	84	743
1342113	144666	144683	N/A	N/A	TTGTTATTAGTTAGAAAT	106	837
1342114	144661	144678	N/A	N/A	ATTAGTTAGAAATCTGAT	88	838
1342115	144691	144708	N/A	N/A	CCTATACAAAATAGAAAT	97	588
1342116	144676	144693	N/A	N/A	AATATATAGTTTGTATT	68	839
1342117	144671	144688	N/A	N/A	ATAGTTTGTATTAGTTA	94	840

1342118	144686	144703	N/A	N/A	ACAAAATAGAAATATATA	117	513
1342119	144656	144673	N/A	N/A	TTAGAAATCTGATATGAC	97	841
1342120	144681	144698	N/A	N/A	ATAGAAATATATAGTTTG	100	744
1342121	144701	144718	N/A	N/A	GCAAGATTATCCTATACA	51	745
1342122	144696	144713	N/A	N/A	ATTATCCTATACAAAATA	70	666
1342123	144646	144663	N/A	N/A	GATATGACAGAACATTTG	74	842
1342124	144615	144632	N/A	N/A	TTCATGATGCTCTCCGTC	67	843
1342125	144613	144630	N/A	N/A	CATGATGCTCTCCGCTCG	50	844
1342126	144617	144634	N/A	N/A	TGTTTCATGATGCTCTCCG	68	845
1342127	144619	144636	N/A	N/A	TTTGTTTCATGATGCTCTC	65	846
1342128	144633	144650	N/A	N/A	ATTTGGTGTTACTTTTTG	67	847
1342129	144621	144638	N/A	N/A	TTTTTGTTTCATGATGCTC	34	848
1342130	144636	144653	N/A	N/A	AACATTTGGTGTTACTTT	82	849
1342131	144641	144658	N/A	N/A	GACAGAACATTTGGTGTT	57	850
1342132	144651	144668	N/A	N/A	AATCTGATATGACAGAAC	58	851
1342133	144609	144626	N/A	N/A	ATGCTCTCCGTCTGTTTC	70	852
1342134	144571	144588	N/A	N/A	TTCTTTTGAAAAAGAAGG	107	853
1342135	144591	144608	N/A	N/A	CCTATCCATTAAGACTTG	56	854
1342136	144606	144623	N/A	N/A	CTCTCCGTCTGTTTCCCT	103	855
1342137	144581	144598	N/A	N/A	AAGACTTGAGTTCTTTTG	51	856
1342138	144601	144618	N/A	N/A	CGTCTGTTTCCCTATCCA	101	857
1342139	144586	144603	N/A	N/A	CCATTAAGACTTGAGTTC	40	858
1342140	144596	144613	N/A	N/A	GTTTCCCTATCCATTAAG	68	859
1342141	144576	144593	N/A	N/A	TTGAGTTCTTTTGAAAAA	98	860
1342142	144611	144628	N/A	N/A	TGATGCTCTCCGTCTGTT	35	861
1342143	144856	144873	N/A	N/A	TACTGTGGTGCAATAATA	69	862
1342144	144536	144553	N/A	N/A	GTTAGGAAATTAAAAATA	94	863
1342145	144556	144573	N/A	N/A	AGGTATTTAAGATTCCT	56	864
1342146	144848	144865	N/A	N/A	TGCAATAATAGTACCCTT	72	865
1342147	144546	144563	N/A	N/A	GATTTCCCTAGGTTAGGAA	62	866
1342148	144561	144578	N/A	N/A	AAAGAAGGTATTTAAGAT	79	867
1342149	144851	144868	N/A	N/A	TGGTGCAATAATAGTACC	80	868
1342150	144541	144558	N/A	N/A	CCTAGGTTAGGAAATTAA	79	869
1342151	144551	144568	N/A	N/A	TTTAAGATTTCCCTAGGTT	56	870
1342152	144566	144583	N/A	N/A	TTGAAAAAGAAGGTATTT	60	871
1342153	144836	144853	N/A	N/A	ACCCTTCCCAATCCCTCC	63	872
1342154	144840	144857	N/A	N/A	TAGTACCCTTCCCAATCC	75	873
1342155	144844	144861	N/A	N/A	ATAATAGTACCCTTCCCA	34	874
1342156	144846	144863	N/A	N/A	CAATAATAGTACCCTTCC	45	875
1342157	144831	144848	N/A	N/A	TCCCAATCCCTCCCTCAC	65	876
1342158	144826	144843	N/A	N/A	ATCCCTCCCTCACCCAC	63	877
1342159	144838	144855	N/A	N/A	GTACCCTTCCCAATCCCT	43	878
1342160	144842	144859	N/A	N/A	AATAGTACCCTTCCCAAT	139	879

Example 3: Activity of human-mouse cross-reactive modified oligonucleotides against mouse SCN1A in primary mouse cerebral neuron cells, single dose, *in vitro*

Certain modified oligonucleotides described above were tested for their effect on mouse SCN1A RNA levels *in vitro*.

The modified oligonucleotides in the tables below are 18 nucleosides in length. Each nucleoside comprises a 2'-MOE sugar moiety. The internucleoside linkages throughout each modified oligonucleotide are phosphorothioate internucleoside linkages. All cytosine nucleobases throughout each modified oligonucleotide are 5-methylcytosines.

"Start site" indicates the 5'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. "Stop site" indicates the 3'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. As shown in the tables below, the modified oligonucleotides are complementary to the human SCN1A genomic sequence, designated herein as SEQ ID NO: 1 (the complement of GENBANK Accession No. NC_000002.12 truncated from nucleotides 165982001 to 166152000) and the mouse SCN1A genomic sequence, designated herein as SEQ ID NO: 3 (the complement of GENBANK Accession No. NC_000068.7 truncated from nucleotides 66268001 to 66444000).

Cultured primary mouse cerebral neuron cells at a density of 60,000 cells per well were treated by free uptake with 8000 nM of modified oligonucleotide. After a treatment period of approximately 3 days, RNA was isolated from the cells and the amount of SCN1A RNA that excludes the mouse form of NIE-1 (NIE-1⁻), and the amount of SCN1A RNA that includes the mouse form of NIE-1 (NIE-1⁺) were measured by quantitative real-time RTPCR. Mouse primer probe set RTS48951 (forward sequence CCCTAAGAGCCTTATCACGATTT, designated herein as SEQ ID NO: 24; reverse sequence GGCAAACCAGAAGCACATTC, designated herein as SEQ ID NO: 25; probe sequence AGGGTGGTTGTGAATGCCCTGTTA, designated herein as SEQ ID NO: 26) was used to measure the amount of SCN1A transcript that excludes the mouse form of NIE-1 (NIE-1⁻). Mouse primer probe set RTS48949 (forward sequence AGCCCTTTATTATGGGTGGTT, designated herein as SEQ ID NO: 21; reverse sequence CCAGAATATAAGGCAAACCAGAAG, designated herein as SEQ ID NO: 22; probe sequence TGGATGGAATTGCTCCTAACAGGGC, designated herein as SEQ ID NO: 23) was used to measure the amount of SCN1A transcript that includes the mouse form of NIE-1 (NIE-1⁺). SCN1A RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. SCN1A NIE-1⁻ RNA and NIE-1⁺ RNA are presented as % of the average of untreated control (%UTC). Values marked with a "‡" result from oligonucleotides that are complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of the modified oligonucleotides complementary to the amplicon region.

As shown in the tables below, certain modified oligonucleotides complementary to a SCN1A nucleic acid increased the amount of SCN1A RNA that excludes the mouse form of NIE-1 (NIE-1⁻) and reduced the amount of SCN1A RNA that includes the mouse form of NIE-1 (NIE-1⁺), compared to untreated control.

Table 12

5 Effect of modified oligonucleotides on the amount of mouse SCN1A RNA excluding NIE-1 (NIE-1⁻) and the amount of mouse SCN1A RNA including NIE-1 (NIE-1⁺) in primary mouse cerebral neuron cells

Compound Number	SEQ ID NO: 1 Start Site Human	SEQ ID NO: 1 Stop Site Human	SEQ ID NO: 3 Start Site Mouse	SEQ ID NO: 3 Stop Site Mouse	Sequence (5' to 3')	SCN1A (% UTC) RTS48949 NIE-1 ⁺	SCN1A (% UTC) RTS48951 NIE-1 ⁻	SEQ ID No.
1342097	144784	144801	150182	150199	TTAAAGGTAGCAAAAGGG	96	69	831
1342104	144761	144778	150159	150176	ACAGTACCCATAATAAAG	68†	248	741
1342105	144706	144723	150104	150121	TTGGAGCAAGATTATCCT	30	549	510
1342106	144721	144738	150119	150136	TCCACCCCATCCAAGTTG	111	155	742
1342107	144766	144783	150164	150181	GTAATACAGTACCCATAA	55†	346	511
1342108	144716	144733	150114	150131	CCCATCCAAGTTGGAGCA	46	349	664
1342110	144711	144728	150109	150126	CCAAGTTGGAGCAAGATT	15	647	587
1342111	144768	144785	150166	150183	GGGTAATACAGTACCCAT	104†	107	665
1366954	144703	144720	150101	150118	GAGCAAGATTATCCTATA	16	644	590
1366958	144722	144739	150120	150137	CTCCACCCCATCCAAGTT	113	122	515
1366971	144762	144779	150160	150177	TACAGTACCCATAATAAA	72†	465	519
1366982	144710	144727	150108	150125	CAAGTTGGAGCAAGATTA	9	696	523
1366986	144765	144782	150163	150180	TAATACAGTACCCATAAT	52†	333	750
1367004	144682	144699	150080	150097	AATAGAAATATATAGTTT	60	264	529
1367019	144757	144774	150155	150172	TACCCATAATAAAGGGCT	54†	125	760
1367043	144712	144729	150110	150127	TCCAAGTTGGAGCAAGAT	54	450	692
1367047	144758	144775	150156	150173	GTACCCATAATAAAGGGC	86†	146	539
1367071	144760	144777	150158	150175	CAGTACCCATAATAAAGG	67†	224	694
1367076	144704	144721	150102	150119	GGAGCAAGATTATCCTAT	29	510	696
1367089	144684	144701	150082	150099	AAAATAGAAATATATAGT	83	180	703
1367092	144709	144726	150107	150124	AAGTTGGAGCAAGATTAT	14	642	778
1367098	144714	144731	150112	150129	CATCCAAGTTGGAGCAAG	41	421	550
1367121	144719	144736	150117	150134	CACCCCATCCAAGTTGGA	110	215	628
1367131	144724	144741	150122	150139	CGCTCCACCCCATCCAAG	82	86	716
1367135	144759	144776	150157	150174	AGTACCCATAATAAAGGG	67†	214	634
1367144	144720	144737	150118	150135	CCACCCCATCCAAGTTGG	81	182	722
1367155	144723	144740	150121	150138	GCTCCACCCCATCCAAGT	128	102	637
1367174	144763	144780	150161	150178	ATACAGTACCCATAATAA	57†	395	642
1367182	144715	144732	150113	150130	CCATCCAAGTTGGAGCAA	44	431	645
1367184	144767	144784	150165	150182	GGTAATACAGTACCCATA	85†	210	646
1367189	144718	144735	150116	150133	ACCCCATCCAAGTTGGAG	117	185	575

