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(54) Title: COMPOSITIONS FOR MODULATING C9ORF72 EXPRESSION

(57) Abstract: Disclosed herein are compositions and methods for reducing expression of C9ORF72 mRNA and protein in an animal with C9ORF72 specific inhibitors. Also disclosed herein are compositions and methods of selectively inhibiting a C9ORF72 pathogenic associated mRNA variant by administering an antisense compound targeting the region beginning at the start site of exon 1A to the start site of exon 1B of a C9ORF72 pre-mRNA. Such methods are useful to treat, prevent, or ameliorate neurodegenerative diseases in an individual in need thereof. Such C9ORF72 specific inhibitors include antisense compounds.



COMPOSITIONS FOR MODULATING C9ORF72 EXPRESSION

5 Sequence Listing

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL0235WOSEQ_ST25.txt created October 11, 2014, which is 444 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 compositions and methods for reducing expression of C9ORF72 mRNA and protein in an animal. Such methods are useful to treat, prevent, or ameliorate neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD),
15 corticalbasal degeneration syndrome (CBD), atypical Parkinsonian syndrome, and olivopontocerellar degeneration (OPCD).

Background

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized
20 clinically by progressive paralysis leading to death from respiratory failure, typically within two to three years of symptom onset (Rowland and Shneider, N. Engl. J. Med., 2001, 344, 1688-1700). ALS is the third most common neurodegenerative disease in the Western world (Hirtz et al., Neurology, 2007, 68, 326-337), and there are currently no effective therapies. Approximately 10% of cases are familial in nature, whereas the bulk of patients diagnosed with the disease are classified
25 as sporadic as they appear to occur randomly throughout the population (Chio et al., Neurology, 2008, 70, 533-537). There is growing recognition, based on clinical, genetic, and epidemiological data, that ALS and frontotemporal dementia (FTD) represent an overlapping continuum of disease, characterized pathologically by the presence of TDP-43 positive inclusions throughout the central nervous system (Lillo and Hodges, J. Clin. Neurosci., 2009, 16, 1131-1135; Neumann et al.,
30 Science, 2006, 314, 130-133).

To date, a number of genes have been discovered as causative for classical familial ALS, for example, SOD1, TARDBP, FUS, OPTN, and VCP (Johnson et al., Neuron, 2010, 68, 857-864;

Kwiatkowski et al., Science, 2009, 323, 1205-1208; Maruyama et al., Nature, 2010, 465, 223-226; Rosen et al., Nature, 1993, 362, 59-62; Sreedharan et al., Science, 2008, 319, 1668-1672; Vance et al., Brain, 2009, 129, 868-876). Recently, linkage analysis of kindreds involving multiple cases of ALS, FTD, and ALS-FTD had suggested that there was an important locus for the disease on the short arm of chromosome 9 (Boxer et al., J. Neurol. Neurosurg. Psychiatry, 2011, 82, 196-203; Morita et al., Neurology, 2006, 66, 839-844; Pearson et al. J. Nerol., 2011, 258, 647-655; Vance et al., Brain, 2006, 129, 868-876). The mutation in the C9ORF72 gene is the most common genetic cause of ALS and FTD. The ALS-FTD causing mutation is a large hexanucleotide (GGGGCC) repeat expansion in the first intron of the C9ORF72 gene (Renton et al., Neuron, 2011, 72, 257-268; DeJesus-Hernandez et al., Neuron, 2011, 72, 245-256). A founder haplotype, covering the C9ORF72 gene, is present in the majority of cases linked to this region (Renton et al., Neuron, 2011, 72, 257-268). This locus on chromosome 9p21 accounts for nearly half of familial ALS and nearly one-quarter of all ALS cases in a cohort of 405 Finnish patients (Laaksovirta et al, Lancet Neurol., 2010, 9, 978-985).

A founder haplotype, covering the C9ORF72 gene, is present in the majority of cases linked to this region.

There are currently no effective therapies to treat such neurodegenerative diseases. Therefore, it is an object to provide compositions and methods for the treatment of such neurodegenerative diseases.

Summary

Provided herein are compositions and methods for modulating levels of C9ORF72 mRNA and protein in cells, tissues, and animals. In certain embodiments, C9ORF72 specific inhibitors modulate expression of C9ORF72 mRNA and protein. In certain embodiments, C9ORF72 specific inhibitors are nucleic acids, proteins, or small molecules.

In certain embodiments, modulation can occur in a cell or tissue. In certain embodiments, the cell or tissue is in an animal. In certain embodiments, the animal is a human. In certain embodiments, C9ORF72 mRNA levels are reduced. In certain embodiments, C9ORF72 protein levels are reduced. In certain embodiments, C9ORF72 associated Repeat Associated Non-ATG Translation (RAN translation) products are reduced. In certain embodiments, the C9ORF72 associated RAN translation products are poly-(glycine-proline), poly-(glycine-alanine), and poly-(glycine-arginine). In certain embodiments, certain C9ORF72 mRNA variants are preferentially

reduced. In certain embodiments, the C9ORF72 mRNA variants preferentially reduced are variants processed from a pre-mRNA containing intron 1. In certain embodiments, intron 1 contains a hexanucleotide repeat expansion. In certain embodiments, the C9ORF72 mRNA variant preferentially reduced is a C9ORF72 pathogenic associated mRNA variant. In certain
5 embodiments, the C9ORF72 pathogenic associated mRNA variant is NM_001256054.1 (SEQ ID NO: 1). In certain embodiments, the hexanucleotide repeat expansion is associated with a C9ORF72 associated disease. In certain embodiments, the hexanucleotide repeat expansion is associated with a C9ORF72 hexanucleotide repeat expansion associated disease. In certain
10 embodiments, the hexanucleotide repeat expansion comprises at least 24 GGGGCC repeats. In certain embodiments, the hexanucleotide repeat expansion is associated with nuclear foci. In certain embodiments, C9ORF72 associated RAN translation products are associated with nuclear foci. In certain embodiments, the C9ORF72 associated RAN translation products are poly-(glycine-proline), poly-(glycine-alanine), and poly-(glycine-arginine). In certain embodiments, the compositions and methods described herein are useful for reducing C9ORF72 mRNA levels,
15 C9ORF72 protein levels, C9ORF72 RAN translation products, and nuclear foci. In certain embodiments, the compositions and methods described herein are useful for selectively reducing C9ORF72 pathogenic associated mRNA variants. Such reduction can occur in a time-dependent manner or in a dose-dependent manner.

Also provided are methods useful for preventing, treating, and ameliorating diseases,
20 disorders, and conditions associated with C9ORF72. In certain embodiments, such diseases, disorders, and conditions associated with C9ORF72 are neurodegenerative diseases. In certain embodiments, the neurodegenerative disease is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), corticalbasal degeneration syndrome (CBD), atypical Parkinsonian syndrome, and olivopontocerellar degeneration (OPCD).

25 Such diseases, disorders, and conditions can have one or more risk factors, causes, or outcomes in common. Certain risk factors and causes for development of a neurodegenerative disease, and, in particular, ALS and FTD, include genetic predisposition and older age.

In certain embodiments, methods of treatment include administering a C9ORF72 specific inhibitor to an individual in need thereof. In certain embodiments, the C9ORF72 specific inhibitor
30 is a nucleic acid. In certain embodiments, the nucleic acid is an antisense compound. In certain embodiments, the antisense compound is a single-stranded antisense oligonucleotide. In certain

embodiments, the single-stranded antisense oligonucleotide is complementary to a C9ORF72 nucleic acid.

Detailed Description

5 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 of the invention, as claimed. Herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the use of “or” means “and/or” unless stated otherwise. Additionally, as used herein, the use of “and” means “and/or” unless stated otherwise. Furthermore, the use of the term “including” as
10 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 limiting the subject matter described. All documents, or portions of documents, cited
15 in this disclosure, including, but not limited to, patents, patent applications, published patent applications, articles, books, treatises, and GENBANK Accession Numbers and associated sequence information obtainable through databases such as National Center for Biotechnology Information (NCBI) and other data referred to throughout in the disclosure herein are hereby expressly incorporated by reference for the portions of the document discussed herein, as well as in their
20 entirety.

Definitions

Unless specific definitions are provided, the nomenclature utilized in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal
25 and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques may be used for chemical synthesis, and chemical analysis.

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

“2’-O-methoxyethyl” (also 2’-MOE and 2’-OCH₂CH₂-OCH₃ and MOE) refers to an O-methoxy-ethyl modification of the 2’ position of a furanose ring. A 2’-O-methoxyethyl modified
30 sugar is a modified sugar.

“2’-MOE nucleoside” (also 2’-O-methoxyethyl nucleoside) means a nucleoside comprising a MOE modified sugar moiety.

“2’-substituted nucleoside” means a nucleoside comprising a substituent at the 2’-position of the furanose ring other than H or OH. In certain embodiments, 2’-substituted nucleosides include nucleosides with bicyclic sugar modifications.

“5-methylcytosine” means a cytosine modified with a methyl group attached to the 5’ position. A 5-methylcytosine is a modified nucleobase.

“About” means within $\pm 7\%$ of a value. For example, if it is stated, “the compounds affected at least about 70% inhibition of C9ORF72”, it is implied that the C9ORF72 levels are inhibited within a range of 63% and 77%.

“Administered concomitantly” refers to the co-administration of two pharmaceutical agents in any manner in which the pharmacological effects of both are manifest in the patient at the same time. Concomitant administration does not require that both pharmaceutical agents be administered in a single pharmaceutical composition, in the same dosage form, or by the same route of administration. The effects of both pharmaceutical agents need not manifest themselves at the same time. The effects need only be overlapping for a period of time and need not be coextensive.

“Administering” means providing a pharmaceutical agent to an animal, and includes, but is not limited to administering by a medical professional and self-administering.

“Amelioration” refers to a lessening, slowing, stopping, or reversing of at least one indicator of the severity of a condition or disease. The severity of indicators may be determined by subjective or objective measures, which are known to those skilled in the art.

“Animal” refers to a human or non-human animal, including, but not limited to, mice, rats, rabbits, dogs, cats, pigs, and non-human primates, including, but not limited to, monkeys and chimpanzees.

“Antibody” refers to a molecule characterized by reacting specifically with an antigen in some way, where the antibody and the antigen are each defined in terms of the other. Antibody may refer to a complete antibody molecule or any fragment or region thereof, such as the heavy chain, the light chain, Fab region, and Fc region.

“Antisense activity” means any detectable or measurable activity attributable to the hybridization of an antisense compound to its target nucleic acid. In certain embodiments, antisense activity is a decrease in the amount or expression of a target nucleic acid or protein encoded by such target nucleic acid.

“Antisense compound” means an oligomeric compound that is capable of undergoing hybridization to a target nucleic acid through hydrogen bonding. Examples of antisense compounds

include single-stranded and double-stranded compounds, such as, antisense oligonucleotides, siRNAs, shRNAs, ssRNAs, and occupancy-based compounds.

“Antisense inhibition” means reduction of target nucleic acid levels in the presence of an antisense compound complementary to a target nucleic acid compared to target nucleic acid levels or in the absence of the antisense compound.

“Antisense mechanisms” are all those mechanisms involving hybridization of a compound with a target nucleic acid, wherein the outcome or effect of the hybridization is either target degradation or target occupancy with concomitant stalling of the cellular machinery involving, for example, transcription or splicing.

“Antisense oligonucleotide” means a single-stranded oligonucleotide having a nucleobase sequence that permits hybridization to a corresponding segment of a target nucleic acid.

“Base complementarity” refers to the capacity for the precise base pairing of nucleobases of an antisense oligonucleotide with corresponding nucleobases in a target nucleic acid (i.e., hybridization), and is mediated by Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen binding between corresponding nucleobases.

“Bicyclic sugar” means a furanose ring modified by the bridging of two atoms. A bicyclic sugar is a modified sugar.

“Bicyclic nucleoside” (also BNA) means a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4'-carbon and the 2'-carbon of the sugar ring.

“C9ORF72 associated disease” means any disease associated with any C9ORF72 nucleic acid or expression product thereof. Such diseases may include a neurodegenerative disease. Such neurodegenerative diseases may include ALS and FTD.

“C9ORF72 associated RAN translation products” means aberrant peptide or di-peptide polymers translated through RAN translation (i.e., repeat-associated, and non-ATG-dependent translation). In certain embodiments, the C9ORF72 associated RAN translation products are any of poly-(glycine-proline), poly-(glycine-alanine), and poly-(glycine-arginine).

“C9ORF72 hexanucleotide repeat expansion associated disease” means any disease associated with a C9ORF72 nucleic acid containing a hexanucleotide repeat expansion. In certain embodiments, the hexanucleotide repeat expansion may comprise GGGGCC, GGGGGG, GGGGGC, or GGGGCG repeated at least 24 times. Such diseases may include a neurodegenerative disease. Such neurodegenerative diseases may include ALS and FTD.

“C9ORF72 nucleic acid” means any nucleic acid encoding C9ORF72. For example, in certain embodiments, a C9ORF72 nucleic acid includes a DNA sequence encoding C9ORF72, an RNA sequence transcribed from DNA encoding C9ORF72 including genomic DNA comprising introns and exons (i.e., pre-mRNA), and an mRNA sequence encoding C9ORF72. “C9ORF72 mRNA” means an mRNA encoding a C9ORF72 protein.

“C9ORF72 pathogenic associated mRNA variant” means the C9ORF72 mRNA variant processed from a C9ORF72 pre-mRNA variant containing the hexanucleotide repeat. A C9ORF72 pre-mRNA contains the hexanucleotide repeat when transcription of the pre-mRNA begins in the region from the start site of exon 1A to the start site of exon 1B, e.g., nucleotides 1107 to 1520 of the genomic sequence (SEQ ID NO: 2, the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, the level of a C9ORF72 pathogenic associated mRNA variant is measured to determine the level of a C9ORF72 pre-mRNA containing the hexanucleotide repeat in a sample.

“C9ORF72 specific inhibitor” refers to any agent capable of specifically inhibiting the expression of C9ORF72 mRNA and/or C9ORF72 protein at the molecular level. For example, C9ORF72 specific inhibitors include nucleic acids (including antisense compounds), siRNAs, aptamers, antibodies, peptides, small molecules, and other agents capable of inhibiting the expression of C9ORF72 mRNA and/or C9ORF72 protein. Similarly, in certain embodiments, C9ORF72 specific inhibitors may affect other molecular processes in an animal.

“Cap structure” or “terminal cap moiety” means chemical modifications, which have been incorporated at either terminus of an antisense compound.

“cEt” or “constrained ethyl” means a bicyclic nucleoside having a sugar moiety comprising a bridge connecting the 4'-carbon and the 2'-carbon, wherein the bridge has the formula: 4'-CH(CH₃)-O-2'.

“Constrained ethyl nucleoside” (also cEt nucleoside) means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-CH(CH₃)-O-2' bridge.

“Chemically distinct region” refers to a region of an antisense compound that is in some way chemically different than another region of the same antisense compound. For example, a region having 2'-O-methoxyethyl nucleosides is chemically distinct from a region having nucleosides without 2'-O-methoxyethyl modifications.

“Chimeric antisense compound” means an antisense compound that has at least two chemically distinct regions, each position having a plurality of subunits.

“Co-administration” means administration of two or more pharmaceutical agents to an individual. The two or more pharmaceutical agents may be in a single pharmaceutical composition, or may be in separate pharmaceutical compositions. Each of the two or more pharmaceutical agents may be administered through the same or different routes of administration. Co-administration
5 encompasses parallel or sequential administration.

“Complementarity” means the capacity for pairing between nucleobases of a first nucleic acid and a second nucleic acid.

“Comprise,” “comprises,” and “comprising” will be understood to imply the inclusion of a stated step or element or group of steps or elements but not the exclusion of any other step or
10 element or group of steps or elements.

“Contiguous nucleobases” means nucleobases immediately adjacent to each other.

“Designing” or “designed to” refer to the process of designing an oligomeric compound that specifically hybridizes with a selected nucleic acid molecule.

“Diluent” means an ingredient in a composition that lacks pharmacological activity, but is
15 pharmaceutically necessary or desirable. For example, in drugs that are injected, the diluent may be a liquid, e.g. saline solution.

“Dose” means a specified quantity of a pharmaceutical agent provided in a single administration, or in a specified time period. In certain embodiments, a dose may be administered in one, two, or more boluses, tablets, or injections. For example, in certain embodiments where
20 subcutaneous administration is desired, the desired dose requires a volume not easily accommodated by a single injection, therefore, two or more injections may be used to achieve the desired dose. In certain embodiments, the pharmaceutical agent is administered by infusion over an extended period of time or continuously. Doses may be stated as the amount of pharmaceutical agent per hour, day, week, or month.

“Effective amount” in the context of modulating an activity or of treating or preventing a condition means the administration of that amount of pharmaceutical agent to a subject in need of such modulation, treatment, or prophylaxis, either in a single dose or as part of a series, that is effective for modulation of that effect, or for treatment or prophylaxis or improvement of that condition. The effective amount may vary among individuals depending on the health and physical
25 condition of the individual to be treated, the taxonomic group of the individuals to be treated, the formulation of the composition, assessment of the individual’s medical condition, and other relevant factors.
30

“Efficacy” means the ability to produce a desired effect.

“Expression” includes all the functions by which a gene’s coded information is converted into structures present and operating in a cell. Such structures include, but are not limited to the products of transcription and translation.

5 “Foci” means a nuclear foci comprising a C9ORF72 transcript. In certain embodiments, a foci comprises at least one C9ORF72 transcript. In certain embodiments, C9ORF72 foci comprise transcripts comprising any of the following hexanucleotide repeats: GGGGCC, GGGGGG, GGGGGC, and/or GGGGCG.

10 “Fully complementary” or “100% complementary” means each nucleobase of a first nucleic acid has a complementary nucleobase in a second nucleic acid. In certain embodiments, a first nucleic acid is an antisense compound and a target nucleic acid is a second nucleic acid.

“Gapmer” means a chimeric antisense compound in which an internal region having a plurality of nucleosides that support RNase H cleavage is positioned between external regions having one or more nucleosides, wherein the nucleosides comprising the internal region are
15 chemically distinct from the nucleoside or nucleosides comprising the external regions. The internal region may be referred to as a “gap” and the external regions may be referred to as the “wings.”

“Gap-narrowed” means a chimeric antisense compound having a gap segment of 9 or fewer contiguous 2’-deoxyribonucleosides positioned between and immediately adjacent to 5’ and 3’ wing segments having from 1 to 6 nucleosides.

20 “Gap-widened” means a chimeric antisense compound having a gap segment of 12 or more contiguous 2’-deoxyribonucleosides positioned between and immediately adjacent to 5’ and 3’ wing segments having from 1 to 6 nucleosides.

“Hexanucleotide repeat expansion” means a series of six bases (for example, GGGGCC, GGGGGG, GGGGCG, or GGGGGC) repeated at least twice. In certain embodiments, the
25 hexanucleotide repeat expansion may be located in intron 1 of a C9ORF72 nucleic acid. In certain embodiments, a pathogenic hexanucleotide repeat expansion includes at least 24 repeats of GGGGCC, GGGGGG, GGGGCG, or GGGGGC in a C9ORF72 nucleic acid and is associated with disease. In certain embodiments, the repeats are consecutive. In certain embodiments, the repeats are interrupted by 1 or more nucleobases. In certain embodiments, a wild-type hexanucleotide
30 repeat expansion includes 23 or fewer repeats of GGGGCC, GGGGGG, GGGGCG, or GGGGGC in a C9ORF72 nucleic acid. In certain embodiments, the repeats are consecutive. In certain embodiments, the repeats are interrupted by 1 or more nucleobases.

“Hybridization” means the annealing of complementary nucleic acid molecules. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an antisense compound and a target nucleic acid. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an antisense oligonucleotide and a nucleic acid target.

5 “Identifying an animal having a C9ORF72 associated disease” means identifying an animal having been diagnosed with a C9ORF72 associated disease or predisposed to develop a C9ORF72 associated disease. Individuals predisposed to develop a C9ORF72 associated disease include those having one or more risk factors for developing a C9ORF72 associated disease, including, having a personal or family history or genetic predisposition of one or more C9ORF72 associated diseases.
10 Such identification may be accomplished by any method including evaluating an individual’s medical history and standard clinical tests or assessments, such as genetic testing.

“Immediately adjacent” means there are no intervening elements between the immediately adjacent elements.

“Individual” means a human or non-human animal selected for treatment or therapy.

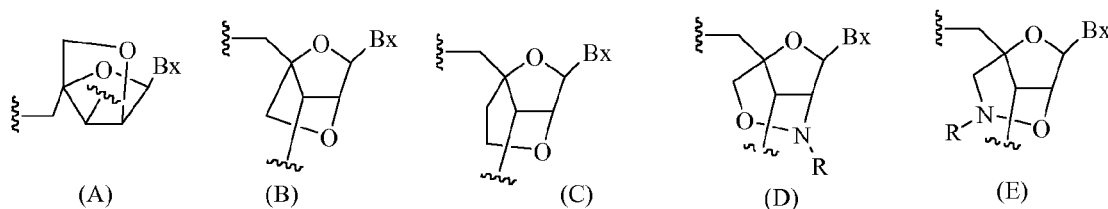
15 “Inhibiting C9ORF72” means reducing the level or expression of a C9ORF72 mRNA and/or protein. In certain embodiments, C9ORF72 mRNA and/or protein levels are inhibited in the presence of an antisense compound targeting C9ORF72, including an antisense oligonucleotide targeting C9ORF72, as compared to expression of C9ORF72 mRNA and/or protein levels in the absence of a C9ORF72 antisense compound, such as an antisense oligonucleotide.

20 “Inhibiting the expression or activity” refers to a reduction or blockade of the expression or activity and does not necessarily indicate a total elimination of expression or activity.

“Internucleoside linkage” refers to the chemical bond between nucleosides.

“Linked nucleosides” means adjacent nucleosides linked together by an internucleoside linkage.

25 “Locked nucleic acid” or “LNA” or “LNA nucleosides” means nucleic acid monomers having a bridge connecting two carbon atoms between the 4’ and 2’ position of the nucleoside sugar unit, thereby forming a bicyclic sugar. Examples of such bicyclic sugar include, but are not limited to A) α -L-Methyleneoxy (4’-CH₂-O-2’) LNA, (B) β -D-Methyleneoxy (4’-CH₂-O-2’) LNA, (C) Ethyleneoxy (4’-(CH₂)₂-O-2’) LNA, (D) Aminooxy (4’-CH₂-O-N(R)-2’) LNA and (E) Oxyamino
30 (4’-CH₂-N(R)-O-2’) LNA, as depicted below.



As used herein, LNA compounds include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the sugar wherein each of the bridges independently comprises 1 or from 2 to 4 linked groups independently selected from $-\text{C}(\text{R}_1)(\text{R}_2)_n-$, $-\text{C}(\text{R}_1)=\text{C}(\text{R}_2)-$, $-\text{C}(\text{R}_1)=\text{N}-$, $-\text{C}(=\text{NR}_1)-$, $-\text{C}(=\text{O})-$, $-\text{C}(=\text{S})-$, $-\text{O}-$, $-\text{Si}(\text{R}_1)_2-$, $-\text{S}(=\text{O})_x-$ and $-\text{N}(\text{R}_1)-$; wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; each R_1 and R_2 is, independently, H, a protecting group, hydroxyl, C_1 - C_{12} alkyl, substituted C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, substituted C_2 - C_{12} alkynyl, C_5 - C_{20} aryl, substituted C_5 - C_{20} aryl, a heterocycle radical, a substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5 - C_7 alicyclic radical, substituted C_5 - C_7 alicyclic radical, halogen, OJ_1 , NJ_1J_2 , SJ_1 , N_3 , COOJ_1 , acyl ($\text{C}(=\text{O})-\text{H}$), substituted acyl, CN, sulfonyl ($\text{S}(=\text{O})_2-\text{J}_1$), or sulfoxyl ($\text{S}(=\text{O})-\text{J}_1$); and each J_1 and J_2 is, independently, H, C_1 - C_{12} alkyl, substituted C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, substituted C_2 - C_{12} alkynyl, C_5 - C_{20} aryl, substituted C_5 - C_{20} aryl, acyl ($\text{C}(=\text{O})-\text{H}$), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1 - C_{12} aminoalkyl, substituted C_1 - C_{12} aminoalkyl or a protecting group.

Examples of 4' - 2' bridging groups encompassed within the definition of LNA include, but are not limited to one of formulae: $-\text{C}(\text{R}_1)(\text{R}_2)_n-$, $-\text{C}(\text{R}_1)(\text{R}_2)_n-\text{O}-$, $-\text{C}(\text{R}_1\text{R}_2)-\text{N}(\text{R}_1)-\text{O}-$ or $-\text{C}(\text{R}_1\text{R}_2)-\text{O}-\text{N}(\text{R}_1)-$. Furthermore, other bridging groups encompassed with the definition of LNA are 4'- CH_2 -2', 4'-(CH_2)₂-2', 4'-(CH_2)₃-2', 4'- CH_2 -O-2', 4'-(CH_2)₂-O-2', 4'- CH_2 -O- $\text{N}(\text{R}_1)$ -2' and 4'- CH_2 - $\text{N}(\text{R}_1)$ -O-2'- bridges, wherein each R_1 and R_2 is, independently, H, a protecting group or C_1 - C_{12} alkyl.

Also included within the definition of LNA according to the invention are LNAs in which the 2'-hydroxyl group of the ribosyl sugar ring is connected to the 4' carbon atom of the sugar ring, thereby forming a methyleneoxy (4'- CH_2 -O-2') bridge to form the bicyclic sugar moiety. The bridge can also be a methylene ($-\text{CH}_2-$) group connecting the 2' oxygen atom and the 4' carbon atom, for which the term methyleneoxy (4'- CH_2 -O-2') LNA is used. Furthermore; in the case of the bicyclic sugar moiety having an ethylene bridging group in this position, the term ethyleneoxy (4'- CH_2CH_2 -O-2') LNA is used. α -L- methyleneoxy (4'- CH_2 -O-2'), an isomer of methyleneoxy (4'- CH_2 -O-2') LNA is also encompassed within the definition of LNA, as used herein.

“Mismatch” or “non-complementary nucleobase” refers to the case when a nucleobase of a first nucleic acid is not capable of pairing with the corresponding nucleobase of a second or target nucleic acid.

“Modified internucleoside linkage” refers to a substitution or any change from a naturally occurring internucleoside bond (*i.e.*, a phosphodiester internucleoside bond).

“Modified nucleobase” means any nucleobase other than adenine, cytosine, guanine, thymidine, or uracil. An “unmodified nucleobase” means the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C), and uracil (U).

“Modified nucleoside” means a nucleoside having, independently, a modified sugar moiety and/or modified nucleobase.

“Modified nucleotide” means a nucleotide having, independently, a modified sugar moiety, modified internucleoside linkage, and/or modified nucleobase.

“Modified oligonucleotide” means an oligonucleotide comprising at least one modified internucleoside linkage, modified sugar, and/or modified nucleobase.

“Modified sugar” means substitution and/or any change from a natural sugar moiety.

“Monomer” means a single unit of an oligomer. Monomers include, but are not limited to, nucleosides and nucleotides, whether naturally occurring or modified.

“Motif” means the pattern of unmodified and modified nucleoside in an antisense compound.

“Natural sugar moiety” means a sugar moiety found in DNA (2'-H) or RNA (2'-OH).

“Naturally occurring internucleoside linkage” means a 3' to 5' phosphodiester linkage.

“Non-complementary nucleobase” refers to a pair of nucleobases that do not form hydrogen bonds with one another or otherwise support hybridization.

“Nucleic acid” refers to molecules composed of monomeric nucleotides. A nucleic acid includes, but is not limited to, ribonucleic acids (RNA), deoxyribonucleic acids (DNA), single-stranded nucleic acids, double-stranded nucleic acids, small interfering ribonucleic acids (siRNA), and microRNAs (miRNA).

“Nucleobase” means a heterocyclic moiety capable of pairing with a base of another nucleic acid.

“Nucleobase complementarity” refers to a nucleobase that is capable of base pairing with another nucleobase. For example, in DNA, adenine (A) is complementary to thymine (T). For example, in RNA, adenine (A) is complementary to uracil (U). In certain embodiments, complementary nucleobase refers to a nucleobase of an antisense compound that is capable of base

pairing with a nucleobase of its target nucleic acid. For example, if a nucleobase at a certain position of an antisense compound is capable of hydrogen bonding with a nucleobase at a certain position of a target nucleic acid, then the position of hydrogen bonding between the oligonucleotide and the target nucleic acid is considered to be complementary at that nucleobase pair.

5 “Nucleobase sequence” means the order of contiguous nucleobases independent of any sugar, linkage, and/or nucleobase modification.

 “Nucleoside” means a nucleobase linked to a sugar.

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

 “Nucleotide” means a nucleoside having a phosphate group covalently linked to the sugar portion of the nucleoside.

 “Off-target effect” refers to an unwanted or deleterious biological effect associated with modulation of RNA or protein expression of a gene other than the intended target nucleic acid.

25 “Oligomeric compound” or “oligomer” means a polymer of linked monomeric subunits which is capable of hybridizing to at least a region of a nucleic acid molecule.

 “Oligonucleotide” means a polymer of linked nucleosides each of which can be modified or unmodified, independent one from another.

 “Parenteral administration” means administration through injection (*e.g.*, bolus injection) or infusion. Parenteral administration includes subcutaneous administration, intravenous administration, intramuscular administration, intraarterial administration, intraperitoneal

administration, or intracranial administration, e.g., intrathecal or intracerebroventricular administration.

“Peptide” means a molecule formed by linking at least two amino acids by amide bonds. Without limitation, as used herein, peptide refers to polypeptides and proteins.

5 “Pharmaceutical agent” means a substance that provides a therapeutic benefit when administered to an individual. For example, in certain embodiments, an antisense oligonucleotide targeted to C9ORF72 is a pharmaceutical agent.

10 “Pharmaceutical composition” means a mixture of substances suitable for administering to a subject. For example, a pharmaceutical composition may comprise an antisense oligonucleotide and a sterile aqueous solution.

“Pharmaceutically acceptable derivative” encompasses pharmaceutically acceptable salts, conjugates, prodrugs or isomers of the compounds described herein.

15 “Pharmaceutically acceptable salts” means physiologically and pharmaceutically acceptable salts of antisense compounds, *i.e.*, salts that retain the desired biological activity of the parent oligonucleotide and do not impart undesired toxicological effects thereto.

“Phosphorothioate linkage” means a linkage between nucleosides where the phosphodiester bond is modified by replacing one of the non-bridging oxygen atoms with a sulfur atom. A phosphorothioate linkage is a modified internucleoside linkage.

20 “Portion” means a defined number of contiguous (*i.e.*, linked) nucleobases of a nucleic acid. In certain embodiments, a portion is a defined number of contiguous nucleobases of a target nucleic acid. In certain embodiments, a portion is a defined number of contiguous nucleobases of an antisense compound.

25 “Prevent” or “preventing” refers to delaying or forestalling the onset or development of a disease, disorder, or condition for a period of time from minutes to days, weeks to months, or indefinitely.

“Prodrug” means a therapeutic agent that is prepared in an inactive form that is converted to an active form within the body or cells thereof by the action of endogenous enzymes or other chemicals or conditions.

30 “Prophylactically effective amount” refers to an amount of a pharmaceutical agent that provides a prophylactic or preventative benefit to an animal.

“Region” is defined as a portion of the target nucleic acid having at least one identifiable structure, function, or characteristic.

“Ribonucleotide” means a nucleotide having a hydroxy at the 2' position of the sugar portion of the nucleotide. Ribonucleotides may be modified with any of a variety of substituents.

“Salts” mean a physiologically and pharmaceutically acceptable salts of antisense compounds, i.e., salts that retain the desired biological activity of the parent oligonucleotide and do not impart undesired toxicological effects thereto.

“Segments” are defined as smaller or sub-portions of regions within a target nucleic acid.

“Shortened” or “truncated” versions of antisense oligonucleotides taught herein have one, two or more nucleosides deleted.

“Side effects” means physiological responses attributable to a treatment other than desired effects. In certain embodiments, side effects include, without limitation, injection site reactions, liver function test abnormalities, renal function abnormalities, liver toxicity, renal toxicity, central nervous system abnormalities, and myopathies.

“Single-stranded oligonucleotide” means an oligonucleotide which is not hybridized to a complementary strand.

“Sites,” as used herein, are defined as unique nucleobase positions within a target nucleic acid.

“Slows progression” means decrease in the development of the disease.

“Specifically hybridizable” refers to an antisense compound having a sufficient degree of complementarity between an antisense oligonucleotide and a target nucleic acid to induce a desired effect, while exhibiting minimal or no effects on non-target nucleic acids under conditions in which specific binding is desired, i.e., under physiological conditions in the case of *in vivo* assays and therapeutic treatments.

“Stringent hybridization conditions” or “stringent conditions” refer to conditions under which an oligomeric compound will hybridize to its target sequence, but to a minimal number of other sequences.

“Subject” means a human or non-human animal selected for treatment or therapy.

“Target” refers to a protein, the modulation of which is desired.

“Target gene” refers to a gene encoding a target.

“Targeting” or “targeted” means the process of design and selection of an antisense compound that will specifically hybridize to a target nucleic acid and induce a desired effect.

“Target nucleic acid,” “target RNA,” and “target RNA transcript” and “nucleic acid target” all mean a nucleic acid capable of being targeted by antisense compounds.

“Target region” means a portion of a target nucleic acid to which one or more antisense compounds is targeted.

“Target segment” means the sequence of nucleotides of a target nucleic acid to which an antisense compound is targeted. “5’ target site” refers to the 5’-most nucleotide of a target segment.
5 “3’ target site” refers to the 3’-most nucleotide of a target segment.

“Therapeutically effective amount” means an amount of a pharmaceutical agent that provides a therapeutic benefit to an individual.

“Treat” or “treating” or “treatment” means administering a composition to effect an alteration or improvement of a disease or condition.

10 “Unmodified nucleobases” means the purine bases adenine (A) and guanine (G), and the pyrimidine bases (T), cytosine (C), and uracil (U).

“Unmodified nucleotide” means a nucleotide composed of naturally occurring nucleobases, sugar moieties, and internucleoside linkages. In certain embodiments, an unmodified nucleotide is an RNA nucleotide (*i.e.* β -D-ribonucleosides) or a DNA nucleotide (*i.e.* β -D-deoxyribonucleoside).

15 “Wing segment” means a plurality of nucleosides modified to impart to an oligonucleotide properties such as enhanced inhibitory activity, increased binding affinity for a target nucleic acid, or resistance to degradation by *in vivo* nucleases.

Certain Embodiments

20 Certain embodiments provide compositions and methods for decreasing total C9ORF72 mRNA and protein expression.

Certain embodiments provide compositions and methods for decreasing C9ORF72 pathogenic associated mRNA variants.

25 Certain embodiments provide methods for the treatment, prevention, or amelioration of diseases, disorders, and conditions associated with C9ORF72 in an individual in need thereof. Also contemplated are methods for the preparation of a medicament for the treatment, prevention, or amelioration of a disease, disorder, or condition associated with C9ORF72. C9ORF72 associated diseases, disorders, and conditions include neurodegenerative diseases. In certain embodiments, the neurodegenerative disease may be ALS or FTD. In certain embodiments, the neurodegenerative
30 disease may be familial or sporadic.

Certain embodiments provide compositions and methods for the treatment, prevention, or amelioration of a C9ORF72 hexanucleotide repeat expansion associated disease. In certain

embodiments, the hexanucleotide repeat expansion may comprise GGGGCC, GGGGGG, GGGGGC, or GGGGCG.

Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases of any of the nucleobase sequences of SEQ ID NOs: SEQ ID NOs: 20-401 and 441-1545.

Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 1107-1520 of SEQ ID NO: 2.

Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 1111-1200 of SEQ ID NO: 2.

Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 1211-1318 of SEQ ID NO: 2.

Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 1326-1540 of SEQ ID NO: 2.

Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 1331-1375 of SEQ ID NO: 2.

Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of
5 nucleobases 1368-1391 of SEQ ID NO: 2

Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of
10 nucleobases 1398-1424 of SEQ ID NO: 2.

Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of
15 nucleobases 1411-1440 of SEQ ID NO: 2.

Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of
20 nucleobases 1429-1481 of SEQ ID NO: 2.

Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of
25 nucleobases 1502-1539 of SEQ ID NO: 2.

Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of
30 nucleobases 1508-1539 of SEQ ID NO: 2.

Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 7860-7906 of SEQ ID NO: 2.

5 Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 7907-9744 of SEQ ID NO: 2.

10 Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 7989-8038 of SEQ ID NO: 2.

15 Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 8020-8135 of SEQ ID NO: 2.

20 Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 8136-8161 of SEQ ID NO: 2.

25 Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 8174-8211 of SEQ ID NO: 2.

30 Provided herein are compounds, comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising 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, at

least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 8213-8325 of SEQ ID NO: 2.

In certain embodiments, the nucleobase sequence of the modified oligonucleotide is at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%,
5 at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% complementary to SEQ ID NO: 1.

In certain embodiments, the modified oligonucleotide is a single-stranded modified oligonucleotide.

10 In certain embodiments at least one internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.

In certain embodiments, at least one modified internucleoside linkage is a phosphorothioate internucleoside linkage.

In certain embodiments, each modified internucleoside linkage is a phosphorothioate
15 internucleoside linkage.

In certain embodiments, at least one internucleoside linkage is a phosphodiester internucleoside linkage.

In certain embodiments, at least one internucleoside linkage is a phosphorothioate linkage and at least one internucleoside linkage is a phosphodiester linkage.

20 In certain embodiments, at least one nucleoside comprises a modified nucleobase.

In certain embodiments, the modified nucleobase is a 5-methylcytosine.

In certain embodiments, at least one nucleoside of the modified oligonucleotide comprises a modified sugar.

In certain embodiments, the at least one modified sugar is a bicyclic sugar.

25 In certain embodiments, the bicyclic sugar comprises a chemical link between the 2' and 4' position of the sugar 4'-CH₂-N(R)-O-2' bridge wherein R is, independently, H, C1-C12 alkyl, or a protecting group.

In certain embodiments, the bicyclic sugar comprises a 4'-CH₂-N(R)-O-2' bridge wherein R is, independently, H, C1-C12 alkyl, or a protecting group.

30 In certain embodiments, at least one modified sugar comprises a 2'-O-methoxyethyl group.

In certain embodiments, the modified sugar comprises a 2'-O(CH₂)₂-OCH₃ group.

In certain embodiments, the modified oligonucleotide comprises:

a gap segment consisting of 10 linked deoxynucleosides;

a 5' wing segment consisting of 5 linked nucleosides; and

a 3' wing segment consisting of 5 linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment
5 and wherein each nucleoside of each wing segment comprises a modified sugar.

In certain embodiments, the modified oligonucleotide comprises:

a gap segment consisting of 8 linked deoxynucleosides;

a 5' wing segment consisting of 5 linked nucleosides; and

a 3' wing segment consisting of 5 linked nucleosides;

10 wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment
and wherein each nucleoside of each wing segment comprises a modified sugar.

In certain embodiments, the modified oligonucleotide comprises sugar modifications in any
of the following patterns: eekkkdddddddkkeee, eekkkdddddddkkeee, ekdddddddekekeee,
kekeddddddddekeke, and ekekdddddddkkeee; wherein,

15 e = a 2'-O-methoxyethyl modified nucleoside

d = a 2'-deoxynucleoside, and

k = a cEt nucleoside.

In certain embodiments, the modified oligonucleotide comprises internucleoside linkages in
any of the following patterns: sooooo:sssssssssooss, sooooo:sssssssssooss, sooooo:sssssssssooss, and
20 sooooo:sssssssssooss; wherein,

s = a phosphorothioate linkage, and

o = a phosphodiester linkage.

In certain embodiments, the modified oligonucleotide consists of 20 linked nucleosides.

In certain embodiments, the modified oligonucleotide consists of 19 linked nucleosides.

25 In certain embodiments, the modified oligonucleotide consists of 18 linked nucleosides.

In certain embodiments, the modified oligonucleotide consists of 17 linked nucleosides.

Provided herein are compositions comprising the compound of any preceding claim or salt thereof and at least one of a pharmaceutically acceptable carrier or diluent.

Provided herein are methods comprising administering to an animal the compound or composition of any preceding claim.

5 In certain embodiments, the animal is a human.

In certain embodiments, administering the compound prevents, treats, ameliorates, or slows progression of a C9ORF72 associated disease, disorder or condition.

10 In certain embodiments, administering the compound prevents, treats, ameliorates, or slows progression of a C9ORF72 hexanucleotide repeat expansion associated disease, disorder or condition.

In certain embodiments, the disease, disorder or condition is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), corticalbasal degeneration syndrome (CBD), atypical Parkinsonian syndrome, and olivopontocerellar degeneration (OPCD).

In certain embodiments, the administering reduces nuclear foci.

15 In certain embodiments, the administering reduces expression of C9ORF72 associated RAN translation products.

In certain embodiments, the C9ORF72 associated RAN translation products are any of poly-(glycine-proline), poly-(glycine-alanine), and poly-(glycine-arginine).

20 Provided herein are uses of the compound or composition of any preceding claim for the manufacture of a medicament for treating a neurodegenerative disorder.

Provided herein are methods of selectively inhibiting a C9ORF72 pathogenic associated mRNA variant by administering an antisense compound targeting the region beginning at the start site of exon 1A to the start site of exon 1B of a C9ORF72 pre-mRNA.

25 *Antisense Compounds*

Oligomeric compounds include, but are not limited to, oligonucleotides, oligonucleosides, oligonucleotide analogs, oligonucleotide mimetics, antisense compounds, antisense oligonucleotides, and siRNAs. An oligomeric compound may be “antisense” to a target nucleic

acid, meaning that it is capable of undergoing hybridization to a target nucleic acid through hydrogen bonding.

In certain embodiments, an antisense compound has a nucleobase sequence that, when written in the 5' to 3' direction, comprises the reverse complement of the target segment of a target nucleic acid to which it is targeted. In certain such embodiments, an antisense oligonucleotide has a nucleobase sequence that, when written in the 5' to 3' direction, comprises the reverse complement of the target segment of a target nucleic acid to which it is targeted.

In certain embodiments, an antisense compound targeted to a C9ORF72 nucleic acid is 12 to 30 subunits in length. In other words, such antisense compounds are from 12 to 30 linked subunits.

In certain embodiments, the antisense compound is 8 to 80, 12 to 50, 15 to 30, 18 to 24, 19 to 22, or 20 linked subunits. In certain embodiments, the antisense compounds are 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, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 linked subunits in length, or a range defined by any two of the above values. In some embodiments the antisense compound is an antisense oligonucleotide, and the linked subunits are nucleosides.

In certain embodiments antisense oligonucleotides targeted to a C9ORF72 nucleic acid may be shortened or truncated. For example, a single subunit may be deleted from the 5' end (5' truncation), or alternatively from the 3' end (3' truncation). A shortened or truncated antisense compound targeted to a C9ORF72 nucleic acid may have two subunits deleted from the 5' end, or alternatively may have two subunits deleted from the 3' end, of the antisense compound. Alternatively, the deleted nucleosides may be dispersed throughout the antisense compound, for example, in an antisense compound having one nucleoside deleted from the 5' end and one nucleoside deleted from the 3' end.

When a single additional subunit is present in a lengthened antisense compound, the additional subunit may be located at the 5' or 3' end of the antisense compound. When two or more additional subunits are present, the added subunits may be adjacent to each other, for example, in an antisense compound having two subunits added to the 5' end (5' addition), or alternatively to the 3' end (3' addition), of the antisense compound. Alternatively, the added subunits may be dispersed throughout the antisense compound, for example, in an antisense compound having one subunit added to the 5' end and one subunit added to the 3' end.

It is possible to increase or decrease the length of an antisense compound, such as an antisense oligonucleotide, and/or introduce mismatch bases without eliminating activity. For example, in Woolf et al. (Proc. Natl. Acad. Sci. USA 89:7305-7309, 1992), a series of antisense oligonucleotides 13-25 nucleobases in length were tested for their ability to induce cleavage of a target RNA in an oocyte injection model. Antisense oligonucleotides 25 nucleobases in length with 8 or 11 mismatch bases near the ends of the antisense oligonucleotides were able to direct specific cleavage of the target mRNA, albeit to a lesser extent than the antisense oligonucleotides that contained no mismatches. Similarly, target specific cleavage was achieved using 13 nucleobase antisense oligonucleotides, including those with 1 or 3 mismatches.

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

Antisense Compound Motifs

In certain embodiments, antisense compounds targeted to a C9ORF72 nucleic acid have chemically modified subunits arranged in patterns, or motifs, to confer to the antisense compounds properties such as enhanced inhibitory activity, increased binding affinity for a target nucleic acid, or resistance to degradation by *in vivo* nucleases.

Chimeric antisense compounds typically contain at least one region modified so as to confer increased resistance to nuclease degradation, increased cellular uptake, increased binding affinity for the target nucleic acid, and/or increased inhibitory activity. A second region of a chimeric antisense compound may optionally serve as a substrate for the cellular endonuclease RNase H, which cleaves the RNA strand of an RNA:DNA duplex.

Antisense compounds having a gapmer motif are considered chimeric antisense compounds. In a gapmer an internal region having a plurality of nucleotides that supports RNaseH

cleavage is positioned between external regions having a plurality of nucleotides that are chemically distinct from the nucleosides of the internal region. In the case of an antisense oligonucleotide having a gapmer motif, the gap segment generally serves as the substrate for endonuclease cleavage, while the wing segments comprise modified nucleosides. In certain embodiments, the regions of a gapmer are differentiated by the types of sugar moieties comprising each distinct region. The types of sugar moieties that are used to differentiate the regions of a gapmer may in some embodiments include β -D-ribonucleosides, β -D-deoxyribonucleosides, 2'-modified nucleosides (such 2'-modified nucleosides may include 2'-MOE, and 2'-O-CH₃, among others), and bicyclic sugar modified nucleosides (such bicyclic sugar modified nucleosides may include those having a 4'-(CH₂)_n-O-2' bridge, where n=1 or n=2 and 4'-CH₂-O-CH₂-2'). Preferably, each distinct region comprises uniform sugar moieties. The wing-gap-wing motif is frequently described as "X-Y-Z", where "X" represents the length of the 5' wing region, "Y" represents the length of the gap region, and "Z" represents the length of the 3' wing region. As used herein, a gapmer described as "X-Y-Z" has a configuration such that the gap segment is positioned immediately adjacent to each of the 5' wing segment and the 3' wing segment. Thus, no intervening nucleotides exist between the 5' wing segment and gap segment, or the gap segment and the 3' wing segment. Any of the antisense compounds described herein can have a gapmer motif. In some embodiments, X and Z are the same, in other embodiments they are different. In a preferred embodiment, Y is between 8 and 15 nucleotides. X, Y or Z can be any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30 or more nucleotides. Thus, gapmers described herein include, but are not limited to, for example 5-10-5, 5-10-4, 4-10-4, 4-10-3, 3-10-3, 2-10-2, 5-9-5, 5-9-4, 4-9-5, 5-8-5, 5-8-4, 4-8-5, 5-7-5, 4-7-5, 5-7-4, or 4-7-4.

In certain embodiments, the antisense compound has a "wingmer" motif, having a wing-gap or gap-wing configuration, i.e. an X-Y or Y-Z configuration as described above for the gapmer configuration. Thus, wingmer configurations described herein include, but are not limited to, for example 5-10, 8-4, 4-12, 12-4, 3-14, 16-2, 18-1, 10-3, 2-10, 1-10, 8-2, 2-13, 5-13, 5-8, or 6-8.

In certain embodiments, antisense compounds targeted to a C9ORF72 nucleic acid possess a 5-10-5 gapmer motif.

In certain embodiments, antisense compounds targeted to a C9ORF72 nucleic acid possess a 5-8-5 gapmer motif.

In certain embodiments, antisense compounds targeted to a C9ORF72 nucleic acid possess sugar modifications in any of the following patterns: eekkkdddddskkeee, eekkkdddddskkeee, ekddddddekekeee, kekedddddddekeke, and ekekddddddekeee; wherein,

e = a 2'-O-methoxyethyl modified nucleoside

5 d = a 2'-deoxynucleoside, and

k = a cEt nucleoside.

In certain embodiments, an antisense compound targeted to a C9ORF72 nucleic acid has a gap-narrowed motif. In certain embodiments, a gap-narrowed antisense oligonucleotide targeted to a C9ORF72 nucleic acid has a gap segment of 9, 8, 7, or 6 2'-deoxynucleotides positioned
 10 immediately adjacent to and between wing segments of 5, 4, 3, 2, or 1 chemically modified nucleosides. In certain embodiments, the chemical modification comprises a bicyclic sugar. In certain embodiments, the bicyclic sugar comprises a 4' to 2' bridge selected from among: 4'-(CH₂)_n-O-2' bridge, wherein n is 1 or 2; and 4'-CH₂-O-CH₂-2'. In certain embodiments, the bicyclic sugar is comprises a 4'-CH(CH₃)-O-2' bridge. In certain embodiments, the chemical modification
 15 comprises a non-bicyclic 2'-modified sugar moiety. In certain embodiments, the non-bicyclic 2'-modified sugar moiety comprises a 2'-O-methylethyl group or a 2'-O-methyl group.

Target Nucleic Acids, Target Regions and Nucleotide Sequences

Nucleotide sequences that encode C9ORF72 include, without limitation, the following: the
 20 complement of GENBANK Accession No. NM_001256054.1 (incorporated herein as SEQ ID NO: 1), GENBANK Accession No. NT_008413.18 truncated from nucleobase 27535000 to 27565000 (incorporated herein as SEQ ID NO: 2), GENBANK Accession No. BQ068108.1 (incorporated herein as SEQ ID NO: 3), GENBANK Accession No. NM_018325.3 (incorporated herein as SEQ ID NO: 4), GENBANK Accession No. DN993522.1 (incorporated herein as SEQ ID NO: 5),
 25 GENBANK Accession No. NM_145005.5 (incorporated herein as SEQ ID NO: 6), GENBANK Accession No. DB079375.1 (incorporated herein as SEQ ID NO: 7), GENBANK Accession No. BU194591.1 (incorporated herein as SEQ ID NO: 8), Sequence Identifier 4141_014_A (incorporated herein as SEQ ID NO: 9), and Sequence Identifier 4008_73_A (incorporated herein as SEQ ID NO: 10), and GENBANK Accession No. NW_001101662.1 truncated from nucleosides
 30 8522000 to 8552000 (incorporated herein as SEQ ID NO: 19).

It is understood that the sequence set forth in each SEQ ID NO in the Examples contained herein is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, antisense compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Antisense compounds described by Isis Number (Isis No) indicate a combination of nucleobase sequence and motif.

In certain embodiments, a target region is a structurally defined region of the target nucleic acid. For example, a target region may encompass a 3' UTR, a 5' UTR, an exon, an intron, an exon/intron junction, a coding region, a translation initiation region, translation termination region, or other defined nucleic acid region. The structurally defined regions for C9ORF72 can be obtained by accession number from sequence databases such as NCBI and such information is incorporated herein by reference. In certain embodiments, a target region may encompass the sequence from a 5' target site of one target segment within the target region to a 3' target site of another target segment within the same target region.

Targeting includes determination of at least one target segment to which an antisense compound hybridizes, such that a desired effect occurs. In certain embodiments, the desired effect is a reduction in mRNA target nucleic acid levels. In certain embodiments, the desired effect is reduction of levels of protein encoded by the target nucleic acid or a phenotypic change associated with the target nucleic acid.

A target region may contain one or more target segments. Multiple target segments within a target region may be overlapping. Alternatively, they may be non-overlapping. In certain embodiments, target segments within a target region are separated by no more than about 300 nucleotides. In certain embodiments, target segments within a target region are separated by a number of nucleotides that is, is about, is no more than, is no more than about, 250, 200, 150, 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10 nucleotides on the target nucleic acid, or is a range defined by any two of the preceding values. In certain embodiments, target segments within a target region are separated by no more than, or no more than about, 5 nucleotides on the target nucleic acid. In certain embodiments, target segments are contiguous. Contemplated are target regions defined by a range having a starting nucleic acid that is any of the 5' target sites or 3' target sites listed herein.

Suitable target segments may be found within a 5' UTR, a coding region, a 3' UTR, an intron, an exon, or an exon/intron junction. Target segments containing a start codon or a stop

codon are also suitable target segments. A suitable target segment may specifically exclude a certain structurally defined region such as the start codon or stop codon.

The determination of suitable target segments may include a comparison of the sequence of a target nucleic acid to other sequences throughout the genome. For example, the BLAST algorithm
5 may be used to identify regions of similarity amongst different nucleic acids. This comparison can prevent the selection of antisense compound sequences that may hybridize in a non-specific manner to sequences other than a selected target nucleic acid (i.e., non-target or off-target sequences).

There may be variation in activity (e.g., as defined by percent reduction of target nucleic acid levels) of the antisense compounds within a target region. In certain embodiments, reductions
10 in C9ORF72 mRNA levels are indicative of inhibition of C9ORF72 expression. Reductions in levels of a C9ORF72 protein are also indicative of inhibition of target mRNA expression. Reduction in the presence of expanded C9ORF72 RNA foci are indicative of inhibition of C9ORF72 expression. Further, phenotypic changes are indicative of inhibition of C9ORF72 expression. For example, improved motor function and respiration may be indicative of inhibition of C9ORF72 expression.

Hybridization

In some embodiments, hybridization occurs between an antisense compound disclosed herein and a C9ORF72 nucleic acid. The most common mechanism of hybridization involves hydrogen bonding (e.g., Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding)
20 between complementary nucleobases of the nucleic acid molecules.

Hybridization can occur under varying conditions. Stringent conditions are sequence-dependent and are determined by the nature and composition of the nucleic acid molecules to be hybridized.

Methods of determining whether a sequence is specifically hybridizable to a target nucleic
25 acid are well known in the art. In certain embodiments, the antisense compounds provided herein are specifically hybridizable with a C9ORF72 nucleic acid.

Complementarity

An antisense compound and a target nucleic acid are complementary to each other when a
30 sufficient number of nucleobases of the antisense compound can hydrogen bond with the corresponding nucleobases of the target nucleic acid, such that a desired effect will occur (e.g., antisense inhibition of a target nucleic acid, such as a C9ORF72 nucleic acid).

Non-complementary nucleobases between an antisense compound and a C9ORF72 nucleic acid may be tolerated provided that the antisense compound remains able to specifically hybridize to a target nucleic acid. Moreover, an antisense compound may hybridize over one or more segments of a C9ORF72 nucleic acid such that intervening or adjacent segments are not involved in the hybridization event (e.g., a loop structure, mismatch or hairpin structure).

In certain embodiments, the antisense compounds provided herein, or a specified portion thereof, are, or are at least, 70%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to a C9ORF72 nucleic acid, a target region, target segment, or specified portion thereof. Percent complementarity of an antisense compound with a target nucleic acid can be determined using routine methods.

For example, an antisense compound in which 18 of 20 nucleobases of the antisense compound are complementary to a target region, and would therefore specifically hybridize, would represent 90 percent complementarity. In this example, the remaining noncomplementary nucleobases may be clustered or interspersed with complementary nucleobases and need not be contiguous to each other or to complementary nucleobases. As such, an antisense compound which is 18 nucleobases in length having 4 (four) noncomplementary nucleobases which are flanked by two regions of complete complementarity with the target nucleic acid would have 77.8% overall complementarity with the target nucleic acid and would thus fall within the scope of the present invention. Percent complementarity of an antisense compound with a region of a target nucleic acid can be determined routinely using BLAST programs (basic local alignment search tools) and PowerBLAST programs known in the art (Altschul et al., J. Mol. Biol., 1990, 215, 403 410; Zhang and Madden, Genome Res., 1997, 7, 649 656). Percent homology, sequence identity or complementarity, can be determined by, for example, the Gap program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, Madison Wis.), using default settings, which uses the algorithm of Smith and Waterman (Adv. Appl. Math., 1981, 2, 482 489).

In certain embodiments, the antisense compounds provided herein, or specified portions thereof, are fully complementary (*i.e.*, 100% complementary) to a target nucleic acid, or specified portion thereof. For example, an antisense compound may be fully complementary to a C9ORF72 nucleic acid, or a target region, or a target segment or target sequence thereof. As used herein, “fully complementary” means each nucleobase of an antisense compound is capable of precise base pairing with the corresponding nucleobases of a target nucleic acid. For example, a 20 nucleobase

antisense compound is fully complementary to a target sequence that is 400 nucleobases long, so long as there is a corresponding 20 nucleobase portion of the target nucleic acid that is fully complementary to the antisense compound. Fully complementary can also be used in reference to a specified portion of the first and /or the second nucleic acid. For example, a 20 nucleobase portion of a 30 nucleobase antisense compound can be “fully complementary” to a target sequence that is 400 nucleobases long. The 20 nucleobase portion of the 30 nucleobase oligonucleotide is fully complementary to the target sequence if the target sequence has a corresponding 20 nucleobase portion wherein each nucleobase is complementary to the 20 nucleobase portion of the antisense compound. At the same time, the entire 30 nucleobase antisense compound may or may not be fully complementary to the target sequence, depending on whether the remaining 10 nucleobases of the antisense compound are also complementary to the target sequence.

The location of a non-complementary nucleobase may be at the 5' end or 3' end of the antisense compound. Alternatively, the non-complementary nucleobase or nucleobases may be at an internal position of the antisense compound. When two or more non-complementary nucleobases are present, they may be contiguous (i.e., linked) or non-contiguous. In one embodiment, a non-complementary nucleobase is located in the wing segment of a gapmer antisense oligonucleotide.

In certain embodiments, antisense compounds that are, or are up to 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleobases in length comprise no more than 4, no more than 3, no more than 2, or no more than 1 non-complementary nucleobase(s) relative to a target nucleic acid, such as a C9ORF72 nucleic acid, or specified portion thereof.

In certain embodiments, antisense compounds that are, or are up to 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleobases in length comprise no more than 6, no more than 5, no more than 4, no more than 3, no more than 2, or no more than 1 non-complementary nucleobase(s) relative to a target nucleic acid, such as a C9ORF72 nucleic acid, or specified portion thereof.

The antisense compounds provided herein also include those which are complementary to a portion of a target nucleic acid. As used herein, “portion” refers to a defined number of contiguous (i.e. linked) nucleobases within a region or segment of a target nucleic acid. A “portion” can also refer to a defined number of contiguous nucleobases of an antisense compound. In certain embodiments, the antisense compounds, are complementary to at least an 8 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 9 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are

complementary to at least a 10 nucleobase portion of a target segment. In certain embodiments, the antisense compounds, are complementary to at least an 11 nucleobase portion of a target segment. In certain embodiments, the antisense compounds, are complementary to at least a 12 nucleobase portion of a target segment. In certain embodiments, the antisense compounds, are complementary to at least a 13 nucleobase portion of a target segment. In certain embodiments, the antisense compounds, are complementary to at least a 14 nucleobase portion of a target segment. In certain embodiments, the antisense compounds, are complementary to at least a 15 nucleobase portion of a target segment. Also contemplated are antisense compounds that are complementary to at least a 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more nucleobase portion of a target segment, or a range defined by any two of these values.

Identity

The antisense compounds provided herein may also have a defined percent identity to a particular nucleotide sequence, SEQ ID NO, or compound represented by a specific Isis number, or portion thereof. As used herein, an antisense compound is identical to the sequence disclosed herein if it has the same nucleobase pairing ability. For example, a RNA which contains uracil in place of thymidine in a disclosed DNA sequence would be considered identical to the DNA sequence since both uracil and thymidine pair with adenine. Shortened and lengthened versions of the antisense compounds described herein as well as compounds having non-identical bases relative to the antisense compounds provided herein also are contemplated. The non-identical bases may be adjacent to each other or dispersed throughout the antisense compound. Percent identity of an antisense compound is calculated according to the number of bases that have identical base pairing relative to the sequence to which it is being compared.

In certain embodiments, the antisense compounds, or portions thereof, are at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to one or more of the antisense compounds or SEQ ID NOs, or a portion thereof, disclosed herein.

In certain embodiments, a portion of the antisense compound is compared to an equal length portion of the target nucleic acid. In certain embodiments, an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleobase portion is compared to an equal length portion of the target nucleic acid.

In certain embodiments, a portion of the antisense oligonucleotide is compared to an equal length portion of the target nucleic acid. In certain embodiments, an 8, 9, 10, 11, 12, 13, 14, 15, 16,

17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleobase portion is compared to an equal length portion of the target nucleic acid.

Modifications

5 A nucleoside is a base-sugar combination. The nucleobase (also known as base) portion of the nucleoside is normally a heterocyclic base moiety. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those nucleosides that include a pentofuranosyl sugar, the phosphate group can be linked to the 2', 3' or 5' hydroxyl moiety of the sugar. Oligonucleotides are formed through the covalent linkage of adjacent
10 nucleosides to one another, to form a linear polymeric oligonucleotide. Within the oligonucleotide structure, the phosphate groups are commonly referred to as forming the internucleoside linkages of the oligonucleotide.

Modifications to antisense compounds encompass substitutions or changes to internucleoside linkages, sugar moieties, or nucleobases. Modified antisense compounds are often
15 preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases, or increased inhibitory activity.

Chemically modified nucleosides may also be employed to increase the binding affinity of a shortened or truncated antisense oligonucleotide for its target nucleic acid. Consequently,
20 comparable results can often be obtained with shorter antisense compounds that have such chemically modified nucleosides.

Modified Internucleoside Linkages

The naturally occurring internucleoside linkage of RNA and DNA is a 3' to 5'
25 phosphodiester linkage. Antisense compounds having one or more modified, i.e. non-naturally occurring, internucleoside linkages are often selected over antisense compounds having naturally occurring internucleoside linkages because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for target nucleic acids, and increased stability in the presence of nucleases.

30 Oligonucleotides having modified internucleoside linkages include internucleoside linkages that retain a phosphorus atom as well as internucleoside linkages that do not have a phosphorus atom. Representative phosphorus containing internucleoside linkages include, but are not limited to,

phosphodiester, phosphotriester, methylphosphonate, phosphoramidate, and phosphorothioates. Methods of preparation of phosphorous-containing and non-phosphorous-containing linkages are well known.

In certain embodiments, antisense compounds targeted to a C9ORF72 nucleic acid
5 comprise one or more modified internucleoside linkages. In certain embodiments, the modified internucleoside linkages are interspersed throughout the antisense compound. In certain embodiments, the modified internucleoside linkages are phosphorothioate linkages. In certain embodiments, each internucleoside linkage of an antisense compound is a phosphorothioate internucleoside linkage. In certain embodiments, the antisense compounds targeted to a C9ORF72
10 nucleic acid comprise at least one phosphodiester linkage and at least one phosphorothioate linkage.

In certain embodiments, antisense compounds targeted to a C9ORF72 nucleic acid possess internucleoside linkages in any of the following patterns: sooooooooooooo, sooooooooooooo, sooooooooooooo, and sooooooooooooo; wherein,

s = a phosphorothioate linkage, and

15 o = a phosphodiester linkage.

Modified Sugar Moieties

Antisense compounds can optionally contain one or more nucleosides wherein the sugar group has been modified. Such sugar modified nucleosides may impart enhanced nuclease stability,
20 increased binding affinity, or some other beneficial biological property to the antisense compounds. In certain embodiments, nucleosides comprise chemically modified ribofuranose ring moieties. Examples of chemically modified ribofuranose rings include without limitation, addition of substituent groups (including 5' and 2' substituent groups, bridging of non-geminal ring atoms to form bicyclic nucleic acids (BNA), replacement of the ribosyl ring oxygen atom with S, N(R), or
25 C(R₁)(R₂) (R, R₁ and R₂ are each independently H, C₁-C₁₂ alkyl or a protecting group) and combinations thereof. Examples of chemically modified sugars include 2'-F-5'-methyl substituted nucleoside (see PCT International Application WO 2008/101157 Published on 8/21/08 for other disclosed 5',2'-bis substituted nucleosides) or replacement of the ribosyl ring oxygen atom with S with further substitution at the 2'-position (see published U.S. Patent Application US2005-0130923,
30 published on June 16, 2005) or alternatively 5'-substitution of a BNA (see PCT International Application WO 2007/134181 Published on 11/22/07 wherein LNA is substituted with for example a 5'-methyl or a 5'-vinyl group).

Examples of nucleosides having modified sugar moieties include without limitation nucleosides comprising 5'-vinyl, 5'-methyl (*R* or *S*), 4'-S, 2'-F, 2'-OCH₃, 2'-OCH₂CH₃, 2'-OCH₂CH₂F and 2'-O(CH₂)₂OCH₃ substituent groups. The substituent at the 2' position can also be selected from allyl, amino, azido, thio, O-allyl, O-C₁-C₁₀ alkyl, OCF₃, OCH₂F, O(CH₂)₂SCH₃,
 5 O(CH₂)₂-O-N(R_m)(R_n), O-CH₂-C(=O)-N(R_m)(R_n), and O-CH₂-C(=O)-N(R₁)-(CH₂)₂-N(R_m)(R_n), where each R₁, R_m and R_n is, independently, H or substituted or unsubstituted C₁-C₁₀ alkyl.

As used herein, "bicyclic nucleosides" refer to modified nucleosides comprising a bicyclic sugar moiety. Examples of bicyclic nucleosides include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In certain embodiments, antisense compounds
 10 provided herein include one or more bicyclic nucleosides comprising a 4' to 2' bridge. Examples of such 4' to 2' bridged bicyclic nucleosides, include but are not limited to one of the formulae: 4'-(CH₂)-O-2' (LNA); 4'-(CH₂)-S-2'; 4'-(CH₂)₂-O-2' (ENA); 4'-CH(CH₃)-O-2' and 4'-CH(CH₂OCH₃)-O-2' (and analogs thereof see U.S. Patent 7,399,845, issued on July 15, 2008); 4'-C(CH₃)(CH₃)-O-2' (and analogs thereof see published International Application WO/2009/006478, published January
 15 8, 2009); 4'-CH₂-N(OCH₃)-2' (and analogs thereof see published International Application WO/2008/150729, published December 11, 2008); 4'-CH₂-O-N(CH₃)-2' (see published U.S. Patent Application US2004-0171570, published September 2, 2004); 4'-CH₂-N(R)-O-2', wherein R is H, C₁-C₁₂ alkyl, or a protecting group (see U.S. Patent 7,427,672, issued on September 23, 2008); 4'-CH₂-C(H)(CH₃)-2' (see Chattopadhyaya *et al.*, *J. Org. Chem.*, 2009, 74, 118-134); and 4'-CH₂-C(=CH₂)-2' (and analogs thereof see published International Application WO 2008/154401, published
 20 on December 8, 2008).

Further reports related to bicyclic nucleosides can also be found in published literature (see for example: Singh *et al.*, *Chem. Commun.*, 1998, 4, 455-456; Koshkin *et al.*, *Tetrahedron*, 1998, 54, 3607-3630; Wahlestedt *et al.*, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, 97, 5633-5638; Kumar *et al.*,
 25 *Bioorg. Med. Chem. Lett.*, 1998, 8, 2219-2222; Singh *et al.*, *J. Org. Chem.*, 1998, 63, 10035-10039; Srivastava *et al.*, *J. Am. Chem. Soc.*, 2007, 129(26) 8362-8379; Elayadi *et al.*, *Curr. Opinion Invest. Drugs*, 2001, 2, 558-561; Braasch *et al.*, *Chem. Biol.*, 2001, 8, 1-7; and Orum *et al.*, *Curr. Opinion Mol. Ther.*, 2001, 3, 239-243; U.S. Patent Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 7,034,133; 7,053,207; 7,399,845; 7,547,684; and 7,696,345; U.S. Patent Publication No.
 30 US2008-0039618; US2009-0012281; U.S. Patent Serial Nos. 60/989,574; 61/026,995; 61/026,998; 61/056,564; 61/086,231; 61/097,787; and 61/099,844; Published PCT International applications WO 1994/014226; WO 2004/106356; WO 2005/021570; WO 2007/134181; WO 2008/150729; WO

2008/154401; and WO 2009/006478. Each of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical sugar configurations including for example α -L-ribofuranose and β -D-ribofuranose (see PCT international application PCT/DK98/00393, published on March 25, 1999 as WO 99/14226).

5 In certain embodiments, bicyclic sugar moieties of BNA nucleosides include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the pentofuranosyl sugar moiety wherein such bridges independently comprises 1 or from 2 to 4 linked groups independently selected from $-[C(R_a)(R_b)]_n-$, $-C(R_a)=C(R_b)-$, $-C(R_a)=N-$, $-C(=O)-$, $-C(=NR_a)-$, $-C(=S)-$, $-O-$, $-Si(R_a)_2-$, $-S(=O)_x-$, and $-N(R_a)-$;

10 wherein:

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

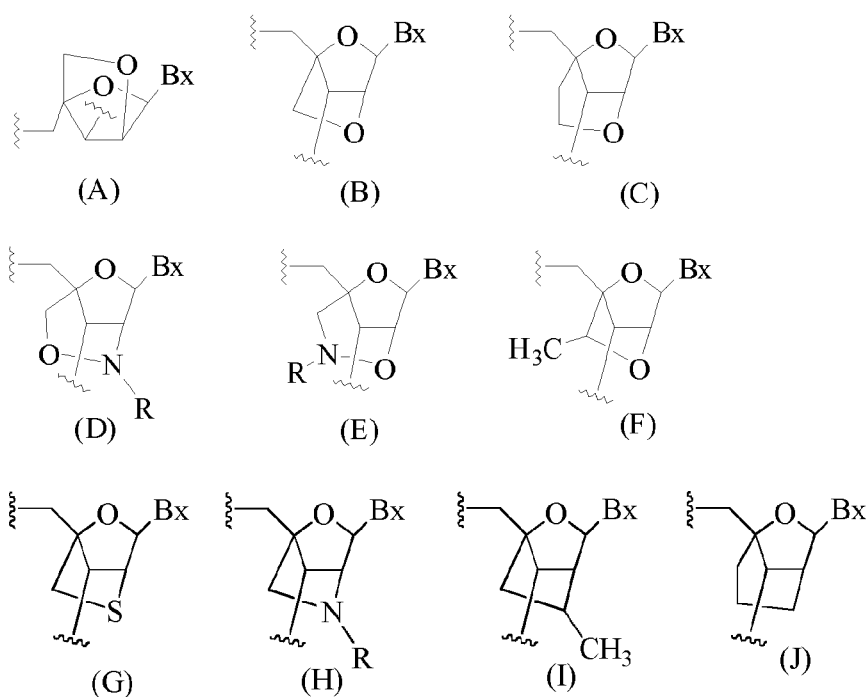
each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1 - C_{12} alkyl, substituted C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, substituted C_2 - C_{12} alkynyl, C_5 - C_{20} aryl, substituted C_5 - C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5 - C_7 alicyclic radical, substituted C_5 - C_7 alicyclic radical, halogen, OJ_1 , NJ_1J_2 , SJ_1 , N_3 , $COOJ_1$, acyl ($C(=O)-H$), substituted acyl, CN, sulfonyl ($S(=O)_2-J_1$), or sulfoxyl ($S(=O)-J_1$); and

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

In certain embodiments, the bridge of a bicyclic sugar moiety is $-[C(R_a)(R_b)]_n-$, $-[C(R_a)(R_b)]_n-O-$, $-C(R_aR_b)-N(R)-O-$ or $-C(R_aR_b)-O-N(R)-$. In certain embodiments, the bridge is 4'-CH₂-2', 4'-(CH₂)₂-2', 4'-(CH₂)₃-2', 4'-CH₂-O-2', 4'-(CH₂)₂-O-2', 4'-CH₂-O-N(R)-2' and 4'-CH₂-N(R)-O-2' wherein each R is, independently, H, a protecting group or C_1 - C_{12} alkyl.

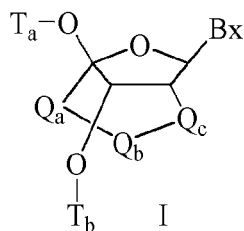
In certain embodiments, bicyclic nucleosides are further defined by isomeric configuration. For example, a nucleoside comprising a 4'-2' methylene-oxy bridge, may be in the α -L configuration or in the β -D configuration. Previously, α -L-methyleneoxy (4'-CH₂-O-2') BNA's have been incorporated into antisense oligonucleotides that showed antisense activity (Frieden *et al.*, *Nucleic Acids Research*, 2003, 21, 6365-6372).

In certain embodiments, bicyclic nucleosides include, but are not limited to, (A) α -L-methyleneoxy (4'-CH₂-O-2') BNA, (B) β -D-methyleneoxy (4'-CH₂-O-2') BNA, (C) ethyleneoxy (4'-(CH₂)₂-O-2') BNA, (D) aminoxy (4'-CH₂-O-N(R)-2') BNA, (E) oxyamino (4'-CH₂-N(R)-O-2') BNA, and (F) methyl(methyleneoxy) (4'-CH(CH₃)-O-2') BNA, (G) methylene-thio (4'-CH₂-S-2') BNA, (H) methylene-amino (4'-CH₂-N(R)-2') BNA, (I) methyl carbocyclic (4'-CH₂-CH(CH₃)-2') BNA, and (J) propylene carbocyclic (4'-(CH₂)₃-2') BNA as depicted below.



wherein Bx is the base moiety and R is independently H, a protecting group or C₁-C₁₂ alkyl.

