OLIGONUCLEOTIDES AND METHODS OF USE FOR TREATING NEUROLOGICAL DISEASES

CROSS REFERENCE

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application No. 62/856,264 filed June 3, 2019; U.S. Provisional Patent Application No. 62/914,252 filed on October 11, 2019; and U.S. Provisional Patent Application No. 62/949,817 filed on December 18, 2019, the entire disclosure of each of which is hereby incorporated by reference in its entirety for all purposes.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on May 29, 2020, is named QRL-002WO_SL.txt and is 378,978 bytes in size.

FIELD OF THE INVENTION

[0003] The present application relates to inhibitors of STMN2 transcripts that include a cryptic exon, including STMN2 antisense oligonucleotide sequences, and methods for treating neurological diseases.

BACKGROUND

[0004] Motor neuron diseases are a class of neurological diseases that result in the degeneration and death of motor neurons – those neurons which coordinate voluntary movement of muscles by the brain. Motor neuron diseases may be sporadic or inherited, and may affect upper motor neurons and/or lower motor neurons. Motor neuron diseases include amyotrophic lateral sclerosis, progressive bulbar palsy, pseudobulbar palsy, primary lateral sclerosis, progressive muscular atrophy, spinal muscular atrophy, and post-polio syndrome.

[0005] Amyotrophic lateral sclerosis (ALS) is a group of motor neuron diseases affecting about 15,000 individuals in the United States of America. ALS is characterized by degeneration and death of upper and lower motor neurons, resulting in loss of voluntary muscle control. Motor neuron death is accompanied by muscle fasciculation and atrophy. Early symptoms of ALS

include muscle cramps, muscle spasticity, muscle weakness (for example, affecting an arm, a leg, neck, or diaphragm), slurred and nasal speech, and difficulty chewing or swallowing. Loss of strength and control over movements, including those necessary for speech, eating, and breathing, eventually occur. Disease progression may be accompanied by weight loss, malnourishment, anxiety, depression, increased risk of pneumonia, muscle cramps, neuropathy, and possibly dementia. Most individuals diagnosed with ALS die of respiratory failure within five years of the first appearance of symptoms. Currently, there is no effective treatment for ALS.

[0006] ALS occurs in individuals of all ages, but is most common in individuals between 55 to 75 years of age, with a slightly higher incidence in males. ALS can be characterized as sporadic or familial. Sporadic ALS appears to occur at random and accounts for more than 90% of all incidences of ALS. Familial ALS accounts for 5-10% of all incidences of ALS.

[0007] FTD refers to a spectrum of progressive neurodegenerative diseases caused by loss of neurons in frontal and temporal lobes of the brain. FTD is characterized by changes in behavior and personality, and language dysfunction. Forms of FTD include behavioral variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA), and nonfluent variant primary progressive aphasia (nfvPPA). ALS with FTD is characterized by symptoms associated with FTD, along with symptoms of ALS such as muscle weakness, atrophy, fasciculation, spasticity, speech impairment (dysarthia), and inability to swallow (dysphagia). Individuals usually succumb to FTD within 5 to 10 years, while ALS with FTD often results in death within 2 to 3 years of the first disease symptoms appearing.

[0008] Like ALS, there is no known cure for FTD, or ALS with FTD, nor a therapeutic known to prevent or retard either disease's progression.

[0009] Thus, there is a pressing need to identify compounds capable of preventing, ameliorating, and treating neurological diseases such as amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD) and/or neuropathies such a chemotherapy induced neuropathy.

[0010] RNA-binding protein transactive response DNA-binding protein 43 (TDP-43) is involved in fundamental RNA processing activities including RNA transcription, splicing, and

transport. TDP-43 binds to thousands of pre-messenger RNA/mRNA targets, with high affinity for GU-rich sequences, including autoregulation of its own mRNA via binding to 3' untranslated region. Reduction in TDP-43 from an otherwise normal adult nervous system alters the splicing or expression levels of more than 1,500 RNAs, including long intron-containing transcripts. *See* Melamed et al., *Nat Neurosci.* (2019), 22(2):180-190.

[0011] In affected neurons in most instances of ALS and approximately 45% of patients with FTD, cytoplasmic accumulation and nuclear loss of TDP-43 have been reported. *See* Melamed et al., *Nat Neurosci.* (2019), 22(2):180-190. Moreover, TDP-43 has been shown to regulate expression of the neuronal growth-associated factor stathmin-2. *See* Melamed (2019); *see also* Klim et al., *Nat Neurosci.* (2019), 22(2):167-179. TDP-43 disruption is shown to drive premature polyadenylation and aberrant splicing in intron 1 of stathmin-2 pre-mRNA, producing truncated mRNA and loss of functional STMN2 protein. *See* Melamed (2019). STMN2 encodes a protein necessary for normal motor neuron outgrowth and repair. *See* Melamed (2019); *see also* Klim (2019).

[0012] The stathmin-2 gene is annotated to contain five constitutive exons (Refseq ID: NM_001199214.1) plus a proposed alternative exon between exons 4 and 5. *See* Melamed (2019); *see also* Klim (2019). Reduction or mutation in TDP-43 induces a new spliced exon, mapping within intron 1. *See* Melamed (2019); *see also* Klim (2019). This new exon (denoted as "exon 2a" or "cryptic exon") appears in STMN2 pre-mRNA when TDP-43 is depleted or endogenous TDP-43 has a N352 mutation. *See* Melamed (2019); *see also* Klim (2019). The cryptic exon in STMN2 pre-mRNA contains a cryptic polyadenylation sequence, which results in premature polyadenylation of the pre-mRNA. *See* Melamed (2019); *see also* Klim (2019). This prematurely polyadenylated RNA includes 227 nucleotides originating from the cryptic exon with its predicted 16 amino acid translation product initiating at the normal AUG codon in exon 1 and ending 11 codons into the cryptic exon. *See* Melamed (2019); *see also* Klim (2019).

[0013] Present invention provides inhibitors of STMN2 transcripts that include a cryptic exon, for treatment of neurological diseases or disorders.

SUMMARY

[0014] Described herein are oligonucleotide inhibitors. In various embodiments, the oligonucleotide targets a transcript for the treatment of neurological diseases, including motor

neuron diseases, and/or neuropathies. For example, inhibitors of the transcript can be used to treat PD, ALS, FTD, and ALS with FTD. In various embodiments, the oligonucleotide inhibitors are antisense oligonucleotides. In various embodiments, the oligonucleotide inhibitors target a Stathmin-2 (STMN2) transcript. In some embodiments, the STMN2 transcript includes a cryptic exon, such as the cryptic exon with a sequence identified below in SEQ ID NO: 447.

[0015] Additionally disclosed herein is a compound comprising an oligonucleotide comprising linked nucleosides with at least a 19 contiguous nucleobase sequence that is at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) complementary to an equal length portion of a transcript with at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to SEQ ID NO: 944, or to a contiguous 19 to 50 nucleobase portion of SEQ ID NO: 944, wherein at least one nucleoside linkage of the linked nucleosides is a non-natural linkage. Additionally disclosed herein is an oligonucleotide comprising linked nucleosides with at least a 19 contiguous nucleobase sequence that is at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) complementary to an equal length portion of a transcript with at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to SEQ ID NO: 944, or to a contiguous 19 to 50 nucleobase portion of SEQ ID NO: 944, wherein at least one nucleoside linkage of the linked nucleosides is a non-natural linkage.

[0016] In various embodiments, the nucleobase sequence comprises a portion of at least 10 contiguous nucleobases that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity with an equal length portion of any one of SEQ ID NOs: 1-446, SEQ ID NOs: 894-918, SEQ ID NOs: 945-1390, or SEQ ID NOs: 1392-1432. In various embodiments, the nucleobase sequence comprises a portion of at least 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleobases that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity with an equal length portion of any one of SEQ ID NOs: 1-446, SEQ ID NOs: 894-918, SEQ ID NOs: 945-1390, or SEQ ID NOs: 1392-1432.

[0017] In various embodiments, the nucleobase sequence comprises a portion of at least 10 contiguous nucleobases that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity with an equal length portion of any one of SEQ ID NOs: 31, 36, 41, 46, 55, 144, 146, 150, 169, 170, 171, 172, 173, 177, 181, 185, 197, 203, 209, 215, 237, 244, 249, 252, 380, 385, 390, 395, 400, 975, 980, 985, 999, 1088, 1090, 1094, 1113, 1114, 1115,

1116, 1117, 1121, 1125, 1129, 1141, 1147, 1153, 1159, 1181, 1188, 1193, 1196, 1324, 1329, 1334, 1339, or 1344, wherein at least one nucleoside linkage of the linked nucleosides is a non-natural linkage. In various embodiments, the nucleobase sequence comprises a portion of at least 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleobases that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity with an equal length portion of any one of SEQ ID NOs: 31, 36, 41, 46, 55, 144, 146, 150, 169, 170, 171, 172, 173, 177, 181, 185, 197, 203, 209, 215, 237, 244, 249, 252, 380, 385, 390, 395, 400, 975, 980, 985, 999, 1088, 1090, 1094, 1113, 1114, 1115, 1116, 1117, 1121, 1125, 1129, 1141, 1147, 1153, 1159, 1181, 1188, 1193, 1196, 1324, 1329, 1334, 1339, or 1344.

[0018] Additionally disclosed herein is a compound comprising an oligonucleotide comprising linked nucleosides with at least a 19 contiguous nucleobase sequence, wherein the nucleobase sequence comprises a portion of at least 10 contiguous nucleobases that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an equal length portion of any one of SEQ ID NOs: 894-918 or SEQ ID NOs: 1392-1432. Additionally disclosed herein is an oligonucleotide comprising linked nucleosides with at least a 19 contiguous nucleobase sequence, wherein the nucleobase sequence comprises a portion of at least 10 contiguous nucleobases that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an equal length portion of any one of SEQ ID NOs: 894-918 or SEQ ID NOs: 1392-1432. In various embodiments, the nucleobase sequence comprises a portion of at least 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleobases that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to of any one of SEQ ID NOs: 894-918 or SEQ ID NOs: 1392-1432.

[0019] Additionally disclosed herein is a compound comprising an oligonucleotide comprising linked nucleosides with at least a 19 contiguous nucleobase sequence, wherein the nucleobase sequence comprises a portion of at least 10 contiguous nucleobases that is at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) complementary to an equal length portion of nucleobases within any one of positions 121-144, 144-168, 146-170, 150-170, 150-172, 150-170, 150-172, 150-174, 169-193, 169-189, 169-191, 170-190, 170-192, 171-191, 171-193, 172-192, 172-194, 170-194, 171-195, 172-196, 173-197, 185-209, 197-221, 237-261, 249-273, 252-276, or 276-300 of SEQ ID NO: 944. Additionally disclosed herein is an oligonucleotide comprising linked nucleosides with a nucleobase sequence with at least a 19 contiguous nucleobase sequence, wherein the nucleobase sequence comprises a portion of at least

10 contiguous nucleobases that is at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) complementary to an equal length portion of nucleobases within any one of positions 121-144, 144-168, 146-170, 150-170, 150-172, 150-174, 169-193, 169-189, 169-191, 170-190, 170-192, 171-191, 171-193, 172-192, 172-194, 170-194, 171-195, 172-196, 173-197, 185-209, 197-221, 237-261, 249-273, 252-276, or 276-300 of SEQ ID NO: 944.

[0020] In various embodiments, the portion of the nucleobase sequence is 100% complementary to an equal length portion of nucleobases within any one of positions 121-144, 144-168, 146-170, 150-170, 150-172, 150-174, 169-193, 169-189, 169-191, 170-190, 170-192, 171-191, 171-193, 172-192, 172-194, 170-194, 171-195, 172-196, 173-197, 185-209, 197-221, 237-261, 249-273, 252-276, or 276-300 of SEQ ID NO: 944. In various embodiments, the portion of the nucleobase sequence is 100% complementary to an equal length portion of nucleobases within any one of positions 144-164, 144-166, 145-167, 146-166, 146-168, 147-165, or 148-168 of SEQ ID NO: 944. In various embodiments, the portion of the nucleobase sequence is 100% complementary to an equal length portion of nucleobases within any one of positions 173-191, 173-193, 173-195, 173-197, 175-195, 175-197, 177-197, or 179-197 of SEQ ID NO: 944.

[0021] In various embodiments, the portion of the nucleobase sequence is 100% complementary to an equal length portion of nucleobases within any one of positions 185-205, 187-209, 189-209, 185-207, 197-217, 197-219, or 191-209 of SEQ ID NO: 944. In various embodiments, the portion of the nucleobase sequence is 100% complementary to an equal length portion of nucleobases within any one of positions 237-255, 237-257, 237-259, 239-259, 239-261, 241-261, 237-257, 249-269, 249-271, 252-272, 252-274, or 243-261 of SEQ ID NO: 944. In various embodiments, the nucleobase sequence comprises a portion of at least 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleobases that is complementary to an equal length portion of nucleobases within any one of positions 121-144, 144-168, 146-170, 150-170, 150-172, 150-174, 169-193, 169-189, 169-191, 170-190, 170-192, 171-191, 171-193, 172-192, 172-194, 170-194, 171-195, 172-196, 173-197, 185-209, 197-221, 237-261, 249-273, 252-276, or 276-300 of SEQ ID NO: 944. In various embodiments, the nucleobase sequence comprises a portion of at least 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleobases that is complementary to an equal length portion of nucleobases within any one of positions 144-164, 144-166, 145-167, 146-166, 146-168, 147-165, 148-168, 173-191, 173-193, 173-195, 173-197, 175-195, 175-197, 177-197, 179-197, 185-205, 185-207, 197-217, 197-219,

187-209, 189-209, 191-209, 237-255, 237-257, 237-259, 239-259, 239-261, 241-261, 237-257, 249-269, 249-271, 252-272, 252-274, or 243-261 of SEQ ID NO: 944.

[0022] In various embodiments, the oligonucleotide is 19 and 40 nucleosides in length. In various embodiments, the oligonucleotide comprises at least one nucleoside linkage selected from the group consisting of a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a phosphorodithioate linkage, a phosphotriester linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothiate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, or any combination(s) thereof. In various embodiments, at least two, three, or four internucleoside linkages of the oligonucleotide are phosphodiester internucleoside linkages. In various embodiments, the oligonucleotide comprises at least two, three, or four modified internucleoside linkages.

[0023] In various embodiments, each of the modified internucleoside linkage of the oligonucleotide is independently selected from a phosphorothioate linkage, a phosphoramidate linkage, a phosphoramidothiate linkage, a phosphorodiamidate. In various embodiments, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages. In various embodiments, the phosphorothioate internucleoside linkage is in one of a *R*p configuration or a *S*p configuration. In various embodiments, the oligonucleotide comprises at least one modified nucleobase. In various embodiments, the at least one modified nucleobase is 5-methyl cytosine, pseudouridine, or 5-methoxyuridine.

[0024] In various embodiments, the oligonucleotide comprises at least one modified sugar moiety. In various embodiments, the modified sugar moiety is one of a 2'-OMe (2'-OCH_3 or 2'-O-methyl) modified sugar moiety, bicyclic sugar moiety, 2'-O-(2-methoxyethyl) (2'-$O(CH_2)_2OCH_3$ (2'MOE)), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

[0025] In various embodiments, wherein the oligonucleotide comprises three linked nucleosides that are linked through phosphodiester internucleoside linkages at the 5' end and three linked nucleosides that are linked through phosphodiester internucleoside linkages at the 3' end. In various embodiments, the oligonucleotide comprises one or more 2'-*O*-(2-methoxyethyl) nucleosides that are linked through phosphorothioate internucleoside linkages. In some embodiments, all cytosine nucleosides in a STMN2 antisense oligonucleotide of the present invention comprise modified sugar moiety comprising 2'-MOE, all nucleosides comprise modified nucleobase 5-methyl cytosine, and all internucleoside linkages are phosphorothioate linkage. In various embodiments, the oligonucleotide comprises three linked nucleosides that are linked through phosphorothioate internucleoside linkages at the 5' end and three linked nucleosides that are linked through phosphorothioate internucleoside linkages at the 3' end. In various embodiments, the oligonucleotide comprises five linked nucleosides that are linked through phosphodiester internucleoside linkages. In various embodiments, the each of the five linked nucleosides are 2'-*O*-(2-methoxyethyl) (2'MOE) nucleosides. In various embodiments, each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'MOE) nucleosides.

[0026] In various embodiments, the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length STMN2 transcript or STMN2 protein. In various embodiments, the oligonucleotide exhibits at least a 100% increase of full length STMN2 transcript or STMN2 protein. In various embodiments, the oligonucleotide exhibits at least a 200% increase of full length STMN2 transcript or STMN2 protein. In various embodiments, the oligonucleotide exhibits at least a 300% increase of full length STMN2 transcript or STMN2 protein. In various embodiments, the oligonucleotide exhibits at least a 400% increase of full length STMN2 transcript or STMN2 protein. In various embodiments, increase of the full length STMN2 protein is measured in comparison to a reduced level of full length STMN2 protein achieved using a TDP43 antisense oligonucleotide. In various embodiments, the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length STMN2 transcript or STMN2 protein. In various embodiments, the oligonucleotide exhibits at least a 50%, 60%, 70%, 80%, or 90% reduction of the STMN2 transcript with the cryptic exon.

[0027] Additionally disclosed herein is a pharmaceutical composition comprising one or more of the oligonucleotides described above, or a pharmaceutically acceptable salt thereof, and a

pharmaceutically acceptable excipient. Additionally disclosed herein is a method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to the patient an oligonucleotide of any of the oligonucleotides described above or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described above.

[0028] In various embodiments, the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, and corticobasal degeneration (CBD). In various embodiments, the neuropathy is chemotherapy induced neuropathy.

[0029] Additionally disclosed herein is a method of restoring axonal outgrowth and/or regeneration of a neuron, the method comprising exposing the motor neuron to an oligonucleotide of any of the oligonucleotides described above or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described above. Additionally disclosed herein is a method of increasing, promoting, stabilizing, or maintaining STMN2 expression and/or function in a neuron, the method comprising exposing the cell to an oligonucleotide of any of the oligonucleotides described above or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described above. In various embodiments, the neuron is a neuron of a patient in need of treatment of a neurological disease and/or a neuropathy. In various embodiments, the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, and corticobasal degeneration (CBD) . In various embodiments, the neuropathy is chemotherapy induced neuropathy.

[0030] In various embodiments, the exposing is performed *in vivo* or *ex vivo*. In various embodiments, the exposing comprises administering a STMN2 oligonucleotide (STMN2 AON) disclosed herein or a pharmaceutical composition thereof to a patient in need thereof. In various embodiments, a STMN2 oligonucleotide or a pharmaceutical composition thereof is administered topically, parenterally (*e.g.*, subcutaneous, intramuscular, intradermal, intraduodenal, or intravenous), intralesionally, intrathecally, intracisternally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, or intraduodenally. In various embodiments, a STMN2 oligonucleotide or a pharmaceutical composition thereof is administered

orally. In various embodiments, a therapeutically effective amount of a STMN2 oligonucleotide or a pharmaceutical composition thereof is administered intrathecally or intracisternally.

[0031] In various embodiments, the patient is a human. In various embodiments, the pharmaceutical composition is suitable for topical, intrathecal, intracisternal, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, intraduodenal, or intravenous), intralesional, oral, pulmonary, intratracheal, intranasal, transdermal, rectal, buccal, sublingual, vaginal, or intraduodenal administration.

[0032] Additionally disclosed herein is a use of a STMN2 oligonucleotide or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described above in the manufacture of a medicament for the treatment of neurological disease or a neuropathy. In various embodiments, the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, and corticobasal degeneration (CBD). In various embodiments, the neuropathy is chemotherapy induced neuropathy.

[0033] Additionally disclosed herein is a method of treating a neurological disease or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a STMN2 oligonucleotide or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described above. In various embodiments, the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, and corticobasal degeneration (CBD). In various embodiments, the neuropathy is chemotherapy induced neuropathy. In various embodiments, the pharmaceutical composition is administered topically, parenterally (*e.g.*, subcutaneous, intramuscular, intradermal, intraduodenal, or intravenous), intralesionally, orally, pulmonarily, rectally, buccally, sublingually, vaginally, intratracheally, intranasally, intracisternally, intrathecally, transdermally, or intraduodenally. In various embodiments, the pharmaceutical composition is administered intrathecally or intracisternally. In various embodiments, a therapeutically effective amount of a STMN2 oligonucleotide or a pharmaceutical composition thereof is administered intrathecally or intracisternally. In various embodiments, the patient is human.

[0034] Additionally disclosed herein is a STMN2 oligonucleotide or a pharmaceutically acceptable salt thereof, for use as a medicament in the treatment of a neurological disease or a neuropathy. In certain embodiments, the present disclosure provides a STMN2 oligonucleotide or a pharmaceutically acceptable salt thereof, for use in the treatment of a neurological disease or a neuropathy. In various embodiments, the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, and corticobasal degeneration (CBD). In various embodiments, the neuropathy is chemotherapy induced neuropathy.

[0035] Additionally disclosed herein is a STMN2 oligonucleotide comprising linked nucleosides with a nucleobase sequence of any one of SEQ ID NOs: 1-446, SEQ ID NOs: 894-918, SEQ ID NOs: 945-1390, or SEQ ID NOs: 1392-1432, or a pharmaceutically acceptable salt thereof; wherein the oligonucleotide comprises at least one nucleoside linkage selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a phosphorodithioate linkage, a phosphotriester linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothiate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one nucleoside of the linked nucleosides is substituted with a component selected from the group consisting of a 2'-*O*-(2-methoxyethyl) nucleoside (2′-*O*-methoxyethylribonucleosides (2′-MOE)), a 2'-*O*-methyl nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA).

[0036] In various embodiments, at least one internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. In various embodiments, the oligonucleotide comprises three linked nucleosides that are linked through phosphodiester internucleoside linkages at the 5' end and three linked nucleosides that are linked through phosphodiester internucleoside linkages at the 3' end. In various embodiments, the oligonucleotide comprises one or more 2'-O-(2-methoxyethyl) nucleosides that are linked through phosphorothioate internucleoside linkages. In various

embodiments, the oligonucleotide comprises five linked nucleosides that are linked through phosphodiester internucleoside linkages. In various embodiments, each of the five linked nucleosides are 2'-*O*-(2-methoxyethyl) (2'MOE) nucleosides. In various embodiments, each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'MOE) nucleosides. In various embodiments, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages, optionally wherein each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[0037] Additionally disclosed herein is a pharmaceutical composition comprising the oligonucleotide of any oligonucleotide described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. Additionally disclosed herein is STMN2 oligonucleotide or a pharmaceutically acceptable salt thereof capable of increasing, restoring, or stabilizing expression of the STMN2 mRNA capable of translation of a functional STMN2 and/or activity and/or function of STMN2 protein in a cell or a human patient of a neurological disease or disorder, wherein the level of increase, restoration, or stabilization of expression and/or activity and/or function is sufficient for use of the oligonucleotide as a medicament for the treatment of neurological disease or disorder. In various embodiments, wherein the oligonucleotide comprises one or more chiral centers and/or double bonds. In various embodiments, the oligonucleotide exist as stereoisomers selected from geometric isomers, enantiomers, and diastereomers.