1367218	144707	144724	150105	150122	GTTGGAGCAAGATTATCC	9	727†	655
1367219	144764	144781	150162	150179	AATACAGTACCCATAATA	97†	511	736
1367221	144683	144700	150081	150098	AAATAGAAATATATAGTT	74	294	656
1367239	144713	144730	150111	150128	ATCCAAGTTGGAGCAAGA	37	514	814
1367241	144717	144734	150115	150132	CCCCATCCAAGTTGGAGC	99	184	815
1367242	144705	144722	150103	150120	TGGAGCAAGATTATCCTA	72	430	816
1369834	144772	144789	150170	150187	AAAGGGGTAATACAGTAC	47	324	880
1369835	144779	144796	150177	150194	GGTAGCAAAAGGGGTAAT	24	463	881
1369836	144774	144791	150172	150189	CAAAAGGGGTAATACAGT	44	448	882
1369838	144771	144788	150169	150186	AAGGGGTAATACAGTACC	69†	283	883
1369840	144781	144798	150179	150196	AAGGTAGCAAAAGGGGTA	102	64	884
1369841	144776	144793	150174	150191	AGCAAAAGGGGTAATACA	19	579	885
1369851	144770	144787	150168	150185	AGGGGTAATACAGTACCC	90†	148	886
1369854	144769	144786	150167	150184	GGGGTAATACAGTACCCA	97†	137	887
1369856	144775	144792	150173	150190	GCAAAAGGGGTAATACAG	48	317	888
1369870	144782	144799	150180	150197	AAAGGTAGCAAAAGGGGT	63	53	889

Example 4: Activity of modified oligonucleotides targeting human SCN1A in HepG2 cells, multiple dose, *in vitro*

Certain modified oligonucleotides described in the studies above were selected and tested at various doses in HepG2 cells.

The modified oligonucleotides were tested in a series of experiments using the same culture conditions. The results for each experiment are presented in separate tables shown below. Cultured HepG2 cells at a density of 20,000 cells per well were transfected using electroporation with modified oligonucleotides diluted to different concentrations as specified in the tables below. After a treatment period of approximately 24 hours, full-length SCN1A RNA levels were measured as previously described using the human RTS48189 primer-probe set. Full-length SCN1A RNA levels were normalized to total RNA, as measured by RIBOGREEN®. Full-length SCN1A RNA is presented as % of the average of untreated control (%UTC). Also provided is the fold increase of full-length SCN1A RNA over the untreated control (fold increase over UTC) at the 20µM dose. As shown in the tables below, certain modified oligonucleotides complementary to SCN1A RNA increased the amount of human full-length SCN1A RNA, compared to untreated control.

Table 13

Effect of modified oligonucleotides on the amount of human full-length SCN1A RNA in HepG2 cells, multiple dose

Compound No.	%UTC				Fold increase over
	312.5 nM	1250 nM	5000 nM	20000 nM	

					UTC @20μM
1342118	78	88	96	73	0.7
1367236	148	91	105	147	1.5
1367011	100	85	85	89	0.9
1366977	81	64	19	41	0.4
1367098	138	80	96	117	1.2
1367121	66	79	95	64	0.6
1367163	81	138	61	115	1.2
1367214	104	81	69	48	0.5
1366982	116	128	142	137	1.4
1367155	89	67	144	126	1.3
1367182	114	80	64	38	0.4
1366952	86	88	66	114	1.1
1367014	80	63	85	49	0.5
1367184	104	71	67	45	0.4
1367240	86	90	95	124	1.2
1366980	78	55	79	73	0.7
1367134	124	58	78	73	0.7
1367147	140	110	123	207	2.1
1367232	121	84	116	72	0.7

Table 14

Effect of modified oligonucleotides on the amount of human full-length SCN1A RNA in HepG2 cells,
multiple dose

Compound No.	%UTC				Fold increase over UTC @20μM
	312.5 nM	1250 nM	5000 nM	20000 nM	
1367020	63	108	64	92	0.9
1366961	98	76	64	62	0.6
1367059	73	138	110	169	1.7
1367040	56	41	53	76	0.8
1367135	110	130	120	136	1.4
1366962	65	99	79	147	1.5
1367107	93	103	93	153	1.5
1367119	101	99	89	86	0.9
1367131	84	167	106	178	1.8
1367032	56	55	103	67	0.7
1366960	89	105	74	38	0.4
1367211	100	113	118	131	1.3

1367092	87	83	179	95	0.9
1367148	86	116	81	44	0.4
1367132	107	117	75	142	1.4
1366956	80	87	58	63	0.6
1367134	89	106	89	83	0.8
1367241	104	110	73	86	0.9

Table 15

Effect of modified oligonucleotides on the amount of human full-length SCN1A RNA expression in HepG2 cells, multiple dose

Compound No.	%UTC				Fold increase over UTC @20 μ M
	312.5 nM	1250 nM	5000 nM	20000 nM	
1367242	197	189	403	388	3.9
1366993	59	78	77	63	0.6
1367118	63	79	65	80	0.8
1367238	77	81	84	65	0.7
1367086	95	65	69	111	1.1
1366994	100	65	69	52	0.5
1367095	113	155	153	170	1.7
1342084	133	100	132	207	2.1
1367052	108	113	118	114	1.1
1342160	103	119	112	66	0.7
1342120	85	79	78	103	1.0
1367226	70	82	125	66	0.7
1342098	92	63	95	78	0.8
1342141	46	76	61	49	0.5
1367199	81	109	133	136	1.4
1342118	120	99	93	95	0.9
1367134	70	61	62	124	1.2
1367239	122	109	105	180	1.8
1342103	115	110	94	90	0.9

Example 5: Activity of human-mouse cross-reactive modified oligonucleotides against mouse SCN1A in primary mouse cerebral neuron cells, multiple dose, *in vitro*

Certain modified oligonucleotides described in the studies above were tested at various doses in primary mouse cerebral neuron cells. The modified oligonucleotides were tested in a series of experiments using the same culture conditions.

Cultured primary mouse cerebral neuron cells at a density of 60,000 cells per well were treated by free uptake with modified oligonucleotides diluted to different concentrations as specified in the tables below. After a treatment period of approximately 3 days, mouse primer probe set RTS48951 (described herein above) was used to measure the amount of mouse SCN1A RNA that excludes NIE-1 (NIE-1⁻), and mouse primer probe set RTS48949 (described herein above) was used to measure the amount of mouse SCN1A RNA that includes NIE-1 (NIE-1⁺). SCN1A RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. SCN1A RNA is presented as % of the average of untreated control (%UTC). Values marked with a “†” result from oligonucleotides that are complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of the modified oligonucleotides complementary to the amplicon region. Also provided is the fold increase of (NIE-1⁻)SCN1A RNA over the untreated control (fold increase over UTC) at the 8μM dose. The half maximal inhibitory concentration (IC₅₀) was calculated using a linear regression on a log/linear plot of the data in Excel; an IC₅₀ of >8μM in the tables below indicates that the value was not calculatable.

As shown in the tables below, certain modified oligonucleotides complementary to a SCN1A nucleic acid increased the amount of SCN1A RNA that excludes the mouse form of NIE-1 (NIE-1⁻) and reduced the amount of SCN1A RNA that includes the mouse form of NIE-1 (NIE-1⁺), compared to untreated control.