In certain embodiments, bicyclic nucleosides are provided having Formula I:



wherein:

Bx is a heterocyclic base moiety;

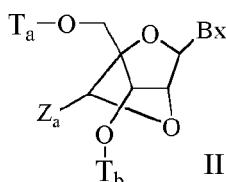
-Q_a-Q_b-Q_c- is -CH₂-N(R_c)-CH₂-, -C(=O)-N(R_c)-CH₂-, -CH₂-O-N(R_c)-, -CH₂-N(R_c)-O- or -N(R_c)-O-CH₂;

R_c is C_1 - C_{12} alkyl or an amino protecting group; and

T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium.

In certain embodiments, bicyclic nucleosides are provided having Formula II:

5



wherein:

B_x is a heterocyclic base moiety;

10

T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

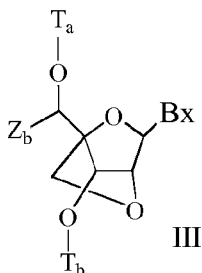
Z_a is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, substituted C_1 - C_6 alkyl, substituted C_2 - C_6 alkenyl, substituted C_2 - C_6 alkynyl, acyl, substituted acyl, substituted amide, thiol or substituted thio.

In one embodiment, each of the substituted groups is, independently, mono or poly

15

substituted with substituent groups independently selected from halogen, oxo, hydroxyl, OJ_e , NJ_eJ_d , SJ_e , N_3 , $OC(=X)J_e$, and $NJ_eC(=X)NJ_eJ_d$, wherein each J_e , J_d and J_e is, independently, H, C_1 - C_6 alkyl, or substituted C_1 - C_6 alkyl and X is O or NJ_e .

In certain embodiments, bicyclic nucleosides are provided having Formula III:



20

wherein:

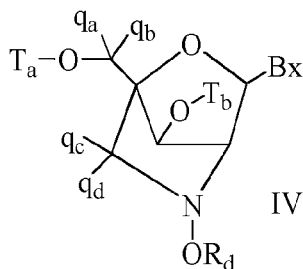
B_x is a heterocyclic base moiety;

T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

25

Z_b is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, substituted C_1 - C_6 alkyl, substituted C_2 - C_6 alkenyl, substituted C_2 - C_6 alkynyl or substituted acyl ($C(=O)-$).

In certain embodiments, bicyclic nucleosides are provided having Formula IV:



wherein:

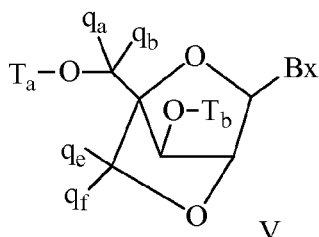
5 Bx is a heterocyclic base moiety;

Ta and Tb are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

Rd is C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, C₂-C₆ alkynyl or substituted C₂-C₆ alkynyl;

10 each qa, qb, qc and qd is, independently, H, halogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, C₂-C₆ alkynyl or substituted C₂-C₆ alkynyl, C₁-C₆ alkoxy, substituted C₁-C₆ alkoxy, acyl, substituted acyl, C₁-C₆ aminoalkyl or substituted C₁-C₆ aminoalkyl;

In certain embodiments, bicyclic nucleosides are provided having Formula V:



15

wherein:

Bx is a heterocyclic base moiety;

Ta and Tb are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

20 qa, qb, qc and qd are each, independently, hydrogen, halogen, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₁-C₁₂ alkoxy, substituted C₁-C₁₂ alkoxy, OJ_j, SJ_j, SOJ_j, SO₂J_j, NJ_jJ_k, N₃, CN, C(=O)OJ_j, C(=O)NJ_jJ_k, C(=O)J_j, O-C(=O)NJ_jJ_k, N(H)C(=NH)NJ_jJ_k, N(H)C(=O)NJ_jJ_k or N(H)C(=S)NJ_jJ_k;

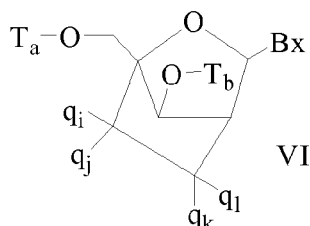
or qc and qd together are =C(q_e)(q_f);

25 q_e and q_f are each, independently, H, halogen, C₁-C₁₂ alkyl or substituted C₁-C₁₂ alkyl.

The synthesis and preparation of the methyleneoxy (4'-CH₂-O-2') BNA monomers adenine, cytosine, guanine, 5-methyl-cytosine, thymine and uracil, along with their oligomerization, and nucleic acid recognition properties have been described (Koshkin *et al.*, *Tetrahedron*, 1998, 54, 3607-3630). BNAs and preparation thereof are also described in WO 98/39352 and WO 99/14226.

5 Analogs of methyleneoxy (4'-CH₂-O-2') BNA and 2'-thio-BNAs, have also been prepared (Kumar *et al.*, *Bioorg. Med. Chem. Lett.*, 1998, 8, 2219-2222). Preparation of locked nucleoside analogs comprising oligodeoxyribonucleotide duplexes as substrates for nucleic acid polymerases has also been described (Wengel *et al.*, WO 99/14226). Furthermore, synthesis of 2'-amino-BNA, a novel conformationally restricted high-affinity oligonucleotide analog has been described in the art
10 (Singh *et al.*, *J. Org. Chem.*, 1998, 63, 10035-10039). In addition, 2'-amino- and 2'-methyldamino-BNA's have been prepared and the thermal stability of their duplexes with complementary RNA and DNA strands has been previously reported.

In certain embodiments, bicyclic nucleosides are provided having Formula VI:



15 wherein:

Bx is a heterocyclic base moiety;

Ta and Tb are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

20 each qi, qj, qk and ql is, independently, H, halogen, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₁-C₁₂ alkoxy, substituted C₁-C₁₂ alkoxy, OJ_j, SJ_j, SOJ_j, SO₂J_j, NJ_jJ_k, N₃, CN, C(=O)OJ_j, C(=O)NJ_jJ_k, C(=O)J_j, O-C(=O)NJ_jJ_k, N(H)C(=NH)NJ_jJ_k, N(H)C(=O)NJ_jJ_k or N(H)C(=S)NJ_jJ_k; and

25 qi and qj or ql and qk together are =C(q_g)(q_h), wherein q_g and q_h are each, independently, H, halogen, C₁-C₁₂ alkyl or substituted C₁-C₁₂ alkyl.

One carbocyclic bicyclic nucleoside having a 4'-(CH₂)₃-2' bridge and the alkenyl analog bridge 4'-CH=CH-CH₂-2' have been described (Freier *et al.*, *Nucleic Acids Research*, 1997, 25(22), 4429-4443 and Albaek *et al.*, *J. Org. Chem.*, 2006, 71, 7731-7740). The synthesis and preparation

of carbocyclic bicyclic nucleosides along with their oligomerization and biochemical studies have also been described (Srivastava *et al.*, *J. Am. Chem. Soc.*, 2007, 129(26), 8362-8379).

As used herein, “4’-2’ bicyclic nucleoside” or “4’ to 2’ bicyclic nucleoside” refers to a bicyclic nucleoside comprising a furanose ring comprising a bridge connecting two carbon atoms of the furanose ring connects the 2’ carbon atom and the 4’ carbon atom of the sugar ring.

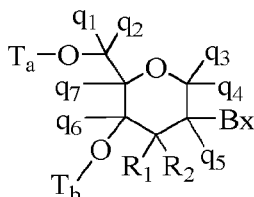
As used herein, “monocyclic nucleosides” refer to nucleosides comprising modified sugar moieties that are not bicyclic sugar moieties. In certain embodiments, the sugar moiety, or sugar moiety analogue, of a nucleoside may be modified or substituted at any position.

As used herein, “2’-modified sugar” means a furanosyl sugar modified at the 2’ position. In certain embodiments, such modifications include substituents selected from: a halide, including, but not limited to substituted and unsubstituted alkoxy, substituted and unsubstituted thioalkyl, substituted and unsubstituted amino alkyl, substituted and unsubstituted alkyl, substituted and unsubstituted allyl, and substituted and unsubstituted alkynyl. In certain embodiments, 2’ modifications are selected from substituents including, but not limited to: $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nF$, $O(CH_2)_nONH_2$, $OCH_2C(=O)N(H)CH_3$, and $O(CH_2)_nON[(CH_2)_nCH_3]_2$, where n and m are from 1 to about 10. Other 2’- substituent groups can also be selected from: C_1 - C_{12} alkyl, substituted alkyl, alkenyl, alkynyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, F, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving pharmacokinetic properties, or a group for improving the pharmacodynamic properties of an antisense compound, and other substituents having similar properties. In certain embodiments, modified nucleosides comprise a 2’-MOE side chain (Baker *et al.*, *J. Biol. Chem.*, 1997, 272, 11944-12000). Such 2’-MOE substitution have been described as having improved binding affinity compared to unmodified nucleosides and to other modified nucleosides, such as 2’- O-methyl, O-propyl, and O-aminopropyl.

Oligonucleotides having the 2’-MOE substituent also have been shown to be antisense inhibitors of gene expression with promising features for *in vivo* use (Martin, *Helv. Chim. Acta*, 1995, 78, 486-504; Altmann *et al.*, *Chimia*, 1996, 50, 168-176; Altmann *et al.*, *Biochem. Soc. Trans.*, 1996, 24, 630-637; and Altmann *et al.*, *Nucleosides Nucleotides*, 1997, 16, 917-926).

As used herein, a “modified tetrahydropyran nucleoside” or “modified THP nucleoside” means a nucleoside having a six-membered tetrahydropyran “sugar” substituted in for the pentofuranosyl residue in normal nucleosides (a sugar surrogate). Modified THP nucleosides

include, but are not limited to, what is referred to in the art as hexitol nucleic acid (HNA), anitol nucleic acid (ANA), manitol nucleic acid (MNA) (see Leumann, *Bioorg. Med. Chem.*, 2002, 10, 841-854), fluoro HNA (F-HNA) or those compounds having Formula VII:



VII

wherein independently for each of said at least one tetrahydropyran nucleoside analog of Formula VII:

Bx is a heterocyclic base moiety;

5 T_a and T_b are each, independently, an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound or one of T_a and T_b is an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound and the other of T_a and T_b is H, a hydroxyl protecting group, a linked conjugate group or a 5' or 3'-terminal group;

10 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 selected from hydrogen, hydroxyl, 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.

15 In certain embodiments, the modified THP nucleosides of Formula VII 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 q₁, q₂, q₃, q₄, q₅, q₆ and q₇ is methyl. In certain embodiments, THP nucleosides of Formula VII are provided wherein one of R₁ and R₂ is fluoro. In certain embodiments, R₁ is fluoro and R₂ is H; R₁ is methoxy and R₂ is H, and R₁ is H and
20 R₂ is methoxyethoxy.

As used herein, "2'-modified" or "2'-substituted" refers to a nucleoside comprising a sugar comprising a substituent at the 2' position other than H or OH. 2'-modified nucleosides, include, but are not limited to, bicyclic nucleosides wherein the bridge connecting two carbon atoms of the sugar ring connects the 2' carbon and another carbon of the sugar ring; and nucleosides with non-

bridging 2'substituents, such as allyl, amino, azido, thio, O-allyl, O-C₁-C₁₀ alkyl, -OCF₃, O-(CH₂)₂-O-CH₃, 2'-O(CH₂)₂SCH₃, O-(CH₂)₂-O-N(R_m)(R_n), or O-CH₂-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H or substituted or unsubstituted C₁-C₁₀ alkyl. 2'-modified nucleosides may further comprise other modifications, for example at other positions of the sugar and/or at the nucleobase.

As used herein, "2'-F" refers to a nucleoside comprising a sugar comprising a fluoro group at the 2' position.

As used herein, "2'-OMe" or "2'-OCH₃" or "2'-O-methyl" each refers to a nucleoside comprising a sugar comprising an -OCH₃ group at the 2' position of the sugar ring.

As used herein, "MOE" or "2'-MOE" or "2'-OCH₂CH₂OCH₃" or "2'-O-methoxyethyl" each refers to a nucleoside comprising a sugar comprising a -OCH₂CH₂OCH₃ group at the 2' position of the sugar ring.

As used herein, "oligonucleotide" refers to a compound comprising a plurality of linked nucleosides. In certain embodiments, one or more of the plurality of nucleosides is modified. In certain embodiments, an oligonucleotide comprises one or more ribonucleosides (RNA) and/or deoxyribonucleosides (DNA).

Many other bicyclo and tricyclo sugar surrogate ring systems are also known in the art that can be used to modify nucleosides for incorporation into antisense compounds (see for example review article: Leumann, *Bioorg. Med. Chem.*, 2002, 10, 841-854).

Such ring systems can undergo various additional substitutions to enhance activity.

Methods for the preparations of modified sugars are well known to those skilled in the art.

In nucleotides having modified sugar moieties, the nucleobase moieties (natural, modified or a combination thereof) are maintained for hybridization with an appropriate nucleic acid target.

In certain embodiments, antisense compounds comprise one or more nucleosides having modified sugar moieties. In certain embodiments, the modified sugar moiety is 2'-MOE. In certain embodiments, the 2'-MOE modified nucleosides are arranged in a gapmer motif. In certain embodiments, the modified sugar moiety is a bicyclic nucleoside having a (4'-CH(CH₃)-O-2') bridging group. In certain embodiments, the (4'-CH(CH₃)-O-2') modified nucleosides are arranged throughout the wings of a gapmer motif.

Compositions and Methods for Formulating Pharmaceutical Compositions

Antisense oligonucleotides may be admixed with pharmaceutically acceptable active or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions are dependent upon a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

An antisense compound targeted to a C9ORF72 nucleic acid can be utilized in pharmaceutical compositions by combining the antisense compound with a suitable pharmaceutically acceptable diluent or carrier. A pharmaceutically acceptable diluent includes phosphate-buffered saline (PBS). PBS is a diluent suitable for use in compositions to be delivered parenterally. Accordingly, in one embodiment, employed in the methods described herein is a pharmaceutical composition comprising an antisense compound targeted to a C9ORF72 nucleic acid and a pharmaceutically acceptable diluent. In certain embodiments, the pharmaceutically acceptable diluent is PBS. In certain embodiments, the antisense compound is an antisense oligonucleotide.

Pharmaceutical compositions comprising antisense compounds encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other oligonucleotide which, upon administration to an animal, including a human, is 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 antisense 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.

A prodrug can include the incorporation of additional nucleosides at one or both ends of an antisense compound which are cleaved by endogenous nucleases within the body, to form the active antisense compound.

Conjugated Antisense Compounds

Antisense compounds may be covalently linked to one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the resulting antisense oligonucleotides. Typical conjugate groups include cholesterol moieties and lipid moieties. Additional conjugate groups include carbohydrates, phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes.

Antisense compounds can also be modified to have one or more stabilizing groups that are generally attached to one or both termini of antisense compounds to enhance properties such as, for example, nuclease stability. Included in stabilizing groups are cap structures. These terminal modifications protect the antisense compound having terminal nucleic acid from exonuclease degradation, and can help in delivery and/or localization within a cell. The cap can be present at the 5'-terminus (5'-cap), or at the 3'-terminus (3'-cap), or can be present on both termini. Cap structures are well known in the art and include, for example, inverted deoxy abasic caps. Further 3' and 5'-stabilizing groups that can be used to cap one or both ends of an antisense compound to impart nuclease stability include those disclosed in WO 03/004602 published on January 16, 2003.

Cell culture and antisense compounds treatment

The effects of antisense compounds on the level, activity or expression of C9ORF72 nucleic acids can be tested *in vitro* in a variety of cell types. Cell types used for such analyses are available from commercial vendors (e.g. American Type Culture Collection, Manassus, VA; Zen-Bio, Inc., Research Triangle Park, NC; Clonetics Corporation, Walkersville, MD) and are cultured according to the vendor's instructions using commercially available reagents (e.g. Invitrogen Life Technologies, Carlsbad, CA). Illustrative cell types include, but are not limited to, HepG2 cells, Hep3B cells, and primary hepatocytes.

In vitro testing of antisense oligonucleotides

Described herein are methods for treatment of cells with antisense oligonucleotides, which can be modified appropriately for treatment with other antisense compounds.

In general, cells are treated with antisense oligonucleotides when the cells reach approximately 60-80% confluency in culture.

One reagent commonly used to introduce antisense oligonucleotides into cultured cells includes the cationic lipid transfection reagent LIPOFECTIN (Invitrogen, Carlsbad, CA). Antisense oligonucleotides are mixed with LIPOFECTIN in OPTI-MEM 1 (Invitrogen, Carlsbad, CA) to achieve the desired final concentration of antisense oligonucleotide and a LIPOFECTIN concentration that typically ranges 2 to 12 ug/mL per 100 nM antisense oligonucleotide.

Another reagent used to introduce antisense oligonucleotides into cultured cells includes LIPOFECTAMINE (Invitrogen, Carlsbad, CA). Antisense oligonucleotide is mixed with LIPOFECTAMINE in OPTI-MEM 1 reduced serum medium (Invitrogen, Carlsbad, CA) to achieve

the desired concentration of antisense oligonucleotide and a LIPOFECTAMINE concentration that typically ranges 2 to 12 ug/mL per 100 nM antisense oligonucleotide.

Another technique used to introduce antisense oligonucleotides into cultured cells includes electroporation.

5 Cells are treated with antisense oligonucleotides by routine methods. Cells are typically harvested 16-24 hours after antisense oligonucleotide treatment, at which time RNA or protein levels of target nucleic acids are measured by methods known in the art and described herein. In general, when treatments are performed in multiple replicates, the data are presented as the average of the replicate treatments.

10 The concentration of antisense oligonucleotide used varies from cell line to cell line. Methods to determine the optimal antisense oligonucleotide concentration for a particular cell line are well known in the art. Antisense oligonucleotides are typically used at concentrations ranging from 1 nM to 300 nM when transfected with LIPOFECTAMINE. Antisense oligonucleotides are used at higher concentrations ranging from 625 to 20,000 nM when transfected using
15 electroporation.

RNA Isolation

RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. Methods of RNA isolation are well known in the art. RNA is prepared using methods well known in the art, for
20 example, using the TRIZOL Reagent (Invitrogen, Carlsbad, CA) according to the manufacturer's recommended protocols.

Analysis of inhibition of target levels or expression

Inhibition of levels or expression of a C9ORF72 nucleic acid can be assayed in a variety of
25 ways known in the art. For example, target nucleic acid levels can be quantitated by, e.g., Northern blot analysis, competitive polymerase chain reaction (PCR), or quantitative real-time PCR. RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. Methods of RNA isolation are well known in the art. Northern blot analysis is also routine in the art. Quantitative real-time PCR can be conveniently accomplished using the commercially available ABI PRISM 7600, 7700,
30 or 7900 Sequence Detection System, available from PE-Applied Biosystems, Foster City, CA and used according to manufacturer's instructions.

Quantitative Real-Time PCR Analysis of Target RNA Levels

Quantitation of target RNA levels may be accomplished by quantitative real-time PCR using the ABI PRISM 7600, 7700, or 7900 Sequence Detection System (PE-Applied Biosystems, Foster City, CA) according to manufacturer's instructions. Methods of quantitative real-time PCR are well known in the art.

Prior to real-time PCR, the isolated RNA is subjected to a reverse transcriptase (RT) reaction, which produces complementary DNA (cDNA) that is then used as the substrate for the real-time PCR amplification. The RT and real-time PCR reactions are performed sequentially in the same sample well. RT and real-time PCR reagents are obtained from Invitrogen (Carlsbad, CA). RT real-time-PCR reactions are carried out by methods well known to those skilled in the art.

Gene (or RNA) target quantities obtained by real time PCR are normalized using either the expression level of a gene whose expression is constant, such as cyclophilin A, or by quantifying total RNA using RIBOGREEN (Invitrogen, Inc. Carlsbad, CA). Cyclophilin A expression is quantified by real time PCR, by being run simultaneously with the target, multiplexing, or separately. Total RNA is quantified using RIBOGREEN RNA quantification reagent (Invitrogen, Inc. Eugene, OR). Methods of RNA quantification by RIBOGREEN are taught in Jones, L.J., et al, (Analytical Biochemistry, 1998, 265, 368-374). A CYTOFLUOR 4000 instrument (PE Applied Biosystems) is used to measure RIBOGREEN fluorescence.

Probes and primers are designed to hybridize to a C9ORF72 nucleic acid. Methods for designing real-time PCR probes and primers are well known in the art, and may include the use of software such as PRIMER EXPRESS Software (Applied Biosystems, Foster City, CA).

Analysis of Protein Levels

Antisense inhibition of C9ORF72 nucleic acids can be assessed by measuring C9ORF72 protein levels. Protein levels of C9ORF72 can be evaluated or quantitated in a variety of ways well known in the art, such as immunoprecipitation, Western blot analysis (immunoblotting), enzyme-linked immunosorbent assay (ELISA), quantitative protein assays, protein activity assays (for example, caspase activity assays), immunohistochemistry, immunocytochemistry or fluorescence-activated cell sorting (FACS). Antibodies directed to a target can be identified and obtained from a variety of sources, such as the MSRS catalog of antibodies (Aerie Corporation, Birmingham, MI), or can be prepared via conventional monoclonal or polyclonal antibody generation methods well

known in the art. Antibodies useful for the detection of mouse, rat, monkey, and human C9ORF72 are commercially available.

In vivo testing of antisense compounds

5 Antisense compounds, for example, antisense oligonucleotides, are tested in animals to assess their ability to inhibit expression of C9ORF72 and produce phenotypic changes, such as, improved motor function and respiration. In certain embodiments, motor function is measured by rotarod, grip strength, pole climb, open field performance, balance beam, hindpaw footprint testing in the animal. In certain embodiments, respiration is measured by whole body plethysmograph,
10 invasive resistance, and compliance measurements in the animal. Testing may be performed in normal animals, or in experimental disease models. For administration to animals, antisense oligonucleotides are formulated in a pharmaceutically acceptable diluent, such as phosphate-buffered saline (PBS) or artificial cerebrospinal fluid (aCSF). Administration includes parenteral routes of administration, such as intraperitoneal, intravenous, and subcutaneous, as well as central
15 routes of administration such as intracerebroventricular or intrathecal. Calculation of antisense oligonucleotide dosage and dosing frequency is within the abilities of those skilled in the art, and depends upon factors such as route of administration and animal body weight. Following a period of treatment with antisense oligonucleotides, RNA is isolated from CNS tissue or CSF and changes in C9ORF72 nucleic acid expression are measured.

Targeting C9ORF72

 Antisense oligonucleotides described herein may hybridize to a C9ORF72 nucleic acid in any stage of RNA processing. For example, described herein are antisense oligonucleotides that are complementary to a pre-mRNA or a mature mRNA. Additionally, antisense oligonucleotides
25 described herein may hybridize to any element of a C9ORF72 nucleic acid. For example, described herein are antisense oligonucleotides that are complementary to an exon, an intron, the 5' UTR, the 3' UTR, a repeat region, a hexanucleotide repeat expansion, a splice junction, an exon:exon splice junction, an exonic splicing silencer (ESS), an exonic splicing enhancer (ESE), exon 1a, exon 1b, exon 1c, exon 1d, exon 1e, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10,
30 exon 11, intron 1, intron 2, intron 3, intron 4, intron 5, intron 6, intron 7, intron 8, intron 9, or intron 10 of a C9ORF72 nucleic acid.

In certain embodiments, antisense oligonucleotides described herein hybridize to all variants of C9ORF72. In certain embodiments, the antisense oligonucleotides described herein selectively hybridize to certain variants of C9ORF72. In certain embodiments, the antisense oligonucleotides described herein selectively hybridize to variants of C9ORF72 containing a hexanucleotide repeat expansion. In certain embodiments, the antisense oligonucleotides described herein selectively hybridize to pre-mRNA variants containing the hexanucleotide repeat. In certain embodiments, pre-mRNA variants of C9ORF72 containing a hexanucleotide repeat expansion include SEQ ID NO: 1-3 and 6-10. In certain embodiments, such hexanucleotide repeat expansion comprises at least 24 repeats of any of GGGGCC, GGGGGG, GGGGGC, or GGGGCG.

In certain embodiments, the antisense oligonucleotides described herein inhibit expression of all variants of C9ORF72. In certain embodiments, the antisense oligonucleotides described herein inhibit expression of all variants of C9ORF72 equally. In certain embodiments, the antisense oligonucleotides described herein preferentially inhibit expression of one or more variants of C9ORF72. In certain embodiments, the antisense oligonucleotides described herein preferentially inhibit expression of variants of C9ORF72 containing a hexanucleotide repeat expansion. In certain embodiments, the antisense oligonucleotides described herein selectively inhibit expression of pre-mRNA variants containing the hexanucleotide repeat. In certain embodiments, the antisense oligonucleotides described herein selectively inhibit expression of C9ORF72 pathogenic associated mRNA variants. In certain embodiments, pre-mRNA variants of C9ORF72 containing a hexanucleotide repeat expansion include SEQ ID NO: 1-3 and 6-10. In certain embodiments, such hexanucleotide repeat expansion comprises at least 24 repeats of any of GGGGCC, GGGGGG, GGGGGC, or GGGGCG. In certain embodiments, the hexanucleotide repeat expansion forms nuclear foci. In certain embodiments, antisense oligonucleotides described herein are useful for reducing nuclear foci. Nuclear foci may be reduced in terms of percent of cells with foci as well as number of foci per cell.

Selective Inhibition of Certain Pathogenic Associated Variants

In certain examples herein, primer probe set RTS3905 detects an mRNA variant (e.g. NM_001256054.1) processed from a pre-mRNA variant containing the hexanucleotide repeat. The mRNA variant processed from a pre-mRNA variant containing the hexanucleotide repeat (i.e., the "C9ORF72 pathogenic associated mRNA variant"). A pre-mRNA contains the hexanucleotide repeat when transcription of the pre-mRNA begins in the region from the start site of exon 1A to the

start site of exon 1B, e.g., nucleotides 1107 to 1520 of the genomic sequence (SEQ ID NO: 2, the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). Oligonucleotides were designed in this region to selectively target the pre-mRNA variant containing the hexanucleotide repeat. RTS3905 measures an mRNA product (i.e. the C9ORF72 pathogenic associated mRNA variant) of the pre-mRNA variant containing the hexanucleotide repeat and, therefore, measures the reduction of the pre-mRNA variant containing the hexanucleotide repeat.

C9ORF72 Features

Antisense oligonucleotides described herein may hybridize to any C9ORF72 variant at any state of processing within any element of the C9ORF72 gene. For example, antisense oligonucleotides described herein may hybridize to an exon, an intron, the 5' UTR, the 3' UTR, a repeat region, a hexanucleotide repeat expansion, a splice junction, an exon:exon splice junction, an exonic splicing silencer (ESS), an exonic splicing enhancer (ESE), exon 1a, exon 1b, exon 1c, exon 1d, exon 1e, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, intron 1, intron 2, intron 3, intron 4, intron 5, intron 6, intron 7, intron 8, intron 9, or intron 10. For example, antisense oligonucleotides may target any of the exons characterized below in Tables 1-5 for the various C9ORF72 variants described below. Antisense oligonucleotides described herein may also target variants not characterized below and such variants are characterized in GENBANK. Moreover, antisense oligonucleotides described herein may also target elements other than exons and such elements are characterized in GENBANK.

Table 1
Functional Segments for NM_001256054.1 (SEQ ID NO: 1)

Exon Number	mRNA start site	mRNA stop site	Start site in reference to SEQ ID NO: 2	Stop site in reference to SEQ ID NO: 2
exon 1C	1	158	1137	1294
exon 2	159	646	7839	8326
exon 3	647	706	9413	9472
exon 4	707	802	12527	12622
exon 5	803	867	13354	13418
exon 6	868	940	14704	14776
exon 7	941	1057	16396	16512

exon 8	1058	1293	18207	18442
exon 9	1294	1351	24296	24353
exon 10	1352	1461	26337	26446
exon 11	1462	3339	26581	28458

Table 2

Functional Segments for NM_018325.3 (SEQ ID NO: 4)

Exon Number	mRNA start site	mRNA stop site	Start site in reference to SEQ ID NO: 2	Stop site in reference to SEQ ID NO: 2
exon 1B	1	63	1510	1572
exon 2	64	551	7839	8326
exon 3	552	611	9413	9472
exon 4	612	707	12527	12622
exon 5	708	772	13354	13418
exon 6	773	845	14704	14776
exon 7	846	962	16396	16512
exon 8	963	1198	18207	18442
exon 9	1199	1256	24296	24353
exon 10	1257	1366	26337	26446
exon 11	1367	3244	26581	28458

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Table 3

Functional Segments for NM_145005.5 (SEQ ID NO: 6)

Exon Number	mRNA start site	mRNA stop site	Start site in reference to SEQ ID NO: 2	Stop site in reference to SEQ ID NO: 2
exon 1A	1	80	1137	1216
exon 2	81	568	7839	8326
exon 3	569	628	9413	9472
exon 4	629	724	12527	12622
exon 5B (exon 5 into intron 5)	725	1871	13354	14500

Table 4

Functional Segments for DB079375.1 (SEQ ID NO: 7)

Exon Number	mRNA start site	mRNA stop site	Start site in reference to SEQ	Stop site in reference to SEQ

			ID NO: 2	ID NO: 2
exon 1E	1	35	1135	1169
exon 2	36	524	7839	8326
exon 3 (EST ends before end of full exon)	525	562	9413	9450

Table 5
Functional Segments for BU194591.1 (SEQ ID NO: 8)

Exon Number	mRNA start site	mRNA stop site	Start site in reference to SEQ ID NO: 2	Stop site in reference to SEQ ID NO: 2
exon 1D	1	36	1241	1279
exon 2	37	524	7839	8326
exon 3	525	584	9413	9472
exon 4	585	680	12527	12622
exon 5B (exon 5 into intron 5)	681	798	13354	13465

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Certain Indications

In certain embodiments, provided herein are methods of treating an individual comprising administering one or more pharmaceutical compositions described herein. In certain embodiments, the individual has a neurodegenerative disease. In certain embodiments, the individual is at risk for developing a neurodegenerative disease, including, but not limited to, ALS or FTD. In certain
10
embodiments, the individual has been identified as having a C9ORF72 associated disease. In certain embodiments, the individual has been identified as having a C9ORF72 hexanucleotide repeat expansion associated disease. In certain embodiments, provided herein are methods for prophylactically reducing C9ORF72 expression in an individual. Certain embodiments include
15
treating an individual in need thereof by administering to an individual a therapeutically effective amount of an antisense compound targeted to a C9ORF72 nucleic acid.

In one embodiment, administration of a therapeutically effective amount of an antisense compound targeted to a C9ORF72 nucleic acid is accompanied by monitoring of C9ORF72 levels in an individual, to determine an individual's response to administration of the antisense compound.
20
An individual's response to administration of the antisense compound may be used by a physician to determine the amount and duration of therapeutic intervention.

In certain embodiments, administration of an antisense compound targeted to a C9ORF72 nucleic acid results in reduction of C9ORF72 expression by at least 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values. In certain embodiments, administration of an antisense compound targeted to a C9ORF72 nucleic acid results in improved motor function and respiration in an animal. In certain embodiments, administration of a C9ORF72 antisense compound improves motor function and respiration by at least 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values.

In certain embodiments, pharmaceutical compositions comprising an antisense compound targeted to C9ORF72 are used for the preparation of a medicament for treating a patient suffering or susceptible to a neurodegenerative disease including ALS and FTD.

Certain Combination Therapies

In certain embodiments, one or more pharmaceutical compositions described herein are co-administered with one or more other pharmaceutical agents. In certain embodiments, such one or more other pharmaceutical agents are designed to treat the same disease, disorder, or condition as the one or more pharmaceutical compositions described herein. In certain embodiments, such one or more other pharmaceutical agents are designed to treat a different disease, disorder, or condition as the one or more pharmaceutical compositions described herein. In certain embodiments, such one or more other pharmaceutical agents are designed to treat an undesired side effect of one or more pharmaceutical compositions described herein. In certain embodiments, one or more pharmaceutical compositions described herein are co-administered with another pharmaceutical agent to treat an undesired effect of that other pharmaceutical agent. In certain embodiments, one or more pharmaceutical compositions described herein are co-administered with another pharmaceutical agent to produce a combinational effect. In certain embodiments, one or more pharmaceutical compositions described herein are co-administered with another pharmaceutical agent to produce a synergistic effect.

In certain embodiments, one or more pharmaceutical compositions described herein and one or more other pharmaceutical agents are administered at the same time. In certain embodiments, one or more pharmaceutical compositions described herein and one or more other pharmaceutical agents are administered at different times. In certain embodiments, one or more pharmaceutical compositions described herein and one or more other pharmaceutical agents are prepared together in

a single formulation. In certain embodiments, one or more pharmaceutical compositions described herein and one or more other pharmaceutical agents are prepared separately.

In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include Riluzole (Rilutek), Lioresal (Lioresal), and
5 Dexpramipexole.

In certain embodiments, pharmaceutical agents that may be co-administered with a C9ORF72 specific inhibitor described herein include, but are not limited to, an additional C9ORF72 inhibitor. In certain embodiments, the co-administered pharmaceutical agent is administered prior to administration of a pharmaceutical composition described herein. In certain embodiments, the co-
10 administered pharmaceutical agent is administered following administration of a pharmaceutical composition described herein. In certain embodiments the co-administered pharmaceutical agent is administered at the same time as a pharmaceutical composition described herein. In certain embodiments the dose of a co-administered pharmaceutical agent is the same as the dose that would
15 be administered if the co-administered pharmaceutical agent was administered alone. In certain embodiments the dose of a co-administered pharmaceutical agent is lower than the dose that would be administered if the co-administered pharmaceutical agent was administered alone. In certain
embodiments the dose of a co-administered pharmaceutical agent is greater than the dose that would be administered if the co-administered pharmaceutical agent was administered alone.

In certain embodiments, the co-administration of a second compound enhances the effect of
20 a first compound, such that co-administration of the compounds results in an effect that is greater than the effect of administering the first compound alone. In other embodiments, the co-administration results in effects that are additive of the effects of the compounds when administered alone. In certain embodiments, the co-administration results in effects that are supra-additive of the effects of the compounds when administered alone. In certain embodiments, the first compound is
25 an antisense compound. In certain embodiments, the second compound is an antisense compound.

Certain Amplicon Regions

Certain antisense oligonucleotides described herein may target the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of these
30 compounds.

Certain Human Therapeutics

The human C9ORF72 antisense oligonucleotides described herein are being evaluated as possible human therapeutics. Various parameters of potency, efficacy, and/or tolerability are being examined. Such parameters include in vitro inhibition of total C9ORF72 RNA expression, in vitro inhibition of C9ORF72 pathogenic associated RNA variant expression, in vitro dose response (IC50), in vivo inhibition of total or pathogenic RNA and/or protein in a transgenic animal containing a human C9ORF72 transgene in relevant tissues (e.g., brain and/or spinal cord), tolerability in mouse, tolerability in rat, and/or tolerability in a primate. Tolerability markers that may be measured include blood and serum chemistry parameters, CSF chemistry parameters, body and organ weights, general observations and/or behavioral tests, and/or biochemical markers such as GFAP and/or AIF1. Acute or long term tolerability may be measured.

Certain Hotspot Regions

1. Nucleobases 1107-1520 of SEQ ID NO: 2

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 1107-1520 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 1107-1520 are a hotspot region. In certain embodiments, nucleobases 1107-1520 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 17, 18, or 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers or 5-8-5 MOE gapmers. In certain embodiments, the antisense oligonucleotides are 17-mer Deoxy, MOE and cEt oligonucleotides. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleotide linkages (e.g., the antisense oligonucleotides have "mixed backbones").

In certain embodiments, nucleobases 1107-1520 are targeted by the following ISIS numbers: 619042-619333, 672581-672714, 672735-672865, 672885-673015, 673035-673165, 673185-673315, and 673335-673465.

In certain embodiments, nucleobases 1107-1520 are targeted by the following SEQ ID NOs: 21-31, 33-50, 52, 54-134, 138-248, 251-319, 325, 744-877, and 898-1028.

In certain embodiments, nucleobases 1107-1520 are targeted by the following ISIS numbers: 619042-619333.

In certain embodiments, nucleobases 1107-1520 are targeted by the following SEQ ID NOs: 21-31, 33-50, 52, 54-134, 138-248, 251-319, and 325.

5 In certain embodiments, antisense oligonucleotides targeting nucleobases 1107-1520 achieve 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%, at least 19%, 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of total C9ORF72 mRNA and/or protein levels in vitro and/or in vivo.

15 In certain embodiments, antisense oligonucleotides targeting nucleobases 1107-1520 achieve 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%, at least 19%, 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%,

at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of C9ORF72 pathogenic associated mRNA variant levels in vitro and/or in vivo.

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2. Nucleobases 1111-1200 of SEQ ID NO: 2

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 1111-1200 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 1111-1200 are a hotspot region. In certain embodiments, nucleobases 1111-1200 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleotide linkages (e.g., the antisense oligonucleotides have “mixed backbones”).

In certain embodiments, nucleobases 1111-1200 are targeted by the following ISIS numbers: 619042-619095.

In certain embodiments, nucleobases 1111-1200 are targeted by the following SEQ ID NOs: 21, 26-31, 33-50, 52, 54-60, 75, 81, and 87-96.

In certain embodiments, antisense oligonucleotides targeting nucleobases 1111-1200 achieve 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%, at least 19%, 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at

least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of total C9ORF72 mRNA and/or protein levels in vitro and/or in vivo.

In certain embodiments, antisense oligonucleotides targeting nucleobases 1111-1200 achieve 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%, at least 19%, 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of C9ORF72 pathogenic associated mRNA variant levels in vitro and/or in vivo.

3. Nucleobases 1211-1318 of SEQ ID NO: 2

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 1211-1318 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 1211-1318 are a hotspot region. In certain embodiments, nucleobases 1211-1318 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside

linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleotide linkages (e.g., the antisense oligonucleotides have “mixed backbones”).

5 In certain embodiments, nucleobases 1211-1318 are targeted by the following ISIS numbers: 619096-619172.

 In certain embodiments, nucleobases 1211-1318 are targeted by the following SEQ ID NOs: 22-25, 70-74, 76-80, 82-86, 99-134, and 138-159.

 In certain embodiments, antisense oligonucleotides targeting nucleobases 1211-1318
10 achieve 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%, at least 19%, 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%,
15 at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least
20 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of total C9ORF72 mRNA and/or protein levels in vitro and/or in vivo.

25 In certain embodiments, antisense oligonucleotides targeting nucleobases 1211-1318 achieve 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%, at least 19%, 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least
30 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least

53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of C9ORF72 pathogenic associated mRNA variant levels in vitro and/or in vivo.

10 **4. Nucleobases 1326-1540 of SEQ ID NO: 2**

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 1326-1540 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 1326-1540 are a hotspot region. In certain embodiments, nucleobases 1326-1540 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 17, 18, or 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers or 5-8-5 MOE gapmers. In certain embodiments, the antisense oligonucleotides are 17-mer Deoxy, MOE and cEt oligonucleotides. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleotide linkages (e.g., the antisense oligonucleotides have “mixed backbones”).

In certain embodiments, nucleobases 1326-1540 are targeted by the following ISIS numbers: 619173-619354, and 672581-673484.

In certain embodiments, nucleobases 1326-1540 are targeted by the following SEQ ID NOs: 97, 98, 160-248, 251-322, 325-343, and 744-1047.

In certain embodiments, nucleobases 1326-1540 are targeted by the following ISIS numbers: 619173-619354.

In certain embodiments, nucleobases 1326-1540 are targeted by the following SEQ ID NOs: 97, 98, 160-248, 251-322, and 325-343.

In certain embodiments, antisense oligonucleotides targeting nucleobases 1326-1540 achieve 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%, at least 19%, 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of total C9ORF72 mRNA and/or protein levels in vitro and/or in vivo.

In certain embodiments, antisense oligonucleotides targeting nucleobases 1326-1540 achieve 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%, at least 19%, 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of C9ORF72 pathogenic associated mRNA variant levels in vitro and/or in vivo.

5. Nucleobases 1331-1375 of SEQ ID NO: 2

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 1331-1375 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 1331-1375 are a hotspot region. In certain embodiments, nucleobases 1331-1375 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleotide linkages (e.g., the antisense oligonucleotides have “mixed backbones”). In certain embodiments, the antisense oligonucleotides comprise the following sugar modification pattern: sooooooooooooo.

In certain embodiments, nucleobases 1331-1375 are targeted by the following ISIS numbers: 619178-619203.

In certain embodiments, nucleobases 1331-1375 are targeted by the following SEQ ID NOs: 165-190.

In certain embodiments, antisense oligonucleotides targeting nucleobases 1331-1375 achieve 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%, at least 19%, 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at

least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of C9ORF72 pathogenic associated mRNA variant levels in vitro and/or in vivo.

5 **6. Nucleobases 1368-1391 of SEQ ID NO: 2**

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 1368-1391 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 1368-1391 are a hotspot region. In certain embodiments, nucleobases 1368-1391 are targeted by
10 antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by
15 phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleotide linkages (e.g., the antisense oligonucleotides have “mixed backbones”). In certain embodiments, the antisense oligonucleotides comprise the following sugar modification pattern: sooooooooooooo.

In certain embodiments, nucleobases 1368-1391 are targeted by the following ISIS
20 numbers: 619215-619219.

In certain embodiments, nucleobases 1368-1391 are targeted by the following SEQ ID NOs: 202-206.

In certain embodiments, antisense oligonucleotides targeting nucleobases 1368-1391 achieve at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least
25 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%, at least 19%, 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at
30 least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at

least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of C9ORF72 pathogenic associated mRNA variant levels in vitro and/or in vivo.

7. Nucleobases 1398-1424 of SEQ ID NO: 2

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 1398-1424 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 1398-1424 are a hotspot region. In certain embodiments, nucleobases 1398-1424 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleotide linkages (e.g., the antisense oligonucleotides have “mixed backbones”). In certain embodiments, the antisense oligonucleotides comprise the following sugar modification pattern: sooooooooooooo.

In certain embodiments, nucleobases 1398-1424 are targeted by the following ISIS numbers: 619245-619252.

In certain embodiments, nucleobases 1398-1424 are targeted by the following SEQ ID NOs: 232-239.

In certain embodiments, antisense oligonucleotides targeting nucleobases 1398-1424 achieve 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%, at least 19%, 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at

least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of C9ORF72 pathogenic associated mRNA variant levels in vitro and/or in vivo.

8. Nucleobases 1411-1440 of SEQ ID NO: 2

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 1411-1440 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 1411-1440 are a hotspot region. In certain embodiments, nucleobases 1411-1440 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleotide linkages (e.g., the antisense oligonucleotides have “mixed backbones”). In certain embodiments, the antisense oligonucleotides comprise the following sugar modification pattern: soooooossssssooss.

In certain embodiments, nucleobases 1411-1440 are targeted by the following ISIS numbers: 619258-619268.

In certain embodiments, nucleobases 1411-1440 are targeted by the following SEQ ID NOs: 244-248, 251-255, and 325.

In certain embodiments, antisense oligonucleotides targeting nucleobases 1411-1440 achieve 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%, at least 19%, 20%, at least 21%, at least 22%, at least 23%, at

least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of C9ORF72 pathogenic associated mRNA variant levels in vitro and/or in vivo.

9. Nucleobases 1429-1481 of SEQ ID NO: 2

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 1429-1481 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 1429-1481 are a hotspot region. In certain embodiments, nucleobases 1429-1481 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleotide linkages (e.g., the antisense oligonucleotides have “mixed backbones”). In certain embodiments, the antisense oligonucleotides comprise the following sugar modification pattern: soooooossssssssooss.

In certain embodiments, nucleobases 1429-1481 are targeted by the following ISIS numbers: 619276-619303.

In certain embodiments, nucleobases 1429-1481 are targeted by the following SEQ ID NOs: 98 and 263-289.

In certain embodiments, antisense oligonucleotides targeting nucleobases 1429-1481 achieve 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%, at least 19%, 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of C9ORF72 pathogenic associated mRNA variant levels in vitro and/or in vivo.

10. Nucleobases 1502-1539 of SEQ ID NO: 2

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 1502-1539 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 1502-1539 are a hotspot region. In certain embodiments, nucleobases 1502-1539 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleotide linkages (e.g., the antisense oligonucleotides have “mixed backbones”). In certain embodiments, the antisense oligonucleotides comprise the following sugar modification pattern: soooooossssssooss.

In certain embodiments, nucleobases 1502-1539 are targeted by the following ISIS numbers: 619335-619353.

In certain embodiments, nucleobases 1502-1539 are targeted by the following SEQ ID NOs: 321, 322, and 326-342.

5 In certain embodiments, antisense oligonucleotides targeting nucleobases 1502-1539 achieve 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%, at least 19%, 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least
10 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at
15 least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of C9ORF72 pathogenic associated
20 mRNA variant levels in vitro and/or in vivo.

11. Nucleobases 1508-1539 of SEQ ID NO: 2

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 1508-1539 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18
25 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 1508-1539 are a hotspot region. In certain embodiments, nucleobases 1508-1539 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the
30 nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense

oligonucleotides are linked by phosphorothioate and phosphodiester internucleotide linkages (e.g., the antisense oligonucleotides have “mixed backbones”). In certain embodiments, the antisense oligonucleotides comprise the following sugar modification pattern: soooooossssssooss.

In certain embodiments, nucleobases 1508-1539 are targeted by the following ISIS
 5 numbers: 619341-619353.

In certain embodiments, nucleobases 1508-1539 are targeted by the following SEQ ID
 NOs: 330-342.

In certain embodiments, antisense oligonucleotides targeting nucleobases 1508-1539
 achieve at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least
 10 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%, at least 19%, 20%, at least 21%, at least 22%, at least 23%, at
 least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least
 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%,
 at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at
 15 least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least
 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%,
 at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at
 least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least
 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%,
 20 at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at
 least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least
 97%, at least 98%, at least 99%, or at least 100% reduction of C9ORF72 pathogenic associated
 mRNA variant levels in vitro and/or in vivo

25 **12. Nucleobases 7860-7906 of SEQ ID NO: 2**

In certain embodiments, antisense oligonucleotides are designed to target nucleobases
 7860-7906 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18
 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 7860-
 7906 are a hotspot region. In certain embodiments, nucleobases 7860-7906 are targeted by
 30 antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20
 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In
 certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the

nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleoside linkages (e.g., the antisense oligonucleotides have “mixed backbones”).

In certain embodiments, nucleobases 7860-7906 are targeted by the following ISIS numbers: 655135-655144.

In certain embodiments, nucleobases 7860-7906 are targeted by the following SEQ ID NOs: 445-454.

In certain embodiments, antisense oligonucleotides targeting nucleobases 7860-7906 achieve at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, or at least 89% reduction of total C9ORF72 mRNA and/or protein levels in vitro and/or in vivo.

13. Nucleobases 7907-7944 of SEQ ID NO: 2

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 7907-7944 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 7907-7944 are a hotspot region. In certain embodiments, nucleobases 7907-7944 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleoside linkages (e.g., the antisense oligonucleotides have “mixed backbones”).

In certain embodiments, nucleobases 7907-7944 are targeted by the following ISIS numbers: 655150-655156.

In certain embodiments, nucleobases 7907-7944 are targeted by the following SEQ ID NOs: 460-467.

In certain embodiments, antisense oligonucleotides targeting nucleobases 7907-7944 achieve at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, or at least 91% reduction of total C9ORF72 mRNA and/or protein levels in vitro and/or in vivo.

14. Nucleobases 7989-8038 of SEQ ID NO: 2

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 7989-8038 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 7989-8038 are a hotspot region. In certain embodiments, nucleobases 7989-8038 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester Internucleoside linkages (e.g., the antisense oligonucleotides have “mixed backbones”).

In certain embodiments, nucleobases 7989-8038 are targeted by the following ISIS numbers: 619411, 619412, 619420, 625183, 627833, and 655173-655180.

In certain embodiments, nucleobases 7989-8038 are targeted by the following SEQ ID NOs: 20, 51, 53, and 484-493.

In certain embodiments, antisense oligonucleotides targeting nucleobases 7989-8038 achieve at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least

49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, or at least 76% reduction of total C9ORF72 mRNA and/or protein levels in vitro and/or in vivo.

In certain embodiments, antisense oligonucleotides targeting nucleobases 7989-8038 achieve at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of C9ORF72 pathogenic associated mRNA variant levels in vitro and/or in vivo.

15. Nucleobases 8020-8135 of SEQ ID NO: 2

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 8020-8135 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 8020-8135 are a hotspot region. In certain embodiments, nucleobases 8020-8135 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleoside linkages (e.g., the antisense oligonucleotides have “mixed backbones”).

In certain embodiments, nucleobases 8020-8135 are targeted by the following ISIS numbers: 619413, 619414, 625255, 627834, 655181-655208.

In certain embodiments, nucleobases 8020-8135 are targeted by the following SEQ ID NOs: 135, 136, 494-511, and 517-528.

In certain embodiments, antisense oligonucleotides targeting nucleobases 8020-8135 achieve 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%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%,

at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, or at least 54% reduction of total C9ORF72 mRNA and/or protein levels in vitro and/or in vivo.

In certain embodiments, antisense oligonucleotides targeting nucleobases 8020-8135 achieve at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of C9ORF72 pathogenic associated mRNA variant levels in vitro and/or in vivo.

16. Nucleobases 8136-8161 of SEQ ID NO: 2

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 8136-8161 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 8136-8161 are a hotspot region. In certain embodiments, nucleobases 8136-8161 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleoside linkages (e.g., the antisense oligonucleotides have “mixed backbones”).

In certain embodiments, nucleobases 8136-8161 are targeted by the following ISIS numbers: 655215-655217.

In certain embodiments, nucleobases 8136-8161 are targeted by the following SEQ ID NOs: 535-537.

In certain embodiments, antisense oligonucleotides targeting nucleobases 8136-8161 achieve at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, or at least 41% reduction of total C9ORF72 mRNA and/or protein levels in vitro and/or in vivo.

5 In certain embodiments, antisense oligonucleotides targeting nucleobases 8136-8161 achieve at least 91%, at least 92%, at least 93%, at least 94%, or at least 95% reduction of C9ORF72 pathogenic associated mRNA variant levels in vitro and/or in vivo.

17. Nucleobases 8174-8211 of SEQ ID NO: 2

10 In certain embodiments, antisense oligonucleotides are designed to target nucleobases 8174-8211 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 8174-8211 are a hotspot region. In certain embodiments, nucleobases 8174-8211 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20
15 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleoside linkages (e.g.,
20 the antisense oligonucleotides have “mixed backbones”).

In certain embodiments, nucleobases 8174-8211 are targeted by the following ISIS numbers: 655228-655234.

25 In certain embodiments, nucleobases 8174-8211 are targeted by the following SEQ ID NOs: 548-554.

In certain embodiments, antisense oligonucleotides targeting nucleobases 8174-8211 achieve at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at
30 least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%,

at least 61%, at least 62%, or at least 63% reduction of total C9ORF72 mRNA and/or protein levels in vitro and/or in vivo.

In certain embodiments, antisense oligonucleotides targeting nucleobases 8174-8211 achieve at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% reduction of C9ORF72 pathogenic associated mRNA variant levels in vitro and/or in vivo.

18. Nucleobases 8213-8325 of SEQ ID NO: 2

In certain embodiments, antisense oligonucleotides are designed to target nucleobases 8213-8325 of SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000). In certain embodiments, nucleobases 8213-8325 are a hotspot region. In certain embodiments, nucleobases 8213-8325 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphodiester internucleoside linkages. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate and phosphodiester internucleoside linkages (e.g., the antisense oligonucleotides have “mixed backbones”).

In certain embodiments, nucleobases 8213-8325 are targeted by the following ISIS numbers: 655235-655270.

In certain embodiments, nucleobases 8213-8325 are targeted by the following SEQ ID NOs: 555-590.

In certain embodiments, antisense oligonucleotides targeting nucleobases 8213-8325 achieve 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%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least

45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, or at least 51% reduction of total C9ORF72 mRNA and/or protein levels in vitro and/or in vivo.

In certain embodiments, antisense oligonucleotides targeting nucleobases 8213-8325 achieve at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, or at least 98% reduction of C9ORF72 pathogenic associated mRNA variant levels in vitro and/or in vivo.

EXAMPLES

Non-limiting disclosure and incorporation by reference

While certain compounds, compositions, and methods described herein have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds described herein and are not intended to limit the same. Each of the references recited in the present application is incorporated herein by reference in its entirety.

Example 1: Antisense inhibition of a human C9ORF72 mRNA variant in HepG2 cells by MOE gapmers

Antisense oligonucleotides targeting a C9ORF72 nucleic acid were designed and tested for their effects on C9ORF72 mRNA in vitro. ISIS 576816, previously tested in US Application No. 61/714,132, filed October 15, 2012, was used as a benchmark oligonucleotide. ISIS 576816 is a 5-10-5 MOE gapmer with phosphorothioate linkages throughout. Cultured HepG2 cells at a density of 20,000 cells per well were transfected using electroporation with 4,000 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3905 (forward primer sequence GGGTCTAGCAAGAGCAGGTG, designated herein as SEQ ID NO: 13; reverse primer sequence GTCTTGGCAACAGCTGGAGAT, designated herein

as SEQ ID NO: 14; probe sequence TGATGTCGACTCTTTGCCCACCGC, designated herein as SEQ ID NO: 15 – a TAQ-man primer probe set) was used. RTS3905 detects an mRNA variant (e.g. NM_001256054.1) processed from a pre-mRNA variant containing the hexanucleotide repeat. The mRNA variant processed from a pre-mRNA variant containing the hexanucleotide repeat is herein the “C9ORF72 pathogenic associated mRNA variant.” A pre-mRNA contains the hexanucleotide repeat when transcription of the pre-mRNA begins in the region from the start site of exon 1A to the start site of exon 1B (generally nucleotides 1107 to 1520 of the genomic sequence: SEQ ID NO: 2, the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000. Therefore, oligonucleotides were designed in this region selectively target the pre-mRNA variant containing the hexanucleotide repeat. RTS3905 measures an mRNA product (i.e. the C9ORF72 pathogenic associated mRNA variant) of the pre-mRNA variant containing the hexanucleotide repeat and, therefore, measures the reduction of the pre-mRNA variant containing the hexanucleotide repeat. The levels of the C9ORF72 pathogenic associated mRNA variant were normalized to the total RNA content of the cell, as measured by RIBOGREEN®. Results are presented as percent inhibition of C9ORF72, relative to untreated control cells. The oligonucleotide marked with an asterisk (*) targets the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of these oligonucleotides.

The chimeric antisense oligonucleotides in the Tables below were designed as 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both the 5' end and on the 3' end comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment comprises a 2'-MOE group. All cytosine residues throughout each oligonucleotide are 5-methylcytosines. The internucleoside linkages for the gapmers are mixed phosphorothioate and phosphodiester linkages. The internucleoside linkages for each gapmer are presented in the Linkage column, where 'o' indicates a phosphodiester linkage and 's' indicates a phosphorothioate linkage.

“Start site” indicates the 5'-most nucleoside to which the gapmer is targeted in the human gene sequence. “Stop site” indicates the 3'-most nucleoside to which the gapmer is targeted human gene sequence. Each antisense oligonucleotide listed in the Table below is targeted to either human C9ORF72 mRNA sequence, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_001256054.1) or the human C9ORF72 genomic sequence, designated herein as SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides

27535000 to 27565000), or both. 'n/a' indicates that the antisense oligonucleotide does not target that particular gene sequence

Table 6
Percent inhibition of the C9ORF72 pathogenic associated mRNA variant compared to PBS
control by antisense oligonucleotides targeting SEQ ID NOs: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	Sequence	Linkage	% inhibition	SEQ ID NO
576816	310	7990	GCCTTACTCTAGGACCAAGA	ssssssssssssssssss	40	20
619060	10	1146	CTTTCCTAGCGGGACACCGT	s0000ssssssssss00ss	34	21
619111	100	1236	AAAAGAGAAGCAACCGGGCA	s0000ssssssssss00ss	34	22
619112	101	1237	CAAAAGAGAAGCAACCGGGC	s0000ssssssssss00ss	38	23
619113	102	1238	CCAAAAGAGAAGCAACCGGG	s0000ssssssssss00ss	44	24
619114	103	1239	CCCAAAAGAGAAGCAACCGG	s0000ssssssssss00ss	100	25
619061	11	1147	TCTTTCCTAGCGGGACACCG	s0000ssssssssss00ss	100	26
619062	12	1148	CTCTTTCCTAGCGGGACACC	s0000ssssssssss00ss	20	27
619063	13	1149	TCTCTTTCCTAGCGGGACAC	s0000ssssssssss00ss	14	28
619064	14	1150	CTCTCTTTCCTAGCGGGACA	s0000ssssssssss00ss	9	29
619065	15	1151	CCTCTCTTTCCTAGCGGGAC	s0000ssssssssss00ss	12	30
619066	16	1152	ACCTCTCTTTCCTAGCGGGA	s0000ssssssssss00ss	0	31
619410*	160	7840	ATCCAAATGCTCCGGAGATA	s0000ssssssssss00ss	96	32
619067	17	1153	CACCTCTCTTTCCTAGCGGG	s0000ssssssssss00ss	0	33
619068	18	1154	GCACCTCTCTTTCCTAGCGG	s0000ssssssssss00ss	24	34
619069	19	1155	CGCACCTCTCTTTCCTAGCG	s0000ssssssssss00ss	39	35
619052	2	1138	GCGGGACACCGTAGGTTACG	s0000ssssssssss00ss	30	36
619070	20	1156	ACGCACCTCTCTTTCCTAGC	s0000ssssssssss00ss	14	37
619071	21	1157	GACGCACCTCTCTTTCCTAG	s0000ssssssssss00ss	7	38
619072	22	1158	TGACGCACCTCTCTTTCCTA	s0000ssssssssss00ss	50	39
619073	23	1159	TTGACGCACCTCTCTTTCCT	s0000ssssssssss00ss	0	40
619074	24	1160	TTTGACGCACCTCTCTTTC	s0000ssssssssss00ss	55	41
619075	25	1161	GTTTGACGCACCTCTCTTTC	s0000ssssssssss00ss	12	42
619076	26	1162	TGTTTGACGCACCTCTCTTT	s0000ssssssssss00ss	65	43
619077	27	1163	CTGTTTGACGCACCTCTCTT	s0000ssssssssss00ss	28	44
619078	28	1164	GCTGTTTGACGCACCTCTCT	s0000ssssssssss00ss	18	45
619079	29	1165	CGCTGTTTGACGCACCTCTC	s0000ssssssssss00ss	14	46
619053	3	1139	AGCGGGACACCGTAGGTTAC	s0000ssssssssss00ss	23	47
619080	30	1166	TCGCTGTTTGACGCACCTCT	s0000ssssssssss00ss	100	48
619081	31	1167	GTCGCTGTTTGACGCACCTC	s0000ssssssssss00ss	23	49
619082	32	1168	TGTCGCTGTTTGACGCACCT	s0000ssssssssss00ss	0	50
619411	324	8004	TGGAGCCCAAATGTGCCTTA	s0000ssssssssss00ss	99	51

619083	33	1169	TTGTCGCTGTTTGACGCACC	s0000ssssssssss00ss	36	52
619412	332	8012	TCTGTCTTTGGAGCCCAAAT	s0000ssssssssss00ss	100	53
619084	34	1170	CTTGTCGCTGTTTGACGCAC	s0000ssssssssss00ss	28	54
619085	35	1171	ACTTGTCGCTGTTTGACGCA	s0000ssssssssss00ss	55	55
619086	36	1172	AACTTGTCGCTGTTTGACGC	s0000ssssssssss00ss	29	56
619087	37	1173	GAACCTTGTCGCTGTTTGACG	s0000ssssssssss00ss	21	57
619088	38	1174	GGAACCTTGTCGCTGTTTGAC	s0000ssssssssss00ss	100	58
619089	39	1175	CGGAACCTTGTCGCTGTTTGA	s0000ssssssssss00ss	67	59
619054	4	1140	TAGCGGGACACCGTAGGTTA	s0000ssssssssss00ss	59	60
619090	40	1176	GCGGAACCTTGTCGCTGTTTG	s0000ssssssssss00ss	8	61
619091	41	1177	GGCGGAACCTTGTCGCTGTTT	s0000ssssssssss00ss	38	62
619092	42	1178	GGGCGGAACCTTGTCGCTGTT	s0000ssssssssss00ss	16	63
619093	43	1179	TGGGCGGAACCTTGTCGCTGT	s0000ssssssssss00ss	22	64
619094	44	1180	GTGGGCGGAACCTTGTCGCTG	s0000ssssssssss00ss	24	65
619095	45	1181	CGTGGGCGGAACCTTGTCGCT	s0000ssssssssss00ss	100	66
619055	5	1141	CTAGCGGGACACCGTAGGTT	s0000ssssssssss00ss	100	67
619056	6	1142	CCTAGCGGGACACCGTAGGT	s0000ssssssssss00ss	11	68
619057	7	1143	TCCTAGCGGGACACCGTAGG	s0000ssssssssss00ss	22	69
619096	75	1211	GACGGCTGACACACCAAGCG	s0000ssssssssss00ss	100	70
619097	76	1212	GGACGGCTGACACACCAAGC	s0000ssssssssss00ss	88	71
619098	77	1213	GGGACGGCTGACACACCAAG	s0000ssssssssss00ss	29	72
619099	78	1214	AGGGACGGCTGACACACCAA	s0000ssssssssss00ss	83	73
619100	79	1215	CAGGGACGGCTGACACACCA	s0000ssssssssss00ss	23	74
619058	8	1144	TTCCTAGCGGGACACCGTAG	s0000ssssssssss00ss	32	75
619101	80	1216	GCAGGGACGGCTGACACACC	s0000ssssssssss00ss	18	76
619102	81	1217	AGCAGGGACGGCTGACACAC	s0000ssssssssss00ss	39	77
619103	82	1218	CAGCAGGGACGGCTGACACA	s0000ssssssssss00ss	39	78
619104	83	1219	GCAGCAGGGACGGCTGACAC	s0000ssssssssss00ss	22	79
619105	84	1220	GGCAGCAGGGACGGCTGACA	s0000ssssssssss00ss	43	80
619059	9	1145	TTTCCTAGCGGGACACCGTA	s0000ssssssssss00ss	4	81
619106	95	1231	AGAAGCAACCGGGCAGCAGG	s0000ssssssssss00ss	54	82
619107	96	1232	GAGAAGCAACCGGGCAGCAG	s0000ssssssssss00ss	100	83
619108	97	1233	AGAGAAGCAACCGGGCAGCA	s0000ssssssssss00ss	32	84
619109	98	1234	AAGAGAAGCAACCGGGCAGC	s0000ssssssssss00ss	30	85
619110	99	1235	AAAGAGAAGCAACCGGGCAG	s0000ssssssssss00ss	44	86
619042	n/a	1111	GTTTTCTATGTGCGATGACG	s0000ssssssssss00ss	6	87
619043	n/a	1112	TGTTTTCTATGTGCGATGAC	s0000ssssssssss00ss	45	88
619044	n/a	1113	CTGTTTTCTATGTGCGATGA	s0000ssssssssss00ss	23	89
619045	n/a	1114	TCTGTTTTCTATGTGCGATG	s0000ssssssssss00ss	10	90
619046	n/a	1115	GTCTGTTTTCTATGTGCGAT	s0000ssssssssss00ss	11	91
619047	n/a	1116	TGTCTGTTTTCTATGTGCGA	s0000ssssssssss00ss	28	92
619048	n/a	1117	CTGTCTGTTTTCTATGTGCG	s0000ssssssssss00ss	34	93
619049	n/a	1118	TCTGTCTGTTTTCTATGTGC	s0000ssssssssss00ss	72	94

619050	n/a	1119	GTCTGTCTGTTTTCTATGTG	sooooooosoooooooooss	37	95
619051	n/a	1120	CGTCTGTCTGTTTTCTATGT	sooooooosoooooooooss	1	96
619253	n/a	1406	TACAGGCTGCGGTTGTTTCC	sooooooosoooooooooss	100	97
619293	n/a	1446	CCCGGCCCTAGCGCGCGAC	sooooooosoooooooooss	98	98

Example 2: Antisense inhibition of a human C9ORF72 mRNA variant in HepG2 cells by MOE gapmers

Additional antisense oligonucleotides targeting a C9ORF72 nucleic acid were designed and tested for their effects on C9ORF72 mRNA in vitro. ISIS 576816, previously tested in US Application No. 61/714,132, filed October 15, 2012, was used as a benchmark oligonucleotide. The antisense oligonucleotides were tested in a series of experiments that had similar 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 1,000 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3905 was used to measure the C9ORF72 pathogenic associated mRNA variant, which is the product of a pre-mRNA containing a hexanucleotide repeat. The levels of the C9ORF72 pathogenic associated mRNA variant were normalized to the total RNA content of the cell, as measured by RIBOGREEN®. Results are presented as percent inhibition of C9ORF72, relative to untreated control cells. The oligonucleotides marked with an asterisk (*) targets the region of the primer probe set. Additional assays may be used to measure the potency and efficacy of these oligonucleotides. 'n.d.' indicates that there was no signal reading in the assay for that particular oligonucleotide.

The chimeric antisense oligonucleotides in the Tables below were designed as 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both the 5' end and on the 3' end comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment comprises a 2'-MOE group. All cytosine residues throughout each oligonucleotide are 5-methylcytosines. The internucleoside linkages for the gapmers are mixed phosphorothioate and phosphodiester linkages. The internucleoside linkages for each gapmer are presented in the Linkage column, where 'o' indicates a phosphodiester linkage and 's' indicates a phosphorothioate linkage.

“Start site” indicates the 5’-most nucleoside to which the gapmer is targeted in the human gene sequence. “Stop site” indicates the 3’-most nucleoside to which the gapmer is targeted human gene sequence. The gapmers of the Tables below also target either human C9ORF72 mRNA sequence, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_001256054.1) or the human C9ORF72 genomic sequence, designated herein as SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000), or both. Some of the gapmers of Table 10 are targeted to GENBANK Accession No. NM_145005.5 (incorporated herein as SEQ ID NO: 3), GENBANK Accession No. DB079375.1 (incorporated herein as SEQ ID NO: 4), or GENBANK Accession No. BU194591.1 (incorporated herein as SEQ ID NO: 5). ‘n/a’ indicates that the antisense oligonucleotide does not target that particular gene sequence.