[0038] Additionally disclosed herein is a method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a STMN2 oligonucleotide or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described above, in combination with a second therapeutic agent selected from Riluzole (Rilutek), Edaravone (Radicava), rivastigmine, donepezil, galantamine, selective serotonin reuptake inhibitor, antipsychotic agents, cholinesterase inhibitors, memantine, benzodiazepine antianxiety drugs, AMX0035 (ELYBRIO), ZILUCOPLAN (RA101495), dual AON intrathecal administration (*e.g.*, BIIB067, BIIB078), BIIB100, levodopa/carbidopa, dopaminergic agents (*e.g.*, ropinirole, pramipexole, rotigotine), medroxyprogesterone, KCNQ2/KCNQ3 openers, anticonvulsants and psychostimulant agents, and/or a therapy (*e.g.*, selected from breathing care, physical therapy, occupational therapy, speech therapy, nutritional support), for treating said neurologic disease.

[0039] In various embodiments, the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease

(AD), Parkinson's disease (PD), Huntington's disease, brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, and corticobasal degeneration (CBD). In various embodiments, the neuropathy is chemotherapy induced neuropathy.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] FIG. 1A is a schematic depiction of portions of the STMN2 transcript and STMN2 antisense oligonucleotides that are designed to target certain portions of the STMN2 transcript. FIG. 1B is another schematic depiction of portions of the STMN2 transcript and STMN2 antisense oligonucleotides that are designed to target certain portions of the STMN2 transcript in SY5Y cells. FIG. 1C is yet another schematic depiction of portions of the STMN2 transcript and STMN2 antisense oligonucleotides that are designed to target certain portions of the STMN2 transcript in human motor neurons. In each of FIG. 1A, 1B, and 1C the solid line represents tested STMN2 AON that increased STMN2-FL mRNA expression by greater than 50% over TDP43 AON treated alone. The dotted line represents tested STMN2 AON that increased STMN2-FL (full length) mRNA less than 50% over TDP43 AON treated alone.

[0041] FIG. 2 is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript in the presence of 6 different STMN2 antisense oligonucleotides (QSN-36, QSN-55, QSN-177, QSN-203, QSN-244, and QSN-395).

[0042] FIG. 3 is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels in the presence of 6 different STMN2 antisense oligonucleotides (QSN-173, QSN-181, QSN-197, QSN-215, QSN-385, and QSN-400).

[0043] FIG. 4 is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript in the presence of 6 different STMN2 antisense oligonucleotides (QSN-173, QSN-181, QSN-197, QSN-215, QSN-385, and QSN-400).

[0044] FIG. 5A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2

transcript with cryptic exon mRNA levels in the presence of 6 different STMN2 antisense oligonucleotides (QSN-185, QSN-209, QSN-237, QSN-252, QSN-380, and QSN-390).

[0045] FIG. 5B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript in the presence of 6 different STMN2 antisense oligonucleotides (QSN-185, QSN-209, QSN-237, QSN-252, QSN-380, and QSN-390).

[0046] FIG. 6A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels in the presence of 2 different STMN2 antisense oligonucleotides (QSN-144 and QSN-237) over two duplicate experiments.

[0047] FIG. 6B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript in the presence of 2 different STMN2 antisense oligonucleotides (QSN-144 and QSN-237) over two duplicate experiments.

[0048] FIG. 7A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels in the presence of 5 different STMN2 antisense oligonucleotides (QSN-36, QSN-173, QSN-177, QSN-181, and QSN-185).

[0049] FIG. 7B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript in the presence of 5 different STMN2 antisense oligonucleotides (QSN-36, QSN-173, QSN-177, QSN-181, and QSN-185).

[0050] FIG. 8A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels in the presence of 5 different STMN2 antisense oligonucleotides (QSN-197, QSN-203, QSN-237, QSN-380, and QSN-395).

[0051] FIG. 8B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2

transcript in the presence of 5 different STMN2 antisense oligonucleotides (QSN-197, QSN-203, QSN-237, QSN-380, and QSN-395).

[0052] FIG. 9A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels in the presence of 3 different STMN2 antisense oligonucleotides (QSN-144, QSN-173, and QSN-237).

[0053] FIG. 9B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript in the presence of 3 different STMN2 antisense oligonucleotides (QSN-144, QSN-173, and QSN-237).

[0054] FIG. 10A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of a QSN-181 STMN2 antisense oligonucleotide.

[0055] FIG. 10B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of a QSN-181 STMN2 antisense oligonucleotide.

[0056] FIG. 11A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of a QSN-185 STMN2 antisense oligonucleotide.

[0057] FIG. 11B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of a QSN-185 STMN2 antisense oligonucleotide.

[0058] FIG. 12A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense,

and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of a QSN-197 STMN2 antisense oligonucleotide.

[0059] FIG. 12B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of a QSN-197 STMN2 antisense oligonucleotide.

[0060] FIG. 13A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of a QSN-144 STMN2 antisense oligonucleotide.

[0061] FIG. 13B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of a QSN-144 STMN2 antisense oligonucleotide.

[0062] FIG. 14A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of a QSN-173 STMN2 antisense oligonucleotide.

[0063] FIG. 14B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript across different dosages of a QSN-173 STMN2 antisense oligonucleotide.

[0064] FIG. 15A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels across different dosages of a QSN-237 STMN2 antisense oligonucleotide.

[0065] FIG. 15B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and

restoration of the full-length STMN2 transcript across different dosages of a QSN-237 STMN2 antisense oligonucleotide.

[0066] FIG. 16 is a protein blot and quantified bar graph showing the normalized quantity of STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript for 2 different STMN2 antisense oligonucleotides (QSN-173 and QSN237).

[0067] FIG. 17A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different variants of a QSN-237 STMN2 antisense oligonucleotide.

[0068] FIG. 17B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different variants of a QSN-237 STMN2 antisense oligonucleotide.

[0069] FIG. 18A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different variants of a QSN-185 STMN2 antisense oligonucleotide.

[0070] FIG. 18B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different variants of a QSN-185 STMN2 antisense oligonucleotide.

[0071] FIG. 19A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different variants of a QSN-173 STMN2 antisense oligonucleotide.

[0072] FIG. 19B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and

restoration of the full-length STMN2 transcript using different variants of a QSN-173 STMN2 antisense oligonucleotide.

[0073] FIG. 20A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different variants of a QSN-237 STMN2 antisense oligonucleotide.

[0074] FIG. 20B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different variants of a QSN-237 STMN2 antisense oligonucleotide.

[0075] FIG. 21A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different variants of a QSN-173 STMN2 antisense oligonucleotide.

[0076] FIG. 21B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different variants of a QSN-173 STMN2 antisense oligonucleotide.

[0077] FIG. 22A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different variants of a QSN-144 STMN2 antisense oligonucleotide.

[0078] FIG. 22B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different variants of a QSN-144 STMN2 antisense oligonucleotide.

[0079] FIG. 23 shows the dose response curve illustrating increasing restoration of full length STMN2 transcript with increasing concentrations of STMN2 AON.

[0080] FIG. 24A shows a Western blot assay demonstrating the qualitative increase of full length STMN2 protein in response to higher concentrations of STMN2 AON.

[0081] FIG. 24B shows the quantitated levels of full length STMN2 protein normalized to GAPDH in response to different concentrations of STMN2 AON.

[0082] FIG. 25A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different QSN-144 STMN2 AONs and AON variants.

[0083] FIG. 25B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different QSN-144 STMN2 AONs and AON variants.

[0084] FIG. 26A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different QSN-173 STMN2 AONs and AON variants.

[0085] FIG. 26B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different QSN-173 STMN2 AONs and AON variants.

[0086] FIG. 27A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different QSN-185 STMN2 AONs and AON variants.

[0087] FIG. 27B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different QSN-185 STMN2 AONs and AON variants.

[0088] FIG. 28A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different QSN-237 STMN2 AONs and AON variants.

[0089] FIG. 28B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different QSN-237 STMN2 AONs and AON variants.

[0090] FIG. 29A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different STMN2 AONs (QSN-31, QSN-41, and QSN-46).

[0091] FIG. 29B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different STMN2 AONs (QSN-31, QSN-41, and QSN-46).

[0092] FIG. 30 is a bar graph showing reversal of cryptic exon induction in human motor neurons using QSN-237 STMN2 antisense oligonucleotide even in view of increasing proteasome inhibition.

[0093] FIGs. 31A and 31B show bar graphs showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels and STMN2 full-length mRNA levels, which demonstrate reduction of the STMN2 transcript with cryptic exon mRNA levels and restoration of the full-length STMN2 transcript using different STMN2 AONs and AON variants.

[0094] FIG 32 is a bar graph showing the results of a western blot analysis of STMN2 protein levels, which demonstrates restoration of the full-length STMN2 protein using different STMN2 AONs and AON variants.

[0095] FIG. 33A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA expression in human motor neurons, which demonstrates

reduction of the STMN2 transcript with cryptic exon mRNA levels using different STMN2 AONs (QSN-31, QSN-41, and QSN-46).

[0096] FIG. 33B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels, which demonstrates restoration of the full-length STMN2 transcript using different STMN2 AONs (QSN-31, QSN-41, and QSN-46).

[0097] FIG. 34A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA expression in human motor neurons, which demonstrates reduction of the STMN2 transcript with cryptic exon mRNA levels using different STMN2 AONs (QSN-146, QSN-150, and QSN-169).

[0098] FIG. 34B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels, which demonstrates the restoration of the full-length STMN2 transcript using different STMN2 AONs (QSN-146, QSN-150, and QSN-169).

[0099] FIG. 34C is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA expression in human motor neurons, which demonstrates reduction of the STMN2 transcript with cryptic exon mRNA levels using different STMN2 AONs (QSN-170, QSN-171, and QSN-172).

[00100] FIG. 34D is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels, which demonstrates the restoration of the full-length STMN2 transcript using different STMN2 AONs (QSN-170, QSN-171, and QSN-172).

[00101] FIG. 34E is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA expression in human motor neurons, which demonstrates reduction of the STMN2 transcript with cryptic exon mRNA levels using different STMN2 AONs (QSN-249).

[00102] FIG. 34F is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels, which demonstrates the restoration of the full-length STMN2 transcript using different STMN2 AONs (QSN-249).

DETAILED DESCRIPTION

[00103] The features and other details of the disclosure will now be more particularly described. Certain terms employed in the specification, examples and appended claims are

collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

[00104] The terms "treat," "treatment," "treating," and the like are used herein to generally mean obtaining a desired pharmacological and/or physiological effect. The effect may be therapeutic in terms of partially or completely curing a disease and/or adverse effect attributed to the disease. The term "treatment" as used herein covers any treatment of a disease in a mammal, particularly a human, and includes: (a) inhibiting the disease, *i.e.*, preventing the disease from increasing in severity or scope; (b) relieving the disease, *i.e.*, causing partial or complete amelioration of the disease; or (c) preventing relapse of the disease, *i.e.*, preventing the disease from returning to an active state following previous successful treatment of symptoms of the disease or treatment of the disease.

[00105] "Preventing" includes delaying the onset of clinical symptoms, complications, or biochemical indicia of the state, disorder, disease, or condition developing in a subject that may be afflicted with or predisposed to the state, disorder, disease, or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder, disease, or condition. "Preventing" includes prophylactically treating a state, disorder, disease, or condition in or developing in a subject, including prophylactically treating clinical symptoms, complications, or biochemical indicia of the state, disorder, disease, or condition in or developing in a subject.

[00106] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" as used herein interchangeably refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

[00107] The term "pharmaceutical composition" as used herein refers to a composition comprising at least one biologically active compound, for example, a STMN2 antisense oligonucleotide (AON), as disclosed herein formulated together with one or more pharmaceutically acceptable excipients.

[00108] "Individual," "patient," or "subject" are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or non-human primates, and most preferably humans. The compounds of the invention can be administered to a mammal, such as a human, but can also be other mammals such as an animal in need of veterinary treatment, *e.g.*, domestic animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, non-human primates, and the like). In some embodiments, the mammal treated in the methods of the invention is desirably a mammal in whom modulation of STMN2 expression and/or activity is desired.

[00109] The term "STMN2 oligonucleotide," "STMN2 antisense oligonucleotide," or "STMN2 AON" refers to an oligonucleotide that is capable of increasing, restoring, or stabilizing full-length STMN2 activity *e.g.*, full length STMN2 expression, for example, full length STMN2 mRNA and/or full length STMN2 protein expression. Generally, a STMN2 oligonucleotide reduces the level of mature STMN2 transcripts with a cryptic exon by targeting a STMN2 transcript comprising a cryptic exon. A patient suffering from ALS, FTD, ALS with FTD, or another neurological or motor neuron disease can be a patient that is diagnosed with the disease or that displays symptoms of the disease. A patient suffering from ALS, FTD, ALS with FTD, or another neurological or motor neuron disease can be a patient that previously suffered from the disease and, after recovering or experiencing complete or partial amelioration of the disease and/or disease symptoms, experiences a complete or partial relapse of the disease or disease symptoms. A patient suffering from ALS, FTD, ALS with FTD, or another neurological or motor neuron disease or condition can be a patient that harbors a genetic mutation associated with manifestation of the disease or condition. For example, a patient suffering from ALS can be a patient that harbors a genetic mutation in any of SOD1, C9orf72, Ataxin 2 (ATXN2), Charged Multivesicular Body Protein 2B (CHMP2B), Dynactin 1 (DCTN1), Human Epidermal Growth Factor Receptor 4 (ERBB4), FIG4 phosphoinositide 5-phosphatase (FIG4), NIMA related kinase 1 (NEK1), Heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1), Neurofilament Heavy (NEFH), Peripherin (PRPH), TAR DNA binding protein 43 (TDP43 or TARDBP), Fused in Sarcoma (FUS), Ubiquilin-2 (UBQLN2), Kinesin Family Member 5A (KIF5A), Valosin-Containing Protein (VCP), Alsin (ALS2), Senataxin (SETX), Sigma Non-Opioid Intracellular Receptor 1 (SIGMAR1), Survival of Motor Neuron 1, Telomeric (SMN1), Spastic Paraplegia 11, Autosomal Recessive (SPG11), Transient Receptor Potential Cation Channel Subfamily M Member 7 (TRPM7), Vesicle-Associated Membrane Protein-Associated Protein B/C (VAPB),

Angiogenin (ANG), Profilin-1 (PFN1), Matrin-3 (MATR3), Coiled-coil-helix-coiled-coil-helix domain Containing 10 (CHCHD10), Tubulin, Alpha 4A (TUBA4A), TBK1, C21orf2, Sequestosome-1 (SQSTM1, also known as Ubiquitin-binding protein p62), and/or optineurin (OPTN), in particular, where the mutation is associated with ALS or a high risk of developing ALS.

[00110] A patient at risk of ALS, FTD, ALS with FTD, or another neurological or motor neuron disease can include those patients with a familial history of the disease or a genetic predisposition to the disease (*e.g.*, a patient that harbors a genetic mutation associated with high disease risk, for example), or patients exposed to environmental factors that increase disease risk. For example, a patient may be at risk of ALS if the patient harbors a mutation in any of genes encoding SOD1, C9orf72, ATXN2, CHMP2B, DCTN1, ERBB4, FIG4, HNRNPA1, NEFH, PRPH, NEK1, TDP43, FUS, UBQLN2, KIF5A, VCP, ALS2, SETX, SIGMAR1, SMN1, SPG11, TRPM7, VAPB, ANG, PFN1, MATR3, CHCHD10, TUBA4A, TBK1, SQSTM1, C21orf2, and/or OPTN, in particular, where the mutation is associated with ALS or high risk of developing ALS. A patient at risk may also include those patients diagnosed with a disease or condition that has a high comorbidity with ALS, FTD, ALS with FTD, or another neurological or motor neuron disease (for example, a patient suffering from dementia, which is significantly associated with higher odds of a family history of ALS, FTD, and of bulbar onset ALS (*see* Trojsi, F., *et al.* (2017) "Comorbidity of dementia with amyotrophic lateral sclerosis (ALS): insights from a large multicenter Italian cohort" *J Neurol* 264: 2224-31)).

[00111] As used herein, "STMN2" (also known as Superior Cervical Ganglion-10 Protein, Stathmin-Like 2, SCGN10, SCG10, Neuronal Growth-Associated Protein, Neuron-Specific Growth-Associated Protein, or Protein SCG10 (Superior Cervical Ganglia NEAR Neural Specific 10) refers to the gene or gene products (*e.g.*, protein or mRNA transcript (including pre-mRNA) encoded by the gene) identified by Entrez Gene ID No. 11075 and allelic variants thereof, as well as orthologs found in non-human species (*e.g.*, non-human primates or mice).

[00112] In the present specification, the term "therapeutically effective amount" means the amount of the subject inhibitor of STMN2 transcripts that include a cryptic exon that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor, or other clinician. The inhibitor of STMN2 transcripts that include a cryptic exons of the invention are administered in therapeutically effective amounts to treat and/or prevent a disease, condition, disorder, or state, for example, ALS, FTD, ALS with

FTD, or another motor neuron disease or neurological disease or condition. Alternatively, a therapeutically effective amount of an inhibitor of STMN2 transcripts that include a cryptic exon is the quantity required to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in the prevention of or a decrease in the symptoms associated with a disease associated with reduced STMN2 activity in the motor neurons.

[00113] The phrase "oligonucleotide that targets a STMN2 transcript" refers to an oligonucleotide that binds to a STMN2 transcript. In various embodiments, the oligonucleotide binds to a region of a STMN2 transcript. Example regions of a STMN2 transcript are shown in Table 1, which show sequences corresponding to regions of branch points (*e.g.*, branch point 1, 2, and 3) a 3' splice acceptor region, an ESE binding region, TDP43 binding sites, a cryptic exon, and a Poly A region. In various embodiments, the oligonucleotide binds to a region of a STMN2 transcript with a cryptic exon, the region being located less than 75 nucleobases upstream or downstream to any of the branch points (*e.g.*, branch point 1, 2, and 3) a 3' splice acceptor region, an ESE binding region, TDP43 binding sites, a cryptic exon, and a Poly A region.

[00114] The term "pharmaceutically acceptable salt(s)" as used herein refers to salts of acidic or basic groups that may be present in inhibitors of STMN2 transcripts that include a cryptic exon used in the present compositions. Inhibitors of STMN2 transcripts that include a cryptic exon included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, including but not limited to malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Inhibitors of STMN2 transcripts that include a cryptic exon included in the present compositions that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, and lithium salts. Pharmaceutically acceptable salts of the disclosure include, for example, pharmaceutically acceptable salts of STMN2 AONs that include

a nucleobase sequence of any of SEQ ID NOs: 1-446, SEQ ID NOs: 894-918, SEQ ID NOs: 945-1390, or SEQ ID NOs: 1392-1432.

[00115] Inhibitors of STMN2 transcripts that include a cryptic exon of the disclosure may contain one or more chiral centers, groups, linkages, and/or double bonds and, therefore, exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers. The term "stereoisomers" when used herein consist of all geometric isomers, enantiomers or diastereomers. These compounds may be designated by the symbols "*R*" or "*S*" (or "*R*p" or "*S*p") depending on the configuration of substituents around the stereogenic atom, for example, a stereogenic carbon, phosphorus, or sulfur atom. In some embodiments, one or more linkages of the compound may have a *R*p or *S*p configuration (*e.g.*, one or more phosphorothioate linkages have either a *R*p or *S*p configuration). The configuration of each phosphorothioate linkage may be independent of another phosphorothioate linkage (*e.g.*, one phosphorothioate linkage has a *R*p configuration and a second phosphorothioate linkage has a *S*p configuration). The present invention encompasses various stereoisomers of these compounds and mixtures thereof. Stereoisomers include enantiomers and diastereomers. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.Individual stereoisomers of inhibitors of STMN2 transcripts that include a cryptic exon of the present invention can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, or (3) direct separation of the mixture of optical enantiomers on chiral chromatographic columns. Stereoisomeric mixtures can also be resolved into their component stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase super critical fluid chromatography, chiral-phase simulated moving bed chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Stereoisomers can also be obtained from stereomerically-pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

[00116] The inhibitors of STMN2 transcripts that include a cryptic exon disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms.

[00117] The disclosure also embraces isotopically labeled compounds of the invention (*i.e.*, isotopically labeled inhibitors of STMN2 transcripts that include a cryptic exon) which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number abundantly found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{33}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

[00118] Certain isotopically labeled disclosed compounds (*e.g.*, those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^{3}H) and carbon-14 (*i.e.*, ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances.

[00119] As used herein, "2'-O-(2-methoxyethyl)" (also 2'-MOE and 2'-O$(CH_2)_2OCH_3$ and MOE) refers to an *O*-methoxyethyl modification of the 2' position of a furanose ring. A 2'-O-(2-methoxyethyl) is used interchangeably as "2'-*O*-methoxyethyl" in the present disclosure. A sugar moiety in a nucleoside modified with 2'-MOE is a modified sugar.

[00120] As used herein, "2'-MOE nucleoside" (also 2'-O-(2-methoxyethyl) nucleoside) means a nucleoside comprising a 2'-MOE modified sugar moiety.

[00121] As used herein, "2'-substituted nucleoside" means a nucleoside comprising a substituent at the 2'-position of the furanose ring other than H or OH. In certain embodiments, 2' substituted nucleosides include nucleosides with bicyclic sugar modifications.

[00122] As used herein, "5-methyl cytosine" (5-MeC) means a cytosine modified with a methyl group attached to the 5 position. A 5-methyl cytosine (5-MeC) is a modified nucleobase.

[00123] As used herein, “bicyclic sugar” means a furanose ring modified by the bridging of two atoms. A bicyclic sugar is a modified sugar.

[00124] As used herein, “bicyclic nucleoside” (also BNA) means a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4'-carbon and the 2'-carbon of the sugar ring.

[00125] As used herein, “cap structure” or “terminal cap moiety” means chemical modifications, which have been incorporated at either terminus of an antisense compound.

[00126] As used herein, “cEt” or “constrained ethyl” means a bicyclic nucleoside having a sugar moiety comprising a bridge connecting the 4'-carbon and the 2'-carbon, wherein the bridge has the formula: 4'-CH(CH_3)—*O*-2'.

[00127] As used herein, “constrained ethyl nucleoside” (also cEt nucleoside) means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-CH(CH_3)—*O*-2' bridge.

[00128] As used herein, “internucleoside linkage” refers to the covalent linkage between adjacent nucleosides in an oligonucleotide. In some embodiments, as used herein, “non-natural linkage” refers to a “modified internucleoside linkage.”

[00129] As used herein, "contiguous" in the context of an oligonucleotide refers to nucleosides, nucleobases, sugar moieties, or internucleoside linkages that are immediately adjacent to each other. For example, “contiguous nucleobases” means nucleobases that are immediately adjacent to each other in a sequence.

[00130] As used herein, “locked nucleic acid” or “LNA” or “LNA nucleosides” means nucleic acid monomers having a bridge (*e.g.*, methylene, ethylene, aminooxy, or oxyimino bridge) connecting two carbon atoms between the 4' and 2' position of the nucleoside sugar unit, thereby forming a bicyclic sugar. Examples of such bicyclic sugar include, but are not limited to A) α-L-Methyleneoxy (4'-CH_2—O-2') LNA, (B) β-D-Methyleneoxy (4'-CH_2—O-2') LNA, (C) Ethyleneoxy (4'-$(CH_2)_2$—O-2') LNA, (D) Aminooxy (4'-CH_2—O—N(R)-2') LNA and (E) Oxyamino (4'-CH_2—N(R)—O-2') LNA.