Table 16

Effect of modified oligonucleotides on the amount of mouse SCN1A RNA excluding NIE-1 (NIE-1⁻) and the amount of SCN1A RNA including (NIE-1⁺) in primary mouse cerebral neuron cells, multiple doses

Compound No.	NIE-1 ⁺					NIE-1 ⁻				
	%UTC				IC ₅₀	%UTC				Fold increase over UTC
	64 nM	320 nM	1600 nM	8000 nM	μM	64 nM	320 nM	1600 nM	8000 nM	8μM
1369834	149	143	126	80	> 8.0	137	162	292	817	8.2
1367174	111†	102†	87†	62†	> 8.0	145	208	344	1059	10.6
1369856	133	142	100	55	> 8.0	149	171	322	968	9.7
1366971	100†	102†	92†	76†	> 8.0	124	170	305	849	8.5
1366986	89†	77†	75†	56†	> 8.0	98	121	250	584	5.8

1342107	79†	76†	74†	44†	> 8.0	122	152	295	805	8.0
1367242	97	80	70	39	4.7	119	169	397	885	8.8
1367219	79†	73†	71†	51†	> 8.0	139	178	353	692	6.9
1367004	81	86	81	75	> 8.0	94	107	181	487	4.9
1369838	149†	130†	130†	80†	> 8.0	127	153	254	409	4.1
1367221	96	103	111	74	> 8.0	94	113	168	444	4.4
1342104	103†	98†	97†	76†	> 8.0	125	126	172	378	3.8
1367071	123†	126†	120†	81†	> 8.0	125	119	174	340	3.4
1367135	140†	115†	88†	93†	> 8.0	94	117	160	321	3.2

Table 17

Effect of modified oligonucleotides on amount of mouse SCN1A RNA including (NIE-1⁺) or excluding NIE-1 (NIE-1⁻) in primary mouse cerebral neuron cells, multiple doses

Compound No.	NIE-1 ⁺					NIE-1 ⁻				
	%UTC				IC ₅₀	%UTC				Fold increase over UTC
	64 nM	320 nM	1600 nM	8000 nM	μM	64 nM	320 nM	1600 nM	8000 nM	8μM
1367218	56	39	22	3	0.1	252	346	634	1084	10.8
1366982	59	41	14	3	0.1	241	336	737	1089	10.9
1367092	60	46	20	2	0.2	225	280	619	1044	10.4
1342110	62	42	16	6	0.2	151	246	366	797	8.0
1366954	51	36	14	4	0.1	170	248	517	770	7.7
1369841	145	110	56	10	2.1	180	233	622	801	8.0
1369835	129	62	43	15	1.2	164	197	447	578	5.8
1342105	81	62	46	13	0.8	143	187	346	683	6.8
1367076	88	72	65	15	1.5	138	184	419	721	7.2
1367239	86	84	63	18	1.8	100	185	427	565	5.7
1367098	92	109	69	31	4.3	80	111	239	477	4.8
1369836	120	97	65	14	2.2	101	95	223	426	4.3
1367182	132	103	81	38	5.4	103	130	254	415	4.1
1367043	108	83	93	39	> 8.0	129	187	352	559	5.6
1342108	136	88	85	45	6.9	99	95	188	351	3.5

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Example 6: Activity of modified oligonucleotides targeting SCN1A in wildtype mice

Wildtype C57BL/6 mice were divided into groups of 4 mice each. Each mouse received a single ICV bolus of Compound No. 1429226 or comparator compound 1367010 at the dose indicated in the tables below. A group of 4 mice received PBS as a negative control.

10 Compound No. 1429226, described hereinabove, is a modified oligonucleotide having a nucleobase sequence of (from 5' to 3') AGTTGGAGCAAGATTATC (SEQ ID NO: 41), wherein each nucleoside

comprises a 2'-NMA sugar moiety, each internucleoside linkage is a phosphorothioate internucleoside linkage, and each cytosine is a 5-methyl cytosine. Comparator compound 1367010, previously described in WO 2019/040923 (incorporated herein by reference) as Compound Ex 20X+1 has a nucleobase sequence of (from 5' to 3') AGTTGGAGCAAGATTATC (SEQ ID NO: 41), wherein each nucleoside comprises a 2'-

5 MOE sugar moiety and each internucleoside linkage is a phosphorothioate internucleoside linkage. SEQ ID NO:41 is 100% complementary to SEQ ID NO: 1, from Start Site 144708 to Stop Site 144725, and is 100% complementary to SEQ ID NO: 3 from Start Site 150106 to Stop Site 150123. "Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is complementary in the

10 target nucleic acid sequence.

Three weeks post treatment mice were sacrificed and RNA was extracted from cortical brain tissue and spinal cord for real-time qPCR analysis of SCN1A RNA using primer probe set RTS48951 (described herein above) to measure the amount of SCN1A RNA that excludes the mouse form of NIE-1 (NIE-1⁻) and primer probe set RTS48949 (described herein above) to measure the amount of SCN1A RNA that includes

15 the mouse form of NIE-1 (NIE-1⁺). SCN1A RNA is presented as % of the average of untreated control (%UTC), normalized to mouse GAPDH. Mouse GAPDH was amplified using primer probe set mGapdh_LTS00102 (forward sequence GGCAAATTCAACGGCACAGT, designated herein as SEQ ID NO: 36; reverse sequence GGGTCTCGCTCCTGGAAGAT, designated herein as SEQ ID NO: 37; probe sequence AAGGCCGAGAATGGGAAGCTTGTCATC, designated herein as SEQ ID NO: 38). Each of

20 Tables 18 and 19 represents a different experiment.

As shown in the tables below, Compound No. 1429226 is more potent than comparator compound 1367010 in this assay.

Table 18

Effect of modified oligonucleotides on the amount of mouse SCN1A excluding NIE-1 (NIE-1⁻) and the

25 amount of mouse SCN1A RNA including (NIE-1⁺) in wildtype mice, multiple doses

Compound No.	Dose (μg)	SPINAL CORD			CORTEX		
		NIE-1 ⁻	NIE-1 ⁺		NIE-1 ⁻	NIE-1 ⁺	
		%UTC	%UTC	ED ₅₀ (μg)	%UTC	%UTC	ED ₅₀ (μg)
1367010	1	82	88	50	111	94	78
	3	93	91		109	96	
	10	98	76		103	95	
	30	90	64		119	84	
	100	103	33		149	38	
	300	104	23		176	13	
	700	108	18		173	3	

Table 19

Effect of modified oligonucleotides on amount of mouse SCN1A excluding NIE-1⁻ (NIE-1⁻) and the amount of mouse SCN1A RNA including (NIE-1⁺) in wildtype mice, multiple doses

5

Compound No.	Dose (μg)	SPINAL CORD			CORTEX		
		NIE-1 ⁻	NIE-1 ⁺		NIE-1 ⁻	NIE-1 ⁺	
		%UTC	%UTC	ED ₅₀ (μg)	%UTC	%UTC	ED ₅₀ (μg)
1429226	1	100	106	14	100	96	21
	3	109	106		123	75	
	10	95	38		109	69	
	30	106	38		162	43	
	100	105	17		164	11	
	300	104	7		162	2	
	700	117	7		172	1	

Example 7: Tolerability of modified oligonucleotides complementary to SCN1A in wild-type mice

Compound No. 1429226 and comparator compound 1367010, both described hereinabove, were tested in wild-type female C57/Bl6 mice to assess the tolerability of the oligonucleotides. Wild-type female C57/Bl6 mice each received a single ICV dose of either 500 μg or 700 μg of modified oligonucleotide, indicated as Dose (μg) in the tables below. Each treatment group consisted of 4 mice. A group of 4 mice received PBS as a negative control for each experiment (identified in separate tables below). At 3 hours post-injection, mice were evaluated according to seven different criteria. The criteria are (1) the mouse was bright, alert, and responsive; (2) the mouse was standing or hunched without stimuli; (3) the mouse showed any movement without stimuli; (4) the mouse demonstrated forward movement after it was lifted; (5) the mouse demonstrated any movement after it was lifted; (6) the mouse responded to tail pinching; (7) regular breathing. For each of the 7 criteria, a mouse was given a subscore of 0 if it met the criteria and 1 if it did not (the functional observational battery score or FOB). After all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. Each of Tables 20-22 represents a different experiment.

As shown in the tables below, Compound No. 1429226 is more tolerable than comparator compound 1367010 in this assay.

Table 20

Tolerability scores in mice

Compound No.	Dose (μg)	FOB 3 hour
PBS	N/A	0
1367010	500	5.75

Table 21

Tolerability scores in mice

Compound No.	Dose (μg)	FOB 3 hour
PBS	N/A	0
1367010	700	7

Table 22

Tolerability scores in mice

Compound No.	Dose (μg)	FOB 3 hour
PBS	N/A	0
1429226	500	4
1429226	700	4

10 Example 8: Design of modified oligonucleotides complementary to a human SCN1A nucleic acid

Modified oligonucleotides complementary to a human SCN1A nucleic acid are designed and synthesized as indicated in Table 23 below.

The modified oligonucleotides in Table 23 are 18, 19, or 20 nucleosides in length, as specified. The modified oligonucleotides comprise 2'-MOE sugar moieties, as specified. The sugar motif for each modified oligonucleotide is provided in the Sugar Motif column, wherein each 'e' represents a 2'-MOE sugar moiety. The internucleoside linkage motif for each modified oligonucleotide is provided in the Internucleoside Linkage Motif column, wherein each 's' represents a phosphorothioate internucleoside linkage, and each 'o' represents a phosphodiester internucleoside linkage. Each cytosine is a 5-methyl cytosine.

Each modified oligonucleotide listed in Table 23 below is 100% complementary to SEQ ID NO: 1 (the complement of GENBANK Accession No. NC_000002.12 truncated from nucleotides 165982001 to 166152000), and to SEQ ID NO: 3 (the complement of GENBANK Accession No. NC_000068.7 truncated from nucleotides 66268001 to 66444000) unless specifically stated otherwise. SEQ ID NO:890 is 100% complementary to SEQ ID NO: 3 from Start Site 150105 to Stop Site 150124. SEQ ID NO:891 is 100%

complementary to SEQ ID NO: 3 from Start Site 150105 to Stop Site 150123. SEQ ID NO:892 is 100% complementary to SEQ ID NO: 3 from Start Site 150106 to Stop Site 150124. “Start site” indicates the 5’-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. “Stop site” indicates the 3’-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence.