Table 7
Percent inhibition of the C9ORF72 pathogenic associated mRNA variant compared to PBS control by antisense oligonucleotides targeting SEQ ID NOs: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	Sequence	Linkage	% inhibition	SEQ ID NO
576816	310	7990	GCCTTACTCTAGGACCAAGA	ssssssssssssssssssss	70	20
619115	104	1240	CCCCAAAAGAGAAGCAACCG	soooooossssssssooss	10	99
619116	105	1241	CCCCAAAAGAGAAGCAACC	soooooossssssssooss	19	100
619117	106	1242	GCCCCAAAAGAGAAGCAAC	soooooossssssssooss	0	101
619118*	107	1243	CGCCCCAAAAGAGAAGCAA	soooooossssssssooss	17	102
619119*	108	1244	CCGCCCCAAAAGAGAAGCA	soooooossssssssooss	14	103
619120*	109	1245	CCCGCCCCAAAAGAGAAGC	soooooossssssssooss	4	104
619121*	110	1246	CCCCGCCCCAAAAGAGAAG	soooooossssssssooss	19	105
619122*	111	1247	ACCCCGCCCCAAAAGAGAA	soooooossssssssooss	47	106
619123*	112	1248	GACCCCGCCCCAAAAGAGA	soooooossssssssooss	11	107
619124*	113	1249	AGACCCCGCCCCAAAAGAG	soooooossssssssooss	16	108
619125*	114	1250	TAGACCCCGCCCCAAAAGA	soooooossssssssooss	15	109
619126*	115	1251	CTAGACCCCGCCCCAAAAG	soooooossssssssooss	43	110
619127*	116	1252	GCTAGACCCCGCCCCAAAA	soooooossssssssooss	67	111
619128*	117	1253	TGCTAGACCCCGCCCCAAA	soooooossssssssooss	85	112
619129*	118	1254	TTGCTAGACCCCGCCCCAA	soooooossssssssooss	41	113
619130*	119	1255	CTTGCTAGACCCCGCCCCA	soooooossssssssooss	62	114
619131*	120	1256	TCTTGCTAGACCCCGCCCC	soooooossssssssooss	95	115
619132*	121	1257	CTCTTGCTAGACCCCGCCCC	soooooossssssssooss	81	116
619133*	122	1258	GCTCTTGCTAGACCCCGCCC	soooooossssssssooss	90	117

619134*	123	1259	TGCTCTTGCTAGACCCCGCC	S0000SSSSSSSSSS00SS	85	118
619135*	124	1260	CTGCTCTTGCTAGACCCCGC	S0000SSSSSSSSSS00SS	81	119
619136*	125	1261	CCTGCTCTTGCTAGACCCCG	S0000SSSSSSSSSS00SS	78	120
619137*	126	1262	ACCTGCTCTTGCTAGACCCC	S0000SSSSSSSSSS00SS	85	121
619138*	127	1263	CACCTGCTCTTGCTAGACCC	S0000SSSSSSSSSS00SS	81	122
619139*	128	1264	ACACCTGCTCTTGCTAGACC	S0000SSSSSSSSSS00SS	77	123
619140*	129	1265	CACACCTGCTCTTGCTAGAC	S0000SSSSSSSSSS00SS	86	124
619141*	130	1266	CCACACCTGCTCTTGCTAGA	S0000SSSSSSSSSS00SS	90	125
619142*	131	1267	CCCACACCTGCTCTTGCTAG	S0000SSSSSSSSSS00SS	98	126
619143*	132	1268	ACCCACACCTGCTCTTGCTA	S0000SSSSSSSSSS00SS	94	127
619144*	133	1269	AACCCACACCTGCTCTTGCT	S0000SSSSSSSSSS00SS	93	128
619145*	134	1270	AAACCCACACCTGCTCTTGC	S0000SSSSSSSSSS00SS	95	129
619146*	135	1271	TAAACCCACACCTGCTCTTG	S0000SSSSSSSSSS00SS	78	130
619147*	136	1272	CTAAACCCACACCTGCTCTT	S0000SSSSSSSSSS00SS	64	131
619148*	137	1273	CCTAAACCCACACCTGCTCT	S0000SSSSSSSSSS00SS	84	132
619149*	138	1274	TCCTAAACCCACACCTGCTC	S0000SSSSSSSSSS00SS	87	133
619150*	139	1275	CTCCTAAACCCACACCTGCT	S0000SSSSSSSSSS00SS	89	134
619413	340	8020	GTACCTGTTCTGTCTTTGGA	S0000SSSSSSSSSS00SS	70	135
619414	353	8033	CCATCACTGAGAAGTACCTG	S0000SSSSSSSSSS00SS	78	136
619415	940	16395	GGCATAATGTTCTGACTATC	S0000SSSSSSSSSS00SS	67	137
619151*	n/a	1276	CCTCCTAAACCCACACCTGC	S0000SSSSSSSSSS00SS	64	138
619152*	n/a	1277	ACCTCCTAAACCCACACCTG	S0000SSSSSSSSSS00SS	45	139
619153*	n/a	1278	CACCTCCTAAACCCACACCT	S0000SSSSSSSSSS00SS	36	140
619154*	n/a	1279	ACACCTCCTAAACCCACACC	S0000SSSSSSSSSS00SS	26	141
619155*	n/a	1280	CACACCTCCTAAACCCACAC	S0000SSSSSSSSSS00SS	50	142
619156*	n/a	1281	ACACACCTCCTAAACCCACA	S0000SSSSSSSSSS00SS	53	143
619157*	n/a	1282	CACACACCTCCTAAACCCAC	S0000SSSSSSSSSS00SS	44	144
619158*	n/a	1283	ACACACACCTCCTAAACCCA	S0000SSSSSSSSSS00SS	65	145
619159*	n/a	1284	AACACACACCTCCTAAACCC	S0000SSSSSSSSSS00SS	9	146
619160*	n/a	1285	AAACACACACCTCCTAAACC	S0000SSSSSSSSSS00SS	0	147
619161*	n/a	1286	AAAACACACACCTCCTAAAC	S0000SSSSSSSSSS00SS	15	148
619162*	n/a	1287	AAAAACACACACCTCCTAAA	S0000SSSSSSSSSS00SS	10	149
619163*	n/a	1288	CAAAAACACACACCTCCTAA	S0000SSSSSSSSSS00SS	7	150
619164*	n/a	1289	ACAAAAACACACACCTCCTA	S0000SSSSSSSSSS00SS	55	151
619165*	n/a	1290	AACAAAAACACACACCTCCT	S0000SSSSSSSSSS00SS	24	152
619166*	n/a	1291	AAACAAAAACACACACCTCC	S0000SSSSSSSSSS00SS	19	153
619167*	n/a	1292	AAAACAAAAACACACACCTC	S0000SSSSSSSSSS00SS	8	154
619168*	n/a	1294	GAAAAACAAAAACACACACC	S0000SSSSSSSSSS00SS	17	155
619169*	n/a	1295	GGAAAAACAAAAACACACAC	S0000SSSSSSSSSS00SS	26	156
619170	n/a	1297	TGGGAAAAACAAAAACACAC	S0000SSSSSSSSSS00SS	30	157
619171	n/a	1298	GTGGGAAAAACAAAAACACA	S0000SSSSSSSSSS00SS	23	158
619172	n/a	1299	GGTGGGAAAAACAAAAACAC	S0000SSSSSSSSSS00SS	22	159
619173	n/a	1326	CTGTGAGAGCAAGTAGTGGG	S0000SSSSSSSSSS00SS	43	160

619174	n/a	1327	ACTGTGAGAGCAAGTAGTGG	s0000ssssssssss00ss	36	161
619175	n/a	1328	TACTGTGAGAGCAAGTAGTG	s0000ssssssssss00ss	24	162
619176	n/a	1329	GTACTGTGAGAGCAAGTAGT	s0000ssssssssss00ss	58	163
619177	n/a	1330	AGTACTGTGAGAGCAAGTAG	s0000ssssssssss00ss	22	164
619178	n/a	1331	GAGTACTGTGAGAGCAAGTA	s0000ssssssssss00ss	100	165
619179	n/a	1332	CGAGTACTGTGAGAGCAAGT	s0000ssssssssss00ss	62	166
619180	n/a	1333	GCGAGTACTGTGAGAGCAAG	s0000ssssssssss00ss	63	167
619181	n/a	1334	AGCGAGTACTGTGAGAGCAA	s0000ssssssssss00ss	36	168
619182	n/a	1335	CAGCGAGTACTGTGAGAGCA	s0000ssssssssss00ss	41	169
619183	n/a	1336	TCAGCGAGTACTGTGAGAGC	s0000ssssssssss00ss	66	170
619184	n/a	1337	CTCAGCGAGTACTGTGAGAG	s0000ssssssssss00ss	28	171
619185	n/a	1338	CCTCAGCGAGTACTGTGAGA	s0000ssssssssss00ss	37	172
619186	n/a	1339	CCCTCAGCGAGTACTGTGAG	s0000ssssssssss00ss	43	173
619187	n/a	1340	ACCCTCAGCGAGTACTGTGA	s0000ssssssssss00ss	84	174
619253	n/a	1406	TACAGGCTGCGGTTGTTTCC	s0000ssssssssss00ss	31	97
619293	n/a	1446	CCCGGCCCTAGCGCGCGAC	s0000ssssssssss00ss	63	98

Table 8
Percent inhibition of the C9ORF72 pathogenic associated mRNA variant compared to PBS control by
antisense oligonucleotides targeting SEQ ID NOs: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	Sequence	Linkage	% inhibition	SEQ ID NO
576816	310	7990	GCCTTACTCTAGGACCAAGA	ssssssssssssssssss	82	20
619188	n/a	1341	CACCCTCAGCGAGTACTGTG	s0000ssssssssss00ss	56	175
619189	n/a	1342	TCACCCTCAGCGAGTACTGT	s0000ssssssssss00ss	66	176
619190	n/a	1343	TTCACCCTCAGCGAGTACTG	s0000ssssssssss00ss	57	177
619191	n/a	1344	GTTTACCCTCAGCGAGTACT	s0000ssssssssss00ss	83	178
619192	n/a	1345	TGTTTACCCTCAGCGAGTAC	s0000ssssssssss00ss	66	179
619193	n/a	1346	TTGTTTACCCTCAGCGAGTA	s0000ssssssssss00ss	57	180
619194	n/a	1347	CTTGTTTACCCTCAGCGAGT	s0000ssssssssss00ss	48	181
619195	n/a	1348	TCTTGTTTACCCTCAGCGAG	s0000ssssssssss00ss	46	182
619196	n/a	1349	TTCTTGTTTACCCTCAGCGA	s0000ssssssssss00ss	66	183
619197	n/a	1350	TTTCTTGTTTACCCTCAGCG	s0000ssssssssss00ss	31	184
619198	n/a	1351	TTTTCTTGTTTACCCTCAGC	s0000ssssssssss00ss	47	185
619199	n/a	1352	CTTTCTTGTTTACCCTCAG	s0000ssssssssss00ss	53	186
619200	n/a	1353	TCTTTCTTGTTTACCCTCA	s0000ssssssssss00ss	46	187
619201	n/a	1354	GTCTTTCTTGTTTACCCTC	s0000ssssssssss00ss	71	188
619202	n/a	1355	GGTCTTTCTTGTTTACCCT	s0000ssssssssss00ss	73	189
619203	n/a	1356	AGGTCTTTCTTGTTTACCC	s0000ssssssssss00ss	79	190
619204	n/a	1357	CAGGTCTTTCTTGTTTACC	s0000ssssssssss00ss	0	191

619205	n/a	1358	TCAGGTCTTTTCTTGTTAC	s0000sssssssssooss	68	192
619206	n/a	1359	ATCAGGTCTTTTCTTGTTCA	s0000sssssssssooss	52	193
619207	n/a	1360	TATCAGGTCTTTTCTTGTTT	s0000sssssssssooss	47	194
619208	n/a	1361	TTATCAGGTCTTTTCTTGTT	s0000sssssssssooss	37	195
619209	n/a	1362	TTTATCAGGTCTTTTCTTGTT	s0000sssssssssooss	31	196
619210	n/a	1363	CTTTATCAGGTCTTTTCTTG	s0000sssssssssooss	24	197
619211	n/a	1364	TCTTTATCAGGTCTTTTCTT	s0000sssssssssooss	37	198
619212	n/a	1365	ATCTTTATCAGGTCTTTTCT	s0000sssssssssooss	34	199
619213	n/a	1366	AATCTTTATCAGGTCTTTTC	s0000sssssssssooss	38	200
619214	n/a	1367	TAATCTTTATCAGGTCTTTT	s0000sssssssssooss	32	201
619215	n/a	1368	TTAATCTTTATCAGGTCTTT	s0000sssssssssooss	55	202
619216	n/a	1369	GTAAATCTTTATCAGGTCTT	s0000sssssssssooss	72	203
619217	n/a	1370	GGTTAATCTTTATCAGGTCT	s0000sssssssssooss	85	204
619218	n/a	1371	TGGTTAATCTTTATCAGGTC	s0000sssssssssooss	82	205
619219	n/a	1372	CTGGTTAATCTTTATCAGGT	s0000sssssssssooss	62	206
619220	n/a	1373	TCTGGTTAATCTTTATCAGG	s0000sssssssssooss	19	207
619221	n/a	1374	TTCTGGTTAATCTTTATCAG	s0000sssssssssooss	31	208
619222	n/a	1375	CTTCTGGTTAATCTTTATCA	s0000sssssssssooss	40	209
619223	n/a	1376	TCTTCTGGTTAATCTTTATC	s0000sssssssssooss	41	210
619224	n/a	1377	TTCTTCTGGTTAATCTTTAT	s0000sssssssssooss	11	211
619225	n/a	1378	TTTCTTCTGGTTAATCTTTA	s0000sssssssssooss	46	212
619226	n/a	1379	TTTTCTTCTGGTTAATCTTT	s0000sssssssssooss	14	213
619227	n/a	1380	GTTTTCTTCTGGTTAATCTT	s0000sssssssssooss	50	214
619228	n/a	1381	TGTTTTCTTCTGGTTAATCT	s0000sssssssssooss	49	215
619229	n/a	1382	TTGTTTTCTTCTGGTTAATC	s0000sssssssssooss	31	216
619230	n/a	1383	CTTGTTTTCTTCTGGTTAAT	s0000sssssssssooss	16	217
619231	n/a	1384	CCTTGTTTTCTTCTGGTTAA	s0000sssssssssooss	23	218
619232	n/a	1385	TCCTTGTTTTCTTCTGGTTA	s0000sssssssssooss	52	219
619233	n/a	1386	CTCCTTGTTTTCTTCTGGTT	s0000sssssssssooss	32	220
619234	n/a	1387	CCTCCTTGTTTTCTTCTGGT	s0000sssssssssooss	59	221
619235	n/a	1388	CCCTCCTTGTTTTCTTCTGG	s0000sssssssssooss	48	222
619236	n/a	1389	TCCCTCCTTGTTTTCTTCTG	s0000sssssssssooss	31	223
619237	n/a	1390	TTCCCTCCTTGTTTTCTTCT	s0000sssssssssooss	24	224
619238	n/a	1391	TTCCCTCCTTGTTTTCTTC	s0000sssssssssooss	42	225
619239	n/a	1392	GTTTCCCTCCTTGTTTTCTT	s0000sssssssssooss	46	226
619240	n/a	1393	TGTTTCCCTCCTTGTTTTCT	s0000sssssssssooss	81	227
619241	n/a	1394	TTGTTTCCCTCCTTGTTTTC	s0000sssssssssooss	53	228
619242	n/a	1395	GTTGTTTCCCTCCTTGTTTT	s0000sssssssssooss	28	229
619243	n/a	1396	GGTTGTTTCCCTCCTTGTTT	s0000sssssssssooss	40	230
619244	n/a	1397	CGGTTGTTTCCCTCCTTGTT	s0000sssssssssooss	31	231
619245	n/a	1398	GCGGTTGTTTCCCTCCTTGT	s0000sssssssssooss	69	232
619246	n/a	1399	TGCGGTTGTTTCCCTCCTTG	s0000sssssssssooss	73	233
619247	n/a	1400	CTGCGGTTGTTTCCCTCCTT	s0000sssssssssooss	90	234

619248	n/a	1401	GCTGCGGTTGTTTCCCTCCT	s0000sssssssssssooss	40	235
619249	n/a	1402	GGCTGCGGTTGTTTCCCTCC	s0000sssssssssssooss	50	236
619250	n/a	1403	AGGCTGCGGTTGTTTCCCTC	s0000sssssssssssooss	61	237
619251	n/a	1404	CAGGCTGCGGTTGTTTCCCT	s0000sssssssssssooss	72	238
619252	n/a	1405	ACAGGCTGCGGTTGTTTCCC	s0000sssssssssssooss	69	239
619253	n/a	1406	TACAGGCTGCGGTTGTTTCC	s0000sssssssssssooss	67	97
619254	n/a	1407	CTACAGGCTGCGGTTGTTTC	s0000sssssssssssooss	43	240
619255	n/a	1408	GCTACAGGCTGCGGTTGTTT	s0000sssssssssssooss	54	241
619256	n/a	1409	TGCTACAGGCTGCGGTTGTT	s0000sssssssssssooss	36	242
619257	n/a	1410	TTGCTACAGGCTGCGGTTGT	s0000sssssssssssooss	29	243
619258	n/a	1411	CTTGCTACAGGCTGCGGTTG	s0000sssssssssssooss	50	244
619259	n/a	1412	GCTTGCTACAGGCTGCGGTT	s0000sssssssssssooss	76	245
619260	n/a	1413	AGCTTGCTACAGGCTGCGGT	s0000sssssssssssooss	80	246
619261	n/a	1414	GAGCTTGCTACAGGCTGCGG	s0000sssssssssssooss	54	247
619262	n/a	1415	AGAGCTTGCTACAGGCTGCG	s0000sssssssssssooss	62	248
619293	n/a	1446	CCCGGCCCTAGCGCGCGAC	s0000sssssssssssooss	64	98
619416	1937	24657 27056	AAAAAACAGTAGTTGTGGTC	s0000sssssssssssooss	78	249
619417	1988	27107	GCCAACTCAGATTTACCTT	s0000sssssssssssooss	86	250

Table 9

Percent inhibition of the C9ORF72 pathogenic associated mRNA variant compared to PBS control by antisense oligonucleotides targeting SEQ ID NOs: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	Sequence	Linkage	% inhibition	SEQ ID NO
576816	310	7990	GCCTTACTCTAGGACCAAGA	ssssssssssssssssssss	71	20
619264	n/a	1417	CCAGAGCTTGCTACAGGCTG	s0000sssssssssssooss	54	251
619265	n/a	1418	TCCAGAGCTTGCTACAGGCT	s0000sssssssssssooss	69	252
619266	n/a	1419	TTCCAGAGCTTGCTACAGGC	s0000sssssssssssooss	70	253
619267	n/a	1420	GTTCCAGAGCTTGCTACAGG	s0000sssssssssssooss	49	254
619268	n/a	1421	AGTTCCAGAGCTTGCTACAG	s0000sssssssssssooss	95	255
619269	n/a	1422	GAGTTCCAGAGCTTGCTACA	s0000sssssssssssooss	36	256
619270	n/a	1423	TGAGTTCCAGAGCTTGCTAC	s0000sssssssssssooss	15	257
619271	n/a	1424	CTGAGTTCCAGAGCTTGCTA	s0000sssssssssssooss	31	258
619272	n/a	1425	CCTGAGTTCCAGAGCTTGCT	s0000sssssssssssooss	41	259
619273	n/a	1426	TCCTGAGTTCCAGAGCTTGC	s0000sssssssssssooss	36	260
619274	n/a	1427	CTCCTGAGTTCCAGAGCTTG	s0000sssssssssssooss	25	261
619275	n/a	1428	ACTCCTGAGTTCCAGAGCTT	s0000sssssssssssooss	50	262
619276	n/a	1429	GACTCCTGAGTTCCAGAGCT	s0000sssssssssssooss	74	263
619277	n/a	1430	CGACTCCTGAGTTCCAGAGC	s0000sssssssssssooss	69	264

619278	n/a	1431	GCGACTCCTGAGTTCCAGAG	s0000s	98	265
619279	n/a	1432	CGCGACTCCTGAGTTCCAGA	s0000s	69	266
619280	n/a	1433	GCGCGACTCCTGAGTTCCAG	s0000s	75	267
619281	n/a	1434	CGCGCGACTCCTGAGTTCCA	s0000s	67	268
619282	n/a	1435	GCGCGCGACTCCTGAGTTCC	s0000s	55	269
619283	n/a	1436	AGCGCGCGACTCCTGAGTTC	s0000s	62	270
619284	n/a	1437	TAGCGCGCGACTCCTGAGTT	s0000s	100	271
619285	n/a	1438	CTAGCGCGCGACTCCTGAGT	s0000s	68	272
619286	n/a	1439	CCTAGCGCGCGACTCCTGAG	s0000s	41	273
619287	n/a	1440	CCCTAGCGCGCGACTCCTGA	s0000s	70	274
619288	n/a	1441	CCCCTAGCGCGCGACTCCTG	s0000s	68	275
619289	n/a	1442	GCCCCTAGCGCGCGACTCCT	s0000s	52	276
619290	n/a	1443	GGCCCCTAGCGCGCGACTCC	s0000s	49	277
619291	n/a	1444	CGGCCCTAGCGCGCGACTC	s0000s	69	278
619292	n/a	1445	CCGGCCCCTAGCGCGCGACT	s0000s	76	279
619293	n/a	1446	CCCGGCCCTAGCGCGCGAC	s0000s	52	98
619294	n/a	1447	CCCCGGCCCCTAGCGCGCGA	s0000s	62	280
619295	n/a	1448	GCCCCGGCCCCTAGCGCGCG	s0000s	68	281
619296	n/a	1449	GGCCCCGGCCCCTAGCGCGC	s0000s	56	282
619297	n/a	1450	CGGCCCGGCCCTAGCGCG	s0000s	71	283
619298	n/a	1451	CCGGCCCCGGCCCCTAGCGC	s0000s	73	284
619299	n/a	1452	CCCGGCCCGGCCCTAGCG	s0000s	51	285
619300	n/a	1453	CCCCGGCCCCGGCCCCTAGC	s0000s	49	286
619301	n/a	1454	GCCCCGGCCCCGGCCCCTAG	s0000s	60	287
619302	n/a	1455	GGCCCCGGCCCCGGCCCCTA	s0000s	48	288
619303	n/a	1462	ACGCCCGGCCCGGCCCG	s0000s	49	289
619304	n/a	1463	CACGCCCGGCCCGGCCCG	s0000s	25	290
619305	n/a	1464	CCACGCCCGGCCCGGCCCG	s0000s	66	291
619306	n/a	1465	ACCACGCCCGGCCCGGCC	s0000s	70	292
619307	n/a	1466	GACCACGCCCGGCCCGGC	s0000s	73	293
619308	n/a	1467	CGACCACGCCCGGCCCGG	s0000s	55	294
619309	n/a	1468	CCGACCACGCCCGGCCCG	s0000s	70	295
619310	n/a	1469	CCCGACCACGCCCGGCCCG	s0000s	50	296
619311	n/a	1470	CCCCGACCACGCCCGGCC	s0000s	45	297
619312	n/a	1471	GCCCCGACCACGCCCGGCC	s0000s	36	298
619313	n/a	1472	CGCCCCGACCACGCCCGGC	s0000s	58	299
619314	n/a	1473	CCGCCCGACCACGCCCGG	s0000s	100	300
619315	n/a	1474	CCCGCCCCGACCACGCCCG	s0000s	44	301
619316	n/a	1475	GCCCGCCCCGACCACGCC	s0000s	97	302
619317	n/a	1476	GGCCCGCCCCGACCACGCC	s0000s	76	303
619318	n/a	1477	GGGCCCGCCCCGACCACGC	s0000s	44	304
619319	n/a	1478	CGGGCCCGCCCCGACCACGC	s0000s	40	305
619320	n/a	1479	CCGGGCCCGCCCCGACCACG	s0000s	50	306

619321	n/a	1480	CCCGGGCCCCGCCCCGACCAC	s0000sssssssssssooss	22	307
619322	n/a	1481	CCCCGGGCCCCGCCCCGACCA	s0000sssssssssssooss	56	308
619323	n/a	1482	CCCCGGGCCCCGCCCCGACC	s0000sssssssssssooss	40	309
619324	n/a	1483	GCCCCCGGGCCCCGCCCCGAC	s0000sssssssssssooss	65	310
619325	n/a	1484	CGCCCCCGGGCCCCGCCCCGA	s0000sssssssssssooss	25	311
619326	n/a	1486	CCCGCCCCCGGGCCCCGCCCC	s0000sssssssssssooss	41	312
619327	n/a	1487	GCCCCGCCCCCGGGCCCCGCCC	s0000sssssssssssooss	36	313
619328	n/a	1488	GGCCCCGCCCCCGGGCCCCGCC	s0000sssssssssssooss	14	314
619329	n/a	1495	CGCCCCCGGGCCCCGCCCCCGG	s0000sssssssssssooss	33	315
619330	n/a	1497	CCCGCCCCCGGGCCCCGCCCC	s0000sssssssssssooss	35	316
619331	n/a	1498	CCCCGCCCCCGGGCCCCGCCCC	s0000sssssssssssooss	42	317
619332	n/a	1499	GCCCCGCCCCCGGGCCCCGCCC	s0000sssssssssssooss	47	318
619333	n/a	1500	AGCCCCGCCCCCGGGCCCCGCC	s0000sssssssssssooss	53	319
619334	n/a	1501	CAGCCCCGCCCCCGGGCCCCGC	s0000sssssssssssooss	32	320
619335	n/a	1502	GCAGCCCCGCCCCCGGGCCCCG	s0000sssssssssssooss	58	321
619336	n/a	1503	CGCAGCCCCGCCCCCGGGCCC	s0000sssssssssssooss	75	322
619418	n/a	27155	CTACACACCAAAGAATGCCA	s0000sssssssssssooss	71	323
619419	n/a	15587	GGAATAAGGTCAGTAGTTCG	s0000sssssssssssooss	72	324
619420	n/a	7990	GCCTTACTCTAGGACCAAGA	s0000sssssssssssooss	100	20
619263	n/a	1416	CAGAGCTTGCTACAGGCTGC	s0000sssssssssssooss	63	325
619253	n/a	1406	TACAGGCTGCGGTTGTTTCC	s0000sssssssssssooss	50	97

Table 10
Percent inhibition of the C9ORF72 pathogenic associated mRNA variant compared to PBS control by
antisense oligonucleotides targeting SEQ ID NOs: 1-5

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 3 Start Site	SEQ ID NO: 4 Start Site	SEQ ID NO: 5 Start Site	Sequence	Linkage	% inhibition	SEQ ID NO
576816	310	7990	232	188	188	GCCTTACTCTAGGACCAAGA	ssssssssssssssssssss	69	20
619253	n/a	1406	n/a	n/a	n/a	TACAGGCTGCGGTTGTTTCC	s0000sssssssssssooss	19	97
619293	n/a	1446	n/a	n/a	n/a	CCCGGCCCCCTAGCGCGCGAC	s0000sssssssssssooss	56	98
619337	n/a	1504	n/a	n/a	n/a	CCGCAGCCCCGCCCCGGGCC	s0000sssssssssssooss	55	326
619338	n/a	1505	n/a	n/a	n/a	ACCGCAGCCCCGCCCCGGGC	s0000sssssssssssooss	62	327
619339	n/a	1506	n/a	n/a	n/a	AACCGCAGCCCCGCCCCGGG	s0000sssssssssssooss	68	328
619340	n/a	1507	n/a	n/a	n/a	CAACCGCAGCCCCGCCCCGG	s0000sssssssssssooss	14	329
619341	n/a	1508	n/a	n/a	n/a	GCAACCGCAGCCCCGCCCCG	s0000sssssssssssooss	95	330
619342	n/a	1509	n/a	n/a	n/a	CGCAACCGCAGCCCCGCCCC	s0000sssssssssssooss	56	331
619343	n/a	1510	n/a	n/a	n/a	CCGCAACCGCAGCCCCGCCC	s0000sssssssssssooss	58	332
619344	n/a	1511	n/a	n/a	n/a	ACCGCAACCGCAGCCCCGCC	s0000sssssssssssooss	51	333
619345	n/a	1512	n/a	n/a	n/a	CACCGCAACCGCAGCCCCGC	s0000sssssssssssooss	97	334
619346	n/a	1513	n/a	n/a	n/a	GCACCGCAACCGCAGCCCCG	s0000sssssssssssooss	49	335

619347	n/a	1514	n/a	n/a	n/a	GGCACCGCAACCGCAGCCCC	sooooooooooooo	100	336
619348	n/a	1515	n/a	n/a	n/a	AGGCACCGCAACCGCAGCCC	sooooooooooooo	46	337
619349	n/a	1516	n/a	n/a	n/a	CAGGCACCGCAACCGCAGCC	sooooooooooooo	100	338
619350	n/a	1517	n/a	n/a	n/a	GCAGGCACCGCAACCGCAGC	sooooooooooooo	55	339
619351	n/a	1518	n/a	n/a	n/a	CGCAGGCACCGCAACCGCAG	sooooooooooooo	63	340
619352	n/a	1519	n/a	n/a	n/a	GCGCAGGCACCGCAACCGCA	sooooooooooooo	42	341
619353	n/a	1520	n/a	n/a	n/a	GGCGCAGGCACCGCAACCGC	sooooooooooooo	95	342
619354	n/a	1521	n/a	n/a	n/a	GGGCGCAGGCACCGCAACCG	sooooooooooooo	23	343
619355*	140	n/a	n/a	n/a	n/a	TCTCCTAAACCCACACCTGC	sooooooooooooo	94	384
619356*	141	n/a	n/a	n/a	n/a	ATCTCCTAAACCCACACCTG	sooooooooooooo	69	385
619357	142	n/a	n/a	n/a	n/a	TATCTCCTAAACCCACACCT	sooooooooooooo	n.d.	386
619358*	143	n/a	n/a	n/a	n/a	ATATCTCCTAAACCCACACC	sooooooooooooo	53	387
619359	144	n/a	n/a	n/a	n/a	GATATCTCCTAAACCCACAC	sooooooooooooo	n.d.	388
619360*	145	n/a	n/a	n/a	n/a	AGATATCTCCTAAACCCACA	sooooooooooooo	30	389
619361*	146	n/a	n/a	n/a	n/a	GAGATATCTCCTAAACCCAC	sooooooooooooo	48	390
619362*	147	n/a	n/a	n/a	n/a	GGAGATATCTCCTAAACCCA	sooooooooooooo	60	391
619363*	148	n/a	n/a	n/a	n/a	CGGAGATATCTCCTAAACCC	sooooooooooooo	26	392
619364*	149	n/a	n/a	n/a	n/a	CCGGAGATATCTCCTAAACC	sooooooooooooo	97	393
619365*	150	n/a	n/a	n/a	n/a	TCCGGAGATATCTCCTAAAC	sooooooooooooo	60	394
619366*	151	n/a	n/a	n/a	n/a	CTCCGGAGATATCTCCTAAA	sooooooooooooo	34	395
619367	152	n/a	n/a	n/a	n/a	GCTCCGGAGATATCTCCTAA	sooooooooooooo	n.d.	396
619368*	153	n/a	n/a	n/a	n/a	TGCTCCGGAGATATCTCCTA	sooooooooooooo	95	397
619369	154	n/a	n/a	n/a	n/a	ATGCTCCGGAGATATCTCCT	sooooooooooooo	n.d.	398
619370*	155	n/a	n/a	n/a	n/a	AATGCTCCGGAGATATCTCC	sooooooooooooo	59	399
619371*	n/a	n/a	n/a	17	n/a	TCTCTCTTCCTAGCGGGAC	sooooooooooooo	0	344
619372*	n/a	n/a	n/a	18	n/a	ATCTCTCTTCCTAGCGGGA	sooooooooooooo	8	345
619373*	n/a	n/a	n/a	19	n/a	TATCTCTCTTCCTAGCGGG	sooooooooooooo	6	346
619374*	n/a	n/a	n/a	20	n/a	ATATCTCTCTTCCTAGCGG	sooooooooooooo	0	347
619375*	n/a	n/a	n/a	21	n/a	GATATCTCTCTTCCTAGCG	sooooooooooooo	8	348
619376*	n/a	n/a	n/a	22	n/a	AGATATCTCTCTTCCTAGC	sooooooooooooo	0	349
619377*	n/a	n/a	n/a	23	n/a	GAGATATCTCTCTTCCTAG	sooooooooooooo	89	350
619378*	n/a	n/a	n/a	24	n/a	GGAGATATCTCTCTTCCTA	sooooooooooooo	1	351
619379*	n/a	n/a	n/a	25	n/a	CGGAGATATCTCTCTTCCT	sooooooooooooo	0	352
619380	n/a	n/a	n/a	26	n/a	CCGGAGATATCTCTCTTTCC	sooooooooooooo	n.d.	353
619381*	n/a	n/a	n/a	27	n/a	TCCGGAGATATCTCTCTTTC	sooooooooooooo	28	354
619382*	n/a	n/a	n/a	28	n/a	CTCCGGAGATATCTCTCTTT	sooooooooooooo	28	355
619383*	n/a	n/a	n/a	29	n/a	GCTCCGGAGATATCTCTCTT	sooooooooooooo	91	356
619384*	n/a	n/a	n/a	30	n/a	TGCTCCGGAGATATCTCTCT	sooooooooooooo	61	357
619385*	n/a	n/a	n/a	31	n/a	ATGCTCCGGAGATATCTCTC	sooooooooooooo	69	358
619386*	n/a	n/a	n/a	32	n/a	AATGCTCCGGAGATATCTCT	sooooooooooooo	75	359
619387	156	n/a	n/a	33	n/a	AAATGCTCCGGAGATATCTC	sooooooooooooo	n.d.	400
619388*	n/a	n/a	n/a	n/a	18	TCTGCTCTTGCTAGACCCCG	sooooooooooooo	50	360
619389	n/a	n/a	n/a	n/a	19	ATCTGCTCTTGCTAGACCCC	sooooooooooooo	n.d.	361

619390*	n/a	n/a	n/a	n/a	20	TATCTGCTCTTGCTAGACCC	sooooooooooooo	5	362
619391*	n/a	n/a	n/a	n/a	21	ATATCTGCTCTTGCTAGACC	sooooooooooooo	0	363
619392*	n/a	n/a	n/a	n/a	22	GATATCTGCTCTTGCTAGAC	sooooooooooooo	0	364
619393*	n/a	n/a	n/a	n/a	23	AGATATCTGCTCTTGCTAGA	sooooooooooooo	6	365
619394*	n/a	n/a	n/a	n/a	24	GAGATATCTGCTCTTGCTAG	sooooooooooooo	57	366
619395*	n/a	n/a	n/a	n/a	25	GGAGATATCTGCTCTTGCTA	sooooooooooooo	6	367
619396*	n/a	n/a	n/a	n/a	26	CGGAGATATCTGCTCTTGCT	sooooooooooooo	0	368
619397*	n/a	n/a	n/a	n/a	27	CCGGAGATATCTGCTCTTGC	sooooooooooooo	0	369
619398*	n/a	n/a	n/a	n/a	28	TCCGGAGATATCTGCTCTTG	sooooooooooooo	22	370
619399*	n/a	n/a	n/a	n/a	29	CTCCGGAGATATCTGCTCTT	sooooooooooooo	14	371
619400*	n/a	n/a	n/a	n/a	30	GCTCCGGAGATATCTGCTCT	sooooooooooooo	46	372
619401*	n/a	n/a	n/a	n/a	31	TGCTCCGGAGATATCTGCTC	sooooooooooooo	40	373
619402*	n/a	n/a	n/a	n/a	32	ATGCTCCGGAGATATCTGCT	sooooooooooooo	79	374
619403*	n/a	n/a	n/a	n/a	33	AATGCTCCGGAGATATCTGC	sooooooooooooo	65	375
619404*	n/a	n/a	n/a	n/a	34	AAATGCTCCGGAGATATCTG	sooooooooooooo	22	376
619405*	n/a	n/a	75	n/a	n/a	TGCTCCGGAGATATCAAGCG	sooooooooooooo	18	377
619406*	n/a	n/a	76	n/a	n/a	ATGCTCCGGAGATATCAAGC	sooooooooooooo	21	378
619407*	n/a	n/a	77	n/a	n/a	AATGCTCCGGAGATATCAAG	sooooooooooooo	98	379
619408	n/a	n/a	78	n/a	n/a	AAATGCTCCGGAGATATCAA	sooooooooooooo	n.d.	380
619409*	n/a	n/a	79	n/a	n/a	CAAATGCTCCGGAGATATCA	sooooooooooooo	98.	381
619421	3132	28251	n/a	n/a	n/a	GGGACACTACAAGGTAGTAT	sooooooooooooo	80	401
619422*	n/a	3452	n/a	n/a	n/a	GGTAACTTCAAACCTTGGG	sooooooooooooo	85.	382
619423	n/a	13642	1013	n/a	n/a	GCCATGATTTCTTGCTGGG	sooooooooooooo	67	383

Example 3: Dose-dependent antisense inhibition of a human C9ORF72 mRNA variant in HepG2 cells

Antisense oligonucleotides from the study described above exhibiting significant *in vitro* inhibition of C9ORF72 mRNA were selected and tested at various doses in HepG2 cells. ISIS 576816 and ISIS 577061, previously tested in US Application No. 61/714,132, filed October 15, 2012, were used as benchmark oligonucleotides. ISIS 576816 and ISIS 577061 are 5-10-5 MOE gapmers with phosphorothioate linkages throughout. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 78.1 nM, 312.5 nM, 1,250.0 nM, or 5,000.0 nM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Human C9ORF72 primer probe set RTS3905 was used to measure the C9ORF72 pathogenic associated mRNA variant. The levels of the C9ORF72 pathogenic associated mRNA variant were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of variant C9ORF72 levels, relative to untreated control cells. 'n.d.' means no data.

The half maximal inhibitory concentration (IC₅₀) of each oligonucleotide is also presented in the Tables below. As illustrated, the C9ORF72 pathogenic associated mRNA variant levels were reduced in a dose-dependent manner in some of the antisense oligonucleotide treated cells.

Table 11

5 **Dose-dependent inhibition of the C9ORF72 pathogenic associated mRNA variant**

ISIS No	78.1 nM	312.5 nM	1250.0 nM	5000.0 nM	IC ₅₀ (μ M)
576816	13	47	92	95	0.4
577061	0	1	23	57	4.2
619049	11	46	34	18	>5.0
619055	14	13	0	0	>5.0
619061	0	2	0	0	>5.0
619080	7	4	0	0	>5.0
619088	0	7	16	16	>5.0
619089	2	0	0	17	>5.0
619095	10	0	0	27	>5.0
619096	16	0	10	27	>5.0
619097	23	55	41	38	>5.0
619099	10	36	46	23	>5.0
619107	15	0	4	33	>5.0
619114	0	0	8	31	>5.0
619253	26	33	66	86	0.5
619293	26	71	n.d.	95	0.2
619410	42	63	86	n.d.	0.1
619411	28	20	96	n.d.	0.3
619412	39	66	93	97	0.1

Table 12

Dose-dependent inhibition of the C9ORF72 pathogenic associated mRNA variant

ISIS No	78.1 nM	312.5 nM	1250.0 nM	5000.0 nM	IC ₅₀ (μ M)
576816	39	84	96	90	0.1
577061	29	0	25	71	3.7
619173	18	46	84	98	0.4
619174	21	36	77	n.d.	0.4
619176	16	29	57	95	0.7
619178	5	31	86	97	0.5
619179	0	16	65	96	0.8
619180	4	24	66	96	0.7
619181	10	34	72	95	0.6

619182	23	32	74	92	0.5
619183	0	26	44	96	1.0
619185	14	34	70	93	0.5
619186	8	32	71	98	0.6
619187	18	36	81	95	0.4
619253	17	22	61	97	0.7
619293	0	49	86	99	0.6
619413	8	48	84	95	0.4
619415	26	67	90	n.d.	0.2

Table 13**Dose-dependent inhibition of the C9ORF72 pathogenic associated mRNA variant**

ISIS No	78.1nM	312.5 nM	1250.0 nM	5000.0 nM	IC ₅₀ (μ M)
576816	0	71	97	n.d.	0.3
577061	0	12	46	82	1.4
619191	66	84	94	98	<0.07
619201	16	64	95	97	0.3
619202	35	78	95	95	0.1
619203	29	55	92	95	0.2
619216	61	55	92	96	<0.07
619217	44	86	83	n.d.	0.1
619218	35	87	93	n.d.	0.1
619240	0	43	52	78	1.0
619245	0	39	85	n.d.	0.5
619246	34	74	96	99	0.1
619247	0	46	92	93	0.6
619251	40	91	93	96	<0.07
619252	24	67	87	n.d.	0.2
619259	7	76	85	98	0.3
619260	16	80	92	99	0.2
619416	13	63	91	92	0.3
619417	45	88	91	97	<0.07

5

Table 14**Dose-dependent inhibition of the C9ORF72 pathogenic associated mRNA variant**

ISIS No	78.1 nM	312.5 nM	1250.0 nM	5000.0 nM	IC ₅₀ (μ M)
576816	38	61	95	98	0.1
577061	0	8	13	77	2.5

619266	0	23	73	98	0.8
619268	5	29	77	97	0.6
619276	31	82	90	91	0.1
619278	35	83	97	99	0.1
619280	66	80	97	96	<0.07
619284	22	55	88	98	0.3
619292	37	79	85	94	0.1
619297	0	68	82	91	0.6
619298	47	89	93	91	<0.07
619307	37	71	96	98	0.1
619314	21	0	61	97	0.8
619316	13	37	71	91	0.5
619317	7	17	68	87	0.8
619336	17	51	64	90	0.5
619418	43	78	89	95	0.1
619419	43	68	94	95	0.1
619420	66	88	100	n.d.	<0.07

Table 15**Dose-dependent inhibition of the C9ORF72 pathogenic associated mRNA variant**

ISIS No	78.1 nM	312.5 nM	1250.0 nM	5000.0 nM	IC₅₀ (μM)
576816	8	48	91	91	0.4
577061	0	13	33	64	2.6
619293	32	77	85	95	0.1
619337	28	42	79	95	0.3
619338	11	55	83	91	0.4
619339	6	42	83	90	0.5
619341	17	14	66	83	0.8
619342	37	57	85	97	0.2
619343	25	51	87	96	0.3
619344	17	27	75	91	0.5
619345	0	18	50	88	1.2
619346	0	22	76	90	0.8
619347	1	8	41	76	1.7
619349	10	12	51	78	1.3
619350	16	46	84	91	0.4
619351	20	21	69	87	0.6
619353	0	13	52	76	1.4
619421	27	78	93	92	0.1
619423	0	53	87	93	0.5

Table 16
Gapmers chosen for further analysis

Isis No	IC ₅₀ (μ M)	Sequence	SEQ ID NO: 2 Start Site	Location	SEQ ID NO
619173	0.4	CTGTGAGAGCAAGTAGTGGG	1326	intron	160
619174	0.4	ACTGTGAGAGCAAGTAGTGG	1327	intron	161
619178	0.5	GAGTACTGTGAGAGCAAGTA	1331	intron	165
619179	0.8	CGAGTACTGTGAGAGCAAGT	1332	intron	166
619181	0.5	AGCGAGTACTGTGAGAGCAA	1334	intron	168
619182	0.5	CAGCGAGTACTGTGAGAGCA	1335	intron	169
619185	0.5	CCTCAGCGAGTACTGTGAGA	1338	intron	172
619186	0.6	CCCTCAGCGAGTACTGTGAG	1339	intron	173
619187	0.4	ACCCTCAGCGAGTACTGTGA	1340	intron	174
619191	<0.07	GTTACCCCTCAGCGAGTACT	1344	intron	178
619201	0.3	GTCTTTTCTTGTTACCCCTC	1354	intron	188
619202	0.1	GGTCTTTTCTTGTTACCCCT	1355	intron	189
619203	0.2	AGGTCTTTTCTTGTTACCCC	1356	intron	190
619216	<0.07	GTAAATCTTTATCAGGTCTT	1369	intron	203
619217	0.1	GGTAAATCTTTATCAGGTCT	1370	intron	204
619218	0.1	TGGTAAATCTTTATCAGGTC	1371	intron	205
619245	0.5	GCGGTTGTTTCCCTCCTTGT	1398	intron	232
619246	0.1	TGCGGTTGTTTCCCTCCTTG	1399	intron	233
619251	<0.07	CAGGCTGCGGTTGTTTCCCT	1404	intron	238
619252	0.2	ACAGGCTGCGGTTGTTTCCC	1405	intron	239
619253	0.5	TACAGGCTGCGGTTGTTTCC	1406	intron	97
619259	0.3	GCTTGCTACAGGCTGCGGTT	1412	intron	245
619260	0.2	AGCTTGCTACAGGCTGCGGT	1413	intron	246
619276	0.1	GACTCCTGAGTTCCAGAGCT	1429	intron	263
619278	0.1	GCGACTCCTGAGTTCCAGAG	1431	intron	265
619280	<0.07	GCGCGACTCCTGAGTTCCAG	1433	intron	267
619284	0.3	TAGCGCGCGACTCCTGAGTT	1437	Intron	271
619292	0.1	CCGGCCCCCTAGCGCGCGACT	1445	intron	279
619293	0.2	CCCGGCCCCCTAGCGCGCGAC	1446	intron	98
619298	<0.07	CCGGCCCCCGCCCCCTAGCGC	1451	intron	284
619307	0.1	GACCACGCCCCGCCCCCGGC	1466	intron	293
619337	0.3	CCGCAGCCCCGCCCCGGGCC	1504	intron:exon1B junction	326
619338	0.4	ACCGCAGCCCCGCCCCGGGC	1505	intron:exon1B junction	327
619339	0.5	AACCGCAGCCCCGCCCCGGG	1506	intron:exon1B junction	328
619342	0.2	CGCAACCGCAGCCCCGCCCC	1509	intron:exon1B	331

				junction	
619343	0.3	CCGCAACCGCAGCCCCGCCC	1510	intron:exon1B junction	332
619344	0.5	ACCGCAACCGCAGCCCCGCC	1511	intron:exon1B junction	333
619350	0.4	GCAGGCACCGCAACCGCAGC	1517	intron:exon1B junction	339
619351	0.6	CGCAGGCACCGCAACCGCAG	1518	intron:exon1B junction	340

Example 4: Antisense inhibition of C9ORF72 by human-rhesus cross-reactive antisense oligonucleotides in LLC-MK2 cells

5 Antisense oligonucleotides targeting a human C9ORF72 nucleic acid and fully cross-reactive with a rhesus C9ORF72 nucleic acid were designed and were tested for their effects on rhesus C9ORF72 mRNA in vitro. ISIS 576816, previously tested in US Application No. 61/714,132, filed October 15, 2012, was used as a benchmark oligonucleotide. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in the tables below. Cultured rhesus

10 LLC-MK2 cells at a density of 20,000 cells per well were transfected using electroporation with 4,000 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3750 (forward sequence TGTGACAGTTGGAATGCAGTGA, designated herein as SEQ ID NO: 16; reverse sequence GCCACTTAAAGCAATCTCTGTCTTG, designated herein as SEQ ID NO: 17; probe

15 sequence TCGACTCTTTGCCACCGCCA, designated herein as SEQ ID NO: 18 – a TAQ-man primer probe set) was used to measure total C9ORF72 mRNA levels. RTS3750 targets exon 2 of the mRNA transcripts and, therefore, measures total mRNA transcripts. C9ORF72 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of C9ORF72, relative to untreated control cells. The oligonucleotides marked with an asterisk (*) target

20 the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of these oligonucleotides. ‘n.d.’ indicates that there was no signal reading in the assay for that particular oligonucleotide. The antisense oligonucleotides were also tested in HepG2 cells in a series of experiments that had similar culture conditions. The results for each experiment are also presented in tables shown below. Cultured HepG2 cells at a density of 20,000 cells per well were transfected using

25 electroporation with 4,000 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3905 was used to measure the C9ORF72 pathogenic associated mRNA variant, which is the product of a pre-mRNA containing a hexanucleotide repeat. The levels of the C9ORF72 pathogenic associated mRNA variant were normalized to the total RNA content of the cell, as measured by

RIBOGREEN®. Results are presented as percent inhibition of C9ORF72, relative to untreated control cells. 'n.d.' means no data.

The chimeric antisense oligonucleotides in the Tables below were designed as 5'-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment comprises ten 2'-

5 deoxynucleosides and is flanked by wing segments on both the 5' end and on the 3' end comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment comprises a 2'-MOE group. All cytosine residues throughout each oligonucleotide are 5-methylcytosines. The internucleoside linkages for the gapmers are mixed phosphorothioate and phosphodiester linkages. The internucleoside linkages for each gapmer are presented in the Linkage column, where 'o' indicates a phosphodiester linkage and 's' indicates a phosphorothioate linkage.

"Start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is targeted human gene sequence. Each antisense oligonucleotide listed in the Tables below is targeted to either human C9ORF72 mRNA sequence, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_001256054.1), the human C9ORF72 genomic sequence, designated herein as SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000), GENBANK Accession No. NM_018325.3 (incorporated herein as SEQ ID NO: 6), or all three. 'n/a' indicates that the antisense oligonucleotide does not target that particular gene sequence.

Table 17
Percent inhibition of human C9ORF72 compared to PBS control by antisense oligonucleotides targeting SEQ ID NOs: 1, 2, and 6

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 6 Start Site	Sequence	Linkage	% inhibition (LLC-MK2) Primer Probe RTS3750	% inhibition (HepG2) Primer Probe RTS3905	SEQ ID NO
576816	310	7990	215	GCCTTACTCTAGGACCAAGA	ssssssssssssssssssss	51	91	20
619343	n/a	1510	1	CCGCAACCGCAGCCCCGCCC	soooooossssssssooss	0	96	332
619420	310	7990	215	GCCTTACTCTAGGACCAAGA	soooooossssssssooss	59	100	20
625183	309	7989	214	CCTTACTCTAGGACCAAGAA	soooooossssssssooss	27	92	484
625249	239	7919	144	AAAGCAATCTCTGTCTTGGC	soooooossssssssooss	78	n.d.	465
625255	364	8044	269	AAGTTATTTCTCCATCACTG	soooooossssssssooss	40	97	502
627833	321	8001	226	AGCCCAAATGTGCCTTACTC	soooooossssssssooss	52	n.d.	487
627834	382	8062	287	GAGTGTGGTTGGCAAGAAAA	soooooossssssssooss	0	61	506
655126	n/a	1548	39	CGCCACCGCCTGCGCCTCCG	soooooossssssssooss	0	96	512
655127	n/a	1551	42	ACTCGCCACCGCCTGCGCCT	soooooossssssssooss	11	93	513
655128	n/a	n/a	45	TCCACTCGCCACCGCCTGCG	soooooossssssssooss	0	60	514

655129	n/a	n/a	48	ATATCCACTCGCCACCGCCT	SOOOOSSSSSSSSSOOSS	1	79	515
655130	n/a	n/a	51	GAGATATCCACTCGCCACCG	SOOOOSSSSSSSSSOOSS	8	45	516
655131*	167	7847	72	TCACATTATCCAAATGCTCC	SOOOOSSSSSSSSSOOSS	36	88	441
655132*	170	7850	75	CTGTCACATTATCCAAATGC	SOOOOSSSSSSSSSOOSS	20	79	442
655133*	173	7853	78	CAACTGTCACATTATCCAAA	SOOOOSSSSSSSSSOOSS	31	82	443
655134*	176	7856	81	TTCCAACTGTCACATTATCC	SOOOOSSSSSSSSSOOSS	43	90	444
655135*	180	7860	85	TGCATTCCAACTGTCACATT	SOOOOSSSSSSSSSOOSS	69	94	445
655136*	183	7863	88	CACTGCATTCCAACTGTCAC	SOOOOSSSSSSSSSOOSS	75	98	446
655137*	186	7866	91	CATCACTGCATTCCAACTGT	SOOOOSSSSSSSSSOOSS	71	95	447
655138	189	7869	94	CGACATCACTGCATTCCAAC	SOOOOSSSSSSSSSOOSS	85	n.d.	448
655139	192	7872	97	AGTCGACATCACTGCATTCC	SOOOOSSSSSSSSSOOSS	89	n.d.	449
655140*	195	7875	100	AAGAGTCGACATCACTGCAT	SOOOOSSSSSSSSSOOSS	81	100	450
655141*	198	7878	103	GCAAAGAGTCGACATCACTG	SOOOOSSSSSSSSSOOSS	68	98	451
655142*	201	7881	106	TGGGCAAAGAGTCGACATCA	SOOOOSSSSSSSSSOOSS	60	98	452
655143*	204	7884	109	CGGTGGGCAAAGAGTCGACA	SOOOOSSSSSSSSSOOSS	69	99	453
655144*	207	7887	112	TGGCGGTGGGCAAAGAGTCG	SOOOOSSSSSSSSSOOSS	60	97	454
655145*	211	7891	116	GAGATGGCGGTGGGCAAAGA	SOOOOSSSSSSSSSOOSS	27	93	455
655146*	214	7894	119	CTGGAGATGGCGGTGGGCAA	SOOOOSSSSSSSSSOOSS	56	99	456
655147*	218	7898	123	ACAGCTGGAGATGGCGGTGG	SOOOOSSSSSSSSSOOSS	17	84	457
655148	221	7901	126	GCAACAGCTGGAGATGGCGG	SOOOOSSSSSSSSSOOSS	34	n.d.	458
655149	224	7904	129	TTGGCAACAGCTGGAGATGG	SOOOOSSSSSSSSSOOSS	27	n.d.	459
655150*	227	7907	132	GTCTTGGCAACAGCTGGAGA	SOOOOSSSSSSSSSOOSS	52	99	460
655151	230	7910	135	TCTGTCTTGGCAACAGCTGG	SOOOOSSSSSSSSSOOSS	60	n.d.	461
655152*	232	7912	137	TCTGTCTTGGCAACAGCT	SOOOOSSSSSSSSSOOSS	65	98	462
655153*	236	7916	141	GCAATCTCTGTCTTGGCAAC	SOOOOSSSSSSSSSOOSS	91	99	463
655154*	237	7917	142	AGCAATCTCTGTCTTGGCAA	SOOOOSSSSSSSSSOOSS	87	99	464
655155*	242	7922	147	CTTAAAGCAATCTCTGTCTT	SOOOOSSSSSSSSSOOSS	80	76	466
655156*	245	7925	150	CCACTTAAAGCAATCTCTGT	SOOOOSSSSSSSSSOOSS	74	86	467
655157	267	7947	172	AGCTGCTAATAAAGGTGATT	SOOOOSSSSSSSSSOOSS	27	90	468
655158	270	7950	175	AGTAGCTGCTAATAAAGGTG	SOOOOSSSSSSSSSOOSS	17	87	469
655159	273	7953	178	AAAAGTAGCTGCTAATAAAG	SOOOOSSSSSSSSSOOSS	6	48	470
655160	276	7956	181	AGCAAAAGTAGCTGCTAATA	SOOOOSSSSSSSSSOOSS	3	87	471
655161	279	7959	184	GTAAGCAAAAGTAGCTGCTA	SOOOOSSSSSSSSSOOSS	30	99	472
655162	282	7962	187	CCAGTAAGCAAAAGTAGCTG	SOOOOSSSSSSSSSOOSS	24	85	473
655163	285	7965	190	GTCCAGTAAGCAAAAGTAG	SOOOOSSSSSSSSSOOSS	15	70	474
655164	286	7966	191	TGTCCCAGTAAGCAAAAGTA	SOOOOSSSSSSSSSOOSS	5	60	475
655165	288	7968	193	ATTGTCCCAGTAAGCAAAAG	SOOOOSSSSSSSSSOOSS	0	46	476
655166	290	7970	195	ATATTGTCCCAGTAAGCAAA	SOOOOSSSSSSSSSOOSS	0	54	477
655167	291	7971	196	AATATTGTCCCAGTAAGCAA	SOOOOSSSSSSSSSOOSS	16	60	478
655168	294	7974	199	AAGAATATTGTCCCAGTAAG	SOOOOSSSSSSSSSOOSS	0	52	479
655169	297	7977	202	ACCAAGAATATTGTCCCAGT	SOOOOSSSSSSSSSOOSS	20	82	480
655170	300	7980	205	AGGACCAAGAATATTGTCCC	SOOOOSSSSSSSSSOOSS	17	54	481
655171	303	7983	208	TCTAGGACCAAGAATATTGT	SOOOOSSSSSSSSSOOSS	0	36	482

655172	306	7986	211	TACTCTAGGACCAAGAATAT	SOOOOSSSSSSSSSOOSS	10	43	483
655173	312	7992	217	GTGCCTTACTCTAGGACCAA	SOOOOSSSSSSSSSOOSS	75	99	485
655174	315	7995	220	AATGTGCCTTACTCTAGGAC	SOOOOSSSSSSSSSOOSS	47	98	486
655175	327	8007	232	CTTTGGAGCCCAAATGTGCC	SOOOOSSSSSSSSSOOSS	21	86	488
655176	330	8010	235	TGCTTTGGAGCCCAAATGT	SOOOOSSSSSSSSSOOSS	21	88	489
655177	333	8013	238	TTCTGTCTTTGGAGCCCAA	SOOOOSSSSSSSSSOOSS	42	97	490
655178	334	8014	239	GTTCTGTCTTTGGAGCCCAA	SOOOOSSSSSSSSSOOSS	66	99	491
655179	336	8016	241	CTGTTCTGTCTTTGGAGCCC	SOOOOSSSSSSSSSOOSS	68	95	492
655180	339	8019	244	TACCTGTTCTGTCTTTGGAG	SOOOOSSSSSSSSSOOSS	29	92	493
655181	342	8022	247	AAGTACCTGTTCTGTCTTTG	SOOOOSSSSSSSSSOOSS	26	76	494
655182	345	8025	250	GAGAAGTACCTGTTCTGTCT	SOOOOSSSSSSSSSOOSS	38	94	495
655183	348	8028	253	ACTGAGAAGTACCTGTTCTG	SOOOOSSSSSSSSSOOSS	23	89	496
655184	350	8030	255	TCACTGAGAAGTACCTGTTT	SOOOOSSSSSSSSSOOSS	19	83	497
655185	351	8031	256	ATCACTGAGAAGTACCTGTT	SOOOOSSSSSSSSSOOSS	40	87	498
655186	354	8034	259	TCCATCACTGAGAAGTACCT	SOOOOSSSSSSSSSOOSS	46	97	499
655187	358	8038	263	TTTCTCCATCACTGAGAAGT	SOOOOSSSSSSSSSOOSS	36	94	500
655188	361	8041	266	TTATTTCTCCATCACTGAGA	SOOOOSSSSSSSSSOOSS	9	82	501
655189	367	8047	272	GAAAAGTTATTTCTCCATCA	SOOOOSSSSSSSSSOOSS	37	96	503
655190	376	8056	281	GGTTGGCAAGAAAAGTTATT	SOOOOSSSSSSSSSOOSS	15	74	504
655191	379	8059	284	TGTGGTTGGCAAGAAAAGTT	SOOOOSSSSSSSSSOOSS	15	62	505
655192	385	8065	290	TTAGAGTGTGGTTGGCAAGA	SOOOOSSSSSSSSSOOSS	12	63	507
655193	388	8068	293	CATTTAGAGTGTGGTTGGCA	SOOOOSSSSSSSSSOOSS	7	89	508
655194	389	8069	294	CCATTTAGAGTGTGGTTGGC	SOOOOSSSSSSSSSOOSS	31	93	509
655195	394	8074	299	TTTCTCCATTTAGAGTGTGG	SOOOOSSSSSSSSSOOSS	19	91	510
655196	397	8077	302	GGATTCTCCATTTAGAGTIG	SOOOOSSSSSSSSSOOSS	8	82	511

Table 18
Percent inhibition of human C9ORF72 compared to PBS control by antisense oligonucleotides
targeting SEQ ID NOs: 1, 2, and 6

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 6 Start Site	Sequence	Linkage	% inhibition (LLC-MK2) Primer Probe RTS3750	% inhibition (HepG2) Primer Probe RTS3905	SEQ ID NO
576816	310	7990	215	GCCTTACTCTAGGACCAAGA	SSSSSSSSSSSSSSSSSS	55	97	20
619420	310	7990	215	GCCTTACTCTAGGACCAAGA	SOOOOSSSSSSSSSOOSS	74	97	20
655197	403	8083	308	TTCGAAGGATTTCTCATTT	SOOOOSSSSSSSSSOOSS	14	87	517
655198	406	8086	311	CATTTCTGAAGGATTTCTCCA	SOOOOSSSSSSSSSOOSS	23	83	518
655199	409	8089	314	CTGCATTTCTGAAGGATTTCT	SOOOOSSSSSSSSSOOSS	42	97	519
655200	412	8092	317	TCTCTGCATTTCTGAAGGATT	SOOOOSSSSSSSSSOOSS	21	87	520
655201	415	8095	320	CACTCTCTGCATTTCTGAAGG	SOOOOSSSSSSSSSOOSS	25	89	521
655202	418	8098	323	CACCACTCTCTGCATTTCTGA	SOOOOSSSSSSSSSOOSS	54	96	522
655203	420	8100	325	AGCACCCTCTCTGCATTTCT	SOOOOSSSSSSSSSOOSS	51	90	523

655204	421	8101	326	TAGCACCCTCTCTGCATTT	S0000SSSSSSSSSSSOOSS	28	94	524
655205	424	8104	329	CTATAGCACCCTCTCTGCA	S0000SSSSSSSSSSSOOSS	17	90	525
655206	427	8107	332	CATCTATAGCACCCTCTCT	S0000SSSSSSSSSSSOOSS	15	83	526
655207	433	8113	338	ACTTTACATCTATAGACCA	S0000SSSSSSSSSSSOOSS	20	85	527
655208	436	8116	341	AAAACCTTTACATCTATAGCA	S0000SSSSSSSSSSSOOSS	25	72	528
655209	443	8123	348	AAGACAAAAAACTTTACATC	S0000SSSSSSSSSSSOOSS	10	45	529
655210	444	8124	349	CAAGACAAAAAACTTTACAT	S0000SSSSSSSSSSSOOSS	0	56	530
655211	446	8126	351	GACAAGACAAAAAACTTTAC	S0000SSSSSSSSSSSOOSS	32	84	531
655212	449	8129	354	TCAGACAAGACAAAAAACTT	S0000SSSSSSSSSSSOOSS	10	74	532
655213	451	8131	356	TTTCAGACAAGACAAAAAAC	S0000SSSSSSSSSSSOOSS	7	54	533
655214	453	8133	358	CTTTTCAGACAAGACAAAAA	S0000SSSSSSSSSSSOOSS	7	57	534
655215	456	8136	361	TCCCTTTTCAGACAAGACAA	S0000SSSSSSSSSSSOOSS	32	91	535
655216	459	8139	364	CACTCCCTTTTCAGACAAGA	S0000SSSSSSSSSSSOOSS	39	91	536
655217	462	8142	367	AATCACTCCCTTTTCAGACA	S0000SSSSSSSSSSSOOSS	41	95	537
655218	465	8145	370	AATAATCACTCCCTTTTCAG	S0000SSSSSSSSSSSOOSS	13	63	538
655219	467	8147	372	ACAATAATCACTCCCTTTTC	S0000SSSSSSSSSSSOOSS	2	60	539
655220	468	8148	373	AACAATAATCACTCCCTTTT	S0000SSSSSSSSSSSOOSS	11	73	540
655221	471	8151	376	TGAAACAATAATCACTCCCT	S0000SSSSSSSSSSSOOSS	17	83	541
655222	474	8154	379	TAATGAAACAATAATCACTC	S0000SSSSSSSSSSSOOSS	1	79	542
655223	477	8157	382	GATTAATGAAACAATAATCA	S0000SSSSSSSSSSSOOSS	12	59	543
655224	482	8162	387	TCAAAGATTAATGAAACAAT	S0000SSSSSSSSSSSOOSS	0	9	544
655225	485	8165	390	CCATCAAAGATTAATGAAAC	S0000SSSSSSSSSSSOOSS	17	81	545
655226	488	8168	393	TTCCATCAAAGATTAATGA	S0000SSSSSSSSSSSOOSS	14	87	546
655227	491	8171	396	CAGTTTCCATCAAAGATTAA	S0000SSSSSSSSSSSOOSS	7	69	547
655228	494	8174	399	TTCCAGTTTCCATCAAAGAT	S0000SSSSSSSSSSSOOSS	25	88	548
655229	497	8177	402	CCATTCCAGTTTCCATCAA	S0000SSSSSSSSSSSOOSS	44	90	549
655230	500	8180	405	TCCCCATTCCAGTTTCCATC	S0000SSSSSSSSSSSOOSS	48	94	550
655231	503	8183	408	CGATCCCCATTCCAGTTTCC	S0000SSSSSSSSSSSOOSS	54	96	551
655232	506	8186	411	CTGCGATCCCCATTCCAGTT	S0000SSSSSSSSSSSOOSS	61	96	552
655233	509	8189	414	GTGCTGCGATCCCCATTCCA	S0000SSSSSSSSSSSOOSS	63	100	553
655234	512	8192	417	TATGTGCTGCGATCCCCATT	S0000SSSSSSSSSSSOOSS	34	94	554
655235	533	8213	438	GGAAGTATAATTGATAGTCC	S0000SSSSSSSSSSSOOSS	25	91	555
655236	536	8216	441	TGTGGAAGTATAATTGATAG	S0000SSSSSSSSSSSOOSS	13	66	556
655237	539	8219	444	GTCTGTGGAAGTATAATTGA	S0000SSSSSSSSSSSOOSS	24	83	557
655238	542	8222	447	TCTGTCTGTGGAAGTATAAT	S0000SSSSSSSSSSSOOSS	51	92	558
655239	545	8225	450	AGTTCTGTCTGTGGAAGTAT	S0000SSSSSSSSSSSOOSS	42	96	559
655240	548	8228	453	CTAAGTTCTGTCTGTGGAAG	S0000SSSSSSSSSSSOOSS	16	88	560
655241	551	8231	456	AAACTAAGTTCTGTCTGTGG	S0000SSSSSSSSSSSOOSS	25	93	561
655242	554	8234	459	TAGAACTAAGTTCTGTCTG	S0000SSSSSSSSSSSOOSS	29	94	562
655243	557	8237	462	AGGTAGAACTAAGTTCTGT	S0000SSSSSSSSSSSOOSS	43	85	563
655244	560	8240	465	GGGAGGTAGAACTAAGTTC	S0000SSSSSSSSSSSOOSS	27	77	564
655245	563	8243	468	AGTGGGAGGTAGAACTAAG	S0000SSSSSSSSSSSOOSS	22	77	565
655246	566	8246	471	TGAAGTGGGAGGTAGAACT	S0000SSSSSSSSSSSOOSS	16	45	566

655247	569	8249	474	CTATGAAGTGGGAGGTAGAA	SOOOOSSSSSSSSSOOSS	14	60	567
655248	572	8252	477	ACTCTATGAAGTGGGAGTA	SOOOOSSSSSSSSSOOSS	30	81	568
655249	574	8254	479	ACACTCTATGAAGTGGGAGG	SOOOOSSSSSSSSSOOSS	34	94	569
655250	575	8255	480	CACACTCTATGAAGTGGGAG	SOOOOSSSSSSSSSOOSS	46	98	570
655251	576	8256	481	ACACACTCTATGAAGTGGGA	SOOOOSSSSSSSSSOOSS	20	94	571
655252	578	8258	483	ACACACACTCTATGAAGTGG	SOOOOSSSSSSSSSOOSS	28	97	572
655253	581	8261	486	TCAACACACACTCTATGAAG	SOOOOSSSSSSSSSOOSS	12	62	573
655254	584	8264	489	CTATCAACACACACTCTATG	SOOOOSSSSSSSSSOOSS	6	68	574
655255	587	8267	492	AATCTATCAACACACACTCT	SOOOOSSSSSSSSSOOSS	16	87	575
655256	590	8270	495	GTTAATCTATCAACACACAC	SOOOOSSSSSSSSSOOSS	28	95	576
655257	592	8272	497	GTGTTAATCTATCAACACAC	SOOOOSSSSSSSSSOOSS	15	76	577
655258	593	8273	498	TGTGTTAATCTATCAACACA	SOOOOSSSSSSSSSOOSS	14	53	578
655259	595	8275	500	TATGTGTTAATCTATCAACA	SOOOOSSSSSSSSSOOSS	11	78	579
655260	596	8276	501	ATATGTGTTAATCTATCAAC	SOOOOSSSSSSSSSOOSS	25	79	580
655261	599	8279	504	ATTATATGTGTTAATCTATC	SOOOOSSSSSSSSSOOSS	11	71	581
655262	602	8282	507	CGGATTATATGTGTTAATCT	SOOOOSSSSSSSSSOOSS	21	91	582
655263	605	8285	510	TTCCGGATTATATGTGTTAA	SOOOOSSSSSSSSSOOSS	15	88	583
655264	608	8288	513	CCTTTCCGGATTATATGTGT	SOOOOSSSSSSSSSOOSS	12	83	584
655265	611	8291	516	CTTCCTTTCCGGATTATATG	SOOOOSSSSSSSSSOOSS	1	69	585
655266	614	8294	519	ATTCTTCCTTTCCGGATTAT	SOOOOSSSSSSSSSOOSS	15	76	586
655267	617	8297	522	CATATTCTTCCTTTCCGGAT	SOOOOSSSSSSSSSOOSS	17	69	587
655268	620	8300	525	ATCCATATTCTTCCTTTCCG	SOOOOSSSSSSSSSOOSS	21	67	588
655269	624	8304	529	ATGCATCCATATTCTTCCTT	SOOOOSSSSSSSSSOOSS	5	73	589
655270	626	8306	531	TTATGCATCCATATTCTTCC	SOOOOSSSSSSSSSOOSS	23	71	590
655271	629	n/a	534	TCCTTATGCATCCATATTCT	SOOOOSSSSSSSSSOOSS	15	64	591
655272	632	n/a	537	CTTTCCTTATGCATCCATAT	SOOOOSSSSSSSSSOOSS	24	66	592
655273	635	n/a	540	TGTCTTTCCTTATGCATCCA	SOOOOSSSSSSSSSOOSS	37	76	593

Table 19
Percent inhibition of human C9ORF72 compared to PBS control by antisense oligonucleotides
targeting SEQ ID NOs: 1, 2, and 6

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 6 Start Site	Sequence	Linkage	% inhibition (LLC-MK2) Primer Probe RTS3750	% inhibition (HepG2) Primer Probe RTS3905	SEQ ID NO
576816	310	7990	215	GCCTTACTCTAGGACCAAGA	SSSSSSSSSSSSSSSSSS	53	95	20
619253	n/a	1406	n/a	TACAGGCTGCGGTTGTTTCC	SOOOOSSSSSSSSSOOSS	0	72	97
619293	n/a	1446	n/a	CCCGGCCCTAGCGCGCGAC	SOOOOSSSSSSSSSOOSS	0	95	98
619422	n/a	3452	n/a	GGTAACTTCAAACCTTG	SOOOOSSSSSSSSSOOSS	0	93	382
655329	n/a	2330	n/a	AGGACCTCCCTCCTGTTTCT	SOOOOSSSSSSSSSOOSS	0	84	594
655330	n/a	2490	n/a	AGAAGTAATGCCAGACAGAT	SOOOOSSSSSSSSSOOSS	0	75	595
655331	n/a	2901	n/a	CTTTGTTTCTCTGAAAGCAA	SOOOOSSSSSSSSSOOSS	16	75	596

655332	n/a	3576	n/a	GTGGTTGGTCCACTGCTATT	sooooooooooooo	28	94	597
655333	n/a	3801	n/a	TTGAGGGAAGCCAAGATTCA	sooooooooooooo	10	77	598
655334	n/a	3975	n/a	AGAGCTGTACAATTATTTTA	sooooooooooooo	13	90	599
655335	n/a	4725	n/a	GGTAATGACACTACTGCTGT	sooooooooooooo	27	96	600
655336	n/a	5970	n/a	GATCCTAATCCTGTCTATGC	sooooooooooooo	0	70	601
655337	n/a	7382	n/a	ACTTGTGGGTTGAATTGTGT	sooooooooooooo	4	66	602
655338	n/a	8310	n/a	TACCTTATGCATCCATATTC	sooooooooooooo	11	62	603
655339	n/a	8409	n/a	GATGTTCACTGCATATAATT	sooooooooooooo	31	88	604
655340	n/a	8464	n/a	CCAGATGTATTTGTATCTAA	sooooooooooooo	41	96	605
655341	n/a	8523	n/a	TAATGTGGAGCTACCATTTC	sooooooooooooo	6	72	606
655342	n/a	8587	n/a	GCTCCCAAGAAGAATCCAGG	sooooooooooooo	44	74	607
655343	n/a	8658	n/a	ACTTACACATAGTAGTAAGC	sooooooooooooo	16	88	608
655344	n/a	8716	n/a	AAAGAGACCAAAGGCTACAT	sooooooooooooo	4	82	609
655345	n/a	8785	n/a	GGAATTCTCTTGGGAACCAT	sooooooooooooo	9	80	610
619420	310	7990	215	GCCTTACTCTAGGACCAAGA	sooooooooooooo	51	98	20
655274	638	n/a	543	TCTTGCTTTTCCTTATGCAT	sooooooooooooo	0	73	611
655275	641	n/a	546	TTTCTTGTCTTTCCTTATG	sooooooooooooo	10	61	612
625344	647	9413	552	TGGACATTTTCTTGTCTTTC	sooooooooooooo	32	94	613
655276	650	9416	555	TTCTGGACATTTTCTTGTCT	sooooooooooooo	8	79	614
655277	653	9419	558	ATCTTCTGGACATTTTCTTG	sooooooooooooo	0	60	615
655278	655	9421	560	TAATCTTCTGGACATTTTCT	sooooooooooooo	0	66	616
655279	659	9425	564	AAGATAATCTTCTGGACATT	sooooooooooooo	5	72	617
655280	662	9428	567	TCTAAGATAATCTTCTGGAC	sooooooooooooo	2	81	618
655281	665	9431	570	CCTTCTAAGATAATCTTCTG	sooooooooooooo	0	19	619
655282	668	9434	573	GTGCCTTCTAAGATAATCTT	sooooooooooooo	4	20	620
655283	671	9437	576	TCTGTGCCTTCTAAGATAAT	sooooooooooooo	9	27	621
655284	674	9440	579	CTCTCTGTGCCTTCTAAGAT	sooooooooooooo	0	35	622
655285	677	9443	582	ATTCTCTCTGTGCCTTCTAA	sooooooooooooo	7	40	623
655286	680	9446	585	TCCATTCTCTCTGTGCCTTC	sooooooooooooo	18	65	624
655287	683	9449	588	TCTTCCATTCTCTCTGTGCC	sooooooooooooo	14	67	625
655288	686	9452	591	TGATCTTCCATTCTCTCTGT	sooooooooooooo	7	65	626
655289	691	n/a	596	GACCCTGATCTTCCATTCTC	sooooooooooooo	12	89	627
655290	694	n/a	599	TCTGACCCTGATCTTCCATT	sooooooooooooo	13	81	628
655291	697	n/a	602	TACTCTGACCCTGATCTTCC	sooooooooooooo	0	82	629
655292	700	n/a	605	TAATACTCTGACCCTGATCT	sooooooooooooo	0	72	630
655293	703	n/a	608	GAATAATACTCTGACCCTGA	sooooooooooooo	0	77	631
655294	709	12529	614	GCATTGGAATAATACTCTGA	sooooooooooooo	0	79	632
655295	712	12532	617	TAAGCATTGGAATAATACTC	sooooooooooooo	8	79	633
655296	715	12535	620	CAGTAAGCATTGGAATAATA	sooooooooooooo	0	66	634
655297	718	12538	623	CTCCAGTAAGCATTGGAATA	sooooooooooooo	12	78	635
655298	721	12541	626	CTTCTCCAGTAAGCATTGGA	sooooooooooooo	0	81	636
655299	724	12544	629	TCACTTCTCCAGTAAGCATT	sooooooooooooo	0	70	637
655300	727	12547	632	GAATCACTTCTCCAGTAAGC	sooooooooooooo	0	75	638

655301	730	12550	635	CAGGAATCACTTCTCCAGTA	sooooooosoooooooooooo	20	85	639
655302	733	12553	638	TTACAGGAATCACTTCTCCA	sooooooosoooooooooooo	0	50	640
655303	736	12556	641	CCATTACAGGAATCACTTCT	sooooooosoooooooooooo	0	57	641
655304	744	12564	649	AAGCAGTTCCATTACAGGAA	sooooooosoooooooooooo	0	83	642
655305	747	12567	652	TGAAAGCAGTTCCATTACAG	sooooooosoooooooooooo	0	55	643
655306	750	12570	655	AGATGAAAGCAGTTCCATTA	sooooooosoooooooooooo	0	82	644
655307	753	12573	658	CATAGATGAAAGCAGTTCCA	sooooooosoooooooooooo	2	83	645
655308	756	12576	661	TTTCATAGATGAAAGCAGTT	sooooooosoooooooooooo	0	59	646
655309	762	12582	667	GTGTGATTTTCATAGATGAAA	sooooooosoooooooooooo	0	39	647
655310	766	12586	671	CACTGTGTGATTTCATAGAT	sooooooosoooooooooooo	10	31	648
655311	769	12589	674	GAACACTGTGTGATTTCATA	sooooooosoooooooooooo	0	80	649
655312	772	12592	677	CAGGAACACTGTGTGATTTC	sooooooosoooooooooooo	0	53	650
655313	778	12598	683	TTTCTTCAGGAACACTGTGT	sooooooosoooooooooooo	0	45	651
655314	781	12601	686	CTATTTCTTCAGGAACACTG	sooooooosoooooooooooo	0	56	652
655315	784	n/a	689	TATCTATTTCTTCAGGAACA	sooooooosoooooooooooo	0	75	653
655316	787	n/a	692	CTATATCTATTTCTTCAGGA	sooooooosoooooooooooo	0	75	654
655317	790	n/a	695	CAGCTATATCTATTTCTTCA	sooooooosoooooooooooo	23	89	655
655318	793	n/a	698	TATCAGCTATATCTATTTCT	sooooooosoooooooooooo	7	80	656
655319	796	n/a	701	CTGTATCAGCTATATCTATT	sooooooosoooooooooooo	34	86	657
655320	799	n/a	704	GTACTGTATCAGCTATATCT	sooooooosoooooooooooo	42	88	658
655321	802	n/a	707	TGAGTACTGTATCAGCTATA	sooooooosoooooooooooo	31	87	659
655322	805	13356	710	CATTGAGTACTGTATCAGCT	sooooooosoooooooooooo	3	84	660
655323	808	13359	713	CATCATTGAGTACTGTATCA	sooooooosoooooooooooo	5	88	661
655324	811	13362	716	CATCATCATTGAGTACTGTA	sooooooosoooooooooooo	17	90	662
655325	814	13365	719	TATCATCATCATTGAGTACT	sooooooosoooooooooooo	2	84	663
655326	817	13368	722	CAATATCATCATCATTGAGT	sooooooosoooooooooooo	0	74	664
655327	822	13373	727	GTCACCAATATCATCATCAT	sooooooosoooooooooooo	6	78	665
655328	848	13399	753	TTGAGAAGAAAGCCTTCATG	sooooooosoooooooooooo	0	42	666
619421	3132	28251	3037	GGGACACTACAAGGTAGTAT	sooooooosoooooooooooo	0	94	401

Table 20
Percent inhibition of human C9ORF72 compared to PBS control by antisense oligonucleotides
targeting SEQ ID NOs: 1, 2, and 6

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 6 Start Site	Sequence	Linkage	% inhibition (LLC-MK2) Primer Probe RTS3750	% inhibition (HepG2) Primer Probe RTS3905	SEQ ID NO
576816	310	7990	215	GCCTTACTCTAGGACCAAGA	sooooooooooooooooooooo	49	97	20
655346	n/a	8861	n/a	ACTATACTGAAATGTAAATA	sooooooosoooooooooooo	4	7	667
655347	n/a	8915	n/a	TATCAAACCTGGAACACAGGA	sooooooosoooooooooooo	16	53	668
655348	n/a	8965	n/a	TGGGCAAAAGCCTTTTAAAA	sooooooosoooooooooooo	13	63	669
655349	n/a	9017	n/a	GCAAACATAGTAAAAAATTA	sooooooosoooooooooooo	6	7	670

655350	n/a	9067	n/a	TTCTCCTGATTTTAAGAGTT	sooooooosooooooooooss	39	90	671
655351	n/a	9117	n/a	AAGAATGACTTGCACTTTTC	sooooooosooooooooooss	25	100	672
655352	n/a	9173	n/a	AAAGATAACTTCACAGAAAA	sooooooosooooooooooss	13	10	673
655353	n/a	9286	n/a	CTTTCTACTTTAGGGAAAAA	sooooooosooooooooooss	16	64	674
655354	n/a	9336	n/a	TTTTTCAATAGACATGTTCT	sooooooosooooooooooss	19	81	675
655355	n/a	9403	n/a	CTTGTCTTTCCTGAGCAAGA	sooooooosooooooooooss	8	54	676
655356	n/a	9455	n/a	ACCTGATCTTCCATTCTCTC	sooooooosooooooooooss	22	81	677
655357	n/a	9576	n/a	CTCCATAAAAGCTCCATTAA	sooooooosooooooooooss	34	52	678
655358	n/a	9640	n/a	TGTTTACTGATTTAACTCTT	sooooooosooooooooooss	34	83	679
655359	n/a	9696	n/a	AACAGAAAAAAAAGGGAGC	sooooooosooooooooooss	18	22	680
655360	n/a	9772	n/a	GTACCTTAAAGAACATATCA	sooooooosooooooooooss	34	100	681
655361	n/a	9920	n/a	AAATGTAAATTGCATGAGTC	sooooooosooooooooooss	7	100	682
655362	n/a	9970	n/a	GGGTAAGAAATATCACTGAC	sooooooosooooooooooss	43	63	683
655363	n/a	10055	n/a	AACCATGCTTCTCAAACCTCT	sooooooosooooooooooss	29	75	684
655364	n/a	10122	n/a	AAGAACTTCTCTGCTTTACA	sooooooosooooooooooss	13	68	685
655365	n/a	10172	n/a	AATGGAAGTAAAAGTGAAGA	sooooooosooooooooooss	7	13	686
655366	n/a	10233	n/a	AACAGCCATGTTTAAATAT	sooooooosooooooooooss	15	37	687
655367	n/a	10283	n/a	TTAAAGTATCATCTGTCTCA	sooooooosooooooooooss	34	74	688
655368	n/a	10364	n/a	CAATTTGGTAAAGGAGATCA	sooooooosooooooooooss	6	48	689
655369	n/a	10418	n/a	ACACAGAATAACTGTCTCTG	sooooooosooooooooooss	16	64	690
655370	n/a	10491	n/a	GCTTATTGACCAGCAAATAA	sooooooosooooooooooss	22	69	691
655371	n/a	10615	n/a	CCCAGTAAAAGCAGAATTTT	sooooooosooooooooooss	24	57	692
655372	n/a	10665	n/a	ATTAATAGTAGTCAACTTAA	sooooooosooooooooooss	20	10	693
655373	n/a	10730	n/a	ACTTGAACCTCTCAGCAGTA	sooooooosooooooooooss	25	62	694
655374	n/a	10786	n/a	AGAAGAGGCTCTAAAAGAAA	sooooooosooooooooooss	7	59	695
655375	n/a	10970	n/a	AAAGGCAACTCCTCCTTTTC	sooooooosooooooooooss	13	78	696
655376	n/a	11020	n/a	ACAGTATTGTTCAAATAAA	sooooooosooooooooooss	18	100	697
655377	n/a	11070	n/a	CAGATGACAGCTACAACCTGA	sooooooosooooooooooss	16	49	698
655378	n/a	11121	n/a	GAATAATGACTAGATCCGTG	sooooooosooooooooooss	26	88	699
655379	n/a	11171	n/a	ATAATTATCATGCCTGTTTA	sooooooosooooooooooss	22	80	700
655380	n/a	11221	n/a	CTTTAGTAACCTCCACAACT	sooooooosooooooooooss	19	26	701
655381	n/a	11313	n/a	GAATTTAAATGTGATGCTAC	sooooooosooooooooooss	15	49	702
655382	n/a	11385	n/a	TGTCAGACCCAGGGCCATTT	sooooooosooooooooooss	40	83	703
655383	n/a	11445	n/a	ACTTATTTTATGAAATGATT	sooooooosooooooooooss	7	3	704
655384	n/a	11513	n/a	TTTTAGCTAAACATATTTTT	sooooooosooooooooooss	2	1	705
655385	n/a	11591	n/a	CAGTCTCATCAGTTTTGTGA	sooooooosooooooooooss	33	83	706
655386	n/a	11641	n/a	TGTAAAGTGTCTCAAATATG	sooooooosooooooooooss	21	39	707
655387	n/a	11711	n/a	CTTGAAATTGTAATTTTGAA	sooooooosooooooooooss	14	42	708
655388	n/a	11798	n/a	AATCAAAATCAGCACATATA	sooooooosooooooooooss	8	46	709
655389	n/a	11871	n/a	ACCAAATAGGTAAGGAAAAC	sooooooosooooooooooss	9	32	710
655390	n/a	11978	n/a	AAAGATCTCCTTTAAATTT	sooooooosooooooooooss	11	29	711
655391	n/a	12053	n/a	CTTTAGAGAGTATGGAATCA	sooooooosooooooooooss	22	71	712
655392	n/a	12334	n/a	CAAAGCTCACTTTTATTCTT	sooooooosooooooooooss	25	70	713

655393	n/a	12384	n/a	ACACAGTATCAAACAAGTCT	sooooooooooooo	29	45	714
655394	n/a	12459	n/a	AAGCTGGGCAATAAAAAATA	sooooooooooooo	0	24	715
655395	n/a	12513	n/a	CTGACCCTGCACAATAAAGT	sooooooooooooo	17	0	716
655396	n/a	12604	n/a	CATCTATTTCTTCAGGAACA	sooooooooooooo	21	74	717
655397	n/a	12681	n/a	GAATATTAATAATATACATA	sooooooooooooo	0	16	718
655398	n/a	12765	n/a	AGGATTTTGTGTGTGCTTAT	sooooooooooooo	30	65	719
655399	n/a	12855	n/a	TTTGTAGGAATTATAAAAGTA	sooooooooooooo	7	61	720
655400	n/a	12924	n/a	ACACAGTTTGTTCAAAAG	sooooooooooooo	13	61	721
655401	n/a	12978	n/a	GGAAACTAAATTTGTGACTA	sooooooooooooo	21	56	722
655402	n/a	13028	n/a	CTCTTAACACTCATAGTGTG	sooooooooooooo	13	52	723
655403	n/a	13084	n/a	GAGACTAACCTAAATGACAA	sooooooooooooo	20	35	724
655404	n/a	13159	n/a	CAAATGTGAAAGCTGGTCAA	sooooooooooooo	8	100	725
655405	n/a	13237	n/a	TAACACACTGCCTTCATTC	sooooooooooooo	17	32	726
655406	n/a	13337	n/a	TATCTAAAATGCATCAAAAA	sooooooooooooo	2	6	727
655407	n/a	13400	n/a	CTTGAGAAGAAAGCCTTCAT	sooooooooooooo	23	42	728
655408	n/a	13471	n/a	CCAAATCTTGTCATAGGTGA	sooooooooooooo	42	95	729
655409	n/a	13550	n/a	TAACACAAATTTAAGCAACA	sooooooooooooo	21	55	730
655410	n/a	13603	n/a	AAATAGCAAAATGGAATAACA	sooooooooooooo	14	55	731
655411	n/a	13662	n/a	AAACCAGAATCAAGCAAGGG	sooooooooooooo	27	73	732
655412	n/a	13722	n/a	CATCTACAGTACAACCTAAT	sooooooooooooo	13	100	733
655413	n/a	13773	n/a	AGATCAGTATAAATATGAAT	sooooooooooooo	1	43	734
655414	n/a	13823	n/a	GTTTAAGGGCACAACTCTT	sooooooooooooo	27	78	735
655415	n/a	13884	n/a	AGGTGTATAGAGAATTCAGG	sooooooooooooo	43	89	736
655416	n/a	13955	n/a	TACTCAATGCTTATAACAAC	sooooooooooooo	26	84	737
655417	n/a	14089	n/a	GGAACCTAACATGTAGGCACT	sooooooooooooo	66	100	738
655418	n/a	14213	n/a	CATAAAAGTGAATACTTTAT	sooooooooooooo	13	0	739
655419	n/a	14281	n/a	AGGCTCTTAGGTTAAACACA	sooooooooooooo	16	79	740
655420	n/a	14331	n/a	GCTGACACTGAACAGATACA	sooooooooooooo	52	84	741
655421	n/a	14392	n/a	CATGTAGAGAGATTAAGTGA	sooooooooooooo	27	42	742
655422	n/a	14452	n/a	ATCATTTAATTAATGTATTT	sooooooooooooo	13	0	743
619420	310	7990	215	GCCTTACTCTAGGACCAAGA	sooooooooooooo	76	98	20

Example 5: Dose-dependent antisense inhibition of human C9ORF72 mRNA in LLC-MK2

Antisense oligonucleotides from the study described above exhibiting significant *in vitro* inhibition of C9ORF72 mRNA were selected and tested at various doses in LLC-MK2 cells. ISIS 576816, previously tested in US Application No. 61/714,132, filed October 15, 2012, was used as a benchmark oligonucleotide. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.33 μ M, 1.00 μ M, 3.00 μ M, or 9.00 μ M concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Human C9ORF72 primer probe set RTS3750 was used to measure total

C9ORF72 mRNA levels. C9ORF72 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN[®]. Results are presented as percent inhibition of C9ORF72 levels, relative to untreated control cells.