[00131] As used herein, LNA compounds include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the sugar wherein each of the bridges

independently comprises 1 or from 2 to 4 linked groups independently selected from —$[C(R_1)(R_2)]_n$ —, —$C(R_1)=C(R_2)$—, —$C(R_1)=N$—, —$C(=NR_1)$—, —$C(=O)$—, —$C(=S)$—, —O—, —$Si(R_1)_2$—, —$S(=O)_x$— and —$N(R_1)$ —; wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; each R_1 and R_2 is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, a heterocycle radical, a substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O) —H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl (S(=O)- J_1); and each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(=O) —H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1-C_{12} aminoalkyl, substituted C_1-C_{12} aminoalkyl or a protecting group.

[00132] Examples of 4'-2' bridging groups encompassed within the definition of LNA include, but are not limited to one of formulae: —$[C(R_1)(R_2)]_n$ —, — $[C(R_1)(R_2)]_n$—O—, — $C(R_1R_2)$—$N(R_1)$—O— or —$C(R_1R_2)$—O—$N(R_1)$—. Furthermore, other bridging groups encompassed with the definition of LNA are 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2—O-2', 4'-$(CH_2)_2$—O-2', 4'-CH_2—O—$N(R_1)$-2' and 4'- CH_2—$N(R_1)$—O-2'- bridges, wherein each R_1 and R_2 is, independently, H, a protecting group or C_1-C_{12} alkyl.

[00133] Also included within the definition of LNA according to the invention are LNAs in which the 2'-hydroxyl group of the ribosyl sugar ring is connected to the 4' carbon atom of the sugar ring, thereby forming a bridge to form the bicyclic sugar moiety. The bridge can also be a methylene (—CH_2—) group connecting the 2' oxygen atom and the 4' carbon atom, for which the term methyleneoxy (4'-CH_2—O-2') LNA is used. Furthermore, in the case of the bicyclic sugar moiety having an ethylene bridging group in this position, the term ethyleneoxy (4'-CH_2CH_2—O-2') LNA is used. 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.

[00134] As used herein, “hotspot region” is a range of nucleobases on a target nucleic acid amenable to oligomeric compound-mediated modulation of the splicing of the target nucleic acid.

[00135] As used herein, “hybridization” means the pairing or annealing of complementary oligonucleotides and/or nucleic acids. While not limited to a particular mechanism, the most

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

[00136] As used herein, "increasing the amount of activity" refers to more transcriptional expression, more accurate splicing resulting in full length mature mRNA and/or protein expression, and/or more activity relative to the transcriptional expression or activity in an untreated or control sample.

[00137] 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.

[00138] As used herein, "linked nucleosides" are nucleosides that are connected through internucleoside linkages in a contiguous sequence (*i.e.*, no additional nucleosides are presented between those that are linked).

[00139] As used herein, "modified internucleoside linkage" refers to a substitution or any change from a naturally occurring internucleoside linkage (*e.g.*, a phosphodiester internucleoside bond). "Phosphorothioate linkage" is a modified internucleoside linkage in which one of the non-bridging oxygen atoms of a phosphodiester internucleoside linkage is replaced with a sulfur atom.

[00140] As used herein, "modified nucleobase" means any nucleobase other than adenine, cytosine, guanine, thymidine, or uracil. Examples of a modified nucleobase include 5-methyl cytosine, pseudouridine, or 5-methoxyuridine. An "unmodified nucleobase" means the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C), and uracil (U).

[00141] As used herein, a "modified nucleoside" means a nucleoside having, independently, a modified sugar moiety and/or modified nucleobase. A universal base is a modified nucleobase that can pair with any one of the five unmodified nucleobases. Modified nucleosides include abasic nucleosides, which lack a nucleobase.

[00142] As used herein, "modified oligonucleotide" means an oligonucleotide comprising at least one modified internucleoside linkage, modified sugar, and/or modified nucleobase.

[00143] As used herein, "modified sugar" or "modified sugar moiety" means a modified furanosyl sugar moiety or a modified sugar moiety having other than a furanosyl moiety that can

link a nucleobase to another group, such as an internucleoside linkage, conjugate group, or terminal group in an oligonucleotide.

[00144] As used herein, “monomer” means a single unit of an oligomer. Monomers include, but are not limited to, nucleosides and nucleotides, whether naturally occurring or modified.

[00145] As used herein, “motif” means the pattern of unmodified and modified nucleosides in an antisense compound.

[00146] As used herein, “natural sugar moiety” means a sugar moiety found in DNA (2'-H) or RNA (2'-OH).

[00147] As used herein, “naturally occurring internucleoside linkage” means a 3' to 5' phosphodiester linkage.

[00148] As used herein, “non-complementary nucleobase” refers to a pair of nucleobases that do not form hydrogen bonds with one another or otherwise support hybridization.

[00149] As used herein, “nucleic acid” refers to molecules composed of monomeric nucleotides. A nucleic acid includes, but is not limited to, ribonucleic acids (RNA), deoxyribonucleic acids (DNA), single-stranded nucleic acids, double-stranded nucleic acids, small interfering ribonucleic acids (siRNA), short-hairpin RNA (shRNA), and microRNAs (miRNA).

[00150] As used herein, “nucleobase” means a heterocyclic moiety capable of pairing with a base of another nucleic acid.

[00151] As used herein, “nucleobase complementarity" refers to a nucleobase that is capable of base pairing with another nucleobase. For example, in DNA, adenine (A) is complementary to thymine (T). For example, in RNA, adenine (A) is complementary to uracil (U). In certain embodiments, complementary nucleobase refers to a nucleobase of an antisense compound that is capable of base pairing with a 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.

[00152] As used herein, "nucleobase sequence" means the order of contiguous nucleobases independent of any sugar, linkage, and/or nucleobase modification.

[00153] As used herein, "nucleoside" means a nucleobase linked to a sugar. The term "nucleoside" also includes a "modified nucleoside" which has independently, a modified sugar moiety and/or modified nucleobase.

[00154] As used herein, "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.

[00155] As used herein, "nucleotide" means a nucleoside having a phosphate group covalently linked to the sugar portion of the nucleoside.

[00156] As used herein, "oligomeric compound" or "oligomer" means a polymer of linked monomeric subunits which is capable of hybridizing to at least a region of a nucleic acid molecule.

[00157] As used herein, "oligonucleotide" means a polymer of linked nucleosides each of which can be modified or unmodified, independent one from another.

Modifications

[00158] A nucleoside is a base-sugar combination. The nucleobase (also known as base) portion of the nucleoside is normally a heterocyclic base moiety. Nucleotides are nucleosides that

further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those nucleosides that include a pentofuranosyl sugar, the phosphate group can be linked to the 2', 3' or 5' hydroxyl moiety of the sugar. Oligonucleotides are formed through the covalent linkage of adjacent nucleosides to one another, to form a linear polymeric oligonucleotide. Within the oligonucleotide structure, the phosphate groups are commonly referred to as forming the internucleoside linkages of the oligonucleotide.

[00159] Modifications to antisense compounds encompass substitutions or changes to internucleoside linkages, sugar moieties, or nucleobases. Modified antisense compounds are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases, or increased inhibitory activity.

[00160] Chemically modified nucleosides may also be employed to increase the binding affinity of a shortened or truncated antisense oligonucleotide for its target nucleic acid. Consequently, comparable results can often be obtained with shorter antisense compounds that have such chemically modified nucleosides.

Modified Internucleoside Linkages

[00161] The naturally occurring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. Antisense compounds having one or more modified, i.e. non-naturally occurring, internucleoside linkages are often selected over antisense compounds having naturally occurring internucleoside linkages because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for target nucleic acids, and increased stability in the presence of nucleases.

[00162] Oligonucleotides having modified internucleoside linkages include internucleoside linkages that retain a phosphorus atom as well as internucleoside linkages that do not have a phosphorus atom. Representative phosphorus containing internucleoside linkages include, but are not limited to, phosphodiesters, phosphotriesters, methylphosphonates, phosphoramidate, and phosphorothioates. Methods of preparation of phosphorus-containing and non- phosphorus-containing linkages are well known.

[00163] In certain embodiments, antisense compounds targeted to a STMN2 nucleic acid comprise one or more modified internucleoside linkages. In certain embodiments, the modified

internucleoside linkages are interspersed throughout the antisense compound. In certain embodiments, the modified internucleoside linkages are phosphorothioate linkages. In certain embodiments, each internucleoside linkage of an antisense compound is a phosphorothioate internucleoside linkage. In certain embodiments, the antisense compounds targeted to a STMN2 nucleic acid comprise at least one phosphodiester linkage and at least one phosphorothioate linkage.

Modified Sugar Moieties

[00164] Antisense compounds can optionally contain one or more nucleosides wherein the sugar group has been modified. Such sugar modified nucleosides may impart enhanced nuclease stability, increased binding affinity, or some other beneficial biological property to the antisense compounds. In certain embodiments, nucleosides comprise chemically modified ribofuranose ring moieties. Examples of chemically modified ribofuranose rings include without limitation, addition of substitutent groups (including 5' and 2' substituent groups, bridging of non-geminal ring atoms to form bicyclic nucleic acids (BNA), replacement of the ribosyl ring oxygen atom with S, N(R), or $C(R_1)(R_2)$ (R, R_1 and R_2 are each independently H, C_1-C_{12} alkyl or a protecting group) and combinations thereof. Examples of chemically modified sugars include 2'-F-5'-methyl substituted nucleoside (*see* PCT International Application WO 2008/101157 Published on Aug. 21, 2008 for other disclosed 5',2'-bis substituted nucleosides) or replacement of the ribosyl ring oxygen atom with S or CF_2 with further substitution at the 2'-position (*see* published U.S. Patent Application US2005-0130923, published on Jun. 16, 2005) or alternatively 5'-substitution of a BNA (*see* PCT International Application WO 2007/134181 Published on Nov. 22, 2007 wherein LNA is substituted with for example a 5'-methyl or a 5'-vinyl group).

[00165] Examples of nucleosides having modified sugar moieties include without limitation nucleosides comprising 5'-vinyl, 5'-methyl (R or 5), 4'-S, 2'-F, 2'-OCH_3, 2'-OCH_2CH_3, 2'-O CH_2 CH_2F and 2'-$O(CH_2)_2OCH_3$ substituent groups. The substituent at the 2' position can also be selected from allyl, amino, azido, thio, O-allyl, O—C_1-C_{10} alkyl, OCF_3, OCH_2F, $O(CH_2)_2S$ CH_3, $O(CH_2)_2$—O—$N(R_m)(R_n)$, O—CH_2—C(=O)—$N(R_m)(R_n)$, and O—CH_2—C(=O)—$N(R_1)$—($CH_2)_2$—$N(R_m)(R_n)$- , where each R_l, R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl.

[00166] Additional examples of modified sugar moieties include a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-O-(2-methoxyethyl) (2'MOE), 2'-deoxy-2'-fluoro nucleoside,

2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt) (4'-CH(CH_3)-O-2'), *S*-constrained ethyl (*S*-cEt) 2'-4'-bridged nucleic acid, 4' -CH_2-O-CH_2-2', 4' -CH_2-N(R)-2', 4'-CH(CH2OCH3)-O-2' ("constrained MOE" or "cMOE"), hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

[00167] As used herein, "bicyclic nucleosides" refer to modified nucleosides comprising a bicyclic sugar moiety. Examples of bicyclic nucleosides include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In certain embodiments, antisense compounds provided herein include one or more bicyclic nucleosides comprising a 4' to 2' bridge. Examples of such 4' to 2' bridged bicyclic nucleosides, include but are not limited to one of the formulae: 4'-(CH_2)—O-2' (LNA); 4'-(CH_2)—S-2'; 4'-(CH_2)$_2$—O-2' (ENA); 4'-CH(CH_3)—O-2' and 4'-CH(CH_2OCH_3)—O-2' (and analogs thereof see U.S. Pat. No. 7,399,845, issued on Jul. 15, 2008); 4'-C(CH_3)(CH_3)—O-2' (and analogs thereof see published International Application WO/2009/006478, published Jan. 8, 2009); 4'-CH_2—N(OCH_3)-2' (and analogs thereof see published International Application WO/2008/150729, published Dec. 11, 2008); 4'-CH_2—O—N(CH_3)-2' (see published U.S. Patent Application US2004-0171570, published Sep. 2, 2004); 4'-CH_2—N(R)—O-2', wherein R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008); 4'-CH_2—C(H)(CH_3)-2' (see Chattopadhyaya et al., J. Org. Chem., 2009, 74, 118-134); and 4'-CH_2—C—(=CH_2)-2' (and analogs thereof see published International Application WO 2008/154401, published on Dec. 8, 2008).

[00168] Further reports related to bicyclic nucleosides can also be found in published literature (*see* for example: Singh et al., Chem. Commun., 1998, 4, 455-456; Koshkin et al., Tetrahedron, 1998, 54, 3607-3630; Wahlestedt et al., Proc. Natl. Acad. Sci. U.S.A., 2000, 97, 5633-5638; Kumar et al., Bioorg. Med. Chem. Lett., 1998, 8, 2219-2222; Singh et al., J. Org. Chem., 1998, 63, 10035-10039; Srivastava et al., J. Am. Chem. Soc., 2007, 129(26) 8362-8379; Elayadi et al., Curr. Opinion Invest. Drugs, 2001, 2, 558-561; Braasch et al., Chem. Biol., 2001, 8, 1-7; and Orum et al., Curr. Opinion Mol. Ther., 2001, 3, 239-243; U.S. Pat. Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 7,034,133; 7,053,207; 7,399,845; 7,547,684; and 7,696,345; U.S. Patent Publication No. US2008-0039618; US2009-0012281; U.S. Patent Ser. No. 60/989,574; 61/026,995; 61/026,998; 61/056,564; 61/086,231; 61/097,787; and 61/099,844; Published PCT International applications WO 1994/014226; WO 2004/106356; WO 2005/021570; WO 2007/134181; WO 2008/150729; WO 2008/154401; and WO 2009/006478. Each of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical

sugar configurations including for example α-L-ribofuranose and β-D-ribofuranose (see PCT international application PCT/DK98/00393, published on Mar. 25, 1999 as WO 99/14226).

[00169] In certain embodiments, bicyclic sugar moieties of BNA nucleosides include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the pentofuranosyl sugar moiety wherein such bridges independently comprises 1 or from 2 to 4 linked groups independently selected from —$[C(R_a)(R_b)]_n$—, —$C(R_a)=C(R_b)$—, —$C(R_a)=N$—, —C(=O)—, —$C(=NR_a)$—, —C(=S) —, —O—, —$Si(R_a)_2$—, —$S(=O)_x$—, and —$N(R_a)$—; wherein:

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

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

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

[00170] In certain embodiments, the bridge of a bicyclic sugar moiety is —$[C(R_a)(R_b)]_n$—, —[—$[C(R_a)(R_b)]_n$—O—, —$C(R_aR_b)$—N(R)—O— or —$C(R_aR_b)$—O—N(R)—. In certain embodiments, the bridge is 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2—O-2', 4'-$(CH_2)_2$—O-2', 4'-CH_2—O—N(R)-2' and 4'-CH_2—N(R)—O-2'- wherein each R is, independently, H, a protecting group or C_1-C_{12} alkyl, each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O)--H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl (S(=O)-J_1).

[00171] In certain embodiments, bicyclic nucleosides are further defined by isomeric configuration. For example, a nucleoside comprising a 4'-2' methylene-oxy bridge, may be in the

α-L configuration or in the β-D configuration. Previously, α-L-methyleneoxy (4'-CH_2—O-2') BNA's have been incorporated into antisense oligonucleotides that showed antisense activity (Frieden et al., Nucleic Acids Research, 2003, 21, 6365-6372).

[00172] In certain embodiments, bicyclic nucleosides include, but are not limited to, α-L-methyleneoxy (4'-CH_2—O-2') BNA, β-D-methyleneoxy (4'-CH_2—O-2') BNA, ethyleneoxy (4'-$(CH_2)_2$—O-2) BNA, aminooxy (4'-CH_2—O—N(R)-2') BNA, oxyamino (4'-CH_2—N(R)—O-2') BNA, methyl(methyleneoxy) (4'-$CH(CH_3)$—O-2') BNA, methylene-thio (4'-CH_2—S-2') BNA, methylene-amino (4'-CH_2—N(R)-2') BNA, methyl carbocyclic (4'-CH_2—$CH(CH_3)$-2') BNA, and propylene carbocyclic (4'-$(CH_2)_3$-2') BNA.

[00173] The present disclosure provide, in some embodiments, methods for treating, ameliorating, or preventing a neurological disease such as, but not limited to, ALS, FTD, or ALS with FTD, or treating, ameliorating, or preventing a neurological disease, condition, or a disorder characterized symptoms associated with a neurological disease such as, but not limited to, ALS, FTD, or ALS with FTD, include methods of administering a pharmaceutically acceptable composition, for example, a pharmaceutically acceptable formulation, that includes one or more inhibitors of STMN2 transcripts that include a cryptic exon, to a patient. Inhibitors of STMN2 transcripts that include a cryptic exon can increase, restore, or stabilize STMN2 activity, for example, STMN2 activity, and/or levels of STMN2 expression, for example, STMN2 mRNA and/or protein expression.

[00174] The present disclosure also provides pharmaceutical compositions comprising inhibitor of STMN2 transcripts that include a cryptic exon as disclosed herein formulated together with one or more pharmaceutically or cosmetically acceptable excipients. These formulations include those suitable for oral, sublingual, intratracheal, intranasal, transdermal, pulmonary, intrathecal, intracisternal, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, intraduodenal, or intravenous) or intralesional, administration, transmucosal (*e.g.*, buccal, vaginal, and rectal), or for topical use, *e.g.*, as part of a composition suitable for applying topically to skin and/or mucous membrane, for example, a composition in the form of a gel, a paste, a wax, a cream, a spray, a liquid, a foam, a lotion, an ointment, a topical solution, a transdermal patch, a powder, a vapor, or a tincture. Although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular inhibitor of STMN2 transcripts that include a cryptic exon being used.

[00175] The present disclosure also provides a pharmaceutical composition comprising an inhibitor of STMN2 transcripts that include a cryptic exon, or a pharmaceutically acceptable salt thereof (for example, a STMN2 AON that includes a nucleobase sequence of any of SEQ ID NOs: 1-446, SEQ ID NOs: 894-918, SEQ ID NOs: 945-1390, or SEQ ID NOs: 1392-1432).

[00176] The present disclosure also provides methods that include the use of pharmaceutical compositions comprising inhibitor of STMN2 transcripts that include a cryptic exon as disclosed herein (*e.g.*, a STMN2 AON of any one of SEQ ID NOs: 1-446, SEQ ID NOs: 894-918, SEQ ID NOs: 945-1390, or SEQ ID NOs: 1392-1432) formulated together with one or more pharmaceutically acceptable excipients. Exemplary compositions provided herein include compositions comprising an inhibitor of STMN2 transcripts that include a cryptic exon, as described above, and one or more pharmaceutically acceptable excipients. Formulations include those suitable for oral, sublingual, intratracheal, intranasal, transdermal, pulmonary, intrathecal, intracisternal, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, intraduodenal, or intravenous) or intralesional, administration, transmucosal (*e.g.*, buccal, vaginal, and rectal), or for topical use. The most suitable form of administration in any given case will depend on the clinical symptoms, complications, or biochemical indicia of the state, disorder, disease, or condition that one is trying to prevent in a subject; the state, disorder, disease, or condition one is trying to prevent in a subject; and/or on the nature of the particular compound and/or the composition being used.

Inhibitors of STMN2 transcripts that include a cryptic exon

[00177] In certain embodiments, STMN2 levels (*e.g.*, STMN2 mRNA or full length STMN2 protein levels) and/or activity (*e.g.*, biological activity, for example, STMN2 activity) can be increased, restored, or stabilized using compounds or compositions that target a STMN2 gene product that includes a cryptic exon (for example, a STMN2 pre-mRNA).

[00178] In some embodiments, an inhibitor of STMN2 transcripts that include a cryptic exon can be, but is not limited to, nucleotide-based inhibitors of STMN2 (for example, STMN2 shRNAs, STMN2 siRNAs, STMN2 PNAs, STMN2 LNAs, 2'-*O*-methyl (2'OMe) STMN2 antisense oligonucleotide (AON), 2'-O-(2-methoxyethyl) (2'MOE) STMN2 AON, or STMN2 morpholino oligomers (*e.g.*, phosphorodiamidate morpholino (PMO))), or compositions that include such compounds. In some embodiments an inhibitor of STMN2 is an antisense oligonucleotide (AON) comprising 2'OMe (*e.g.*, an STMN2 AON comprising one or more 2'OMe

modified sugar), MOE (*e.g.*, an STMN2 AON comprising one or more MOE modified sugar (*e.g.*, 2'-MOE)), PNA (*e.g.*, a STMN2 AON comprising one or more *N*-(2-aminoethyl)-glycine units linked by amide bonds or carbonyl methylene linkage as repeating units in place of a sugar-phosphate backbone), LNA (*e.g.*, a STMN2 AON comprising one or more locked ribose, and can be a mixture of 2'-deoxy nucleotides or 2'OMe nucleotides), c-ET (*e.g.*, a STMN2 AON comprising one or more cET sugar), cMOE (*e.g.*, a STMN2 AON comprising one or more cMOE sugar), morpholino oligomer (*e.g.*, a STMN2 AON comprising a backbone comprising one or more PMO), deoxy-2'-fluoro nucleoside (*e.g.*, a STMN2 AON comprising one or more 2'-fluoro-β-D-arabinonucleoside), ENA (*e.g.*, a STMN2 AON comprising one or more ENA modified sugar), HNA (*e.g.*, a STMN2 AON comprising one or more HNA modified sugar), or tcDNA (*e.g.*, a STMN2 AON comprising one or more tcDNA modified sugar). In some embodiments, a STMN2 AON comprises one or more phosphorothioate linkage, phosphodiester linkage, phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, phosphorodiamidate morpholino (PMO) linkage ("morpholino linkage"), peptide nucleic acid (PNA) linkage, or any combination of phosphorothioate linkage, phosphodiester linkage, a phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, phosphorodiamidate morpholino (PMO) (morpholino) linkage, and PNA linkage. In some embodiments, a STMN2 AON comprises one or more phosphorothioate linkage, phosphodiester linkage, or a combination of phosphorothioate and phosphodiester linkages.

STMN2 Antisense Therapeutics

[00179] Antisense therapeutics are a class of nucleic acid-based compounds that can be used to modulate a STMN2 mRNA or STMN2 transcript (for example, a STMN2 pre-mRNA comprising a cryptic exon). Antisense therapeutics may be single- or double-stranded deoxyribonucleic acid (DNA)-based, ribonucleic acid (RNA)-based, or DNA/RNA chemical analogue compounds. In general, antisense therapeutics are designed to include a nucleobase sequence that is complementary or nearly complementary to an mRNA or pre-mRNA sequence transcribed from a given gene in order to promote binding between the antisense therapeutic and the pre-mRNA or mRNA. In certain embodiments, antisense therapeutics act by binding to an mRNA or pre-mRNA, thereby inhibiting protein translation, altering pre-mRNA splicing into mature mRNA (*e.g.,* by preventing appropriate proteins such as splicing activator proteins from binding), and/or causing destruction of mRNA. In certain embodiments, the antisense therapeutic nucleobase sequence is complementary to a portion of a targeted gene's or mRNA's sense sequence. In

certain embodiments, STMN2 antisense therapeutics described herein are oligonucleotide-based compounds that include an oligonucleotide sequence complementary to a pre-mRNA sense, or a portion thereof. In certain embodiments, STMN2 antisense therapeutics described herein can also be nucleotide chemical analog-based compounds. Synthetic oligonucleotides as therapeutic agents has evolved into broad applications involving multiple modalities. These applications include ribozymes, small interfering RNA (siRNA), microRNA, aptamers, non-coding RNA, splicing modulation, targeting toxic repeats, gene editing, and immune modulations. The STMN2 oligonucleotides (STMN2 AONs) of the present disclosure prevent aberrant or mis-splicing by targeting a STMN2 transcript (*e.g.*, STMN2 pre-mRNA (*e.g.*, SEQ ID NO: 944)).