Table 23

2’-MOE modified oligonucleotides with mixed PS/PO internucleoside linkages

Compound Number	Nucleobase Sequence (5' to 3')	Sugar Motif (5' to 3')	Internucleoside Linkage Motif (5' to 3')	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No.
1472459	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	soosoooooooooooo	144708	144725	41
1472453	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sosooooooooooooo	144708	144725	41
1472454	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	soosoooooooooooo	144708	144725	41
1472455	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sosooooooooooooo	144708	144725	41
1472460	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sssooooooooooooo	144708	144725	41
1472462	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sssooooooooooooo	144708	144725	41
1472463	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sssooooooooooooo	144708	144725	41
1472464	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sssooooooooooooo	144708	144725	41
1472456	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sooooooooooooooooo	144708	144725	41
1472457	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sooooooooooooooooo	144708	144725	41
1472458	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sooooooooooooooooo	144708	144725	41
1472466	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sooooooooooooooooo	144708	144725	41
1472467	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sooooooooooooooooo	144708	144725	41
1472461	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sssooooooooooooo	144708	144725	41
1472468	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sssooooooooooooo	144708	144725	41
1472472	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sssooooooooooooo	144708	144725	41
1472469	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sssooooooooooooo	144708	144725	41
1472470	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sssooooooooooooo	144708	144725	41
1472473	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sssooooooooooooo	144708	144725	41
1472471	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sssooooooooooooo	144708	144725	41
1472465	AGTTGGAGCAAGATTATC	eeeeeeeeeeeeeeeeee	sssooooooooooooo	144708	144725	41

1472452	AAGTTGGAGCAAGATTAT CC	eeeeeeeeeeeeeeeeeeee	osssssssssssssso	144707	144726	890
1472451	AGTTGGAGCAAGATTATC C	eeeeeeeeeeeeeeeeeeee	ssssssssssssssso	144707	144725	891
1472450	AAGTTGGAGCAAGATTAT C	eeeeeeeeeeeeeeeeeeee	osssssssssssssss	144708	144726	892

Example 9: Activity and tolerability of modified oligonucleotides complementary to human SCN1A in wild-type mice

Treatment

5 Modified oligonucleotides described in Table 23 were tested in wild-type female C57/Bl6 mice to assess the tolerability and activity of the oligonucleotides. Wild-type female C57/Bl6 mice each received a single ICV dose of 700 µg of modified oligonucleotide as listed in the table below. Each treatment group consisted of 3 mice. A group of 4 mice received PBS as a negative control.

Activity

10 Eight weeks post treatment mice were sacrificed and RNA was extracted from cortical brain tissue for quantitative real-time RTPCR analysis of SCN1A RNA using primer probe set RTS48951 (described herein above) to measure the amount of SCN1A RNA that excludes the mouse form of NIE-1 (NIE-1⁻) and primer probe set RTS48949 (described herein above) to measure the amount of SCN1A RNA that includes the mouse form of NIE-1 (NIE-1⁺). SCN1A RNA is presented as % of the average of the PBS control

15 (%control), normalized to mouse GAPDH. Mouse GAPDH was amplified using primer probe set mGapdh_LTS00102 (described herein above). As shown in Table 24 below, the compounds demonstrate activity in this assay.

Table 24

Effect of modified oligonucleotides on amount of mouse SCN1A excluding NIE-1 (NIE-1⁻) and the amount of mouse SCN1A RNA including (NIE-1⁺) in wildtype mice, single dose

Compound No.	CORTEX	
	NIE-1 ⁻	NIE-1 ⁺
	%control	%control
PBS	100	100
1472450	154	8
1472451	169	3
1472452	171	9
1472453	158	2
1472454	139	8
1472455	156	4

1472456	170	4
1472457	178	2
1472458	197	4
1472459	199	12
1472460	178	2
1472461	185	5
1472462	192	6
1472463	197	4
1472464	198	2
1472465	175	4
1472466	162	1
1472467	169	4
1472468	169	2
1472469	148	4
1472470	145	4
1472471	150	3
1472472	150	4
1472473	152	1

Tolerability

At 3 hours post-injection, mice were evaluated according to seven different criteria. The criteria are (1) the mouse was bright, alert, and responsive; (2) the mouse was standing or hunched without stimuli; (3) the mouse showed any movement without stimuli; (4) the mouse demonstrated forward movement after it was lifted; (5) the mouse demonstrated any movement after it was lifted; (6) the mouse responded to tail pinching; (7) regular breathing. For each of the 7 criteria, a mouse was given a subscore of 0 if it met the criteria and 1 if it did not (the functional observational battery score or FOB). After all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. As shown in the data provided in Table 21 above, and Table 25 below, the compounds described in Table 23 are more tolerable than comparator compound 1367010 in this assay.

Table 25

Tolerability scores in mice

Compound No.	FOB 3 hour
PBS	0
1472450	3.33
1472451	3.00
1472452	2.33
1472453	1.00
1472454	2.33

1472455	1.33
1472456	1.00
1472457	2.67
1472458	1.33
1472459	1.67
1472460	1.67
1472461	2.00
1472462	2.67
1472463	2.67
1472464	2.00
1472465	3.67
1472466	2.67
1472467	3.67
1472468	3.33
1472469	2.67
1472470	2.67
1472471	3.00
1472472	2.67
1472473	3.33

Example 10: Tolerability of modified oligonucleotides complementary to human SCN1A in rats, 3 hour study

5 Modified oligonucleotides described in Table 23 above, and comparator compound 1367010, were tested in rats to assess the tolerability of the oligonucleotides. Sprague Dawley rats each received a single intrathecal (IT) dose of 3 mg of oligonucleotide listed in the table below. Each treatment group consisted of 4 rats. A group of 4 rats received PBS as a negative control. At 3 hours post-injection, movement in 7 different parts of the body were evaluated for each rat. The 7 body parts are (1) the rat's tail; (2) the rat's posterior posture; (3) the rat's hind limbs; (4) the rat's hind paws; (5) the rat's forepaws; (6) the rat's anterior posture; (7) the rat's head. For each of the 7 different body parts, each rat was given a sub-score of 0 if the body part was moving or 1 if the body part was paralyzed (the functional observational battery score or FOB). After each of the 7 body parts were evaluated, the sub-scores were summed for each rat and then averaged for each group. For example, if a rat's tail, head, and all other evaluated body parts were moving 3 hours after the 3 mg IT dose, it would get a summed score of 0. If another rat was not moving its tail 3 hours after the 3 mg IT

10

15

dose but all other evaluated body parts were moving, it would receive a score of 1. Results are presented as the average score for each treatment group.

Table 26
Tolerability scores in rats (n=4) at 3 mg dose

Compound No.	3 hr. FOB
PBS	0.00
1367010	6.00

Table 27
Tolerability scores in rats (n=4) at 3 mg dose

Compound No.	3 hr. FOB
PBS	0.00
1472450	1.00
1472451	2.00
1472452	2.75
1472453	2.25
1472454	3.00
1472455	1.50
1472456	2.25
1472457	2.25
1472458	3.00
1472459	2.25
1472460	2.75
1472461	2.25
1472462	2.25
1472463	1.50
1472464	1.25
1472465	2.25
1472466	3.00
1472467	2.25
1472468	4.00
1472469	1.75
1472470	3.00
1472471	2.25
1472472	2.25
1472473	0.00

Example 11: Tolerability of modified oligonucleotides complementary to human SCN1A in rats, long-term assessment

In separate studies run under the same conditions, modified oligonucleotides described in Table 23 and comparator compound 1367010 were tested in Sprague Dawley rats to assess long-term tolerability. Sprague Dawley rats each received a single intrathecal (IT) delivered dose of 3 mg of oligonucleotide or PBS. Beginning 1-week post-treatment, each animal was weighed and evaluated weekly by a trained observer for adverse events. Adverse events are defined as neurological dysfunction not typical in PBS-treated control animals, including, but not limited to: abnormal limb splay, abnormal gait, tremors, abnormal respiration, paralysis, and spasticity. The onset of the adverse event is defined as the week post-dosing when the dysfunction was first recorded. If no adverse event was achieved, there is no onset (-). If the animal died prior to 1-week due to acute toxicity, long term adverse effects could not be verified, and such cases are marked with a 'Ø' symbol. Similar tolerability assessments are described in Ostergaard et al., *Nucleic Acids Res.*, 2013 Nov, 41(21), 9634–9650 and Southwell et al., *Mol Ther.*, 2014 Dec, 22(12), 2093–2106.

At the end of the study, the rats are sacrificed and tissues were collected. Histopathology was performed on sections of cerebellum using calbindin stain. The calbindin stained cerebellum sections were evaluated for Purkinje cell loss. Purkinje cell loss was observed in calbindin stained cerebellum sections as indicated in the table below. Cerebellum and spinal cord were also evaluated using an antibody specific for modified oligonucleotides. Animals demonstrating no oligonucleotide uptake were excluded from histopathology analysis. Histology was not completed for animals that were sacrificed early due to adverse events. In cases where purkinje cell loss could not be evaluated due to death of mice in less than a week post treatment, the values are indicated as 'N/A'. Additionally, cortical GFAP, a marker of astrogliosis (Abdelhak, et al., *Scientific Reports*, 2018, 8, 14798), was measured using RT-PCR, and average elevations >2-fold are noted below. In cases where GFAP levels could not be evaluated due to death of mice in less than a week post treatment, the values are indicated as 'N/A'.