As shown in Table 21, total C9ORF72 mRNA levels were reduced in a dose-dependent manner in the antisense oligonucleotide treated cells.

Table 21

Dose-dependent inhibition of total C9ORF72 mRNA transcript levels in LLC-MK2 cells

ISIS No	0.33 μM	1.00 μM	3.00 μM	9.00 μM
576816	0	33	55	66
619411	15	43	67	87
619412	9	30	55	84
619413	17	27	58	79
619414	13	49	75	83
619415	15	41	62	57
619416	29	47	70	81
619420	17	49	70	85
619423	25	52	71	82
627833	4	31	63	82
655173	37	72	86	90
655178	9	35	71	86
655179	30	50	52	84
655202	1	12	41	72
655231	0	28	43	71
655232	17	45	64	76
655233	19	30	62	80
655420	24	28	49	78

The antisense oligonucleotides were also selected and tested at various doses in HepG2 cells. . ISIS 576816, previously tested in US Application No. 61/714,132, filed October 15, 2012, was used as a benchmark oligonucleotide. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.11 μM, 0.33 μM, 1.00 μM, or 3.00 μM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Human C9ORF72 primer probe set RTS3750 was used to measure total C9ORF72 mRNA levels. C9ORF72 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN[®]. Results are presented as percent inhibition of C9ORF72 levels, relative to untreated control cells.

As shown in Table 22, total C9ORF72 mRNA levels were reduced in a dose-dependent manner in the antisense oligonucleotide treated cells.

Table 22

Dose-dependent inhibition of total C9ORF72 mRNA transcript levels in HepG2 cells

ISIS No	0.11 μM	0.33 μM	1.00 μM	3.00 μM
576816	16	32	71	90
619411	11	41	71	91
619412	24	44	79	92
619413	0	18	59	84
619414	16	51	76	92
619415	16	38	72	85
619416	16	36	47	80
619420	15	47	75	91
619423	24	50	81	89
627833	0	29	69	90
655173	24	56	88	96
655178	25	48	81	92
655179	16	43	79	87
655202	17	19	61	84
655231	14	45	68	84
655232	13	38	69	79
655233	17	30	65	86
655420	19	35	60	86

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Example 6: Design of mixed backbone 5-8-5 MOE gapmers and deoxy, MOE, and cEt oligonucleotides targeting human C9ORF72

Additional antisense oligonucleotides were designed targeting a C9ORF72 nucleic acid. The newly designed chimeric antisense oligonucleotides in the Tables below were designed as 5-8-5 MOE gapmers, 5-10-5 MOE gapmers, or deoxy, MOE, and cEt gapmers.

The 5-8-5 MOE gapmers are 18 nucleosides in length, wherein the central gap segment comprises of eight 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE modification. The linkages between the nucleosides are described in the Linkage column; 'o' indicates a phosphodiester linkage and 's' indicates a phosphorothioate linkage. All cytosine residues throughout each gapmer are 5-methylcytosines.

The 5-10-5 MOE gapmers are 20 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction

comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE modification. The linkages between the nucleosides are described in the Linkage column; 'o' indicates a phosphodiester linkage and 's' indicates a phosphorothioate linkage. All cytosine residues throughout each gapmer are 5-methylcytosines.

The deoxy, MOE, and cEt oligonucleotides are 17 nucleosides in length wherein the nucleoside has either a MOE sugar modification, a cEt sugar modification, or a deoxyribose sugar. The 'Chemistry' column describes the sugar modifications of each oligonucleotide; 'k' indicates a cEt nucleoside; 'd' indicates deoxyribonucleosides, the number indicates the number of deoxyribonucleosides; and 'e' indicates a 2'-MOE nucleoside. The internucleoside linkages throughout each gapmer are either phosphorothioate linkages or phosphodiester linkages. The linkages between the nucleosides are described in the Linkage column; 'o' indicates a phosphodiester linkage and 's' indicates a phosphorothioate linkage. All cytosine residues throughout each gapmer are 5-methylcytosines.

"Start site" indicates the 5'-most nucleoside to which the antisense oligonucleotide is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the antisense oligonucleotide is targeted in the human gene sequence. Each antisense oligonucleotide listed in the Tables 23-29 below is targeted to the human C9ORF72 genomic sequence, designated herein as SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000. Table 30 presents a 5-10-5 gapmer that is targeted to C9ORF72 mRNA sequence, SEQ ID NO: 1 (GENBANK Accession No. NM_001256054.1).

Table 23

5-8-5 MOE gapmers targeting SEQ ID NO: 2

ISIS NO	Sequence	Linkage	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
672581	GTGAGAGCAAGTAGTGGG	sooooooooooooo	1326	1343	744
672582	TGTGAGAGCAAGTAGTGG	sooooooooooooo	1327	1344	745
672583	CTGTGAGAGCAAGTAGTG	sooooooooooooo	1328	1345	746
672584	ACTGTGAGAGCAAGTAGT	sooooooooooooo	1329	1346	747
672585	TACTGTGAGAGCAAGTAG	sooooooooooooo	1330	1347	748
672586	GTACTGTGAGAGCAAGTA	sooooooooooooo	1331	1348	749
672587	AGTACTGTGAGAGCAAGT	sooooooooooooo	1332	1349	750
672588	GAGTACTGTGAGAGCAAG	sooooooooooooo	1333	1350	751
672589	CGAGTACTGTGAGAGCAA	sooooooooooooo	1334	1351	752
672590	GCGAGTACTGTGAGAGCA	sooooooooooooo	1335	1352	753
672591	AGCGAGTACTGTGAGAGC	sooooooooooooo	1336	1353	754
672592	CAGCGAGTACTGTGAGAG	sooooooooooooo	1337	1354	755
672593	TCAGCGAGTACTGTGAGA	sooooooooooooo	1338	1355	756

672594	CTCAGCGAGTACTGTGAG	sooooooooooooo	1339	1356	757
672595	CCTCAGCGAGTACTGTGA	sooooooooooooo	1340	1357	758
672596	CCCTCAGCGAGTACTGTG	sooooooooooooo	1341	1358	759
672597	ACCCTCAGCGAGTACTGT	sooooooooooooo	1342	1359	760
672598	CACCCTCAGCGAGTACTG	sooooooooooooo	1343	1360	761
672599	TCACCCTCAGCGAGTACT	sooooooooooooo	1344	1361	762
672600	TTCACCCTCAGCGAGTAC	sooooooooooooo	1345	1362	763
672601	GTTTACCCTCAGCGAGTA	sooooooooooooo	1346	1363	764
672602	TGTTACCCTCAGCGAGT	sooooooooooooo	1347	1364	765
672603	TTGTTACCCTCAGCGAG	sooooooooooooo	1348	1365	766
672604	CTTGTTACCCTCAGCGA	sooooooooooooo	1349	1366	767
672605	TCTTGTTACCCTCAGCG	sooooooooooooo	1350	1367	768
672606	TTCTTGTTACCCTCAGC	sooooooooooooo	1351	1368	769
672607	TTTCTTGTTACCCTCAG	sooooooooooooo	1352	1369	770
672608	TTTTCTTGTTACCCTCA	sooooooooooooo	1353	1370	771
672609	CTTTCTTGTTACCCTC	sooooooooooooo	1354	1371	772
672610	TCTTTCTTGTTACCCT	sooooooooooooo	1355	1372	773
672611	GTCTTTCTTGTTACCC	sooooooooooooo	1356	1373	774
672612	GGTCTTTCTTGTTACC	sooooooooooooo	1357	1374	775
672613	AGGTCTTTCTTGTTAC	sooooooooooooo	1358	1375	776
672614	CAGGTCTTTCTTGTTCA	sooooooooooooo	1359	1376	777
672615	TCAGGTCTTTCTTGTT	sooooooooooooo	1360	1377	778
672616	ATCAGGTCTTTCTTGTT	sooooooooooooo	1361	1378	779
672617	TATCAGGTCTTTCTTGT	sooooooooooooo	1362	1379	780
672618	TTATCAGGTCTTTCTTG	sooooooooooooo	1363	1380	781
672619	TTTATCAGGTCTTTCTT	sooooooooooooo	1364	1381	782
672620	AATCTTTATCAGGTCTT	sooooooooooooo	1368	1385	783
672621	TAATCTTTATCAGGTCT	sooooooooooooo	1369	1386	784
672622	TTAATCTTTATCAGGTCT	sooooooooooooo	1370	1387	785
672623	GTTAATCTTTATCAGGTC	sooooooooooooo	1371	1388	786
672624	GGTTAATCTTTATCAGGT	sooooooooooooo	1372	1389	787
672625	TGGTTAATCTTTATCAGG	sooooooooooooo	1373	1390	788
672626	CTGGTTAATCTTTATCAG	sooooooooooooo	1374	1391	789
672627	TCTGGTTAATCTTTATCA	sooooooooooooo	1375	1392	790
672628	TTCTGGTTAATCTTTATC	sooooooooooooo	1376	1393	791
672629	TCCCTCCTTGTTTCTTC	sooooooooooooo	1391	1408	792
672630	TTTCCCTCCTTGTTTCT	sooooooooooooo	1393	1410	793
672631	GTTTCCCTCCTTGTTTCT	sooooooooooooo	1394	1411	794
672632	TGTTTCCCTCCTTGTTT	sooooooooooooo	1395	1412	795
672633	TTGTTTCCCTCCTTGTTT	sooooooooooooo	1396	1413	796
672634	GTTGTTTCCCTCCTTGTT	sooooooooooooo	1397	1414	797

672635	GGTTGTTTCCCTCCTTGT	sooooooooooooo	1398	1415	798
672636	CGGTTGTTTCCCTCCTTG	sooooooooooooo	1399	1416	799
672637	GCGGTTGTTTCCCTCCTT	sooooooooooooo	1400	1417	800
672638	TGCGGTTGTTTCCCTCCT	sooooooooooooo	1401	1418	801
672639	CTGCGGTTGTTTCCCTCC	sooooooooooooo	1402	1419	802
672640	GCTGCGGTTGTTTCCCTC	sooooooooooooo	1403	1420	803
672641	GGCTGCGGTTGTTTCCCT	sooooooooooooo	1404	1421	804
672642	AGGCTGCGGTTGTTTCCC	sooooooooooooo	1405	1422	805
672643	CAGGCTGCGGTTGTTTCC	sooooooooooooo	1406	1423	806
672644	ACAGGCTGCGGTTGTTTC	sooooooooooooo	1407	1424	807
672645	TACAGGCTGCGGTTGTTT	sooooooooooooo	1408	1425	808
672646	CTACAGGCTGCGGTTGTT	sooooooooooooo	1409	1426	809
672647	GCTACAGGCTGCGGTTGT	sooooooooooooo	1410	1427	810
672648	TGCTACAGGCTGCGGTTG	sooooooooooooo	1411	1428	811
672649	TTGCTACAGGCTGCGGTT	sooooooooooooo	1412	1429	812
672650	CTTGCTACAGGCTGCGGT	sooooooooooooo	1413	1430	813
672651	GCTTGCTACAGGCTGCGG	sooooooooooooo	1414	1431	814
672652	AGCTTGCTACAGGCTGCG	sooooooooooooo	1415	1432	815
672653	GAGCTTGCTACAGGCTGC	sooooooooooooo	1416	1433	816
672654	AGAGCTTGCTACAGGCTG	sooooooooooooo	1417	1434	817
672655	CAGAGCTTGCTACAGGCT	sooooooooooooo	1418	1435	818
672656	CCAGAGCTTGCTACAGGC	sooooooooooooo	1419	1436	819
672657	TCCAGAGCTTGCTACAGG	sooooooooooooo	1420	1437	820
672658	TTCCAGAGCTTGCTACAG	sooooooooooooo	1421	1438	821
672659	GTTCCAGAGCTTGCTACA	sooooooooooooo	1422	1439	822
672660	AGTTCCAGAGCTTGCTAC	sooooooooooooo	1423	1440	823
672661	GAGTTCCAGAGCTTGCTA	sooooooooooooo	1424	1441	824
672662	TGAGTTCCAGAGCTTGCT	sooooooooooooo	1425	1442	825
672663	CTGAGTTCCAGAGCTTGC	sooooooooooooo	1426	1443	826
672664	CCTGAGTTCCAGAGCTTG	sooooooooooooo	1427	1444	827
672665	TCCTGAGTTCCAGAGCTT	sooooooooooooo	1428	1445	828
672666	CTCCTGAGTTCCAGAGCT	sooooooooooooo	1429	1446	829
672667	ACTCCTGAGTTCCAGAGC	sooooooooooooo	1430	1447	830
672668	GACTCCTGAGTTCCAGAG	sooooooooooooo	1431	1448	831
672669	CGACTCCTGAGTTCCAGA	sooooooooooooo	1432	1449	832
672670	GCGACTCCTGAGTTCCAG	sooooooooooooo	1433	1450	833
672671	CGCGACTCCTGAGTTCCA	sooooooooooooo	1434	1451	834
672672	GCGCGACTCCTGAGTTCC	sooooooooooooo	1435	1452	835
672673	CGCGCGACTCCTGAGTTC	sooooooooooooo	1436	1453	836
672674	GCGCGCGACTCCTGAGTT	sooooooooooooo	1437	1454	837
672675	AGCGCGCGACTCCTGAGT	sooooooooooooo	1438	1455	838

672676	TAGCGCGCGACTCCTGAG	sooooooooooooo	1439	1456	839
672677	CTAGCGCGCGACTCCTGA	sooooooooooooo	1440	1457	840
672678	CCTAGCGCGCGACTCCTG	sooooooooooooo	1441	1458	841
672679	CCCTAGCGCGCGACTCCT	sooooooooooooo	1442	1459	842
672680	CCCCTAGCGCGCGACTCC	sooooooooooooo	1443	1460	843
672681	GCCCCTAGCGCGCGACTC	sooooooooooooo	1444	1461	844
672682	GGCCCCTAGCGCGCGACT	sooooooooooooo	1445	1462	845
672683	CGGCCCCTAGCGCGCGAC	sooooooooooooo	1446	1463	846
672684	CCGGCCCCTAGCGCGCGA	sooooooooooooo	1447	1464	847
672685	CCCGGCCCCTAGCGCGCG	sooooooooooooo	1448	1465	848
672686	CCCCGGCCCCTAGCGCGC	sooooooooooooo	1449	1466	849
672687	GCCCCGGCCCCTAGCGCG	sooooooooooooo	1450	1467	850
672688	GGCCCCGGCCCCTAGCGC	sooooooooooooo	1451	1468	851
672689	CGGCCCCGGCCCCTAGCG	sooooooooooooo	1452	1469	852
672690	CCGGCCCCGGCCCCTAGC	sooooooooooooo	1453	1470	853
672691	CCCGGCCCCGGCCCCTAG	sooooooooooooo	1454	1471	854
672692	CCCCGGCCCCGGCCCCTA	sooooooooooooo	1455	1472	855
672693	ACGCCCCGGCCCCGGCCC	sooooooooooooo	1464	1481	856
672694	CACGCCCCGGCCCCGGCC	sooooooooooooo	1465	1482	857
672695	CCACGCCCCGGCCCCGGC	sooooooooooooo	1466	1483	858
672696	ACCACGCCCCGGCCCCGG	sooooooooooooo	1467	1484	859
672697	GACCACGCCCCGGCCCCG	sooooooooooooo	1468	1485	860
672698	CGACCACGCCCCGGCCCC	sooooooooooooo	1469	1486	861
672699	CCGACCACGCCCCGGCCC	sooooooooooooo	1470	1487	862
672700	CCCGACCACGCCCCGGCC	sooooooooooooo	1471	1488	863
672701	CCCCGACCACGCCCCGGC	sooooooooooooo	1472	1489	864
672702	GCCCCGACCACGCCCCGG	sooooooooooooo	1473	1490	865
672703	CGCCCCGACCACGCCCCG	sooooooooooooo	1474	1491	866
672704	CCGCCCCGACCACGCCCC	sooooooooooooo	1475	1492	867
672705	CCCGCCCCGACCACGCCC	sooooooooooooo	1476	1493	868
672706	GCCCGCCCCGACCACGCC	sooooooooooooo	1477	1494	869
672707	GGCCCGCCCCGACCACGC	sooooooooooooo	1478	1495	870
672708	GGGCCCGCCCCGACCACG	sooooooooooooo	1479	1496	871
672709	CGGGCCCGCCCCGACCAC	sooooooooooooo	1480	1497	872
672710	CCGGGCCCGCCCCGACCA	sooooooooooooo	1481	1498	873
672711	CCCGGGCCCGCCCCGACC	sooooooooooooo	1482	1499	874
672712	CCCCGGGCCCGCCCCGAC	sooooooooooooo	1483	1500	875
672713	AGCCCCGCCCGGGCCCCG	sooooooooooooo	1502	1519	876
672714	CAGCCCCGCCCGGGCCCC	sooooooooooooo	1503	1520	877
672715	GCAGCCCCGCCCGGGGCC	sooooooooooooo	1504	1521	878
672716	CGCAGCCCCGCCCGGGGC	sooooooooooooo	1505	1522	879

672717	CCGCAGCCCCGCCCCGGG	sooooooooooooo	1506	1523	880
672718	ACCGCAGCCCCGCCCCGG	sooooooooooooo	1507	1524	881
672719	AACCGCAGCCCCGCCCCG	sooooooooooooo	1508	1525	882
672720	CAACCGCAGCCCCGCCCC	sooooooooooooo	1509	1526	883
672721	GCAACCGCAGCCCCGCCC	sooooooooooooo	1510	1527	884
672722	CGCAACCGCAGCCCCGCC	sooooooooooooo	1511	1528	885
672723	CCGCAACCGCAGCCCCGC	sooooooooooooo	1512	1529	886
672724	ACCGCAACCGCAGCCCCG	sooooooooooooo	1513	1530	887
672725	CACCGCAACCGCAGCCCC	sooooooooooooo	1514	1531	888
672726	GCACCGCAACCGCAGCCC	sooooooooooooo	1515	1532	889
672727	GGCACCGCAACCGCAGCC	sooooooooooooo	1516	1533	890
672728	AGGCACCGCAACCGCAGC	sooooooooooooo	1517	1534	891
672729	CAGGCACCGCAACCGCAG	sooooooooooooo	1518	1535	892
672730	GCAGGCACCGCAACCGCA	sooooooooooooo	1519	1536	893
672731	CGCAGGCACCGCAACCGC	sooooooooooooo	1520	1537	894
672732	GCGCAGGCACCGCAACCG	sooooooooooooo	1521	1538	895
672733	GGCGCAGGCACCGCAACC	sooooooooooooo	1522	1539	896
672734	GGGCGCAGGCACCGCAAC	sooooooooooooo	1523	1540	897

Table 24

Deoxy, MOE and cEt oligonucleotides targeting SEQ ID NO: 2

ISIS NO	Sequence	Chemistry	Linkage	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
672735	TGAGAGCAAGTAGTGGG	eeekk-d7-kkeee	sooooooooooooo	1326	1342	898
672736	GTGAGAGCAAGTAGTGG	eeekk-d7-kkeee	sooooooooooooo	1327	1343	899
672737	TGTGAGAGCAAGTAGTG	eeekk-d7-kkeee	sooooooooooooo	1328	1344	900
672738	CTGTGAGAGCAAGTAGT	eeekk-d7-kkeee	sooooooooooooo	1329	1345	901
672739	ACTGTGAGAGCAAGTAG	eeekk-d7-kkeee	sooooooooooooo	1330	1346	902
672740	TACTGTGAGAGCAAGTA	eeekk-d7-kkeee	sooooooooooooo	1331	1347	903
672741	GTACTGTGAGAGCAAGT	eeekk-d7-kkeee	sooooooooooooo	1332	1348	904
672742	AGTACTGTGAGAGCAAG	eeekk-d7-kkeee	sooooooooooooo	1333	1349	905
672743	GAGTACTGTGAGAGCAA	eeekk-d7-kkeee	sooooooooooooo	1334	1350	906
672744	CGAGTACTGTGAGAGCA	eeekk-d7-kkeee	sooooooooooooo	1335	1351	907
672745	GCGAGTACTGTGAGAGC	eeekk-d7-kkeee	sooooooooooooo	1336	1352	908
672746	AGCGAGTACTGTGAGAG	eeekk-d7-kkeee	sooooooooooooo	1337	1353	909
672747	CAGCGAGTACTGTGAGA	eeekk-d7-kkeee	sooooooooooooo	1338	1354	910
672748	TCAGCGAGTACTGTGAG	eeekk-d7-kkeee	sooooooooooooo	1339	1355	911
672749	CTCAGCGAGTACTGTGA	eeekk-d7-kkeee	sooooooooooooo	1340	1356	912
672750	CCTCAGCGAGTACTGTG	eeekk-d7-kkeee	sooooooooooooo	1341	1357	913
672751	CCCTCAGCGAGTACTGT	eeekk-d7-kkeee	sooooooooooooo	1342	1358	914

672752	ACCCTCAGCGAGTACTG	eeekk-d7-kkeee	soossssssssooss	1343	1359	915
672753	CACCCTCAGCGAGTACT	eeekk-d7-kkeee	soossssssssooss	1344	1360	916
672754	TCACCCTCAGCGAGTAC	eeekk-d7-kkeee	soossssssssooss	1345	1361	917
672755	TTCACCCTCAGCGAGTA	eeekk-d7-kkeee	soossssssssooss	1346	1362	918
672756	GTTTACCCTCAGCGAGT	eeekk-d7-kkeee	soossssssssooss	1347	1363	919
672757	TGTTTACCCTCAGCGAG	eeekk-d7-kkeee	soossssssssooss	1348	1364	920
672758	TTGTTTACCCTCAGCGA	eeekk-d7-kkeee	soossssssssooss	1349	1365	921
672759	CTTGTTTACCCTCAGCG	eeekk-d7-kkeee	soossssssssooss	1350	1366	922
672760	TCTTGTTTACCCTCAGC	eeekk-d7-kkeee	soossssssssooss	1351	1367	923
672761	TTCTTGTTTACCCTCAG	eeekk-d7-kkeee	soossssssssooss	1352	1368	924
672762	TTTCTTGTTTACCCTCA	eeekk-d7-kkeee	soossssssssooss	1353	1369	925
672763	TTTTCTTGTTTACCCTC	eeekk-d7-kkeee	soossssssssooss	1354	1370	926
672764	CTTTTCTTGTTTACCCT	eeekk-d7-kkeee	soossssssssooss	1355	1371	927
672765	TCTTTTCTTGTTTACCC	eeekk-d7-kkeee	soossssssssooss	1356	1372	928
672766	GTCTTTTCTTGTTTACC	eeekk-d7-kkeee	soossssssssooss	1357	1373	929
672767	GGTCTTTTCTTGTTTAC	eeekk-d7-kkeee	soossssssssooss	1358	1374	930
672768	AGGTCTTTTCTTGTTCA	eeekk-d7-kkeee	soossssssssooss	1359	1375	931
672769	CAGGTCTTTTCTTGTTT	eeekk-d7-kkeee	soossssssssooss	1360	1376	932
672770	TCAGGTCTTTTCTTGTT	eeekk-d7-kkeee	soossssssssooss	1361	1377	933
672771	ATCAGGTCTTTTCTTGT	eeekk-d7-kkeee	soossssssssooss	1362	1378	934
672772	TATCAGGTCTTTTCTTG	eeekk-d7-kkeee	soossssssssooss	1363	1379	935
672773	TTATCAGGTCTTTTCTT	eeekk-d7-kkeee	soossssssssooss	1364	1380	936
672774	ATCTTTATCAGGTCTTT	eeekk-d7-kkeee	soossssssssooss	1368	1384	937
672775	AATCTTTATCAGGTCTT	eeekk-d7-kkeee	soossssssssooss	1369	1385	938
672776	TAATCTTTATCAGGTCT	eeekk-d7-kkeee	soossssssssooss	1370	1386	939
672777	TTAATCTTTATCAGGTC	eeekk-d7-kkeee	soossssssssooss	1371	1387	940
672778	GTTAATCTTTATCAGGT	eeekk-d7-kkeee	soossssssssooss	1372	1388	941
672779	GGTTAATCTTTATCAGG	eeekk-d7-kkeee	soossssssssooss	1373	1389	942
672780	TGGTTAATCTTTATCAG	eeekk-d7-kkeee	soossssssssooss	1374	1390	943
672781	CTGGTTAATCTTTATCA	eeekk-d7-kkeee	soossssssssooss	1375	1391	944
672782	TCTGGTTAATCTTTATC	eeekk-d7-kkeee	soossssssssooss	1376	1392	945
672783	CCCTCCTTGTTTTCTTC	eeekk-d7-kkeee	soossssssssooss	1391	1407	946
672784	TCCCTCCTTGTTTTCTT	eeekk-d7-kkeee	soossssssssooss	1392	1408	947
672785	TTCCCTCCTTGTTTTCT	eeekk-d7-kkeee	soossssssssooss	1393	1409	948
672786	TTCCCTCCTTGTTTTTC	eeekk-d7-kkeee	soossssssssooss	1394	1410	949
672787	GTTTCCCTCCTTGTTTT	eeekk-d7-kkeee	soossssssssooss	1395	1411	950
672788	TGTTTCCCTCCTTGTTTT	eeekk-d7-kkeee	soossssssssooss	1396	1412	951
672789	TTGTTTCCCTCCTTGTT	eeekk-d7-kkeee	soossssssssooss	1397	1413	952
672790	GGTTGTTTCCCTCCTTG	eeekk-d7-kkeee	soossssssssooss	1399	1415	953
672791	CGTTGTTTCCCTCCTT	eeekk-d7-kkeee	soossssssssooss	1400	1416	954
672792	GCGTTGTTTCCCTCCT	eeekk-d7-kkeee	soossssssssooss	1401	1417	955

672793	TGCGGTTGTTTCCCTCC	eeekk-d7-kkeee	sooooooooooooo	1402	1418	956
672794	CTGCGGTTGTTTCCCTC	eeekk-d7-kkeee	sooooooooooooo	1403	1419	957
672795	GCTGCGGTTGTTTCCCT	eeekk-d7-kkeee	sooooooooooooo	1404	1420	958
672796	GGCTGCGGTTGTTTCCC	eeekk-d7-kkeee	sooooooooooooo	1405	1421	959
672797	AGGCTGCGGTTGTTTCC	eeekk-d7-kkeee	sooooooooooooo	1406	1422	960
672798	CAGGCTGCGGTTGTTTC	eeekk-d7-kkeee	sooooooooooooo	1407	1423	961
672799	ACAGGCTGCGGTTGTTT	eeekk-d7-kkeee	sooooooooooooo	1408	1424	962
672800	TACAGGCTGCGGTTGTT	eeekk-d7-kkeee	sooooooooooooo	1409	1425	963
672801	CTACAGGCTGCGGTTGT	eeekk-d7-kkeee	sooooooooooooo	1410	1426	964
672802	GCTACAGGCTGCGGTTG	eeekk-d7-kkeee	sooooooooooooo	1411	1427	965
672803	TGCTACAGGCTGCGGTT	eeekk-d7-kkeee	sooooooooooooo	1412	1428	966
672804	TTGCTACAGGCTGCGGT	eeekk-d7-kkeee	sooooooooooooo	1413	1429	967
672805	CTTGCTACAGGCTGCGG	eeekk-d7-kkeee	sooooooooooooo	1414	1430	968
672806	GCTTGCTACAGGCTGCG	eeekk-d7-kkeee	sooooooooooooo	1415	1431	969
672807	AGCTTGCTACAGGCTGC	eeekk-d7-kkeee	sooooooooooooo	1416	1432	970
672808	GAGCTTGCTACAGGCTG	eeekk-d7-kkeee	sooooooooooooo	1417	1433	971
672809	AGAGCTTGCTACAGGCT	eeekk-d7-kkeee	sooooooooooooo	1418	1434	972
672810	CAGAGCTTGCTACAGGC	eeekk-d7-kkeee	sooooooooooooo	1419	1435	973
672811	CCAGAGCTTGCTACAGG	eeekk-d7-kkeee	sooooooooooooo	1420	1436	974
672812	TCCAGAGCTTGCTACAG	eeekk-d7-kkeee	sooooooooooooo	1421	1437	975
672813	TTCCAGAGCTTGCTACA	eeekk-d7-kkeee	sooooooooooooo	1422	1438	976
672814	GTTCCAGAGCTTGCTAC	eeekk-d7-kkeee	sooooooooooooo	1423	1439	977
672815	AGTTCCAGAGCTTGCTA	eeekk-d7-kkeee	sooooooooooooo	1424	1440	978
672816	GAGTTCCAGAGCTTGCT	eeekk-d7-kkeee	sooooooooooooo	1425	1441	979
672817	TGAGTTCCAGAGCTTGC	eeekk-d7-kkeee	sooooooooooooo	1426	1442	980
672818	CTGAGTTCCAGAGCTTG	eeekk-d7-kkeee	sooooooooooooo	1427	1443	981
672819	CCTGAGTTCCAGAGCTT	eeekk-d7-kkeee	sooooooooooooo	1428	1444	982
672820	TCCTGAGTTCCAGAGCT	eeekk-d7-kkeee	sooooooooooooo	1429	1445	983
672821	CTCCTGAGTTCCAGAGC	eeekk-d7-kkeee	sooooooooooooo	1430	1446	984
672822	ACTCCTGAGTTCCAGAG	eeekk-d7-kkeee	sooooooooooooo	1431	1447	985
672823	GA CTCCTGAGTTCCAGA	eeekk-d7-kkeee	sooooooooooooo	1432	1448	986
672824	CGACTCCTGAGTTCCAG	eeekk-d7-kkeee	sooooooooooooo	1433	1449	987
672825	GCGACTCCTGAGTTCCA	eeekk-d7-kkeee	sooooooooooooo	1434	1450	988
672826	CGCGACTCCTGAGTTCC	eeekk-d7-kkeee	sooooooooooooo	1435	1451	989
672827	GCGCGACTCCTGAGTTC	eeekk-d7-kkeee	sooooooooooooo	1436	1452	990
672828	CGCGCGACTCCTGAGTT	eeekk-d7-kkeee	sooooooooooooo	1437	1453	991
672829	GCGCGCGACTCCTGAGT	eeekk-d7-kkeee	sooooooooooooo	1438	1454	992
672830	AGCGCGCGACTCCTGAG	eeekk-d7-kkeee	sooooooooooooo	1439	1455	993
672831	TAGCGCGCGACTCCTGA	eeekk-d7-kkeee	sooooooooooooo	1440	1456	994
672832	CTAGCGCGCGACTCCTG	eeekk-d7-kkeee	sooooooooooooo	1441	1457	995
672833	CCTAGCGCGCGACTCCT	eeekk-d7-kkeee	sooooooooooooo	1442	1458	996

672834	CCCTAGCGCGCGACTCC	eeekk-d7-kkeee	soossssssssooss	1443	1459	997
672835	CCCCTAGCGCGCGACTC	eeekk-d7-kkeee	soossssssssooss	1444	1460	998
672836	GCCCCTAGCGCGCGACT	eeekk-d7-kkeee	soossssssssooss	1445	1461	999
672837	GGCCCCTAGCGCGCGAC	eeekk-d7-kkeee	soossssssssooss	1446	1462	1000
672838	CGGCCCTAGCGCGCGA	eeekk-d7-kkeee	soossssssssooss	1447	1463	1001
672839	CCGGCCCCTAGCGCGCG	eeekk-d7-kkeee	soossssssssooss	1448	1464	1002
672840	CCCGGCCCTAGCGCGC	eeekk-d7-kkeee	soossssssssooss	1449	1465	1003
672841	CCCCGGCCCCTAGCGCG	eeekk-d7-kkeee	soossssssssooss	1450	1466	1004
672842	GCCCCGGCCCCTAGCGC	eeekk-d7-kkeee	soossssssssooss	1451	1467	1005
672843	GGCCCCGGCCCCTAGCG	eeekk-d7-kkeee	soossssssssooss	1452	1468	1006
672844	CGGCCCGGCCCTAGC	eeekk-d7-kkeee	soossssssssooss	1453	1469	1007
672845	CCGGCCCCGGCCCCTAG	eeekk-d7-kkeee	soossssssssooss	1454	1470	1008
672846	CCCGGCCCGGCCCTA	eeekk-d7-kkeee	soossssssssooss	1455	1471	1009
672847	ACGCCCGGCCCGGCC	eeekk-d7-kkeee	soossssssssooss	1465	1481	1010
672848	CACGCCCGGCCCGGC	eeekk-d7-kkeee	soossssssssooss	1466	1482	1011
672849	CCACGCCCGGCCCGG	eeekk-d7-kkeee	soossssssssooss	1467	1483	1012
672850	ACCACGCCCGGCCCG	eeekk-d7-kkeee	soossssssssooss	1468	1484	1013
672851	GACCACGCCCGGCC	eeekk-d7-kkeee	soossssssssooss	1469	1485	1014
672852	CGACCACGCCCGGCC	eeekk-d7-kkeee	soossssssssooss	1470	1486	1015
672853	CCGACCACGCCCGGCC	eeekk-d7-kkeee	soossssssssooss	1471	1487	1016
672854	CCCGACCACGCCCGGC	eeekk-d7-kkeee	soossssssssooss	1472	1488	1017
672855	CCCCGACCACGCCCGG	eeekk-d7-kkeee	soossssssssooss	1473	1489	1018
672856	GCCCCGACCACGCCCG	eeekk-d7-kkeee	soossssssssooss	1474	1490	1019
672857	CGCCCCGACCACGCC	eeekk-d7-kkeee	soossssssssooss	1475	1491	1020
672858	CCGCCCGACCACGCC	eeekk-d7-kkeee	soossssssssooss	1476	1492	1021
672859	CCCGCCCCGACCACGCC	eeekk-d7-kkeee	soossssssssooss	1477	1493	1022
672860	GCCCGCCCCGACCACGC	eeekk-d7-kkeee	soossssssssooss	1478	1494	1023
672861	GGCCCGCCCCGACCACG	eeekk-d7-kkeee	soossssssssooss	1479	1495	1024
672862	GGGCCCGCCCCGACCAC	eeekk-d7-kkeee	soossssssssooss	1480	1496	1025
672863	CGGGCCCGCCCCGACCA	eeekk-d7-kkeee	soossssssssooss	1481	1497	1026
672864	CCGGGCCCGCCCCGACC	eeekk-d7-kkeee	soossssssssooss	1482	1498	1027
672865	CCCGGGCCCGCCCCGAC	eeekk-d7-kkeee	soossssssssooss	1483	1499	1028
672866	GCAGCCCCGCCCGGGC	eeekk-d7-kkeee	soossssssssooss	1505	1521	1029
672867	CGCAGCCCCGCCCGGG	eeekk-d7-kkeee	soossssssssooss	1506	1522	1030
672868	CCGAGCCCCGCCCGG	eeekk-d7-kkeee	soossssssssooss	1507	1523	1031
672869	ACCGCAGCCCCGCCCG	eeekk-d7-kkeee	soossssssssooss	1508	1524	1032
672870	AACCGCAGCCCCGCC	eeekk-d7-kkeee	soossssssssooss	1509	1525	1033
672871	CAACCGCAGCCCCGCC	eeekk-d7-kkeee	soossssssssooss	1510	1526	1034
672872	GCAACCGCAGCCCCGC	eeekk-d7-kkeee	soossssssssooss	1511	1527	1035
672873	CGCAACCGCAGCCCCGC	eeekk-d7-kkeee	soossssssssooss	1512	1528	1036
672874	CCGCAACCGCAGCCCCG	eeekk-d7-kkeee	soossssssssooss	1513	1529	1037

672875	ACCGCAACCGCAGCCCC	eeekk-d7-kkeee	sooooooooooooo	1514	1530	1038
672876	CACCGCAACCGCAGCCC	eeekk-d7-kkeee	sooooooooooooo	1515	1531	1039
672877	GCACCGCAACCGCAGCC	eeekk-d7-kkeee	sooooooooooooo	1516	1532	1040
672878	GGCACCGCAACCGCAGC	eeekk-d7-kkeee	sooooooooooooo	1517	1533	1041
672879	AGGCACCGCAACCGCAG	eeekk-d7-kkeee	sooooooooooooo	1518	1534	1042
672880	CAGGCACCGCAACCGCA	eeekk-d7-kkeee	sooooooooooooo	1519	1535	1043
672881	GCAGGCACCGCAACCGC	eeekk-d7-kkeee	sooooooooooooo	1520	1536	1044
672882	CGCAGGCACCGCAACCG	eeekk-d7-kkeee	sooooooooooooo	1521	1537	1045
672883	GCGCAGGCACCGCAACC	eeekk-d7-kkeee	sooooooooooooo	1522	1538	1046
672884	GGCGCAGGCACCGCAAC	eeekk-d7-kkeee	sooooooooooooo	1523	1539	1047

Table 25

Deoxy, MOE and cEt oligonucleotides targeting SEQ ID NO: 2

ISIS NO	Sequence	Chemistry	Linkage	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
672885	TGAGAGCAAGTAGTGGG	eekk-d8-kkeee	sooooooooooooo	1326	1342	898
672886	GTGAGAGCAAGTAGTGG	eekk-d8-kkeee	sooooooooooooo	1327	1343	899
672887	TGTGAGAGCAAGTAGTG	eekk-d8-kkeee	sooooooooooooo	1328	1344	900
672888	CTGTGAGAGCAAGTAGT	eekk-d8-kkeee	sooooooooooooo	1329	1345	901
672889	ACTGTGAGAGCAAGTAG	eekk-d8-kkeee	sooooooooooooo	1330	1346	902
672890	TACTGTGAGAGCAAGTA	eekk-d8-kkeee	sooooooooooooo	1331	1347	903
672891	GTACTGTGAGAGCAAGT	eekk-d8-kkeee	sooooooooooooo	1332	1348	904
672892	AGTACTGTGAGAGCAAG	eekk-d8-kkeee	sooooooooooooo	1333	1349	905
672893	GAGTACTGTGAGAGCAA	eekk-d8-kkeee	sooooooooooooo	1334	1350	906
672894	CGAGTACTGTGAGAGCA	eekk-d8-kkeee	sooooooooooooo	1335	1351	907
672895	GCGAGTACTGTGAGAGC	eekk-d8-kkeee	sooooooooooooo	1336	1352	908
672896	AGCGAGTACTGTGAGAG	eekk-d8-kkeee	sooooooooooooo	1337	1353	909
672897	CAGCGAGTACTGTGAGA	eekk-d8-kkeee	sooooooooooooo	1338	1354	910
672898	TCAGCGAGTACTGTGAG	eekk-d8-kkeee	sooooooooooooo	1339	1355	911
672899	CTCAGCGAGTACTGTGA	eekk-d8-kkeee	sooooooooooooo	1340	1356	912
672900	CCTCAGCGAGTACTGTG	eekk-d8-kkeee	sooooooooooooo	1341	1357	913
672901	CCCTCAGCGAGTACTGT	eekk-d8-kkeee	sooooooooooooo	1342	1358	914
672902	ACCCTCAGCGAGTACTG	eekk-d8-kkeee	sooooooooooooo	1343	1359	915
672903	CACCCTCAGCGAGTACT	eekk-d8-kkeee	sooooooooooooo	1344	1360	916
672904	TCACCCTCAGCGAGTAC	eekk-d8-kkeee	sooooooooooooo	1345	1361	917
672905	TTCACCCTCAGCGAGTA	eekk-d8-kkeee	sooooooooooooo	1346	1362	918
672906	GTTCACCCTCAGCGAGT	eekk-d8-kkeee	sooooooooooooo	1347	1363	919
672907	TGTTACCCTCAGCGAG	eekk-d8-kkeee	sooooooooooooo	1348	1364	920
672908	TTGTTACCCTCAGCGA	eekk-d8-kkeee	sooooooooooooo	1349	1365	921

672909	CTTGTTACCCCTCAGCG	eekk-d8-kkeee	sooooooooooooo	1350	1366	922
672910	TCTTGTTACCCCTCAGC	eekk-d8-kkeee	sooooooooooooo	1351	1367	923
672911	TTCTTGTTACCCCTCAG	eekk-d8-kkeee	sooooooooooooo	1352	1368	924
672912	TTTCTTGTTACCCCTCA	eekk-d8-kkeee	sooooooooooooo	1353	1369	925
672913	TTTTCTTGTTACCCCTC	eekk-d8-kkeee	sooooooooooooo	1354	1370	926
672914	CTTTTCTTGTTACCCCT	eekk-d8-kkeee	sooooooooooooo	1355	1371	927
672915	TCTTTTCTTGTTACCC	eekk-d8-kkeee	sooooooooooooo	1356	1372	928
672916	GTCTTTTCTTGTTACCC	eekk-d8-kkeee	sooooooooooooo	1357	1373	929
672917	GGTCTTTTCTTGTTAC	eekk-d8-kkeee	sooooooooooooo	1358	1374	930
672918	AGGTCTTTTCTTGTTCA	eekk-d8-kkeee	sooooooooooooo	1359	1375	931
672919	CAGGTCTTTTCTTGTT	eekk-d8-kkeee	sooooooooooooo	1360	1376	932
672920	TCAGGTCTTTTCTTGTT	eekk-d8-kkeee	sooooooooooooo	1361	1377	933
672921	ATCAGGTCTTTTCTTGT	eekk-d8-kkeee	sooooooooooooo	1362	1378	934
672922	TATCAGGTCTTTTCTTG	eekk-d8-kkeee	sooooooooooooo	1363	1379	935
672923	TTATCAGGTCTTTTCTT	eekk-d8-kkeee	sooooooooooooo	1364	1380	936
672924	ATCTTTATCAGGTCTTT	eekk-d8-kkeee	sooooooooooooo	1368	1384	937
672925	AATCTTTATCAGGTCTT	eekk-d8-kkeee	sooooooooooooo	1369	1385	938
672926	TAATCTTTATCAGGTCT	eekk-d8-kkeee	sooooooooooooo	1370	1386	939
672927	TTAATCTTTATCAGGTC	eekk-d8-kkeee	sooooooooooooo	1371	1387	940
672928	GTTAATCTTTATCAGGT	eekk-d8-kkeee	sooooooooooooo	1372	1388	941
672929	GGTTAATCTTTATCAGG	eekk-d8-kkeee	sooooooooooooo	1373	1389	942
672930	TGGTTAATCTTTATCAG	eekk-d8-kkeee	sooooooooooooo	1374	1390	943
672931	CTGGTTAATCTTTATCA	eekk-d8-kkeee	sooooooooooooo	1375	1391	944
672932	TCTGGTTAATCTTTATC	eekk-d8-kkeee	sooooooooooooo	1376	1392	945
672933	CCCTCCTTGTTTTCTTC	eekk-d8-kkeee	sooooooooooooo	1391	1407	946
672934	TCCCTCCTTGTTTTCTT	eekk-d8-kkeee	sooooooooooooo	1392	1408	947
672935	TTCCCTCCTTGTTTTCT	eekk-d8-kkeee	sooooooooooooo	1393	1409	948
672936	TTTCCCTCCTTGTTTTCT	eekk-d8-kkeee	sooooooooooooo	1394	1410	949
672937	GTTTCCCTCCTTGTTTT	eekk-d8-kkeee	sooooooooooooo	1395	1411	950
672938	TGTTTCCCTCCTTGTTTT	eekk-d8-kkeee	sooooooooooooo	1396	1412	951
672939	TTGTTTCCCTCCTTGTT	eekk-d8-kkeee	sooooooooooooo	1397	1413	952
672940	GGTTGTTTCCCTCCTTG	eekk-d8-kkeee	sooooooooooooo	1399	1415	953
672941	CGGTTGTTTCCCTCCTT	eekk-d8-kkeee	sooooooooooooo	1400	1416	954
672942	GCGGTTGTTTCCCTCCT	eekk-d8-kkeee	sooooooooooooo	1401	1417	955
672943	TGCGGTTGTTTCCCTCC	eekk-d8-kkeee	sooooooooooooo	1402	1418	956
672944	CTGCGGTTGTTTCCCTC	eekk-d8-kkeee	sooooooooooooo	1403	1419	957
672945	GCTGCGGTTGTTTCCCT	eekk-d8-kkeee	sooooooooooooo	1404	1420	958
672946	GGCTGCGGTTGTTTCCC	eekk-d8-kkeee	sooooooooooooo	1405	1421	959
672947	AGGCTGCGGTTGTTTCC	eekk-d8-kkeee	sooooooooooooo	1406	1422	960
672948	CAGGCTGCGGTTGTTTC	eekk-d8-kkeee	sooooooooooooo	1407	1423	961
672949	ACAGGCTGCGGTTGTTT	eekk-d8-kkeee	sooooooooooooo	1408	1424	962

672950	TACAGGCTGCGGTTGTT	eekk-d8-kkeee	sooooooooooooo	1409	1425	963
672951	CTACAGGCTGCGGTTGT	eekk-d8-kkeee	sooooooooooooo	1410	1426	964
672952	GCTACAGGCTGCGGTTG	eekk-d8-kkeee	sooooooooooooo	1411	1427	965
672953	TGCTACAGGCTGCGGTT	eekk-d8-kkeee	sooooooooooooo	1412	1428	966
672954	TTGCTACAGGCTGCGGT	eekk-d8-kkeee	sooooooooooooo	1413	1429	967
672955	CTTGCTACAGGCTGCGG	eekk-d8-kkeee	sooooooooooooo	1414	1430	968
672956	GCTTGCTACAGGCTGCG	eekk-d8-kkeee	sooooooooooooo	1415	1431	969
672957	AGCTTGCTACAGGCTGC	eekk-d8-kkeee	sooooooooooooo	1416	1432	970
672958	GAGCTTGCTACAGGCTG	eekk-d8-kkeee	sooooooooooooo	1417	1433	971
672959	AGAGCTTGCTACAGGCT	eekk-d8-kkeee	sooooooooooooo	1418	1434	972
672960	CAGAGCTTGCTACAGGC	eekk-d8-kkeee	sooooooooooooo	1419	1435	973
672961	CCAGAGCTTGCTACAGG	eekk-d8-kkeee	sooooooooooooo	1420	1436	974
672962	TCCAGAGCTTGCTACAG	eekk-d8-kkeee	sooooooooooooo	1421	1437	975
672963	TTCCAGAGCTTGCTACA	eekk-d8-kkeee	sooooooooooooo	1422	1438	976
672964	GTTCCAGAGCTTGCTAC	eekk-d8-kkeee	sooooooooooooo	1423	1439	977
672965	AGTTCCAGAGCTTGCTA	eekk-d8-kkeee	sooooooooooooo	1424	1440	978
672966	GAGTTCCAGAGCTTGCT	eekk-d8-kkeee	sooooooooooooo	1425	1441	979
672967	TGAGTTCCAGAGCTTGC	eekk-d8-kkeee	sooooooooooooo	1426	1442	980
672968	CTGAGTTCCAGAGCTTG	eekk-d8-kkeee	sooooooooooooo	1427	1443	981
672969	CCTGAGTTCCAGAGCTT	eekk-d8-kkeee	sooooooooooooo	1428	1444	982
672970	TCCTGAGTTCCAGAGCT	eekk-d8-kkeee	sooooooooooooo	1429	1445	983
672971	CTCCTGAGTTCCAGAGC	eekk-d8-kkeee	sooooooooooooo	1430	1446	984
672972	ACTCCTGAGTTCCAGAG	eekk-d8-kkeee	sooooooooooooo	1431	1447	985
672973	GACTCCTGAGTTCCAGA	eekk-d8-kkeee	sooooooooooooo	1432	1448	986
672974	CGACTCCTGAGTTCCAG	eekk-d8-kkeee	sooooooooooooo	1433	1449	987
672975	GCGACTCCTGAGTTCCA	eekk-d8-kkeee	sooooooooooooo	1434	1450	988
672976	CGCGACTCCTGAGTTCC	eekk-d8-kkeee	sooooooooooooo	1435	1451	989
672977	GCGCGACTCCTGAGTTC	eekk-d8-kkeee	sooooooooooooo	1436	1452	990
672978	CGCGCGACTCCTGAGTT	eekk-d8-kkeee	sooooooooooooo	1437	1453	991
672979	GCGCGCGACTCCTGAGT	eekk-d8-kkeee	sooooooooooooo	1438	1454	992
672980	AGCGCGCGACTCCTGAG	eekk-d8-kkeee	sooooooooooooo	1439	1455	993
672981	TAGCGCGCGACTCCTGA	eekk-d8-kkeee	sooooooooooooo	1440	1456	994
672982	CTAGCGCGCGACTCCTG	eekk-d8-kkeee	sooooooooooooo	1441	1457	995
672983	CCTAGCGCGCGACTCCT	eekk-d8-kkeee	sooooooooooooo	1442	1458	996
672984	CCCTAGCGCGCGACTCC	eekk-d8-kkeee	sooooooooooooo	1443	1459	997
672985	CCCCTAGCGCGCGACTC	eekk-d8-kkeee	sooooooooooooo	1444	1460	998
672986	GCCCCTAGCGCGCGACT	eekk-d8-kkeee	sooooooooooooo	1445	1461	999
672987	GGCCCCTAGCGCGCGAC	eekk-d8-kkeee	sooooooooooooo	1446	1462	1000
672988	CGGCCCTAGCGCGCGCA	eekk-d8-kkeee	sooooooooooooo	1447	1463	1001
672989	CCGGCCCCTAGCGCGCG	eekk-d8-kkeee	sooooooooooooo	1448	1464	1002
672990	CCCGGCCCTAGCGCGC	eekk-d8-kkeee	sooooooooooooo	1449	1465	1003

672991	CCCCGGCCCCTAGCGCG	eekk-d8-kkeee	soosoooooooooss	1450	1466	1004
672992	GCCCCGGCCCCTAGCGC	eekk-d8-kkeee	soosoooooooooss	1451	1467	1005
672993	GGCCCCGGCCCCTAGCG	eekk-d8-kkeee	soosoooooooooss	1452	1468	1006
672994	CGGCCCCGGCCCCTAGC	eekk-d8-kkeee	soosoooooooooss	1453	1469	1007
672995	CCGGCCCCGGCCCCTAG	eekk-d8-kkeee	soosoooooooooss	1454	1470	1008
672996	CCCGGCCCCGGCCCCTA	eekk-d8-kkeee	soosoooooooooss	1455	1471	1009
672997	ACGCCCCGGCCCCGGCC	eekk-d8-kkeee	soosoooooooooss	1465	1481	1010
672998	CACGCCCCGGCCCCGGC	eekk-d8-kkeee	soosoooooooooss	1466	1482	1011
672999	CCACGCCCCGGCCCCGG	eekk-d8-kkeee	soosoooooooooss	1467	1483	1012
673000	ACCACGCCCCGGCCCCG	eekk-d8-kkeee	soosoooooooooss	1468	1484	1013
673001	GACCACGCCCCGGCCCC	eekk-d8-kkeee	soosoooooooooss	1469	1485	1014
673002	CGACCACGCCCCGGCCC	eekk-d8-kkeee	soosoooooooooss	1470	1486	1015
673003	CCGACCACGCCCCGGCC	eekk-d8-kkeee	soosoooooooooss	1471	1487	1016
673004	CCCGACCACGCCCCGGC	eekk-d8-kkeee	soosoooooooooss	1472	1488	1017
673005	CCCCGACCACGCCCCGG	eekk-d8-kkeee	soosoooooooooss	1473	1489	1018
673006	GCCCCGACCACGCCCCG	eekk-d8-kkeee	soosoooooooooss	1474	1490	1019
673007	CGCCCCGACCACGCCCC	eekk-d8-kkeee	soosoooooooooss	1475	1491	1020
673008	CCGCCCCGACCACGCCC	eekk-d8-kkeee	soosoooooooooss	1476	1492	1021
673009	CCCGCCCCGACCACGCC	eekk-d8-kkeee	soosoooooooooss	1477	1493	1022
673010	GCCCGCCCCGACCACGC	eekk-d8-kkeee	soosoooooooooss	1478	1494	1023
673011	GGCCCGCCCCGACCACG	eekk-d8-kkeee	soosoooooooooss	1479	1495	1024
673012	GGGCCCGCCCCGACCAC	eekk-d8-kkeee	soosoooooooooss	1480	1496	1025
673013	CGGGCCCGCCCCGACCA	eekk-d8-kkeee	soosoooooooooss	1481	1497	1026
673014	CCGGGCCCGCCCCGACC	eekk-d8-kkeee	soosoooooooooss	1482	1498	1027
673015	CCCGGGCCCGCCCCGAC	eekk-d8-kkeee	soosoooooooooss	1483	1499	1028
673016	GCAGCCCCGCCCCGGGC	eekk-d8-kkeee	soosoooooooooss	1505	1521	1029
673017	CGCAGCCCCGCCCCGGG	eekk-d8-kkeee	soosoooooooooss	1506	1522	1030
673018	CCGCAGCCCCGCCCCGG	eekk-d8-kkeee	soosoooooooooss	1507	1523	1031
673019	ACCGCAGCCCCGCCCCG	eekk-d8-kkeee	soosoooooooooss	1508	1524	1032
673020	AACCGCAGCCCCGCCCC	eekk-d8-kkeee	soosoooooooooss	1509	1525	1033
673021	CAACCGCAGCCCCGCCC	eekk-d8-kkeee	soosoooooooooss	1510	1526	1034
673022	GCAACCGCAGCCCCGCC	eekk-d8-kkeee	soosoooooooooss	1511	1527	1035
673023	CGCAACCGCAGCCCCGC	eekk-d8-kkeee	soosoooooooooss	1512	1528	1036
673024	CCGCAACCGCAGCCCCG	eekk-d8-kkeee	soosoooooooooss	1513	1529	1037
673025	ACCGCAACCGCAGCCCC	eekk-d8-kkeee	soosoooooooooss	1514	1530	1038
673026	CACCGCAACCGCAGCCC	eekk-d8-kkeee	soosoooooooooss	1515	1531	1039
673027	GCACCGCAACCGCAGCC	eekk-d8-kkeee	soosoooooooooss	1516	1532	1040
673028	GGCACCGCAACCGCAGC	eekk-d8-kkeee	soosoooooooooss	1517	1533	1041
673029	AGGCACCGCAACCGCAG	eekk-d8-kkeee	soosoooooooooss	1518	1534	1042
673030	CAGGCACCGCAACCGCA	eekk-d8-kkeee	soosoooooooooss	1519	1535	1043
673031	GCAGGCACCGCAACCGC	eekk-d8-kkeee	soosoooooooooss	1520	1536	1044

673032	CGCAGGCACCGCAACCG	eekk-d8-kkeee	sooooooooooooo	1521	1537	1045
673033	GCGCAGGCACCGCAACC	eekk-d8-kkeee	sooooooooooooo	1522	1538	1046
673034	GGCGCAGGCACCGCAAC	eekk-d8-kkeee	sooooooooooooo	1523	1539	1047

Table 26

Deoxy, MOE and cEt oligonucleotides targeting SEQ ID NO: 2

ISIS NO	Sequence	Chemistry	Linkage	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
673035	TGAGAGCAAGTAGTGGG	ek-d8-ekekeee	sooooooooooooo	1326	1342	898
673036	GTGAGAGCAAGTAGTGG	ek-d8-ekekeee	sooooooooooooo	1327	1343	899
673037	TGTGAGAGCAAGTAGTG	ek-d8-ekekeee	sooooooooooooo	1328	1344	900
673038	CTGTGAGAGCAAGTAGT	ek-d8-ekekeee	sooooooooooooo	1329	1345	901
673039	ACTGTGAGAGCAAGTAG	ek-d8-ekekeee	sooooooooooooo	1330	1346	902
673040	TACTGTGAGAGCAAGTA	ek-d8-ekekeee	sooooooooooooo	1331	1347	903
673041	GTACTGTGAGAGCAAGT	ek-d8-ekekeee	sooooooooooooo	1332	1348	904
673042	AGTACTGTGAGAGCAAG	ek-d8-ekekeee	sooooooooooooo	1333	1349	905
673043	GAGTACTGTGAGAGCAA	ek-d8-ekekeee	sooooooooooooo	1334	1350	906
673044	CGAGTACTGTGAGAGCA	ek-d8-ekekeee	sooooooooooooo	1335	1351	907
673045	GCGAGTACTGTGAGAGC	ek-d8-ekekeee	sooooooooooooo	1336	1352	908
673046	AGCGAGTACTGTGAGAG	ek-d8-ekekeee	sooooooooooooo	1337	1353	909
673047	CAGCGAGTACTGTGAGA	ek-d8-ekekeee	sooooooooooooo	1338	1354	910
673048	TCAGCGAGTACTGTGAG	ek-d8-ekekeee	sooooooooooooo	1339	1355	911
673049	CTCAGCGAGTACTGTGA	ek-d8-ekekeee	sooooooooooooo	1340	1356	912
673050	CCTCAGCGAGTACTGTG	ek-d8-ekekeee	sooooooooooooo	1341	1357	913
673051	CCCTCAGCGAGTACTGT	ek-d8-ekekeee	sooooooooooooo	1342	1358	914
673052	ACCTCAGCGAGTACTG	ek-d8-ekekeee	sooooooooooooo	1343	1359	915
673053	CACCCTCAGCGAGTACT	ek-d8-ekekeee	sooooooooooooo	1344	1360	916
673054	TCACCCTCAGCGAGTAC	ek-d8-ekekeee	sooooooooooooo	1345	1361	917
673055	TTCACCCTCAGCGAGTA	ek-d8-ekekeee	sooooooooooooo	1346	1362	918
673056	GTTTACCCTCAGCGAGT	ek-d8-ekekeee	sooooooooooooo	1347	1363	919
673057	TGTTTACCCTCAGCGAG	ek-d8-ekekeee	sooooooooooooo	1348	1364	920
673058	TTGTTTACCCTCAGCGA	ek-d8-ekekeee	sooooooooooooo	1349	1365	921
673059	CTTGTTTACCCTCAGCG	ek-d8-ekekeee	sooooooooooooo	1350	1366	922
673060	TCTTGTTTACCCTCAGC	ek-d8-ekekeee	sooooooooooooo	1351	1367	923
673061	TTCTTGTTTACCCTCAG	ek-d8-ekekeee	sooooooooooooo	1352	1368	924
673062	TTTCTTGTTTACCCTCA	ek-d8-ekekeee	sooooooooooooo	1353	1369	925
673063	TTTTCTTGTTTACCCTC	ek-d8-ekekeee	sooooooooooooo	1354	1370	926
673064	CTTTTCTTGTTTACCCT	ek-d8-ekekeee	sooooooooooooo	1355	1371	927
673065	TCTTTTCTTGTTTACCC	ek-d8-ekekeee	sooooooooooooo	1356	1372	928
673066	GTCTTTTCTTGTTTACC	ek-d8-ekekeee	sooooooooooooo	1357	1373	929

673067	GGTCTTTTCTTGTTTAC	ek-d8-ekekeee	sooooooooooooo	1358	1374	930
673068	AGGTCTTTTCTTGTTCA	ek-d8-ekekeee	sooooooooooooo	1359	1375	931
673069	CAGGTCTTTTCTTGTTT	ek-d8-ekekeee	sooooooooooooo	1360	1376	932
673070	TCAGGTCTTTTCTTGTT	ek-d8-ekekeee	sooooooooooooo	1361	1377	933
673071	ATCAGGTCTTTTCTTGTT	ek-d8-ekekeee	sooooooooooooo	1362	1378	934
673072	TATCAGGTCTTTTCTTG	ek-d8-ekekeee	sooooooooooooo	1363	1379	935
673073	TTATCAGGTCTTTTCTT	ek-d8-ekekeee	sooooooooooooo	1364	1380	936
673074	ATCTTTATCAGGTCTTT	ek-d8-ekekeee	sooooooooooooo	1368	1384	937
673075	AATCTTTATCAGGTCTT	ek-d8-ekekeee	sooooooooooooo	1369	1385	938
673076	TAATCTTTATCAGGTCT	ek-d8-ekekeee	sooooooooooooo	1370	1386	939
673077	TTAATCTTTATCAGGTC	ek-d8-ekekeee	sooooooooooooo	1371	1387	940
673078	GTTAATCTTTATCAGGT	ek-d8-ekekeee	sooooooooooooo	1372	1388	941
673079	GGTTAATCTTTATCAGG	ek-d8-ekekeee	sooooooooooooo	1373	1389	942
673080	TGGTTAATCTTTATCAG	ek-d8-ekekeee	sooooooooooooo	1374	1390	943
673081	CTGGTTAATCTTTATCA	ek-d8-ekekeee	sooooooooooooo	1375	1391	944
673082	TCTGGTTAATCTTTATC	ek-d8-ekekeee	sooooooooooooo	1376	1392	945
673083	CCCTCCTTGTTTTCTTC	ek-d8-ekekeee	sooooooooooooo	1391	1407	946
673084	TCCCTCCTTGTTTTCTT	ek-d8-ekekeee	sooooooooooooo	1392	1408	947
673085	TTCCCTCCTTGTTTTCT	ek-d8-ekekeee	sooooooooooooo	1393	1409	948
673086	TTTCCCTCCTTGTTTTT	ek-d8-ekekeee	sooooooooooooo	1394	1410	949
673087	GTTTCCCTCCTTGTTTT	ek-d8-ekekeee	sooooooooooooo	1395	1411	950
673088	TGTTTCCCTCCTTGTTT	ek-d8-ekekeee	sooooooooooooo	1396	1412	951
673089	TTGTTTCCCTCCTTGTT	ek-d8-ekekeee	sooooooooooooo	1397	1413	952
673090	GGTTGTTTCCCTCCTTG	ek-d8-ekekeee	sooooooooooooo	1399	1415	953
673091	CGGTTGTTTCCCTCCTT	ek-d8-ekekeee	sooooooooooooo	1400	1416	954
673092	GCGGTTGTTTCCCTCCT	ek-d8-ekekeee	sooooooooooooo	1401	1417	955
673093	TGCGGTTGTTTCCCTCC	ek-d8-ekekeee	sooooooooooooo	1402	1418	956
673094	CTGCGGTTGTTTCCCTC	ek-d8-ekekeee	sooooooooooooo	1403	1419	957
673095	GCTGCGGTTGTTTCCCT	ek-d8-ekekeee	sooooooooooooo	1404	1420	958
673096	GGCTGCGGTTGTTTCCC	ek-d8-ekekeee	sooooooooooooo	1405	1421	959
673097	AGGCTGCGGTTGTTTCC	ek-d8-ekekeee	sooooooooooooo	1406	1422	960
673098	CAGGCTGCGGTTGTTTC	ek-d8-ekekeee	sooooooooooooo	1407	1423	961
673099	ACAGGCTGCGGTTGTTT	ek-d8-ekekeee	sooooooooooooo	1408	1424	962
673100	TACAGGCTGCGGTTGTT	ek-d8-ekekeee	sooooooooooooo	1409	1425	963
673101	CTACAGGCTGCGGTTGT	ek-d8-ekekeee	sooooooooooooo	1410	1426	964
673102	GCTACAGGCTGCGGTTG	ek-d8-ekekeee	sooooooooooooo	1411	1427	965
673103	TGCTACAGGCTGCGGTT	ek-d8-ekekeee	sooooooooooooo	1412	1428	966
673104	TTGCTACAGGCTGCGGT	ek-d8-ekekeee	sooooooooooooo	1413	1429	967
673105	CTTGCTACAGGCTGCGG	ek-d8-ekekeee	sooooooooooooo	1414	1430	968
673106	GCTTGCTACAGGCTGCG	ek-d8-ekekeee	sooooooooooooo	1415	1431	969
673107	AGCTTGCTACAGGCTGC	ek-d8-ekekeee	sooooooooooooo	1416	1432	970
673108	GAGCTTGCTACAGGCTG	ek-d8-ekekeee	sooooooooooooo	1417	1433	971
673109	AGAGCTTGCTACAGGCT	ek-d8-ekekeee	sooooooooooooo	1418	1434	972