[00180] Antisense oligonucleotides (AONs) are short oligonucleotide-based sequences that include an oligonucleotide sequence complementary to a target RNA sequence. In certain embodiments, AONs are between 8 to 50 nucleotides in length, for example, 8, 10, 15, 20, 25, 30, 35, 40, 45, or 45 nucleotides in length. In certain embodiments, the AONs are 25 nucleotides in length. In certain embodiments, AONs may include chemically modified nucleosides (for example, 2'-*O*-methylated nucleosides or 2'-*O*-(2-methoxyethyl) nucleosides (2′-*O*-methoxyethylribonucleosides (2′-MOE))) as well as modified internucleoside linkages (for example, phosphorothioate linkages). In certain embodiments, STMN2 AONs described herein include oligonucleotide sequences that are complementary to STMN2 RNA sequences. In certain embodiments, STMN2 AONs described herein can include chemically modified nucleosides and modified internucleoside linkages (for example, phosphorothioate linkages).

[00181] Peptide nucleic acids (PNAs) are short, artificially synthesized polymers with a structure that mimics DNA or RNA. PNAs include a backbone composed of repeating N-(2-aminoethyl)-glycine units linked by peptide bonds. In certain embodiments, STMN2 PNAs described herein can be used as antisense therapeutics that bind to STMN2 RNA sequences with high specificity and increase, restore, and/or stabilize STMN2 levels (*e.g.*, STMN2 mRNA or protein levels) and/or activity (*e.g.*, biological activity, for example, STMN2 activity).

[00182] Locked nucleic acids (LNAs) are oligonucleotide sequences that include one or more modified RNA nucleotides in which the ribose moiety is modified with an extra bridge connecting the 2' oxygen and 4' carbon. LNAs are believed to have higher Tm's than analogous oligonucleotide sequences. In certain embodiments, STMN2 LNAs described herein can be used as antisense therapeutics that bind to STMN2 RNA sequences with high specificity and repress premature polyadenylation of STMN2 pre-mRNA, and increase, restore, and/or stabilize STMN2

levels (*e.g.*, STMN2 mRNA or protein levels) and/or activity (*e.g.*, biological activity, for example, STMN2 activity).

[00183] Morpholino oligomers are oligonucleotide compounds that include DNA bases attached to a backbone of methylenemorpholine rings linked through phosphorodiamidate groups. In certain embodiments, morpholino oligomers of the present invention can be designed to bind to specific STMN2 pre-mRNA sequence of interest, thereby repressing premature polyadenylation of the pre-mRNA, and increase, restore, and/or stabilize STMN2 levels (*e.g.*, STMN2 mRNA or protein levels) and/or activity (*e.g.*, biological activity, for example, STMN2 activity). In certain embodiments, STMN2 morpholino oligomers described herein can be used as antisense therapeutics that bind to STMN2 pre-mRNA sequences with high specificity and repress premature polyadenylation of STMN2 pre-mRNA, and increase, restore, and/or stabilize STMN2 levels (*e.g.*, STMN2 mRNA or protein levels) and/or activity (*e.g.*, biological activity, for example, STMN2 activity). In certain embodiments, STMN2 morpholino oligomers described herein can also be used to bind STMN2 pre-mRNA sequences, altering STMN2 pre-mRNA splicing and STMN2 gene expression, and increase, restore, and/or stabilize STMN2 levels (*e.g.*, STMN2 mRNA or protein levels) and/or activity (*e.g.*, biological activity, for example, STMN2 activity).

[00184] In some embodiments, STMN2 antisense therapeutics include a STMN2 AON comprising 2'OMe (*e.g.*, an STMN2 AON comprising one or more 2'OMe modified sugar), MOE (*e.g.*, an STMN2 AON comprising one or more MOE modified sugar (*e.g.*, 2'-MOE)), PNA (*e.g.*, a STMN2 AON comprising one or more *N*-(2-aminoethyl)-glycine units linked by amide bonds or carbonyl methylene linkage as repeating units in place of a sugar-phosphate backbone), LNA (*e.g.*, a STMN2 AON comprising one or more locked ribose, and can be a mixture of 2'-deoxy nucleotides or 2'OMe nucleotides), c-ET (*e.g.*, a STMN2 AON comprising one or more cET sugar), cMOE (*e.g.*, a STMN2 AON comprising one or more cMOE sugar), morpholino oligomer (*e.g.*, a STMN2 AON comprising a backbone comprising one or more PMO), deoxy-2'-fluoro nucleoside (*e.g.*, a STMN2 AON comprising one or more 2'-fluoro-β-D-arabinonucleoside), ENA (*e.g.*, a STMN2 AON comprising one or more ENA modified sugar), HNA (*e.g.*, a STMN2 AON comprising one or more HNA modified sugar), or tcDNA (*e.g.*, a STMN2 AON comprising one or more tcDNA modified sugar). In some embodiments, a STMN2 AON comprises one or more phosphorothioate linkage, phosphodiester linkage, phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, morpholino linkage, PNA linkage, or any combination of

phosphorothioate linkage, phosphodiester linkage, a phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, morpholino linkage, and PNA linkage. In some embodiments, a STMN2 AON comprises one or more phosphorothioate linkage, phosphodiester linkage, or a combination of phosphorothioate and phosphodiester linkages.

STMN2 Antisense Oligonucleotides

[00185] In certain embodiments, a STMN2 antisense oligonucleotide, such as disclosed herein, may be an oligonucleotide sequence of 5 to 100 nucleotides in length, for example, 10 to 40 nucleotides in length, for example, 14 to 40 nucleotides in length, 10 to 30 nucleotides in length, for example, 14 to 30 nucleotides in length, for example, 14 to 25 or 15 to 22 nucleotides in length, or 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides in length. In certain embodiments, the AONs are 25 nucleotides in length. In certain embodiments, STMN2 antisense oligonucleotides (AONs) described herein are short synthetic oligonucleotide sequence complementary to a STMN2 transcript (*e.g.*, pre-mRNA), a portion of a STMN2 transcript, or a STMN2 gene sequence.

[00186] In some embodiments, a STMN2 AON includes a nucleobase sequence that is 80%, 85%, 90%, 95%, or 100% complementary to the STMN2 transcript (*e.g.*, STMN2 pre-mRNA) that includes a cryptic exon. In some embodiments, the nucleobase sequence of the STMN2 antisense oligonucleotide is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleobases that are 80%, 85%, 90%, 95%, or 100% complementary to an equal length portion of nucleobases in a portion of the STMN2 transcript that includes a cryptic exon. AON binding specificity can be assessed via measurement of parameters such as dissociation constant, melting temperature (Tm), or other criteria such as changes in protein or RNA expression levels or other assays that measure STMN2 activity or expression.

[00187] In some embodiments, a STMN2 AON can include a non-duplexed oligonucleotide. In some embodiments, a STMN2 AON can include a duplex of two oligonucleotides where the first oligonucleotide includes a nucleobase sequence that is completely or almost completely complementary to a STMN2 pre-mRNA sequence and the second oligonucleotide includes a nucleobase sequence that is complementary to the nucleobase sequence of the first oligonucleotide.

[00188] In some embodiments, a STMN2 AON can target STMN2 pre-mRNAs that include a cryptic exon produced from STMN2 genes of one or more species. For example, a STMN2 AON can target a STMN2 pre-mRNA, which includes a cryptic exon, of a mammalian STMN2 gene, for example, a human (*i.e.*, *Homo sapiens*) STMN2 gene. In particular embodiments, the STMN2 AON targets a human STMN2 pre-mRNA, which includes a cryptic exon. In some embodiments, the STMN2 AON includes a nucleobase sequence that is complementary to a nucleobase sequence of a STMN2 gene or a STMN2 pre-mRNA, which includes a cryptic exon, or a portion thereof.

[00189] STMN2 AONs described herein include antisense oligonucleotides comprising the oligonucleotide sequences listed in Table 1 below:

Table 1. STMN2 AON Sequences

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

16	TACCAGAGCTTACCAGGAGGGATAC		GTATCCCTCCTGGTAAGCTCTGGTA SEQ ID NO: 463
17	ATACCAGAGCTTACCAGGAGGGATA		TATCCCTCCTGGTAAGCTCTGGTAT SEQ ID NO: 464
18	AATACCAGAGCTTACCAGGAGGGAT		ATCCCTCCTGGTAAGCTCTGGTATT SEQ ID NO: 465
19	TAATACCAGAGCTTACCAGGAGGGA		TCCCTCCTGGTAAGCTCTGGTATTA SEQ ID NO: 466
20	ATAATACCAGAGCTTACCAGGAGGG		CCCTCCTGGTAAGCTCTGGTATTAT SEQ ID NO: 467
21	CATAATACCAGAGCTTACCAGGAGG		CCTCCTGGTAAGCTCTGGTATTATG SEQ ID NO: 468
22	ACATAATACCAGAGCTTACCAGGAG		CTCCTGGTAAGCTCTGGTATTATGT SEQ ID NO: 469
23	GACATAATACCAGAGCTTACCAGGA		TCCTGGTAAGCTCTGGTATTATGTC SEQ ID NO: 470
24	AGACATAATACCAGAGCTTACCAGG		CCTGGTAAGCTCTGGTATTATGTCT SEQ ID NO: 471
25	AAGACATAATACCAGAGCTTACCAG		CTGGTAAGCTCTGGTATTATGTCTT SEQ ID NO: 472
26	TAAGACATAATACCAGAGCTTACCA		TGGTAAGCTCTGGTATTATGTCTTA SEQ ID NO: 473
27	TTAAGACATAATACCAGAGCTTACC		GGTAAGCTCTGGTATTATGTCTTAA SEQ ID NO: 474
28	GTTAAGACATAATACCAGAGCTTAC		GTAAGCTCTGGTATTATGTCTTAAC SEQ ID NO: 475
29	TGTTAAGACATAATACCAGAGCTTA		TAAGCTCTGGTATTATGTCTTAACA SEQ ID NO: 476
30	ATGTTAAGACATAATACCAGAGCTT	branch point 1	AAGCTCTGGTATTATGTCTTAACAT SEQ ID NO: 477
31	AATGTTAAGACATAATACCAGAGCT	branch point 1	AGCTCTGGTATTATGTCTTAACATT SEQ ID NO: 478
32	AAATGTTAAGACATAATACCAGAGC	branch point 1	GCTCTGGTATTATGTCTTAACATTT SEQ ID NO: 479
33	AAAATGTTAAGACATAATACCAGAG	branch point 1	CTCTGGTATTATGTCTTAACATTTT SEQ ID NO: 480
34	AAAAATGTTAAGACATAATACCAGA	branch point 1	TCTGGTATTATGTCTTAACATTTTT SEQ ID NO: 481
35	TAAAAATGTTAAGACATAATACCAG	branch point 1	CTGGTATTATGTCTTAACATTTTTA SEQ ID NO: 482
36	TTAAAAATGTTAAGACATAATACCA	branch point 1	TGGTATTATGTCTTAACATTTTTAA SEQ ID NO: 483
37	TTTAAAAATGTTAAGACATAATACC	branch point 1	GGTATTATGTCTTAACATTTTTAAA SEQ ID NO: 484
38	ATTTAAAAATGTTAAGACATAATAC	branch point 1	GTATTATGTCTTAACATTTTTAAAT SEQ ID NO: 485
39	GATTTAAAAATGTTAAGACATAATA	branch point 1	TATTATGTCTTAACATTTTTAAATC SEQ ID NO: 486
40	AGATTTAAAAATGTTAAGACATAAT	branch point 1	ATTATGTCTTAACATTTTTAAATCT SEQ ID NO: 487

41	TAGATTTAAAAATGTTAAGACATAA	branch point 1	TTATGTCTTAACATTTTTAAATCTA SEQ ID NO: 488
42	ATAGATTTAAAAATGTTAAGACATA	branch point 1	TATGTCTTAACATTTTTAAATCTAT SEQ ID NO: 489
43	CATAGATTTAAAAATGTTAAGACAT	branch point 1	ATGTCTTAACATTTTTAAATCTATG SEQ ID NO: 490
44	CCATAGATTTAAAAATGTTAAGACA	branch point 1	TGTCTTAACATTTTTAAATCTATGG SEQ ID NO: 491
45	ACCATAGATTTAAAAATGTTAAGAC	branch point 1	GTCTTAACATTTTTAAATCTATGGT SEQ ID NO: 492
46	TACCATAGATTTAAAAATGTTAAGA	branch point 1	TCTTAACATTTTTAAATCTATGGTA SEQ ID NO: 493
47	TTACCATAGATTTAAAAATGTTAAG		CTTAACATTTTTAAATCTATGGTAA SEQ ID NO: 494
48	ATTACCATAGATTTAAAAATGTTAA		TTAACATTTTTAAATCTATGGTAAT SEQ ID NO: 495
49	GATTACCATAGATTTAAAAATGTTA		TAACATTTTTAAATCTATGGTAATC SEQ ID NO: 496
50	AGATTACCATAGATTTAAAAATGTT	Branch point 2	AACATTTTTAAATCTATGGTAATCT SEQ ID NO: 497
51	AAGATTACCATAGATTTAAAAATGT	Branch point 2	ACATTTTTAAATCTATGGTAATCTT SEQ ID NO: 498
52	AAAGATTACCATAGATTTAAAAATG	Branch point 2	CATTTTTAAATCTATGGTAATCTTT SEQ ID NO: 499
53	TAAAGATTACCATAGATTTAAAAAT	Branch point 2	ATTTTTAAATCTATGGTAATCTTTA SEQ ID NO: 500
54	GTAAAGATTACCATAGATTTAAAAA	Branch point 2	TTTTTAAATCTATGGTAATCTTTAC SEQ ID NO: 501
55	TGTAAAGATTACCATAGATTTAAAA	Branch point 2	TTTTAAATCTATGGTAATCTTTACA SEQ ID NO: 502
56	TTGTAAAGATTACCATAGATTTAAA	Branch point 2	TTTAAATCTATGGTAATCTTTACAA SEQ ID NO: 503
57	TTTGTAAAGATTACCATAGATTTAA	Branch point 2	TTAAATCTATGGTAATCTTTACAAA SEQ ID NO: 504
58	TTTTGTAAAGATTACCATAGATTTA	Branch point 2	TAAATCTATGGTAATCTTTACAAAA SEQ ID NO: 505
59	ATTTTGTAAAGATTACCATAGATTT	Branch point 2	AAATCTATGGTAATCTTTACAAAAT SEQ ID NO: 506
60	TATTTTGTAAAGATTACCATAGATT	Branch point 2	AATCTATGGTAATCTTTACAAAATA SEQ ID NO: 507
61	ATATTTTGTAAAGATTACCATAGAT	Branch point 2	ATCTATGGTAATCTTTACAAAATAT SEQ ID NO: 508
62	AATATTTTGTAAAGATTACCATAGA	Branch point 2	TCTATGGTAATCTTTACAAAATATT SEQ ID NO: 509
63	AAATATTTTGTAAAGATTACCATAG	Branch point 2	CTATGGTAATCTTTACAAAATATTT SEQ ID NO: 510
64	AAAATATTTTGTAAAGATTACCATA	Branch point 2	TATGGTAATCTTTACAAAATATTTT SEQ ID NO: 511
65	TAAAATATTTTGTAAAGATTACCAT	Branch point 2	ATGGTAATCTTTACAAAATATTTTA SEQ ID NO: 512

66	GTAAAATATTTTGTAAAGATTACCA	Branch point 2	TGGTAATCTTTACAAAATATTTTAC SEQ ID NO: 513
67	AGTAAAATATTTTGTAAAGATTACC		GGTAATCTTTACAAAATATTTTACT SEQ ID NO: 514
68	AAGTAAAATATTTTGTAAAGATTAC		GTAATCTTTACAAAATATTTTACTT SEQ ID NO: 515
69	GAAGTAAAATATTTTGTAAAGATTA		TAATCTTTACAAAATATTTTACTTC SEQ ID NO: 516
70	GGAAGTAAAATATTTTGTAAAGATT		AATCTTTACAAAATATTTTACTTCC SEQ ID NO: 517
71	CGGAAGTAAAATATTTTGTAAAGAT		ATCTTTACAAAATATTTTACTTCCG SEQ ID NO: 518
72	TCGGAAGTAAAATATTTTGTAAAGA		TCTTTACAAAATATTTTACTTCCGA SEQ ID NO: 519
73	TTCGGAAGTAAAATATTTTGTAAAG		CTTTACAAAATATTTTACTTCCGAA SEQ ID NO: 520
74	GTTCGGAAGTAAAATATTTTGTAAA		TTTACAAAATATTTTACTTCCGAAC SEQ ID NO: 521
75	AGTTCGGAAGTAAAATATTTTGTAA		TTACAAAATATTTTACTTCCGAACT SEQ ID NO: 522
76	GAGTTCGGAAGTAAAATATTTTGTA		TACAAAATATTTTACTTCCGAACTC SEQ ID NO: 523
77	TGAGTTCGGAAGTAAAATATTTTGT		ACAAAATATTTTACTTCCGAACTCA SEQ ID NO: 524
78	ATGAGTTCGGAAGTAAAATATTTTG		CAAAATATTTTACTTCCGAACTCAT SEQ ID NO: 525
79	TATGAGTTCGGAAGTAAAATATTTT		AAAATATTTTACTTCCGAACTCATA SEQ ID NO: 526
80	ATATGAGTTCGGAAGTAAAATATTT		AAATATTTTACTTCCGAACTCATAT SEQ ID NO: 527
81	TATATGAGTTCGGAAGTAAAATATT		AATATTTTACTTCCGAACTCATATA SEQ ID NO: 528
82	GTATATGAGTTCGGAAGTAAAATAT		ATATTTTACTTCCGAACTCATATAC SEQ ID NO: 529
83	GGTATATGAGTTCGGAAGTAAAATA		TATTTTACTTCCGAACTCATATACC SEQ ID NO: 530
84	AGGTATATGAGTTCGGAAGTAAAAT		ATTTTACTTCCGAACTCATATACCT SEQ ID NO: 531
85	CAGGTATATGAGTTCGGAAGTAAAA		TTTTACTTCCGAACTCATATACCTG SEQ ID NO: 532
86	CCAGGTATATGAGTTCGGAAGTAAA		TTTACTTCCGAACTCATATACCTGG SEQ ID NO: 533
87	CCCAGGTATATGAGTTCGGAAGTAA		TTACTTCCGAACTCATATACCTGGG SEQ ID NO: 534
88	CCCCAGGTATATGAGTTCGGAAGTA		TACTTCCGAACTCATATACCTGGGG SEQ ID NO: 535
89	TCCCCAGGTATATGAGTTCGGAAGT		ACTTCCGAACTCATATACCTGGGGA SEQ ID NO: 536
90	ATCCCCAGGTATATGAGTTCGGAAG		CTTCCGAACTCATATACCTGGGGAT SEQ ID NO: 537
91	AATCCCCAGGTATATGAGTTCGGAA		TTCCGAACTCATATACCTGGGGATT

			SEQ ID NO: 538
92	AAATCCCCAGGTATATGAGTTCGGA		TCCGAACTCATATACCTGGGGATTT SEQ ID NO: 539
93	AAAATCCCCAGGTATATGAGTTCGG		CCGAACTCATATACCTGGGGATTTT SEQ ID NO: 540
94	TAAAATCCCCAGGTATATGAGTTCG		CGAACTCATATACCTGGGGATTTTA SEQ ID NO: 541
95	ATAAAATCCCCAGGTATATGAGTTC		GAACTCATATACCTGGGGATTTTAT SEQ ID NO: 542
96	AATAAAATCCCCAGGTATATGAGTT		AACTCATATACCTGGGGATTTTATT SEQ ID NO: 543
97	TAATAAAATCCCCAGGTATATGAGT		ACTCATATACCTGGGGATTTTATTA SEQ ID NO: 544
98	GTAATAAAATCCCCAGGTATATGAG		CTCATATACCTGGGGATTTTATTAC SEQ ID NO: 545
99	AGTAATAAAATCCCCAGGTATATGA		TCATATACCTGGGGATTTTATTACT SEQ ID NO: 546
100	GAGTAATAAAATCCCCAGGTATATG		CATATACCTGGGGATTTTATTACTC SEQ ID NO: 547
101	AGAGTAATAAAATCCCCAGGTATAT		ATATACCTGGGGATTTTATTACTCT SEQ ID NO: 548
102	CAGAGTAATAAAATCCCCAGGTATA		TATACCTGGGGATTTTATTACTCTG SEQ ID NO: 549
103	CCAGAGTAATAAAATCCCCAGGTAT		ATACCTGGGGATTTTATTACTCTGG SEQ ID NO: 550
104	CCCAGAGTAATAAAATCCCCAGGTA		TACCTGGGGATTTTATTACTCTGGG SEQ ID NO: 551
105	TCCCAGAGTAATAAAATCCCCAGGT		ACCTGGGGATTTTATTACTCTGGGA SEQ ID NO: 552
106	TTCCCAGAGTAATAAAATCCCCAGG		CCTGGGGATTTTATTACTCTGGGAA SEQ ID NO: 553
107	ATTCCCAGAGTAATAAAATCCCCAG		CTGGGGATTTTATTACTCTGGGAAT SEQ ID NO: 554
108	AATTCCCAGAGTAATAAAATCCCCA		TGGGGATTTTATTACTCTGGGAATT SEQ ID NO: 555
109	TAATTCCCAGAGTAATAAAATCCCC		GGGGATTTTATTACTCTGGGAATTA SEQ ID NO: 556
110	ATAATTCCCAGAGTAATAAAATCCC		GGGATTTTATTACTCTGGGAATTAT SEQ ID NO: 557
111	CATAATTCCCAGAGTAATAAAATCC		GGATTTTATTACTCTGGGAATTATG SEQ ID NO: 558
112	ACATAATTCCCAGAGTAATAAAATC		GATTTTATTACTCTGGGAATTATGT SEQ ID NO: 559
113	CACATAATTCCCAGAGTAATAAAAT		ATTTTATTACTCTGGGAATTATGTG SEQ ID NO: 560
114	ACACATAATTCCCAGAGTAATAAAA		TTTTATTACTCTGGGAATTATGTGT SEQ ID NO: 561
115	AACACATAATTCCCAGAGTAATAAA		TTTATTACTCTGGGAATTATGTGTT SEQ ID NO: 562
116	GAACACATAATTCCCAGAGTAATAA		TTATTACTCTGGGAATTATGTGTTC SEQ ID NO: 563