Table 28
Long-term tolerability in rats at 3 mg dose

Compound Number	Adverse event onset, weeks post-treatment, individual animals	Purkinje cell loss (# animals with loss/# animals tested)	Cortex GFAP mRNA >2-fold PBS Control
PBS	-,-,-,-	0/4	100

1367010	Ø, Ø, Ø, Ø	N/A	N/A
1472450	-, -, -, -	0/4	151
1472451	-, 7, -, -	2/4	128
1472452	-, -, 7, -	0/4	112
1472453	-, -, -, -	1/4	100
1472454	-, -, -, -	0/4	136
1472455	-, -, -, -	0/4	116
1472456	-, -, -, 7	0/4	140
1472457	-, -, -, -	0/4	135
1472458	-, -, -, 3	0/4	118
1472459	-, -, -, -	0/4	129
1472460	-, -, -, -	1/4	130
1472461	-, -, -, -	0/4	130
1472462	-, -, -, -	0/4	130
1472463	-, -, -, -	0/4	118
1472464	-, -, -, -	0/4	111
1472465	-, -, -, -	0/4	119
1472466	7, -, 7, 7	1/4	159
1472467	-, -, -, -	0/4	120
1472468	-, -, -	0/3	148
1472469	-, -, -, -	0/4	123
1472470	-, -, -, -	0/4	150
1472471	-, -, -, -	0/4	142
1472472	-, -, -, -	0/4	125
1472473	-, -, -, -	0/4	115

Example 12: Design of modified oligonucleotides complementary to a human SCN1A nucleic acid

Modified oligonucleotides complementary to a human SCN1A nucleic acid were designed and synthesized as indicated in Table 29 below.

The modified oligonucleotides in Table 29 are 18 nucleosides in length. Each nucleoside comprises a 2'-NMA sugar moiety. The internucleoside linkages throughout each modified oligonucleotide are phosphorothioate internucleoside linkages. All cytosine nucleobases throughout each modified oligonucleotide are 5-methylcytosines.

Each modified oligonucleotide listed in Table 29 below is 100% complementary to SEQ ID NO: 1 (the complement of GENBANK Accession No. NC_000002.12 truncated from nucleotides 165982001 to 166152000). "Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence.

Table 29

2'-NMA modified oligonucleotides with uniform phosphorothioate internucleoside linkages

Compound Number	Nucleobase Sequence (5' to 3')	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No.
1521407	GGTAGCAAAAGGGGTAAT	144779	144796	881
1521408	AGCAAAAGGGGTAATACA	144776	144793	885
1521409	GCAAAAGGGGTAATACAG	144775	144792	888
1521410	CAAAAGGGGTAATACAGT	144774	144791	882
1521411	AAAGGGGTAATACAGTAC	144772	144789	880
1521412	AAGGGGTAATACAGTACC	144771	144788	883
1521413	GTAATACAGTACCCATAA	144766	144783	511
1521414	TAATACAGTACCCATAAT	144765	144782	750
1521415	AATACAGTACCCATAATA	144764	144781	736
1521416	ATACAGTACCCATAATAA	144763	144780	642
1521417	TACAGTACCCATAATAAA	144762	144779	519
1521418	ACAGTACCCATAATAAAG	144761	144778	741
1521419	CCCATCCAAGTTGGAGCA	144716	144733	664
1521420	CCATCCAAGTTGGAGCAA	144715	144732	645
1521421	CATCCAAGTTGGAGCAAG	144714	144731	550
1521422	ATCCAAGTTGGAGCAAGA	144713	144730	814
1521423	TCCAAGTTGGAGCAAGAT	144712	144729	692
1521424	CCAAGTTGGAGCAAGATT	144711	144728	587
1521425	CAAGTTGGAGCAAGATTA	144710	144727	523
1521426	AAGTTGGAGCAAGATTAT	144709	144726	778
1521428	TTGGAGCAAGATTATCCT	144706	144723	510
1521429	TGGAGCAAGATTATCCTA	144705	144722	816
1521430	GGAGCAAGATTATCCTAT	144704	144721	696
1521431	GAGCAAGATTATCCTATA	144703	144720	590

Example 13: Activity of modified oligonucleotides targeting SCN1A in wildtype mice

Wildtype C57BL/6 mice were divided into groups of 3 mice each. Each mouse received a single
 5 ICV bolus of 50 µg of modified oligonucleotide. A group of 4 mice received PBS as a negative control.

Compound No. 1367010, previously described in WO 2019/040923 and herein above, was added as a comparator compound.

Two weeks post treatment mice were sacrificed and RNA was extracted from cortical brain tissue for
 10 real-time qPCR analysis of SCN1A RNA using primer probe set RTS48951 (described herein above) to
 measure the amount of SCN1A RNA that excludes the mouse form of NIE-1 (NIE-1⁻) and primer probe set
 RTS48869 (forward sequence GCTCAAGCTCATCTCGCT, designated herein as SEQ ID NO: 27; reverse
 sequence AGCTCCGCAAGAAACATCC, designated herein as SEQ ID NO: 28; probe sequence
 TTCGATTTTGTGGTGGTCATCCTCTCC, designated herein as SEQ ID NO: 29) to measure the total
 amount of SCN1A mRNA transcript. SCN1A RNA is presented as % of the average of the PBS control

(%control), normalized to mouse GAPDH. Mouse GAPDH was amplified using primer probe set mGapdh_LTS00102 (described herein above).

Table 30

Effect of modified oligonucleotides on the amount of mouse SCN1A excluding NIE-1 (NIE-1⁻) and the amount of total mouse SCN1A mRNA in wildtype mice, single dose

Compound No.	CORTEX	
	NIE-1 ⁻	Total SCN1A mRNA
PBS	100	100
1367010	120	126
1429226	142	142
1521407	129	130
1521408	131	121
1521409	126	112
1521410	135	118
1521411	125	111
1521412	123	117
1521413	117	116
1521414	103	114
1521415	143	132
1521416	113	111
1521417	106	104
1521418	110	105
1521419	125	128
1521420	114	119
1521421	134	127
1521422	116	112
1521423	132	122
1521424	120	117
1521425	128	136
1521426	119	126
1521428	119	121
1521429	129	120
1521430	117	116
1521431	111	116

CLAIMS:

1. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 85% complementary to an equal length portion of a SCN1A nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.
2. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or 18 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs 41-889, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.
3. The oligomeric compound of claim 1 or claim 2, wherein the modified oligonucleotide has a nucleobase sequence that is at least 90%, 95%, or 100% complementary to the nucleobase sequence of SEQ ID NO: 1 or SEQ ID NO: 2 when measured across the entire nucleobase sequence of the modified oligonucleotide.
4. The oligomeric compound of any of claims 1-3, wherein the modified oligonucleotide has a nucleobase sequence comprising a portion of at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 18 contiguous nucleobases, wherein the portion is complementary to SEQ ID NO: 13.
5. The oligomeric compound of any of claims 1-4 wherein the modified oligonucleotide comprises at least one modified sugar moiety.
6. The oligomeric compound of claim 5, wherein the modified oligonucleotide comprises at least one bicyclic sugar moiety.
7. The oligomeric compound of claim 6, wherein the bicyclic sugar moiety has a 4'-2' bridge, wherein the 4'-2' bridge is selected from -CH₂-O-; and -CH(CH₃)-O-.
8. The oligomeric compound of any of claims 5-7, wherein the modified oligonucleotide comprises at least one non-bicyclic modified sugar moiety.
9. The oligomeric compound of claim 8, wherein the non-bicyclic modified sugar moiety is any of a 2'-MOE sugar moiety, a 2'-NMA sugar moiety, a 2'-OMe sugar moiety, or a 2'-F sugar moiety.
10. The oligomeric compound any of claims 5-9, wherein the modified oligonucleotide comprises at least one sugar surrogate.

11. The oligomeric compound of claim 10, wherein the sugar surrogate is any of morpholino, modified morpholino, PNA, THP, and F-HNA.
12. The oligomeric compound of claim 5, wherein each nucleoside of the modified oligonucleotide comprises a modified sugar moiety.
13. The oligomeric compound of claim 12, wherein each modified sugar moiety is a 2'-MOE sugar moiety.
14. The oligomeric compound of claim 12, wherein each modified sugar moiety is a 2'-NMA sugar moiety.
15. The oligomeric compound of any of claims 1-14, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.
16. The oligomeric compound of any of claims 1-14, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.
17. The oligomeric compound of claim 15 or claim 16, wherein at least one modified internucleoside linkage is a phosphorothioate internucleoside linkage.
18. The oligomeric compound of claim 15 or claim 17 wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.
19. The oligomeric compound of any of claims 15, 17, or 18, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage and a phosphorothioate internucleoside linkage.
20. The oligomeric compound of claim 16, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.
21. The oligomeric compound of any of claims 1-20, wherein the modified oligonucleotide comprises at least one modified nucleobase.
22. The oligomeric compound of claim 21, wherein the modified nucleobase is a 5-methyl cytosine.
23. The oligomeric compound of any of claims 1-22, wherein the modified oligonucleotide consists of 12-22, 12-20, 14-20, 15-25, 16-20, 18-22 or 18-20 linked nucleosides.
24. The oligomeric compound of any of claims 1-23, wherein the modified oligonucleotide consists of 16, 17, or 18 linked nucleosides.
25. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $A_{ns} G_{ns} T_{ns} T_{ns} G_{ns} G_{ns} A_{ns} G_{ns} {}^mC_{ns} A_{ns} A_{ns} G_{ns} A_{ns} T_{ns} T_{ns} A_{ns} T_{ns} {}^mC_n$ (SEQ ID NO: 41), wherein,

A = an adenine nucleobase,

${}^mC$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

n = a 2'-NMA sugar moiety, and

s = a phosphorothioate internucleoside linkage.