673110	CAGAGCTTGCTACAGGC	ek-d8-ekekeee	sooooooooooooo	1419	1435	973
673111	CCAGAGCTTGCTACAGG	ek-d8-ekekeee	sooooooooooooo	1420	1436	974
673112	TCCAGAGCTTGCTACAG	ek-d8-ekekeee	sooooooooooooo	1421	1437	975
673113	TTCCAGAGCTTGCTACA	ek-d8-ekekeee	sooooooooooooo	1422	1438	976
673114	GTTCCAGAGCTTGCTAC	ek-d8-ekekeee	sooooooooooooo	1423	1439	977
673115	AGTTCCAGAGCTTGCTA	ek-d8-ekekeee	sooooooooooooo	1424	1440	978
673116	GAGTTCCAGAGCTTGCT	ek-d8-ekekeee	sooooooooooooo	1425	1441	979
673117	TGAGTTCCAGAGCTTGC	ek-d8-ekekeee	sooooooooooooo	1426	1442	980
673118	CTGAGTTCCAGAGCTTG	ek-d8-ekekeee	sooooooooooooo	1427	1443	981
673119	CCTGAGTTCCAGAGCTT	ek-d8-ekekeee	sooooooooooooo	1428	1444	982
673120	TCCTGAGTTCCAGAGCT	ek-d8-ekekeee	sooooooooooooo	1429	1445	983
673121	CTCCTGAGTTCCAGAGC	ek-d8-ekekeee	sooooooooooooo	1430	1446	984
673122	ACTCCTGAGTTCCAGAG	ek-d8-ekekeee	sooooooooooooo	1431	1447	985
673123	GACTCCTGAGTTCCAGA	ek-d8-ekekeee	sooooooooooooo	1432	1448	986
673124	CGACTCCTGAGTTCCAG	ek-d8-ekekeee	sooooooooooooo	1433	1449	987
673125	GCGACTCCTGAGTTCCA	ek-d8-ekekeee	sooooooooooooo	1434	1450	988
673126	CGCGACTCCTGAGTTCC	ek-d8-ekekeee	sooooooooooooo	1435	1451	989
673127	GCGCGACTCCTGAGTTC	ek-d8-ekekeee	sooooooooooooo	1436	1452	990
673128	CGCGCGACTCCTGAGTT	ek-d8-ekekeee	sooooooooooooo	1437	1453	991
673129	GCGCGCGACTCCTGAGT	ek-d8-ekekeee	sooooooooooooo	1438	1454	992
673130	AGCGCGCGACTCCTGAG	ek-d8-ekekeee	sooooooooooooo	1439	1455	993
673131	TAGCGCGCGACTCCTGA	ek-d8-ekekeee	sooooooooooooo	1440	1456	994
673132	CTAGCGCGCGACTCCTG	ek-d8-ekekeee	sooooooooooooo	1441	1457	995
673133	CCTAGCGCGCGACTCCT	ek-d8-ekekeee	sooooooooooooo	1442	1458	996
673134	CCCTAGCGCGCGACTCC	ek-d8-ekekeee	sooooooooooooo	1443	1459	997
673135	CCCCTAGCGCGCGACTC	ek-d8-ekekeee	sooooooooooooo	1444	1460	998
673136	GCCCCTAGCGCGCGACT	ek-d8-ekekeee	sooooooooooooo	1445	1461	999
673137	GGCCCCTAGCGCGCGAC	ek-d8-ekekeee	sooooooooooooo	1446	1462	1000
673138	CGGCCCCTAGCGCGCGA	ek-d8-ekekeee	sooooooooooooo	1447	1463	1001
673139	CCGGCCCCTAGCGCGCG	ek-d8-ekekeee	sooooooooooooo	1448	1464	1002
673140	CCCGGCCCCTAGCGCGC	ek-d8-ekekeee	sooooooooooooo	1449	1465	1003
673141	CCCCGGCCCCTAGCGCG	ek-d8-ekekeee	sooooooooooooo	1450	1466	1004
673142	GCCCCGGCCCCTAGCGC	ek-d8-ekekeee	sooooooooooooo	1451	1467	1005
673143	GGCCCCGGCCCCTAGCG	ek-d8-ekekeee	sooooooooooooo	1452	1468	1006
673144	CGGCCCCGGCCCCTAGC	ek-d8-ekekeee	sooooooooooooo	1453	1469	1007
673145	CCGGCCCCGGCCCCTAG	ek-d8-ekekeee	sooooooooooooo	1454	1470	1008
673146	CCCGGCCCCGGCCCCTA	ek-d8-ekekeee	sooooooooooooo	1455	1471	1009
673147	ACGCCCCGGCCCCGGCC	ek-d8-ekekeee	sooooooooooooo	1465	1481	1010
673148	CACGCCCCGGCCCCGGC	ek-d8-ekekeee	sooooooooooooo	1466	1482	1011
673149	CCACGCCCCGGCCCCGG	ek-d8-ekekeee	sooooooooooooo	1467	1483	1012
673150	ACCACGCCCCGGCCCCG	ek-d8-ekekeee	sooooooooooooo	1468	1484	1013
673151	GACCACGCCCCGGCCCC	ek-d8-ekekeee	sooooooooooooo	1469	1485	1014
673152	CGACCACGCCCCGGCCC	ek-d8-ekekeee	sooooooooooooo	1470	1486	1015

673153	CCGACCACGCCCCGGCC	ek-d8-ekekeee	sossssssssoooss	1471	1487	1016
673154	CCCGACCACGCCCCGGC	ek-d8-ekekeee	sossssssssoooss	1472	1488	1017
673155	CCCCGACCACGCCCCGG	ek-d8-ekekeee	sossssssssoooss	1473	1489	1018
673156	GCCCCGACCACGCCCCG	ek-d8-ekekeee	sossssssssoooss	1474	1490	1019
673157	CGCCCCGACCACGCCCC	ek-d8-ekekeee	sossssssssoooss	1475	1491	1020
673158	CCGCCCCGACCACGCCC	ek-d8-ekekeee	sossssssssoooss	1476	1492	1021
673159	CCCGCCCCGACCACGCC	ek-d8-ekekeee	sossssssssoooss	1477	1493	1022
673160	GCCCCGCCCCGACCACGC	ek-d8-ekekeee	sossssssssoooss	1478	1494	1023
673161	GGCCCCGCCCCGACCACG	ek-d8-ekekeee	sossssssssoooss	1479	1495	1024
673162	GGGCCCCGCCCCGACCAC	ek-d8-ekekeee	sossssssssoooss	1480	1496	1025
673163	CGGGCCCCGCCCCGACCA	ek-d8-ekekeee	sossssssssoooss	1481	1497	1026
673164	CCGGGCCCCGCCCCGACC	ek-d8-ekekeee	sossssssssoooss	1482	1498	1027
673165	CCCGGGCCCCGCCCCGAC	ek-d8-ekekeee	sossssssssoooss	1483	1499	1028
673166	GCAGCCCCGCCCCGGGC	ek-d8-ekekeee	sossssssssoooss	1505	1521	1029
673167	CGCAGCCCCGCCCCGGG	ek-d8-ekekeee	sossssssssoooss	1506	1522	1030
673168	CCGCAGCCCCGCCCCGG	ek-d8-ekekeee	sossssssssoooss	1507	1523	1031
673169	ACCGCAGCCCCGCCCCG	ek-d8-ekekeee	sossssssssoooss	1508	1524	1032
673170	AACCGCAGCCCCGCCCC	ek-d8-ekekeee	sossssssssoooss	1509	1525	1033
673171	CAACCGCAGCCCCGCC	ek-d8-ekekeee	sossssssssoooss	1510	1526	1034
673172	GCAACCGCAGCCCCGCC	ek-d8-ekekeee	sossssssssoooss	1511	1527	1035
673173	CGCAACCGCAGCCCCGC	ek-d8-ekekeee	sossssssssoooss	1512	1528	1036
673174	CCGCAACCGCAGCCCCG	ek-d8-ekekeee	sossssssssoooss	1513	1529	1037
673175	ACCGCAACCGCAGCCCC	ek-d8-ekekeee	sossssssssoooss	1514	1530	1038
673176	CACCGCAACCGCAGCCC	ek-d8-ekekeee	sossssssssoooss	1515	1531	1039
673177	GCACCGCAACCGCAGCC	ek-d8-ekekeee	sossssssssoooss	1516	1532	1040
673178	GGCACCGCAACCGCAGC	ek-d8-ekekeee	sossssssssoooss	1517	1533	1041
673179	AGGCACCGCAACCGCAG	ek-d8-ekekeee	sossssssssoooss	1518	1534	1042
673180	CAGGCACCGCAACCGCA	ek-d8-ekekeee	sossssssssoooss	1519	1535	1043
673181	GCAGGCACCGCAACCGC	ek-d8-ekekeee	sossssssssoooss	1520	1536	1044
673182	CGCAGGCACCGCAACCG	ek-d8-ekekeee	sossssssssoooss	1521	1537	1045
673183	GCGCAGGCACCGCAACC	ek-d8-ekekeee	sossssssssoooss	1522	1538	1046
673184	GGCGCAGGCACCGCAAC	ek-d8-ekekeee	sossssssssoooss	1523	1539	1047

Table 27

Deoxy, MOE and cEt oligonucleotides targeting SEQ ID NO: 2

ISIS NO	Sequence	Chemistry	Linkage	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
673185	TGAGAGCAAGTAGTGGG	keke-d8-ekeke	soossssssssooss	1326	1342	898
673186	GTGAGAGCAAGTAGTGG	keke-d8-ekeke	soossssssssooss	1327	1343	899
673187	TGTGAGAGCAAGTAGTG	keke-d8-ekeke	soossssssssooss	1328	1344	900

673188	CTGTGAGAGCAAGTAGT	keke-d8-ekeke	sooooooooooooo	1329	1345	901
673189	ACTGTGAGAGCAAGTAG	keke-d8-ekeke	sooooooooooooo	1330	1346	902
673190	TACTGTGAGAGCAAGTA	keke-d8-ekeke	sooooooooooooo	1331	1347	903
673191	GTAAGTGAGAGCAAGT	keke-d8-ekeke	sooooooooooooo	1332	1348	904
673192	AGTACTGTGAGAGCAAG	keke-d8-ekeke	sooooooooooooo	1333	1349	905
673193	GAGTACTGTGAGAGCAA	keke-d8-ekeke	sooooooooooooo	1334	1350	906
673194	CGAGTACTGTGAGAGCA	keke-d8-ekeke	sooooooooooooo	1335	1351	907
673195	GCGAGTACTGTGAGAGC	keke-d8-ekeke	sooooooooooooo	1336	1352	908
673196	AGCGAGTACTGTGAGAG	keke-d8-ekeke	sooooooooooooo	1337	1353	909
673197	CAGCGAGTACTGTGAGA	keke-d8-ekeke	sooooooooooooo	1338	1354	910
673198	TCAGCGAGTACTGTGAG	keke-d8-ekeke	sooooooooooooo	1339	1355	911
673199	CTCAGCGAGTACTGTGA	keke-d8-ekeke	sooooooooooooo	1340	1356	912
673200	CCTCAGCGAGTACTGTG	keke-d8-ekeke	sooooooooooooo	1341	1357	913
673201	CCCTCAGCGAGTACTGT	keke-d8-ekeke	sooooooooooooo	1342	1358	914
673202	ACCCTCAGCGAGTACTG	keke-d8-ekeke	sooooooooooooo	1343	1359	915
673203	CACCCTCAGCGAGTACT	keke-d8-ekeke	sooooooooooooo	1344	1360	916
673204	TCACCCTCAGCGAGTAC	keke-d8-ekeke	sooooooooooooo	1345	1361	917
673205	TTCACCCTCAGCGAGTA	keke-d8-ekeke	sooooooooooooo	1346	1362	918
673206	GTTACCCTCAGCGAGT	keke-d8-ekeke	sooooooooooooo	1347	1363	919
673207	TGTTACCCTCAGCGAG	keke-d8-ekeke	sooooooooooooo	1348	1364	920
673208	TTGTTACCCTCAGCGA	keke-d8-ekeke	sooooooooooooo	1349	1365	921
673209	CTTGTTACCCTCAGCG	keke-d8-ekeke	sooooooooooooo	1350	1366	922
673210	TCTTGTTACCCTCAGC	keke-d8-ekeke	sooooooooooooo	1351	1367	923
673211	TTCTTGTTACCCTCAG	keke-d8-ekeke	sooooooooooooo	1352	1368	924
673212	TTTCTTGTTACCCTCA	keke-d8-ekeke	sooooooooooooo	1353	1369	925
673213	TTTTCTTGTTACCCTC	keke-d8-ekeke	sooooooooooooo	1354	1370	926
673214	CTTTTCTTGTTACCCT	keke-d8-ekeke	sooooooooooooo	1355	1371	927
673215	TCTTTTCTTGTTACCC	keke-d8-ekeke	sooooooooooooo	1356	1372	928
673216	GTCTTTTCTTGTTACC	keke-d8-ekeke	sooooooooooooo	1357	1373	929
673217	GGTCTTTTCTTGTTAC	keke-d8-ekeke	sooooooooooooo	1358	1374	930
673218	AGGTCTTTTCTTGTTCA	keke-d8-ekeke	sooooooooooooo	1359	1375	931
673219	CAGGTCTTTTCTTGTT	keke-d8-ekeke	sooooooooooooo	1360	1376	932
673220	TCAGGTCTTTTCTTGTT	keke-d8-ekeke	sooooooooooooo	1361	1377	933
673221	ATCAGGTCTTTTCTTGT	keke-d8-ekeke	sooooooooooooo	1362	1378	934
673222	TATCAGGTCTTTTCTTG	keke-d8-ekeke	sooooooooooooo	1363	1379	935
673223	TTATCAGGTCTTTTCTT	keke-d8-ekeke	sooooooooooooo	1364	1380	936
673224	ATCTTTATCAGGTCTTT	keke-d8-ekeke	sooooooooooooo	1368	1384	937
673225	AATCTTTATCAGGTCTT	keke-d8-ekeke	sooooooooooooo	1369	1385	938
673226	TAATCTTTATCAGGTCT	keke-d8-ekeke	sooooooooooooo	1370	1386	939
673227	TTAATCTTTATCAGGTC	keke-d8-ekeke	sooooooooooooo	1371	1387	940
673228	GTAAATCTTTATCAGGT	keke-d8-ekeke	sooooooooooooo	1372	1388	941

673229	GGTTAATCTTTATCAGG	keke-d8-ekeke	sooooooooooooo	1373	1389	942
673230	TGGTTAATCTTTATCAG	keke-d8-ekeke	sooooooooooooo	1374	1390	943
673231	CTGGTTAATCTTTATCA	keke-d8-ekeke	sooooooooooooo	1375	1391	944
673232	TCTGGTTAATCTTTATC	keke-d8-ekeke	sooooooooooooo	1376	1392	945
673233	CCCTCCTTGTTTTCTTC	keke-d8-ekeke	sooooooooooooo	1391	1407	946
673234	TCCCTCCTTGTTTTCTT	keke-d8-ekeke	sooooooooooooo	1392	1408	947
673235	TTCCCTCCTTGTTTTCT	keke-d8-ekeke	sooooooooooooo	1393	1409	948
673236	TTTCCCTCCTTGTTTTCT	keke-d8-ekeke	sooooooooooooo	1394	1410	949
673237	GTTTCCCTCCTTGTTTT	keke-d8-ekeke	sooooooooooooo	1395	1411	950
673238	TGTTTCCCTCCTTGTTT	keke-d8-ekeke	sooooooooooooo	1396	1412	951
673239	TTGTTTCCCTCCTTGTT	keke-d8-ekeke	sooooooooooooo	1397	1413	952
673240	GGTTGTTTCCCTCCTTG	keke-d8-ekeke	sooooooooooooo	1399	1415	953
673241	CGGTTGTTTCCCTCCTT	keke-d8-ekeke	sooooooooooooo	1400	1416	954
673242	GCGGTTGTTTCCCTCCT	keke-d8-ekeke	sooooooooooooo	1401	1417	955
673243	TGCGGTTGTTTCCCTCC	keke-d8-ekeke	sooooooooooooo	1402	1418	956
673244	CTGCGGTTGTTTCCCTC	keke-d8-ekeke	sooooooooooooo	1403	1419	957
673245	GCTGCGGTTGTTTCCCT	keke-d8-ekeke	sooooooooooooo	1404	1420	958
673246	GGCTGCGGTTGTTTCCC	keke-d8-ekeke	sooooooooooooo	1405	1421	959
673247	AGGCTGCGGTTGTTTCC	keke-d8-ekeke	sooooooooooooo	1406	1422	960
673248	CAGGCTGCGGTTGTTTC	keke-d8-ekeke	sooooooooooooo	1407	1423	961
673249	ACAGGCTGCGGTTGTTT	keke-d8-ekeke	sooooooooooooo	1408	1424	962
673250	TACAGGCTGCGGTTGTT	keke-d8-ekeke	sooooooooooooo	1409	1425	963
673251	CTACAGGCTGCGGTTGT	keke-d8-ekeke	sooooooooooooo	1410	1426	964
673252	GCTACAGGCTGCGGTTG	keke-d8-ekeke	sooooooooooooo	1411	1427	965
673253	TGCTACAGGCTGCGGTT	keke-d8-ekeke	sooooooooooooo	1412	1428	966
673254	TTGCTACAGGCTGCGGT	keke-d8-ekeke	sooooooooooooo	1413	1429	967
673255	CTTGCTACAGGCTGCGG	keke-d8-ekeke	sooooooooooooo	1414	1430	968
673256	GCTTGCTACAGGCTGCG	keke-d8-ekeke	sooooooooooooo	1415	1431	969
673257	AGCTTGCTACAGGCTGC	keke-d8-ekeke	sooooooooooooo	1416	1432	970
673258	GAGCTTGCTACAGGCTG	keke-d8-ekeke	sooooooooooooo	1417	1433	971
673259	AGAGCTTGCTACAGGCT	keke-d8-ekeke	sooooooooooooo	1418	1434	972
673260	CAGAGCTTGCTACAGGC	keke-d8-ekeke	sooooooooooooo	1419	1435	973
673261	CCAGAGCTTGCTACAGG	keke-d8-ekeke	sooooooooooooo	1420	1436	974
673262	TCCAGAGCTTGCTACAG	keke-d8-ekeke	sooooooooooooo	1421	1437	975
673263	TTCCAGAGCTTGCTACA	keke-d8-ekeke	sooooooooooooo	1422	1438	976
673264	GTTCCAGAGCTTGCTAC	keke-d8-ekeke	sooooooooooooo	1423	1439	977
673265	AGTTCCAGAGCTTGCTA	keke-d8-ekeke	sooooooooooooo	1424	1440	978
673266	GAGTTCCAGAGCTTGCT	keke-d8-ekeke	sooooooooooooo	1425	1441	979
673267	TGAGTTCCAGAGCTTGC	keke-d8-ekeke	sooooooooooooo	1426	1442	980
673268	CTGAGTTCCAGAGCTTG	keke-d8-ekeke	sooooooooooooo	1427	1443	981
673269	CCTGAGTTCCAGAGCTT	keke-d8-ekeke	sooooooooooooo	1428	1444	982

673270	TCCTGAGTTCCAGAGCT	keke-d8-ekeke	sooooooooooooo	1429	1445	983
673271	CTCCTGAGTTCCAGAGC	keke-d8-ekeke	sooooooooooooo	1430	1446	984
673272	ACTCCTGAGTTCCAGAG	keke-d8-ekeke	sooooooooooooo	1431	1447	985
673273	GACTCCTGAGTTCCAGA	keke-d8-ekeke	sooooooooooooo	1432	1448	986
673274	CGACTCCTGAGTTCCAG	keke-d8-ekeke	sooooooooooooo	1433	1449	987
673275	GCGACTCCTGAGTTCCA	keke-d8-ekeke	sooooooooooooo	1434	1450	988
673276	CGCGACTCCTGAGTTCC	keke-d8-ekeke	sooooooooooooo	1435	1451	989
673277	GCGCGACTCCTGAGTTC	keke-d8-ekeke	sooooooooooooo	1436	1452	990
673278	CGCGCGACTCCTGAGTT	keke-d8-ekeke	sooooooooooooo	1437	1453	991
673279	GCGCGCGACTCCTGAGT	keke-d8-ekeke	sooooooooooooo	1438	1454	992
673280	AGCGCGCGACTCCTGAG	keke-d8-ekeke	sooooooooooooo	1439	1455	993
673281	TAGCGCGCGACTCCTGA	keke-d8-ekeke	sooooooooooooo	1440	1456	994
673282	CTAGCGCGCGACTCCTG	keke-d8-ekeke	sooooooooooooo	1441	1457	995
673283	CCTAGCGCGCGACTCCT	keke-d8-ekeke	sooooooooooooo	1442	1458	996
673284	CCCTAGCGCGCGACTCC	keke-d8-ekeke	sooooooooooooo	1443	1459	997
673285	CCCCTAGCGCGCGACTC	keke-d8-ekeke	sooooooooooooo	1444	1460	998
673286	GCCCCTAGCGCGCGACT	keke-d8-ekeke	sooooooooooooo	1445	1461	999
673287	GGCCCCTAGCGCGCGAC	keke-d8-ekeke	sooooooooooooo	1446	1462	1000
673288	CGGCCCCTAGCGCGCGA	keke-d8-ekeke	sooooooooooooo	1447	1463	1001
673289	CCGGCCCCTAGCGCGCG	keke-d8-ekeke	sooooooooooooo	1448	1464	1002
673290	CCCGGCCCCTAGCGCGC	keke-d8-ekeke	sooooooooooooo	1449	1465	1003
673291	CCCCGGCCCCTAGCGCG	keke-d8-ekeke	sooooooooooooo	1450	1466	1004
673292	GCCCCGGCCCCTAGCGC	keke-d8-ekeke	sooooooooooooo	1451	1467	1005
673293	GGCCCCGGCCCCTAGCG	keke-d8-ekeke	sooooooooooooo	1452	1468	1006
673294	CGGCCCCGGCCCCTAGC	keke-d8-ekeke	sooooooooooooo	1453	1469	1007
673295	CCGGCCCCGGCCCCTAG	keke-d8-ekeke	sooooooooooooo	1454	1470	1008
673296	CCCGGCCCCGGCCCCCTA	keke-d8-ekeke	sooooooooooooo	1455	1471	1009
673297	ACGCCCCGGCCCCGGCC	keke-d8-ekeke	sooooooooooooo	1465	1481	1010
673298	CACGCCCCGGCCCCGGC	keke-d8-ekeke	sooooooooooooo	1466	1482	1011
673299	CCACGCCCCGGCCCCGG	keke-d8-ekeke	sooooooooooooo	1467	1483	1012
673300	ACCACGCCCCGGCCCCG	keke-d8-ekeke	sooooooooooooo	1468	1484	1013
673301	GACCACGCCCCGGCCCC	keke-d8-ekeke	sooooooooooooo	1469	1485	1014
673302	CGACCACGCCCCGGCCC	keke-d8-ekeke	sooooooooooooo	1470	1486	1015
673303	CCGACCACGCCCCGGCC	keke-d8-ekeke	sooooooooooooo	1471	1487	1016
673304	CCCGACCACGCCCCGGC	keke-d8-ekeke	sooooooooooooo	1472	1488	1017
673305	CCCCGACCACGCCCCGG	keke-d8-ekeke	sooooooooooooo	1473	1489	1018
673306	GCCCCGACCACGCCCCG	keke-d8-ekeke	sooooooooooooo	1474	1490	1019
673307	CGCCCCGACCACGCCCC	keke-d8-ekeke	sooooooooooooo	1475	1491	1020
673308	CCGCCCCGACCACGCCC	keke-d8-ekeke	sooooooooooooo	1476	1492	1021
673309	CCCGCCCCGACCACGCC	keke-d8-ekeke	sooooooooooooo	1477	1493	1022
673310	GCCCGCCCCGACCACGC	keke-d8-ekeke	sooooooooooooo	1478	1494	1023

673311	GGCCCGCCCCGACCACG	keke-d8-ekeke	sooooooooooooo	1479	1495	1024
673312	GGGCCCCGCCCCGACCAC	keke-d8-ekeke	sooooooooooooo	1480	1496	1025
673313	CGGGCCCCGCCCCGACCA	keke-d8-ekeke	sooooooooooooo	1481	1497	1026
673314	CCGGGCCCCGCCCCGACC	keke-d8-ekeke	sooooooooooooo	1482	1498	1027
673315	CCCGGGCCCCGCCCCGAC	keke-d8-ekeke	sooooooooooooo	1483	1499	1028
673316	GCAGCCCCGCCCCGGGC	keke-d8-ekeke	sooooooooooooo	1505	1521	1029
673317	CGCAGCCCCGCCCCGGG	keke-d8-ekeke	sooooooooooooo	1506	1522	1030
673318	CCGCAGCCCCGCCCCGG	keke-d8-ekeke	sooooooooooooo	1507	1523	1031
673319	ACCGCAGCCCCGCCCCG	keke-d8-ekeke	sooooooooooooo	1508	1524	1032
673320	AACCGCAGCCCCGCCCC	keke-d8-ekeke	sooooooooooooo	1509	1525	1033
673321	CAACCGCAGCCCCGCC	keke-d8-ekeke	sooooooooooooo	1510	1526	1034
673322	GCAACCGCAGCCCCGCC	keke-d8-ekeke	sooooooooooooo	1511	1527	1035
673323	CGCAACCGCAGCCCCGC	keke-d8-ekeke	sooooooooooooo	1512	1528	1036
673324	CCGCAACCGCAGCCCCG	keke-d8-ekeke	sooooooooooooo	1513	1529	1037
673325	ACCGCAACCGCAGCCCC	keke-d8-ekeke	sooooooooooooo	1514	1530	1038
673326	CACCGCAACCGCAGCCC	keke-d8-ekeke	sooooooooooooo	1515	1531	1039
673327	GCACCGCAACCGCAGCC	keke-d8-ekeke	sooooooooooooo	1516	1532	1040
673328	GGCACCGCAACCGCAGC	keke-d8-ekeke	sooooooooooooo	1517	1533	1041
673329	AGGCACCGCAACCGCAG	keke-d8-ekeke	sooooooooooooo	1518	1534	1042
673330	CAGGCACCGCAACCGCA	keke-d8-ekeke	sooooooooooooo	1519	1535	1043
673331	GCAGGCACCGCAACCGC	keke-d8-ekeke	sooooooooooooo	1520	1536	1044
673332	CGCAGGCACCGCAACCG	keke-d8-ekeke	sooooooooooooo	1521	1537	1045
673333	GCGCAGGCACCGCAACC	keke-d8-ekeke	sooooooooooooo	1522	1538	1046
673334	GGCGCAGGCACCGCAAC	keke-d8-ekeke	sooooooooooooo	1523	1539	1047

Table 28

Deoxy, MOE and cEt oligonucleotides targeting SEQ ID NO: 2

ISIS NO	Sequence	Chemistry	Linkage	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
673335	TGAGAGCAAGTAGTGGG	ekek-d8-kekee	sooooooooooooo	1326	1342	898
673336	GTGAGAGCAAGTAGTGG	ekek-d8-kekee	sooooooooooooo	1327	1343	899
673337	TGTGAGAGCAAGTAGTG	ekek-d8-kekee	sooooooooooooo	1328	1344	900
673338	CTGTGAGAGCAAGTAGT	ekek-d8-kekee	sooooooooooooo	1329	1345	901
673339	ACTGTGAGAGCAAGTAG	ekek-d8-kekee	sooooooooooooo	1330	1346	902
673340	TACTGTGAGAGCAAGTA	ekek-d8-kekee	sooooooooooooo	1331	1347	903
673341	GTACTGTGAGAGCAAGT	ekek-d8-kekee	sooooooooooooo	1332	1348	904
673342	AGTACTGTGAGAGCAAG	ekek-d8-kekee	sooooooooooooo	1333	1349	905
673343	GAGTACTGTGAGAGCAA	ekek-d8-kekee	sooooooooooooo	1334	1350	906
673344	CGAGTACTGTGAGAGCA	ekek-d8-kekee	sooooooooooooo	1335	1351	907

673345	GCGAGTACTGTGAGAGC	ekek-d8-kekee	sooooooooooooo	1336	1352	908
673346	AGCGAGTACTGTGAGAG	ekek-d8-kekee	sooooooooooooo	1337	1353	909
673347	CAGCGAGTACTGTGAGA	ekek-d8-kekee	sooooooooooooo	1338	1354	910
673348	TCAGCGAGTACTGTGAG	ekek-d8-kekee	sooooooooooooo	1339	1355	911
673349	CTCAGCGAGTACTGTGA	ekek-d8-kekee	sooooooooooooo	1340	1356	912
673350	CCTCAGCGAGTACTGTG	ekek-d8-kekee	sooooooooooooo	1341	1357	913
673351	CCCTCAGCGAGTACTGT	ekek-d8-kekee	sooooooooooooo	1342	1358	914
673352	ACCCTCAGCGAGTACTG	ekek-d8-kekee	sooooooooooooo	1343	1359	915
673353	CACCCTCAGCGAGTACT	ekek-d8-kekee	sooooooooooooo	1344	1360	916
673354	TCACCCTCAGCGAGTAC	ekek-d8-kekee	sooooooooooooo	1345	1361	917
673355	TTCACCCTCAGCGAGTA	ekek-d8-kekee	sooooooooooooo	1346	1362	918
673356	GTTCACCCTCAGCGAGT	ekek-d8-kekee	sooooooooooooo	1347	1363	919
673357	TGTTACCCTCAGCGAG	ekek-d8-kekee	sooooooooooooo	1348	1364	920
673358	TTGTTACCCTCAGCGA	ekek-d8-kekee	sooooooooooooo	1349	1365	921
673359	CTTGTTACCCTCAGCG	ekek-d8-kekee	sooooooooooooo	1350	1366	922
673360	TCTTGTTACCCTCAGC	ekek-d8-kekee	sooooooooooooo	1351	1367	923
673361	TTCTTGTTACCCTCAG	ekek-d8-kekee	sooooooooooooo	1352	1368	924
673362	TTTCTTGTTACCCTCA	ekek-d8-kekee	sooooooooooooo	1353	1369	925
673363	TTTTCTTGTTACCCTC	ekek-d8-kekee	sooooooooooooo	1354	1370	926
673364	CTTTCTTGTTACCCT	ekek-d8-kekee	sooooooooooooo	1355	1371	927
673365	TCTTTCTTGTTACCC	ekek-d8-kekee	sooooooooooooo	1356	1372	928
673366	GTCTTTCTTGTTACC	ekek-d8-kekee	sooooooooooooo	1357	1373	929
673367	GGTCTTTCTTGTTAC	ekek-d8-kekee	sooooooooooooo	1358	1374	930
673368	AGGTCTTTCTTGTTCA	ekek-d8-kekee	sooooooooooooo	1359	1375	931
673369	CAGGTCTTTCTTGTT	ekek-d8-kekee	sooooooooooooo	1360	1376	932
673370	TCAGGTCTTTCTTGTT	ekek-d8-kekee	sooooooooooooo	1361	1377	933
673371	ATCAGGTCTTTCTTGT	ekek-d8-kekee	sooooooooooooo	1362	1378	934
673372	TATCAGGTCTTTCTTG	ekek-d8-kekee	sooooooooooooo	1363	1379	935
673373	TTATCAGGTCTTTCTT	ekek-d8-kekee	sooooooooooooo	1364	1380	936
673374	ATCTTATCAGGTCTTT	ekek-d8-kekee	sooooooooooooo	1368	1384	937
673375	AATCTTATCAGGTCTT	ekek-d8-kekee	sooooooooooooo	1369	1385	938
673376	TAATCTTATCAGGTCT	ekek-d8-kekee	sooooooooooooo	1370	1386	939
673377	TTAATCTTATCAGGTC	ekek-d8-kekee	sooooooooooooo	1371	1387	940
673378	GTTAATCTTATCAGGT	ekek-d8-kekee	sooooooooooooo	1372	1388	941
673379	GGTTAATCTTATCAGG	ekek-d8-kekee	sooooooooooooo	1373	1389	942
673380	TGGTTAATCTTATCAG	ekek-d8-kekee	sooooooooooooo	1374	1390	943
673381	CTGGTTAATCTTATCA	ekek-d8-kekee	sooooooooooooo	1375	1391	944
673382	TCTGGTTAATCTTATC	ekek-d8-kekee	sooooooooooooo	1376	1392	945
673383	CCCTCCTTGTTTCTTC	ekek-d8-kekee	sooooooooooooo	1391	1407	946
673384	TCCCTCCTTGTTTCTT	ekek-d8-kekee	sooooooooooooo	1392	1408	947
673385	TTCCCTCCTTGTTTCT	ekek-d8-kekee	sooooooooooooo	1393	1409	948

673386	TTTCCCTCCTTGTTTTTC	ekek-d8-kekee	sooooooooooooo	1394	1410	949
673387	GTTTCCCTCCTTGTTTT	ekek-d8-kekee	sooooooooooooo	1395	1411	950
673388	TGTTTCCCTCCTTGTTT	ekek-d8-kekee	sooooooooooooo	1396	1412	951
673389	TTGTTTCCCTCCTTGTT	ekek-d8-kekee	sooooooooooooo	1397	1413	952
673390	GGTTGTTTCCCTCCTTG	ekek-d8-kekee	sooooooooooooo	1399	1415	953
673391	CGGTTGTTTCCCTCCTT	ekek-d8-kekee	sooooooooooooo	1400	1416	954
673392	GCGGTTGTTTCCCTCCT	ekek-d8-kekee	sooooooooooooo	1401	1417	955
673393	TGCGGTTGTTTCCCTCC	ekek-d8-kekee	sooooooooooooo	1402	1418	956
673394	CTGCGGTTGTTTCCCTC	ekek-d8-kekee	sooooooooooooo	1403	1419	957
673395	GCTGCGGTTGTTTCCCT	ekek-d8-kekee	sooooooooooooo	1404	1420	958
673396	GGCTGCGGTTGTTTCCC	ekek-d8-kekee	sooooooooooooo	1405	1421	959
673397	AGGCTGCGGTTGTTTCC	ekek-d8-kekee	sooooooooooooo	1406	1422	960
673398	CAGGCTGCGGTTGTTTC	ekek-d8-kekee	sooooooooooooo	1407	1423	961
673399	ACAGGCTGCGGTTGTTT	ekek-d8-kekee	sooooooooooooo	1408	1424	962
673400	TACAGGCTGCGGTTGTT	ekek-d8-kekee	sooooooooooooo	1409	1425	963
673401	CTACAGGCTGCGGTTGT	ekek-d8-kekee	sooooooooooooo	1410	1426	964
673402	GCTACAGGCTGCGGTTG	ekek-d8-kekee	sooooooooooooo	1411	1427	965
673403	TGCTACAGGCTGCGGTT	ekek-d8-kekee	sooooooooooooo	1412	1428	966
673404	TTGCTACAGGCTGCGGT	ekek-d8-kekee	sooooooooooooo	1413	1429	967
673405	CTTGCTACAGGCTGCGG	ekek-d8-kekee	sooooooooooooo	1414	1430	968
673406	GCTTGCTACAGGCTGCG	ekek-d8-kekee	sooooooooooooo	1415	1431	969
673407	AGCTTGCTACAGGCTGC	ekek-d8-kekee	sooooooooooooo	1416	1432	970
673408	GAGCTTGCTACAGGCTG	ekek-d8-kekee	sooooooooooooo	1417	1433	971
673409	AGAGCTTGCTACAGGCT	ekek-d8-kekee	sooooooooooooo	1418	1434	972
673410	CAGAGCTTGCTACAGGC	ekek-d8-kekee	sooooooooooooo	1419	1435	973
673411	CCAGAGCTTGCTACAGG	ekek-d8-kekee	sooooooooooooo	1420	1436	974
673412	TCCAGAGCTTGCTACAG	ekek-d8-kekee	sooooooooooooo	1421	1437	975
673413	TTCCAGAGCTTGCTACA	ekek-d8-kekee	sooooooooooooo	1422	1438	976
673414	GTTCCAGAGCTTGCTAC	ekek-d8-kekee	sooooooooooooo	1423	1439	977
673415	AGTTCCAGAGCTTGCTA	ekek-d8-kekee	sooooooooooooo	1424	1440	978
673416	GAGTTCCAGAGCTTGCT	ekek-d8-kekee	sooooooooooooo	1425	1441	979
673417	TGAGTTCCAGAGCTTGCT	ekek-d8-kekee	sooooooooooooo	1426	1442	980
673418	CTGAGTTCCAGAGCTTG	ekek-d8-kekee	sooooooooooooo	1427	1443	981
673419	CCTGAGTTCCAGAGCTT	ekek-d8-kekee	sooooooooooooo	1428	1444	982
673420	TCCTGAGTTCCAGAGCT	ekek-d8-kekee	sooooooooooooo	1429	1445	983
673421	CTCCTGAGTTCCAGAGC	ekek-d8-kekee	sooooooooooooo	1430	1446	984
673422	ACTCCTGAGTTCCAGAG	ekek-d8-kekee	sooooooooooooo	1431	1447	985
673423	GA CTCTGAGTTCCAGA	ekek-d8-kekee	sooooooooooooo	1432	1448	986
673424	CGACTCCTGAGTTCCAG	ekek-d8-kekee	sooooooooooooo	1433	1449	987
673425	GCGACTCCTGAGTTCCA	ekek-d8-kekee	sooooooooooooo	1434	1450	988
673426	CGCGACTCCTGAGTTCC	ekek-d8-kekee	sooooooooooooo	1435	1451	989

673427	GCGCGACTCCTGAGTTC	ekek-d8-kekee	sooooooooooooo	1436	1452	990
673428	CGCGCGACTCCTGAGTT	ekek-d8-kekee	sooooooooooooo	1437	1453	991
673429	GCGCGCGACTCCTGAGT	ekek-d8-kekee	sooooooooooooo	1438	1454	992
673430	AGCGCGCGACTCCTGAG	ekek-d8-kekee	sooooooooooooo	1439	1455	993
673431	TAGCGCGCGACTCCTGA	ekek-d8-kekee	sooooooooooooo	1440	1456	994
673432	CTAGCGCGCGACTCCTG	ekek-d8-kekee	sooooooooooooo	1441	1457	995
673433	CCTAGCGCGCGACTCCT	ekek-d8-kekee	sooooooooooooo	1442	1458	996
673434	CCCTAGCGCGCGACTCC	ekek-d8-kekee	sooooooooooooo	1443	1459	997
673435	CCCCTAGCGCGCGACTC	ekek-d8-kekee	sooooooooooooo	1444	1460	998
673436	GCCCCTAGCGCGCGACT	ekek-d8-kekee	sooooooooooooo	1445	1461	999
673437	GGCCCCTAGCGCGCGAC	ekek-d8-kekee	sooooooooooooo	1446	1462	1000
673438	CGGCCCCTAGCGCGCGA	ekek-d8-kekee	sooooooooooooo	1447	1463	1001
673439	CCGGCCCCTAGCGCGCG	ekek-d8-kekee	sooooooooooooo	1448	1464	1002
673440	CCCGGCCCCTAGCGCGC	ekek-d8-kekee	sooooooooooooo	1449	1465	1003
673441	CCCCGGCCCCTAGCGCG	ekek-d8-kekee	sooooooooooooo	1450	1466	1004
673442	GCCCCGGCCCCTAGCGC	ekek-d8-kekee	sooooooooooooo	1451	1467	1005
673443	GGCCCCGGCCCCTAGCG	ekek-d8-kekee	sooooooooooooo	1452	1468	1006
673444	CGGCCCCGGCCCCTAGC	ekek-d8-kekee	sooooooooooooo	1453	1469	1007
673445	CCGGCCCCGGCCCCTAG	ekek-d8-kekee	sooooooooooooo	1454	1470	1008
673446	CCCGGCCCCGGCCCCTA	ekek-d8-kekee	sooooooooooooo	1455	1471	1009
673447	ACGCCCCGGCCCCGGCC	ekek-d8-kekee	sooooooooooooo	1465	1481	1010
673448	CACGCCCCGGCCCCGGC	ekek-d8-kekee	sooooooooooooo	1466	1482	1011
673449	CCACGCCCCGGCCCCGG	ekek-d8-kekee	sooooooooooooo	1467	1483	1012
673450	ACCACGCCCCGGCCCCG	ekek-d8-kekee	sooooooooooooo	1468	1484	1013
673451	GACCACGCCCCGGCCCC	ekek-d8-kekee	sooooooooooooo	1469	1485	1014
673452	CGACCACGCCCCGGCCC	ekek-d8-kekee	sooooooooooooo	1470	1486	1015
673453	CCGACCACGCCCCGGCC	ekek-d8-kekee	sooooooooooooo	1471	1487	1016
673454	CCCGACCACGCCCCGGC	ekek-d8-kekee	sooooooooooooo	1472	1488	1017
673455	CCCCGACCACGCCCCGG	ekek-d8-kekee	sooooooooooooo	1473	1489	1018
673456	GCCCCGACCACGCCCCG	ekek-d8-kekee	sooooooooooooo	1474	1490	1019
673457	CGCCCCGACCACGCCCC	ekek-d8-kekee	sooooooooooooo	1475	1491	1020
673458	CCGCCCCGACCACGCCC	ekek-d8-kekee	sooooooooooooo	1476	1492	1021
673459	CCCGCCCCGACCACGCC	ekek-d8-kekee	sooooooooooooo	1477	1493	1022
673460	GCCCGCCCCGACCACGC	ekek-d8-kekee	sooooooooooooo	1478	1494	1023
673461	GGCCCGCCCCGACCACG	ekek-d8-kekee	sooooooooooooo	1479	1495	1024
673462	GGGCCCGCCCCGACCAC	ekek-d8-kekee	sooooooooooooo	1480	1496	1025
673463	CGGGCCCGCCCCGACCA	ekek-d8-kekee	sooooooooooooo	1481	1497	1026
673464	CCGGCCCGCCCCGACC	ekek-d8-kekee	sooooooooooooo	1482	1498	1027
673465	CCCGGGCCCGCCCCGAC	ekek-d8-kekee	sooooooooooooo	1483	1499	1028
673466	GCAGCCCCGCCCCGGGC	ekek-d8-kekee	sooooooooooooo	1505	1521	1029
673467	CGCAGCCCCGCCCCGGG	ekek-d8-kekee	sooooooooooooo	1506	1522	1030

673468	CCGCAGCCCCGCCCCGG	ekek-d8-kekee	sooooooooooooo	1507	1523	1031
673469	ACCGCAGCCCCGCCCCG	ekek-d8-kekee	sooooooooooooo	1508	1524	1032
673470	AACCGCAGCCCCGCCCC	ekek-d8-kekee	sooooooooooooo	1509	1525	1033
673471	CAACCGCAGCCCCGCCC	ekek-d8-kekee	sooooooooooooo	1510	1526	1034
673472	GCAACCGCAGCCCCGCC	ekek-d8-kekee	sooooooooooooo	1511	1527	1035
673473	CGCAACCGCAGCCCCGC	ekek-d8-kekee	sooooooooooooo	1512	1528	1036
673474	CCGCAACCGCAGCCCCG	ekek-d8-kekee	sooooooooooooo	1513	1529	1037
673475	ACCGCAACCGCAGCCCC	ekek-d8-kekee	sooooooooooooo	1514	1530	1038
673476	CACCGCAACCGCAGCCC	ekek-d8-kekee	sooooooooooooo	1515	1531	1039
673477	GCACCGCAACCGCAGCC	ekek-d8-kekee	sooooooooooooo	1516	1532	1040
673478	GGACCGCAACCGCAGC	ekek-d8-kekee	sooooooooooooo	1517	1533	1041
673479	AGGACCGCAACCGCAG	ekek-d8-kekee	sooooooooooooo	1518	1534	1042
673480	CAGGACCGCAACCGCA	ekek-d8-kekee	sooooooooooooo	1519	1535	1043
673481	GCAGGACCGCAACCGC	ekek-d8-kekee	sooooooooooooo	1520	1536	1044
673482	CGCAGGACCGCAACCG	ekek-d8-kekee	sooooooooooooo	1521	1537	1045
673483	GCGCAGGACCGCAACC	ekek-d8-kekee	sooooooooooooo	1522	1538	1046
673484	GGCGCAGGACCGCAAC	ekek-d8-kekee	sooooooooooooo	1523	1539	1047

Table 29

5-10-5 MOE gapmers targeting SEQ ID NO: 2

ISIS NO	Sequence	Linkage	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
653222	CCACTCGCCACCGCCTGCGC	sooooooooooooo	1553	1572	1048
653223	TGCATTCTTAAGCAATGTGT	sooooooooooooo	5325	5344	1049
655016	CCCGGCCCGGCCCGGCC	sooooooooooooo	1458	1477	1050
655017	CCCCGGCCCCGGCCCCGCC	sooooooooooooo	1459	1478	1051
671081	TTACATCTATAGCACTC	sooooooooooooo	8110	8129	1052
671082	TCACTCCCTTTTCAGACAAG	sooooooooooooo	8140	8159	1053
671083	AACTAAGTTCTGTCTGTGA	sooooooooooooo	8230	8249	1054
671084	ATACAGGACTAAAGTGCTTC	sooooooooooooo	14316	14335	1055

5

Table 30

5-10-5 MOE gapmers targeting SEQ ID NO: 1

ISIS NO	Sequence	Linkage	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO
672561	CTCTGACCCTGATCTTCAT	sooooooooooooo	695	714	1056

Example 7: In vivo rodent inhibition and tolerability with treatment of C9ORF72 antisense oligonucleotides

In order to assess the tolerability of inhibition of C9ORF72 expression *in vivo*, antisense oligonucleotides targeting a murine C9ORF72 nucleic acid were designed and assessed in mouse and rat models.

ISIS 571883 was designed as a 5-10-5 MOE gapmer, 20 nucleosides in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both the 5' end and on the 3' end comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a MOE modification. The internucleoside linkages are phosphorothioate linkages. All cytosine residues throughout the gapmer are 5-methylcytosines. ISIS 571883 has a target start site of nucleoside 33704 on the murine C9ORF72 genomic sequence, designated herein as SEQ ID NO: 11 (the complement of GENBANK Accession No. NT_166289.1 truncated from nucleosides 3587000 to 3625000).

ISIS 603538 was designed as a 5-10-5 MOE gapmer, 20 nucleosides in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both the 5' end and on the 3' end comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a MOE modification. The internucleoside linkages are either phosphorothioate linkages or phosphate ester linkages (Gs Ao Co Co Gs Cs Ts Ts Gs As Gs Ts Ts Ts Gs Co Co Ao Cs A; wherein 's' denotes a phosphorothioate internucleoside linkage, 'o' denotes a phosphate ester linkage; and A, G, C, T denote the relevant nucleosides). All cytosine residues throughout the gapmer are 5-methylcytosines. ISIS 603538 has a target start site of nucleoside 2872 on the rat C9ORF72 mRNA sequence, designated herein as SEQ ID NO: 12 (GENBANK Accession No. NM_001007702.1).

Mouse experiment 1

Groups of 4 C57BL/6 mice each were injected with 50 µg, 100 µg, 300 µg, 500 µg, or 700 µg of ISIS 571883 administered via an intracerebroventricular bolus injection. A control group of four C57/BL6 mice were similarly treated with PBS. Animals were anesthetized with 3% isoflurane and placed in a stereotactic frame. After sterilizing the surgical site, each mouse was injected -0.2 mm antero-posterior from the bregma and 3 mm dorsoventral to the bregma with the above-mentioned doses of ISIS 571883 using a Hamilton syringe. The incision was closed with sutures. The mice were allowed to recover for 14 days, after which animals were euthanized according to a humane protocol approved by the Institutional Animal Care and Use Committee. Brain and spinal cord tissue were harvested and snap frozen in liquid nitrogen. Prior to freezing, brain tissue was cut transversely five sections using a mouse brain matrix.

RNA analysis

RNA was extracted from a 2-3 mm brain section posterior to the injection site, from brain frontal cortex and from the lumbar section of the spinal cord tissue for analysis of C9ORF72 mRNA expression. C9ORF72 mRNA expression was measured by RT-PCR. The data is presented in Table 31. The results indicate that treatment with increasing doses of ISIS 571883 resulted in dose-dependent inhibition of C9ORF72 mRNA expression.

The induction of the microglial marker AIF-1 as a measure of CNS toxicity was also assessed. The data is presented in Table 32. The results indicate that treatment with increasing doses of ISIS 571883 did not result in significant increases in AIF-1 mRNA expression. Hence, the injection of ISIS 571883 was deemed tolerable in this model.

Table 31

Percentage inhibition of C9ORF72 mRNA expression compared to the PBS control

Dose (μ g)	Posterior brain	Cortex	Spinal cord
50	22	8	46
100	22	12	47
300	55	47	67
500	61	56	78
700	65	65	79

Table 32

Percentage expression of AIF-1 mRNA expression compared to the PBS control

Dose (μ g)	Posterior brain	Spinal cord
50	102	89
100	105	111
300	107	98
500	131	124
700	122	116

Mouse experiment 2

Groups of 4 C57BL/6 mice each were injected with 500 μ g of ISIS 571883 administered via an intracerebroventricular bolus injection in a procedure similar to that described above. A control group of four C57/BL6 mice were similarly treated with PBS. The mice were tested at regular time points after ICV administration.

Behavior analysis

Two standard assays to assess motor behavior were employed; the rotarod assay and grip strength assay. In case of the rotarod assays, the time of latency to fall was measured. The data for the assays is presented in Tables 33 and 34. The results indicate that there were no significant changes in the motor

behavior of the mice as a result of antisense inhibition of ISIS 571883 or due to the ICV injection. Hence, antisense inhibition of C9ORF72 was deemed tolerable in this model.

Table 33**Latency to fall (sec) in the rotarod assay**

Weeks after injection	PBS	ISIS 571883
0	66	66
4	91	70
8	94	84

5

Table 34**Mean hindlimb grip strength (g) in the grip strength assay**

Weeks after injection	PBS	ISIS 571883
0	57	63
1	65	51
2	51	52
3	51	51
4	59	72
5	60	64
6	61	72
7	67	68
8	66	70
9	63	61
10	48	46

Rat experiment

10 Groups of 4 Sprague-Dawley rats each were injected with 700 µg, 1,000 µg, or 3,000 µg of ISIS 603538 administered via an intrathecal bolus injection. A control group of four Sprague-Dawley rats were similarly treated with PBS. Animals were anesthetized with 3% isoflurane and placed in a stereotactic frame. After sterilizing the surgical site, each rat was injected with 30 µL of ASO solution administered via 8 cm intrathecal catheter 2 cm into the spinal canal with a 50 µL flush. The rats were allowed to recover for 4 weeks, after which animals were euthanized according to a humane protocol approved by the Institutional Animal Care and Use Committee.

RNA analysis

20 RNA was extracted from a 2-3 mm brain section posterior to the injection stie, from brain frontal cortex, and from the cervical and lumbar sections of the spinal cord tissue for analysis of C9ORF72 mRNA expression. C9ORF72 mRNA expression was measured by RT-PCR. The data is presented in Table 35. The results indicate that treatment with increasing doses of ISIS 603538 resulted in dose-dependent inhibition of C9ORF72 mRNA expression.

The induction of the microglial marker AIF-1 as a measure of CNS toxicity was also assessed. The data is presented in Table 36. The results indicate that treatment with increasing doses of ISIS 603538 did not result in significant increases in AIF-1 mRNA expression. Hence, the injection of ISIS 603538 was deemed tolerable in this model.

5

Table 35

Percentage inhibition of C9ORF72 mRNA expression compared to the PBS control

Dose (μg)	Brain (1 mm section)	Cortex	Spinal cord (lumbar)	Spinal cord (cervical)
700	21	4	86	74
1000	53	49	88	82
3000	64	62	88	80

Table 36

Percentage expression of AIF-1 mRNA expression compared to the PBS control

Dose (μg)	Brain (1 mm section)	Cortex	Spinal cord (lumbar)	Spinal cord (cervical)
700	97	119	98	89
1000	105	113	122	96
3000	109	141	156	115

10

Body weight analysis

Body weights of the rats were measured at regular time point intervals. The data is presented in Table 37. The results indicate that treatment with increasing doses of ISIS 603538 did not have any significant changes in the body weights of the rats.

15

Table 37

Body weights of the rats (% initial body weight)

	Dose (μg)	Week 1	Week 2	Week 3	Week 4	Week 5
PBS		100	94	103	105	109
ISIS 603538	700	100	94	98	103	107
	1000	100	95	97	101	103
	3000	100	92	98	102	105

Example 8: Antisense inhibition of C9ORF72 by 5-8-5 MOE gapmers with mixed backbones and Deoxy, MOE and cEt antisense oligonucleotides with mixed backbones

20

Antisense oligonucleotides described in Example 6 hereinabove (see Table 23 and Table 24 hereinabove) were tested in HepG2 cells in a series of experiments that had similar culture conditions. ISIS 576816, previously tested in PCT/US2013/065073 (claiming priority to US Application No. 61/714,132, filed October 15, 2012, was used as a benchmark oligonucleotide for study with deoxy, MOE, and cEt antisense

oligonucleotides. The results for each experiment are presented in tables shown below. Cultured HepG2 cells at a density of 20,000 cells per well were transfected using electroporation with 500 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3905 was used to measure the C9ORF72 pathogenic associated mRNA variant, which is the product of a pre-mRNA containing a hexanucleotide repeat. The levels of the C9ORF72 pathogenic associated mRNA variant were normalized to the total RNA content of the cell, as measured by RIBOGREEN®. Results are presented as percent inhibition of C9ORF72, relative to untreated control cells.

Table 38

Percent inhibition of the C9ORF72 pathogenic associated mRNA variant compared to PBS control by 5-8-5 MOE gapmers with mixed backbones targeting SEQ ID NO: 2

ISIS NO	Sequence	Linkage	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	% inhibition	SEQ ID NO
672581	GTGAGAGCAAGTAGTGGG	sooooooooooooo	1326	1343	11	744
672582	TGTGAGAGCAAGTAGTGG	sooooooooooooo	1327	1344	32	745
672583	CTGTGAGAGCAAGTAGTG	sooooooooooooo	1328	1345	14	746
672584	ACTGTGAGAGCAAGTAGT	sooooooooooooo	1329	1346	1	747
672585	TACTGTGAGAGCAAGTAG	sooooooooooooo	1330	1347	14	748
672586	GTACTGTGAGAGCAAGTA	sooooooooooooo	1331	1348	22	749
672587	AGTACTGTGAGAGCAAGT	sooooooooooooo	1332	1349	0	750
672588	GAGTACTGTGAGAGCAAG	sooooooooooooo	1333	1350	8	751
672589	CGAGTACTGTGAGAGCAA	sooooooooooooo	1334	1351	15	752
672590	GCGAGTACTGTGAGAGCA	sooooooooooooo	1335	1352	13	753
672591	AGCGAGTACTGTGAGAGC	sooooooooooooo	1336	1353	32	754
672592	CAGCGAGTACTGTGAGAG	sooooooooooooo	1337	1354	39	755
672593	TCAGCGAGTACTGTGAGA	sooooooooooooo	1338	1355	15	756
672594	CTCAGCGAGTACTGTGAG	sooooooooooooo	1339	1356	14	757
672595	CCTCAGCGAGTACTGTGA	sooooooooooooo	1340	1357	40	758
672596	CCCTCAGCGAGTACTGTG	sooooooooooooo	1341	1358	28	759
672597	ACCCTCAGCGAGTACTGT	sooooooooooooo	1342	1359	30	760
672598	CACCCTCAGCGAGTACTG	sooooooooooooo	1343	1360	46	761
672599	TCACCCTCAGCGAGTACT	sooooooooooooo	1344	1361	40	762
672600	TTCACCCTCAGCGAGTAC	sooooooooooooo	1345	1362	25	763
672601	GTTCACCCTCAGCGAGTA	sooooooooooooo	1346	1363	15	764
672602	TGTTACCCTCAGCGAGT	sooooooooooooo	1347	1364	35	765
672603	TTGTTACCCTCAGCGAG	sooooooooooooo	1348	1365	22	766
672604	CTTGTTACCCTCAGCGA	sooooooooooooo	1349	1366	6	767
672605	TCTTGTTACCCTCAGCG	sooooooooooooo	1350	1367	26	768

672606	TTCTTGTTACCCCTCAGC	sooooooooooooo	1351	1368	11	769
672607	TTTCTTGTTACCCCTCAG	sooooooooooooo	1352	1369	9	770
672608	TTTTCTTGTTACCCCTCA	sooooooooooooo	1353	1370	36	771
672609	CTTTTCTTGTTACCCCTC	sooooooooooooo	1354	1371	25	772
672610	TCTTTTCTTGTTACCCCT	sooooooooooooo	1355	1372	16	773
672611	GTCTTTTCTTGTTACCC	sooooooooooooo	1356	1373	45	774
672612	GGTCTTTTCTTGTTACCC	sooooooooooooo	1357	1374	15	775
672613	AGGTCTTTTCTTGTTAC	sooooooooooooo	1358	1375	10	776
672614	CAGGTCTTTTCTTGTTCA	sooooooooooooo	1359	1376	25	777
672615	TCAGGTCTTTTCTTGTT	sooooooooooooo	1360	1377	21	778
672616	ATCAGGTCTTTTCTTGTT	sooooooooooooo	1361	1378	15	779
672617	TATCAGGTCTTTTCTTGT	sooooooooooooo	1362	1379	27	780
672618	TTATCAGGTCTTTTCTTG	sooooooooooooo	1363	1380	14	781
672619	TTTATCAGGTCTTTTCTT	sooooooooooooo	1364	1381	46	782
672620	AATCTTTATCAGGTCTTT	sooooooooooooo	1368	1385	31	783
672621	TAATCTTTATCAGGTCTT	sooooooooooooo	1369	1386	12	784
672622	TTAATCTTTATCAGGTCT	sooooooooooooo	1370	1387	27	785
672623	GTTAATCTTTATCAGGTC	sooooooooooooo	1371	1388	9	786
672624	GGTTAATCTTTATCAGGT	sooooooooooooo	1372	1389	53	787
672625	TGGTTAATCTTTATCAGG	sooooooooooooo	1373	1390	17	788
672626	CTGGTTAATCTTTATCAG	sooooooooooooo	1374	1391	11	789
672627	TCTGGTTAATCTTTATCA	sooooooooooooo	1375	1392	16	790
672628	TTCTGGTTAATCTTTATC	sooooooooooooo	1376	1393	22	791
672629	TCCCTCCTTGTTTTCTTC	sooooooooooooo	1391	1408	0	792
672630	TTTCCCTCCTTGTTTTCT	sooooooooooooo	1393	1410	8	793
672631	GTTTCCCTCCTTGTTTTTC	sooooooooooooo	1394	1411	0	794
672632	TGTTTCCCTCCTTGTTTT	sooooooooooooo	1395	1412	25	795
672633	TTGTTTCCCTCCTTGTTT	sooooooooooooo	1396	1413	0	796
672634	GTTGTTTCCCTCCTTGTT	sooooooooooooo	1397	1414	10	797
672635	GGTTGTTTCCCTCCTTG	sooooooooooooo	1398	1415	15	798
672636	CGGTTGTTTCCCTCCTTG	sooooooooooooo	1399	1416	49	799
672637	GCGGTTGTTTCCCTCCTT	sooooooooooooo	1400	1417	49	800
672638	TGCGGTTGTTTCCCTCCT	sooooooooooooo	1401	1418	23	801
672639	CTGCGGTTGTTTCCCTCC	sooooooooooooo	1402	1419	21	802
672640	GCTGCGGTTGTTTCCCTC	sooooooooooooo	1403	1420	52	803
672641	GGCTGCGGTTGTTTCCCT	sooooooooooooo	1404	1421	23	804
672642	AGGCTGCGGTTGTTTCCC	sooooooooooooo	1405	1422	35	805
672643	CAGGCTGCGGTTGTTTCC	sooooooooooooo	1406	1423	22	806
672644	ACAGGCTGCGGTTGTTTC	sooooooooooooo	1407	1424	27	807
672645	TACAGGCTGCGGTTGTTT	sooooooooooooo	1408	1425	21	808
672646	CTACAGGCTGCGGTTGTT	sooooooooooooo	1409	1426	18	809

672647	GCTACAGGCTGCGGTTGT	soooSSSSSSSSsooss	1410	1427	16	810
672648	TGCTACAGGCTGCGGTTG	soooSSSSSSSSsooss	1411	1428	10	811
672649	TTGCTACAGGCTGCGGTT	soooSSSSSSSSsooss	1412	1429	0	812
672650	CTTGCTACAGGCTGCGGT	soooSSSSSSSSsooss	1413	1430	27	813
672651	GCTTGCTACAGGCTGCGG	soooSSSSSSSSsooss	1414	1431	53	814
672652	AGCTTGCTACAGGCTGCG	soooSSSSSSSSsooss	1415	1432	38	815
672653	GAGCTTGCTACAGGCTGC	soooSSSSSSSSsooss	1416	1433	7	816
672654	AGAGCTTGCTACAGGCTG	soooSSSSSSSSsooss	1417	1434	7	817
672655	CAGAGCTTGCTACAGGCT	soooSSSSSSSSsooss	1418	1435	15	818
672656	CCAGAGCTTGCTACAGGC	soooSSSSSSSSsooss	1419	1436	22	819
672657	TCCAGAGCTTGCTACAGG	soooSSSSSSSSsooss	1420	1437	43	820
672658	TTCCAGAGCTTGCTACAG	soooSSSSSSSSsooss	1421	1438	20	821
672659	GTTCCAGAGCTTGCTACA	soooSSSSSSSSsooss	1422	1439	12	822
672660	AGTTCCAGAGCTTGCTAC	soooSSSSSSSSsooss	1423	1440	11	823
672661	GAGTTCCAGAGCTTGCTA	soooSSSSSSSSsooss	1424	1441	39	824
672662	TGAGTTCCAGAGCTTGCT	soooSSSSSSSSsooss	1425	1442	18	825
672663	CTGAGTTCCAGAGCTTGC	soooSSSSSSSSsooss	1426	1443	26	826
672664	CCTGAGTTCCAGAGCTTG	soooSSSSSSSSsooss	1427	1444	69	827
672665	TCCTGAGTTCCAGAGCTT	soooSSSSSSSSsooss	1428	1445	56	828
672666	CTCCTGAGTTCCAGAGCT	soooSSSSSSSSsooss	1429	1446	28	829
672667	ACTCCTGAGTTCCAGAGC	soooSSSSSSSSsooss	1430	1447	51	830
672668	GACTCCTGAGTTCCAGAG	soooSSSSSSSSsooss	1431	1448	39	831
672669	CGACTCCTGAGTTCCAGA	soooSSSSSSSSsooss	1432	1449	32	832
672670	GCGACTCCTGAGTTCCAG	soooSSSSSSSSsooss	1433	1450	66	833
672671	CGCGACTCCTGAGTTCCA	soooSSSSSSSSsooss	1434	1451	67	834
672672	GCGCGACTCCTGAGTTCC	soooSSSSSSSSsooss	1435	1452	48	835
672673	CGCGCGACTCCTGAGTTC	soooSSSSSSSSsooss	1436	1453	38	836
672674	GCGCGCGACTCCTGAGTT	soooSSSSSSSSsooss	1437	1454	53	837
672675	AGCGCGCGACTCCTGAGT	soooSSSSSSSSsooss	1438	1455	58	838
672676	TAGCGCGCGACTCCTGAG	soooSSSSSSSSsooss	1439	1456	55	839
672677	CTAGCGCGCGACTCCTGA	soooSSSSSSSSsooss	1440	1457	47	840
672678	CCTAGCGCGCGACTCCTG	soooSSSSSSSSsooss	1441	1458	56	841
672679	CCCTAGCGCGCGACTCCT	soooSSSSSSSSsooss	1442	1459	74	842
672680	CCCCTAGCGCGCGACTCC	soooSSSSSSSSsooss	1443	1460	43	843
672681	GCCCCTAGCGCGCGACTC	soooSSSSSSSSsooss	1444	1461	53	844
672682	GGCCCCCTAGCGCGCGACT	soooSSSSSSSSsooss	1445	1462	42	845
672683	CGGCCCCCTAGCGCGCGAC	soooSSSSSSSSsooss	1446	1463	69	846
672684	CCGGCCCCCTAGCGCGCGA	soooSSSSSSSSsooss	1447	1464	29	847
672685	CCCGCCCCCTAGCGCGCG	soooSSSSSSSSsooss	1448	1465	21	848
672686	CCCCGCCCCCTAGCGCGC	soooSSSSSSSSsooss	1449	1466	35	849
672687	GCCCCGGCCCCCTAGCGCG	soooSSSSSSSSsooss	1450	1467	41	850

672688	GGCCCCGGCCCCTAGCGC	sooooooooooooo	1451	1468	46	851
672689	CGGCCCCGGCCCCTAGCG	sooooooooooooo	1452	1469	28	852
672690	CCGGCCCCGGCCCCTAGC	sooooooooooooo	1453	1470	33	853
672691	CCCGGCCCCGGCCCCTAG	sooooooooooooo	1454	1471	10	854
672692	CCCCGGCCCCGGCCCCTA	sooooooooooooo	1455	1472	35	855
672693	ACGCCCCGGCCCCGGCCC	sooooooooooooo	1464	1481	57	856
672694	CACGCCCCGGCCCCGGCC	sooooooooooooo	1465	1482	39	857
672695	CCACGCCCCGGCCCCGGC	sooooooooooooo	1466	1483	48	858
672696	ACCACGCCCCGGCCCCGG	sooooooooooooo	1467	1484	39	859
672697	GACCACGCCCCGGCCCCG	sooooooooooooo	1468	1485	54	860
672698	CGACCACGCCCCGGCCCC	sooooooooooooo	1469	1486	48	861
672699	CCGACCACGCCCCGGCCC	sooooooooooooo	1470	1487	52	862
672700	CCCGACCACGCCCCGGCC	sooooooooooooo	1471	1488	67	863
672701	CCCCGACCACGCCCCGGC	sooooooooooooo	1472	1489	42	864
672702	GCCCCGACCACGCCCCGG	sooooooooooooo	1473	1490	11	865
672703	CGCCCCGACCACGCCCCG	sooooooooooooo	1474	1491	23	866
672704	CCGCCCCGACCACGCCCC	sooooooooooooo	1475	1492	50	867
672705	CCCGCCCCGACCACGCCC	sooooooooooooo	1476	1493	23	868
672706	GCCCGCCCCGACCACGCC	sooooooooooooo	1477	1494	24	869
672707	GGCCCGCCCCGACCACGC	sooooooooooooo	1478	1495	44	870
672708	GGGCCCGCCCCGACCACG	sooooooooooooo	1479	1496	29	871
672709	CGGGCCCGCCCCGACCAC	sooooooooooooo	1480	1497	7	872
672710	CCGGGCCCGCCCCGACCA	sooooooooooooo	1481	1498	30	873
672711	CCCGGGCCCGCCCCGACC	sooooooooooooo	1482	1499	16	874
672712	CCCCGGGCCCGCCCCGAC	sooooooooooooo	1483	1500	14	875
672713	AGCCCCGCCCGGGCCCG	sooooooooooooo	1502	1519	32	876
672714	CAGCCCCGCCCGGGGCC	sooooooooooooo	1503	1520	22	877
672715	GCAGCCCCGCCCGGGCC	sooooooooooooo	1504	1521	1	878
672716	CGCAGCCCCGCCCGGGC	sooooooooooooo	1505	1522	29	879
672717	CCGCAGCCCCGCCCGGG	sooooooooooooo	1506	1523	51	880
672718	ACCGCAGCCCCGCCCGG	sooooooooooooo	1507	1524	45	881
672719	AACCGCAGCCCCGCCCG	sooooooooooooo	1508	1525	12	882
672720	CAACCGCAGCCCCGCCCC	sooooooooooooo	1509	1526	7	883
672721	GCAACCGCAGCCCCGCC	sooooooooooooo	1510	1527	38	884
672722	CGCAACCGCAGCCCCGCC	sooooooooooooo	1511	1528	34	885
672723	CCGCAACCGCAGCCCCGC	sooooooooooooo	1512	1529	58	886
672724	ACCGCAACCGCAGCCCCG	sooooooooooooo	1513	1530	39	887
672725	CACCGCAACCGCAGCCCC	sooooooooooooo	1514	1531	43	888
672726	GCACCGCAACCGCAGCCC	sooooooooooooo	1515	1532	41	889
672727	GGCACCGCAACCGCAGCC	sooooooooooooo	1516	1533	18	890
672728	AGGCACCGCAACCGCAGC	sooooooooooooo	1517	1534	53	891

672729	CAGGCACCGCAACCGCAG	sooooooooooooo	1518	1535	26	892
672730	GCAGGCACCGCAACCGCA	sooooooooooooo	1519	1536	54	893
672731	CGCAGGCACCGCAACCGC	sooooooooooooo	1520	1537	41	894
672732	GCGCAGGCACCGCAACCG	sooooooooooooo	1521	1538	46	895
672733	GGCGCAGGCACCGCAACC	sooooooooooooo	1522	1539	7	896
672734	GGGCGCAGGCACCGCAAC	sooooooooooooo	1523	1540	26	897

Table 39

Percent inhibition of the C9ORF72 pathogenic associated mRNA variant compared to PBS control by Deoxy, MOE and cEt antisense oligonucleotides with mixed backbones targeting SEQ ID NO: 2

ISIS NO	Sequence	Chemistry	Linkage	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	% inhibition	SEQ ID NO
576816	GCCTTACTCTAGGACCAAGA	eeee-d10-eeee	ssssssssssssssss	7990	8009	71	20
672735	TGAGAGCAAGTAGTGGG	eeekk-d7-kkee	sooooooooooooo	1326	1342	5	898
672736	GTGAGAGCAAGTAGTGG	eeekk-d7-kkee	sooooooooooooo	1327	1343	35	899
672737	TGTGAGAGCAAGTAGTG	eeekk-d7-kkee	sooooooooooooo	1328	1344	0	900
672738	CTGTGAGAGCAAGTAGT	eeekk-d7-kkee	sooooooooooooo	1329	1345	63	901
672739	ACTGTGAGAGCAAGTAG	eeekk-d7-kkee	sooooooooooooo	1330	1346	0	902
672740	TACTGTGAGAGCAAGTA	eeekk-d7-kkee	sooooooooooooo	1331	1347	65	903
672741	GTACTGTGAGAGCAAGT	eeekk-d7-kkee	sooooooooooooo	1332	1348	13	904
672742	AGTACTGTGAGAGCAAG	eeekk-d7-kkee	sooooooooooooo	1333	1349	46	905
672743	GAGTACTGTGAGAGCAA	eeekk-d7-kkee	sooooooooooooo	1334	1350	55	906
672744	CGAGTACTGTGAGAGCA	eeekk-d7-kkee	sooooooooooooo	1335	1351	76	907
672745	GCGAGTACTGTGAGAGC	eeekk-d7-kkee	sooooooooooooo	1336	1352	11	908
672746	AGCGAGTACTGTGAGAG	eeekk-d7-kkee	sooooooooooooo	1337	1353	11	909
672747	CAGCGAGTACTGTGAGA	eeekk-d7-kkee	sooooooooooooo	1338	1354	51	910
672748	TCAGCGAGTACTGTGAG	eeekk-d7-kkee	sooooooooooooo	1339	1355	20	911
672749	CTCAGCGAGTACTGTGA	eeekk-d7-kkee	sooooooooooooo	1340	1356	12	912
672750	CCTCAGCGAGTACTGTG	eeekk-d7-kkee	sooooooooooooo	1341	1357	2	913
672751	CCCTCAGCGAGTACTGT	eeekk-d7-kkee	sooooooooooooo	1342	1358	39	914
672752	ACCCTCAGCGAGTACTG	eeekk-d7-kkee	sooooooooooooo	1343	1359	27	915
672753	CACCCTCAGCGAGTACT	eeekk-d7-kkee	sooooooooooooo	1344	1360	33	916
672754	TCACCCTCAGCGAGTAC	eeekk-d7-kkee	sooooooooooooo	1345	1361	0	917
672755	TTCACCCTCAGCGAGTA	eeekk-d7-kkee	sooooooooooooo	1346	1362	13	918
672756	GTTCACCCTCAGCGAGT	eeekk-d7-kkee	sooooooooooooo	1347	1363	45	919
672757	TGTTACCCTCAGCGAG	eeekk-d7-kkee	sooooooooooooo	1348	1364	11	920
672758	TTGTTACCCTCAGCGA	eeekk-d7-kkee	sooooooooooooo	1349	1365	0	921
672759	CTTGTTACCCTCAGCG	eeekk-d7-kkee	sooooooooooooo	1350	1366	12	922
672760	TCTTGTTACCCTCAGC	eeekk-d7-kkee	sooooooooooooo	1351	1367	21	923