117	AGAACACATAATTCCCAGAGTAATA		TATTACTCTGGGAATTATGTGTTCT SEQ ID NO: 564
118	CAGAACACATAATTCCCAGAGTAAT		ATTACTCTGGGAATTATGTGTTCTG SEQ ID NO: 565
119	GCAGAACACATAATTCCCAGAGTAA		TTACTCTGGGAATTATGTGTTCTGC SEQ ID NO: 566
120	GGCAGAACACATAATTCCCAGAGTA		TACTCTGGGAATTATGTGTTCTGCC SEQ ID NO: 567
121	GGGCAGAACACATAATTCCCAGAGT		ACTCTGGGAATTATGTGTTCTGCCC SEQ ID NO: 568
122	GGGGCAGAACACATAATTCCCAGAG		CTCTGGGAATTATGTGTTCTGCCCC SEQ ID NO: 569
123	TGGGGCAGAACACATAATTCCCAGA		TCTGGGAATTATGTGTTCTGCCCCA SEQ ID NO: 570
124	ATGGGGCAGAACACATAATTCCCAG		CTGGGAATTATGTGTTCTGCCCCAT SEQ ID NO: 571
125	GATGGGGCAGAACACATAATTCCCA		TGGGAATTATGTGTTCTGCCCCATC SEQ ID NO: 572
126	TGATGGGGCAGAACACATAATTCCC		GGGAATTATGTGTTCTGCCCCATCA SEQ ID NO: 573
127	GTGATGGGGCAGAACACATAATTCC		GGAATTATGTGTTCTGCCCCATCAC SEQ ID NO: 574
128	AGTGATGGGGCAGAACACATAATTC		GAATTATGTGTTCTGCCCCATCACT SEQ ID NO: 575
129	GAGTGATGGGGCAGAACACATAATT	Branch point 3	AATTATGTGTTCTGCCCCATCACTC SEQ ID NO: 576
130	AGAGTGATGGGGCAGAACACATAAT	Branch point 3	ATTATGTGTTCTGCCCCATCACTCT SEQ ID NO: 577
131	GAGAGTGATGGGGCAGAACACATAA	Branch point 3	TTATGTGTTCTGCCCCATCACTCTC SEQ ID NO: 578
132	AGAGAGTGATGGGGCAGAACACATA	Branch point 3	TATGTGTTCTGCCCCATCACTCTCT SEQ ID NO: 579
133	GAGAGAGTGATGGGGCAGAACACAT	Branch point 3	ATGTGTTCTGCCCCATCACTCTCTC SEQ ID NO: 580
134	AGAGAGAGTGATGGGGCAGAACACA	Branch point 3	TGTGTTCTGCCCCATCACTCTCTCT SEQ ID NO: 581
135	AAGAGAGAGTGATGGGGCAGAACAC	Branch point 3	GTGTTCTGCCCCATCACTCTCTCTT SEQ ID NO: 582
136	TAAGAGAGAGTGATGGGGCAGAACA	Branch point 3	TGTTCTGCCCCATCACTCTCTCTTA SEQ ID NO: 583
137	TTAAGAGAGAGTGATGGGGCAGAAC	Branch point 3	GTTCTGCCCCATCACTCTCTCTTAA SEQ ID NO: 584
138	ATTAAGAGAGAGTGATGGGGCAGAA	Branch point 3	TTCTGCCCCATCACTCTCTCTTAAT SEQ ID NO: 585
139	AATTAAGAGAGAGTGATGGGGCAGA	Branch point 3	TCTGCCCCATCACTCTCTCTTAATT SEQ ID NO: 586
140	CAATTAAGAGAGAGTGATGGGGCAG	Branch point 3	CTGCCCCATCACTCTCTCTTAATTG SEQ ID NO: 587
141	CCAATTAAGAGAGAGTGATGGGGCA	Branch point 3	TGCCCCATCACTCTCTCTTAATTGG SEQ ID NO: 588

142	TCCAATTAAGAGAGAGTGATGGGGC	Branch point 3	GCCCCATCACTCTCTCTTAATTGGA SEQ ID NO: 589
143	ATCCAATTAAGAGAGAGTGATGGGG	Branch point 3	CCCCATCACTCTCTCTTAATTGGAT SEQ ID NO: 590
144	AATCCAATTAAGAGAGAGTGATGGG	Branch point 3	CCCATCACTCTCTCTTAATTGGATT SEQ ID NO: 591
145	AAATCCAATTAAGAGAGAGTGATGG	Branch point 3	CCATCACTCTCTCTTAATTGGATTT SEQ ID NO: 592
146	AAAATCCAATTAAGAGAGAGTGATG		CATCACTCTCTCTTAATTGGATTTT SEQ ID NO: 593
147	AAAAATCCAATTAAGAGAGAGTGAT		ATCACTCTCTCTTAATTGGATTTTT SEQ ID NO: 594
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162	TATGAATATAATTTTAAAAATCCAA		TTGGATTTTTAAAATTATATTCATA SEQ ID NO: 609
163	ATATGAATATAATTTTAAAAATCCA		TGGATTTTTAAAATTATATTCATAT SEQ ID NO: 610
164	AATATGAATATAATTTTAAAAATCC		GGATTTTTAAAATTATATTCATATT SEQ ID NO: 611
165	CAATATGAATATAATTTTAAAAATC		GATTTTTAAAATTATATTCATATTG SEQ ID NO: 612
166	GCAATATGAATATAATTTTAAAAAT		ATTTTTAAAATTATATTCATATTGC SEQ ID NO: 613
167	TGCAATATGAATATAATTTTAAAAA		TTTTTAAAATTATATTCATATTGCA

			SEQ ID NO: 614
168	CTGCAATATGAATATAATTTTAAAA		TTTTAAAATTATATTCATATTGCAG SEQ ID NO: 615
169	CCTGCAATATGAATATAATTTTAAA		TTTAAAATTATATTCATATTGCAGG SEQ ID NO: 616
170	TCCTGCAATATGAATATAATTTTAA		TTAAAATTATATTCATATTGCAGGA SEQ ID NO: 617
171	GTCCTGCAATATGAATATAATTTTA	Acceptor site	TAAAATTATATTCATATTGCAGGAC SEQ ID NO: 618
172	AGTCCTGCAATATGAATATAATTTT	Acceptor site	AAAATTATATTCATATTGCAGGACT SEQ ID NO: 619
173	GAGTCCTGCAATATGAATATAATTT	Acceptor site	AAATTATATTCATATTGCAGGACTC SEQ ID NO: 620
174	CGAGTCCTGCAATATGAATATAATT	Acceptor site	AATTATATTCATATTGCAGGACTCG SEQ ID NO: 621
175	CCGAGTCCTGCAATATGAATATAAT	Acceptor site	ATTATATTCATATTGCAGGACTCGG SEQ ID NO: 622
176	GCCGAGTCCTGCAATATGAATATAA	Acceptor site	TTATATTCATATTGCAGGACTCGGC SEQ ID NO: 623
177	TGCCGAGTCCTGCAATATGAATATA	Acceptor site	TATATTCATATTGCAGGACTCGGCA SEQ ID NO: 624
178	CTGCCGAGTCCTGCAATATGAATAT	Acceptor site	ATATTCATATTGCAGGACTCGGCAG SEQ ID NO: 625
179	TCTGCCGAGTCCTGCAATATGAATA	Acceptor site	TATTCATATTGCAGGACTCGGCAGA SEQ ID NO: 626
180	TTCTGCCGAGTCCTGCAATATGAAT	Acceptor site	ATTCATATTGCAGGACTCGGCAGAA SEQ ID NO: 627
181	CTTCTGCCGAGTCCTGCAATATGAA	Acceptor site	TTCATATTGCAGGACTCGGCAGAAG SEQ ID NO: 628
182	TCTTCTGCCGAGTCCTGCAATATGA	Acceptor site	TCATATTGCAGGACTCGGCAGAAGA SEQ ID NO: 629
183	GTCTTCTGCCGAGTCCTGCAATATG	Acceptor site	CATATTGCAGGACTCGGCAGAAGAC SEQ ID NO: 630
184	GGTCTTCTGCCGAGTCCTGCAATAT	Acceptor site	ATATTGCAGGACTCGGCAGAAGACC SEQ ID NO: 631
185	AGGTCTTCTGCCGAGTCCTGCAATA	Acceptor site	TATTGCAGGACTCGGCAGAAGACCT SEQ ID NO: 632
186	AAGGTCTTCTGCCGAGTCCTGCAAT	Acceptor site	ATTGCAGGACTCGGCAGAAGACCTT SEQ ID NO: 633
187	GAAGGTCTTCTGCCGAGTCCTGCAA	Acceptor site	TTGCAGGACTCGGCAGAAGACCTTC SEQ ID NO: 634
188	CGAAGGTCTTCTGCCGAGTCCTGCA	Acceptor site	TGCAGGACTCGGCAGAAGACCTTCG SEQ ID NO: 635
189	TCGAAGGTCTTCTGCCGAGTCCTGC	Acceptor site	GCAGGACTCGGCAGAAGACCTTCGA SEQ ID NO: 636
190	CTCGAAGGTCTTCTGCCGAGTCCTG	Acceptor site	CAGGACTCGGCAGAAGACCTTCGAG SEQ ID NO: 637
191	TCTCGAAGGTCTTCTGCCGAGTCCT	ESE Binding	AGGACTCGGCAGAAGACCTTCGAGA SEQ ID NO: 638
192	CTCTCGAAGGTCTTCTGCCGAGTCC	ESE Binding	GGACTCGGCAGAAGACCTTCGAGAG SEQ ID NO: 639

193	TCTCTCGAAGGTCTTCTGCCGAGTC	ESE Binding	GACTCGGCAGAAGACCTTCGAGAGA SEQ ID NO: 640
194	TTCTCTCGAAGGTCTTCTGCCGAGT	ESE Binding	ACTCGGCAGAAGACCTTCGAGAGAA SEQ ID NO: 641
195	TTTCTCTCGAAGGTCTTCTGCCGAG	ESE Binding	CTCGGCAGAAGACCTTCGAGAGAAA SEQ ID NO: 642
196	CTTTCTCTCGAAGGTCTTCTGCCGA	ESE Binding	TCGGCAGAAGACCTTCGAGAGAAAG SEQ ID NO: 643
197	CCTTTCTCTCGAAGGTCTTCTGCCG	ESE Binding	CGGCAGAAGACCTTCGAGAGAAAGG SEQ ID NO: 644
198	ACCTTTCTCTCGAAGGTCTTCTGCC	ESE Binding	GGCAGAAGACCTTCGAGAGAAAGGT SEQ ID NO: 645
199	TACCTTTCTCTCGAAGGTCTTCTGC	ESE Binding	GCAGAAGACCTTCGAGAGAAAGGTA SEQ ID NO: 646
200	CTACCTTTCTCTCGAAGGTCTTCTG	ESE Binding	CAGAAGACCTTCGAGAGAAAGGTAG SEQ ID NO: 647
201	TCTACCTTTCTCTCGAAGGTCTTCT	ESE Binding	AGAAGACCTTCGAGAGAAAGGTAGA SEQ ID NO: 648
202	TTCTACCTTTCTCTCGAAGGTCTTC	ESE Binding	GAAGACCTTCGAGAGAAAGGTAGAA SEQ ID NO: 649
203	TTTCTACCTTTCTCTCGAAGGTCTT	ESE Binding	AAGACCTTCGAGAGAAAGGTAGAAA SEQ ID NO: 650
204	TTTTCTACCTTTCTCTCGAAGGTCT	ESE Binding	AGACCTTCGAGAGAAAGGTAGAAAA SEQ ID NO: 651
205	ATTTTCTACCTTTCTCTCGAAGGTC	ESE Binding	GACCTTCGAGAGAAAGGTAGAAAAT SEQ ID NO: 652
206	TATTTTCTACCTTTCTCTCGAAGGT	ESE Binding	ACCTTCGAGAGAAAGGTAGAAAATA SEQ ID NO: 653
207	TTATTTTCTACCTTTCTCTCGAAGG	ESE Binding	CCTTCGAGAGAAAGGTAGAAAATAA SEQ ID NO: 654
208	CTTATTTTCTACCTTTCTCTCGAAG	ESE Binding	CTTCGAGAGAAAGGTAGAAAATAAG SEQ ID NO: 655
209	TCTTATTTTCTACCTTTCTCTCGAA	ESE Binding	TTCGAGAGAAAGGTAGAAAATAAGA SEQ ID NO: 656
210	TTCTTATTTTCTACCTTTCTCTCGA	ESE Binding	TCGAGAGAAAGGTAGAAAATAAGAA SEQ ID NO: 657
211	ATTCTTATTTTCTACCTTTCTCTCG	ESE Binding	CGAGAGAAAGGTAGAAAATAAGAAT SEQ ID NO: 658
212	AATTCTTATTTTCTACCTTTCTCTC	ESE Binding	GAGAGAAAGGTAGAAAATAAGAATT SEQ ID NO: 659
213	AAATTCTTATTTTCTACCTTTCTCT	ESE Binding	AGAGAAAGGTAGAAAATAAGAATTT SEQ ID NO: 660
214	CAAATTCTTATTTTCTACCTTTCTC	ESE Binding	GAGAAAGGTAGAAAATAAGAATTTG SEQ ID NO: 661
215	CCAAATTCTTATTTTCTACCTTTCT	ESE Binding	AGAAAGGTAGAAAATAAGAATTTGG SEQ ID NO: 662
216	GCCAAATTCTTATTTTCTACCTTTC	ESE Binding	GAAAGGTAGAAAATAAGAATTTGGC SEQ ID NO: 663
217	AGCCAAATTCTTATTTTCTACCTTT	ESE Binding	AAAGGTAGAAAATAAGAATTTGGCT SEQ ID NO: 664

218	GAGCCAAATTCTTATTTTCTACCTT	ESE Binding	AAGGTAGAAAATAAGAATTTGGCTC SEQ ID NO: 665
219	AGAGCCAAATTCTTATTTTCTACCT	ESE Binding	AGGTAGAAAATAAGAATTTGGCTCT SEQ ID NO: 666
220	GAGAGCCAAATTCTTATTTTCTACC	ESE Binding	GGTAGAAAATAAGAATTTGGCTCTC SEQ ID NO: 667
221	AGAGAGCCAAATTCTTATTTTCTAC	ESE Binding	GTAGAAAATAAGAATTTGGCTCTCT SEQ ID NO: 668
222	CAGAGAGCCAAATTCTTATTTTCTA		TAGAAAATAAGAATTTGGCTCTCTG SEQ ID NO: 669
223	ACAGAGAGCCAAATTCTTATTTTCT		AGAAAATAAGAATTTGGCTCTCTGT SEQ ID NO: 670
224	CACAGAGAGCCAAATTCTTATTTTC		GAAAATAAGAATTTGGCTCTCTGTG SEQ ID NO: 671
225	ACACAGAGAGCCAAATTCTTATTTT		AAAATAAGAATTTGGCTCTCTGTGT SEQ ID NO: 672
226	CACACAGAGAGCCAAATTCTTATTT	Overlaps TDP-43 site 1	AAATAAGAATTTGGCTCTCTGTGTG SEQ ID NO: 673
227	TCACACAGAGAGCCAAATTCTTATT	Overlaps TDP-43 site 1	AATAAGAATTTGGCTCTCTGTGTGA SEQ ID NO: 674
228	CTCACACAGAGAGCCAAATTCTTAT	Overlaps TDP-43 site 1	ATAAGAATTTGGCTCTCTGTGTGAG SEQ ID NO: 675
229	GCTCACACAGAGAGCCAAATTCTTA	Overlaps TDP-43 site 1	TAAGAATTTGGCTCTCTGTGTGAGC SEQ ID NO: 676
230	TGCTCACACAGAGAGCCAAATTCTT	Overlaps TDP-43 site 1	AAGAATTTGGCTCTCTGTGTGAGCA SEQ ID NO: 677
231	ATGCTCACACAGAGAGCCAAATTCT	Overlaps TDP-43 site 1	AGAATTTGGCTCTCTGTGTGAGCAT SEQ ID NO: 678
232	CATGCTCACACAGAGAGCCAAATTC	Overlaps TDP-43 site 1	GAATTTGGCTCTCTGTGTGAGCATG SEQ ID NO: 679
233	ACATGCTCACACAGAGAGCCAAATT	Overlaps TDP-43 site 1	AATTTGGCTCTCTGTGTGAGCATGT SEQ ID NO: 680
234	CACATGCTCACACAGAGAGCCAAAT	Overlaps TDP-43 site 1	ATTTGGCTCTCTGTGTGAGCATGTG SEQ ID NO: 681
235	ACACATGCTCACACAGAGAGCCAAA	Overlaps TDP-43 site 1	TTTGGCTCTCTGTGTGAGCATGTGT SEQ ID NO: 682
236	CACACATGCTCACACAGAGAGCCAA	Overlaps TDP-43 site 1 & 2	TTGGCTCTCTGTGTGAGCATGTGTG SEQ ID NO: 683

237	GCACACATGCTCACACAGAGAGCCA	Overlaps TDP-43 site 1 & 2	TGGCTCTCTGTGTGAGCATGTGTGC SEQ ID NO: 684
238	CGCACACATGCTCACACAGAGAGCC	Overlaps TDP-43 site 1 & 2	GGCTCTCTGTGTGAGCATGTGTGCG SEQ ID NO: 685
239	ACGCACACATGCTCACACAGAGAGC	Overlaps TDP-43 site 1 & 2	GCTCTCTGTGTGAGCATGTGTGCGT SEQ ID NO: 686
240	CACGCACACATGCTCACACAGAGAG	Overlaps TDP-43 site 1 & 2	CTCTCTGTGTGAGCATGTGTGCGTG SEQ ID NO: 687
241	ACACGCACACATGCTCACACAGAGA	Overlaps TDP-43 site 1 & 2	TCTCTGTGTGAGCATGTGTGCGTGT SEQ ID NO: 688
242	CACACGCACACATGCTCACACAGAG	Overlaps TDP-43 site 1 & 2	CTCTGTGTGAGCATGTGTGCGTGTG SEQ ID NO: 689
243	ACACACGCACACATGCTCACACAGA	Overlaps TDP-43 site 1 & 2	TCTGTGTGAGCATGTGTGCGTGTGT SEQ ID NO: 690
244	CACACACGCACACATGCTCACACAG	Overlaps TDP-43 site 1 & 2 & 3	CTGTGTGAGCATGTGTGCGTGTGTG SEQ ID NO: 691
245	GCACACACGCACACATGCTCACACA	Overlaps TDP-43 site 1 & 2 & 3	TGTGTGAGCATGTGTGCGTGTGTGC SEQ ID NO: 692
246	CGCACACACGCACACATGCTCACAC	Overlaps TDP-43 site 2 & 3	GTGTGAGCATGTGTGCGTGTGTGCG SEQ ID NO: 693
247	TCGCACACACGCACACATGCTCACA	Overlaps TDP-43 site 2 & 3	TGTGAGCATGTGTGCGTGTGTGCGA SEQ ID NO: 694
248	CTCGCACACACGCACACATGCTCAC	Overlaps TDP-43 site 2 & 3	GTGAGCATGTGTGCGTGTGTGCGAG SEQ ID NO: 695
249	TCTCGCACACACGCACACATGCTCA	Overlaps TDP-43	TGAGCATGTGTGCGTGTGTGCGAGA SEQ ID NO: 696

		site 2 & 3	
250	CTCTCGCACACACGCACACATGCTC	Overlaps TDP-43 site 2 & 3	GAGCATGTGTGCGTGTGTGCGAGAG SEQ ID NO: 697
251	TCTCTCGCACACACGCACACATGCT	Overlaps TDP-43 site 2 & 3	AGCATGTGTGCGTGTGTGCGAGAGA SEQ ID NO: 698
252	CTCTCTCGCACACACGCACACATGC	Overlaps TDP-43 site 2 & 3	GCATGTGTGCGTGTGTGCGAGAGAG SEQ ID NO: 699
253	TCTCTCTCGCACACACGCACACATG	Overlaps TDP-43 site 2 & 3	CATGTGTGCGTGTGTGCGAGAGAGA SEQ ID NO: 700
254	CTCTCTCTCGCACACACGCACACAT	Overlaps TDP-43 site 2 & 3	ATGTGTGCGTGTGTGCGAGAGAGAG SEQ ID NO: 701
255	TCTCTCTCTCGCACACACGCACACA	Overlaps TDP-43 site 2 & 3	TGTGTGCGTGTGTGCGAGAGAGAGA SEQ ID NO: 702
256	CTCTCTCTCTCGCACACACGCACAC	Overlaps TDP-43 site 3	GTGTGCGTGTGTGCGAGAGAGAGAG SEQ ID NO: 703
257	TCTCTCTCTCTCGCACACACGCACA	Overlaps TDP-43 site 3	TGTGCGTGTGTGCGAGAGAGAGAGA SEQ ID NO: 704
258	GTCTCTCTCTCTCGCACACACGCAC	Overlaps TDP-43 site 3	GTGCGTGTGTGCGAGAGAGAGAGAC SEQ ID NO: 705
259	TGTCTCTCTCTCTCGCACACACGCA	Overlaps TDP-43 site 3	TGCGTGTGTGCGAGAGAGAGAGACA SEQ ID NO: 706
260	CTGTCTCTCTCTCTCGCACACACGC	Overlaps TDP-43 site 3	GCGTGTGTGCGAGAGAGAGAGACAG SEQ ID NO: 707
261	TCTGTCTCTCTCTCTCGCACACACG	Overlaps TDP-43 site 3	CGTGTGTGCGAGAGAGAGAGACAGA SEQ ID NO: 708
262	GTCTGTCTCTCTCTCTCGCACACAC	Overlaps TDP-43 site 3	GTGTGTGCGAGAGAGAGAGACAGAC SEQ ID NO: 709
263	TGTCTGTCTCTCTCTCTCGCACACA	Overlaps TDP-43 site 3	TGTGTGCGAGAGAGAGAGACAGACA SEQ ID NO: 710
264	CTGTCTGTCTCTCTCTCTCGCACAC		GTGTGCGAGAGAGAGAGACAGACAG