26. An oligomeric compound comprising a modified oligonucleotide according to any one of the following chemical notations (5' to 3'):

- i) $A_{es}G_{eo}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- ii) $A_{es}G_{eo}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- iii) $A_{es}G_{eo}T_{es}T_{es}G_{es}G_{eo}A_{es}G_{es}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- iv) $A_{es}G_{eo}T_{es}T_{es}G_{es}G_{es}A_{es}G_{eo}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- v) $A_{es}G_{es}T_{es}T_{es}G_{eo}G_{es}A_{es}G_{es}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- vi) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{eo}^mC_{eo}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- vii) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{es}A_{eo}A_{eo}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- viii) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{es}A_{es}A_{es}G_{eo}A_{eo}T_{es}T_{es}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- ix) $A_{es}G_{eo}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{es}A_{eo}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- x) $A_{es}G_{eo}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{es}A_{es}A_{es}G_{eo}A_{es}T_{es}T_{es}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- xi) $A_{es}G_{eo}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{eo}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- xii) $A_{es}G_{es}T_{eo}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{eo}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- xiii) $A_{es}G_{es}T_{es}T_{es}G_{eo}G_{es}A_{es}G_{es}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{eo}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- xiv) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{eo}A_{eo}G_{es}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- xv) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{eo}G_{es}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{eo}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- xvi) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{eo}A_{es}A_{es}G_{es}A_{es}T_{eo}T_{es}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- xvii) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{eo}A_{es}A_{es}G_{es}A_{es}T_{es}T_{eo}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- xviii) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{es}A_{es}A_{eo}G_{es}A_{es}T_{es}T_{eo}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- xix) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{es}A_{es}A_{es}G_{eo}A_{es}T_{eo}T_{es}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- xx) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{es}A_{es}A_{es}G_{es}A_{eo}T_{es}T_{eo}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- xxi) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{eo}T_{eo}A_{es}T_{es}^mC_e$ (SEQ ID NO: 41);
- xxii) $A_{eo}A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}^mC_{eo}^mC_e$ (SEQ ID NO: 890);
- xxiii) $A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}^mC_{eo}^mC_e$ (SEQ ID NO: 891);
- xxiv) $A_{eo}A_{es}G_{es}T_{es}T_{es}G_{es}G_{es}A_{es}G_{es}^mC_{es}A_{es}A_{es}G_{es}A_{es}T_{es}T_{es}A_{es}T_{es}^mC_e$ (SEQ ID NO: 892);
- xxv) $G_{ns}G_{ns}T_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}A_{ns}A_{ns}G_{ns}G_{ns}G_{ns}G_{ns}T_{ns}A_{ns}A_{ns}T_{ns}$ (SEQ ID NO: 881);
- xxvi) $A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}A_{ns}A_{ns}G_{ns}G_{ns}G_{ns}G_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}^mC_{ns}A_{ns}$ (SEQ ID NO: 885);
- xxvii) $G_{ns}^mC_{ns}A_{ns}A_{ns}A_{ns}A_{ns}G_{ns}G_{ns}G_{ns}G_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}^mC_{ns}A_{ns}G_{ns}$ (SEQ ID NO: 888);
- xxviii) $^mC_{ns}A_{ns}A_{ns}A_{ns}A_{ns}G_{ns}G_{ns}G_{ns}G_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}^mC_{ns}A_{ns}G_{ns}T_{ns}$ (SEQ ID NO: 882);
- xxix) $A_{ns}A_{ns}A_{ns}G_{ns}G_{ns}G_{ns}G_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}^mC_{ns}$ (SEQ ID NO: 880);

- xxx) $A_{ns}A_{ns}G_{ns}G_{ns}G_{ns}G_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}^mC_{ns}^mC_n$ (SEQ ID NO: 883);
- xxxii) $G_{ns}T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}^mC_{ns}^mC_{ns}A_{ns}T_{ns}A_{ns}A_n$ (SEQ ID NO: 511);
- xxxiii) $T_{ns}A_{ns}A_{ns}T_{ns}A_{ns}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}^mC_{ns}^mC_{ns}A_{ns}T_{ns}A_{ns}A_nT_n$ (SEQ ID NO: 750);
- xxxiiii) $A_{ns}A_{ns}T_{ns}A_{ns}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}^mC_{ns}^mC_{ns}A_{ns}T_{ns}A_{ns}A_nT_{ns}A_n$ (SEQ ID NO: 736);
- xxxiv) $A_{ns}T_{ns}A_{ns}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}^mC_{ns}^mC_{ns}A_{ns}T_{ns}A_{ns}A_nT_{ns}A_{ns}A_n$ (SEQ ID NO: 642);
- xxxv) $T_{ns}A_{ns}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}^mC_{ns}^mC_{ns}A_{ns}T_{ns}A_{ns}A_nT_{ns}A_{ns}A_nA_n$ (SEQ ID NO: 519);
- xxxvi) $A_{ns}^mC_{ns}A_{ns}G_{ns}T_{ns}A_{ns}^mC_{ns}^mC_{ns}A_{ns}T_{ns}A_{ns}A_nT_{ns}A_{ns}A_nA_nG_n$ (SEQ ID NO: 741);
- xxxvii) $^mC_{ns}^mC_{ns}^mC_{ns}A_{ns}T_{ns}^mC_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_n$ (SEQ ID NO: 664);
- xxxviii) $^mC_{ns}^mC_{ns}A_{ns}T_{ns}^mC_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_n$ (SEQ ID NO: 645);
- xxxix) $^mC_{ns}A_{ns}T_{ns}^mC_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_nG_n$ (SEQ ID NO: 550);
- xl) $A_{ns}T_{ns}^mC_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_n$ (SEQ ID NO: 814);
- xli) $T_{ns}^mC_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_nT_n$ (SEQ ID NO: 692);
- xlvi) $^mC_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_nT_{ns}T_n$ (SEQ ID NO: 587);
- xlvi) $^mC_{ns}A_{ns}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_nT_{ns}T_nA_n$ (SEQ ID NO: 523);
- xlii) $A_{ns}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_nT_{ns}T_nA_n$ (SEQ ID NO: 778);
- xlvi) $T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_nT_{ns}T_{ns}A_{ns}T_{ns}^mC_{ns}^mC_{ns}T_n$ (SEQ ID NO: 510);
- xlvi) $T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_nT_{ns}T_{ns}A_{ns}T_{ns}^mC_{ns}^mC_{ns}T_{ns}A_n$ (SEQ ID NO: 816);
- xlvi) $G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_nT_{ns}T_{ns}A_{ns}T_{ns}^mC_{ns}^mC_{ns}T_{ns}A_nT_n$ (SEQ ID NO: 696); or
- xlvi) $G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_nT_{ns}T_{ns}A_{ns}T_{ns}^mC_{ns}^mC_{ns}T_{ns}A_nT_{ns}A_n$ (SEQ ID NO: 590),

wherein,

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

n = a 2'-NMA sugar moiety.

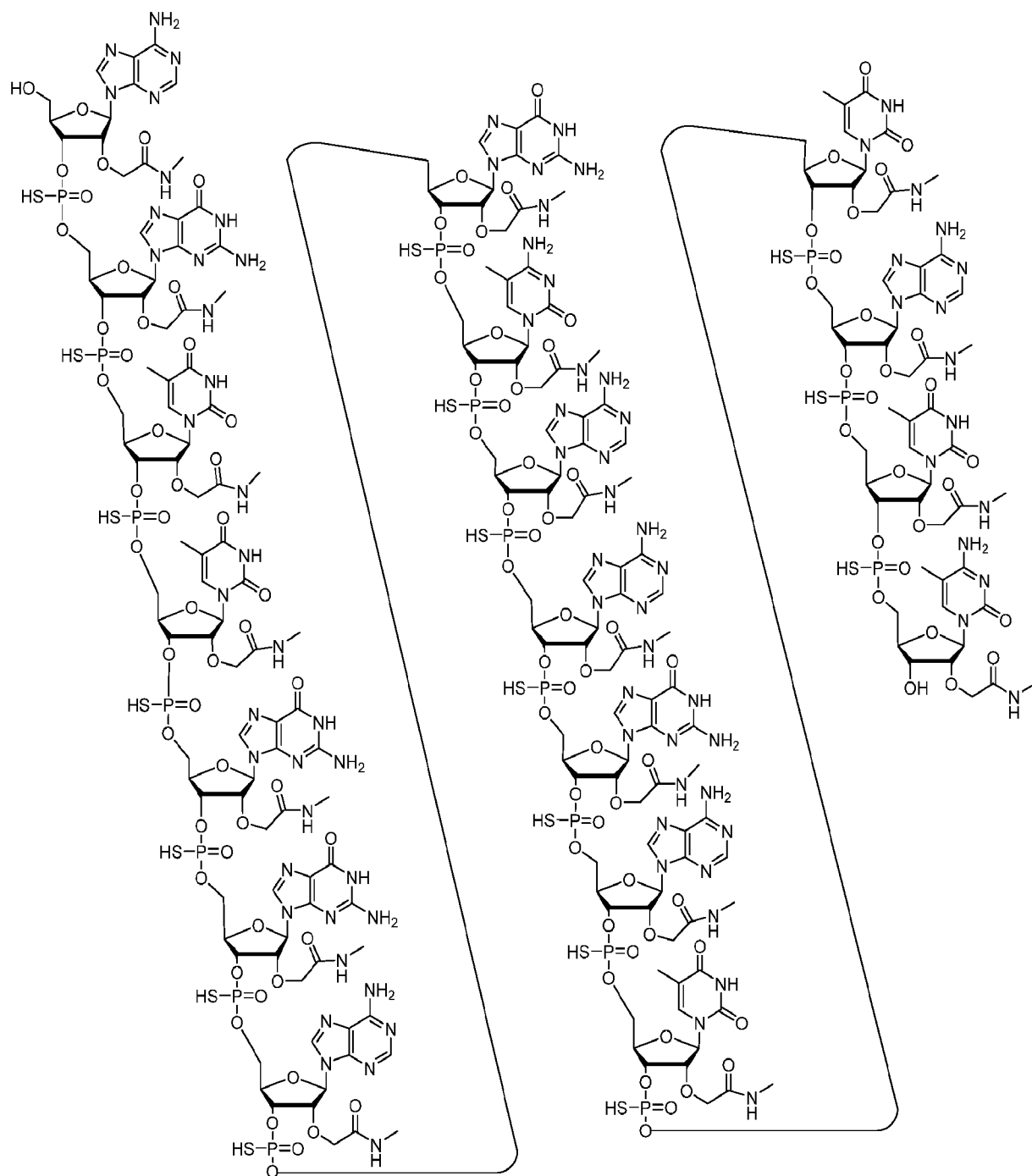
o = a phosphodiester internucleoside linkage, and

s = a phosphorothioate internucleoside linkage.