672761	TTCTTGTTACCCCTCAG	eeekk-d7-kkeee	sooooooooooooo	1352	1368	0	924
672762	TTTCTTGTTACCCCTCA	eeekk-d7-kkeee	sooooooooooooo	1353	1369	34	925
672763	TTTTCTTGTTACCCCTC	eeekk-d7-kkeee	sooooooooooooo	1354	1370	16	926
672764	CTTTTCTTGTTACCCCT	eeekk-d7-kkeee	sooooooooooooo	1355	1371	2	927
672765	TCTTTTCTTGTTACCCC	eeekk-d7-kkeee	sooooooooooooo	1356	1372	24	928
672766	GTCTTTTCTTGTTACCC	eeekk-d7-kkeee	sooooooooooooo	1357	1373	28	929
672767	GGTCTTTTCTTGTTAC	eeekk-d7-kkeee	sooooooooooooo	1358	1374	30	930
672768	AGGTCTTTTCTTGTTCA	eeekk-d7-kkeee	sooooooooooooo	1359	1375	14	931
672769	CAGGTCTTTTCTTGTTT	eeekk-d7-kkeee	sooooooooooooo	1360	1376	20	932
672770	TCAGGTCTTTTCTTGTT	eeekk-d7-kkeee	sooooooooooooo	1361	1377	2	933
672771	ATCAGGTCTTTTCTTG	eeekk-d7-kkeee	sooooooooooooo	1362	1378	0	934
672772	TATCAGGTCTTTTCTTG	eeekk-d7-kkeee	sooooooooooooo	1363	1379	23	935
672773	TTATCAGGTCTTTTCTT	eeekk-d7-kkeee	sooooooooooooo	1364	1380	39	936
672774	ATCTTTATCAGGTCTTT	eeekk-d7-kkeee	sooooooooooooo	1368	1384	92	937
672775	AATCTTTATCAGGTCTT	eeekk-d7-kkeee	sooooooooooooo	1369	1385	61	938
672776	TAATCTTTATCAGGTCT	eeekk-d7-kkeee	sooooooooooooo	1370	1386	2	939
672777	TTAATCTTTATCAGGTC	eeekk-d7-kkeee	sooooooooooooo	1371	1387	33	940
672778	GTTAATCTTTATCAGGT	eeekk-d7-kkeee	sooooooooooooo	1372	1388	53	941
672779	GGTTAATCTTTATCAGG	eeekk-d7-kkeee	sooooooooooooo	1373	1389	40	942
672780	TGGTTAATCTTTATCAG	eeekk-d7-kkeee	sooooooooooooo	1374	1390	26	943
672781	CTGGTTAATCTTTATCA	eeekk-d7-kkeee	sooooooooooooo	1375	1391	25	944
672782	TCTGGTTAATCTTTATC	eeekk-d7-kkeee	sooooooooooooo	1376	1392	44	945
672783	CCCTCCTTGTTTTCTTC	eeekk-d7-kkeee	sooooooooooooo	1391	1407	37	946
672784	TCCCTCCTTGTTTTCTT	eeekk-d7-kkeee	sooooooooooooo	1392	1408	10	947
672785	TTCCCTCCTTGTTTTCT	eeekk-d7-kkeee	sooooooooooooo	1393	1409	0	948
672786	TTTCCCTCCTTGTTTTC	eeekk-d7-kkeee	sooooooooooooo	1394	1410	0	949
672787	GTTTCCCTCCTTGTTTT	eeekk-d7-kkeee	sooooooooooooo	1395	1411	0	950
672788	TGTTTCCCTCCTTGTTT	eeekk-d7-kkeee	sooooooooooooo	1396	1412	0	951
672789	TTGTTTCCCTCCTTGTT	eeekk-d7-kkeee	sooooooooooooo	1397	1413	0	952
672790	GGTTGTTTCCCTCCTTG	eeekk-d7-kkeee	sooooooooooooo	1399	1415	33	953
672791	CGGTTGTTTCCCTCCTT	eeekk-d7-kkeee	sooooooooooooo	1400	1416	0	954
672792	GCGGTTGTTTCCCTCCT	eeekk-d7-kkeee	sooooooooooooo	1401	1417	23	955
672793	TGCGGTTGTTTCCCTCC	eeekk-d7-kkeee	sooooooooooooo	1402	1418	0	956
672794	CTGCGGTTGTTTCCCTC	eeekk-d7-kkeee	sooooooooooooo	1403	1419	25	957
672795	GCTGCGGTTGTTTCCCT	eeekk-d7-kkeee	sooooooooooooo	1404	1420	5	958
672796	GGCTGCGGTTGTTTCCC	eeekk-d7-kkeee	sooooooooooooo	1405	1421	16	959
672797	AGGCTGCGGTTGTTTCC	eeekk-d7-kkeee	sooooooooooooo	1406	1422	7	960
672798	CAGGCTGCGGTTGTTTC	eeekk-d7-kkeee	sooooooooooooo	1407	1423	0	961
672799	ACAGGCTGCGGTTGTTT	eeekk-d7-kkeee	sooooooooooooo	1408	1424	28	962
672800	TACAGGCTGCGGTTGTT	eeekk-d7-kkeee	sooooooooooooo	1409	1425	33	963
672801	CTACAGGCTGCGGTTGT	eeekk-d7-kkeee	sooooooooooooo	1410	1426	53	964

672802	GCTACAGGCTGCGGTTG	eeekk-d7-kkeee	sooooooooooooo	1411	1427	0	965
672803	TGCTACAGGCTGCGGTT	eeekk-d7-kkeee	sooooooooooooo	1412	1428	0	966
672804	TTGCTACAGGCTGCGGT	eeekk-d7-kkeee	sooooooooooooo	1413	1429	0	967
672805	CTTGCTACAGGCTGCGG	eeekk-d7-kkeee	sooooooooooooo	1414	1430	1	968
672806	GCTTGCTACAGGCTGCG	eeekk-d7-kkeee	sooooooooooooo	1415	1431	58	969
672807	AGCTTGCTACAGGCTGC	eeekk-d7-kkeee	sooooooooooooo	1416	1432	0	970
672808	GAGCTTGCTACAGGCTG	eeekk-d7-kkeee	sooooooooooooo	1417	1433	0	971
672809	AGAGCTTGCTACAGGCT	eeekk-d7-kkeee	sooooooooooooo	1418	1434	71	972
672810	CAGAGCTTGCTACAGGC	eeekk-d7-kkeee	sooooooooooooo	1419	1435	18	973
672811	CCAGAGCTTGCTACAGG	eeekk-d7-kkeee	sooooooooooooo	1420	1436	0	974
672812	TCCAGAGCTTGCTACAG	eeekk-d7-kkeee	sooooooooooooo	1421	1437	19	975
672813	TTCCAGAGCTTGCTACA	eeekk-d7-kkeee	sooooooooooooo	1422	1438	19	976
672814	GTTCCAGAGCTTGCTAC	eeekk-d7-kkeee	sooooooooooooo	1423	1439	0	977
672815	AGTTCCAGAGCTTGCTA	eeekk-d7-kkeee	sooooooooooooo	1424	1440	0	978
672816	GAGTTCCAGAGCTTGCT	eeekk-d7-kkeee	sooooooooooooo	1425	1441	14	979
672817	TGAGTTCCAGAGCTTGCT	eeekk-d7-kkeee	sooooooooooooo	1426	1442	31	980
672818	CTGAGTTCCAGAGCTTG	eeekk-d7-kkeee	sooooooooooooo	1427	1443	21	981
672819	CCTGAGTTCCAGAGCTT	eeekk-d7-kkeee	sooooooooooooo	1428	1444	19	982
672820	TCCTGAGTTCCAGAGCT	eeekk-d7-kkeee	sooooooooooooo	1429	1445	46	983
672821	CTCCTGAGTTCCAGAGC	eeekk-d7-kkeee	sooooooooooooo	1430	1446	7	984
672822	ACTCCTGAGTTCCAGAG	eeekk-d7-kkeee	sooooooooooooo	1431	1447	13	985
672823	GACTCCTGAGTTCCAGA	eeekk-d7-kkeee	sooooooooooooo	1432	1448	19	986
672824	CGACTCCTGAGTTCCAG	eeekk-d7-kkeee	sooooooooooooo	1433	1449	23	987
672825	GCGACTCCTGAGTTCCA	eeekk-d7-kkeee	sooooooooooooo	1434	1450	0	988
672826	CGCGACTCCTGAGTTCC	eeekk-d7-kkeee	sooooooooooooo	1435	1451	19	989
672827	GCGCGACTCCTGAGTTC	eeekk-d7-kkeee	sooooooooooooo	1436	1452	31	990
672828	CGCGCGACTCCTGAGTT	eeekk-d7-kkeee	sooooooooooooo	1437	1453	63	991
672829	GCGCGCGACTCCTGAGT	eeekk-d7-kkeee	sooooooooooooo	1438	1454	28	992
672830	AGCGCGCGACTCCTGAG	eeekk-d7-kkeee	sooooooooooooo	1439	1455	58	993
672831	TAGCGCGCGACTCCTGA	eeekk-d7-kkeee	sooooooooooooo	1440	1456	42	994
672832	CTAGCGCGCGACTCCTG	eeekk-d7-kkeee	sooooooooooooo	1441	1457	42	995
672833	CCTAGCGCGCGACTCCT	eeekk-d7-kkeee	sooooooooooooo	1442	1458	24	996
672834	CCCTAGCGCGCGACTCC	eeekk-d7-kkeee	sooooooooooooo	1443	1459	58	997
672835	CCCCTAGCGCGCGACTC	eeekk-d7-kkeee	sooooooooooooo	1444	1460	40	998
672836	GCCCCTAGCGCGCGACT	eeekk-d7-kkeee	sooooooooooooo	1445	1461	0	999
672837	GGCCCCTAGCGCGCGAC	eeekk-d7-kkeee	sooooooooooooo	1446	1462	2	1000
672838	CGGCCCTAGCGCGCGA	eeekk-d7-kkeee	sooooooooooooo	1447	1463	72	1001
672839	CCGGCCCCTAGCGCGCG	eeekk-d7-kkeee	sooooooooooooo	1448	1464	0	1002
672840	CCCGGCCCTAGCGCGCG	eeekk-d7-kkeee	sooooooooooooo	1449	1465	28	1003
672841	CCCCGGCCCCTAGCGCG	eeekk-d7-kkeee	sooooooooooooo	1450	1466	28	1004
672842	GCCCCGGCCCCTAGCGCG	eeekk-d7-kkeee	sooooooooooooo	1451	1467	0	1005

672843	GGCCCCGGCCCCTAGCG	eeekk-d7-kkeee	sooooooooooooo	1452	1468	23	1006
672844	CGGCCCCGGCCCCTAGC	eeekk-d7-kkeee	sooooooooooooo	1453	1469	26	1007
672845	CCGGCCCCGGCCCCTAG	eeekk-d7-kkeee	sooooooooooooo	1454	1470	24	1008
672846	CCCGGCCCCGGCCCCTA	eeekk-d7-kkeee	sooooooooooooo	1455	1471	9	1009
672847	ACGCCCCGGCCCCGGCC	eeekk-d7-kkeee	sooooooooooooo	1465	1481	3	1010
672848	CACGCCCCGGCCCCGGC	eeekk-d7-kkeee	sooooooooooooo	1466	1482	19	1011
672849	CCACGCCCCGGCCCCGG	eeekk-d7-kkeee	sooooooooooooo	1467	1483	50	1012
672850	ACCACGCCCCGGCCCCG	eeekk-d7-kkeee	sooooooooooooo	1468	1484	0	1013
672851	GACCACGCCCCGGCCCC	eeekk-d7-kkeee	sooooooooooooo	1469	1485	3	1014
672852	CGACCACGCCCCGGCCC	eeekk-d7-kkeee	sooooooooooooo	1470	1486	9	1015
672853	CCGACCACGCCCCGGCC	eeekk-d7-kkeee	sooooooooooooo	1471	1487	24	1016
672854	CCCGACCACGCCCCGGC	eeekk-d7-kkeee	sooooooooooooo	1472	1488	9	1017
672855	CCCCGACCACGCCCCGG	eeekk-d7-kkeee	sooooooooooooo	1473	1489	18	1018
672856	GCCCCGACCACGCCCCG	eeekk-d7-kkeee	sooooooooooooo	1474	1490	8	1019
672857	CGCCCCGACCACGCCCC	eeekk-d7-kkeee	sooooooooooooo	1475	1491	0	1020
672858	CCGCCCCGACCACGCCC	eeekk-d7-kkeee	sooooooooooooo	1476	1492	48	1021
672859	CCCGCCCCGACCACGCC	eeekk-d7-kkeee	sooooooooooooo	1477	1493	28	1022
672860	GCCCGCCCCGACCACGC	eeekk-d7-kkeee	sooooooooooooo	1478	1494	0	1023
672861	GGCCCGCCCCGACCACG	eeekk-d7-kkeee	sooooooooooooo	1479	1495	33	1024
672862	GGGCCCGCCCCGACCAC	eeekk-d7-kkeee	sooooooooooooo	1480	1496	32	1025
672863	CGGGCCCGCCCCGACCA	eeekk-d7-kkeee	sooooooooooooo	1481	1497	0	1026
672864	CCGGGCCCGCCCCGACC	eeekk-d7-kkeee	sooooooooooooo	1482	1498	0	1027
672865	CCCGGGCCCGCCCCGAC	eeekk-d7-kkeee	sooooooooooooo	1483	1499	11	1028
672866	GCAGCCCCGCCCCGGGC	eeekk-d7-kkeee	sooooooooooooo	1505	1521	23	1029
672867	CGCAGCCCCGCCCCGGG	eeekk-d7-kkeee	sooooooooooooo	1506	1522	26	1030
672868	CCGCAGCCCCGCCCCGG	eeekk-d7-kkeee	sooooooooooooo	1507	1523	2	1031
672869	ACCGCAGCCCCGCCCCG	eeekk-d7-kkeee	sooooooooooooo	1508	1524	8	1032
672870	AACCGCAGCCCCGCCCC	eeekk-d7-kkeee	sooooooooooooo	1509	1525	7	1033
672871	CAACCGCAGCCCCGCCC	eeekk-d7-kkeee	sooooooooooooo	1510	1526	1	1034
672872	GCAACCGCAGCCCCGCC	eeekk-d7-kkeee	sooooooooooooo	1511	1527	37	1035
672873	CGCAACCGCAGCCCCGC	eeekk-d7-kkeee	sooooooooooooo	1512	1528	20	1036
672874	CCGCAACCGCAGCCCCG	eeekk-d7-kkeee	sooooooooooooo	1513	1529	23	1037
672875	ACCGCAACCGCAGCCCC	eeekk-d7-kkeee	sooooooooooooo	1514	1530	8	1038
672876	CACCGCAACCGCAGCCC	eeekk-d7-kkeee	sooooooooooooo	1515	1531	22	1039
672877	GCACCGCAACCGCAGCC	eeekk-d7-kkeee	sooooooooooooo	1516	1532	19	1040
672878	GGACCGCAACCGCAGC	eeekk-d7-kkeee	sooooooooooooo	1517	1533	25	1041
672879	AGGCACCGCAACCGCAG	eeekk-d7-kkeee	sooooooooooooo	1518	1534	21	1042
672880	CAGGCACCGCAACCGCA	eeekk-d7-kkeee	sooooooooooooo	1519	1535	12	1043
672881	GCAGGCACCGCAACCGC	eeekk-d7-kkeee	sooooooooooooo	1520	1536	18	1044
672882	CGCAGGCACCGCAACCG	eeekk-d7-kkeee	sooooooooooooo	1521	1537	15	1045
672883	GCGCAGGCACCGCAACC	eeekk-d7-kkeee	sooooooooooooo	1522	1538	0	1046

672884	GGCGCAGGCACCGCAAC	eeekk-d7-kkeee	soossssssssooss	1523	1539	0	1047

Example 9: Dose-dependent antisense inhibition of human C9ORF72 mRNA in HepG2 cells

Antisense oligonucleotides from the study described in Example 8 hereinabove exhibiting significant *in vitro* inhibition of C9ORF72 mRNA were selected and tested at various doses in HepG2 cells. ISIS

5 576816, previously tested in PCT/US2013/065073 (claiming priority to US Application No. 61/714,132, filed October 15, 2012, was used as a benchmark oligonucleotide. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.11 μ M, 0.33 μ M, 1.00 μ M, or 3.00 μ M concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Human primer probe set

10 RTS3905 was used to measure the C9ORF72 pathogenic associated mRNA variant, which is the product of a pre-mRNA containing a hexanucleotide repeat. C9ORF72 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN[®]. Results are presented as percent inhibition of C9ORF72 levels, relative to untreated control cells.

As shown in Tables 39 and 40, total C9ORF72 mRNA levels were reduced in a dose-dependent

15 manner in some of the antisense oligonucleotide treated cells.

Table 39

Dose-dependent inhibition of the C9ORF72 pathogenic associated mRNA variant transcript levels in HepG2 cells

ISIS No	0.11 μ M	0.33 μ M	1.00 μ M	3.00 μ M
672651	12	39	63	88
672611	13	50	59	79
672602	16	36	62	79
672624	25	54	80	95
672657	19	30	53	75
672582	0	0	20	57
672683	33	57	73	84
672595	39	39	66	88
576816	23	53	78	87
672640	17	26	56	84
672599	28	59	69	87
672637	36	50	66	88
672592	16	38	37	65
672636	24	39	69	88
672652	26	48	63	94

672619	8	12	6	0
672608	12	45	37	59
672598	21	9	55	69
672642	28	35	59	72

Table 40

Dose-dependent inhibition of the C9ORF72 pathogenic associated mRNA variant transcript levels in HepG2 cells

ISIS No	0.11 μM	0.33 μM	1.00 μM	3.00 μM
672679	2	52	81	95
672693	14	41	53	83
672681	27	42	63	87
672683	10	35	64	82
672678	24	56	77	91
672699	17	31	46	83
672664	7	28	58	87
672665	35	46	62	75
576816	15	55	71	84
672671	36	66	79	87
672676	33	53	71	77
672700	25	45	68	81
672730	24	41	59	80
672670	25	40	60	75
672697	11	41	64	80
672723	30	48	68	88
672728	11	44	49	68
672675	41	48	74	88
672674	19	34	55	61

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Example 10: Antisense inhibition of C9ORF72 by Deoxy, MOE and cEt antisense oligonucleotides with mixed backbones

Antisense oligonucleotides described in Example 6 hereinabove (see Tables 25-28 hereinabove) were tested in HepG2 cells in a series of experiments that had similar culture conditions. ISIS 576816, which was previously tested in PCT/US2013/065073 (claiming priority to US Application No. 61/714,132, filed October 15, 2012) was used as a benchmark oligonucleotide for study with deoxy, MOE, and cEt antisense oligonucleotides. The results for each experiment are presented in tables shown below. Cultured HepG2

10

cells at a density of 20,000 cells per well were transfected using electroporation with 700 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3905 was used to measure the C9ORF72 pathogenic associated mRNA variant, which is the product of a pre-mRNA containing a hexanucleotide repeat. The levels of the C9ORF72 pathogenic associated mRNA variant were normalized to the total RNA content of the cell, as measured by RIBOGREEN®. Results are presented as percent inhibition of C9ORF72, relative to untreated control cells.

Table 41

Percent inhibition of the C9ORF72 pathogenic associated mRNA variant compared to PBS control by Deoxy, MOE and cEt antisense oligonucleotides with mixed backbones targeting SEQ ID NO: 2

ISIS NO	Sequence	Chemistry	Linkage	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	% inhibition	SEQ ID NO
576816	GCCTTACTCTAGGACCAAGA	eeeee-d10-eeee	ssssssssssssssssss	7990	8009	52	20
672885	TGAGAGCAAGTAGTGGG	eekk-d8-kkee	soossssssssooss	1326	1342	10	898
672886	GTGAGAGCAAGTAGTGG	eekk-d8-kkee	soossssssssooss	1327	1343	24	899
672887	TGTGAGAGCAAGTAGTG	eekk-d8-kkee	soossssssssooss	1328	1344	38	900
672888	CTGTGAGAGCAAGTAGT	eekk-d8-kkee	soossssssssooss	1329	1345	37	901
672889	ACTGTGAGAGCAAGTAG	eekk-d8-kkee	soossssssssooss	1330	1346	16	902
672890	TACTGTGAGAGCAAGTA	eekk-d8-kkee	soossssssssooss	1331	1347	26	903
672891	GTACTGTGAGAGCAAGT	eekk-d8-kkee	soossssssssooss	1332	1348	38	904
672892	AGTACTGTGAGAGCAAG	eekk-d8-kkee	soossssssssooss	1333	1349	44	905
672893	GAGTACTGTGAGAGCAA	eekk-d8-kkee	soossssssssooss	1334	1350	57	906
672894	CGAGTACTGTGAGAGCA	eekk-d8-kkee	soossssssssooss	1335	1351	62	907
672895	GCGAGTACTGTGAGAGC	eekk-d8-kkee	soossssssssooss	1336	1352	39	908
672896	AGCGAGTACTGTGAGAG	eekk-d8-kkee	soossssssssooss	1337	1353	54	909
672897	CAGCGAGTACTGTGAGA	eekk-d8-kkee	soossssssssooss	1338	1354	57	910
672898	TCAGCGAGTACTGTGAG	eekk-d8-kkee	soossssssssooss	1339	1355	23	911
672899	CTCAGCGAGTACTGTGA	eekk-d8-kkee	soossssssssooss	1340	1356	34	912
672900	CCTCAGCGAGTACTGTG	eekk-d8-kkee	soossssssssooss	1341	1357	33	913
672901	CCCTCAGCGAGTACTGT	eekk-d8-kkee	soossssssssooss	1342	1358	32	914
672902	ACCCTCAGCGAGTACTG	eekk-d8-kkee	soossssssssooss	1343	1359	62	915

672903	CACCCTCAGCGAGTACT	eekk-d8-kkeee	sooooooooooooo	1344	1360	59	916
672904	TCACCCTCAGCGAGTAC	eekk-d8-kkeee	sooooooooooooo	1345	1361	52	917
672905	TTCACCCTCAGCGAGTA	eekk-d8-kkeee	sooooooooooooo	1346	1362	50	918
672906	GTTACACCCTCAGCGAGT	eekk-d8-kkeee	sooooooooooooo	1347	1363	38	919
672907	TGTTACACCCTCAGCGAG	eekk-d8-kkeee	sooooooooooooo	1348	1364	20	920
672908	TTGTTACACCCTCAGCGA	eekk-d8-kkeee	sooooooooooooo	1349	1365	57	921
672909	CTTGTTACACCCTCAGCG	eekk-d8-kkeee	sooooooooooooo	1350	1366	66	922
672910	TCCTTGTTACACCCTCAGC	eekk-d8-kkeee	sooooooooooooo	1351	1367	47	923
672911	TTCTTGTTACACCCTCAG	eekk-d8-kkeee	sooooooooooooo	1352	1368	37	924
672912	TTTCTTGTTACACCCTCA	eekk-d8-kkeee	sooooooooooooo	1353	1369	36	925
672913	TTTTCTTGTTACACCCTC	eekk-d8-kkeee	sooooooooooooo	1354	1370	34	926
672914	CTTTCTTGTTACACCCT	eekk-d8-kkeee	sooooooooooooo	1355	1371	35	927
672915	TCTTTCTTGTTACACC	eekk-d8-kkeee	sooooooooooooo	1356	1372	41	928
672916	GTCTTTCTTGTTACACC	eekk-d8-kkeee	sooooooooooooo	1357	1373	34	929
672917	GGTCTTTCTTGTTACAC	eekk-d8-kkeee	sooooooooooooo	1358	1374	23	930
672918	AGGTCTTTCTTGTTCA	eekk-d8-kkeee	sooooooooooooo	1359	1375	31	931
672919	CAGGTCTTTCTTGTTTC	eekk-d8-kkeee	sooooooooooooo	1360	1376	51	932
672920	TCAGGTCTTTCTTGTT	eekk-d8-kkeee	sooooooooooooo	1361	1377	15	933
672921	ATCAGGTCTTTCTTGTT	eekk-d8-kkeee	sooooooooooooo	1362	1378	0	934
672922	TATCAGGTCTTTCTTG	eekk-d8-kkeee	sooooooooooooo	1363	1379	31	935
672923	TTATCAGGTCTTTCTT	eekk-d8-kkeee	sooooooooooooo	1364	1380	14	936
672924	ATCTTTATCAGGTCTTT	eekk-d8-kkeee	sooooooooooooo	1368	1384	71	937
672925	AATCTTTATCAGGTCTT	eekk-d8-kkeee	sooooooooooooo	1369	1385	72	938
672926	TAATCTTTATCAGGTCT	eekk-d8-kkeee	sooooooooooooo	1370	1386	40	939
672927	TAAATCTTTATCAGGTC	eekk-d8-kkeee	sooooooooooooo	1371	1387	66	940
672928	GTTAATCTTTATCAGGT	eekk-d8-kkeee	sooooooooooooo	1372	1388	56	941
672929	GGTTAATCTTTATCAGG	eekk-d8-kkeee	sooooooooooooo	1373	1389	80	942
672930	TGGTTAATCTTTATCAG	eekk-d8-kkeee	sooooooooooooo	1374	1390	48	943
672931	CTGGTTAATCTTTATCA	eekk-d8-kkeee	sooooooooooooo	1375	1391	48	944
672932	TCTGGTTAATCTTTATC	eekk-d8-kkeee	sooooooooooooo	1376	1392	54	945
672933	CCCTCCTTGTTTTCTTC	eekk-d8-kkeee	sooooooooooooo	1391	1407	18	946
672934	TCCCTCCTTGTTTTCTT	eekk-d8-kkeee	sooooooooooooo	1392	1408	7	947
672935	TTCCCTCCTTGTTTTCT	eekk-d8-kkeee	sooooooooooooo	1393	1409	10	948

672936	TTTCCCTCCTTGTTTC	eekk-d8-kkeee	sooooooooooooo	1394	1410	0	949
672937	GTTTCCCTCCTTGTTTT	eekk-d8-kkeee	sooooooooooooo	1395	1411	0	950
672938	TGTTTCCCTCCTTGTTT	eekk-d8-kkeee	sooooooooooooo	1396	1412	9	951
672939	TTGTTTCCCTCCTTGTT	eekk-d8-kkeee	sooooooooooooo	1397	1413	27	952
672940	GGTTGTTTCCCTCCTTG	eekk-d8-kkeee	sooooooooooooo	1399	1415	49	953
672941	CGGTTGTTTCCCTCCTT	eekk-d8-kkeee	sooooooooooooo	1400	1416	17	954
672942	GCGGTTGTTTCCCTCCT	eekk-d8-kkeee	sooooooooooooo	1401	1417	10	955
672943	TGCGGTTGTTTCCCTCC	eekk-d8-kkeee	sooooooooooooo	1402	1418	33	956
672944	CTGCGGTTGTTTCCCTC	eekk-d8-kkeee	sooooooooooooo	1403	1419	29	957
672945	GCTGCGGTTGTTTCCCT	eekk-d8-kkeee	sooooooooooooo	1404	1420	23	958
672946	GGCTGCGGTTGTTTCCC	eekk-d8-kkeee	sooooooooooooo	1405	1421	15	959
672947	AGGCTGCGGTTGTTTCC	eekk-d8-kkeee	sooooooooooooo	1406	1422	24	960
672948	CAGGCTGCGGTTGTTTC	eekk-d8-kkeee	sooooooooooooo	1407	1423	49	961
672949	ACAGGCTGCGGTTGTTT	eekk-d8-kkeee	sooooooooooooo	1408	1424	35	962
672950	TACAGGCTGCGGTTGTT	eekk-d8-kkeee	sooooooooooooo	1409	1425	37	963
672951	CTACAGGCTGCGGTTGT	eekk-d8-kkeee	sooooooooooooo	1410	1426	4	964
672952	GCTACAGGCTGCGGTTG	eekk-d8-kkeee	sooooooooooooo	1411	1427	4	965
672953	TGCTACAGGCTGCGGTT	eekk-d8-kkeee	sooooooooooooo	1412	1428	24	966
672954	TTGCTACAGGCTGCGGT	eekk-d8-kkeee	sooooooooooooo	1413	1429	8	967
672955	CTTGCTACAGGCTGCGG	eekk-d8-kkeee	sooooooooooooo	1414	1430	28	968
672956	GCTTGCTACAGGCTGCG	eekk-d8-kkeee	sooooooooooooo	1415	1431	8	969
672957	AGCTTGCTACAGGCTGC	eekk-d8-kkeee	sooooooooooooo	1416	1432	5	970
672958	GAGCTTGCTACAGGCTG	eekk-d8-kkeee	sooooooooooooo	1417	1433	4	971
672959	AGAGCTTGCTACAGGCT	eekk-d8-kkeee	sooooooooooooo	1418	1434	0	972
672960	CAGAGCTTGCTACAGGC	eekk-d8-kkeee	sooooooooooooo	1419	1435	12	973
672961	CCAGAGCTTGCTACAGG	eekk-d8-kkeee	sooooooooooooo	1420	1436	36	974
672962	TCCAGAGCTTGCTACAG	eekk-d8-kkeee	sooooooooooooo	1421	1437	0	975
672963	TTCCAGAGCTTGCTACA	eekk-d8-kkeee	sooooooooooooo	1422	1438	11	976
672964	GTTCCAGAGCTTGCTAC	eekk-d8-kkeee	sooooooooooooo	1423	1439	8	977
672965	AGTTCCAGAGCTTGCTA	eekk-d8-kkeee	sooooooooooooo	1424	1440	19	978
672966	GAGTTCCAGAGCTTGCT	eekk-d8-kkeee	sooooooooooooo	1425	1441	48	979
672967	TGAGTTCCAGAGCTTGC	eekk-d8-kkeee	sooooooooooooo	1426	1442	41	980
672968	CTGAGTTCCAGAGCTTG	eekk-d8-kkeee	sooooooooooooo	1427	1443	54	981

672969	CCTGAGTTCCAGAGCTT	eekk-d8-kkeee	sooooooooooooo	1428	1444	58	982
672970	TCCTGAGTTCCAGAGCT	eekk-d8-kkeee	sooooooooooooo	1429	1445	12	983
672971	CTCCTGAGTTCCAGAGC	eekk-d8-kkeee	sooooooooooooo	1430	1446	23	984
672972	ACTCCTGAGTTCCAGAG	eekk-d8-kkeee	sooooooooooooo	1431	1447	30	985
672973	GACTCCTGAGTTCCAGA	eekk-d8-kkeee	sooooooooooooo	1432	1448	39	986
672974	CGACTCCTGAGTTCCAG	eekk-d8-kkeee	sooooooooooooo	1433	1449	41	987
672975	GCGACTCCTGAGTTCCA	eekk-d8-kkeee	sooooooooooooo	1434	1450	31	988
672976	CGCGACTCCTGAGTTCC	eekk-d8-kkeee	sooooooooooooo	1435	1451	56	989
672977	GCGCGACTCCTGAGTTC	eekk-d8-kkeee	sooooooooooooo	1436	1452	31	990
672978	CGCGCGACTCCTGAGTT	eekk-d8-kkeee	sooooooooooooo	1437	1453	45	991
672979	GCGCGCGACTCCTGAGT	eekk-d8-kkeee	sooooooooooooo	1438	1454	29	992
672980	AGCGCGCGACTCCTGAG	eekk-d8-kkeee	sooooooooooooo	1439	1455	48	993
672981	TAGCGCGCGACTCCTGA	eekk-d8-kkeee	sooooooooooooo	1440	1456	68	994
672982	CTAGCGCGCGACTCCTG	eekk-d8-kkeee	sooooooooooooo	1441	1457	59	995
672983	CCTAGCGCGCGACTCCT	eekk-d8-kkeee	sooooooooooooo	1442	1458	62	996
672984	CCCTAGCGCGCGACTCC	eekk-d8-kkeee	sooooooooooooo	1443	1459	69	997
672985	CCCCTAGCGCGCGACTC	eekk-d8-kkeee	sooooooooooooo	1444	1460	65	998
672986	GCCCCTAGCGCGCGACT	eekk-d8-kkeee	sooooooooooooo	1445	1461	34	999
672987	GGCCCCTAGCGCGCGAC	eekk-d8-kkeee	sooooooooooooo	1446	1462	22	1000
672988	CGGCCCCTAGCGCGCGA	eekk-d8-kkeee	sooooooooooooo	1447	1463	16	1001
672989	CCGGCCCCTAGCGCGCG	eekk-d8-kkeee	sooooooooooooo	1448	1464	24	1002
672990	CCCGGCCCCTAGCGCGC	eekk-d8-kkeee	sooooooooooooo	1449	1465	10	1003
672991	CCCCGGCCCCTAGCGCG	eekk-d8-kkeee	sooooooooooooo	1450	1466	24	1004
672992	GCCCCGGCCCCTAGCGC	eekk-d8-kkeee	sooooooooooooo	1451	1467	29	1005
672993	GGCCCCGGCCCCTAGCG	eekk-d8-kkeee	sooooooooooooo	1452	1468	24	1006
672994	CGGCCCCGGCCCCTAGC	eekk-d8-kkeee	sooooooooooooo	1453	1469	25	1007
672995	CCGGCCCCGGCCCCTAG	eekk-d8-kkeee	sooooooooooooo	1454	1470	28	1008
672996	CCCGGCCCCGGCCCCTA	eekk-d8-kkeee	sooooooooooooo	1455	1471	25	1009
672997	ACGCCCCGGCCCCGGCC	eekk-d8-kkeee	sooooooooooooo	1465	1481	21	1010
672998	CACGCCCCGGCCCCGGC	eekk-d8-kkeee	sooooooooooooo	1466	1482	17	1011
672999	CCACGCCCCGGCCCCGG	eekk-d8-kkeee	sooooooooooooo	1467	1483	30	1012
673000	ACCACGCCCCGGCCCCG	eekk-d8-kkeee	sooooooooooooo	1468	1484	29	1013
673001	GACCACGCCCCGGCCCC	eekk-d8-kkeee	sooooooooooooo	1469	1485	25	1014

673002	CGACCACGCCCCGGCCC	eekk-d8-kkeee	sooooooooooooo	1470	1486	37	1015
673003	CCGACCACGCCCCGGCC	eekk-d8-kkeee	sooooooooooooo	1471	1487	23	1016
673004	CCCGACCACGCCCCGGC	eekk-d8-kkeee	sooooooooooooo	1472	1488	21	1017
673005	CCCCGACCACGCCCCGG	eekk-d8-kkeee	sooooooooooooo	1473	1489	9	1018
673006	GCCCCGACCACGCCCCG	eekk-d8-kkeee	sooooooooooooo	1474	1490	13	1019
673007	CGCCCCGACCACGCCCC	eekk-d8-kkeee	sooooooooooooo	1475	1491	17	1020
673008	CCGCCCCGACCACGCCC	eekk-d8-kkeee	sooooooooooooo	1476	1492	20	1021
673009	CCCGCCCCGACCACGCC	eekk-d8-kkeee	sooooooooooooo	1477	1493	36	1022
673010	GCCCGCCCCGACCACGC	eekk-d8-kkeee	sooooooooooooo	1478	1494	16	1023
673011	GGCCCGCCCCGACCACG	eekk-d8-kkeee	sooooooooooooo	1479	1495	3	1024
673012	GGGCCCCGCCCGACCAC	eekk-d8-kkeee	sooooooooooooo	1480	1496	21	1025
673013	CGGGCCCCGCCCGACCA	eekk-d8-kkeee	sooooooooooooo	1481	1497	4	1026
673014	CCGGGCCCCGCCCGACC	eekk-d8-kkeee	sooooooooooooo	1482	1498	21	1027
673015	CCCGGGCCCCGCCCGAC	eekk-d8-kkeee	sooooooooooooo	1483	1499	15	1028
673016	GCAGCCCCGCCCGGGC	eekk-d8-kkeee	sooooooooooooo	1505	1521	3	1029
673017	CGCAGCCCCGCCCGGG	eekk-d8-kkeee	sooooooooooooo	1506	1522	7	1030
673018	CCGCAGCCCCGCCCGG	eekk-d8-kkeee	sooooooooooooo	1507	1523	7	1031
673019	ACCGCAGCCCCGCCCG	eekk-d8-kkeee	sooooooooooooo	1508	1524	8	1032
673020	AACCGCAGCCCCGCCCC	eekk-d8-kkeee	sooooooooooooo	1509	1525	42	1033
673021	CAACCGCAGCCCCGCCC	eekk-d8-kkeee	sooooooooooooo	1510	1526	58	1034
673022	GCAACCGCAGCCCCGCC	eekk-d8-kkeee	sooooooooooooo	1511	1527	44	1035
673023	CGCAACCGCAGCCCCGC	eekk-d8-kkeee	sooooooooooooo	1512	1528	46	1036
673024	CCGCAACCGCAGCCCCG	eekk-d8-kkeee	sooooooooooooo	1513	1529	26	1037
673025	ACCGCAACCGCAGCCCC	eekk-d8-kkeee	sooooooooooooo	1514	1530	20	1038
673026	CACCGCAACCGCAGCCC	eekk-d8-kkeee	sooooooooooooo	1515	1531	52	1039
673027	GCACCGCAACCGCAGCC	eekk-d8-kkeee	sooooooooooooo	1516	1532	22	1040
673028	GGCACCGCAACCGCAGC	eekk-d8-kkeee	sooooooooooooo	1517	1533	32	1041
673029	AGGCACCGCAACCGCAG	eekk-d8-kkeee	sooooooooooooo	1518	1534	27	1042
673030	CAGGCACCGCAACCGCA	eekk-d8-kkeee	sooooooooooooo	1519	1535	32	1043
673031	GCAGGCACCGCAACCGC	eekk-d8-kkeee	sooooooooooooo	1520	1536	38	1044
673032	CGCAGGCACCGCAACCG	eekk-d8-kkeee	sooooooooooooo	1521	1537	54	1045
673033	GCGCAGGCACCGCAACC	eekk-d8-kkeee	sooooooooooooo	1522	1538	24	1046
673034	GGCGCAGGCACCGCAAC	eekk-d8-kkeee	sooooooooooooo	1523	1539	17	1047

Table 42

Percent inhibition of the C9ORF72 pathogenic associated mRNA variant compared to PBS control by Deoxy, MOE and cEt antisense oligonucleotides with mixed backbones targeting SEQ ID NO: 2

ISIS NO	Sequence	Chemistry	Linkage	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	% inhibition	SEQ ID NO
576816	GCCTTACTCTAGGACCAAGA	eeee-d10-eeee	ssssssssssssssssss	7990	8009	75	20
673035	TGAGAGCAAGTAGTGGG	ek-d8-ekekeee	sossssssssssoooss	1326	1342	47	898
673036	GTGAGAGCAAGTAGTGG	ek-d8-ekekeee	sossssssssssoooss	1327	1343	57	899
673037	TGTGAGAGCAAGTAGTG	ek-d8-ekekeee	sossssssssssoooss	1328	1344	39	900
673038	CTGTGAGAGCAAGTAGT	ek-d8-ekekeee	sossssssssssoooss	1329	1345	48	901
673039	ACTGTGAGAGCAAGTAG	ek-d8-ekekeee	sossssssssssoooss	1330	1346	35	902
673040	TACTGTGAGAGCAAGTA	ek-d8-ekekeee	sossssssssssoooss	1331	1347	40	903
673041	GTACTGTGAGAGCAAGT	ek-d8-ekekeee	sossssssssssoooss	1332	1348	35	904
673042	AGTACTGTGAGAGCAAG	ek-d8-ekekeee	sossssssssssoooss	1333	1349	26	905
673043	GAGTACTGTGAGAGCAA	ek-d8-ekekeee	sossssssssssoooss	1334	1350	44	906
673044	CGAGTACTGTGAGAGCA	ek-d8-ekekeee	sossssssssssoooss	1335	1351	44	907
673045	GCGAGTACTGTGAGAGC	ek-d8-ekekeee	sossssssssssoooss	1336	1352	36	908
673046	AGCGAGTACTGTGAGAG	ek-d8-ekekeee	sossssssssssoooss	1337	1353	37	909
673047	CAGCGAGTACTGTGAGA	ek-d8-ekekeee	sossssssssssoooss	1338	1354	66	910
673048	TCAGCGAGTACTGTGAG	ek-d8-ekekeee	sossssssssssoooss	1339	1355	22	911
673049	CTCAGCGAGTACTGTGA	ek-d8-ekekeee	sossssssssssoooss	1340	1356	49	912
673050	CCTCAGCGAGTACTGTG	ek-d8-ekekeee	sossssssssssoooss	1341	1357	53	913
673051	CCCTCAGCGAGTACTGT	ek-d8-ekekeee	sossssssssssoooss	1342	1358	52	914
673052	ACCCTCAGCGAGTACTG	ek-d8-ekekeee	sossssssssssoooss	1343	1359	20	915
673053	CACCCTCAGCGAGTACT	ek-d8-ekekeee	sossssssssssoooss	1344	1360	66	916
673054	TCACCCTCAGCGAGTAC	ek-d8-ekekeee	sossssssssssoooss	1345	1361	50	917
673055	TTCACCCTCAGCGAGTA	ek-d8-ekekeee	sossssssssssoooss	1346	1362	35	918
673056	GTTCACCCTCAGCGAGT	ek-d8-ekekeee	sossssssssssoooss	1347	1363	46	919
673057	TGTTACCCTCAGCGAG	ek-d8-ekekeee	sossssssssssoooss	1348	1364	51	920
673058	TTGTTACCCTCAGCGA	ek-d8-ekekeee	sossssssssssoooss	1349	1365	57	921
673059	CTTGTTACCCTCAGCG	ek-d8-ekekeee	sossssssssssoooss	1350	1366	50	922

673060	TCTTGTTACCCCTCAGC	ek-d8-ekekeee	sossssssssoooss	1351	1367	41	923
673061	TTCTTGTTACCCCTCAG	ek-d8-ekekeee	sossssssssoooss	1352	1368	14	924
673062	TTTCTTGTTACCCCTCA	ek-d8-ekekeee	sossssssssoooss	1353	1369	28	925
673063	TTTTCTTGTTACCCCTC	ek-d8-ekekeee	sossssssssoooss	1354	1370	38	926
673064	CTTTTCTTGTTACCCCT	ek-d8-ekekeee	sossssssssoooss	1355	1371	38	927
673065	TCTTTTCTTGTTACCC	ek-d8-ekekeee	sossssssssoooss	1356	1372	30	928
673066	GTCTTTTCTTGTTACCC	ek-d8-ekekeee	sossssssssoooss	1357	1373	47	929
673067	GGTCTTTTCTTGTTAC	ek-d8-ekekeee	sossssssssoooss	1358	1374	63	930
673068	AGGTCTTTTCTTGTTCA	ek-d8-ekekeee	sossssssssoooss	1359	1375	71	931
673069	CAGGTCTTTTCTTGTT	ek-d8-ekekeee	sossssssssoooss	1360	1376	41	932
673070	TCAGGTCTTTTCTTGTT	ek-d8-ekekeee	sossssssssoooss	1361	1377	24	933
673071	ATCAGGTCTTTTCTTGT	ek-d8-ekekeee	sossssssssoooss	1362	1378	53	934
673072	TATCAGGTCTTTTCTTG	ek-d8-ekekeee	sossssssssoooss	1363	1379	44	935
673073	TTATCAGGTCTTTTCTT	ek-d8-ekekeee	sossssssssoooss	1364	1380	28	936
673074	ATCTTTATCAGGTCTTT	ek-d8-ekekeee	sossssssssoooss	1368	1384	57	937
673075	AATCTTTATCAGGTCTT	ek-d8-ekekeee	sossssssssoooss	1369	1385	49	938
673076	TAATCTTTATCAGGTCT	ek-d8-ekekeee	sossssssssoooss	1370	1386	40	939
673077	TTAATCTTTATCAGGTC	ek-d8-ekekeee	sossssssssoooss	1371	1387	33	940
673078	GTAAATCTTTATCAGGT	ek-d8-ekekeee	sossssssssoooss	1372	1388	46	941
673079	GGTAAATCTTTATCAGG	ek-d8-ekekeee	sossssssssoooss	1373	1389	87	942
673080	TGGTAAATCTTTATCAG	ek-d8-ekekeee	sossssssssoooss	1374	1390	35	943
673081	CTGGTAAATCTTTATCA	ek-d8-ekekeee	sossssssssoooss	1375	1391	56	944
673082	TCTGGTAAATCTTTATC	ek-d8-ekekeee	sossssssssoooss	1376	1392	59	945
673083	CCCTCCTTGTTTTCTTC	ek-d8-ekekeee	sossssssssoooss	1391	1407	11	946
673084	TCCCTCCTTGTTTTCTT	ek-d8-ekekeee	sossssssssoooss	1392	1408	10	947
673085	TTCCCTCCTTGTTTTCT	ek-d8-ekekeee	sossssssssoooss	1393	1409	8	948
673086	TTTCCCTCCTTGTTTTCT	ek-d8-ekekeee	sossssssssoooss	1394	1410	26	949
673087	GTTTCCCTCCTTGTTTT	ek-d8-ekekeee	sossssssssoooss	1395	1411	25	950
673088	TGTTTCCCTCCTTGTTT	ek-d8-ekekeee	sossssssssoooss	1396	1412	62	951
673089	TTGTTTCCCTCCTTGTT	ek-d8-ekekeee	sossssssssoooss	1397	1413	51	952
673090	GGTTGTTTCCCTCCTTG	ek-d8-ekekeee	sossssssssoooss	1399	1415	34	953
673091	CGGTTGTTTCCCTCCTT	ek-d8-ekekeee	sossssssssoooss	1400	1416	13	954
673092	GCGGTTGTTTCCCTCCT	ek-d8-ekekeee	sossssssssoooss	1401	1417	37	955

673093	TGCGGTTGTTTCCCTCC	ek-d8-ekekeee	sossssssssoooss	1402	1418	49	956
673094	CTGCGGTTGTTTCCCTC	ek-d8-ekekeee	sossssssssoooss	1403	1419	15	957
673095	GCTGCGGTTGTTTCCCT	ek-d8-ekekeee	sossssssssoooss	1404	1420	17	958
673096	GGCTGCGGTTGTTTCCC	ek-d8-ekekeee	sossssssssoooss	1405	1421	33	959
673097	AGGCTGCGGTTGTTTCC	ek-d8-ekekeee	sossssssssoooss	1406	1422	43	960
673098	CAGGCTGCGGTTGTTTC	ek-d8-ekekeee	sossssssssoooss	1407	1423	53	961
673099	ACAGGCTGCGGTTGTTT	ek-d8-ekekeee	sossssssssoooss	1408	1424	21	962
673100	TACAGGCTGCGGTTGTT	ek-d8-ekekeee	sossssssssoooss	1409	1425	23	963
673101	CTACAGGCTGCGGTTGT	ek-d8-ekekeee	sossssssssoooss	1410	1426	16	964
673102	GCTACAGGCTGCGGTTG	ek-d8-ekekeee	sossssssssoooss	1411	1427	24	965
673103	TGCTACAGGCTGCGGTT	ek-d8-ekekeee	sossssssssoooss	1412	1428	41	966
673104	TTGCTACAGGCTGCGGT	ek-d8-ekekeee	sossssssssoooss	1413	1429	30	967
673105	CTTGCTACAGGCTGCGG	ek-d8-ekekeee	sossssssssoooss	1414	1430	13	968
673106	GCTTGCTACAGGCTGCG	ek-d8-ekekeee	sossssssssoooss	1415	1431	7	969
673107	AGCTTGCTACAGGCTGC	ek-d8-ekekeee	sossssssssoooss	1416	1432	7	970
673108	GAGCTTGCTACAGGCTG	ek-d8-ekekeee	sossssssssoooss	1417	1433	23	971
673109	AGAGCTTGCTACAGGCT	ek-d8-ekekeee	sossssssssoooss	1418	1434	38	972
673110	CAGAGCTTGCTACAGGC	ek-d8-ekekeee	sossssssssoooss	1419	1435	22	973
673111	CCAGAGCTTGCTACAGG	ek-d8-ekekeee	sossssssssoooss	1420	1436	14	974
673112	TCCAGAGCTTGCTACAG	ek-d8-ekekeee	sossssssssoooss	1421	1437	11	975
673113	TTCCAGAGCTTGCTACA	ek-d8-ekekeee	sossssssssoooss	1422	1438	24	976
673114	GTTCCAGAGCTTGCTAC	ek-d8-ekekeee	sossssssssoooss	1423	1439	37	977
673115	AGTTCCAGAGCTTGCTA	ek-d8-ekekeee	sossssssssoooss	1424	1440	34	978
673116	GAGTTCCAGAGCTTGCT	ek-d8-ekekeee	sossssssssoooss	1425	1441	21	979
673117	TGAGTTCCAGAGCTTGC	ek-d8-ekekeee	sossssssssoooss	1426	1442	47	980
673118	CTGAGTTCCAGAGCTTG	ek-d8-ekekeee	sossssssssoooss	1427	1443	27	981
673119	CCTGAGTTCCAGAGCTT	ek-d8-ekekeee	sossssssssoooss	1428	1444	44	982
673120	TCCTGAGTTCCAGAGCT	ek-d8-ekekeee	sossssssssoooss	1429	1445	39	983
673121	CTCCTGAGTTCCAGAGC	ek-d8-ekekeee	sossssssssoooss	1430	1446	37	984
673122	ACTCCTGAGTTCCAGAG	ek-d8-ekekeee	sossssssssoooss	1431	1447	40	985
673123	GA CTCCTGAGTTCCAGA	ek-d8-ekekeee	sossssssssoooss	1432	1448	26	986
673124	CGACTCCTGAGTTCCAG	ek-d8-ekekeee	sossssssssoooss	1433	1449	36	987
673125	GCGACTCCTGAGTTCCA	ek-d8-ekekeee	sossssssssoooss	1434	1450	55	988

673126	CGCGACTCCTGAGTTCC	ek-d8-ekekeee	sossssssssoooss	1435	1451	55	989
673127	GCGCGACTCCTGAGTTC	ek-d8-ekekeee	sossssssssoooss	1436	1452	64	990
673128	CGCGCGACTCCTGAGTT	ek-d8-ekekeee	sossssssssoooss	1437	1453	59	991
673129	GCGCGCGACTCCTGAGT	ek-d8-ekekeee	sossssssssoooss	1438	1454	42	992
673130	AGCGCGCGACTCCTGAG	ek-d8-ekekeee	sossssssssoooss	1439	1455	60	993
673131	TAGCGCGCGACTCCTGA	ek-d8-ekekeee	sossssssssoooss	1440	1456	59	994
673132	CTAGCGCGCGACTCCTG	ek-d8-ekekeee	sossssssssoooss	1441	1457	49	995
673133	CCTAGCGCGCGACTCCT	ek-d8-ekekeee	sossssssssoooss	1442	1458	62	996
673134	CCCTAGCGCGCGACTCC	ek-d8-ekekeee	sossssssssoooss	1443	1459	62	997
673135	CCCCTAGCGCGCGACTC	ek-d8-ekekeee	sossssssssoooss	1444	1460	65	998
673136	GCCCCTAGCGCGCGACT	ek-d8-ekekeee	sossssssssoooss	1445	1461	27	999
673137	GGCCCCTAGCGCGCGAC	ek-d8-ekekeee	sossssssssoooss	1446	1462	6	1000
673138	CGGCCCTAGCGCGCGA	ek-d8-ekekeee	sossssssssoooss	1447	1463	26	1001
673139	CCGGCCCCTAGCGCGCG	ek-d8-ekekeee	sossssssssoooss	1448	1464	15	1002
673140	CCCGGCCCTAGCGCGC	ek-d8-ekekeee	sossssssssoooss	1449	1465	24	1003
673141	CCCCGGCCCCTAGCGCG	ek-d8-ekekeee	sossssssssoooss	1450	1466	27	1004
673142	GCCCCGGCCCCTAGCGC	ek-d8-ekekeee	sossssssssoooss	1451	1467	28	1005
673143	GGCCCCGGCCCCTAGCG	ek-d8-ekekeee	sossssssssoooss	1452	1468	28	1006
673144	CGGCCCGGCCCTAGC	ek-d8-ekekeee	sossssssssoooss	1453	1469	49	1007
673145	CCGGCCCCGGCCCCTAG	ek-d8-ekekeee	sossssssssoooss	1454	1470	24	1008
673146	CCCGGCCCGGCCCTA	ek-d8-ekekeee	sossssssssoooss	1455	1471	32	1009
673147	ACGCCCGGCCCGGCC	ek-d8-ekekeee	sossssssssoooss	1465	1481	12	1010
673148	CACGCCCGGCCCGGC	ek-d8-ekekeee	sossssssssoooss	1466	1482	4	1011
673149	CCACGCCCGGCCCGG	ek-d8-ekekeee	sossssssssoooss	1467	1483	18	1012
673150	ACCACGCCCGGCCCG	ek-d8-ekekeee	sossssssssoooss	1468	1484	5	1013
673151	GACCACGCCCGGCC	ek-d8-ekekeee	sossssssssoooss	1469	1485	20	1014
673152	CGACCACGCCCGGCC	ek-d8-ekekeee	sossssssssoooss	1470	1486	52	1015
673153	CCGACCACGCCCGGCC	ek-d8-ekekeee	sossssssssoooss	1471	1487	4	1016
673154	CCCGACCACGCCCGGC	ek-d8-ekekeee	sossssssssoooss	1472	1488	9	1017
673155	CCCCGACCACGCCCGG	ek-d8-ekekeee	sossssssssoooss	1473	1489	23	1018
673156	GCCCCGACCACGCCCG	ek-d8-ekekeee	sossssssssoooss	1474	1490	9	1019
673157	CGCCCCGACCACGCC	ek-d8-ekekeee	sossssssssoooss	1475	1491	22	1020
673158	CCGCCCGACCACGCC	ek-d8-ekekeee	sossssssssoooss	1476	1492	27	1021

673159	CCCGCCCCGACCACGCC	ek-d8-ekekeee	sossssssssoooss	1477	1493	49	1022
673160	GCCCGCCCCGACCACGC	ek-d8-ekekeee	sossssssssoooss	1478	1494	33	1023
673161	GGCCCGCCCCGACCACG	ek-d8-ekekeee	sossssssssoooss	1479	1495	7	1024
673162	GGGCCCCGCCCCGACCAC	ek-d8-ekekeee	sossssssssoooss	1480	1496	8	1025
673163	CGGGCCCCGCCCCGACCA	ek-d8-ekekeee	sossssssssoooss	1481	1497	12	1026
673164	CCGGGCCCCGCCCCGACC	ek-d8-ekekeee	sossssssssoooss	1482	1498	2	1027
673165	CCCGGGCCCCGCCCCGAC	ek-d8-ekekeee	sossssssssoooss	1483	1499	13	1028
673166	GCAGCCCCGCCCCGGGC	ek-d8-ekekeee	sossssssssoooss	1505	1521	7	1029
673167	CGCAGCCCCGCCCCGGG	ek-d8-ekekeee	sossssssssoooss	1506	1522	14	1030
673168	CCGCAGCCCCGCCCCGG	ek-d8-ekekeee	sossssssssoooss	1507	1523	17	1031
673169	ACCGCAGCCCCGCCCCG	ek-d8-ekekeee	sossssssssoooss	1508	1524	44	1032
673170	AACCGCAGCCCCGCCCC	ek-d8-ekekeee	sossssssssoooss	1509	1525	40	1033
673171	CAACCGCAGCCCCGCCC	ek-d8-ekekeee	sossssssssoooss	1510	1526	45	1034
673172	GCAACCGCAGCCCCGCC	ek-d8-ekekeee	sossssssssoooss	1511	1527	28	1035
673173	CGCAACCGCAGCCCCGC	ek-d8-ekekeee	sossssssssoooss	1512	1528	31	1036
673174	CCGCAACCGCAGCCCCG	ek-d8-ekekeee	sossssssssoooss	1513	1529	38	1037
673175	ACCGCAACCGCAGCCCC	ek-d8-ekekeee	sossssssssoooss	1514	1530	47	1038
673176	CACCGCAACCGCAGCCC	ek-d8-ekekeee	sossssssssoooss	1515	1531	37	1039
673177	GCACCGCAACCGCAGCC	ek-d8-ekekeee	sossssssssoooss	1516	1532	41	1040
673178	GGCACCGCAACCGCAGC	ek-d8-ekekeee	sossssssssoooss	1517	1533	34	1041
673179	AGGCACCGCAACCGCAG	ek-d8-ekekeee	sossssssssoooss	1518	1534	19	1042
673180	CAGGCACCGCAACCGCA	ek-d8-ekekeee	sossssssssoooss	1519	1535	36	1043
673181	GCAGGCACCGCAACCGC	ek-d8-ekekeee	sossssssssoooss	1520	1536	33	1044
673182	CGCAGGCACCGCAACCG	ek-d8-ekekeee	sossssssssoooss	1521	1537	37	1045
673183	GCGCAGGCACCGCAACC	ek-d8-ekekeee	sossssssssoooss	1522	1538	6	1046
673184	GGCGCAGGCACCGCAAC	ek-d8-ekekeee	sossssssssoooss	1523	1539	11	1047

Table 43

Percent inhibition of the C9ORF72 pathogenic associated mRNA variant compared to PBS control by Deoxy, MOE and cEt antisense oligonucleotides with mixed backbones targeting SEQ ID NO: 2

ISIS NO	Sequence	Chemistry	Linkage	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	% inhibition	SEQ ID NO
576816	GCCTTACTCTAGGACCAAGA	eeeee-d10-eeee	ssssssssssssssssssss	7990	8009	79	20
673185	TGAGAGCAAGTAGTGGG	keke-d8-ekeke	soossssssssooss	1326	1342	37	898
673186	GTGAGAGCAAGTAGTG	keke-d8-ekeke	soossssssssooss	1327	1343	39	899
673187	TGTGAGAGCAAGTAGTG	keke-d8-ekeke	soossssssssooss	1328	1344	33	900
673188	CTGTGAGAGCAAGTAGT	keke-d8-ekeke	soossssssssooss	1329	1345	40	901
673189	ACTGTGAGAGCAAGTAG	keke-d8-ekeke	soossssssssooss	1330	1346	26	902
673190	TACTGTGAGAGCAAGTA	keke-d8-ekeke	soossssssssooss	1331	1347	23	903
673191	GTACTGTGAGAGCAAGT	keke-d8-ekeke	soossssssssooss	1332	1348	50	904
673192	AGTACTGTGAGAGCAAG	keke-d8-ekeke	soossssssssooss	1333	1349	39	905
673193	GAGTACTGTGAGAGCAA	keke-d8-ekeke	soossssssssooss	1334	1350	69	906
673194	CGAGTACTGTGAGAGCA	keke-d8-ekeke	soossssssssooss	1335	1351	72	907
673195	GCGAGTACTGTGAGAGC	keke-d8-ekeke	soossssssssooss	1336	1352	51	908
673196	AGCGAGTACTGTGAGAG	keke-d8-ekeke	soossssssssooss	1337	1353	51	909
673197	CAGCGAGTACTGTGAGA	keke-d8-ekeke	soossssssssooss	1338	1354	59	910
673198	TCAGCGAGTACTGTGAG	keke-d8-ekeke	soossssssssooss	1339	1355	33	911
673199	CTCAGCGAGTACTGTGA	keke-d8-ekeke	soossssssssooss	1340	1356	32	912
673200	CCTCAGCGAGTACTGTG	keke-d8-ekeke	soossssssssooss	1341	1357	46	913
673201	CCCTCAGCGAGTACTGT	keke-d8-ekeke	soossssssssooss	1342	1358	53	914
673202	ACCCTCAGCGAGTACTG	keke-d8-ekeke	soossssssssooss	1343	1359	58	915
673203	CACCCTCAGCGAGTACT	keke-d8-ekeke	soossssssssooss	1344	1360	68	916
673204	TCACCCTCAGCGAGTAC	keke-d8-ekeke	soossssssssooss	1345	1361	70	917
673205	TTCACCCTCAGCGAGTA	keke-d8-ekeke	soossssssssooss	1346	1362	47	918
673206	GTTACCCTCAGCGAGT	keke-d8-ekeke	soossssssssooss	1347	1363	65	919
673207	TGTTACCCTCAGCGAG	keke-d8-ekeke	soossssssssooss	1348	1364	31	920
673208	TTGTTACCCTCAGCGA	keke-d8-ekeke	soossssssssooss	1349	1365	51	921
673209	CTTGTTACCCTCAGCG	keke-d8-ekeke	soossssssssooss	1350	1366	49	922

673210	TCTTGTTACCCCTCAGC	keke-d8-ekeke	sooooooooooooo	1351	1367	61	923
673211	TTCTTGTTACCCCTCAG	keke-d8-ekeke	sooooooooooooo	1352	1368	49	924
673212	TTTCTTGTTACCCCTCA	keke-d8-ekeke	sooooooooooooo	1353	1369	42	925
673213	TTTTCTTGTTACCCCTC	keke-d8-ekeke	sooooooooooooo	1354	1370	36	926
673214	CTTTTCTTGTTACCCCT	keke-d8-ekeke	sooooooooooooo	1355	1371	41	927
673215	TCTTTTCTTGTTACCCC	keke-d8-ekeke	sooooooooooooo	1356	1372	41	928
673216	GTCTTTTCTTGTTACCC	keke-d8-ekeke	sooooooooooooo	1357	1373	36	929
673217	GGTCTTTTCTTGTTAC	keke-d8-ekeke	sooooooooooooo	1358	1374	29	930
673218	AGGTCTTTTCTTGTTCA	keke-d8-ekeke	sooooooooooooo	1359	1375	50	931
673219	CAGGTCTTTTCTTGTT	keke-d8-ekeke	sooooooooooooo	1360	1376	60	932
673220	TCAGGTCTTTTCTTGTT	keke-d8-ekeke	sooooooooooooo	1361	1377	34	933
673221	ATCAGGTCTTTTCTTGT	keke-d8-ekeke	sooooooooooooo	1362	1378	33	934
673222	TATCAGGTCTTTTCTTG	keke-d8-ekeke	sooooooooooooo	1363	1379	31	935
673223	TTATCAGGTCTTTTCTT	keke-d8-ekeke	sooooooooooooo	1364	1380	10	936
673224	ATCTTTATCAGGTCTTT	keke-d8-ekeke	sooooooooooooo	1368	1384	61	937
673225	AATCTTTATCAGGTCTT	keke-d8-ekeke	sooooooooooooo	1369	1385	74	938
673226	TAATCTTTATCAGGTCT	keke-d8-ekeke	sooooooooooooo	1370	1386	62	939
673227	TTAATCTTTATCAGGTC	keke-d8-ekeke	sooooooooooooo	1371	1387	51	940
673228	GTAAATCTTTATCAGGT	keke-d8-ekeke	sooooooooooooo	1372	1388	73	941
673229	GGTTAATCTTTATCAGG	keke-d8-ekeke	sooooooooooooo	1373	1389	66	942
673230	TGGTTAATCTTTATCAG	keke-d8-ekeke	sooooooooooooo	1374	1390	38	943
673231	CTGGTTAATCTTTATCA	keke-d8-ekeke	sooooooooooooo	1375	1391	41	944
673232	TCTGGTTAATCTTTATC	keke-d8-ekeke	sooooooooooooo	1376	1392	37	945
673233	CCCTCCTTGTTTTCTTC	keke-d8-ekeke	sooooooooooooo	1391	1407	26	946
673234	TCCCTCCTTGTTTTCTT	keke-d8-ekeke	sooooooooooooo	1392	1408	10	947
673235	TTCCCTCCTTGTTTTCT	keke-d8-ekeke	sooooooooooooo	1393	1409	20	948
673236	TTCCCTCCTTGTTTTCT	keke-d8-ekeke	sooooooooooooo	1394	1410	1	949
673237	GTTTCCCTCCTTGTTTT	keke-d8-ekeke	sooooooooooooo	1395	1411	7	950
673238	TGTTTCCCTCCTTGTTT	keke-d8-ekeke	sooooooooooooo	1396	1412	26	951
673239	TTGTTTCCCTCCTTGTT	keke-d8-ekeke	sooooooooooooo	1397	1413	28	952
673240	GGTTGTTTCCCTCCTTG	keke-d8-ekeke	sooooooooooooo	1399	1415	70	953
673241	CGGTTGTTTCCCTCCTT	keke-d8-ekeke	sooooooooooooo	1400	1416	36	954
673242	GCGGTTGTTTCCCTCCT	keke-d8-ekeke	sooooooooooooo	1401	1417	21	955

673243	TGCGGTTGTTTCCCTCC	keke-d8-ekeke	sooooooooooooo	1402	1418	24	956
673244	CTGCGGTTGTTTCCCTC	keke-d8-ekeke	sooooooooooooo	1403	1419	41	957
673245	GCTGCGGTTGTTTCCCT	keke-d8-ekeke	sooooooooooooo	1404	1420	23	958
673246	GGCTGCGGTTGTTTCCC	keke-d8-ekeke	sooooooooooooo	1405	1421	39	959
673247	AGGCTGCGGTTGTTTCC	keke-d8-ekeke	sooooooooooooo	1406	1422	50	960
673248	CAGGCTGCGGTTGTTTC	keke-d8-ekeke	sooooooooooooo	1407	1423	32	961
673249	ACAGGCTGCGGTTGTTT	keke-d8-ekeke	sooooooooooooo	1408	1424	28	962
673250	TACAGGCTGCGGTTGTT	keke-d8-ekeke	sooooooooooooo	1409	1425	41	963
673251	CTACAGGCTGCGGTTGT	keke-d8-ekeke	sooooooooooooo	1410	1426	18	964
673252	GCTACAGGCTGCGGTTG	keke-d8-ekeke	sooooooooooooo	1411	1427	28	965
673253	TGCTACAGGCTGCGGTT	keke-d8-ekeke	sooooooooooooo	1412	1428	28	966
673254	TTGCTACAGGCTGCGGT	keke-d8-ekeke	sooooooooooooo	1413	1429	9	967
673255	CTTGCTACAGGCTGCGG	keke-d8-ekeke	sooooooooooooo	1414	1430	34	968
673256	GCTTGCTACAGGCTGCG	keke-d8-ekeke	sooooooooooooo	1415	1431	28	969
673257	AGCTTGCTACAGGCTGC	keke-d8-ekeke	sooooooooooooo	1416	1432	25	970
673258	GAGCTTGCTACAGGCTG	keke-d8-ekeke	sooooooooooooo	1417	1433	23	971
673259	AGAGCTTGCTACAGGCT	keke-d8-ekeke	sooooooooooooo	1418	1434	0	972
673260	CAGAGCTTGCTACAGGC	keke-d8-ekeke	sooooooooooooo	1419	1435	4	973
673261	CCAGAGCTTGCTACAGG	keke-d8-ekeke	sooooooooooooo	1420	1436	40	974
673262	TCCAGAGCTTGCTACAG	keke-d8-ekeke	sooooooooooooo	1421	1437	35	975
673263	TTCCAGAGCTTGCTACA	keke-d8-ekeke	sooooooooooooo	1422	1438	23	976
673264	GTTCCAGAGCTTGCTAC	keke-d8-ekeke	sooooooooooooo	1423	1439	36	977
673265	AGTTCAGAGCTTGCTA	keke-d8-ekeke	sooooooooooooo	1424	1440	54	978
673266	GAGTTCAGAGCTTGCT	keke-d8-ekeke	sooooooooooooo	1425	1441	32	979
673267	TGAGTTCAGAGCTTGCT	keke-d8-ekeke	sooooooooooooo	1426	1442	32	980
673268	CTGAGTTCAGAGCTTG	keke-d8-ekeke	sooooooooooooo	1427	1443	44	981
673269	CCTGAGTTCAGAGCTT	keke-d8-ekeke	sooooooooooooo	1428	1444	70	982
673270	TCCTGAGTTCAGAGCT	keke-d8-ekeke	sooooooooooooo	1429	1445	43	983
673271	CTCCTGAGTTCAGAGC	keke-d8-ekeke	sooooooooooooo	1430	1446	41	984
673272	ACTCCTGAGTTCAGAG	keke-d8-ekeke	sooooooooooooo	1431	1447	23	985
673273	GACTCCTGAGTTCAGA	keke-d8-ekeke	sooooooooooooo	1432	1448	48	986
673274	CGACTCCTGAGTTCAG	keke-d8-ekeke	sooooooooooooo	1433	1449	34	987
673275	GCGACTCCTGAGTCCA	keke-d8-ekeke	sooooooooooooo	1434	1450	64	988

673276	CGCGACTCCTGAGTTCC	keke-d8-ekeke	sooooooooooooo	1435	1451	65	989
673277	GCGCGACTCCTGAGTTC	keke-d8-ekeke	sooooooooooooo	1436	1452	62	990
673278	CGCGCGACTCCTGAGTT	keke-d8-ekeke	sooooooooooooo	1437	1453	45	991
673279	GCGCGCGACTCCTGAGT	keke-d8-ekeke	sooooooooooooo	1438	1454	52	992
673280	AGCGCGCGACTCCTGAG	keke-d8-ekeke	sooooooooooooo	1439	1455	65	993
673281	TAGCGCGCGACTCCTGA	keke-d8-ekeke	sooooooooooooo	1440	1456	89	994
673282	CTAGCGCGCGACTCCTG	keke-d8-ekeke	sooooooooooooo	1441	1457	69	995
673283	CCTAGCGCGCGACTCCT	keke-d8-ekeke	sooooooooooooo	1442	1458	68	996
673284	CCCTAGCGCGCGACTCC	keke-d8-ekeke	sooooooooooooo	1443	1459	73	997
673285	CCCCTAGCGCGCGACTC	keke-d8-ekeke	sooooooooooooo	1444	1460	70	998
673286	GCCCCTAGCGCGCGACT	keke-d8-ekeke	sooooooooooooo	1445	1461	45	999
673287	GGCCCCTAGCGCGCGAC	keke-d8-ekeke	sooooooooooooo	1446	1462	33	1000
673288	CGGCCCCTAGCGCGCGA	keke-d8-ekeke	sooooooooooooo	1447	1463	29	1001
673289	CCGGCCCCTAGCGCGCG	keke-d8-ekeke	sooooooooooooo	1448	1464	0	1002
673290	CCCGGCCCCTAGCGCGC	keke-d8-ekeke	sooooooooooooo	1449	1465	31	1003
673291	CCCCGGCCCCTAGCGCG	keke-d8-ekeke	sooooooooooooo	1450	1466	28	1004
673292	GCCCCGGCCCCTAGCGC	keke-d8-ekeke	sooooooooooooo	1451	1467	12	1005
673293	GGCCCCGGCCCCTAGCG	keke-d8-ekeke	sooooooooooooo	1452	1468	29	1006
673294	CGGCCCCGGCCCCTAGC	keke-d8-ekeke	sooooooooooooo	1453	1469	39	1007
673295	CCGGCCCCGGCCCCTAG	keke-d8-ekeke	sooooooooooooo	1454	1470	28	1008
673296	CCCGGCCCCGGCCCCTA	keke-d8-ekeke	sooooooooooooo	1455	1471	4	1009
673297	ACGCCCCGGCCCCGGCC	keke-d8-ekeke	sooooooooooooo	1465	1481	17	1010
673298	CACGCCCCGGCCCCGGC	keke-d8-ekeke	sooooooooooooo	1466	1482	35	1011
673299	CCACGCCCCGGCCCCGG	keke-d8-ekeke	sooooooooooooo	1467	1483	28	1012
673300	ACCACGCCCCGGCCCCG	keke-d8-ekeke	sooooooooooooo	1468	1484	21	1013
673301	GACCACGCCCCGGCCCC	keke-d8-ekeke	sooooooooooooo	1469	1485	28	1014
673302	CGACCACGCCCCGGCCC	keke-d8-ekeke	sooooooooooooo	1470	1486	46	1015
673303	CCGACCACGCCCCGGCC	keke-d8-ekeke	sooooooooooooo	1471	1487	40	1016
673304	CCCGACCACGCCCCGGC	keke-d8-ekeke	sooooooooooooo	1472	1488	16	1017
673305	CCCCGACCACGCCCCGG	keke-d8-ekeke	sooooooooooooo	1473	1489	11	1018
673306	GCCCCGACCACGCCCCG	keke-d8-ekeke	sooooooooooooo	1474	1490	13	1019
673307	CGCCCCGACCACGCCCC	keke-d8-ekeke	sooooooooooooo	1475	1491	43	1020
673308	CCGCCCCGACCACGCCC	keke-d8-ekeke	sooooooooooooo	1476	1492	20	1021

673309	CCCGCCCCGACCACGCC	keke-d8-ekeke	soossssssssooss	1477	1493	16	1022
673310	GCCCGCCCCGACCACGC	keke-d8-ekeke	soossssssssooss	1478	1494	44	1023
673311	GGCCCGCCCCGACCACG	keke-d8-ekeke	soossssssssooss	1479	1495	33	1024
673312	GGGCCCCCCCCGACCAC	keke-d8-ekeke	soossssssssooss	1480	1496	1	1025
673313	CGGGCCCCCCCCGACCA	keke-d8-ekeke	soossssssssooss	1481	1497	0	1026
673314	CCGGGCCCCCCCCGACC	keke-d8-ekeke	soossssssssooss	1482	1498	0	1027
673315	CCCGGGCCCCCCCCGAC	keke-d8-ekeke	soossssssssooss	1483	1499	8	1028
673316	GCAGCCCCGCCCCGGGC	keke-d8-ekeke	soossssssssooss	1505	1521	31	1029
673317	CGCAGCCCCGCCCCGGG	keke-d8-ekeke	soossssssssooss	1506	1522	4	1030
673318	CCGCAGCCCCGCCCCGG	keke-d8-ekeke	soossssssssooss	1507	1523	18	1031
673319	ACCGCAGCCCCGCCCCG	keke-d8-ekeke	soossssssssooss	1508	1524	16	1032
673320	AACCGCAGCCCCGCCCC	keke-d8-ekeke	soossssssssooss	1509	1525	39	1033
673321	CAACCGCAGCCCCGCCC	keke-d8-ekeke	soossssssssooss	1510	1526	50	1034
673322	GCAACCGCAGCCCCGCC	keke-d8-ekeke	soossssssssooss	1511	1527	45	1035
673323	CGCAACCGCAGCCCCGC	keke-d8-ekeke	soossssssssooss	1512	1528	56	1036
673324	CCGCAACCGCAGCCCCG	keke-d8-ekeke	soossssssssooss	1513	1529	10	1037
673325	ACCGCAACCGCAGCCCC	keke-d8-ekeke	soossssssssooss	1514	1530	43	1038
673326	CACCGCAACCGCAGCCC	keke-d8-ekeke	soossssssssooss	1515	1531	49	1039
673327	GCACCGCAACCGCAGCC	keke-d8-ekeke	soossssssssooss	1516	1532	35	1040
673328	GGCACCGCAACCGCAGC	keke-d8-ekeke	soossssssssooss	1517	1533	24	1041
673329	AGGCACCGCAACCGCAG	keke-d8-ekeke	soossssssssooss	1518	1534	52	1042
673330	CAGGCACCGCAACCGCA	keke-d8-ekeke	soossssssssooss	1519	1535	38	1043
673331	GCAGGCACCGCAACCGC	keke-d8-ekeke	soossssssssooss	1520	1536	51	1044
673332	CGCAGGCACCGCAACCG	keke-d8-ekeke	soossssssssooss	1521	1537	59	1045
673333	GCGCAGGCACCGCAACC	keke-d8-ekeke	soossssssssooss	1522	1538	24	1046
673334	GGCGCAGGCACCGCAAC	keke-d8-ekeke	soossssssssooss	1523	1539	18	1047