			SEQ ID NO: 711
265	GCTGTCTGTCTCTCTCTCTCGCACA		TGTGCGAGAGAGAGAGACAGACAGC SEQ ID NO: 712
266	GGCTGTCTGTCTCTCTCTCTCGCAC		GTGCGAGAGAGAGAGACAGACAGCC SEQ ID NO: 713
267	AGGCTGTCTGTCTCTCTCTCTCGCA		TGCGAGAGAGAGAGACAGACAGCCT SEQ ID NO: 714
268	CAGGCTGTCTGTCTCTCTCTCTCGC		GCGAGAGAGAGAGACAGACAGCCTG SEQ ID NO: 715
269	GCAGGCTGTCTGTCTCTCTCTCTCG		CGAGAGAGAGAGACAGACAGCCTGC SEQ ID NO: 716
270	GGCAGGCTGTCTGTCTCTCTCTCTC		GAGAGAGAGAGACAGACAGCCTGCC SEQ ID NO: 717
271	AGGCAGGCTGTCTGTCTCTCTCTCT		AGAGAGAGAGACAGACAGCCTGCCT SEQ ID NO: 718
272	TAGGCAGGCTGTCTGTCTCTCTCTC		GAGAGAGAGACAGACAGCCTGCCTA SEQ ID NO: 719
273	TTAGGCAGGCTGTCTGTCTCTCTCT		AGAGAGAGACAGACAGCCTGCCTAA SEQ ID NO: 720
274	CTTAGGCAGGCTGTCTGTCTCTCTC		GAGAGAGACAGACAGCCTGCCTAAG SEQ ID NO: 721
275	TCTTAGGCAGGCTGTCTGTCTCTCT		AGAGAGACAGACAGCCTGCCTAAGA SEQ ID NO: 722
276	TTCTTAGGCAGGCTGTCTGTCTCTC		GAGAGACAGACAGCCTGCCTAAGAA SEQ ID NO: 723
277	CTTCTTAGGCAGGCTGTCTGTCTCT		AGAGACAGACAGCCTGCCTAAGAAG SEQ ID NO: 724
278	TCTTCTTAGGCAGGCTGTCTGTCTC		GAGACAGACAGCCTGCCTAAGAAGA SEQ ID NO: 725
279	TTCTTCTTAGGCAGGCTGTCTGTCT		AGACAGACAGCCTGCCTAAGAAGAA SEQ ID NO: 726
280	TTTCTTCTTAGGCAGGCTGTCTGTC		GACAGACAGCCTGCCTAAGAAGAAA SEQ ID NO: 727
281	ATTTCTTCTTAGGCAGGCTGTCTGT		ACAGACAGCCTGCCTAAGAAGAAAT SEQ ID NO: 728
282	CATTTCTTCTTAGGCAGGCTGTCTG		CAGACAGCCTGCCTAAGAAGAAATG SEQ ID NO: 729
283	TCATTTCTTCTTAGGCAGGCTGTCT		AGACAGCCTGCCTAAGAAGAAATGA SEQ ID NO: 730
284	TTCATTTCTTCTTAGGCAGGCTGTC		GACAGCCTGCCTAAGAAGAAATGAA SEQ ID NO: 731
285	ATTCATTTCTTCTTAGGCAGGCTGT		ACAGCCTGCCTAAGAAGAAATGAAT SEQ ID NO: 732
286	CATTCATTTCTTCTTAGGCAGGCTG		CAGCCTGCCTAAGAAGAAATGAATG SEQ ID NO: 733
287	ACATTCATTTCTTCTTAGGCAGGCT		AGCCTGCCTAAGAAGAAATGAATGT SEQ ID NO: 734
288	CACATTCATTTCTTCTTAGGCAGGC		GCCTGCCTAAGAAGAAATGAATGTG SEQ ID NO: 735
289	TCACATTCATTTCTTCTTAGGCAGG		CCTGCCTAAGAAGAAATGAATGTGA SEQ ID NO: 736

290	TTCACATTCATTTCTTCTTAGGCAG		CTGCCTAAGAAGAAATGAATGTGAA SEQ ID NO: 737
291	ATTCACATTCATTTCTTCTTAGGCA		TGCCTAAGAAGAAATGAATGTGAAT SEQ ID NO: 738
292	CATTCACATTCATTTCTTCTTAGGC		GCCTAAGAAGAAATGAATGTGAATG SEQ ID NO: 739
293	GCATTCACATTCATTTCTTCTTAGG		CCTAAGAAGAAATGAATGTGAATGC SEQ ID NO: 740
294	CGCATTCACATTCATTTCTTCTTAG		CTAAGAAGAAATGAATGTGAATGCG SEQ ID NO: 741
295	CCGCATTCACATTCATTTCTTCTTA		TAAGAAGAAATGAATGTGAATGCGG SEQ ID NO: 742
296	GCCGCATTCACATTCATTTCTTCTT		AAGAAGAAATGAATGTGAATGCGGC SEQ ID NO: 743
297	AGCCGCATTCACATTCATTTCTTCT		AGAAGAAATGAATGTGAATGCGGCT SEQ ID NO: 744
298	AAGCCGCATTCACATTCATTTCTTC		GAAGAAATGAATGTGAATGCGGCTT SEQ ID NO: 745
299	CAAGCCGCATTCACATTCATTTCTT		AAGAAATGAATGTGAATGCGGCTTG SEQ ID NO: 746
300	ACAAGCCGCATTCACATTCATTTCT		AGAAATGAATGTGAATGCGGCTTGT SEQ ID NO: 747
301	CACAAGCCGCATTCACATTCATTTC		GAAATGAATGTGAATGCGGCTTGTG SEQ ID NO: 748
302	CCACAAGCCGCATTCACATTCATTT		AAATGAATGTGAATGCGGCTTGTGG SEQ ID NO: 749
303	GCCACAAGCCGCATTCACATTCATT		AATGAATGTGAATGCGGCTTGTGGC SEQ ID NO: 750
304	TGCCACAAGCCGCATTCACATTCAT		ATGAATGTGAATGCGGCTTGTGGCA SEQ ID NO: 751
305	GTGCCACAAGCCGCATTCACATTCA		TGAATGTGAATGCGGCTTGTGGCAC SEQ ID NO: 752
306	TGTGCCACAAGCCGCATTCACATTC		GAATGTGAATGCGGCTTGTGGCACA SEQ ID NO: 753
307	CTGTGCCACAAGCCGCATTCACATT		AATGTGAATGCGGCTTGTGGCACAG SEQ ID NO: 754
308	ACTGTGCCACAAGCCGCATTCACAT		ATGTGAATGCGGCTTGTGGCACAGT SEQ ID NO: 755
309	AACTGTGCCACAAGCCGCATTCACA		TGTGAATGCGGCTTGTGGCACAGTT SEQ ID NO: 756
310	CAACTGTGCCACAAGCCGCATTCAC		GTGAATGCGGCTTGTGGCACAGTTG SEQ ID NO: 757
311	TCAACTGTGCCACAAGCCGCATTCA		TGAATGCGGCTTGTGGCACAGTTGA SEQ ID NO: 758
312	GTCAACTGTGCCACAAGCCGCATTC		GAATGCGGCTTGTGGCACAGTTGAC SEQ ID NO: 759
313	TGTCAACTGTGCCACAAGCCGCATT		AATGCGGCTTGTGGCACAGTTGACA SEQ ID NO: 760
314	TTGTCAACTGTGCCACAAGCCGCAT		ATGCGGCTTGTGGCACAGTTGACAA SEQ ID NO: 761
315	CTTGTCAACTGTGCCACAAGCCGCA		TGCGGCTTGTGGCACAGTTGACAAG

			SEQ ID NO: 762
316	CCTTGTCAACTGTGCCACAAGCCGC		GCGGCTTGTGGCACAGTTGACAAGG SEQ ID NO: 763
317	TCCTTGTCAACTGTGCCACAAGCCG		CGGCTTGTGGCACAGTTGACAAGGA SEQ ID NO: 764
318	ATCCTTGTCAACTGTGCCACAAGCC		GGCTTGTGGCACAGTTGACAAGGAT SEQ ID NO: 765
319	CATCCTTGTCAACTGTGCCACAAGC		GCTTGTGGCACAGTTGACAAGGATG SEQ ID NO: 766
320	TCATCCTTGTCAACTGTGCCACAAG		CTTGTGGCACAGTTGACAAGGATGA SEQ ID NO: 767
321	ATCATCCTTGTCAACTGTGCCACAA		TTGTGGCACAGTTGACAAGGATGAT SEQ ID NO: 768
322	TATCATCCTTGTCAACTGTGCCACA		TGTGGCACAGTTGACAAGGATGATA SEQ ID NO: 769
323	TTATCATCCTTGTCAACTGTGCCAC		GTGGCACAGTTGACAAGGATGATAA SEQ ID NO: 770
324	TTTATCATCCTTGTCAACTGTGCCA		TGGCACAGTTGACAAGGATGATAAA SEQ ID NO: 771
325	ATTTATCATCCTTGTCAACTGTGCC		GGCACAGTTGACAAGGATGATAAAT SEQ ID NO: 772
326	GATTTATCATCCTTGTCAACTGTGC		GCACAGTTGACAAGGATGATAAATC SEQ ID NO: 773
327	TGATTTATCATCCTTGTCAACTGTG		CACAGTTGACAAGGATGATAAATCA SEQ ID NO: 774
328	TTGATTTATCATCCTTGTCAACTGT		ACAGTTGACAAGGATGATAAATCAA SEQ ID NO: 775
329	ATTGATTTATCATCCTTGTCAACTG		CAGTTGACAAGGATGATAAATCAAT SEQ ID NO: 776
330	TATTGATTTATCATCCTTGTCAACT		AGTTGACAAGGATGATAAATCAATA SEQ ID NO: 777
331	TTATTGATTTATCATCCTTGTCAAC		GTTGACAAGGATGATAAATCAATAA SEQ ID NO: 778
332	ATTATTGATTTATCATCCTTGTCAA		TTGACAAGGATGATAAATCAATAAT SEQ ID NO: 779
333	CATTATTGATTTATCATCCTTGTCA		TGACAAGGATGATAAATCAATAATG SEQ ID NO: 780
334	GCATTATTGATTTATCATCCTTGTC		GACAAGGATGATAAATCAATAATGC SEQ ID NO: 781
335	TGCATTATTGATTTATCATCCTTGT		ACAAGGATGATAAATCAATAATGCA SEQ ID NO: 782
336	TTGCATTATTGATTTATCATCCTTG		CAAGGATGATAAATCAATAATGCAA SEQ ID NO: 783
337	CTTGCATTATTGATTTATCATCCTT		AAGGATGATAAATCAATAATGCAAG SEQ ID NO: 784
338	GCTTGCATTATTGATTTATCATCCT		AGGATGATAAATCAATAATGCAAGC SEQ ID NO: 785
339	AGCTTGCATTATTGATTTATCATCC		GGATGATAAATCAATAATGCAAGCT SEQ ID NO: 786
340	AAGCTTGCATTATTGATTTATCATC		GATGATAAATCAATAATGCAAGCTT SEQ ID NO: 787

341	TAAGCTTGCATTATTGATTTATCAT		ATGATAAATCAATAATGCAAGCTTA SEQ ID NO: 788
342	GTAAGCTTGCATTATTGATTTATCA		TGATAAATCAATAATGCAAGCTTAC SEQ ID NO: 789
343	AGTAAGCTTGCATTATTGATTTATC		GATAAATCAATAATGCAAGCTTACT SEQ ID NO: 790
344	TAGTAAGCTTGCATTATTGATTTAT		ATAAATCAATAATGCAAGCTTACTA SEQ ID NO: 791
345	ATAGTAAGCTTGCATTATTGATTTA		TAAATCAATAATGCAAGCTTACTAT SEQ ID NO: 792
346	GATAGTAAGCTTGCATTATTGATTT		AAATCAATAATGCAAGCTTACTATC SEQ ID NO: 793
347	TGATAGTAAGCTTGCATTATTGATT		AATCAATAATGCAAGCTTACTATCA SEQ ID NO: 794
348	ATGATAGTAAGCTTGCATTATTGAT		ATCAATAATGCAAGCTTACTATCAT SEQ ID NO: 795
349	AATGATAGTAAGCTTGCATTATTGA		TCAATAATGCAAGCTTACTATCATT SEQ ID NO: 796
350	AAATGATAGTAAGCTTGCATTATTG		CAATAATGCAAGCTTACTATCATTT SEQ ID NO: 797
351	TAAATGATAGTAAGCTTGCATTATT		AATAATGCAAGCTTACTATCATTTA SEQ ID NO: 798
352	ATAAATGATAGTAAGCTTGCATTAT		ATAATGCAAGCTTACTATCATTTAT SEQ ID NO: 799
353	CATAAATGATAGTAAGCTTGCATTA		TAATGCAAGCTTACTATCATTTATG SEQ ID NO: 800
354	TCATAAATGATAGTAAGCTTGCATT		AATGCAAGCTTACTATCATTTATGA SEQ ID NO: 801
355	TTCATAAATGATAGTAAGCTTGCAT		ATGCAAGCTTACTATCATTTATGAA SEQ ID NO: 802
356	ATTCATAAATGATAGTAAGCTTGCA		TGCAAGCTTACTATCATTTATGAAT SEQ ID NO: 803
357	TATTCATAAATGATAGTAAGCTTGC		GCAAGCTTACTATCATTTATGAATA SEQ ID NO: 804
358	CTATTCATAAATGATAGTAAGCTTG		CAAGCTTACTATCATTTATGAATAG SEQ ID NO: 805
359	GCTATTCATAAATGATAGTAAGCTT		AAGCTTACTATCATTTATGAATAGC SEQ ID NO: 806
360	TGCTATTCATAAATGATAGTAAGCT		AGCTTACTATCATTTATGAATAGCA SEQ ID NO: 807
361	TTGCTATTCATAAATGATAGTAAGC		GCTTACTATCATTTATGAATAGCAA SEQ ID NO: 808
362	ATTGCTATTCATAAATGATAGTAAG		CTTACTATCATTTATGAATAGCAAT SEQ ID NO: 809
363	TATTGCTATTCATAAATGATAGTAA		TTACTATCATTTATGAATAGCAATA SEQ ID NO: 810
364	GTATTGCTATTCATAAATGATAGTA		TACTATCATTTATGAATAGCAATAC SEQ ID NO: 811
365	AGTATTGCTATTCATAAATGATAGT		ACTATCATTTATGAATAGCAATACT SEQ ID NO: 812
366	CAGTATTGCTATTCATAAATGATAG		CTATCATTTATGAATAGCAATACTG

			SEQ ID NO: 813
367	TCAGTATTGCTATTCATAAATGATA		TATCATTTATGAATAGCAATACTGA SEQ ID NO: 814
368	TTCAGTATTGCTATTCATAAATGAT		ATCATTTATGAATAGCAATACTGAA SEQ ID NO: 815
369	CTTCAGTATTGCTATTCATAAATGA		TCATTTATGAATAGCAATACTGAAG SEQ ID NO: 816
370	TCTTCAGTATTGCTATTCATAAATG		CATTTATGAATAGCAATACTGAAGA SEQ ID NO: 817
371	TTCTTCAGTATTGCTATTCATAAAT		ATTTATGAATAGCAATACTGAAGAA SEQ ID NO: 818
372	TTTCTTCAGTATTGCTATTCATAAA		TTTATGAATAGCAATACTGAAGAAA SEQ ID NO: 819
373	ATTTCTTCAGTATTGCTATTCATAA		TTATGAATAGCAATACTGAAGAAAT SEQ ID NO: 820
374	AATTTCTTCAGTATTGCTATTCATA		TATGAATAGCAATACTGAAGAAATT SEQ ID NO: 821
375	TAATTTCTTCAGTATTGCTATTCAT		ATGAATAGCAATACTGAAGAAATTA SEQ ID NO: 822
376	TTAATTTCTTCAGTATTGCTATTCA		TGAATAGCAATACTGAAGAAATTAA SEQ ID NO: 823
377	TTTAATTTCTTCAGTATTGCTATTC	polyA signal	GAATAGCAATACTGAAGAAATTAAA SEQ ID NO: 824
378	TTTTAATTTCTTCAGTATTGCTATT	polyA signal	AATAGCAATACTGAAGAAATTAAAA SEQ ID NO: 825
379	GTTTTAATTTCTTCAGTATTGCTAT	polyA signal	ATAGCAATACTGAAGAAATTAAAAC SEQ ID NO: 826
380	TGTTTTAATTTCTTCAGTATTGCTA	polyA signal	TAGCAATACTGAAGAAATTAAAACA SEQ ID NO: 827
381	TTGTTTTAATTTCTTCAGTATTGCT	polyA signal	AGCAATACTGAAGAAATTAAAACAA SEQ ID NO: 828
382	TTTGTTTTAATTTCTTCAGTATTGC	polyA signal	GCAATACTGAAGAAATTAAAACAAA SEQ ID NO: 829
383	TTTTGTTTTAATTTCTTCAGTATTG	polyA signal	CAATACTGAAGAAATTAAAACAAAA SEQ ID NO: 830
384	CTTTTGTTTTAATTTCTTCAGTATT	polyA signal	AATACTGAAGAAATTAAAACAAAAG SEQ ID NO: 831
385	TCTTTTGTTTTAATTTCTTCAGTAT	polyA signal	ATACTGAAGAAATTAAAACAAAAGA SEQ ID NO: 832
386	ATCTTTTGTTTTAATTTCTTCAGTA	polyA signal	TACTGAAGAAATTAAAACAAAAGAT SEQ ID NO: 833
387	AATCTTTTGTTTTAATTTCTTCAGT	polyA signal	ACTGAAGAAATTAAAACAAAAGATT SEQ ID NO: 834
388	CAATCTTTTGTTTTAATTTCTTCAG	polyA signal	CTGAAGAAATTAAAACAAAAGATTG SEQ ID NO: 835
389	GCAATCTTTTGTTTTAATTTCTTCA	polyA signal	TGAAGAAATTAAAACAAAAGATTGC SEQ ID NO: 836
390	AGCAATCTTTTGTTTTAATTTCTTC	polyA signal	GAAGAAATTAAAACAAAAGATTGCT SEQ ID NO: 837
391	CAGCAATCTTTTGTTTTAATTTCTT	polyA signal	AAGAAATTAAAACAAAAGATTGCTG SEQ ID NO: 838

392	ACAGCAATCTTTTGTTTTAATTTCT	polyA signal	AGAAATTAAAACAAAAGATTGCTGT SEQ ID NO: 839
393	GACAGCAATCTTTTGTTTTAATTTC	polyA signal	GAAATTAAAACAAAAGATTGCTGTC SEQ ID NO: 840
394	AGACAGCAATCTTTTGTTTTAATTT	polyA signal	AAATTAAAACAAAAGATTGCTGTCT SEQ ID NO: 841
395	GAGACAGCAATCTTTTGTTTTAATT	polyA signal and site	AATTAAAACAAAAGATTGCTGTCTC SEQ ID NO: 842
396	TGAGACAGCAATCTTTTGTTTTAAT	polyA signal and site	ATTAAAACAAAAGATTGCTGTCTCA SEQ ID NO: 843
397	TTGAGACAGCAATCTTTTGTTTTAA	polyA site	TTAAAACAAAAGATTGCTGTCTCAA SEQ ID NO: 844
398	ATTGAGACAGCAATCTTTTGTTTTA	polyA site	TAAAACAAAAGATTGCTGTCTCAAT SEQ ID NO: 845
399	TATTGAGACAGCAATCTTTTGTTTT	polyA site	AAAACAAAAGATTGCTGTCTCAATA SEQ ID NO: 846
400	ATATTGAGACAGCAATCTTTTGTTT	polyA site	AAACAAAAGATTGCTGTCTCAATAT SEQ ID NO: 847
401	TATATTGAGACAGCAATCTTTTGTT	polyA site	AACAAAAGATTGCTGTCTCAATATA SEQ ID NO: 848
402	ATATATTGAGACAGCAATCTTTTGT	polyA site	ACAAAAGATTGCTGTCTCAATATAT SEQ ID NO: 849
403	GATATATTGAGACAGCAATCTTTTG	polyA site	CAAAAGATTGCTGTCTCAATATATC SEQ ID NO: 850
404	AGATATATTGAGACAGCAATCTTTT	polyA site	AAAAGATTGCTGTCTCAATATATCT SEQ ID NO: 851
405	AAGATATATTGAGACAGCAATCTTT	polyA site	AAAGATTGCTGTCTCAATATATCTT SEQ ID NO: 852
406	TAAGATATATTGAGACAGCAATCTT	polyA site	AAGATTGCTGTCTCAATATATCTTA SEQ ID NO: 853
407	ATAAGATATATTGAGACAGCAATCT	polyA site	AGATTGCTGTCTCAATATATCTTAT SEQ ID NO: 854
408	TATAAGATATATTGAGACAGCAATC	polyA site	GATTGCTGTCTCAATATATCTTATA SEQ ID NO: 855
409	ATATAAGATATATTGAGACAGCAAT	polyA site	ATTGCTGTCTCAATATATCTTATAT SEQ ID NO: 856
410	AATATAAGATATATTGAGACAGCAA	polyA site	TTGCTGTCTCAATATATCTTATATT SEQ ID NO: 857
411	AAATATAAGATATATTGAGACAGCA	polyA site	TGCTGTCTCAATATATCTTATATTT SEQ ID NO: 858
412	TAAATATAAGATATATTGAGACAGC	polyA site	GCTGTCTCAATATATCTTATATTTA SEQ ID NO: 859
413	ATAAATATAAGATATATTGAGACAG		CTGTCTCAATATATCTTATATTTAT SEQ ID NO: 860
414	AATAAATATAAGATATATTGAGACA		TGTCTCAATATATCTTATATTTATT SEQ ID NO: 861
415	TAATAAATATAAGATATATTGAGAC		GTCTCAATATATCTTATATTTATTA SEQ ID NO: 862
416	ATAATAAATATAAGATATATTGAGA		TCTCAATATATCTTATATTTATTAT

			SEQ ID NO: 863
417	AATAATAAATATAAGATATATTGAG		CTCAATATATCTTATATTTATTATT SEQ ID NO: 864
418	AAATAATAAATATAAGATATATTGA		TCAATATATCTTATATTTATTATTT SEQ ID NO: 865
419	TAAATAATAAATATAAGATATATTG		CAATATATCTTATATTTATTATTTA SEQ ID NO: 866
420	GTAAATAATAAATATAAGATATATT		AATATATCTTATATTTATTATTTAC SEQ ID NO: 867
421	GGTAAATAATAAATATAAGATATAT		ATATATCTTATATTTATTATTTACC SEQ ID NO: 868
422	TGGTAAATAATAAATATAAGATATA		TATATCTTATATTTATTATTTACCA SEQ ID NO: 869
423	TTGGTAAATAATAAATATAAGATAT		ATATCTTATATTTATTATTTACCAA SEQ ID NO: 870
424	TTTGGTAAATAATAAATATAAGATA		TATCTTATATTTATTATTTACCAAA SEQ ID NO: 871
425	ATTTGGTAAATAATAAATATAAGAT		ATCTTATATTTATTATTTACCAAAT SEQ ID NO: 872
426	AATTTGGTAAATAATAAATATAAGA		TCTTATATTTATTATTTACCAAATT SEQ ID NO: 873
427	TAATTTGGTAAATAATAAATATAAG		CTTATATTTATTATTTACCAAATTA SEQ ID NO: 874
428	ATAATTTGGTAAATAATAAATATAA		TTATATTTATTATTTACCAAATTAT SEQ ID NO: 875
429	AATAATTTGGTAAATAATAAATATA		TATATTTATTATTTACCAAATTATT SEQ ID NO: 876
430	GAATAATTTGGTAAATAATAAATAT		ATATTTATTATTTACCAAATTATTC SEQ ID NO: 877
431	AGAATAATTTGGTAAATAATAAATA		TATTTATTATTTACCAAATTATTCT SEQ ID NO: 878
432	TAGAATAATTTGGTAAATAATAAAT		ATTTATTATTTACCAAATTATTCTA SEQ ID NO: 879
433	TTAGAATAATTTGGTAAATAATAAA		TTTATTATTTACCAAATTATTCTAA SEQ ID NO: 880
434	CTTAGAATAATTTGGTAAATAATAA		TTATTATTTACCAAATTATTCTAAG SEQ ID NO: 881
435	TCTTAGAATAATTTGGTAAATAATA		TATTATTTACCAAATTATTCTAAGA SEQ ID NO: 882
436	CTCTTAGAATAATTTGGTAAATAAT		ATTATTTACCAAATTATTCTAAGAG SEQ ID NO: 883
437	ACTCTTAGAATAATTTGGTAAATAA		TTATTTACCAAATTATTCTAAGAGT SEQ ID NO: 884
438	TACTCTTAGAATAATTTGGTAAATA		TATTTACCAAATTATTCTAAGAGTA SEQ ID NO: 885
439	ATACTCTTAGAATAATTTGGTAAAT		ATTTACCAAATTATTCTAAGAGTAT SEQ ID NO: 886
440	AATACTCTTAGAATAATTTGGTAAA		TTTACCAAATTATTCTAAGAGTATT SEQ ID NO: 887
441	AAATACTCTTAGAATAATTTGGTAA		TTACCAAATTATTCTAAGAGTATTT SEQ ID NO: 888