27. The oligomeric compound of any of claims 1-26, wherein the oligomeric compound is a singled-stranded oligomeric compound.
28. The oligomeric compound of any of claims 1-27 consisting of the modified oligonucleotide.
29. The oligomeric compound of any of claims 1-28 comprising a conjugate group comprising a conjugate moiety and a conjugate linker.

30. The oligomeric compound of claim 29, wherein the conjugate group comprises a GalNAc cluster comprising 1-3 GalNAc ligands.
31. The oligomeric compound of claim 29 or claim 30, wherein the conjugate linker consists of a single bond.
32. The oligomeric compound of claim 29, wherein the conjugate linker is cleavable.
33. The oligomeric compound of claim 29, wherein the conjugate linker comprises 1-3 linker-nucleosides.
34. The oligomeric compound of any of claims 29-33, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.
35. The oligomeric compound of any of claims 29-33, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.
36. The oligomeric compound of any of claims 1-27 or 29-35 comprising a terminal group.
37. The oligomeric compound of any of claims 1-32 or 34-35, wherein the oligomeric compound does not comprise linker-nucleosides.

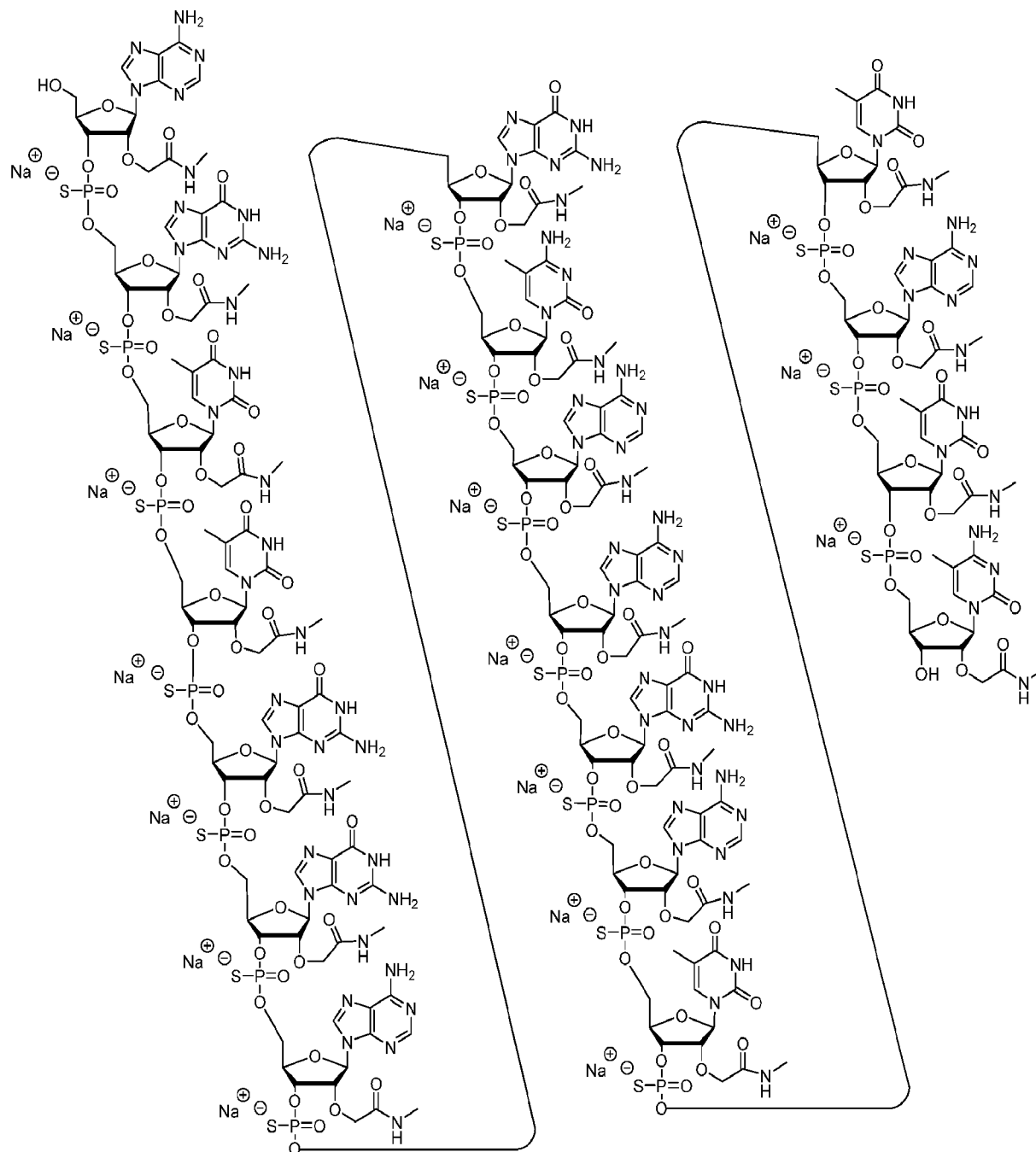
38. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 41) or a salt thereof.

39. The modified oligonucleotide of claim 38, which is the sodium salt or the potassium salt.

40. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 41).

41. A chirally enriched population of modified oligonucleotides of any of claims 38-40, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.
42. The chirally enriched population of claim 41, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (Sp) configuration.

43. The chirally enriched population of claim 41, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*Rp*) configuration.
44. The chirally enriched population of claim 41, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.
45. The chirally enriched population of claim 44, wherein the population is enriched for modified oligonucleotides having the (*Sp*) configuration at each phosphorothioate internucleoside linkage or for modified oligonucleotides having the (*Rp*) configuration at each phosphorothioate internucleoside linkage.
46. The chirally enriched population of claim 44, wherein the population is enriched for modified oligonucleotides having the (*Rp*) configuration at one particular phosphorothioate internucleoside linkage and the (*Sp*) configuration at each of the remaining phosphorothioate internucleoside linkages.
47. The chirally enriched population of claim 44, wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the *Sp*, *Sp*, and *Rp* configurations, in the 5' to 3' direction.
48. A population of modified oligonucleotides of any of claims 38-40, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.
49. A pharmaceutical composition comprising the oligomeric compound of any of claims 1-37, the modified oligonucleotide of any of claims 38-40, the chirally-enriched population of any of claims 41-47, or the population of modified oligonucleotides of claim 48, and a pharmaceutically acceptable diluent or carrier.
50. The pharmaceutical composition of claim 49, comprising a pharmaceutically acceptable diluent and wherein the pharmaceutically acceptable diluent is artificial CSF (aCSF) or PBS.
51. The pharmaceutical composition of claim 50, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial CSF (aCSF).
52. The pharmaceutical composition of claim 50, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.
53. A method of modulating splicing of an SCN1A RNA in a cell comprising contacting the cell with an oligomeric compound of any of claims 1-37, a modified oligonucleotide of any of claims 38-40, a chirally-enriched population of any of claims 41-47, a population of modified oligonucleotides of claim 48, or a pharmaceutical composition of any of claims 49-52.
54. The method of claim 53, wherein the amount of SCN1A RNA that includes an NIE is reduced.

55. The method of claim 54, wherein the amount of SCN1A RNA that includes NIE-1 is reduced.
56. The method of any of claims 53-55, wherein the amount of SCN1A RNA that excludes an NIE is increased.
57. The method of any of claims 53-56, wherein the amount of SCN1A RNA that excludes NIE-1 is increased.
58. A method of increasing the amount of full-length SCN1A RNA in a cell, comprising contacting the cell with an oligomeric compound of any of claims 1-37, a modified oligonucleotide of any of claims 38-40, a chirally-enriched population of any of claims 41-47, a population of modified oligonucleotides of claim 48, or a pharmaceutical composition of any of claims 49-52.
59. A method of increasing SCN1A RNA lacking NIE-1 in a cell, tissue, or organ, comprising contacting a cell, tissue, or organ with an oligomeric compound of any of claims 1-37, a modified oligonucleotide of any of claims 38-40, a chirally-enriched population of any of claims 41-47, a population of modified oligonucleotides of claim 48, or a pharmaceutical composition of any of claims 49-52.
60. The method of any of claims 53-59, wherein the cell is in vitro.
61. The method of any of claims 53-59, wherein the cell is in an animal.
62. A method of ameliorating a disease associated with SCN1A comprising administering to a subject having or at risk for developing a disease associated with SCN1A a therapeutically effective amount of a pharmaceutical composition according to any of claims 49-52, and thereby treating the disease associated with SCN1A.
63. The method of claim 62, comprising identifying a subject having or at risk for developing a disease associated SCN1A.
64. The method of claim 62 or claim 63, wherein the disease associated with SCN1A is a developmental or epileptic encephalopathic disease.
65. The method of claim 64, wherein the developmental or epileptic encephalopathic disease is Dravet Syndrome.
66. The method of claim 64, wherein the developmental or epileptic encephalopathic disease is any of Genetic Epilepsy with Febrile Seizures Plus (GEFS+), febrile seizures, Idiopathic/Generic Generalized Epilepsies (IGE/GGE), Temporal Lobe Epilepsy, Myoclonic Astatic Epilepsy (MAE), Lennox-Gastaut Syndrome, or Migrating Partial Epilepsy of Infancy (MMPSE).
67. The method of any of claims 64-66, wherein at least one symptom of the developmental or epileptic encephalopathic disease is ameliorated.