Table 44

Percent inhibition of the C9ORF72 pathogenic associated mRNA variant compared to PBS control by Deoxy, MOE and cEt antisense oligonucleotides with mixed backbones targeting SEQ ID NO: 2

ISIS NO	Sequence	Chemistry	Linkage	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	% inhibition	SEQ ID NO
576816	GCCTTACTCTAGGACCAAGA	ceeee-d10- eeee	ssssssssssssssssss	7990	8009	60	20
673335	TGAGAGCAAGTAGTGGG	ekek-d8-kekee	soossssssssooss	1326	1342	28	898
673336	GTGAGAGCAAGTAGTGG	ekek-d8-kekee	soossssssssooss	1327	1343	27	899
673337	TGTGAGAGCAAGTAGTG	ekek-d8-kekee	soossssssssooss	1328	1344	32	900
673338	CTGTGAGAGCAAGTAGT	ekek-d8-kekee	soossssssssooss	1329	1345	43	901
673339	ACTGTGAGAGCAAGTAG	ekek-d8-kekee	soossssssssooss	1330	1346	22	902
673340	TACTGTGAGAGCAAGTA	ekek-d8-kekee	soossssssssooss	1331	1347	20	903
673341	GTA CTGTGAGAGCAAGT	ekek-d8-kekee	soossssssssooss	1332	1348	53	904
673342	AGTACTGTGAGAGCAAG	ekek-d8-kekee	soossssssssooss	1333	1349	20	905
673343	GAGTACTGTGAGAGCAA	ekek-d8-kekee	soossssssssooss	1334	1350	50	906
673344	CGAGTACTGTGAGAGCA	ekek-d8-kekee	soossssssssooss	1335	1351	45	907
673345	GCGAGTACTGTGAGAGC	ekek-d8-kekee	soossssssssooss	1336	1352	45	908
673346	AGCGAGTACTGTGAGAG	ekek-d8-kekee	soossssssssooss	1337	1353	53	909
673347	CAGCGAGTACTGTGAGA	ekek-d8-kekee	soossssssssooss	1338	1354	35	910
673348	TCAGCGAGTACTGTGAG	ekek-d8-kekee	soossssssssooss	1339	1355	36	911
673349	CTCAGCGAGTACTGTGA	ekek-d8-kekee	soossssssssooss	1340	1356	19	912
673350	CCTCAGCGAGTACTGTG	ekek-d8-kekee	soossssssssooss	1341	1357	21	913
673351	CCCTCAGCGAGTACTGT	ekek-d8-kekee	soossssssssooss	1342	1358	46	914
673352	ACCCTCAGCGAGTACTG	ekek-d8-kekee	soossssssssooss	1343	1359	43	915
673353	CACCCTCAGCGAGTACT	ekek-d8-kekee	soossssssssooss	1344	1360	46	916
673354	TCACCCTCAGCGAGTAC	ekek-d8-kekee	soossssssssooss	1345	1361	40	917
673355	TTCACCCTCAGCGAGTA	ekek-d8-kekee	soossssssssooss	1346	1362	33	918
673356	GTTACCCTCAGCGAGT	ekek-d8-kekee	soossssssssooss	1347	1363	11	919
673357	TGTTACCCTCAGCGAG	ekek-d8-kekee	soossssssssooss	1348	1364	34	920
673358	TTGTTACCCTCAGCGA	ekek-d8-kekee	soossssssssooss	1349	1365	47	921
673359	CTTGTTACCCTCAGCG	ekek-d8-kekee	soossssssssooss	1350	1366	54	922

673360	TCTTGTTACCCCTCAGC	ekek-d8-kekee	sooooooooooooo	1351	1367	26	923
673361	TTCTTGTTACCCCTCAG	ekek-d8-kekee	sooooooooooooo	1352	1368	36	924
673362	TTTCTTGTTACCCCTCA	ekek-d8-kekee	sooooooooooooo	1353	1369	29	925
673363	TTTTCTTGTTACCCCTC	ekek-d8-kekee	sooooooooooooo	1354	1370	29	926
673364	CTTTTCTTGTTACCCCT	ekek-d8-kekee	sooooooooooooo	1355	1371	23	927
673365	TCTTTTCTTGTTACCCC	ekek-d8-kekee	sooooooooooooo	1356	1372	36	928
673366	GTCTTTTCTTGTTACCC	ekek-d8-kekee	sooooooooooooo	1357	1373	27	929
673367	GGTCTTTTCTTGTTAC	ekek-d8-kekee	sooooooooooooo	1358	1374	21	930
673368	AGGTCTTTTCTTGTTCA	ekek-d8-kekee	sooooooooooooo	1359	1375	29	931
673369	CAGGTCTTTTCTTGTT	ekek-d8-kekee	sooooooooooooo	1360	1376	65	932
673370	TCAGGTCTTTTCTTGTT	ekek-d8-kekee	sooooooooooooo	1361	1377	2	933
673371	ATCAGGTCTTTTCTTGT	ekek-d8-kekee	sooooooooooooo	1362	1378	23	934
673372	TATCAGGTCTTTTCTTG	ekek-d8-kekee	sooooooooooooo	1363	1379	40	935
673373	TTATCAGGTCTTTTCTT	ekek-d8-kekee	sooooooooooooo	1364	1380	13	936
673374	ATCTTTATCAGGTCTTT	ekek-d8-kekee	sooooooooooooo	1368	1384	76	937
673375	AATCTTTATCAGGTCTT	ekek-d8-kekee	sooooooooooooo	1369	1385	62	938
673376	TAATCTTTATCAGGTCT	ekek-d8-kekee	sooooooooooooo	1370	1386	39	939
673377	TTAATCTTTATCAGGTC	ekek-d8-kekee	sooooooooooooo	1371	1387	71	940
673378	GTTAATCTTTATCAGGT	ekek-d8-kekee	sooooooooooooo	1372	1388	61	941
673379	GGTTAATCTTTATCAGG	ekek-d8-kekee	sooooooooooooo	1373	1389	74	942
673380	TGGTTAATCTTTATCAG	ekek-d8-kekee	sooooooooooooo	1374	1390	24	943
673381	CTGGTTAATCTTTATCA	ekek-d8-kekee	sooooooooooooo	1375	1391	32	944
673382	TCTGGTTAATCTTTATC	ekek-d8-kekee	sooooooooooooo	1376	1392	38	945
673383	CCCTCCTTGTTTTCTTC	ekek-d8-kekee	sooooooooooooo	1391	1407	21	946
673384	TCCCTCCTTGTTTTCTT	ekek-d8-kekee	sooooooooooooo	1392	1408	0	947
673385	TTCCCTCCTTGTTTTCT	ekek-d8-kekee	sooooooooooooo	1393	1409	0	948
673386	TTTCCCTCCTTGTTTTCT	ekek-d8-kekee	sooooooooooooo	1394	1410	5	949
673387	GTTTCCCTCCTTGTTTT	ekek-d8-kekee	sooooooooooooo	1395	1411	0	950
673388	TGTTTCCCTCCTTGTTTT	ekek-d8-kekee	sooooooooooooo	1396	1412	0	951
673389	TTGTTTCCCTCCTTGTT	ekek-d8-kekee	sooooooooooooo	1397	1413	22	952
673390	GGTTGTTTCCCTCCTTG	ekek-d8-kekee	sooooooooooooo	1399	1415	55	953
673391	CGGTTGTTTCCCTCCTT	ekek-d8-kekee	sooooooooooooo	1400	1416	25	954
673392	GCGGTTGTTTCCCTCCT	ekek-d8-kekee	sooooooooooooo	1401	1417	19	955

673393	TGCGGTTGTTCCCTCC	ekek-d8-kekee	sooooooooooooo	1402	1418	0	956
673394	CTGCGGTTGTTCCCTC	ekek-d8-kekee	sooooooooooooo	1403	1419	13	957
673395	GCTGCGGTTGTTCCCT	ekek-d8-kekee	sooooooooooooo	1404	1420	19	958
673396	GGCTGCGGTTGTTCCC	ekek-d8-kekee	sooooooooooooo	1405	1421	27	959
673397	AGGCTGCGGTTGTTCC	ekek-d8-kekee	sooooooooooooo	1406	1422	13	960
673398	CAGGCTGCGGTTGTTTC	ekek-d8-kekee	sooooooooooooo	1407	1423	22	961
673399	ACAGGCTGCGGTTGTTT	ekek-d8-kekee	sooooooooooooo	1408	1424	5	962
673400	TACAGGCTGCGGTTGTT	ekek-d8-kekee	sooooooooooooo	1409	1425	0	963
673401	CTACAGGCTGCGGTTGT	ekek-d8-kekee	sooooooooooooo	1410	1426	0	964
673402	GCTACAGGCTGCGGTTG	ekek-d8-kekee	sooooooooooooo	1411	1427	39	965
673403	TGCTACAGGCTGCGGTT	ekek-d8-kekee	sooooooooooooo	1412	1428	20	966
673404	TTGCTACAGGCTGCGGT	ekek-d8-kekee	sooooooooooooo	1413	1429	24	967
673405	CTTGCTACAGGCTGCGG	ekek-d8-kekee	sooooooooooooo	1414	1430	0	968
673406	GCTTGCTACAGGCTGCG	ekek-d8-kekee	sooooooooooooo	1415	1431	18	969
673407	AGCTTGCTACAGGCTGC	ekek-d8-kekee	sooooooooooooo	1416	1432	3	970
673408	GAGCTTGCTACAGGCTG	ekek-d8-kekee	sooooooooooooo	1417	1433	13	971
673409	AGAGCTTGCTACAGGCT	ekek-d8-kekee	sooooooooooooo	1418	1434	29	972
673410	CAGAGCTTGCTACAGGC	ekek-d8-kekee	sooooooooooooo	1419	1435	22	973
673411	CCAGAGCTTGCTACAGG	ekek-d8-kekee	sooooooooooooo	1420	1436	24	974
673412	TCCAGAGCTTGCTACAG	ekek-d8-kekee	sooooooooooooo	1421	1437	4	975
673413	TTCCAGAGCTTGCTACA	ekek-d8-kekee	sooooooooooooo	1422	1438	0	976
673414	GTTCCAGAGCTTGCTAC	ekek-d8-kekee	sooooooooooooo	1423	1439	19	977
673415	AGTTCCAGAGCTTGCTA	ekek-d8-kekee	sooooooooooooo	1424	1440	0	978
673416	GAGTTCCAGAGCTTGCT	ekek-d8-kekee	sooooooooooooo	1425	1441	48	979
673417	TGAGTTCCAGAGCTTGC	ekek-d8-kekee	sooooooooooooo	1426	1442	14	980
673418	CTGAGTTCCAGAGCTTG	ekek-d8-kekee	sooooooooooooo	1427	1443	37	981
673419	CCTGAGTTCCAGAGCTT	ekek-d8-kekee	sooooooooooooo	1428	1444	80	982
673420	TCCTGAGTTCCAGAGCT	ekek-d8-kekee	sooooooooooooo	1429	1445	26	983
673421	CTCCTGAGTTCCAGAGC	ekek-d8-kekee	sooooooooooooo	1430	1446	5	984
673422	ACTCCTGAGTTCCAGAG	ekek-d8-kekee	sooooooooooooo	1431	1447	23	985
673423	GACTCCTGAGTTCCAGA	ekek-d8-kekee	sooooooooooooo	1432	1448	37	986
673424	CGACTCCTGAGTTCCAG	ekek-d8-kekee	sooooooooooooo	1433	1449	5	987
673425	GCGACTCCTGAGTTCCA	ekek-d8-kekee	sooooooooooooo	1434	1450	39	988

673426	CGCGACTCCTGAGTTCC	ekek-d8-kekee	sooooooooooooo	1435	1451	46	989
673427	GCGCGACTCCTGAGTTC	ekek-d8-kekee	sooooooooooooo	1436	1452	50	990
673428	CGCGCGACTCCTGAGTT	ekek-d8-kekee	sooooooooooooo	1437	1453	19	991
673429	GCGCGCGACTCCTGAGT	ekek-d8-kekee	sooooooooooooo	1438	1454	13	992
673430	AGCGCGCGACTCCTGAG	ekek-d8-kekee	sooooooooooooo	1439	1455	51	993
673431	TAGCGCGCGACTCCTGA	ekek-d8-kekee	sooooooooooooo	1440	1456	83	994
673432	CTAGCGCGCGACTCCTG	ekek-d8-kekee	sooooooooooooo	1441	1457	60	995
673433	CCTAGCGCGCGACTCCT	ekek-d8-kekee	sooooooooooooo	1442	1458	37	996
673434	CCCTAGCGCGCGACTCC	ekek-d8-kekee	sooooooooooooo	1443	1459	60	997
673435	CCCCTAGCGCGCGACTC	ekek-d8-kekee	sooooooooooooo	1444	1460	62	998
673436	GCCCCTAGCGCGCGACT	ekek-d8-kekee	sooooooooooooo	1445	1461	41	999
673437	GGCCCCTAGCGCGCGAC	ekek-d8-kekee	sooooooooooooo	1446	1462	8	1000
673438	CGGCCCCTAGCGCGCGA	ekek-d8-kekee	sooooooooooooo	1447	1463	31	1001
673439	CCGGCCCCTAGCGCGCG	ekek-d8-kekee	sooooooooooooo	1448	1464	18	1002
673440	CCCGGCCCCTAGCGCGC	ekek-d8-kekee	sooooooooooooo	1449	1465	6	1003
673441	CCCCGGCCCCTAGCGCG	ekek-d8-kekee	sooooooooooooo	1450	1466	23	1004
673442	GCCCCGGCCCCTAGCGC	ekek-d8-kekee	sooooooooooooo	1451	1467	8	1005
673443	GGCCCCGGCCCCTAGCG	ekek-d8-kekee	sooooooooooooo	1452	1468	18	1006
673444	CGGCCCCGGCCCCTAGC	ekek-d8-kekee	sooooooooooooo	1453	1469	28	1007
673445	CCGGCCCCGGCCCCTAG	ekek-d8-kekee	sooooooooooooo	1454	1470	9	1008
673446	CCCGGCCCCGGCCCCTA	ekek-d8-kekee	sooooooooooooo	1455	1471	5	1009
673447	ACGCCCCGGCCCCGGCC	ekek-d8-kekee	sooooooooooooo	1465	1481	23	1010
673448	CACGCCCCGGCCCCGGC	ekek-d8-kekee	sooooooooooooo	1466	1482	14	1011
673449	CCACGCCCCGGCCCCGG	ekek-d8-kekee	sooooooooooooo	1467	1483	35	1012
673450	ACCACGCCCCGGCCCCG	ekek-d8-kekee	sooooooooooooo	1468	1484	30	1013
673451	GACCACGCCCCGGCCCC	ekek-d8-kekee	sooooooooooooo	1469	1485	0	1014
673452	CGACCACGCCCCGGCCC	ekek-d8-kekee	sooooooooooooo	1470	1486	15	1015
673453	CCGACCACGCCCCGGCC	ekek-d8-kekee	sooooooooooooo	1471	1487	42	1016
673454	CCCGACCACGCCCCGGC	ekek-d8-kekee	sooooooooooooo	1472	1488	19	1017
673455	CCCCGACCACGCCCCGG	ekek-d8-kekee	sooooooooooooo	1473	1489	21	1018
673456	GCCCCGACCACGCCCCG	ekek-d8-kekee	sooooooooooooo	1474	1490	9	1019
673457	CGCCCCGACCACGCCCC	ekek-d8-kekee	sooooooooooooo	1475	1491	45	1020
673458	CCGCCCCGACCACGCCC	ekek-d8-kekee	sooooooooooooo	1476	1492	14	1021

673459	CCCGCCCCGACCACGCC	ekek-d8-kekee	sooooooooooooo	1477	1493	2	1022
673460	GCCCGCCCCGACCACGC	ekek-d8-kekee	sooooooooooooo	1478	1494	28	1023
673461	GGCCCGCCCCGACCACG	ekek-d8-kekee	sooooooooooooo	1479	1495	19	1024
673462	GGGCCCGCCCCGACCAC	ekek-d8-kekee	sooooooooooooo	1480	1496	26	1025
673463	CGGGCCCGCCCCGACCA	ekek-d8-kekee	sooooooooooooo	1481	1497	12	1026
673464	CCGGGCCCGCCCCGACC	ekek-d8-kekee	sooooooooooooo	1482	1498	18	1027
673465	CCCGGGCCCGCCCCGAC	ekek-d8-kekee	sooooooooooooo	1483	1499	19	1028
673466	GCAGCCCCGCCCCGGGC	ekek-d8-kekee	sooooooooooooo	1505	1521	11	1029
673467	CGCAGCCCCGCCCCGGG	ekek-d8-kekee	sooooooooooooo	1506	1522	40	1030
673468	CCGCAGCCCCGCCCCGG	ekek-d8-kekee	sooooooooooooo	1507	1523	12	1031
673469	ACCGCAGCCCCGCCCCG	ekek-d8-kekee	sooooooooooooo	1508	1524	26	1032
673470	AACCGCAGCCCCGCCCC	ekek-d8-kekee	sooooooooooooo	1509	1525	36	1033
673471	CAACCGCAGCCCCGCCC	ekek-d8-kekee	sooooooooooooo	1510	1526	63	1034
673472	GCAACCGCAGCCCCGCC	ekek-d8-kekee	sooooooooooooo	1511	1527	35	1035
673473	CGCAACCGCAGCCCCGC	ekek-d8-kekee	sooooooooooooo	1512	1528	51	1036
673474	CCGCAACCGCAGCCCCG	ekek-d8-kekee	sooooooooooooo	1513	1529	27	1037
673475	ACCGCAACCGCAGCCCC	ekek-d8-kekee	sooooooooooooo	1514	1530	49	1038
673476	CACCGCAACCGCAGCCC	ekek-d8-kekee	sooooooooooooo	1515	1531	34	1039
673477	GCACCGCAACCGCAGCC	ekek-d8-kekee	sooooooooooooo	1516	1532	36	1040
673478	GGCACCGCAACCGCAGC	ekek-d8-kekee	sooooooooooooo	1517	1533	22	1041
673479	AGGCACCGCAACCGCAG	ekek-d8-kekee	sooooooooooooo	1518	1534	23	1042
673480	CAGGCACCGCAACCGCA	ekek-d8-kekee	sooooooooooooo	1519	1535	27	1043
673481	GCAGGCACCGCAACCGC	ekek-d8-kekee	sooooooooooooo	1520	1536	41	1044
673482	CGCAGGCACCGCAACCG	ekek-d8-kekee	sooooooooooooo	1521	1537	60	1045
673483	GCGCAGGCACCGCAACC	ekek-d8-kekee	sooooooooooooo	1522	1538	22	1046
673484	GGCGCAGGCACCGCAAC	ekek-d8-kekee	sooooooooooooo	1523	1539	11	1047

Example 11: Dose-dependent antisense inhibition of human C9ORF72 mRNA in HepG2 cells

Antisense oligonucleotides from the study described in Example 10 hereinabove exhibiting
5 significant *in vitro* inhibition of C9ORF72 mRNA were selected and tested at various doses in HepG2 cells. ISIS 576816, which was previously tested in PCT/US2013/065073 (claiming priority to US Application No. 61/714,132, filed October 15, 2012) was used as a benchmark oligonucleotide. Cells were plated at a density

of 20,000 cells per well and transfected using electroporation with 0.185 μM , 0.56 μM , 1.67 μM , or 5.00 μM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3905 was used to measure the C9ORF72 pathogenic associated mRNA variant, which is the product of a pre-mRNA containing a hexanucleotide repeat. C9ORF72 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN[®]. Results are presented as percent inhibition of C9ORF72 levels, relative to untreated control cells.

As shown in Tables 45-52, total C9ORF72 mRNA levels were reduced in a dose-dependent manner in some of the antisense oligonucleotide treated cells.

Table 45

Dose-dependent inhibition of the C9ORF72 pathogenic associated mRNA variant transcript levels in HepG2 cells

ISIS No	0.185 μM	0.56 μM	1.67 μM	5.00 μM	IC ₅₀ (μM)
576816	21	66	82	91	0.5
672893	4	50	83	82	0.8
672894	13	55	70	88	0.7
672896	13	57	81	89	0.6
672897	2	38	72	79	1.1
672902	20	40	83	88	0.7
672903	19	44	73	80	0.8
672904	16	35	49	85	1.2
672905	15	30	67	82	1.0
672908	41	49	79	83	0.4
672909	20	54	72	90	0.6
672919	31	58	69	92	0.5
672924	34	60	89	97	0.4
672925	41	58	88	94	0.3
672927	31	78	81	92	0.3
672928	30	62	79	92	0.4
672929	51	71	89	94	0.1
672932	10	54	83	88	0.7
672940	14	36	58	87	1.0

Table 46

Dose-dependent inhibition of the C9ORF72 pathogenic associated mRNA variant transcript levels in HepG2 cells

ISIS No	0.185 μM	0.56 μM	1.67 μM	5.00 μM	IC ₅₀ (μM)
576816	24	51	78	88	0.6
672948	17	27	52	65	1.8
672966	1	36	77	73	1.1
672967	24	36	44	75	1.4
672968	15	46	69	83	0.8
672969	1	39	66	93	1.0
672976	47	65	74	80	0.2
672978	36	32	52	76	1.0
672980	24	45	77	86	0.6
672981	48	74	86	93	0.1
672982	42	63	91	90	0.2
672983	38	56	83	92	0.4
672984	33	53	72	88	0.5
672985	38	46	66	78	0.6
673021	43	48	76	79	0.4
673022	2	52	58	89	1.0
673023	44	36	76	78	0.5
673026	22	77	70	76	0.4
673032	19	37	55	80	1.1

5

Table 47

Dose-dependent inhibition of the C9ORF72 pathogenic associated mRNA variant transcript levels in HepG2 cells

ISIS No	0.185 μM	0.56 μM	1.67 μM	5.00 μM	IC ₅₀ (μM)
576816	48	49	80	95	0.3
673036	38	54	73	88	0.4
673047	27	75	93	87	0.3
673050	6	66	83	82	0.6
673051	31	57	69	85	0.5
673053	17	59	76	92	0.6
673054	15	45	76	90	0.7

673057	37	67	64	81	0.3
673058	35	62	79	87	0.4
673067	59	74	98	97	<0.2
673068	37	71	85	95	0.3
673071	43	5	59	64	1.9
673074	37	44	89	89	0.4
673079	41	71	89	95	0.2
673081	21	37	80	76	0.8
673082	27	58	87	92	0.4
673088	63	79	96	97	<0.2
673089	11	41	71	83	0.9
673098	15	61	68	93	0.6

Table 48

Dose-dependent inhibition of the C9ORF72 pathogenic associated mRNA variant transcript levels in HepG2 cells

ISIS No	0.185 μM	0.56 μM	1.67 μM	5.00 μM	IC ₅₀ (μM)
576816	43	71	80	93	0.2
673098	18	53	81	88	0.6
673117	22	45	76	80	0.7
673119	17	47	65	90	0.8
673125	33	64	79	79	0.4
673126	41	56	70	82	0.4
673127	46	85	92	96	<0.2
673128	32	71	88	99	0.3
673130	42	69	91	91	0.2
673131	34	62	74	99	0.4
673132	47	44	75	89	0.4
673133	54	61	78	84	<0.2
673134	41	62	77	77	0.3
673135	28	60	77	82	0.5
673144	24	58	64	92	0.6
673152	18	59	70	72	0.7
673159	4	50	75	80	0.9
673171	17	43	58	86	0.9
673175	30	45	76	78	0.6

Table 49

Dose-dependent inhibition of the C9ORF72 pathogenic associated mRNA variant transcript levels in HepG2 cells

ISIS No	0.185 μM	0.56 μM	1.67 μM	5.00 μM	IC ₅₀ (μM)
576816	22	69	78	93	0.4
673193	60	74	90	89	<0.2
673194	15	54	75	77	0.7
673196	36	38	71	73	0.7
673197	28	39	68	78	0.8
673201	0	40	69	91	1.0
673202	9	50	77	89	0.7
673203	40	52	84	98	0.4
673204	44	67	91	92	0.2
673206	27	40	70	90	0.7
673210	22	43	79	94	0.6
673211	0	45	53	85	1.2
673219	27	36	67	88	0.8
673224	41	65	86	95	0.3
673225	34	73	78	97	0.3
673226	19	59	83	94	0.5
673228	8	67	79	94	0.6
673229	46	76	89	86	<0.2
673240	18	58	75	93	0.6

5

Table 50

Dose-dependent inhibition of the C9ORF72 pathogenic associated mRNA variant transcript levels in HepG2 cells

ISIS No	0.185 μM	0.56 μM	1.67 μM	5.00 μM	IC ₅₀ (μM)
576816	31	65	81	89	0.4
673265	24	43	73	83	0.7
673269	12	58	81	89	0.6
673275	31	57	63	94	0.5
673276	33	56	69	91	0.5
673277	37	51	65	66	0.6
673279	11	57	68	86	0.8

673280	38	60	80	95	0.3
673281	51	83	92	86	<0.2
673282	60	73	93	95	<0.2
673283	59	66	94	96	<0.2
673284	45	59	78	91	0.3
673285	30	59	78	86	0.4
673321	10	44	72	79	0.9
673323	43	54	76	86	0.3
673326	0	46	72	81	0.8
673329	15	30	64	76	1.2
673331	47	40	66	79	0.5
673332	58	49	71	78	<0.2

Table 51

Dose-dependent inhibition of the C9ORF72 pathogenic associated mRNA variant transcript levels in HepG2 cells

ISIS No	0.185 μM	0.56 μM	1.67 μM	5.00 μM	IC ₅₀ (μM)
576816	38	61	75	92	0.3
673338	0	13	48	61	2.6
673341	29	39	66	82	0.8
673343	38	33	58	81	0.8
673344	29	40	69	72	0.8
673345	24	11	51	66	2.2
673346	19	27	52	74	1.4
673351	17	40	61	82	1.0
673352	18	36	62	71	1.2
673353	29	38	47	74	1.2
673358	11	39	63	71	1.2
673359	15	46	51	65	1.4
673369	17	33	55	70	1.4
673374	42	62	77	87	0.3
673375	28	66	79	94	0.4
673377	32	51	77	87	0.5
673378	32	47	76	89	0.5
673379	33	58	76	83	0.4
673390	21	40	57	74	1.1

Table 52

Dose-dependent inhibition of the C9ORF72 pathogenic associated mRNA variant transcript levels in HepG2 cells

ISIS No	0.185 μM	0.56 μM	1.67 μM	5.00 μM	IC ₅₀ (μM)
576816	6	54	75	88	0.7
673416	31	51	61	67	0.7
673419	16	34	41	67	2.0
673426	31	62	53	68	0.7
673427	41	52	52	59	0.8
673430	27	46	76	83	0.6
673431	49	68	83	96	0.2
673432	43	72	72	86	0.2
673434	41	70	80	90	0.2
673435	8	48	71	69	1.0
673436	15	20	65	66	1.6
673453	18	49	57	72	1.0
673457	0	19	43	63	2.5
673467	12	25	35	42	>5.0
673471	13	45	57	79	1.0
673473	13	48	62	92	0.8
673475	23	30	65	61	1.4
673481	26	33	52	41	>5.0
673482	14	45	56	75	1.1

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Example 12: Antisense inhibition of C9ORF72 by human-rhesus cross-reactive antisense oligonucleotides in LLC-MK2 cells by mixed backbone 5-8-5 MOE and 5-10-5 MOE gapmers

Antisense oligonucleotides targeting a human C9ORF72 nucleic acid and cross-reactive with a rhesus C9ORF72 nucleic acid were designed and tested for their effects on rhesus C9ORF72 mRNA expression in vitro. ISIS 576816, previously tested in US Application No. 61/714,132, filed October 15, 2012, was used as a benchmark oligonucleotide. ISIS 619420, which is the mixed backbone version of ISIS 576816, described in Example 2 hereinabove was also tested. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cultured LLC-MK2 cells at a density of 20,000 cells per well were transfected using electroporation with 3,500 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time

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PCR. Human primer probe set RTS3750 (a TAQ-man primer probe set) was used to measure total C9ORF72 mRNA levels. RTS3750 targets exon 2 of the mRNA transcripts and, therefore, measures total mRNA transcripts. In cases where the oligonucleotide overlapped the amplicon of the primer probe set RTS3750 (see, e.g., Table 53), an alternative primer probe set, RTS3760_MGB (forward sequence

5 TTCCAATGCTTACTGGAGAAGTGA, designated herein as SEQ ID NO: 1546; reverse sequence GGAACACTGTGTGATTTTCATAGATGA, designated herein as SEQ ID NO: 1547; probe sequence TCCTGTAATGGAACTGC, designated herein as SEQ ID NO: 1548 – a TAQ-man primer probe set) was used to measure total mRNA transcripts. The levels of the C9ORF72 mRNA were normalized to the total RNA content of the cell, as measured by RIBOGREEN®. Results are presented as percent inhibition of

10 rhesus C9ORF72 mRNA expression, relative to untreated control cells. The oligonucleotides marked with as asterisk (*) target the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of these oligonucleotides. ‘n.d.’ indicates that there was no signal reading in the assay for that particular oligonucleotide.

The newly designed chimeric antisense oligonucleotides in the Tables below were designed as 5-8-5

15 MOE gapmers and 5-10-5 MOE gapmers.

The 5-8-5 MOE gapmers are 18 nucleosides in length, wherein the central gap segment comprises eight 2'-deoxynucleosides and is flanked by wing segments on both the 5' end and the 3' end comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE group. All cytosine residues throughout each gapmer are 5-methylcytosines. The internucleoside

20 linkages for the gapmers are mixed phosphorothioate and phosphodiester linkages. The internucleoside linkages for each gapmer are presented in the Linkage column, where ‘o’ indicates a phosphodiester linkage and ‘s’ indicates a phosphorothioate linkage.

The 5-10-5 MOE gapmers are 20 nucleosides in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both the 5' end and the 3' end comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE group. All cytosine residues throughout each gapmer are 5-methylcytosines. The internucleoside

25 linkages for the gapmers are mixed phosphorothioate and phosphodiester linkages. The internucleoside linkages for each gapmer are presented in the Linkage column, where ‘o’ indicates a phosphodiester linkage and ‘s’ indicates a phosphorothioate linkage.

30 “Start site” indicates the 5'-most nucleoside to which the gapmer is targeted in the gene sequence. “Stop site” indicates the 3'-most nucleoside to which the gapmer is targeted in the gene sequence. Each gapmer listed in the Tables below is targeted to one or more of human C9ORF72 mRNA sequence, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_001256054.1), human C9ORF72 genomic sequence, designated herein as SEQ ID NO: 2 (the complement of GENBANK

Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000), and rhesus C9ORF72 genomic sequence designated herein as SEQ ID NO: 19 (GENBANK Accession No. NW_001101662.1 truncated from nucleosides 8522000 to 8552000). The 'Mismatches' column indicates the number of mismatches the human antisense oligonucleotide has with the rhesus genomic sequence. 'n/a' in the rhesus sequence columns indicates that the human oligonucleotide has more than 3 mismatches with the rhesus genomic sequence. Where the 'Mismatches' column is not provided in a Table, it is understood that the human oligonucleotides of the Table are fully cross-reactive with the rhesus genomic sequence.

Table 53

Percent inhibition of the C9ORF72 mRNA levels compared to PBS control by antisense oligonucleotides targeting SEQ ID NOs: 1, 2 and 19

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 19 Start Site	Sequence	Linkage	Motif	% inhibition (RTS3750)	% inhibition (RTS3760_MGB)	SEQ ID NO
576816	310	7990	8043	GCCTTACTCTAGGACCAAGA	ssssssssssssssssss	5-10-5	60	54	20
619420	310	7990	8043	GCCTTACTCTAGGACCAAGA	soooooossssssooss	5-10-5	69	68	20
688005*	221	7901	7954	AACAGCTGGAGATGGCGG	soooooossssssooss	5-8-5	12	36	1057
688006*	222	7902	7955	CAACAGCTGGAGATGGCG	soooooossssssooss	5-8-5	29	20	1058
688007*	223	7903	7956	GCAACAGCTGGAGATGGC	soooooossssssooss	5-8-5	46	33	1059
688008*	224	7904	7957	GGCAACAGCTGGAGATGG	soooooossssssooss	5-8-5	59	41	1060
688009*	225	7905	7958	TGGCAACAGCTGGAGATG	soooooossssssooss	5-8-5	43	24	1061
688010*	226	7906	7959	TTGGCAACAGCTGGAGAT	soooooossssssooss	5-8-5	31	0	1062
688011*	227	7907	7960	CTTGGCAACAGCTGGAGA	soooooossssssooss	5-8-5	45	18	1063
688012*	228	7908	7961	TCTTGGCAACAGCTGGAG	soooooossssssooss	5-8-5	67	0	1064
688013*	229	7909	7962	GTCTTGGCAACAGCTGGA	soooooossssssooss	5-8-5	48	13	1065
688014*	230	7910	7963	TGTCTTGGCAACAGCTGG	soooooossssssooss	5-8-5	16	16	1066
688015*	231	7911	7964	CTGTCTTGGCAACAGCTG	soooooossssssooss	5-8-5	75	33	1067
688016*	232	7912	7965	TCTGTCTTGGCAACAGCT	soooooossssssooss	5-8-5	37	36	1068
688017*	233	7913	7966	CTCTGTCTTGGCAACAGC	soooooossssssooss	5-8-5	59	28	1069
688018*	234	7914	7967	TCTCTGTCTTGGCAACAG	soooooossssssooss	5-8-5	40	36	1070
688019*	235	7915	7968	ATCTCTGTCTTGGCAACA	soooooossssssooss	5-8-5	34	31	1071
688020*	236	7916	7969	AATCTCTGTCTTGGCAAC	soooooossssssooss	5-8-5	30	26	1072
688021*	237	7917	7970	CAATCTCTGTCTTGGCAA	soooooossssssooss	5-8-5	58	0	1073
688022*	238	7918	7971	GCAATCTCTGTCTTGGCA	soooooossssssooss	5-8-5	90	52	1074
688023*	239	7919	7972	AGCAATCTCTGTCTTGGC	soooooossssssooss	5-8-5	92	73	1075
688024*	240	7920	7973	AAGCAATCTCTGTCTTGG	soooooossssssooss	5-8-5	74	24	1076
688025*	241	7921	7974	AAAGCAATCTCTGTCTTG	soooooossssssooss	5-8-5	76	0	1077
688026*	242	7922	7975	TAAAGCAATCTCTGTCTT	soooooossssssooss	5-8-5	28	6	1078

688027*	243	7923	7976	TTAAAGCAATCTCTGTCT	sooooooooooooo	5-8-5	32	18	1079
688028*	244	7924	7977	CTTAAAGCAATCTCTGTC	sooooooooooooo	5-8-5	41	4	1080
688029*	245	7925	7978	ACTTAAAGCAATCTCTGT	sooooooooooooo	5-8-5	63	0	1081
688030*	246	7926	7979	CACTTAAAGCAATCTCTG	sooooooooooooo	5-8-5	26	31	1082
688031*	247	7927	7980	CCACTTAAAGCAATCTCT	sooooooooooooo	5-8-5	73	33	1083
688032	267	7947	8000	CTGCTAATAAAGGTGATT	sooooooooooooo	5-8-5	24	34	1084
688033	268	7948	8001	GCTGCTAATAAAGGTGAT	sooooooooooooo	5-8-5	11	18	1085
688034	269	7949	8002	AGCTGCTAATAAAGGTGA	sooooooooooooo	5-8-5	40	34	1086
688035	270	7950	8003	TAGCTGCTAATAAAGGTG	sooooooooooooo	5-8-5	46	1	1087
688036	271	7951	8004	GTAGCTGCTAATAAAGGT	sooooooooooooo	5-8-5	13	17	1088
688037	272	7952	8005	AGTAGCTGCTAATAAAGG	sooooooooooooo	5-8-5	0	0	1089
688038	273	7953	8006	AAGTAGCTGCTAATAAAG	sooooooooooooo	5-8-5	0	0	1090
688039	274	7954	8007	AAAGTAGCTGCTAATAAA	sooooooooooooo	5-8-5	0	3	1091
688040	275	7955	8008	AAAAGTAGCTGCTAATAA	sooooooooooooo	5-8-5	0	0	1092
688041	276	7956	8009	CAAAAGTAGCTGCTAATA	sooooooooooooo	5-8-5	0	0	1093
688042	277	7957	8010	GCAAAAGTAGCTGCTAAT	sooooooooooooo	5-8-5	32	31	1094
688043	278	7958	8011	AGCAAAAGTAGCTGCTAA	sooooooooooooo	5-8-5	18	14	1095
688044	279	7959	8012	AAGCAAAAGTAGCTGCTA	sooooooooooooo	5-8-5	17	24	1096
688045	280	7960	8013	TAAGCAAAAGTAGCTGCT	sooooooooooooo	5-8-5	38	7	1097
688046	281	7961	8014	GTAAGCAAAAGTAGCTGC	sooooooooooooo	5-8-5	37	38	1098
688047	282	7962	8015	AGTAAGCAAAAGTAGCTG	sooooooooooooo	5-8-5	12	33	1099
688048	283	7963	8016	CAGTAAGCAAAAGTAGCT	sooooooooooooo	5-8-5	17	29	1100
688049	284	7964	8017	CCAGTAAGCAAAAGTAGC	sooooooooooooo	5-8-5	17	0	1101
688050	285	7965	8018	CCCAGTAAGCAAAAGTAG	sooooooooooooo	5-8-5	7	27	1102
688051	286	7966	8019	TCCCAGTAAGCAAAAGTA	sooooooooooooo	5-8-5	0	0	1103
688052	287	7967	8020	GTCCCAGTAAGCAAAAGT	sooooooooooooo	5-8-5	16	24	1104
688053	288	7968	8021	TGTCCCAGTAAGCAAAAG	sooooooooooooo	5-8-5	0	0	1105
688054	289	7969	8022	TTGTCCCAGTAAGCAAAA	sooooooooooooo	5-8-5	9	10	1106
688055	290	7970	8023	ATTGTCCCAGTAAGCAAA	sooooooooooooo	5-8-5	6	15	1107
688056	291	7971	8024	TATTGTCCCAGTAAGCAA	sooooooooooooo	5-8-5	21	0	1108
688057	292	7972	8025	ATATTGTCCCAGTAAGCA	sooooooooooooo	5-8-5	11	4	1109
688058	293	7973	8026	AATATTGTCCCAGTAAGC	sooooooooooooo	5-8-5	23	29	1110
688059	294	7974	8027	GAATATTGTCCCAGTAAG	sooooooooooooo	5-8-5	5	13	1111
688060	295	7975	8028	AGAATATTGTCCCAGTAA	sooooooooooooo	5-8-5	0	31	1112
688061	296	7976	8029	AAGAATATTGTCCCAGTA	sooooooooooooo	5-8-5	0	16	1113
688062	297	7977	8030	CAAGAATATTGTCCCAGT	sooooooooooooo	5-8-5	29	0	1114
688063	298	7978	8031	CCAAGAATATTGTCCCAG	sooooooooooooo	5-8-5	26	42	1115
688064	299	7979	8032	ACCAAGAATATTGTCCCA	sooooooooooooo	5-8-5	19	11	1116
688065	300	7980	8033	GACCAAGAATATTGTCCC	sooooooooooooo	5-8-5	31	26	1117
688066	301	7981	8034	GGACCAAGAATATTGTCC	sooooooooooooo	5-8-5	0	0	1118
688067	302	7982	8035	AGGACCAAGAATATTGTC	sooooooooooooo	5-8-5	5	10	1119
688068	303	7983	8036	TAGGACCAAGAATATTGT	sooooooooooooo	5-8-5	20	13	1120
688069	304	7984	8037	CTAGGACCAAGAATATTG	sooooooooooooo	5-8-5	0	22	1121

688070	305	7985	8038	TCTAGGACCAAGAATATT	sooooooooooooo	5-8-5	0	0	1122
688071	306	7986	8039	CTCTAGGACCAAGAATAT	sooooooooooooo	5-8-5	5	18	1123
688072	307	7987	8040	ACTCTAGGACCAAGAATA	sooooooooooooo	5-8-5	17	27	1124
688073	308	7988	8041	TACTCTAGGACCAAGAAT	sooooooooooooo	5-8-5	13	8	1125
688074	309	7989	8042	TTACTCTAGGACCAAGAA	sooooooooooooo	5-8-5	0	0	1126
688075	310	7990	8043	CTTACTCTAGGACCAAGA	sooooooooooooo	5-8-5	0	0	1127
688076	311	7991	8044	CCTTACTCTAGGACCAAG	sooooooooooooo	5-8-5	45	71	1128
688077	312	7992	8045	GCCTTACTCTAGGACCAA	sooooooooooooo	5-8-5	62	67	1129
688078	313	7993	8046	TGCCTTACTCTAGGACCA	sooooooooooooo	5-8-5	33	30	1130
688079	314	7994	8047	GTGCCTTACTCTAGGACC	sooooooooooooo	5-8-5	59	49	1131
688080	315	7995	8048	TGTGCCTTACTCTAGGAC	sooooooooooooo	5-8-5	47	41	1132
688081	316	7996	8049	ATGTGCCTTACTCTAGGA	sooooooooooooo	5-8-5	44	13	1133
688082	317	7997	8050	AATGTGCCTTACTCTAGG	sooooooooooooo	5-8-5	6	0	1134

Table 54

Percent inhibition of the C9ORF72 mRNA levels compared to PBS control by antisense oligonucleotides targeting SEQ ID NOs: 1, 2 and 19

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 19 Start Site	Sequence	Linkage	Motif	% inhibition (RTS3750)	SEQ ID NO
576816	310	7990	8043	GCCTTACTCTAGGACCAAGA	ssssssssssssssss	5-10-5	58	20
619420	310	7990	8043	GCCTTACTCTAGGACCAAGA	sooooooooooooo	5-10-5	70	20
688078	313	7993	8046	TGCCTTACTCTAGGACCA	sooooooooooooo	5-8-5	50	1130
688083	318	7998	8051	AAATGTGCCTTACTCTAG	sooooooooooooo	5-8-5	7	1135
688084	319	7999	8052	CAAATGTGCCTTACTCTA	sooooooooooooo	5-8-5	11	1136
688085	320	8000	8053	CCAAATGTGCCTTACTCT	sooooooooooooo	5-8-5	29	1137
688086	321	8001	8054	CCCAAATGTGCCTTACTC	sooooooooooooo	5-8-5	43	1138
688087	322	8002	8055	GCCCAAATGTGCCTTACT	sooooooooooooo	5-8-5	58	1139
688088	323	8003	8056	AGCCCAAATGTGCCTTAC	sooooooooooooo	5-8-5	66	1140
688089	324	8004	8057	GAGCCCAAATGTGCCTTA	sooooooooooooo	5-8-5	61	1141
688090	325	8005	8058	GGAGCCCAAATGTGCCTT	sooooooooooooo	5-8-5	52	1142
688091	326	8006	8059	TGGAGCCCAAATGTGCCT	sooooooooooooo	5-8-5	34	1143
688092	327	8007	8060	TTGGAGCCCAAATGTGCC	sooooooooooooo	5-8-5	15	1144
688093	328	8008	8061	TTTGGAGCCCAAATGTGC	sooooooooooooo	5-8-5	31	1145
688094	329	8009	8062	CTTTGGAGCCCAAATGTG	sooooooooooooo	5-8-5	23	1146
688095	330	8010	8063	TCTTTGGAGCCCAAATGT	sooooooooooooo	5-8-5	13	1147
688096	331	8011	8064	GTCTTTGGAGCCCAAATG	sooooooooooooo	5-8-5	30	1148
688097	332	8012	8065	TGTCTTTGGAGCCCAAAT	sooooooooooooo	5-8-5	32	1149
688098	333	8013	8066	CTGTCTTTGGAGCCCAA	sooooooooooooo	5-8-5	48	1150
688099	334	8014	8067	TCTGTCTTTGGAGCCCAA	sooooooooooooo	5-8-5	62	1151

688100	335	8015	8068	TTCTGTCTTTGGAGCCCA	s000ssssssss00ss	5-8-5	61	1152
688101	336	8016	8069	GTTCTGTCTTTGGAGCCC	s000ssssssss00ss	5-8-5	77	1153
688102	337	8017	8070	TGTTCTGTCTTTGGAGCC	s000ssssssss00ss	5-8-5	58	1154
688103	338	8018	8071	CTGTTCTGTCTTTGGAGC	s000ssssssss00ss	5-8-5	57	1155
688104	339	8019	8072	CCTGTTCTGTCTTTGGAG	s000ssssssss00ss	5-8-5	55	1156
688105	340	8020	8073	ACCTGTTCTGTCTTTGGA	s000ssssssss00ss	5-8-5	51	1157
688106	341	8021	8074	TACCTGTTCTGTCTTTGG	s000ssssssss00ss	5-8-5	42	1158
688107	342	8022	8075	GTACCTGTTCTGTCTTTG	s000ssssssss00ss	5-8-5	49	1159
688108	343	8023	8076	AGTACCTGTTCTGTCTTT	s000ssssssss00ss	5-8-5	25	1160
688109	344	8024	8077	AAGTACCTGTTCTGTCTT	s000ssssssss00ss	5-8-5	22	1161
688110	345	8025	8078	GAAGTACCTGTTCTGTCT	s000ssssssss00ss	5-8-5	42	1162
688111	346	8026	8079	AGAAGTACCTGTTCTGTC	s000ssssssss00ss	5-8-5	21	1163
688112	347	8027	8080	GAGAAGTACCTGTTCTGT	s000ssssssss00ss	5-8-5	22	1164
688113	348	8028	8081	TGAGAAGTACCTGTTCTG	s000ssssssss00ss	5-8-5	13	1165
688114	349	8029	8082	CTGAGAAGTACCTGTTCT	s000ssssssss00ss	5-8-5	25	1166
688115	350	8030	8083	ACTGAGAAGTACCTGTTT	s000ssssssss00ss	5-8-5	14	1167
688116	351	8031	8084	CACTGAGAAGTACCTGTT	s000ssssssss00ss	5-8-5	36	1168
688117	352	8032	8085	TCACTGAGAAGTACCTGT	s000ssssssss00ss	5-8-5	28	1169
688118	353	8033	8086	ATCACTGAGAAGTACCTG	s000ssssssss00ss	5-8-5	36	1170
688119	354	8034	8087	CATCACTGAGAAGTACCT	s000ssssssss00ss	5-8-5	32	1171
688120	355	8035	8088	CCATCACTGAGAAGTACC	s000ssssssss00ss	5-8-5	44	1172
688121	356	8036	8089	TCCATCACTGAGAAGTAC	s000ssssssss00ss	5-8-5	31	1173
688122	357	8037	8090	CTCCATCACTGAGAAGTA	s000ssssssss00ss	5-8-5	56	1174
688123	358	8038	8091	TCTCCATCACTGAGAAGT	s000ssssssss00ss	5-8-5	53	1175
688124	359	8039	8092	TTCTCCATCACTGAGAAG	s000ssssssss00ss	5-8-5	14	1176
688125	360	8040	8093	TTTCTCCATCACTGAGAA	s000ssssssss00ss	5-8-5	12	1177
688126	361	8041	8094	ATTTCTCCATCACTGAGA	s000ssssssss00ss	5-8-5	18	1178
688127	362	8042	8095	TATTTCTCCATCACTGAG	s000ssssssss00ss	5-8-5	11	1179
688128	364	8044	8097	GTTATTTCTCCATCACTG	s000ssssssss00ss	5-8-5	40	1180
688129	365	8045	8098	AGTTATTTCTCCATCACT	s000ssssssss00ss	5-8-5	37	1181
688130	366	8046	8099	AAGTTATTTCTCCATCAC	s000ssssssss00ss	5-8-5	20	1182
688131	367	8047	8100	AAAGTTATTTCTCCATCA	s000ssssssss00ss	5-8-5	22	1183
688132	368	8048	8101	AAAAGTTATTTCTCCATC	s000ssssssss00ss	5-8-5	31	1184
688133	369	8049	8102	GAAAAGTTATTTCTCCAT	s000ssssssss00ss	5-8-5	19	1185
688134	371	8051	8104	AAGAAAAGTTATTTCTCC	s000ssssssss00ss	5-8-5	34	1186
688135	372	8052	8105	CAAGAAAAGTTATTTCTC	s000ssssssss00ss	5-8-5	0	1187
688136	373	8053	8106	GCAAGAAAAGTTATTTCT	s000ssssssss00ss	5-8-5	21	1188
688137	374	8054	8107	GGCAAGAAAAGTTATTTT	s000ssssssss00ss	5-8-5	51	1189
688138	375	8055	8108	TGGCAAGAAAAGTTATTT	s000ssssssss00ss	5-8-5	42	1190
688139	376	8056	8109	TTGGCAAGAAAAGTTATT	s000ssssssss00ss	5-8-5	13	1191
688140	377	8057	8110	GTTGGCAAGAAAAGTTAT	s000ssssssss00ss	5-8-5	16	1192
688141	378	8058	8111	GGTTGGCAAGAAAAGTTA	s000ssssssss00ss	5-8-5	23	1193
688142	379	8059	8112	TGGTTGGCAAGAAAAGTT	s000ssssssss00ss	5-8-5	7	1194

688143	380	8060	8113	GTGGTTGGCAAGAAAAGT	s000ssssssssss00ss	5-8-5	30	1195
688144	381	8061	8114	TGTGGTTGGCAAGAAAAG	s000ssssssssss00ss	5-8-5	12	1196
688145	382	8062	8115	GTGTGGTTGGCAAGAAA	s000ssssssssss00ss	5-8-5	7	1197
688146	383	8063	8116	AGTGTGGTTGGCAAGAAA	s000ssssssssss00ss	5-8-5	0	1198
688147	384	8064	8117	GAGTGTGGTTGGCAAGAA	s000ssssssssss00ss	5-8-5	27	1199
688148	385	8065	8118	AGAGTGTGGTTGGCAAGA	s000ssssssssss00ss	5-8-5	17	1200
688149	386	8066	8119	TAGAGTGTGGTTGGCAAG	s000ssssssssss00ss	5-8-5	17	1201
688150	387	8067	8120	TTAGAGTGTGGTTGGCAA	s000ssssssssss00ss	5-8-5	20	1202
688151	388	8068	8121	TTTAGAGTGTGGTTGGCA	s000ssssssssss00ss	5-8-5	22	1203
688152	389	8069	8122	ATTTAGAGTGTGGTTGGC	s000ssssssssss00ss	5-8-5	47	1204
688153	390	8070	8123	CATTTAGAGTGTGGTTGG	s000ssssssssss00ss	5-8-5	21	1205
688154	391	8071	8124	CCATTTAGAGTGTGGTTG	s000ssssssssss00ss	5-8-5	23	1206
688155	392	8072	8125	TCCATTTAGAGTGTGGTT	s000ssssssssss00ss	5-8-5	9	1207
688156	393	8073	8126	CTCCATTTAGAGTGTGGT	s000ssssssssss00ss	5-8-5	25	1208
688157	394	8074	8127	TCTCCATTTAGAGTGTGG	s000ssssssssss00ss	5-8-5	41	1209
688158	395	8075	8128	TTCTCCATTTAGAGTGTG	s000ssssssssss00ss	5-8-5	19	1210
688159	396	8076	8129	TTTCTCCATTTAGAGTGT	s000ssssssssss00ss	5-8-5	0	1211

Table 55

Percent inhibition of the C9ORF72 mRNA levels compared to PBS control by antisense oligonucleotides targeting SEQ ID NOs: 1, 2 and 19

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 19 Start Site	Sequence	Linkage	Motif	% inhibition (RTS3750)	SEQ ID NO
576816	310	7990	8043	GCCTTACTCTAGGACCAAGA	ssssssssssssssssss	5-10-5	57	20
619420	310	7990	8043	GCCTTACTCTAGGACCAAGA	s000ssssssssss00ss	5-10-5	64	20
688078	313	7993	8046	TGCCTTACTCTAGGACCA	s000ssssssssss00ss	5-8-5	37	1130
688160	397	8077	8130	ATTTCTCCATTTAGAGTG	s000ssssssssss00ss	5-8-5	0	1212
688161	398	8078	8131	GATTTCTCCATTTAGAGT	s000ssssssssss00ss	5-8-5	9	1213
688162	399	8079	8132	GGATTTCTCCATTTAGAG	s000ssssssssss00ss	5-8-5	2	1214
688163	400	8080	8133	AGGATTTCTCCATTTAGA	s000ssssssssss00ss	5-8-5	0	1215
688164	401	8081	8134	AAGGATTTCTCCATTTAG	s000ssssssssss00ss	5-8-5	12	1216
688165	402	8082	8135	GAAGGATTTCTCCATTTA	s000ssssssssss00ss	5-8-5	0	1217
688166	403	8083	8136	CGAAGGATTTCTCCATTT	s000ssssssssss00ss	5-8-5	18	1218
688167	404	8084	8137	TCGAAGGATTTCTCCATT	s000ssssssssss00ss	5-8-5	12	1219
688168	405	8085	8138	TTCGAAGGATTTCTCCAT	s000ssssssssss00ss	5-8-5	6	1220
688169	406	8086	8139	TTTCGAAGGATTTCTCCA	s000ssssssssss00ss	5-8-5	0	1221
688170	407	8087	8140	ATTTCTGAAGGATTTCTCC	s000ssssssssss00ss	5-8-5	8	1222
688171	408	8088	8141	CATTTCTGAAGGATTTCTC	s000ssssssssss00ss	5-8-5	16	1223
688172	409	8089	8142	GCATTTCTGAAGGATTTCT	s000ssssssssss00ss	5-8-5	55	1224

688173	410	8090	8143	TGCATTTCTGAAGGATTTC	SOOOSSSSSSSSOOSS	5-8-5	0	1225
688174	411	8091	8144	CTGCATTTCTGAAGGATTT	SOOOSSSSSSSSOOSS	5-8-5	25	1226
688175	412	8092	8145	TCTGCATTTCTGAAGGATT	SOOOSSSSSSSSOOSS	5-8-5	33	1227
688176	413	8093	8146	CTCTGCATTTCTGAAGGAT	SOOOSSSSSSSSOOSS	5-8-5	12	1228
688177	414	8094	8147	TCTCTGCATTTCTGAAGGA	SOOOSSSSSSSSOOSS	5-8-5	14	1229
688178	415	8095	8148	CTCTCTGCATTTCTGAAGG	SOOOSSSSSSSSOOSS	5-8-5	5	1230
688179	416	8096	8149	ACTCTCTGCATTTCTGAAG	SOOOSSSSSSSSOOSS	5-8-5	0	1231
688180	417	8097	8150	CACTCTCTGCATTTCTGAA	SOOOSSSSSSSSOOSS	5-8-5	12	1232
688181	418	8098	8151	CCACTCTCTGCATTTCTGA	SOOOSSSSSSSSOOSS	5-8-5	40	1233
688182	419	8099	8152	ACCACTCTCTGCATTTCTG	SOOOSSSSSSSSOOSS	5-8-5	40	1234
688183	420	8100	8153	CACCACTCTCTGCATTTCT	SOOOSSSSSSSSOOSS	5-8-5	45	1235
688184	421	8101	8154	GCACCACTCTCTGCATTT	SOOOSSSSSSSSOOSS	5-8-5	24	1236
688185	422	8102	8155	AGCACCACTCTCTGCATT	SOOOSSSSSSSSOOSS	5-8-5	12	1237
688186	423	8103	8156	TAGCACCACTCTCTGCAT	SOOOSSSSSSSSOOSS	5-8-5	21	1238
688187	424	8104	8157	ATAGCACCACTCTCTGCA	SOOOSSSSSSSSOOSS	5-8-5	25	1239
688188	425	8105	8158	TATAGCACCACTCTCTGC	SOOOSSSSSSSSOOSS	5-8-5	12	1240
688189	426	8106	8159	CTATAGCACCACTCTCTG	SOOOSSSSSSSSOOSS	5-8-5	0	1241
688190	427	8107	8160	TCTATAGCACCACTCTCT	SOOOSSSSSSSSOOSS	5-8-5	0	1242
688191	428	8108	8161	ATCTATAGCACCACTCTC	SOOOSSSSSSSSOOSS	5-8-5	20	1243
688192	429	8109	8162	CATCTATAGCACCACTCT	SOOOSSSSSSSSOOSS	5-8-5	0	1244
688193	430	8110	8163	ACATCTATAGCACCACTC	SOOOSSSSSSSSOOSS	5-8-5	31	1245
688194	431	8111	8164	TACATCTATAGCACCACT	SOOOSSSSSSSSOOSS	5-8-5	4	1246
688195	432	8112	8165	TTACATCTATAGCACCA	SOOOSSSSSSSSOOSS	5-8-5	32	1247
688196	433	8113	8166	TTTACATCTATAGCACCA	SOOOSSSSSSSSOOSS	5-8-5	37	1248
688197	434	8114	8167	CTTTACATCTATAGCACC	SOOOSSSSSSSSOOSS	5-8-5	25	1249
688198	435	8115	8168	ACTTTACATCTATAGCAC	SOOOSSSSSSSSOOSS	5-8-5	0	1250
688199	436	8116	8169	AACTTTACATCTATAGCA	SOOOSSSSSSSSOOSS	5-8-5	9	1251
688200	437	8117	8170	AAACTTTACATCTATAGC	SOOOSSSSSSSSOOSS	5-8-5	8	1252
688201	438	8118	8171	AAAACCTTTACATCTATAG	SOOOSSSSSSSSOOSS	5-8-5	4	1253
688202	440	8120	8173	AAAAAATTTACATCTAT	SOOOSSSSSSSSOOSS	5-8-5	8	1254
688203	441	8121	8174	CAAAAAATTTACATCTA	SOOOSSSSSSSSOOSS	5-8-5	4	1255
688204	442	8122	8175	ACAAAAAATTTACATCT	SOOOSSSSSSSSOOSS	5-8-5	0	1256
688205	443	8123	8176	GACAAAAAATTTACATC	SOOOSSSSSSSSOOSS	5-8-5	0	1257
688206	446	8126	8179	CAAGACAAAAAATTTAC	SOOOSSSSSSSSOOSS	5-8-5	5	1258
688207	448	8128	8181	GACAAGACAAAAAATTT	SOOOSSSSSSSSOOSS	5-8-5	27	1259
688208	449	8129	8182	AGACAAGACAAAAAATTT	SOOOSSSSSSSSOOSS	5-8-5	9	1260
688209	450	8130	8183	CAGACAAGACAAAAAAT	SOOOSSSSSSSSOOSS	5-8-5	0	1261
688210	451	8131	8184	TCAGACAAGACAAAAAAC	SOOOSSSSSSSSOOSS	5-8-5	11	1262
688211	452	8132	8185	TTTCAGACAAGACAAAAA	SOOOSSSSSSSSOOSS	5-8-5	0	1263
688212	454	8134	8187	TTTTTCAGACAAGACAAA	SOOOSSSSSSSSOOSS	5-8-5	0	1264
688213	455	8135	8188	CTTTTCAGACAAGACAAA	SOOOSSSSSSSSOOSS	5-8-5	0	1265
688214	456	8136	8189	CCTTTTCAGACAAGACAA	SOOOSSSSSSSSOOSS	5-8-5	30	1266
688215	457	8137	8190	CCCTTTTCAGACAAGACA	SOOOSSSSSSSSOOSS	5-8-5	31	1267

688216	458	8138	8191	TCCCTTTTCAGACAAGAC	sooooooooooooo	5-8-5	24	1268
688217	459	8139	8192	CTCCCTTTTCAGACAAGA	sooooooooooooo	5-8-5	47	1269
688218	460	8140	8193	ACTCCCTTTTCAGACAAG	sooooooooooooo	5-8-5	34	1270
688219	461	8141	8194	CACTCCCTTTTCAGACAA	sooooooooooooo	5-8-5	5	1271
688220	462	8142	8195	TCACTCCCTTTTCAGACA	sooooooooooooo	5-8-5	15	1272
688221	463	8143	8196	ATCACTCCCTTTTCAGAC	sooooooooooooo	5-8-5	14	1273
688222	464	8144	8197	AATCACTCCCTTTTCAGA	sooooooooooooo	5-8-5	18	1274
688223	465	8145	8198	TAATCACTCCCTTTTCAG	sooooooooooooo	5-8-5	14	1275
688224	466	8146	8199	ATAATCACTCCCTTTTCA	sooooooooooooo	5-8-5	15	1276
688225	467	8147	8200	AATAATCACTCCCTTTTC	sooooooooooooo	5-8-5	8	1277
688226	468	8148	8201	CAATAATCACTCCCTTTT	sooooooooooooo	5-8-5	9	1278
688227	469	8149	8202	ACAATAATCACTCCCTTT	sooooooooooooo	5-8-5	24	1279
688228	470	8150	8203	AACAATAATCACTCCCTT	sooooooooooooo	5-8-5	21	1280
688229	471	8151	8204	AAACAATAATCACTCCCT	sooooooooooooo	5-8-5	21	1281
688230	472	8152	8205	GAAACAATAATCACTCCC	sooooooooooooo	5-8-5	36	1282
688231	473	8153	8206	TGAAACAATAATCACTCC	sooooooooooooo	5-8-5	7	1283
688232	474	8154	8207	ATGAAACAATAATCACTC	sooooooooooooo	5-8-5	20	1284
688233	475	8155	8208	AATGAAACAATAATCACT	sooooooooooooo	5-8-5	0	1285
688234	476	8156	8209	TAATGAAACAATAATCAC	sooooooooooooo	5-8-5	16	1286
688235	477	8157	8210	TTAATGAAACAATAATCA	sooooooooooooo	5-8-5	0	1287
688236	478	8158	8211	ATTAATGAAACAATAATC	sooooooooooooo	5-8-5	0	1288

Table 56

Percent inhibition of the C9ORF72 mRNA levels compared to PBS control by antisense oligonucleotides targeting SEQ ID NOs: 1, 2 and 19

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 19 Start Site	Sequence	Linkage	Motif	% inhibition (RTS3750)	SEQ ID NO
576816	310	7990	8043	GCCTTACTCTAGGACCAAGA	ssssssssssssssss	5-10-5	61	20
619420	310	7990	8043	GCCTTACTCTAGGACCAAGA	sooooooooooooo	5-10-5	75	20
688078	313	7993	8046	TGCCTTACTCTAGGACCA	sooooooooooooo	5-8-5	67	1130
688237	485	8165	8218	ATCAAAGATTAATGAAAC	sooooooooooooo	5-8-5	43	1289
688238	486	8166	8219	CATCAAAGATTAATGAAA	sooooooooooooo	5-8-5	0	1290
688239	487	8167	8220	CCATCAAAGATTAATGAA	sooooooooooooo	5-8-5	42	1291
688240	488	8168	8221	TCCATCAAAGATTAATGA	sooooooooooooo	5-8-5	46	1292
688241	489	8169	8222	TTCCATCAAAGATTAATG	sooooooooooooo	5-8-5	0	1293
688242	490	8170	8223	TTTCCATCAAAGATTAAT	sooooooooooooo	5-8-5	55	1294
688243	491	8171	8224	GTTTCCATCAAAGATTAA	sooooooooooooo	5-8-5	49	1295
688244	492	8172	8225	AGTTTCCATCAAAGATTA	sooooooooooooo	5-8-5	44	1296
688245	493	8173	8226	CAGTTTCCATCAAAGATT	sooooooooooooo	5-8-5	0	1297

688246	494	8174	8227	CCAGTTTCCATCAAAGAT	sooooooooooooo	5-8-5	46	1298
688247	495	8175	8228	TCCAGTTTCCATCAAAGA	sooooooooooooo	5-8-5	46	1299
688248	496	8176	8229	TTCCAGTTTCCATCAAAG	sooooooooooooo	5-8-5	59	1300
688249	497	8177	8230	ATTCCAGTTTCCATCAAA	sooooooooooooo	5-8-5	48	1301
688250	498	8178	8231	CATTCCAGTTTCCATCAA	sooooooooooooo	5-8-5	54	1302
688251	499	8179	8232	CCATTCCAGTTTCCATCA	sooooooooooooo	5-8-5	59	1303
688252	500	8180	8233	CCCATTCCAGTTTCCATC	sooooooooooooo	5-8-5	67	1304
688253	501	8181	8234	CCCCATTCCAGTTTCCAT	sooooooooooooo	5-8-5	58	1305
688254	502	8182	8235	TCCCCATTCCAGTTTCCA	sooooooooooooo	5-8-5	55	1306
688255	503	8183	8236	ATCCCCATTCCAGTTTCC	sooooooooooooo	5-8-5	61	1307
688256	504	8184	8237	GATCCCCATTCCAGTTTC	sooooooooooooo	5-8-5	51	1308
688257	505	8185	8238	CGATCCCCATTCCAGTTT	sooooooooooooo	5-8-5	49	1309
688258	506	8186	8239	GCGATCCCCATTCCAGTT	sooooooooooooo	5-8-5	43	1310
688259	507	8187	8240	TGCGATCCCCATTCCAGT	sooooooooooooo	5-8-5	51	1311
688260	508	8188	8241	CTGCGATCCCCATTCCAG	sooooooooooooo	5-8-5	70	1312
688261	509	8189	8242	GCTGCGATCCCCATTCCA	sooooooooooooo	5-8-5	72	1313
688262	510	8190	8243	TGCTGCGATCCCCATTCC	sooooooooooooo	5-8-5	49	1314
688263	511	8191	8244	GTGCTGCGATCCCCATT	sooooooooooooo	5-8-5	0	1315
688264	512	8192	8245	TGTGCTGCGATCCCCATT	sooooooooooooo	5-8-5	58	1316
688265	513	8193	8246	ATGTGCTGCGATCCCCAT	sooooooooooooo	5-8-5	66	1317
688266	514	8194	8247	TATGTGCTGCGATCCCCA	sooooooooooooo	5-8-5	63	1318
688267	533	8213	8266	AAGTATAATTGATAGTCC	sooooooooooooo	5-8-5	49	1319
688268	534	8214	8267	GAAGTATAATTGATAGTC	sooooooooooooo	5-8-5	50	1320
688269	535	8215	8268	GGAAGTATAATTGATAGT	sooooooooooooo	5-8-5	39	1321
688270	536	8216	8269	TGGAAGTATAATTGATAG	sooooooooooooo	5-8-5	43	1322
688271	537	8217	8270	GTGGAAGTATAATTGATA	sooooooooooooo	5-8-5	49	1323
688272	538	8218	8271	TGTGGAAGTATAATTGAT	sooooooooooooo	5-8-5	40	1324
688273	539	8219	8272	CTGTGGAAGTATAATTGA	sooooooooooooo	5-8-5	34	1325
688274	540	8220	8273	TCTGTGGAAGTATAATTG	sooooooooooooo	5-8-5	0	1326
688275	541	8221	8274	GTCTGTGGAAGTATAATT	sooooooooooooo	5-8-5	0	1327
688276	542	8222	8275	TGTCTGTGGAAGTATAAT	sooooooooooooo	5-8-5	66	1328
688277	543	8223	8276	CTGTCTGTGGAAGTATAA	sooooooooooooo	5-8-5	0	1329
688278	544	8224	8277	TCTGTCTGTGGAAGTATA	sooooooooooooo	5-8-5	63	1330
688279	545	8225	8278	TTCTGTCTGTGGAAGTAT	sooooooooooooo	5-8-5	55	1331
688280	546	8226	8279	GTTCTGTCTGTGGAAGTA	sooooooooooooo	5-8-5	78	1332
688281	547	8227	8280	AGTTCTGTCTGTGGAAGT	sooooooooooooo	5-8-5	63	1333
688282	548	8228	8281	AAGTTCTGTCTGTGGAAG	sooooooooooooo	5-8-5	50	1334
688283	549	8229	8282	TAAGTTCTGTCTGTGGAA	sooooooooooooo	5-8-5	0	1335
688284	550	8230	8283	CTAAGTTCTGTCTGTGGA	sooooooooooooo	5-8-5	55	1336
688285	551	8231	8284	ACTAAGTTCTGTCTGTGG	sooooooooooooo	5-8-5	69	1337
688286	552	8232	8285	AACTAAGTTCTGTCTGTG	sooooooooooooo	5-8-5	66	1338
688287	553	8233	8286	AACTAAGTTCTGTCTGT	sooooooooooooo	5-8-5	43	1339
688288	554	8234	8287	GAACTAAGTTCTGTCTG	sooooooooooooo	5-8-5	37	1340

688289	555	8235	8288	AGAACTAAGTTCTGTCT	sooooooooooooo	5-8-5	47	1341
688290	556	8236	8289	TAGAACTAAGTTCTGTC	sooooooooooooo	5-8-5	50	1342
688291	557	8237	8290	GTAGAACTAAGTTCTGT	sooooooooooooo	5-8-5	47	1343
688292	558	8238	8291	GGTAGAACTAAGTTCTG	sooooooooooooo	5-8-5	46	1344
688293	559	8239	8292	AGGTAGAACTAAGTTCT	sooooooooooooo	5-8-5	59	1345
688294	560	8240	8293	GAGGTAGAACTAAGTTC	sooooooooooooo	5-8-5	48	1346
688295	561	8241	8294	GGAGGTAGAACTAAGTT	sooooooooooooo	5-8-5	47	1347
688296	562	8242	8295	GGGAGGTAGAACTAAGT	sooooooooooooo	5-8-5	43	1348
688297	563	8243	8296	TGGGAGGTAGAACTAAG	sooooooooooooo	5-8-5	49	1349
688298	564	8244	8297	GTGGGAGGTAGAACTAA	sooooooooooooo	5-8-5	51	1350
688299	565	8245	8298	AGTGGGAGGTAGAACTA	sooooooooooooo	5-8-5	45	1351
688300	566	8246	8299	AAGTGGGAGGTAGAACT	sooooooooooooo	5-8-5	40	1352
688301	567	8247	8300	GAAGTGGGAGGTAGAAAC	sooooooooooooo	5-8-5	39	1353
688302	568	8248	8301	TGAAGTGGGAGGTAGAAA	sooooooooooooo	5-8-5	0	1354
688303	569	8249	8302	ATGAAGTGGGAGGTAGAA	sooooooooooooo	5-8-5	42	1355
688304	570	8250	8303	TATGAAGTGGGAGGTAGA	sooooooooooooo	5-8-5	32	1356
688305	571	8251	8304	CTATGAAGTGGGAGGTAG	sooooooooooooo	5-8-5	47	1357
688306	572	8252	8305	TCTATGAAGTGGGAGGTA	sooooooooooooo	5-8-5	33	1358
688307	573	8253	8306	CTCTATGAAGTGGGAGGT	sooooooooooooo	5-8-5	55	1359
688308	574	8254	8307	ACTCTATGAAGTGGGAGG	sooooooooooooo	5-8-5	51	1360
688309	575	8255	8308	CACCTCTATGAAGTGGGAG	sooooooooooooo	5-8-5	59	1361
688310	576	8256	8309	ACACTCTATGAAGTGGGA	sooooooooooooo	5-8-5	58	1362
688311	577	8257	8310	CACACTCTATGAAGTGGG	sooooooooooooo	5-8-5	59	1363
688312	578	8258	8311	ACACACTCTATGAAGTGG	sooooooooooooo	5-8-5	42	1364
688313	579	8259	8312	CACACACTCTATGAAGTG	sooooooooooooo	5-8-5	40	1365

Table 57

Percent inhibition of the C9ORF72 mRNA levels compared to PBS control by antisense oligonucleotides targeting SEQ ID NOs: 1, 2 and 19

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 19 Start Site	Mismatches with SEQ ID NO: 19	Sequence	Linkage	Motif	% inhibition (RTS3750)	SEQ ID NO
576816	310	7990	8043	0	GCCTTACTCTAGGACCAAGA	ssssssssssssssssss	5-10-5	47	20
619420	310	7990	8043	0	GCCTTACTCTAGGACCAAGA	sooooooooooooo	5-10-5	51	20
688078	313	7993	8046	0	TGCCTTACTCTAGGACCA	sooooooooooooo	5-8-5	32	1130
688314	580	8260	8313	0	ACACACACTCTATGAAGT	sooooooooooooo	5-8-5	9	1366
688315	691	n/a	9505	1	CCCTGATCTTCCATTCTC	sooooooooooooo	5-8-5	21	1367
688316	692	n/a	9506	2	ACCCTGATCTTCCATTCT	sooooooooooooo	5-8-5	2	1368
688317	693	n/a	9507	3	GACCCTGATCTTCCATTCT	sooooooooooooo	5-8-5	16	1369
688318	694	n/a	9508	3	TGACCCTGATCTTCCATT	sooooooooooooo	5-8-5	18	1370
688319	695	n/a	n/a	n/a	CTGACCCTGATCTTCCAT	sooooooooooooo	5-8-5	5	1371