442	GAAATACTCTTAGAATAATTTGGTA		TACCAAATTATTCTAAGAGTATTTC SEQ ID NO: 889
443	AGAAATACTCTTAGAATAATTTGGT		ACCAAATTATTCTAAGAGTATTTCT SEQ ID NO: 890
444	AAGAAATACTCTTAGAATAATTTGG		CCAAATTATTCTAAGAGTATTTCTT SEQ ID NO: 891
445	GAAGAAATACTCTTAGAATAATTTG		CAAATTATTCTAAGAGTATTTCTTC SEQ ID NO: 892
446	GGAAGAAATACTCTTAGAATAATTT		AAATTATTCTAAGAGTATTTCTTCC SEQ ID NO: 893

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

[00190] Table 2 below identifies additional STMN2 AON sequences:

Table 2. Additional STMN2 AON Sequences

SEQ ID NO:	AON Sequence* (5' →3')
945	GGAGGGAUACCUGUAUAUUACAAGU
946	AGGAGGGAUACCUGUAUAUUACAAG
947	CAGGAGGGAUACCUGUAUAUUACAA
948	CCAGGAGGGAUACCUGUAUAUUACA
949	ACCAGGAGGGAUACCUGUAUAUUAC
950	UACCAGGAGGGAUACCUGUAUAUUA
951	UUACCAGGAGGGAUACCUGUAUAUU
952	CUUACCAGGAGGGAUACCUGUAUAU
953	GCUUACCAGGAGGGAUACCUGUAUA
954	AGCUUACCAGGAGGGAUACCUGUAU
955	GAGCUUACCAGGAGGGAUACCUGUA
956	AGAGCUUACCAGGAGGGAUACCUGU
957	CAGAGCUUACCAGGAGGGAUACCUG
958	CCAGAGCUUACCAGGAGGGAUACCU
959	ACCAGAGCUUACCAGGAGGGAUACC
960	UACCAGAGCUUACCAGGAGGGAUAC
961	AUACCAGAGCUUACCAGGAGGGAUA

962	AAUACCAGAGCUUACCAGGAGGGAU
963	UAAUACCAGAGCUUACCAGGAGGGA
964	AUAAUACCAGAGCUUACCAGGAGGG
965	CAUAAUACCAGAGCUUACCAGGAGG
966	ACAUAAUACCAGAGCUUACCAGGAG
967	GACAUAAUACCAGAGCUUACCAGGA
968	AGACAUAAUACCAGAGCUUACCAGG
969	AAGACAUAAUACCAGAGCUUACCAG
970	UAAGACAUAAUACCAGAGCUUACCA
971	UUAAGACAUAAUACCAGAGCUUACC
972	GUUAAGACAUAAUACCAGAGCUUAC
973	UGUUAAGACAUAAUACCAGAGCUUA
974	AUGUUAAGACAUAAUACCAGAGCUU
975	AAUGUUAAGACAUAAUACCAGAGCU
976	AAAUGUUAAGACAUAAUACCAGAGC
977	AAAAUGUUAAGACAUAAUACCAGAG
978	AAAAAUGUUAAGACAUAAUACCAGA
979	UAAAAAUGUUAAGACAUAAUACCAG
980	UUAAAAAUGUUAAGACAUAAUACCA
981	UUUAAAAAUGUUAAGACAUAAUACC
982	AUUUAAAAAUGUUAAGACAUAAUAC
983	GAUUUAAAAAUGUUAAGACAUAAUA
984	AGAUUUAAAAAUGUUAAGACAUAAU
985	UAGAUUUAAAAAUGUUAAGACAUAA
986	AUAGAUUUAAAAAUGUUAAGACAUA
987	CAUAGAUUUAAAAAUGUUAAGACAU
988	CCAUAGAUUUAAAAAUGUUAAGACA
989	ACCAUAGAUUUAAAAAUGUUAAGAC
990	UACCAUAGAUUUAAAAAUGUUAAGA
991	UUACCAUAGAUUUAAAAAUGUUAAG
992	AUUACCAUAGAUUUAAAAAUGUUAA
993	GAUUACCAUAGAUUUAAAAAUGUUA
994	AGAUUACCAUAGAUUUAAAAAUGUU
995	AAGAUUACCAUAGAUUUAAAAAUGU
996	AAAGAUUACCAUAGAUUUAAAAAUG
997	UAAAGAUUACCAUAGAUUUAAAAAU
998	GUAAAGAUUACCAUAGAUUUAAAAA
999	UGUAAAGAUUACCAUAGAUUUAAAA
1000	UUGUAAAGAUUACCAUAGAUUUAAA
1001	UUUGUAAAGAUUACCAUAGAUUUAA
1002	UUUUGUAAAGAUUACCAUAGAUUUA
1003	AUUUUGUAAAGAUUACCAUAGAUUU

1004	UAUUUUGUAAAGAUUACCAUAGAUU
1005	AUAUUUUGUAAAGAUUACCAUAGAU
1006	AAUAUUUUGUAAAGAUUACCAUAGA
1007	AAAUAUUUUGUAAAGAUUACCAUAG
1008	AAAAUAUUUUGUAAAGAUUACCAUA
1009	UAAAAUAUUUUGUAAAGAUUACCAU
1010	GUAAAAUAUUUUGUAAAGAUUACCA
1011	AGUAAAAUAUUUUGUAAAGAUUACC
1012	AAGUAAAAUAUUUUGUAAAGAUUAC
1013	GAAGUAAAAUAUUUUGUAAAGAUUA
1014	GGAAGUAAAAUAUUUUGUAAAGAUU
1015	CGGAAGUAAAAUAUUUUGUAAAGAU
1016	UCGGAAGUAAAAUAUUUUGUAAAGA
1017	UUCGGAAGUAAAAUAUUUUGUAAAG
1018	GUUCGGAAGUAAAAUAUUUUGUAAA
1019	AGUUCGGAAGUAAAAUAUUUUGUAA
1020	GAGUUCGGAAGUAAAAUAUUUUGUA
1021	UGAGUUCGGAAGUAAAAUAUUUUGU
1022	AUGAGUUCGGAAGUAAAAUAUUUUG
1023	UAUGAGUUCGGAAGUAAAAUAUUUU
1024	AUAUGAGUUCGGAAGUAAAAUAUUU
1025	UAUAUGAGUUCGGAAGUAAAAUAUU
1026	GUAUAUGAGUUCGGAAGUAAAAUAU
1027	GGUAUAUGAGUUCGGAAGUAAAAUA
1028	AGGUAUAUGAGUUCGGAAGUAAAAU
1029	CAGGUAUAUGAGUUCGGAAGUAAAA
1030	CCAGGUAUAUGAGUUCGGAAGUAAA
1031	CCCAGGUAUAUGAGUUCGGAAGUAA
1032	CCCCAGGUAUAUGAGUUCGGAAGUA
1033	UCCCCAGGUAUAUGAGUUCGGAAGU
1034	AUCCCCAGGUAUAUGAGUUCGGAAG
1035	AAUCCCCAGGUAUAUGAGUUCGGAA
1036	AAAUCCCCAGGUAUAUGAGUUCGGA
1037	AAAAUCCCCAGGUAUAUGAGUUCGG
1038	UAAAAUCCCCAGGUAUAUGAGUUCG
1039	AUAAAAUCCCCAGGUAUAUGAGUUC
1040	AAUAAAAUCCCCAGGUAUAUGAGUU
1041	UAAUAAAAUCCCCAGGUAUAUGAGU
1042	GUAAUAAAAUCCCCAGGUAUAUGAG
1043	AGUAAUAAAAUCCCCAGGUAUAUGA
1044	GAGUAAUAAAAUCCCCAGGUAUAUG
1045	AGAGUAAUAAAAUCCCCAGGUAUAU

1046	CAGAGUAAUAAAAUCCCCAGGUAUA
1047	CCAGAGUAAUAAAAUCCCCAGGUAU
1048	CCCAGAGUAAUAAAAUCCCCAGGUA
1049	UCCCAGAGUAAUAAAAUCCCCAGGU
1050	UUCCCAGAGUAAUAAAAUCCCCAGG
1051	AUUCCCAGAGUAAUAAAAUCCCCAG
1052	AAUUCCCAGAGUAAUAAAAUCCCCA
1053	UAAUUCCCAGAGUAAUAAAAUCCCC
1054	AUAAUUCCCAGAGUAAUAAAAUCCC
1055	CAUAAUUCCCAGAGUAAUAAAAUCC
1056	ACAUAAUUCCCAGAGUAAUAAAAUC
1057	CACAUAAUUCCCAGAGUAAUAAAAU
1058	ACACAUAAUUCCCAGAGUAAUAAAA
1059	AACACAUAAUUCCCAGAGUAAUAAA
1060	GAACACAUAAUUCCCAGAGUAAUAA
1061	AGAACACAUAAUUCCCAGAGUAAUA
1062	CAGAACACAUAAUUCCCAGAGUAAU
1063	GCAGAACACAUAAUUCCCAGAGUAA
1064	GGCAGAACACAUAAUUCCCAGAGUA
1065	GGGCAGAACACAUAAUUCCCAGAGU
1066	GGGGCAGAACACAUAAUUCCCAGAG
1067	UGGGGCAGAACACAUAAUUCCCAGA
1068	AUGGGGCAGAACACAUAAUUCCCAG
1069	GAUGGGGCAGAACACAUAAUUCCCA
1070	UGAUGGGGCAGAACACAUAAUUCCC
1071	GUGAUGGGGCAGAACACAUAAUUCC
1072	AGUGAUGGGGCAGAACACAUAAUUC
1073	GAGUGAUGGGGCAGAACACAUAAUU
1074	AGAGUGAUGGGGCAGAACACAUAAU
1075	GAGAGUGAUGGGGCAGAACACAUAA
1076	AGAGAGUGAUGGGGCAGAACACAUA
1077	GAGAGAGUGAUGGGGCAGAACACAU
1078	AGAGAGAGUGAUGGGGCAGAACACA
1079	AAGAGAGAGUGAUGGGGCAGAACAC
1080	UAAGAGAGAGUGAUGGGGCAGAACA
1081	UUAAGAGAGAGUGAUGGGGCAGAAC
1082	AUUAAGAGAGAGUGAUGGGGCAGAA
1083	AAUUAAGAGAGAGUGAUGGGGCAGA
1084	CAAUUAAGAGAGAGUGAUGGGGCAG
1085	CCAAUUAAGAGAGAGUGAUGGGGCA
1086	UCCAAUUAAGAGAGAGUGAUGGGGC
1087	AUCCAAUUAAGAGAGAGUGAUGGGG

1088	AAUCCAAUUAAGAGAGAGUGAUGGG
1089	AAAUCCAAUUAAGAGAGAGUGAUGG
1090	AAAAUCCAAUUAAGAGAGAGUGAUG
1091	AAAAAUCCAAUUAAGAGAGAGUGAU
1092	UAAAAAUCCAAUUAAGAGAGAGUGA
1093	UUAAAAAUCCAAUUAAGAGAGAGUG
1094	UUUAAAAAUCCAAUUAAGAGAGAGU
1095	UUUUAAAAAUCCAAUUAAGAGAGAG
1096	AUUUUAAAAAUCCAAUUAAGAGAGA
1097	AAUUUUAAAAAUCCAAUUAAGAGAG
1098	UAAUUUUAAAAAUCCAAUUAAGAGA
1099	AUAAUUUUAAAAAUCCAAUUAAGAG
1100	UAUAAUUUUAAAAAUCCAAUUAAGA
1101	AUAUAAUUUUAAAAAUCCAAUUAAG
1102	AAUAUAAUUUUAAAAAUCCAAUUAA
1103	GAAUAUAAUUUUAAAAAUCCAAUUA
1104	UGAAUAUAAUUUUAAAAAUCCAAUU
1105	AUGAAUAUAAUUUUAAAAAUCCAAU
1106	UAUGAAUAUAAUUUUAAAAAUCCAA
1107	AUAUGAAUAUAAUUUUAAAAAUCCA
1108	AAUAUGAAUAUAAUUUUAAAAAUCC
1109	CAAUAUGAAUAUAAUUUUAAAAAUC
1110	GCAAUAUGAAUAUAAUUUUAAAAAU
1111	UGCAAUAUGAAUAUAAUUUUAAAAA
1112	CUGCAAUAUGAAUAUAAUUUUAAAA
1113	CCUGCAAUAUGAAUAUAAUUUUAAA
1114	UCCUGCAAUAUGAAUAUAAUUUUAA
1115	GUCCUGCAAUAUGAAUAUAAUUUUA
1116	AGUCCUGCAAUAUGAAUAUAAUUUU
1117	GAGUCCUGCAAUAUGAAUAUAAUUU
1118	CGAGUCCUGCAAUAUGAAUAUAAUU
1119	CCGAGUCCUGCAAUAUGAAUAUAAU
1120	GCCGAGUCCUGCAAUAUGAAUAUAA
1121	UGCCGAGUCCUGCAAUAUGAAUAUA
1122	CUGCCGAGUCCUGCAAUAUGAAUAU
1123	UCUGCCGAGUCCUGCAAUAUGAAUA
1124	UUCUGCCGAGUCCUGCAAUAUGAAU
1125	CUUCUGCCGAGUCCUGCAAUAUGAA
1126	UCUUCUGCCGAGUCCUGCAAUAUGA
1127	GUCUUCUGCCGAGUCCUGCAAUAUG
1128	GGUCUUCUGCCGAGUCCUGCAAUAU
1129	AGGUCUUCUGCCGAGUCCUGCAAUA

1130	AAGGUCUUCUGCCGAGUCCUGCAAU
1131	GAAGGUCUUCUGCCGAGUCCUGCAA
1132	CGAAGGUCUUCUGCCGAGUCCUGCA
1133	UCGAAGGUCUUCUGCCGAGUCCUGC
1134	CUCGAAGGUCUUCUGCCGAGUCCUG
1135	UCUCGAAGGUCUUCUGCCGAGUCCU
1136	CUCUCGAAGGUCUUCUGCCGAGUCC
1137	UCUCUCGAAGGUCUUCUGCCGAGUC
1138	UUCUCUCGAAGGUCUUCUGCCGAGU
1139	UUUCUCUCGAAGGUCUUCUGCCGAG
1140	CUUUCUCUCGAAGGUCUUCUGCCGA
1141	CCUUUCUCUCGAAGGUCUUCUGCCG
1142	ACCUUUCUCUCGAAGGUCUUCUGCC
1143	UACCUUUCUCUCGAAGGUCUUCUGC
1144	CUACCUUUCUCUCGAAGGUCUUCUG
1145	UCUACCUUUCUCUCGAAGGUCUUCU
1146	UUCUACCUUUCUCUCGAAGGUCUUC
1147	UUUCUACCUUUCUCUCGAAGGUCUU
1148	UUUUCUACCUUUCUCUCGAAGGUCU
1149	AUUUUCUACCUUUCUCUCGAAGGUC
1150	UAUUUUCUACCUUUCUCUCGAAGGU
1151	UUAUUUUCUACCUUUCUCUCGAAGG
1152	CUUAUUUUCUACCUUUCUCUCGAAG
1153	UCUUAUUUUCUACCUUUCUCUCGAA
1154	UUCUUAUUUUCUACCUUUCUCUCGA
1155	AUUCUUAUUUUCUACCUUUCUCUCG
1156	AAUUCUUAUUUUCUACCUUUCUCUC
1157	AAAUUCUUAUUUUCUACCUUUCUCU
1158	CAAAUUCUUAUUUUCUACCUUUCUC
1159	CCAAAUUCUUAUUUUCUACCUUUCU
1160	GCCAAAUUCUUAUUUUCUACCUUUC
1161	AGCCAAAUUCUUAUUUUCUACCUUU
1162	GAGCCAAAUUCUUAUUUUCUACCUU
1163	AGAGCCAAAUUCUUAUUUUCUACCU
1164	GAGAGCCAAAUUCUUAUUUUCUACC
1165	AGAGAGCCAAAUUCUUAUUUUCUAC
1166	CAGAGAGCCAAAUUCUUAUUUUCUA
1167	ACAGAGAGCCAAAUUCUUAUUUUCU
1168	CACAGAGAGCCAAAUUCUUAUUUUC
1169	ACACAGAGAGCCAAAUUCUUAUUUU
1170	CACACAGAGAGCCAAAUUCUUAUUU
1171	UCACACAGAGAGCCAAAUUCUUAUU

1172	CUCACACAGAGAGCCAAAUUCUUAU
1173	GCUCACACAGAGAGCCAAAUUCUUA
1174	UGCUCACACAGAGAGCCAAAUUCUU
1175	AUGCUCACACAGAGAGCCAAAUUCU
1176	CAUGCUCACACAGAGAGCCAAAUUC
1177	ACAUGCUCACACAGAGAGCCAAAUU
1178	CACAUGCUCACACAGAGAGCCAAAU
1179	ACACAUGCUCACACAGAGAGCCAAA
1180	CACACAUGCUCACACAGAGAGCCAA
1181	GCACACAUGCUCACACAGAGAGCCA
1182	CGCACACAUGCUCACACAGAGAGCC
1183	ACGCACACAUGCUCACACAGAGAGC
1184	CACGCACACAUGCUCACACAGAGAG
1185	ACACGCACACAUGCUCACACAGAGA
1186	CACACGCACACAUGCUCACACAGAG
1187	ACACACGCACACAUGCUCACACAGA
1188	CACACACGCACACAUGCUCACACAG
1189	GCACACACGCACACAUGCUCACACA
1190	CGCACACACGCACACAUGCUCACAC
1191	UCGCACACACGCACACAUGCUCACA
1192	CUCGCACACACGCACACAUGCUCAC
1193	UCUCGCACACACGCACACAUGCUCA
1194	CUCUCGCACACACGCACACAUGCUC
1195	UCUCUCGCACACACGCACACAUGCU
1196	CUCUCUCGCACACACGCACACAUGC
1197	UCUCUCUCGCACACACGCACACAUG
1198	CUCUCUCUCGCACACACGCACACAU
1199	UCUCUCUCUCGCACACACGCACACA
1200	CUCUCUCUCUCGCACACACGCACAC
1201	UCUCUCUCUCUCGCACACACGCACA
1202	GUCUCUCUCUCUCGCACACACGCAC
1203	UGUCUCUCUCUCUCGCACACACGCA
1204	CUGUCUCUCUCUCUCGCACACACGC
1205	UCUGUCUCUCUCUCUCGCACACACG
1206	GUCUGUCUCUCUCUCUCGCACACAC
1207	UGUCUGUCUCUCUCUCUCGCACACA
1208	CUGUCUGUCUCUCUCUCUCGCACAC
1209	GCUGUCUGUCUCUCUCUCUCGCACA
1210	GGCUGUCUGUCUCUCUCUCUCGCAC
1211	AGGCUGUCUGUCUCUCUCUCUCGCA
1212	CAGGCUGUCUGUCUCUCUCUCUCGC
1213	GCAGGCUGUCUGUCUCUCUCUCUCG

1214	GGCAGGCUGUCUGUCUCUCUCUCUC
1215	AGGCAGGCUGUCUGUCUCUCUCUCU
1216	UAGGCAGGCUGUCUGUCUCUCUCUC
1217	UUAGGCAGGCUGUCUGUCUCUCUCU
1218	CUUAGGCAGGCUGUCUGUCUCUCUC
1219	UCUUAGGCAGGCUGUCUGUCUCUCU
1220	UUCUUAGGCAGGCUGUCUGUCUCUC
1221	CUUCUUAGGCAGGCUGUCUGUCUCU
1222	UCUUCUUAGGCAGGCUGUCUGUCUC
1223	UUCUUCUUAGGCAGGCUGUCUGUCU
1224	UUUCUUCUUAGGCAGGCUGUCUGUC
1225	AUUUCUUCUUAGGCAGGCUGUCUGU
1226	CAUUUCUUCUUAGGCAGGCUGUCUG
1227	UCAUUUCUUCUUAGGCAGGCUGUCU
1228	UUCAUUUCUUCUUAGGCAGGCUGUC
1229	AUUCAUUUCUUCUUAGGCAGGCUGU
1230	CAUUCAUUUCUUCUUAGGCAGGCUG
1231	ACAUUCAUUUCUUCUUAGGCAGGCU
1232	CACAUUCAUUUCUUCUUAGGCAGGC
1233	UCACAUUCAUUUCUUCUUAGGCAGG
1234	UUCACAUUCAUUUCUUCUUAGGCAG
1235	AUUCACAUUCAUUUCUUCUUAGGCA
1236	CAUUCACAUUCAUUUCUUCUUAGGC
1237	GCAUUCACAUUCAUUUCUUCUUAGG
1238	CGCAUUCACAUUCAUUUCUUCUUAG
1239	CCGCAUUCACAUUCAUUUCUUCUUA
1240	GCCGCAUUCACAUUCAUUUCUUCUU
1241	AGCCGCAUUCACAUUCAUUUCUUCU
1242	AAGCCGCAUUCACAUUCAUUUCUUC
1243	CAAGCCGCAUUCACAUUCAUUUCUU
1244	ACAAGCCGCAUUCACAUUCAUUUCU
1245	CACAAGCCGCAUUCACAUUCAUUUC
1246	CCACAAGCCGCAUUCACAUUCAUUU
1247	GCCACAAGCCGCAUUCACAUUCAUU
1248	UGCCACAAGCCGCAUUCACAUUCAU
1249	GUGCCACAAGCCGCAUUCACAUUCA
1250	UGUGCCACAAGCCGCAUUCACAUUC
1251	CUGUGCCACAAGCCGCAUUCACAUU
1252	ACUGUGCCACAAGCCGCAUUCACAU
1253	AACUGUGCCACAAGCCGCAUUCACA
1254	CAACUGUGCCACAAGCCGCAUUCAC
1255	UCAACUGUGCCACAAGCCGCAUUCA