68. The method of claim 67, wherein the symptom is any of seizures, behavioral and developmental delays, movement and balance dysfunctions, motor and cognitive dysfunctions, delayed language and speech, visual motor integration dysfunctions, visual perception dysfunctions, executive dysfunctions, growth and nutrition issues, sleeping difficulties, chronic infections, sensory integration disorders, or dysautonomia.
69. The method of claim 68, wherein the seizures are frequent or prolonged.
70. The method of claim 68 or claim 69, wherein the seizure is any of convulsive, myoclonic, absence, focal, obtundation status, or tonic.
71. The method of any of claims 62-70, wherein the pharmaceutical composition is administered to the central nervous system or systemically.
72. The method of claim 71, wherein the pharmaceutical composition is administered to the central nervous system and systemically.
73. The method of any of claims 62-71, wherein the pharmaceutical composition is administered any of intrathecally, systemically, subcutaneously, or intramuscularly.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US21/19960

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C12N 15/113; C07H 21/00; A61K 31/7125; A61K 31/712; A61K 31/7115 (2021.01)

CPC - C12N 15/1138; C07H 21/00; A61K 31/7125; A61K 31/712; A61K 31/7115; C12N 2310/11; C12N 2310/315; C12N 2310/321; C12N 2310/3341

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2020/0024606 A1 (STOKE THERAPEUTICS, INC.) 23 January 2020; paragraph [0003], [0134], [0140], [0447]; Table 5	1-3
---		25
Y		
Y	US 2019/0365919 A1 (SAREPTA THERAPEUTICS, INC.) 5 December 2019; paragraphs [0147], [0237]	25
A	US 2020/0024603 A1 (STOKE THERAPEUTICS, INC.) 23 January 2020; entire document	1-3, 25
A	WO 2020/041348 A1 (ROGCON, INC.) 27 February 2020; entire document	1-3, 25
A	(BENDER, AC et al.) Focal Scn1a knockdown induces cognitive impairment without seizures. Neurobiology of disease. June 2013, Vol. 54; pages 297-307; DOI: 10.1016/j.nbd.2012.12.021	1-3, 25

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

02 July 2021 (02.07.2021)

Date of mailing of the international search report

AUG 05 2021

Name and mailing address of the ISA/US

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Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US21/19960

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US21/19960

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-24, 27-37, 49-73
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
-***-Please See Supplemental Page-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Groups I+, Claims 1-3, 25, 26, 38-48 and a modified oligonucleotide: Ans Gns Tns Tns Gns Gns Ans Gns mCns Ans Ans Gns
Ans Tns Tns Ans Tns mCn (SEQ ID NO: 41), wherein: A = an adenine nucleobase, me = a 5-methyl cytosine nucleobase, G = a
guanine nucleobase, T = a thymine nucleobase, n = a 2'-NMA sugar moiety, and s = a phosphorothioate internucleoside
linkage (oligonucleotide)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

---Continued From Box No. III: Observations where unity of invention is lacking---

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-3, 25, 26, 38-48 and a modified oligonucleotide: Ans Gns Tns Tns Gns Gns Ans Gns mCns Ans Ans Gns Ans Tns Tns Ans Tns mCn (SEQ ID NO: 41), wherein: A = an adenine nucleobase, me = a 5-methyl cytosine nucleobase, G = a guanine nucleobase, T = a thymine nucleobase, n = a 2'-NMA sugar moiety, and s = a phosphorothioate internucleoside linkage (oligonucleotide) are directed toward oligomeric compounds and populations thereof.

The oligomeric compounds and populations thereof will be searched to the extent they encompass a modified oligonucleotide: Ans Gns Tns Tns Gns Gns Ans Gns mCns Ans Ans Gns Ans Tns Tns Ans Tns mCn (SEQ ID NO: 41), wherein: A = an adenine nucleobase, me = a 5-methyl cytosine nucleobase, G = a guanine nucleobase, T = a thymine nucleobase, n = a 2'-NMA sugar moiety, and s = a phosphorothioate internucleoside linkage (first exemplary oligonucleotide). Applicant is invited to elect additional oligonucleotide(s), with specified chemical modification(s) at specified site(s) of a SEQ ID NO: 41, such that the structure and sequence of each elected species is fully specified (i.e. no optional or variable atoms, bonds, nucleobases or substituents), where available as an option within at least one searchable claim, to be searched. Additional oligonucleotide(s) will be searched upon the payment of additional fees. It is believed that claims 1, 2-3 (each in-part), and 25 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a modified oligonucleotide: Ans Gns Tns Tns Gns Gns Ans Gns mCns Ans Ans Gns Ans Tns Tns Ans Tns mCn (SEQ ID NO: 41), wherein: A = an adenine nucleobase, me = a 5-methyl cytosine nucleobase, G = a guanine nucleobase, T = a thymine nucleobase, n = a 2'-NMA sugar moiety, and s = a phosphorothioate internucleoside linkage (oligonucleotide). Applicants must specify the searchable claims that encompass any additionally elected oligonucleotide(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be AesGeoTeoTesGesGesAesGesmCesAesAesGesAesTesTesAesTesmCe (SEQ ID NO: 41); wherein, A = an adenine nucleobase, me = a 5-methyl cytosine nucleobase, G = a guanine nucleobase, T = a thymine nucleobase, e = a 2'-MOE sugar moiety, n = a 2'-NMA sugar moiety, o = a phosphodiester internucleoside linkage, and s = a phosphorothioate internucleoside linkage.

Groups I+ share the technical features including: an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 85% complementary to an equal length portion of a SCN1A nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage; an oligomeric compound comprising SEQ ID NO. 41; an oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: A = an adenine nucleobase, me = a 5-methyl cytosine nucleobase, G = a guanine nucleobase, T = a thymine nucleobase, n = a 2'-NMA sugar moiety, s = a phosphorothioate internucleoside linkage, e = a 2'-MOE sugar moiety, and o = a phosphodiester internucleoside linkage; a chirally enriched population of modified oligonucleotides, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration; and a population of modified oligonucleotides, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereo random.

However, these shared technical features are previously disclosed by US 2020/0024606 A1 to Stoke Therapeutics, Inc. (hereinafter 'Stoke'), in view of WO 2020/041348 A1 to Rogcon, Inc. (hereinafter 'Rogcon').

Stoke discloses an oligomeric compound comprising a modified oligonucleotide (an antisense oligomer (oligomeric compound) comprising at least one modified sugar moiety (modified oligonucleotide); paragraph [0003]) consisting of 12 to 30 linked nucleosides (consisting of 11 (12) to 30 linked nucleosides; paragraph [0003]) wherein the nucleobase sequence of the modified oligonucleotide is at least 85% complementary to an equal length portion of a SCN1A nucleic acid (wherein the nucleobase sequence of the modified oligonucleotide is at least 85% complementary to an equal length portion of a SCN1A nucleic acid; paragraph [0003]), and wherein the modified oligonucleotide comprises at least one modified sugar moiety (wherein the modified oligonucleotide comprises at least one modified sugar moiety; paragraph [0003]); an oligomeric compound comprising SEQ ID NO. 41 (an oligomeric compound comprising SEQ ID NO. 42 (SEQ ID NO: 41); paragraph [0003], Table 5, wherein SEQ ID NO: 42 is 100% identical to Applicant's SEQ ID NO: 41); an oligomeric compound comprising a modified oligonucleotide (an oligomeric compound comprising a modified oligonucleotide; paragraph [0003]) according to the following chemical notation: A = an adenine nucleobase (according to the following chemical notation: A = an adenine nucleobase; paragraph [0134]), me = a 5-methyl cytosine nucleobase (a 5-methyl cytosine nucleobase; paragraph [0134]), G = a guanine nucleobase (a guanine nucleobase; paragraph [0134]), T = a thymine nucleobase (a thymine nucleobase; paragraph [0134]), s = a phosphorothioate internucleoside linkage (a phosphorothioate internucleoside linkage; paragraph [0135]), e = a 2'-MOE sugar moiety (a 2'-MOE sugar moiety; paragraphs [0011], [0139]), and o = a phosphodiester internucleoside linkage (a phosphodiester internucleoside linkage; paragraph [0135]); a chirally enriched population of modified oligonucleotides, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration (a wherein the chiral stereochemistry of each internucleotide linkage is nonrandom (a chirally enriched population of modified oligonucleotides, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration); paragraph [0136]) and a population of modified oligonucleotides, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereo random (a population of modified oligonucleotides, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereo random; paragraph [0136]).

Stoke does not disclose a 2'-NMA sugar moiety.

Rogcon discloses compounds and compositions useful to treat, prevent, delay, or ameliorate a SCN1A related disease (compounds and compositions useful to treat, prevent, delay, or ameliorate a SCN1A related disease; abstract), wherein the compounds comprise NMA comprising nucleosides (wherein the compounds comprise NMA comprising nucleosides; page 31, lines 4-7).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the disclosure of

---Continued Within the Next Supplemental Box---

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US21/19960

-Continued from previous Supplemental Box-

Stoke to have included the use of alternative 2' sugar modifications, including NMA modifications, as disclosed by Rogcon, in order to produce oligomeric compounds with enhanced activity and resistance to nuclease degradation.

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Stoke and Rogcon references, unity of invention is lacking.