688320	696	n/a	n/a	n/a	TCTGACCCTGATCTTCCA	SOOOSSSSSSSSSOOSS	5-8-5	11	1372
688321	697	n/a	n/a	n/a	CTCTGACCCTGATCTTCC	SOOOSSSSSSSSSOOSS	5-8-5	21	1373
688322	698	n/a	n/a	n/a	ACTCTGACCCTGATCTTC	SOOOSSSSSSSSSOOSS	5-8-5	26	1374
688323	699	n/a	n/a	n/a	TACTCTGACCCTGATCTT	SOOOSSSSSSSSSOOSS	5-8-5	6	1375
688324	700	n/a	12554	3	ATACTCTGACCCTGATCT	SOOOSSSSSSSSSOOSS	5-8-5	7	1376
688325	701	n/a	12555	2	AATACTCTGACCCTGATC	SOOOSSSSSSSSSOOSS	5-8-5	0	1377
687955	n/a	13641	13680	0	ATGATTTCTTGTCTGGGA	SOOOSSSSSSSSSOOSS	5-8-5	31	1378
687956	n/a	13642	13681	0	CATGATTTCTTGTCTGGG	SOOOSSSSSSSSSOOSS	5-8-5	38	1379
687957	n/a	13643	13682	0	CCATGATTTCTTGTCTGG	SOOOSSSSSSSSSOOSS	5-8-5	12	1380
687958	n/a	13644	13683	0	GCCATGATTTCTTGTCTG	SOOOSSSSSSSSSOOSS	5-8-5	27	1381
687959	n/a	13645	13684	0	GGCCATGATTTCTTGTCT	SOOOSSSSSSSSSOOSS	5-8-5	26	1382
687960	n/a	13646	13685	0	GGGCCATGATTTCTTGTCT	SOOOSSSSSSSSSOOSS	5-8-5	18	1383
687961	n/a	14089	14136	0	AACTAACATGTAGGCACT	SOOOSSSSSSSSSOOSS	5-8-5	38	1384
687962	n/a	14090	14137	0	GAACTAACATGTAGGCAC	SOOOSSSSSSSSSOOSS	5-8-5	57	1385
687963	n/a	14091	14138	0	GGAACTAACATGTAGGCA	SOOOSSSSSSSSSOOSS	5-8-5	63	1386
687964	n/a	14092	14139	0	AGGAACTAACATGTAGGC	SOOOSSSSSSSSSOOSS	5-8-5	29	1387
687965	n/a	14302	14349	0	CTTCTGATTCAAGCCATT	SOOOSSSSSSSSSOOSS	5-8-5	25	1388
687966	n/a	14303	14350	0	GCTTCTGATTCAAGCCAT	SOOOSSSSSSSSSOOSS	5-8-5	51	1389
687967	n/a	14304	14351	0	TGCTTCTGATTCAAGCCA	SOOOSSSSSSSSSOOSS	5-8-5	46	1390
687968	n/a	14305	14352	0	GTGCTTCTGATTCAAGCC	SOOOSSSSSSSSSOOSS	5-8-5	21	1391
687969	n/a	14306	14353	0	AGTGCTTCTGATTCAAGC	SOOOSSSSSSSSSOOSS	5-8-5	36	1392
687970	n/a	14307	14354	0	AAGTGCTTCTGATTCAAG	SOOOSSSSSSSSSOOSS	5-8-5	25	1393
687971	n/a	14308	14355	0	AAAGTGCTTCTGATTCAA	SOOOSSSSSSSSSOOSS	5-8-5	28	1394
687972	n/a	14309	14356	0	TAAAGTGCTTCTGATTCA	SOOOSSSSSSSSSOOSS	5-8-5	0	1395
687973	n/a	14310	14357	0	CTAAAGTGCTTCTGATTC	SOOOSSSSSSSSSOOSS	5-8-5	25	1396
687974	n/a	14311	14358	0	ACTAAAGTGCTTCTGATT	SOOOSSSSSSSSSOOSS	5-8-5	17	1397
687975	n/a	14312	14359	0	GACTAAAGTGCTTCTGAT	SOOOSSSSSSSSSOOSS	5-8-5	33	1398
687976	n/a	14313	14360	0	GGACTAAAGTGCTTCTGA	SOOOSSSSSSSSSOOSS	5-8-5	47	1399
687977	n/a	14314	14361	0	AGGACTAAAGTGCTTCTG	SOOOSSSSSSSSSOOSS	5-8-5	44	1400
687978	n/a	14315	14362	0	CAGGACTAAAGTGCTTCT	SOOOSSSSSSSSSOOSS	5-8-5	57	1401
687979	n/a	14316	14363	0	ACAGGACTAAAGTGCTTC	SOOOSSSSSSSSSOOSS	5-8-5	31	1402
687980	n/a	14317	14364	0	TACAGGACTAAAGTGCTT	SOOOSSSSSSSSSOOSS	5-8-5	24	1403
687981	n/a	14318	14365	0	ATACAGGACTAAAGTGCT	SOOOSSSSSSSSSOOSS	5-8-5	21	1404
687982	n/a	14319	14366	0	GATACAGGACTAAAGTGC	SOOOSSSSSSSSSOOSS	5-8-5	15	1405
687983	n/a	14320	14367	0	AGATACAGGACTAAAGTG	SOOOSSSSSSSSSOOSS	5-8-5	8	1406
687984	n/a	14321	14368	0	CAGATACAGGACTAAAGT	SOOOSSSSSSSSSOOSS	5-8-5	1	1407
687985	n/a	14322	14369	0	ACAGATACAGGACTAAAG	SOOOSSSSSSSSSOOSS	5-8-5	10	1408
687986	n/a	14323	14370	0	AACAGATACAGGACTAAA	SOOOSSSSSSSSSOOSS	5-8-5	11	1409
687987	n/a	14324	14371	0	GAACAGATACAGGACTAA	SOOOSSSSSSSSSOOSS	5-8-5	20	1410
687988	n/a	14325	14372	0	TGAACAGATACAGGACTA	SOOOSSSSSSSSSOOSS	5-8-5	25	1411
687989	n/a	14326	14373	0	CTGAACAGATACAGGACT	SOOOSSSSSSSSSOOSS	5-8-5	12	1412
687990	n/a	14327	14374	0	ACTGAACAGATACAGGAC	SOOOSSSSSSSSSOOSS	5-8-5	25	1413
687991	n/a	14328	14375	0	CACTGAACAGATACAGGA	SOOOSSSSSSSSSOOSS	5-8-5	8	1414

687992	n/a	14329	14376	0	ACACTGAACAGATACAGG	sooooooooooooo	5-8-5	10	1415
687993	n/a	14330	14377	0	GACACTGAACAGATACAG	sooooooooooooo	5-8-5	13	1416
687994	n/a	14331	14378	0	TGACACTGAACAGATACA	sooooooooooooo	5-8-5	25	1417
687995	n/a	14332	14379	0	CTGACACTGAACAGATAC	sooooooooooooo	5-8-5	35	1418
687996	n/a	14333	14380	0	GCTGACACTGAACAGATA	sooooooooooooo	5-8-5	24	1419
687997	n/a	14334	14381	0	GGCTGACACTGAACAGAT	sooooooooooooo	5-8-5	40	1420
687998	n/a	14335	14382	0	AGGCTGACACTGAACAGA	sooooooooooooo	5-8-5	10	1421
687999	n/a	14336	14383	0	AAGGCTGACACTGAACAG	sooooooooooooo	5-8-5	3	1422
688000	n/a	14337	14384	0	AAAGGCTGACACTGAACA	sooooooooooooo	5-8-5	18	1423
688001	n/a	14338	14385	0	GAAAGGCTGACACTGAAC	sooooooooooooo	5-8-5	17	1424
688002	n/a	14339	14386	0	TGAAAGGCTGACACTGAA	sooooooooooooo	5-8-5	12	1425
688003	n/a	14358	14405	0	TGGGATTTAAATGATGT	sooooooooooooo	5-8-5	17	1426
688004	n/a	14359	14406	0	ATGGGATTTAAATGATG	sooooooooooooo	5-8-5	11	1427
688326	n/a	13402	13443	0	CTTGAGAAGAAAGCCTTC	sooooooooooooo	5-8-5	6	1428
688327	n/a	14287	14334	0	ATTAAGGCTCTTAGGTTA	sooooooooooooo	5-8-5	0	1429
688328	n/a	13499	13530	0	GTAGACAGTCTGTTATTT	sooooooooooooo	5-8-5	27	1430
688329	n/a	14397	14444	0	TGACATGTAGAGAGATTA	sooooooooooooo	5-8-5	43	1431
688330	n/a	13827	13866	0	TGGTTTAAGGGCACAAAC	sooooooooooooo	5-8-5	0	1432
688331	n/a	13403	13444	0	ACTTGAGAAGAAAGCCTT	sooooooooooooo	5-8-5	27	1433
688332	n/a	14257	14304	0	CCTCTGATACTCCATCAT	sooooooooooooo	5-8-5	28	1434
688333	n/a	13471	13502	0	AAATCTTGTATAGGTGA	sooooooooooooo	5-8-5	21	1435
688334	n/a	13410	13451	0	AATTCTTACTTGAGAAGA	sooooooooooooo	5-8-5	7	1436
688335	n/a	13885	13924	0	GGTGTATAGAGAATTCAG	sooooooooooooo	5-8-5	41	1437
688336	n/a	14250	14297	0	TACTCCATCATGAGCCTA	sooooooooooooo	5-8-5	35	1438
688337	n/a	13788	13827	0	GCTGGATGGAAAAAGATC	sooooooooooooo	5-8-5	12	1439
688338	n/a	13517	13548	0	GTCCCTAGAACAATCTAA	sooooooooooooo	5-8-5	28	1440
688339	n/a	14405	14452	0	GAAGAAATTGACATGTAG	sooooooooooooo	5-8-5	12	1441
688340	n/a	13724	13763	0	CATCTACAGTACAACCTTA	sooooooooooooo	5-8-5	4	1442

Table 58

Percent inhibition of the C9ORF72 mRNA levels compared to PBS control by antisense oligonucleotides targeting SEQ ID NOs: 1, 2 and 19

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 19 Start Site	Sequence	Linkage	Motif	% inhibition (RTS3750)	SEQ ID NO
688341	233	7913	7966	ATCTCTGTCTTGGAACAGC	sooooooooooooo	5-10-5	57	1443
688342	234	7914	7967	AATCTCTGTCTTGGAACAG	sooooooooooooo	5-10-5	35	1444
688343	235	7915	7968	CAATCTCTGTCTTGGAACA	sooooooooooooo	5-10-5	36	1445
655153	236	7916	7969	GCAATCTCTGTCTTGGAAC	sooooooooooooo	5-10-5	89	463
655154	237	7917	7970	AGCAATCTCTGTCTTGCAA	sooooooooooooo	5-10-5	81	464

688344	238	7918	7971	AAGCAATCTCTGTCTTGGCA	s0000sssssssssooss	5-10-5	83	1446
655172	306	7986	8039	TACTCTAGGACCAAGAATAT	s0000sssssssssooss	5-10-5	10	483
688345	307	7987	8040	TTACTCTAGGACCAAGAATA	s0000sssssssssooss	5-10-5	1	1447
688346	308	7988	8041	CTTACTCTAGGACCAAGAAT	s0000sssssssssooss	5-10-5	10	1448
625183	309	7989	8042	CCTTACTCTAGGACCAAGAA	s0000sssssssssooss	5-10-5	44	484
576816	310	7990	8043	GCCTTACTCTAGGACCAAGA	ssssssssssssssssss	5-10-5	56	20
619420	310	7990	8043	GCCTTACTCTAGGACCAAGA	s0000sssssssssooss	5-10-5	73	20
688347	311	7991	8044	TGCCTTACTCTAGGACCAAG	s0000sssssssssooss	5-10-5	62	1449
655173	312	7992	8045	GTGCCTTACTCTAGGACCAA	s0000sssssssssooss	5-10-5	59	485
688348	313	7993	8046	TGTGCCTTACTCTAGGACCA	s0000sssssssssooss	5-10-5	62	1450
688349	314	7994	8047	ATGTGCCTTACTCTAGGACC	s0000sssssssssooss	5-10-5	62	1451
655174	315	7995	8048	AATGTGCCTTACTCTAGGAC	s0000sssssssssooss	5-10-5	60	486
688350	319	7999	8052	CCCAAATGTGCCTTACTCTA	s0000sssssssssooss	5-10-5	41	1452
688351	320	8000	8053	GCCCAAATGTGCCTTACTCT	s0000sssssssssooss	5-10-5	62	1453
627833	321	8001	8054	AGCCCAAATGTGCCTTACTC	s0000sssssssssooss	5-10-5	51	487
688352	322	8002	8055	GAGCCCAAATGTGCCTTACT	s0000sssssssssooss	5-10-5	66	1454
688353	323	8003	8056	GGAGCCCAAATGTGCCTTAC	s0000sssssssssooss	5-10-5	48	1455
619411	324	8004	8057	TGGAGCCCAAATGTGCCTTA	s0000sssssssssooss	5-10-5	67	51
688354	325	8005	8058	TTGGAGCCCAAATGTGCCTT	s0000sssssssssooss	5-10-5	53	1456
627608	326	8006	8059	TTTGGAGCCCAAATGTGCCT	s0000sssssssssooss	5-10-5	42	1457
655175	327	8007	8060	CTTTGGAGCCCAAATGTGCC	s0000sssssssssooss	5-10-5	26	488
655176	330	8010	8063	TGTCTTTGGAGCCCAAATGT	s0000sssssssssooss	5-10-5	33	489
688355	331	8011	8064	CTGTCTTTGGAGCCCAAATG	s0000sssssssssooss	5-10-5	56	1458
619412	332	8012	8065	TCTGTCTTTGGAGCCCAAAT	s0000sssssssssooss	5-10-5	60	53
655177	333	8013	8066	TTCTGTCTTTGGAGCCCAA	s0000sssssssssooss	5-10-5	47	490
655178	334	8014	8067	GTTCTGTCTTTGGAGCCCAA	s0000sssssssssooss	5-10-5	67	491
688356	335	8015	8068	TGTTCTGTCTTTGGAGCCCA	s0000sssssssssooss	5-10-5	60	1459
655179	336	8016	8069	CTGTTCTGTCTTTGGAGCCC	s0000sssssssssooss	5-10-5	59	492
688357	337	8017	8070	CCTGTTCTGTCTTTGGAGCC	s0000sssssssssooss	5-10-5	50	1460
688358	338	8018	8071	ACCTGTTCTGTCTTTGGAGC	s0000sssssssssooss	5-10-5	44	1461
655180	339	8019	8072	TACCTGTTCTGTCTTTGGAG	s0000sssssssssooss	5-10-5	42	493
619413	340	8020	8073	GTACCTGTTCTGTCTTTGGA	s0000sssssssssooss	5-10-5	56	135
688359	341	8021	8074	AGTACCTGTTCTGTCTTTGG	s0000sssssssssooss	5-10-5	38	1462
655181	342	8022	8075	AAGTACCTGTTCTGTCTTTG	s0000sssssssssooss	5-10-5	31	494
655185	351	8031	8084	ATCACTGAGAAGTACCTGTT	s0000sssssssssooss	5-10-5	32	498
688360	352	8032	8085	CATCACTGAGAAGTACCTGT	s0000sssssssssooss	5-10-5	53	1463
619414	353	8033	8086	CCATCACTGAGAAGTACCTG	s0000sssssssssooss	5-10-5	48	136
655186	354	8034	8087	TCCATCACTGAGAAGTACCT	s0000sssssssssooss	5-10-5	56	499
688361	355	8035	8088	CTCCATCACTGAGAAGTACC	s0000sssssssssooss	5-10-5	54	1464
655201	415	8095	8148	CACTCTCTGCATTTTCGAAGG	s0000sssssssssooss	5-10-5	32	521
688362	416	8096	8149	CCACTCTCTGCATTTTCGAAG	s0000sssssssssooss	5-10-5	39	1465
688363	417	8097	8150	ACCACTCTCTGCATTTTCGAA	s0000sssssssssooss	5-10-5	37	1466
655202	418	8098	8151	CACCACTCTCTGCATTTTCGA	s0000sssssssssooss	5-10-5	50	522

688364	419	8099	8152	GCACCACTCTCTGCATTTTCG	s0000sssssssssssooss	5-10-5	56	1467
655203	420	8100	8153	AGCACCACTCTCTGCATTTTC	s0000sssssssssssooss	5-10-5	56	523
655204	421	8101	8154	TAGCACCACTCTCTGCATTT	s0000sssssssssssooss	5-10-5	25	524
688365	422	8102	8155	ATAGCACCACTCTCTGCATT	s0000sssssssssssooss	5-10-5	29	1468
688366	423	8103	8156	TATAGCACCACTCTCTGCAT	s0000sssssssssssooss	5-10-5	31	1469
655206	427	8107	8160	CATCTATAGCACCACTCTCT	s0000sssssssssssooss	5-10-5	20	526
688367	428	8108	8161	ACATCTATAGCACCACTCTC	s0000sssssssssssooss	5-10-5	28	1470
688368	429	8109	8162	TACATCTATAGCACCACTCT	s0000sssssssssssooss	5-10-5	24	1471
671081	430	8110	8163	TTACATCTATAGCACCACTC	s0000sssssssssssooss	5-10-5	26	1052
688369	431	8111	8164	TTTACATCTATAGCACCACT	s0000sssssssssssooss	5-10-5	40	1472
688370	432	8112	8165	CTTTACATCTATAGCACCA	s0000sssssssssssooss	5-10-5	43	1473
655207	433	8113	8166	ACTTTACATCTATAGACCA	s0000sssssssssssooss	5-10-5	33	527
688371	434	8114	8167	AACTTTACATCTATAGCAC	s0000sssssssssssooss	5-10-5	15	1474
688372	435	8115	8168	AACTTTACATCTATAGCAC	s0000sssssssssssooss	5-10-5	24	1475
655208	436	8116	8169	AAAACCTTTACATCTATAG	s0000sssssssssssooss	5-10-5	28	528
655215	456	8136	8189	TCCCTTTTCAGACAAGACAA	s0000sssssssssssooss	5-10-5	35	535
688373	457	8137	8190	CTCCCTTTTCAGACAAGACA	s0000sssssssssssooss	5-10-5	42	1476
688374	458	8138	8191	ACTCCCTTTTCAGACAAGAC	s0000sssssssssssooss	5-10-5	57	1477
655216	459	8139	8192	CACTCCCTTTTCAGACAAGA	s0000sssssssssssooss	5-10-5	51	536
671082	460	8140	8193	TCACTCCCTTTTCAGACAAG	s0000sssssssssssooss	5-10-5	45	1053
688375	461	8141	8194	ATCACTCCCTTTTCAGACAA	s0000sssssssssssooss	5-10-5	39	1478
655217	462	8142	8195	AATCACTCCCTTTTCAGACA	s0000sssssssssssooss	5-10-5	45	537
688376	463	8143	8196	TAATCACTCCCTTTTCAGAC	s0000sssssssssssooss	5-10-5	7	1479
688377	464	8144	8197	ATAATCACTCCCTTTTCAGA	s0000sssssssssssooss	5-10-5	1	1480
655218	465	8145	8198	AATAATCACTCCCTTTTCAG	s0000sssssssssssooss	5-10-5	23	538
655230	500	8180	8233	TCCCCATTCCAGTTTCCATC	s0000sssssssssssooss	5-10-5	57	550
688378	501	8181	8234	ATCCCCATTCCAGTTTCCAT	s0000sssssssssssooss	5-10-5	60	1481
688379	502	8182	8235	GATCCCCATTCCAGTTTCCA	s0000sssssssssssooss	5-10-5	55	1482
655231	503	8183	8236	CGATCCCCATTCCAGTTTCC	s0000sssssssssssooss	5-10-5	58	551
688380	504	8184	8237	GCGATCCCCATTCCAGTTTC	s0000sssssssssssooss	5-10-5	56	1483
688381	505	8185	8238	TGCGATCCCCATTCCAGTTT	s0000sssssssssssooss	5-10-5	46	1484

Table 59

Percent inhibition of the C9ORF72 mRNA levels compared to PBS control by antisense
oligonucleotides targeting SEQ ID NOs: 1, 2 and 19

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 19 Start Site	Mismatches with SEQ ID NO: 19	Sequence	Linkage	Motif	% inhibition (RTS3750)	SEQ ID NO
576816	310	7990	8043	0	GCCTTACTCTAGGACCAAGA	ssssssssssssssssssss	5-10-5	53	20
619420	310	7990	8043	0	GCCTTACTCTAGGACCAAGA	s0000sssssssssssooss	5-10-5	54	20
655173	312	7992	8045	0	GTGCCTTACTCTAGGACCAA	s0000sssssssssssooss	5-10-5	77	485

655232	506	8186	8239	0	CTGCGATCCCCATTCCAGTT	s0000sssssssssssooss	5-10-5	46	552
688382	507	8187	8240	0	GCTGCGATCCCCATTCCAGT	s0000sssssssssssooss	5-10-5	65	1485
688383	508	8188	8241	0	TGCTGCGATCCCCATTCCAG	s0000sssssssssssooss	5-10-5	60	1486
655233	509	8189	8242	0	GTGCTGCGATCCCCATTCCA	s0000sssssssssssooss	5-10-5	57	553
688384	510	8190	8243	0	TGTGCTGCGATCCCCATTCC	s0000sssssssssssooss	5-10-5	45	1487
688385	511	8191	8244	0	ATGTGCTGCGATCCCCATTCT	s0000sssssssssssooss	5-10-5	68	1488
655234	512	8192	8245	0	TATGTGCTGCGATCCCCATT	s0000sssssssssssooss	5-10-5	32	554
655240	548	8228	8281	0	CTAAGTTCTGTCTGTGGAAG	s0000sssssssssssooss	5-10-5	23	560
688386	549	8229	8282	0	ACTAAGTTCTGTCTGTGGAA	s0000sssssssssssooss	5-10-5	45	1489
671083	550	8230	8283	0	AACTAAGTTCTGTCTGTGGA	s0000sssssssssssooss	5-10-5	41	1054
655241	551	8231	8284	0	AAACTAAGTTCTGTCTGTGG	s0000sssssssssssooss	5-10-5	28	561
688387	552	8232	8285	0	GAAACTAAGTTCTGTCTGTG	s0000sssssssssssooss	5-10-5	49	1490
688388	553	8233	8286	0	AGAACTAAGTTCTGTCTGT	s0000sssssssssssooss	5-10-5	46	1491
655242	554	8234	8287	0	TAGAACTAAGTTCTGTCTGT	s0000sssssssssssooss	5-10-5	25	562
655289	691	n/a	9505	3	GACCCTGATCTTCCATTCTC	s0000sssssssssssooss	5-10-5	34	627
688389	692	n/a	9506	3	TGACCCTGATCTTCCATTCT	s0000sssssssssssooss	5-10-5	19	1492
688390	693	n/a	n/a	n/a	CTGACCCTGATCTTCCATTCT	s0000sssssssssssooss	5-10-5	21	1493
655290	694	n/a	n/a	n/a	TCTGACCCTGATCTTCCATT	s0000sssssssssssooss	5-10-5	67	628
672561	695	n/a	n/a	n/a	CTCTGACCCTGATCTTCCAT	s0000sssssssssssooss	5-10-5	25	1056
625345	696	n/a	n/a	n/a	ACTCTGACCCTGATCTTCCA	s0000sssssssssssooss	5-10-5	15	1494
655291	697	n/a	n/a	n/a	TACTCTGACCCTGATCTTCC	s0000sssssssssssooss	5-10-5	18	629
688391	698	n/a	n/a	n/a	ATACTCTGACCCTGATCTTC	s0000sssssssssssooss	5-10-5	40	1495
688392	699	n/a	n/a	n/a	AATACTCTGACCCTGATCTT	s0000sssssssssssooss	5-10-5	8	1496
619423	n/a	13642	13681	0	GCCATGATTTCTTGTCTGGG	s0000sssssssssssooss	5-10-5	77	383
655417	n/a	14089	14136	0	GGAACATAACATGTAGGCACT	s0000sssssssssssooss	5-10-5	83	738
655420	n/a	14331	14378	0	GCTGACACTGAACAGATACA	s0000sssssssssssooss	5-10-5	51	741
655422	n/a	14452	14499	0	ATCATTTAATTAATGTATTT	s0000sssssssssssooss	5-10-5	33	743
671084	n/a	14316	14363	0	ATACAGGACTAAAGTGCTTC	s0000sssssssssssooss	5-10-5	74	1055
688393	n/a	13641	13680	0	CCATGATTTCTTGTCTGGGA	s0000sssssssssssooss	5-10-5	54	1497
688394	n/a	13643	13682	0	GGCCATGATTTCTTGTCTGG	s0000sssssssssssooss	5-10-5	52	1498
688395	n/a	13644	13683	0	GGGCCATGATTTCTTGTCTG	s0000sssssssssssooss	5-10-5	46	1499
688396	n/a	13731	13770	0	ACTTAAGTTCATCTACAGTA	s0000sssssssssssooss	5-10-5	18	1500
688397	n/a	13792	13831	0	TCCACTGCTGGATGGAAAAA	s0000sssssssssssooss	5-10-5	20	1501
688398	n/a	13968	14007	0	ATATTATTTATCTTACTCAA	s0000sssssssssssooss	5-10-5	32	1502
688399	n/a	13982	14021	0	GTCTAAGTGCTTTATATTA	s0000sssssssssssooss	5-10-5	30	1503
688400	n/a	14090	14137	0	AGGAACTAACATGTAGGCAC	s0000sssssssssssooss	5-10-5	87	1504
688401	n/a	14122	14169	0	ATATAAGATAATACATGTAA	s0000sssssssssssooss	5-10-5	6	1505
688402	n/a	14243	14290	0	CATCATGAGCCTAAAGGAAA	s0000sssssssssssooss	5-10-5	22	1506
688403	n/a	14244	14291	0	CCATCATGAGCCTAAAGGAA	s0000sssssssssssooss	5-10-5	37	1507
688404	n/a	14300	14347	0	CTTCTGATTCAAGCCATTAA	s0000sssssssssssooss	5-10-5	76	1508
688405	n/a	14302	14349	0	TGCTTCTGATTCAAGCCATT	s0000sssssssssssooss	5-10-5	55	1509
688406	n/a	14303	14350	0	GTGCTTCTGATTCAAGCCAT	s0000sssssssssssooss	5-10-5	50	1510
688407	n/a	14304	14351	0	AGTGCTTCTGATTCAAGCCA	s0000sssssssssssooss	5-10-5	68	1511

688408	n/a	14305	14352	0	AAGTGCTTCTGATTCAAGCC	sooooooosoooooooooss	5-10-5	41	1512
688409	n/a	14306	14353	0	AAAGTGCTTCTGATTCAAGC	sooooooosoooooooooss	5-10-5	18	1513
688410	n/a	14307	14354	0	TAAAGTGCTTCTGATTCAAG	sooooooosoooooooooss	5-10-5	29	1514
688411	n/a	14308	14355	0	CTAAAGTGCTTCTGATTCAA	sooooooosoooooooooss	5-10-5	43	1515
688412	n/a	14309	14356	0	ACTAAAGTGCTTCTGATTCA	sooooooosoooooooooss	5-10-5	33	1516
688413	n/a	14310	14357	0	GACTAAAGTGCTTCTGATTCT	sooooooosoooooooooss	5-10-5	49	1517
688414	n/a	14311	14358	0	GGACTAAAGTGCTTCTGATT	sooooooosoooooooooss	5-10-5	49	1518
688415	n/a	14312	14359	0	AGGACTAAAGTGCTTCTGAT	sooooooosoooooooooss	5-10-5	55	1519
688416	n/a	14313	14360	0	CAGGACTAAAGTGCTTCTGA	sooooooosoooooooooss	5-10-5	71	1520
688417	n/a	14314	14361	0	ACAGGACTAAAGTGCTTCTG	sooooooosoooooooooss	5-10-5	66	1521
688418	n/a	14315	14362	0	TACAGGACTAAAGTGCTTCT	sooooooosoooooooooss	5-10-5	61	1522
688419	n/a	14317	14364	0	GATACAGGACTAAAGTGCTT	sooooooosoooooooooss	5-10-5	76	1523
688420	n/a	14318	14365	0	AGATACAGGACTAAAGTGCT	sooooooosoooooooooss	5-10-5	46	1524
688421	n/a	14319	14366	0	CAGATACAGGACTAAAGTGC	sooooooosoooooooooss	5-10-5	53	1525
688422	n/a	14320	14367	0	ACAGATACAGGACTAAAGTG	sooooooosoooooooooss	5-10-5	23	1526
688423	n/a	14321	14368	0	AACAGATACAGGACTAAAGT	sooooooosoooooooooss	5-10-5	28	1527
688424	n/a	14322	14369	0	GAACAGATACAGGACTAAAG	sooooooosoooooooooss	5-10-5	26	1528
688425	n/a	14323	14370	0	TGAACAGATACAGGACTAAA	sooooooosoooooooooss	5-10-5	13	1529
688426	n/a	14324	14371	0	CTGAACAGATACAGGACTAA	sooooooosoooooooooss	5-10-5	27	1530
688427	n/a	14325	14372	0	ACTGAACAGATACAGGACTA	sooooooosoooooooooss	5-10-5	37	1531
688428	n/a	14326	14373	0	CACTGAACAGATACAGGACT	sooooooosoooooooooss	5-10-5	35	1532
688429	n/a	14327	14374	0	ACACTGAACAGATACAGGAC	sooooooosoooooooooss	5-10-5	28	1533
688430	n/a	14328	14375	0	GACACTGAACAGATACAGGA	sooooooosoooooooooss	5-10-5	39	1534
688431	n/a	14329	14376	0	TGACACTGAACAGATACAGG	sooooooosoooooooooss	5-10-5	38	1535
688432	n/a	14330	14377	0	CTGACACTGAACAGATACAG	sooooooosoooooooooss	5-10-5	64	1536
688433	n/a	14332	14379	0	GGCTGACACTGAACAGATAC	sooooooosoooooooooss	5-10-5	50	1537
688434	n/a	14333	14380	0	AGGCTGACACTGAACAGATA	sooooooosoooooooooss	5-10-5	18	1538
688435	n/a	14334	14381	0	AAGGCTGACACTGAACAGAT	sooooooosoooooooooss	5-10-5	45	1539
688436	n/a	14335	14382	0	AAAGGCTGACACTGAACAGA	sooooooosoooooooooss	5-10-5	28	1540
688437	n/a	14336	14383	0	GAAAGGCTGACACTGAACAG	sooooooosoooooooooss	5-10-5	18	1541
688438	n/a	14337	14384	0	TGAAAGGCTGACACTGAACA	sooooooosoooooooooss	5-10-5	23	1542
688439	n/a	14358	14405	0	AATGGGATTTAAATGATGT	sooooooosoooooooooss	5-10-5	26	1543
688440	n/a	14359	14406	0	AAATGGGATTTAAATGATG	sooooooosoooooooooss	5-10-5	30	1544
688441	n/a	14360	14407	0	CAAATGGGATTTAAATGAT	sooooooosoooooooooss	5-10-5	16	1545

Table 60

Percent inhibition of the C9ORF72 mRNA levels compared to PBS control by antisense oligonucleotides targeting SEQ ID NOs: 1, 2 and 19

ISIS NO	SEQ ID NO: 1 Start	SEQ ID NO: 2 Start	SEQ ID NO: 19 Start	Sequence	Linkage	Motif	% inhibition (RTS3750)	SEQ ID NO

	Site	Site	Site					
576816	310	7990	8043	GCCTTACTCTAGGACCAAGA	ssssssssssssssssss	5-10-5	62	20
619420	310	7990	8043	GCCTTACTCTAGGACCAAGA	s0000ssssssssss00ss	5-10-5	75	20
688078	313	7993	8046	TGCCTTACTCTAGGACCA	s000ssssssssss00ss	5-8-5	67	1130
688237	485	8165	8218	ATCAAAGATTAATGAAAC	s000ssssssssss00ss	5-8-5	42	1289
688238	486	8166	8219	CATCAAAGATTAATGAAA	s000ssssssssss00ss	5-8-5	0	1290
688239	487	8167	8220	CCATCAAAGATTAATGAA	s000ssssssssss00ss	5-8-5	39	1291
688240	488	8168	8221	TCCATCAAAGATTAATGA	s000ssssssssss00ss	5-8-5	45	1292
688241	489	8169	8222	TTCCATCAAAGATTAATG	s000ssssssssss00ss	5-8-5	0	1293
688242	490	8170	8223	TTTCCATCAAAGATTAAT	s000ssssssssss00ss	5-8-5	53	1294
688243	491	8171	8224	GTTTCCATCAAAGATTAA	s000ssssssssss00ss	5-8-5	46	1295
688244	492	8172	8225	AGTTTCCATCAAAGATTA	s000ssssssssss00ss	5-8-5	43	1296
688245	493	8173	8226	CAGTTTCCATCAAAGATT	s000ssssssssss00ss	5-8-5	0	1297
688246	494	8174	8227	CCAGTTTCCATCAAAGAT	s000ssssssssss00ss	5-8-5	44	1298
688247	495	8175	8228	TCCAGTTTCCATCAAAGA	s000ssssssssss00ss	5-8-5	46	1299
688248	496	8176	8229	TTCCAGTTTCCATCAAAG	s000ssssssssss00ss	5-8-5	58	1300
688249	497	8177	8230	ATTCCAGTTTCCATCAAA	s000ssssssssss00ss	5-8-5	46	1301
688250	498	8178	8231	CATTCCAGTTTCCATCAA	s000ssssssssss00ss	5-8-5	50	1302
688251	499	8179	8232	CCATTCCAGTTTCCATCA	s000ssssssssss00ss	5-8-5	58	1303
688252	500	8180	8233	CCCATTCCAGTTTCCATC	s000ssssssssss00ss	5-8-5	66	1304
688253	501	8181	8234	CCCCATTCCAGTTTCCAT	s000ssssssssss00ss	5-8-5	59	1305
688254	502	8182	8235	TCCCCATTCCAGTTTCCA	s000ssssssssss00ss	5-8-5	52	1306
688255	503	8183	8236	ATCCCCATTCCAGTTTCC	s000ssssssssss00ss	5-8-5	61	1307
688256	504	8184	8237	GATCCCCATTCCAGTTTC	s000ssssssssss00ss	5-8-5	50	1308
688257	505	8185	8238	CGATCCCCATTCCAGTTT	s000ssssssssss00ss	5-8-5	48	1309
688258	506	8186	8239	GCGATCCCCATTCCAGTT	s000ssssssssss00ss	5-8-5	44	1310
688259	507	8187	8240	TGCGATCCCCATTCCAGT	s000ssssssssss00ss	5-8-5	49	1311
688260	508	8188	8241	CTGCGATCCCCATTCCAG	s000ssssssssss00ss	5-8-5	70	1312
688261	509	8189	8242	GCTGCGATCCCCATTCCA	s000ssssssssss00ss	5-8-5	72	1313
688262	510	8190	8243	TGCTGCGATCCCCATTCC	s000ssssssssss00ss	5-8-5	47	1314
688263	511	8191	8244	GTGCTGCGATCCCCATT	s000ssssssssss00ss	5-8-5	0	1315
688264	512	8192	8245	TGTGCTGCGATCCCCATT	s000ssssssssss00ss	5-8-5	56	1316
688265	513	8193	8246	ATGTGCTGCGATCCCCAT	s000ssssssssss00ss	5-8-5	65	1317
688266	514	8194	8247	TATGTGCTGCGATCCCCA	s000ssssssssss00ss	5-8-5	61	1318
688267	533	8213	8266	AAGTATAATTGATAGTCC	s000ssssssssss00ss	5-8-5	47	1319
688268	534	8214	8267	GAAGTATAATTGATAGTC	s000ssssssssss00ss	5-8-5	48	1320
688269	535	8215	8268	GGAAGTATAATTGATAGT	s000ssssssssss00ss	5-8-5	35	1321
688270	536	8216	8269	TGGAAGTATAATTGATAG	s000ssssssssss00ss	5-8-5	41	1322
688271	537	8217	8270	GTGGAAGTATAATTGATA	s000ssssssssss00ss	5-8-5	48	1323
688272	538	8218	8271	TGTGGAAGTATAATTGAT	s000ssssssssss00ss	5-8-5	42	1324

688273	539	8219	8272	CTGTGGAAGTATAATTGA	s000ssssssss00ss	5-8-5	32	1325
688274	540	8220	8273	TCTGTGGAAGTATAATTG	s000ssssssss00ss	5-8-5	0	1326
688275	541	8221	8274	GTCTGTGGAAGTATAATT	s000ssssssss00ss	5-8-5	0	1327
688276	542	8222	8275	TGTCTGTGGAAGTATAAT	s000ssssssss00ss	5-8-5	65	1328
688277	543	8223	8276	CTGTCTGTGGAAGTATAA	s000ssssssss00ss	5-8-5	0	1329
688278	544	8224	8277	TCTGTCTGTGGAAGTATA	s000ssssssss00ss	5-8-5	62	1330
688279	545	8225	8278	TTCTGTCTGTGGAAGTAT	s000ssssssss00ss	5-8-5	55	1331
688280	546	8226	8279	GTTCTGTCTGTGGAAGTA	s000ssssssss00ss	5-8-5	77	1332
688281	547	8227	8280	AGTTCTGTCTGTGGAAGT	s000ssssssss00ss	5-8-5	63	1333
688282	548	8228	8281	AAGTTCTGTCTGTGGAAG	s000ssssssss00ss	5-8-5	49	1334
688283	549	8229	8282	TAAGTTCTGTCTGTGGAA	s000ssssssss00ss	5-8-5	0	1335
688284	550	8230	8283	CTAAGTTCTGTCTGTGGA	s000ssssssss00ss	5-8-5	54	1336
688285	551	8231	8284	ACTAAGTTCTGTCTGTGG	s000ssssssss00ss	5-8-5	69	1337
688286	552	8232	8285	AACTAAGTTCTGTCTGTG	s000ssssssss00ss	5-8-5	65	1338
688287	553	8233	8286	AACTAAGTTCTGTCTGT	s000ssssssss00ss	5-8-5	40	1339
688288	554	8234	8287	GAACTAAGTTCTGTCTG	s000ssssssss00ss	5-8-5	36	1340
688289	555	8235	8288	AGAACTAAGTTCTGTCT	s000ssssssss00ss	5-8-5	47	1341
688290	556	8236	8289	TAGAACTAAGTTCTGTC	s000ssssssss00ss	5-8-5	48	1342
688291	557	8237	8290	GTAGAACTAAGTTCTGT	s000ssssssss00ss	5-8-5	45	1343
688292	558	8238	8291	GGTAGAACTAAGTTCTG	s000ssssssss00ss	5-8-5	44	1344
688293	559	8239	8292	AGGTAGAACTAAGTTCT	s000ssssssss00ss	5-8-5	58	1345
688294	560	8240	8293	GAGGTAGAACTAAGTTC	s000ssssssss00ss	5-8-5	45	1346
688295	561	8241	8294	GGAGGTAGAACTAAGTT	s000ssssssss00ss	5-8-5	47	1347
688296	562	8242	8295	GGGAGGTAGAACTAAGT	s000ssssssss00ss	5-8-5	44	1348
688297	563	8243	8296	TGGGAGGTAGAACTAAG	s000ssssssss00ss	5-8-5	47	1349
688298	564	8244	8297	GTGGGAGGTAGAACTAA	s000ssssssss00ss	5-8-5	53	1350
688299	565	8245	8298	AGTGGGAGGTAGAACTA	s000ssssssss00ss	5-8-5	43	1351
688300	566	8246	8299	AAGTGGGAGGTAGAACT	s000ssssssss00ss	5-8-5	36	1352
688301	567	8247	8300	GAAGTGGGAGGTAGAAAC	s000ssssssss00ss	5-8-5	41	1353
688302	568	8248	8301	TGAAGTGGGAGGTAGAAA	s000ssssssss00ss	5-8-5	0	1354
688303	569	8249	8302	ATGAAGTGGGAGGTAGAA	s000ssssssss00ss	5-8-5	41	1355
688304	570	8250	8303	TATGAAGTGGGAGGTAGA	s000ssssssss00ss	5-8-5	31	1356
688305	571	8251	8304	CTATGAAGTGGGAGGTAG	s000ssssssss00ss	5-8-5	46	1357
688306	572	8252	8305	TCTATGAAGTGGGAGGTA	s000ssssssss00ss	5-8-5	30	1358
688307	573	8253	8306	CTCTATGAAGTGGGAGGT	s000ssssssss00ss	5-8-5	54	1359
688308	574	8254	8307	ACTCTATGAAGTGGGAGG	s000ssssssss00ss	5-8-5	50	1360
688309	575	8255	8308	CACTCTATGAAGTGGGAG	s000ssssssss00ss	5-8-5	60	1361
688310	576	8256	8309	ACACTCTATGAAGTGGGA	s000ssssssss00ss	5-8-5	56	1362
688311	577	8257	8310	CACACTCTATGAAGTGGG	s000ssssssss00ss	5-8-5	57	1363
688312	578	8258	8311	ACACACTCTATGAAGTGG	s000ssssssss00ss	5-8-5	41	1364
688313	579	8259	8312	CACACACTCTATGAAGTG	s000ssssssss00ss	5-8-5	38	1365

Example 13: Dose-dependent antisense inhibition of human C9ORF72 mRNA in HepG2 cells

Antisense oligonucleotides from the study described above exhibiting significant in vitro inhibition of C9ORF72 mRNA were selected and tested at various doses in HepG2 cells. ISIS 619420 described in Example 2 hereinabove was also tested. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.33 μ M, 1.00 μ M, 3.00 μ M, or 9.00 μ M concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3750 was used to measure the total C9ORF72 mRNA levels. C9ORF72 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN[®]. Results are presented as percent inhibition of C9ORF72 levels, relative to untreated control cells.

The half maximal inhibitory concentration (IC₅₀) of each oligonucleotide is also presented in the Tables below. As shown in the Tables below, total C9ORF72 mRNA levels were reduced in a dose-dependent manner in some of the antisense oligonucleotide treated cells.

Table 61**Dose-dependent inhibition of total C9ORF72 mRNA levels in HepG2 cells**

ISIS No	0.33 μ M	1.00 μ M	3.00 μ M	9.00 μ M	IC ₅₀ (μ M)
619411	55	68	89	90	<0.3
619420	41	74	87	95	0.4
655178	45	63	84	92	0.4
687962	48	61	83	86	0.4
687963	34	53	77	76	0.8
687978	50	60	70	65	<0.3
688077	49	63	70	86	0.3
688088	51	72	86	92	<0.3
688089	51	66	76	85	<0.3
688099	41	66	73	85	0.5
688100	44	64	79	86	0.4
688101	53	64	77	74	<0.3
688102	29	43	52	62	2.4
688172	31	47	77	88	1.0
688261	35	41	50	49	6.7
688347	41	60	79	89	0.5
688348	57	61	85	92	<0.3
688352	51	64	71	75	<0.3

Table 62**Dose-dependent inhibition of total C9ORF72 mRNA levels in HepG2 cells**

ISIS No	0.33 μM	1.00 μM	3.00 μM	9.00 μM	IC ₅₀ (μM)
619412	48	69	83	87	0.3
619413	34	33	47	85	1.8
619420	53	72	80	84	<0.3
655173	48	62	76	89	0.4
655174	38	59	82	79	0.6
655179	47	68	83	80	0.3
655186	40	53	82	85	0.6
655203	28	61	87	79	0.7
655230	36	59	77	89	0.7
655231	49	69	78	81	<0.3
688349	40	63	84	79	0.5
688351	47	74	81	88	0.3
688355	50	56	79	83	0.4
688356	47	64	78	85	0.3
688364	29	44	57	78	1.5
688374	38	50	79	70	0.8
688378	41	67	85	87	0.4
688379	39	42	83	83	0.8
688380	50	62	68	82	0.3

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Table 63**Dose-dependent inhibition of total C9ORF72 mRNA levels in HepG2 cells**

ISIS No	0.33 μM	1.00 μM	3.00 μM	9.00 μM	IC ₅₀ (μM)
619420	37	39	87	92	0.3
619423	55	73	84	82	<0.3
655173	53	83	82	94	<0.3
655233	34	28	41	79	2.4
655290	16	27	68	78	2.0
655417	73	42	87	84	<0.3
688022	51	71	80	76	<0.3
688360	32	63	85	72	0.6
688361	46	70	34	85	0.5
688382	42	58	79	81	0.5
688383	43	63	80	87	0.5
688385	41	60	82	84	0.5

688400	61	81	85	85	<0.3
688404	38	62	78	81	0.6
688407	37	53	71	85	0.8
688415	43	18	79	73	1.3
688416	48	74	73	81	<0.3
688417	33	61	67	74	0.8
688418	34	55	77	82	0.8

Example 14: Tolerability of antisense oligonucleotides targeting human C9ORF72 in mice

Antisense oligonucleotides from the Examples above were tested in a standard mouse model to assess tolerability of the oligonucleotides. The rodents were assessed by standard FOB assays and measurement of GFAP and/or AIF expression levels.

Groups of mice were administered a single ICV dose of 700 µg of ISIS oligonucleotides.

Mouse FOB assay

At 3 hours, one week, 2 weeks, 4 weeks, 6 weeks, and 8 weeks post injection, each mouse was evaluated according to 7 different criteria. The 7 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 a tail pinch; (7) regular breathing. For each of the 7 different criteria, each mouse was given a sub-score of 0 if it met the criteria or 1 if it did not. After all of the 7 criteria were evaluated, the sub-scores were summed for each mouse and then averaged for each group. For example, if a mouse was bright, alert, and responsive 3 hours after the 700 µg ICV dose, and met all other other criteria, it would get a summed score of 0. If another mouse was not bright, alert, and responsive 3 hours after the 700 µg ICV dose but met all other criteria, it would receive a score of 1.

The results are presented as individual scores for each mouse in each group. The expression levels of GFAP and AIF1 in the thoracic spinal cord of the mice were assessed by qRT-PCR after 8 weeks.

Study 1 with cEt oligonucleotides

The oligonucleotides tested in this study are presented in the Table below. The FOB scores are given below.

Table 64

Antisense oligonucleotides targeted to SEQ ID NO: 2

ISIS No	Start Site
672744	1335
672747	1338
672774	1368
672775	1369
672778	1372
672779	1373
672831	1440
672908	1349
672909	1350
672919	1360
672924	1368
672925	1369
672927	1371
672928	1372
672929	1373
672976	1435
672980	1439
672981	1440

Table 65**FOB scores in C57/Bl6 mice**

	3 hr
PBS	0, 0, 0, 0
672744	7, 7, 7, 7
672747	7, 7, 7, 7
672774	5, 5, 5, 5
672775	5, 7, 5, 7
672778	1, 7, 1, 1
672779	7, 2, 5, 7
672831	7, 7, 7, 7
672908	6, 1, 1, 1
672909	6, 6, 6, 4
672919	5, 5, 5, 5
672924	4, 6, 7, 6
672925	4, 4, 4, 4
672927	0, 0, 0, 0
672928	0, 0, 0, 0
672929	7, 7, 7, 7
672976	5, 7, 7, 7

672980	2, 2, 2, 2
672981	6, 6, 6, 6

Study 2 with cEt oligonucleotides

The oligonucleotides tested in this study are presented in the Table below. The FOB scores are given below.

5

Table 66

Antisense oligonucleotides targeted to SEQ ID NO: 2

ISIS No	Start Site of SEQ ID NO: 2
672982	1441
672983	1442
672984	1443
672985	1444
673021	1510
673023	1512
673026	1515
673036	1327
673047	1338
673057	1348
673058	1349
673067	1358
673068	1359
673074	1368
673079	1373
673082	1376
673088	1396
673125	1434
673126	1435
673127	1436
672832	1441

Table 67

FOB scores in C57/Bl6 mice

	3 hr
PBS	0, 0, 0, 0
672982	7, 7, 7, 7

672983	5, 7, 5, 7
672984	4, 6, 6, 6
672985	5, 4, 4, 4
673021	5, 5, 5, 5
673023	7, 7, 7, 7
673026	0, 0, 0, 0
673036	7, 7, 7, 7
673047	5, 5, 5, 6
673057	5, 0, 5, 7
673058	3, 3, 3, 3
673067	7, 0, 0, 6
673068	6, 6, 6, 6
673074	1, 1, 1, 1
673079	6, 6, 7, 6
673082	1, 3, 0, 3
673088	6, 6, 6, 6
673125	0, 0, 0, 0
673126	0, 0, 0, 0
673127	7, 7, 7, 7
672832	6, 6, 6, 7

Study 3 with cEt oligonucleotides

The oligonucleotides tested in this study are presented in the Table below. The FOB scores are given below.

5

Table 68

Antisense oligonucleotides targeted to SEQ ID NO: 2

ISIS No	Start Site of SEQ ID NO: 2
673131	1440
673132	1441
673133	1442
673134	1443
673135	1444
673193	1334
673203	1344
673204	1345
673224	1368
673225	1369
673226	1370
673228	1372

673229	1373
673275	1434
673276	1435
673280	1439

Table 69**FOB scores in C57/Bl6 mice**

	3 hr
PBS	0, 0, 0, 0
673131	4, 4, 4, 5
673132	4, 4, 4, 4
673133	4, 3, 4, 3
673134	5, 6, 3, 6
673135	5, 3, 4, 5
673193	6, 6, 6, 6
673203	4, 3, 4, 4
673204	2, 3, 2, 2
673224	5, 5, 5, 5
673225	1, 2, 2, 2
673226	1, 1, 1, 1
673228	2, 2, 2, 2
673229	6, 6, 6, 6
673275	1, 1, 1, 1
673276	3, 3, 3, 3
673280	1, 1, 1, 1

5 Study 4 with cEt oligonucleotides

The oligonucleotides tested in this study are presented in the Table below. The FOB scores are given below.

Table 70**Antisense oligonucleotides targeted to SEQ ID NO: 2**

ISIS No	Start Site of SEQ ID NO: 2
673128	1437
673130	1439
673281	1440
673282	1441

673283	1442
673284	1443
673285	1444
673323	1512
673331	1520
673332	1521
673374	1368
673375	1369
673377	1371
673378	1372
673379	1373
673430	1439
673431	1440
673432	1441
673434	1443

Table 71**FOB scores in C57/Bl6 mice**

	3 hr
PBS	0, 0, 0, 0
673128	0, 0, 0, 0
673130	0, 0, 0, 0
673281	7, 7, 7, 7
673282	7, 7, 7, 7
673283	5, 6, 6, 7
673284	5, 0, 0, 0
673285	3, 3, 3, 3
673323	7, 7, 7, 7
673331	7, 7, 7, 7
673332	7, 7, 7, 7
673374	7, 7, 7, 7
673375	2, 3, 2, 3
673377	0, 0, 0, 0
673378	1, 1, 1, 1
673379	4, 6, 6, 7
673430	7, 7, 7, 7
673431	7, 7, 7, 7
673432	7, 6, 6, 7
673434	7, 7, 7, 7

Study 1 with MOE oligonucleotides

The oligonucleotides tested in this study are presented in the Table below. The FOB scores are given below.

5

Table 72**Antisense oligonucleotides targeted to SEQ ID NO: 2**

ISIS No	Start Site of SEQ ID NO: 2
619253	1406
619293	1446
619322	1481
619352	1519
619353	1520
619410	7840
619414	8033
619420	7990
619421	28251
619422	3452
619423	13642
653222	1553
653223	5325
655016	1458
655017	1459

Table 73**FOB scores in C57/Bl6 mice**

	3 hrs
PBS	0,0,0,0
619253	3,3,7,7
619293	6,4,2,4
619322	2,2,2,4
619352	0,0,7,0
619353	6,4,7,6
619410	7,3,3,3
619414	6,6,6,6
619420	7,7,7,7
619421	1,1,1,1
619422	5,5,5,5
619423	6,6,6,6
653222	3,3,3,3
653223	1,1,7,1

655016	5,5,3,3
655017	0,0,0,0

Study 2 with MOE oligonucleotides

The oligonucleotides tested in this study are presented in the Table below. The FOB scores are given below.

5

Table 74

Antisense oligonucleotides targeted to SEQ ID NO: 2

ISIS No	Start Site of SEQ ID NO: 2
619173	1326
619174	1327
619178	1331
619179	1332
619180	1333
619181	1334
619182	1335
619185	1338
619186	1339
619187	1340
619191	1344
619201	1354
619202	1355
619203	1356
619216	1369
619217	1370

Table 75

FOB scores in C57/Bl6 mice

	3 hrs
PBS	0,0,0,0
619173	7,7,7,7
619174	7,7,7,7
619178	7,7,7,7
619179	7,7,7,7
619180	7,7,7,7
619181	7,7,7,7
619182	7,7,7,7
619185	7,6,6,7
619186	6,6,6,7
619187	5,7,5,7

619191	5,5,3,5
619201	3,3,3,1
619202	6,6,6,6
619203	5,1,5,5
619216	4,4,4,4
619217	2,2,2,2

Study 3 with MOE oligonucleotides

The oligonucleotides tested in this study are presented in the Table below. The FOB scores are given below.

5

Table 76

Antisense oligonucleotides targeted to SEQ ID NO: 2

ISIS No	Start Site of SEQ ID NO: 2
619218	1371
619245	1398
619246	1399
619247	1400
619251	1404
619252	1405
619259	1412
619260	1413
619276	1429
619278	1431
619280	1433
619284	1437
619292	1445
619297	1450
619298	1451
619307	1466

Table 77

FOB scores in C57/Bl6 mice

	3 hrs
PBS	0,0,0,0
619218	4,2,7,7
619245	4,4,4,4

619246	4,5,5,4
619247	1,1,1,1
619251	4,7,4,4
619252	6,6,6,0
619259	6,6,4,5
619260	4,4,4,4
619276	3,3,4,4
619278	4,7,2,7
619280	7,7,7,7
619284	0,0,0,0
619292	6,5,5,5
619297	7,4,4,4
619298	0,0,0,0
619307	0,0,0,0

Study 4 with MOE oligonucleotides

The oligonucleotides tested in this study are presented in the Table below. The FOB scores are given below.

5

Table 78

Antisense oligonucleotides targeted to SEQ ID NO: 2

ISIS No	Start Site of SEQ ID NO: 2
619266	1419
619268	1421
619316	1475
619317	1476
619336	1503
619337	1504
619338	1505
619339	1506
619341	1508
619342	1509
619343	1510
619344	1511
619346	1513
619350	1517
619351	1518
619413	8020

Table 79

FOB scores in C57/Bl6 mice

	3 hrs
PBS	0,0,0,0
619266	2,2,2,2
619268	6,6,7,7
619316	5,5,5,7
619317	2,3,3,4
619336	1,1,1,7
619338	0,0,7,7
619339	0,5,7,7
619341	7,7,7,7
619342	6,6,6,6
619343	6,6,6,6
619344	7,7,7,7
619346	5,5,7,7
619350	6,6,7,7
619351	6,6,7,7
619413	7,6,7,6

5 Example 15: Tolerability of antisense oligonucleotides targeting human C9ORF72 in rats

Antisense oligonucleotides from the Examples above were tested in a standard rat model to assess tolerability of the oligonucleotides. The rodents were assessed by standard FOB assays and measurement of GFAP and/or AIF expression levels. Groups of Sprague-Dawley rats were administered intrathecally with 2,000 µg or 3,000 µg of ISIS oligonucleotide as specified in the Tables below.

10 Rat FOB assay

At 3 hours, one week, 2 weeks, 4 weeks, 6 weeks, and 8 weeks post injection the movement of 7 different parts of the body was evaluated for each rat. The 7 body parts were (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; and (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. After each of the 7 body parts was evaluated, the sub-scores were summed for each rat and then averaged for each group. Saline treated rats generally receive a score of 0.

Study 1 with 5-10-5 MOE oligonucleotides at 3,000 µg

The oligonucleotides tested in this study are presented in the Table below. The FOB scores are given below.

Table 80
Antisense oligonucleotides targeted to SEQ ID NO: 2

ISIS No	Start Site of SEQ ID NO: 2
619185	1338
619186	1339
619187	1340
619191	1344
619201	1354
619203	1356
619217	1370
619218	1371
619251	1404
619252	1405
619259	1412
619266	1419
619268	1421
619278	1431
619284	1437
619346	1513
619350	1517
619351	1518

5

Table 81
FOB scores in Sprague-Dawley rats

	3 hrs
PBS	0,0,0
619185	7,7,6
619186	0,6,6
619187	7,0,6
619191	6,0,0
619201	1,4,4
619203	5,1,5
619217	4,4,4
619218	4,2,4
619251	6,6,6
619252	6,6,6
619259	0,6,6
619266	4,4,3

619268	6,6,6
619278	6,6,6
619284	1
619346	0,0,6
619350	4,0,3
619351	3,3,3

Study 2 with 5-10-5 MOE oligonucleotides at 3,000 µg

The oligonucleotides tested in this study are presented in the Table below. The FOB scores are given below.

5

Table 82

Antisense oligonucleotides targeted to SEQ ID NO: 2

ISIS No	Start Site of SEQ ID NO: 2
619176	1329
619183	1336
619253	1406
619260	1413
619276	1429
619292	1445
619293	1446
619307	1466
619317	1476
619338	1505
619339	1506
619342	1509

Table 83

FOB scores in Sprague-Dawley rats

	3 hrs
PBS	0,1,1
619176	7,7,6
619183	6,6,6
619253	7,6,6
619260	6,5,5
619276	4,5,5
619292	6,6,0

619293	ND
619307	ND
619317	6,6,7
619338	7,7,7
619339	7,6,3
619342	6,6,6

Study 3 with 5-8-5 MOE oligonucleotides at 3,000 µg

The oligonucleotides tested in this study are presented in the Table below. The FOB scores are given below.

5

Table 84

Antisense oligonucleotides targeted to SEQ ID NO: 2

ISIS No	Start Site of SEQ ID NO: 2
672595	1340
672599	1344
672602	1347
672624	1372
672636	1399
672637	1400
672640	1403
672642	1405
672651	1414
672652	1415

Table 85

FOB scores in Sprague-Dawley rats

	3 hr
PBS	0, 0, 0, 0
672595	4, 0, 3, 0, 4, 4, 4
672599	3, 0, 3, 0, 1, 3
672602	3, 3, 1, 0, 0, 3
672624	3, 0, 0, 7, 3, 3, 3
672636	5, 5, 5, 5
672637	1, 1, 2, 1
672640	6, 6, 5, 1, 6, 0
672642	6, 7, 0, 7, 6, 6
672651	6, 1, 1, 6, 3, 2, 3
672652	6, 1, 1, 5, 4, 4

Study 4 with 5-8-5 MOE oligonucleotides at 3,000 µg

The oligonucleotides tested in this study are presented in the Table below. The FOB scores are given below.

Table 86**Antisense oligonucleotides targeted to SEQ ID NO: 2**

ISIS No	Start Site of SEQ ID NO: 2
672664	1427
672665	1428
672670	1433
672671	1434
672675	1438
672676	1439
672678	1441
672679	1442
672681	1444
672683	1446
672693	1464
672697	1468
672699	1470
672700	1471
672723	1512
672730	1519

Table 87**FOB scores in Sprague-Dawley rats**

ISIS No	3 hr
PBS	1, 1, 1, 0
672664	6, 6, 6, 5
672665	4, 0, 4, 0, 4, 1
672670	4, 2, 4, 4
672671	4, 0, 0, 2, 5, 3
672675	3, 3, 0, 2, 1, 1
672676	1, 5, 0, 1, 1, 4
672678	0, 6, 6, 4, 6, 6
672679	3, 0, 0, 2, 3, 4
672681	1, 2, 2, 2

672683	0, 2, 5, 5, 0, 4
672693	ND
672697	6, 6, 6, 6
672699	0, 0, 3, 4, 4, 1
672700	4, 7, 4, 4
672723	4, 4, 4, 4
672730	2, 2, 3, 3

Study 5 with 5-10-5 MOE oligonucleotides at 3,000 µg

The oligonucleotides tested in this study are presented in the Table below. The FOB scores are given below and indicate that several oligonucleotides were tolerable in this model.

5

Table 88

Antisense oligonucleotides targeted to SEQ ID NO: 2

ISIS No	Start Site of SEQ ID NO: 2
619411	8004
619412	8012
627833	8001
655153	7916
655173	7992
655178	8014
655179	8016
655202	8098
655231	8183
655232	8186
655233	8189
655417	14089
655420	14331
671081	8110
671082	8140
671083	8230
671084	14316
672561	mRNA

Table 89

FOB scores in Sprague-Dawley rats

	3 hr
PBS	0,0,0,0
619411	6,6,6,6
619412	4,6,6,0
627833	6,6,6,1

655153	6,6,6,1
655173	6,6,6,0
655178	5,5,6,6
655179	6,6,6,6
655202	6,0,6,6
655231	4,4,4,4
655232	0,0,0,0
655233	6,6,6,6
655417	1,6,6,7
655420	5,7,5,5
671081	5,5,5,5
671082	5,6,5,7
671083	7,6,7,6
671084	6,0,4,3
672561	4,4,4,1

Study 6 with 5-8-5 MOE oligonucleotides at 2,000 µg

The oligonucleotides tested in this study are presented in the Table below. The FOB scores are given below and indicate that several oligonucleotides were tolerable in this model.

5

Table 90

Antisense oligonucleotides targeted to SEQ ID NO: 2

ISIS No	Start Site of SEQ ID NO: 2
687978	14315
688022	7918
688077	7992
688088	8003
688089	8004
688099	8014
688100	8015

Table 91

FOB scores in Sprague-Dawley rats

	3 hr
PBS	0, 0, 0, 0
687978	3, 3, 3, 3
688022	3, 3, 3, 3

688077	0, 3, 1, 3, 3, 3
688088	3, 0, 3, 3, 3
688089	1, 3, 3, 3, 3
688099	3, 4, 0, 3, 3
688100	0, 3, 4, 4

Study 7 with 5-8-5 and 5-10-5 MOE oligonucleotides at 2,000 µg

The oligonucleotides tested in this study are presented in the Table below. The FOB scores are given below and indicate that several oligonucleotides were tolerable in this model.

5

Table 92

Antisense oligonucleotides targeted to SEQ ID NO: 2

ISIS No	Start Site of SEQ ID NO: 2
688101	8016
688348	7993
688356	8015
688380	8184
688382	8187
688400	14090
688407	14304
688415	14312
688416	14313
688417	14314

Table 93

FOB scores in Sprague-Dawley rats

	3 hr
PBS	0, 0, 0, 0
688101	3, 2, 2, 2
688348	2, 1, 2, 2
688356	3, 3, 3, 3
688380	0, 0, 1, 0
688382	2, 2, 2, 2
688400	0, 3, 3, 3
688407	2, 2, 2, 2
688415	3, 0, 3, 3
688416	3, 3, 3, 3

688417	4, 4, 3, 3

Example 16: Acute Tolerability of oligonucleotides from WO 2014/062691

Oligonucleotides described in WO 2014/062691 were tested in an acute tolerability study in mice. The tested oligonucleotides include ISIS 576816, ISIS 576974, ISIS 577061, ISIS 577065, and ISIS 577083, which are 5-10-5 MOE gapmers with a full phosphorothioate backbone and each cytosine is a 5-methylcytosine. The sequences are provided in the Table below. Mice were separated into groups of 3 or 4 mice. Each mouse in each group of mice was administered a single ICV dose of either 700ug of the oligonucleotides in the table below. At 3 hours post injection, each mouse was evaluated according to 7 different criteria. The 7 criteria are (1) the mouse was bright, alert, and responsive; (2) the mouse was standing or hunched without stimuli; (3) the mouse shows any movement without stimuli (4) the mouse demonstrates forward movement after its lifted; (5) the mouse demonstrates any movement after its lifted; (6) the mouse responds to a tail pinch; (7) regular breathing. For each of the 7 different criteria, each mouse was given a sub-score of 0 if it met the criteria or 1 if it did not. After all of the 7 criteria were evaluated, the sub-scores were summed for each mouse and then averaged for each group. For example, if a mouse was bright, alert, and responsive 3 hours after the ICV dose, and met all other other criteria, it would get a summed score of 0. If another mouse was not bright, alert, and responsive 3 hours after the dose but met all other criteria, it would receive a score of 1. Saline treated mice generally receive a score of 0. Results are presented as the average score for each treatment group in the Table below. These results demonstrate that ISIS 576816, ISIS 576974, ISIS 577061, ISIS 577065, and ISIS 577083 were poorly tolerated.

Table 94

Antisense oligonucleotides from WO 2014/062691

ISIS No	Sequence	SEQ ID NO
576816	GCCTTACTCTAGGACCAAGA	20
576974	GGGACACTACAAGGTAGTAT	401
577061	TACAGGCTGCGGTTGTTTCC	97
577065	CCCGGCCCTAGCGCGCGAC	98
577083	GGTAACTTCAAACCTTTGGG	382

Table 95
FOB scores in mice

	3 hrs	5 hrs
576816	7,7,7	7,7,7
576974	6,5,6	7,5,7
577061	7,7,7	7,7,7
577065	6,6,6	7,7,7
577083	7,7,7	7,7,7

Gapmers from the studies described above, including compounds ISIS 576816, ISIS 576974, ISIS 577061, ISIS 577065, and ISIS 577083 which were previously disclosed in WO 2014/062691, are tested for tolerability in Sprague-Dawley rats. Rats are injected intrathecally with 3 mg of a single dose of ISIS oligonucleotide. A control group of rats is injected intrathecally with PBS. Acute tolerability is assessed 3 hours post-dose using a functional observational battery (FOB). This score is used to evaluate the acute tolerability of a compound with lower scores denoting better tolerated compounds. Control animals usually have a score of '0' or '1'. At 3 hours post injection, the rats are observed by placing each rat on the cage top and evaluating certain functions, assigning a number of '0' or '1' depending on whether the rat exhibits normal function in the region of interest (0) or does not (1) for each function, and then adding the total scores. Seven regions are assessed, including tail, hind paws, hind legs, hind end, front posture, fore paws, and head.

Poor acute tolerability in mice is generally predictive of poor acute tolerability in rats. For example, ISIS 619185 (see Example 14 hereinabove) had an acute tolerability score of 7,6,6,6 (4 animals) in mouse, and an acute tolerability score of 7,7,6 (3 animals) in rats (See Example 15 hereinabove). ISIS 619342 (see Example 14 hereinabove) had an acute tolerability score of 6,6,6,6 (4 animals) in mouse, and an acute tolerability score of 6,6,6 (3 animals) in rats (see Example 15 hereinabove). Both compounds were deemed to be poorly tolerated acutely. It is therefore expected that the compounds ISIS 576816, ISIS 576974, ISIS 577061, ISIS 577065, and ISIS 577083, which were previously disclosed in WO 2014/062691, will show similarly high FOB scores in rats as they did in mice.

CLAIMS

What is claimed is:

1. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 consecutive nucleobases complementary to an equal length portion of nucleobases 1429-1481 of SEQ ID NO: 2, wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to an equal length portion of a C9ORF72 nucleic acid, wherein the modified oligonucleotide is capable of reducing expression of C9ORF72 mRNA and/or protein levels, and wherein the modified oligonucleotide is a gapmer.
2. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 consecutive nucleobases of any of the nucleobase sequences of SEQ ID NOs: 98, 263-289 and 829-856, wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to an equal length portion of a C9ORF72 nucleic acid, wherein the modified oligonucleotide is capable of reducing expression of C9ORF72 mRNA and/or protein levels, and wherein the modified oligonucleotide is a gapmer.
3. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising any of the nucleobase sequences of SEQ ID NOs: 98, 263-289 and 829-856, wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to an equal length portion of a C9ORF72 nucleic acid, wherein the modified oligonucleotide is capable of reducing expression of C9ORF72 mRNA and/or protein levels, and wherein the modified oligonucleotide is a gapmer.
4. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of SEQ ID NO: 844, wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to an equal length portion of a C9ORF72 nucleic acid, wherein the modified oligonucleotide is capable of reducing expression of C9ORF72 mRNA and/or protein levels, and wherein the modified oligonucleotide is a gapmer.

5. The compound of any one of claims 1-4, wherein the modified oligonucleotide is a single-stranded modified oligonucleotide.
6. The compound of any one of claims 1-5, wherein at least one internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage, optionally wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.
7. The compound of claim 6, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage, optionally wherein the modified internucleoside linkage is a phosphorothioate linkage.
8. The compound of any one of claims 1-6, wherein at least one internucleoside linkage of the modified oligonucleotide is a phosphodiester internucleoside linkage.
9. The compound of any one of claims 1-8, wherein at least one nucleobase of the modified oligonucleotide comprises a modified nucleobase, optionally wherein the modified nucleobase is a 5-methylcytosine.
10. The compound of any one of claim 1-9, wherein at least one nucleoside of the modified oligonucleotide comprises a modified sugar.
11. The compound of claim 10, wherein each nucleoside of the modified oligonucleotide comprises a modified sugar.
12. The compound of claim 10, wherein the modified sugar is a bicyclic sugar, optionally wherein each bicyclic sugar comprises a chemical bridge between the 4' and 2' positions of the sugar, wherein each chemical bridge is independently selected from: 4'-CH(R)-O-2' and 4'-(CH₂)₂-O-2', wherein R is independently selected from H, C₁-C₆ alkyl, and C₁-C₆ alkoxy, preferably wherein at least one chemical bridge is 4'-CH(R)-O-2' and wherein:
 - a. R is methyl;
 - b. R is H; or
 - c. R is -CH₂-O-CH₃.

13. The compound of claim 12, wherein at least one modified sugar comprises a 2'-O-methoxyethyl group or a 2'-O-methyl group, or wherein each modified sugar comprises a 2'-O-methoxyethyl group or a 2'-O-methyl group.

14. The compound of any one of claims 1-13, wherein the modified oligonucleotide comprises:

a gap segment consisting of 10 linked deoxynucleosides;

a 5' wing segment consisting of 5 linked nucleosides; and

a 3' wing segment consisting of 5 linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar; or

a gap segment consisting of 8 linked deoxynucleosides;

a 5' wing segment consisting of 5 linked nucleosides; and

a 3' wing segment consisting of 5 linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

15. The compound of any one of claims 1-14, wherein the modified oligonucleotide comprises sugar modifications in any of the following patterns: eekkkddddddekkee, eekkkddddddekkee, ekkkddddddekekeee, kekkddddddekeke, and ekekddddddekeee; wherein,

e = a 2'-O-methoxyethyl modified nucleoside,

d = a 2'-deoxynucleoside, and

k = a cEt nucleoside.

16. The compound of any one of claims 1-15, wherein the modified oligonucleotide comprises internucleoside linkages in any of the following patterns: soooooossssssooss, soooooossssssooss, soooooossssooss, and soooooossssooss; wherein,

s = a phosphorothioate linkage, and

o = a phosphodiester linkage.

17. The compound of any one of claims 1-16, wherein the modified oligonucleotide consists of 20, 19, 18, or 17 linked nucleosides.

18. The compound of any one of claims 1-17, wherein the modified oligonucleotide has a nucleobase sequence complementary to a region of C9ORF72 other than a hexanucleotide repeat expansion, wherein the hexanucleotide repeat expansion comprises any of GGGGCC, GGGGGG, GGGGCG, and GGGGGC.

19. The compound of any one of claims 1-18, consisting of the modified oligonucleotide.

20. A double-stranded compound comprising the compound of any one of claims 1-4 and 6-19.

21. A conjugated antisense compound comprising the compound of any one of claims 1-19 or the double-stranded compound of claim 20.

22. A single-stranded modified oligonucleotide consisting of 18 linked nucleosides and having a nucleobase sequence comprising 18 consecutive nucleobases of the nucleobase sequence of SEQ ID NO: 844, wherein the modified oligonucleotide comprises:

a gap segment consisting of 8 linked deoxynucleosides;

a 5' wing segment consisting of 4 linked nucleosides; and

a 3' wing segment consisting of 6 linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar, and wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage, at least one internucleoside linkage is a phosphodiester internucleoside linkage, and each cytosine is a 5-methylcytosine.

23. A composition comprising a compound of any one of claims 1-19, a conjugated antisense compound of claim 21, a double-stranded compound of claim 20, or a modified oligonucleotide of claim 22 and at least one of a pharmaceutically acceptable carrier or diluent.

24. The composition of claim 23, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS), and/or wherein the modified oligonucleotide of the compound is a sodium salt.

25. Use of the compound of any one of claims 1-19, a conjugated antisense compound of claim 21, a double-stranded compound of claim 20, a modified oligonucleotide of claim 22, or a composition of claim 23 or claim 24, in the manufacture of a medicament for treating a neurodegenerative disorder.

26. A method of treating a neurodegenerative disorder which comprises administering to a subject an effective amount of the compound of any one of claims 1-19, a conjugated antisense compound of claim 21, a double-stranded compound of claim 20, a modified oligonucleotide of claim 22, or a composition of claim 23 or claim 24.

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