1256	GUCAACUGUGCCACAAGCCGCAUUC
1257	UGUCAACUGUGCCACAAGCCGCAUU
1258	UUGUCAACUGUGCCACAAGCCGCAU
1259	CUUGUCAACUGUGCCACAAGCCGCA
1260	CCUUGUCAACUGUGCCACAAGCCGC
1261	UCCUUGUCAACUGUGCCACAAGCCG
1262	AUCCUUGUCAACUGUGCCACAAGCC
1263	CAUCCUUGUCAACUGUGCCACAAGC
1264	UCAUCCUUGUCAACUGUGCCACAAG
1265	AUCAUCCUUGUCAACUGUGCCACAA
1266	UAUCAUCCUUGUCAACUGUGCCACA
1267	UUAUCAUCCUUGUCAACUGUGCCAC
1268	UUUAUCAUCCUUGUCAACUGUGCCA
1269	AUUUAUCAUCCUUGUCAACUGUGCC
1270	GAUUUAUCAUCCUUGUCAACUGUGC
1271	UGAUUUAUCAUCCUUGUCAACUGUG
1272	UUGAUUUAUCAUCCUUGUCAACUGU
1273	AUUGAUUUAUCAUCCUUGUCAACUG
1274	UAUUGAUUUAUCAUCCUUGUCAACU
1275	UUAUUGAUUUAUCAUCCUUGUCAAC
1276	AUUAUUGAUUUAUCAUCCUUGUCAA
1277	CAUUAUUGAUUUAUCAUCCUUGUCA
1278	GCAUUAUUGAUUUAUCAUCCUUGUC
1279	UGCAUUAUUGAUUUAUCAUCCUUGU
1280	UUGCAUUAUUGAUUUAUCAUCCUUG
1281	CUUGCAUUAUUGAUUUAUCAUCCUU
1282	GCUUGCAUUAUUGAUUUAUCAUCCU
1283	AGCUUGCAUUAUUGAUUUAUCAUCC
1284	AAGCUUGCAUUAUUGAUUUAUCAUC
1285	UAAGCUUGCAUUAUUGAUUUAUCAU
1286	GUAAGCUUGCAUUAUUGAUUUAUCA
1287	AGUAAGCUUGCAUUAUUGAUUUAUC
1288	UAGUAAGCUUGCAUUAUUGAUUUAU
1289	AUAGUAAGCUUGCAUUAUUGAUUUA
1290	GAUAGUAAGCUUGCAUUAUUGAUUU
1291	UGAUAGUAAGCUUGCAUUAUUGAUU
1292	AUGAUAGUAAGCUUGCAUUAUUGAU
1293	AAUGAUAGUAAGCUUGCAUUAUUGA
1294	AAAUGAUAGUAAGCUUGCAUUAUUG
1295	UAAAUGAUAGUAAGCUUGCAUUAUU
1296	AUAAAUGAUAGUAAGCUUGCAUUAU
1297	CAUAAAUGAUAGUAAGCUUGCAUUA

1298	UCAUAAAUGAUAGUAAGCUUGCAUU
1299	UUCAUAAAUGAUAGUAAGCUUGCAU
1300	AUUCAUAAAUGAUAGUAAGCUUGCA
1301	UAUUCAUAAAUGAUAGUAAGCUUGC
1302	CUAUUCAUAAAUGAUAGUAAGCUUG
1303	GCUAUUCAUAAAUGAUAGUAAGCUU
1304	UGCUAUUCAUAAAUGAUAGUAAGCU
1305	UUGCUAUUCAUAAAUGAUAGUAAGC
1306	AUUGCUAUUCAUAAAUGAUAGUAAG
1307	UAUUGCUAUUCAUAAAUGAUAGUAA
1308	GUAUUGCUAUUCAUAAAUGAUAGUA
1309	AGUAUUGCUAUUCAUAAAUGAUAGU
1310	CAGUAUUGCUAUUCAUAAAUGAUAG
1311	UCAGUAUUGCUAUUCAUAAAUGAUA
1312	UUCAGUAUUGCUAUUCAUAAAUGAU
1313	CUUCAGUAUUGCUAUUCAUAAAUGA
1314	UCUUCAGUAUUGCUAUUCAUAAAUG
1315	UUCUUCAGUAUUGCUAUUCAUAAAU
1316	UUUCUUCAGUAUUGCUAUUCAUAAA
1317	AUUUCUUCAGUAUUGCUAUUCAUAA
1318	AAUUUCUUCAGUAUUGCUAUUCAUA
1319	UAAUUUCUUCAGUAUUGCUAUUCAU
1320	UUAAUUUCUUCAGUAUUGCUAUUCA
1321	UUUAAUUUCUUCAGUAUUGCUAUUC
1322	UUUUAAUUUCUUCAGUAUUGCUAUU
1323	GUUUUAAUUUCUUCAGUAUUGCUAU
1324	UGUUUUAAUUUCUUCAGUAUUGCUA
1325	UUGUUUUAAUUUCUUCAGUAUUGCU
1326	UUUGUUUUAAUUUCUUCAGUAUUGC
1327	UUUUGUUUUAAUUUCUUCAGUAUUG
1328	CUUUUGUUUUAAUUUCUUCAGUAUU
1329	UCUUUUGUUUUAAUUUCUUCAGUAU
1330	AUCUUUUGUUUUAAUUUCUUCAGUA
1331	AAUCUUUUGUUUUAAUUUCUUCAGU
1332	CAAUCUUUUGUUUUAAUUUCUUCAG
1333	GCAAUCUUUUGUUUUAAUUUCUUCA
1334	AGCAAUCUUUUGUUUUAAUUUCUUC
1335	CAGCAAUCUUUUGUUUUAAUUUCUU
1336	ACAGCAAUCUUUUGUUUUAAUUUCU
1337	GACAGCAAUCUUUUGUUUUAAUUUC
1338	AGACAGCAAUCUUUUGUUUUAAUUU
1339	GAGACAGCAAUCUUUUGUUUUAAUU

1340	UGAGACAGCAAUCUUUUGUUUUAAU
1341	UUGAGACAGCAAUCUUUUGUUUUAA
1342	AUUGAGACAGCAAUCUUUUGUUUUA
1343	UAUUGAGACAGCAAUCUUUUGUUUU
1344	AUAUUGAGACAGCAAUCUUUUGUUU
1345	UAUAUUGAGACAGCAAUCUUUUGUU
1346	AUAUAUUGAGACAGCAAUCUUUUGU
1347	GAUAUAUUGAGACAGCAAUCUUUUG
1348	AGAUAUAUUGAGACAGCAAUCUUUU
1349	AAGAUAUAUUGAGACAGCAAUCUUU
1350	UAAGAUAUAUUGAGACAGCAAUCUU
1351	AUAAGAUAUAUUGAGACAGCAAUCU
1352	UAUAAGAUAUAUUGAGACAGCAAUC
1353	AUAUAAGAUAUAUUGAGACAGCAAU
1354	AAUAUAAGAUAUAUUGAGACAGCAA
1355	AAAUAUAAGAUAUAUUGAGACAGCA
1356	UAAAUAUAAGAUAUAUUGAGACAGC
1357	AUAAAUAUAAGAUAUAUUGAGACAG
1358	AAUAAAUAUAAGAUAUAUUGAGACA
1359	UAAUAAAUAUAAGAUAUAUUGAGAC
1360	AUAAUAAAUAUAAGAUAUAUUGAGA
1361	AAUAAUAAAUAUAAGAUAUAUUGAG
1362	AAAUAAUAAAUAUAAGAUAUAUUGA
1363	UAAAUAAUAAAUAUAAGAUAUAUUG
1364	GUAAAUAAUAAAUAUAAGAUAUAUU
1365	GGUAAAUAAUAAAUAUAAGAUAUAU
1366	UGGUAAAUAAUAAAUAUAAGAUAUA
1367	UUGGUAAAUAAUAAAUAUAAGAUAU
1368	UUUGGUAAAUAAUAAAUAUAAGAUA
1369	AUUUGGUAAAUAAUAAAUAUAAGAU
1370	AAUUUGGUAAAUAAUAAAUAUAAGA
1371	UAAUUUGGUAAAUAAUAAAUAUAAG
1372	AUAAUUUGGUAAAUAAUAAAUAUAA
1373	AAUAAUUUGGUAAAUAAUAAAUAUA
1374	GAAUAAUUUGGUAAAUAAUAAAUAU
1375	AGAAUAAUUUGGUAAAUAAUAAAUA
1376	UAGAAUAAUUUGGUAAAUAAUAAAU
1377	UUAGAAUAAUUUGGUAAAUAAUAAA
1378	CUUAGAAUAAUUUGGUAAAUAAUAA
1379	UCUUAGAAUAAUUUGGUAAAUAAUA
1380	CUCUUAGAAUAAUUUGGUAAAUAAU
1381	ACUCUUAGAAUAAUUUGGUAAAUAA

1382	UACUCUUAGAAUAAUUUGGUAAAUA
1383	AUACUCUUAGAAUAAUUUGGUAAAU
1384	AAUACUCUUAGAAUAAUUUGGUAAA
1385	AAAUACUCUUAGAAUAAUUUGGUAA
1386	GAAAUACUCUUAGAAUAAUUUGGUA
1387	AGAAAUACUCUUAGAAUAAUUUGGU
1388	AAGAAAUACUCUUAGAAUAAUUUGG
1389	GAAGAAAUACUCUUAGAAUAAUUUG
1390	GGAAGAAAUACUCUUAGAAUAAUUU

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothiate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00191] Table 3 below identifies exemplary STMN2 AON sequences:

Table 3. Exemplary STMN2 AON Sequences

SEQ ID NO: (legacy ID*)	Oligonucleotide sequence (5'→3')
SEQ ID NO: 31 (QSN-31)	AATGTTAAGACATAATACCAGAGCT
SEQ ID NO: 36 (QSN-36)	TTAAAAATGTTAAGACATAATACCA
SEQ ID NO: 41 (QSN-41)	TAGATTTAAAAATGTTAAGACATAA
SEQ ID NO: 46 (QSN-46)	TACCATAGATTTAAAAATGTTAAGA
SEQ ID NO: 55 (QSN-55)	TGTAAAGATTACCATAGATTTAAAA
SEQ ID NO: 144 (QSN-144)	AATCCAATTAAGAGAGAGTGATGGG
SEQ ID NO: 146 (QSN-146)	AAAATCCAATTAAGAGAGAGTGATG
SEQ ID NO: 150 (QSN-150)	TTTAAAAATCCAATTAAGAGAGAGT

SEQ ID NO: 169 (QSN-169)	CCTGCAATATGAATATAATTTTAAA
SEQ ID NO: 170 (QSN-170)	TCCTGCAATATGAATATAATTTTAA
SEQ ID NO: 171 (QSN-171)	GTCCTGCAATATGAATATAATTTTA
SEQ ID NO: 172 (QSN-172)	AGTCCTGCAATATGAATATAATTTT
SEQ ID NO: 173 (QSN-173)	GAGTCCTGCAATATGAATATAATTT
SEQ ID NO: 177 (QSN-177)	TGCCGAGTCCTGCAATATGAATATA
SEQ ID NO: 181 (QSN-181)	CTTCTGCCGAGTCCTGCAATATGAA
SEQ ID NO: 185 (QSN-185)	AGGTCTTCTGCCGAGTCCTGCAATA
SEQ ID NO: 197 (QSN-197)	CCTTTCTCTCGAAGGTCTTCTGCCG
SEQ ID NO: 203 (QSN-203)	TTTCTACCTTTCTCTCGAAGGTCTT
SEQ ID NO: 209 (QSN-209)	TCTTATTTTCTACCTTTCTCTCGAA
SEQ ID NO: 215 (QSN-215)	CCAAATTCTTATTTTCTACCTTTCT
SEQ ID NO: 237 (QSN-237)	GCACACATGCTCACACAGAGAGCCA
SEQ ID NO: 244 (QSN-244)	CACACACGCACACATGCTCACACAG
SEQ ID NO: 249 (QSN-249)	TCTCGCACACACGCACACATGCTCA
SEQ ID NO: 252 (QSN-252)	CTCTCTCGCACACACGCACACATGC
SEQ ID NO: 380 (QSN-380)	TGTTTTAATTTCTTCAGTATTGCTA
SEQ ID NO: 385 (QSN-385)	TCTTTTGTTTTAATTTCTTCAGTAT
SEQ ID NO: 390 (QSN-390)	AGCAATCTTTTGTTTTAATTTCTTC
SEQ ID NO: 395 (QSN-395)	GAGACAGCAATCTTTTGTTTTAATT
SEQ ID NO: 400 (QSN-400)	ATATTGAGACAGCAATCTTTTGTTT

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

[00192] In some embodiments, all internucleoside linkages of the STMN2 AON oligonucleotides listed in Table 3 are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and each "C" is replaced with a 5-MeC. For example, in some embodiments, all internucleoside linkages of the QSN-31 STMN2 AON (SEQ ID NO: 31) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-36 STMN2 AON (SEQ ID NO: 36) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-55 STMN2 AON (SEQ ID NO: 55) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-144 STMN2 AON (SEQ ID NO: 144) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-173 STMN2 AON (SEQ ID NO: 173) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-177 STMN2 AON (SEQ ID NO: 177) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-181 STMN2 AON (SEQ ID NO: 181) oligonucleotide are phosphorothioate linkages, and each of the

linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-185 STMN2 AON (SEQ ID NO: 185) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-197 STMN2 AON (SEQ ID NO: 197) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-203 STMN2 AON (SEQ ID NO: 203) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-209 STMN2 AON (SEQ ID NO: 209) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-215 STMN2 AON (SEQ ID NO: 215) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-237 STMN2 AON (SEQ ID NO: 237) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-244 STMN2 AON (SEQ ID NO: 244) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-252 STMN2 AON (SEQ ID NO: 252) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-380 STMN2 AON (SEQ ID NO: 380) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-385 STMN2 AON (SEQ ID NO: 385) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some

embodiments, all internucleoside linkages of the QSN-390 STMN2 AON (SEQ ID NO: 390) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-395 STMN2 AON (SEQ ID NO: 395) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-400 STMN2 AON (SEQ ID NO: 400) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-169 STMN2 AON (SEQ ID NO: 169) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-170 STMN2 AON (SEQ ID NO: 170) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-171 STMN2 AON (SEQ ID NO: 171) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-172 STMN2 AON (SEQ ID NO: 172) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-249 STMN2 AON (SEQ ID NO: 249) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC.

[00193] In some embodiments, all internucleoside linkages of the STMN2 AON oligonucleotides listed in Table 3 are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. For example, in some embodiments, all internucleoside linkages of the QSN-31 STMN2 AON (SEQ ID NO: 31) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In

some embodiments, all internucleoside linkages of the QSN-36 STMN2 AON (SEQ ID NO: 36) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-55 STMN2 AON (SEQ ID NO: 55) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-144 STMN2 AON (SEQ ID NO: 144) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-173 STMN2 AON (SEQ ID NO: 173) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-177 STMN2 AON (SEQ ID NO: 177) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-181 STMN2 AON (SEQ ID NO: 181) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-185 STMN2 AON (SEQ ID NO: 185) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-197 STMN2 AON (SEQ ID NO: 197) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-203 STMN2 AON (SEQ ID NO: 203) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-209 STMN2 AON (SEQ ID NO: 209) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-215 STMN2 AON (SEQ ID NO:

215) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-237 STMN2 AON (SEQ ID NO: 237) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-244 STMN2 AON (SEQ ID NO: 244) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-252 STMN2 AON (SEQ ID NO: 252) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-O-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-380 STMN2 AON (SEQ ID NO: 380) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-385 STMN2 AON (SEQ ID NO: 385) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-390 STMN2 AON (SEQ ID NO: 390) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-395 STMN2 AON (SEQ ID NO: 395) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-400 STMN2 AON (SEQ ID NO: 400) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-169 STMN2 AON (SEQ ID NO: 169) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-170 STMN2 AON (SEQ ID NO: 170) oligonucleotide are phosphorothioate

linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-171 STMN2 AON (SEQ ID NO: 171) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-172 STMN2 AON (SEQ ID NO: 172) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and none of the 'C" is replaced with 5-MeC. In some embodiments, all internucleoside linkages of the QSN-249 STMN2 AON (SEQ ID NO: 249) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and not all or none of the 'C" is replaced with 5-MeC.

[00194] Table 4 below identifies additional exemplary STMN2 AON sequences:

Table 4. Additional Exemplary STMN2 AON Sequences

SEQ ID NO:	Oligonucleotide sequence (5'→3')
SEQ ID NO: 975	AAUGUUAAGACAUAAUACCAGAGCU
SEQ ID NO: 980	UUAAAAAUGUUAAGACAUAAUACCA
SEQ ID NO: 985	UAGAUUUAAAAAUGUUAAGACAUAA
SEQ ID NO: 990	UACCAUAGAUUUAAAAAUGUUAAGA
SEQ ID NO: 999	UGUAAAGAUUACCAUAGAUUUAAAA
SEQ ID NO: 1088	AAUCCAAUUAAGAGAGAGUGAUGGG
SEQ ID NO: 1090	AAAAUCCAAUUAAGAGAGAGUGAUG
SEQ ID NO: 1094	UUUAAAAAUCCAAUUAAGAGAGAGU
SEQ ID NO: 1113	CCUGCAAUAUGAAUAUAAUUUUAAA
SEQ ID NO: 1114	UCCUGCAAUAUGAAUAUAAUUUUAA
SEQ ID NO: 1115	GUCCUGCAAUAUGAAUAUAAUUUUA
SEQ ID NO: 1116	AGUCCUGCAAUAUGAAUAUAAUUUU
SEQ ID NO: 1117	GAGUCCUGCAAUAUGAAUAUAAUUU
SEQ ID NO: 1121	UGCCGAGUCCUGCAAUAUGAAUAUA
SEQ ID NO: 1125	CUUCUGCCGAGUCCUGCAAUAUGAA
SEQ ID NO: 1129	AGGUCUUCUGCCGAGUCCUGCAAUA
SEQ ID NO: 1141	CCUUUCUCUCGAAGGUCUUCUGCCG
SEQ ID NO: 1147	UUUCUACCUUUCUCUCGAAGGUCUU
SEQ ID NO: 1153	UCUUAUUUUCUACCUUUCUCUCGAA
SEQ ID NO: 1159	CCAAAUUCUUAUUUUCUACCUUUCU
SEQ ID NO: 1181	GCACACAUGCUCACACAGAGAGCCA
SEQ ID NO: 1188	CACACACGCACACAUGCUCACACAG

SEQ ID NO: 1193	UCUCGCACACACGCACACAUGCUCA
SEQ ID NO: 1196	CUCUCUCGCACACACGCACACAUGC
SEQ ID NO: 1324	UGUUUUAAUUUCUUCAGUAUUGCUA
SEQ ID NO: 1329	UCUUUUGUUUUAAUUUCUUCAGUAU
SEQ ID NO: 1334	AGCAAUCUUUUGUUUUAAUUUCUUC
SEQ ID NO: 1339	GAGACAGCAAUCUUUUGUUUUAAUU
SEQ ID NO: 1344	AUAUUGAGACAGCAAUCUUUUGUUU

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

Full Length STMN2 Transcript

[00195] As described herein, the disclosure provides a method of restoring full length STMN2 transcript expression in a cell, where the method includes exposing the cell to an inhibitor of STMN2 transcripts that include a cryptic exon or contacting the cell with an inhibitor of STMN2 transcripts that include a cryptic exon. Such an inhibitor can sterically block splice machinery, sterically mimic TDP43 binding, and/or repress premature polyadenylation of STMN2 pre-mRNA, and increase, restore, and/or stabilize levels of full length STMN2 transcript.

[00196] In various embodiments, the full length STMN2 transcript comprises a sequence with accession number NM_001199214.2, identified below as SEQ ID NO: 1433.

A TGGCTAAAAC AGCAATGGCC TACAAGGAAA AAATGAAGGA GCTGTCCATG
CTGTCACTGA TCTGCTCTTG CTTTTACCCG GAACCTCGCA ACATCAACAT
CTATACTTAC GATGATATGG AAGTGAAGCA AATCAACAAA CGTGCCTCTG
GCCAGGCTTT TGAGCTGATC TTGAAGCCAC CATCTCCTAT CTCAGAAGCC
CCACGAACTT TAGCTTCTCC AAAGAAGAAA GACCTGTCCC TGGAGGAGAT
CCAGAAGAAA CTGGAGGCTG CAGAGGAAAG AAGAAAGTCT CAGGAGGCCC
AGGTGCTGAA ACAATTGGCA GAGAAGAGGG AACACGAGCG AGAAGTCCTT

CAGAAGGCTT TGGAGGAGAA CAACAACTTC AGCAAGATGG CGGAGGAAAA GCTGATCCTG AAAATGGAAC AAATTAAGGA AAACCGTGAG GCTAATCTAG CTGCTATTAT TGAACGTCTG CAGGAAAAGC TGGTCAAGTT TATTTCTTCT GAACTAAAAG AATCTATAGA GTCTCAATTT CTGGAGCTTC AGAGGGAAGG AGAGAAGCAA TGA

(SEQ ID NO: 1433)

[00197] In various embodiments, the full length STMN2 protein comprises an amino acid sequence with accession number NP_001186143.1, identified below as SEQ ID NO: 1434.

MAKTAMAYKE KMKELSMLSL ICSCFYPEPR NINIYTYDDM EVKQINKRAS GQAFELILKP PSPISEAPRT LASPKKKDLS LEEIQKKLEA AEERRKSQEA QVLKQLAEKR EHEREVLQKA LEENNNFSKM AEEKLILKME QIKENREANL AAIIERLQEK LVKFISSELK ESIESQFLEL QREGEKQ

(SEQ ID NO: 1434)

[00198] In various embodiments, the full length STMN2 transcript comprises a sequence with accession number NM_007029.4, identified below as SEQ ID NO: 1435.

A TGGCTAAAAC AGCAATGGCC TACAAGGAAA AAATGAAGGA GCTGTCCATG CTGTCACTGA TCTGCTCTTG CTTTTACCCG GAACCTCGCA ACATCAACAT CTATACTTAC GATGATATGG AAGTGAAGCA AATCAACAAA CGTGCCTCTG GCCAGGCTTT TGAGCTGATC TTGAAGCCAC CATCTCCTAT CTCAGAAGCC CCACGAACTT TAGCTTCTCC AAAGAAGAAA GACCTGTCCC TGGAGGAGAT CCAGAAGAAA CTGGAGGCTG CAGAGGAAAG AAGAAAGTCT CAGGAGGCCC AGGTGCTGAA ACAATTGGCA GAGAAGAGGG AACACGAGCG AGAAGTCCTT CAGAAGGCTT TGGAGGAGAA CAACAACTTC AGCAAGATGG CGGAGGAAAA GCTGATCCTG AAAATGGAAC AAATTAAGGA AAACCGTGAG GCTAATCTAG CTGCTATTAT TGAACGTCTG CAGGAAAAGG AGAGGCATGC TGCGGAGGTG CGCAGGAACA AGGAACTCCA GGTTGAACTG TCTGGCTGA

(SEQ ID NO: 1435)

[00199] In various embodiments, the full length STMN2 protein comprises an amino acid sequence with accession number NP_008960.2, identified below as SEQ ID NO: 1436.

MAKTAMAYKE KMKELSMLSL ICSCFYPEPR NINIYTYDDM EVKQINKRAS GQAFELILKP PSPISEAPRT LASPKKKDLS LEEIQKKLEA AEERRKSQEA QVLKQLAEKR EHEREVLQKA LEENNNFSKM AEEKLILKME QIKENREANL AAIIERLQEK ERHAAEVRRN KELQVELSG

(SEQ ID NO: 1436)

[00200] In various embodiments, the full length STMN2 transcript comprises a sequence with accession number XM_005251142.2, identified below as SEQ ID NO: 1437.

ATGGCCTAC AAGGAAAAAA TGAAGGAGCT GTCCATGCTG TCACTGATCT GCTCTTGCTT TTACCCGGAA CCTCGCAACA TCAACATCTA TACTTACGAT GATATGGAAG TGAAGCAAAT CAACAAACGT GCCTCTGGCC AGGCTTTTGA GCTGATCTTG AAGCCACCAT CTCCTATCTC AGAAGCCCCA CGAACTTTAG CTTCTCCAAA GAAGAAAGAC CTGTCCCTGG AGGAGATCCA GAAGAAACTG GAGGCTGCAG AGGAAAGAAG AAAGTCTCAG GAGGCCCAGG TGCTGAAACA ATTGGCAGAG AAGAGGGAAC ACGAGCGAGA AGTCCTTCAG AAGGCTTTGG AGGAGAACAA CAACTTCAGC AAGATGGCGG AGGAAAAGCT GATCCTGAAA ATGGAACAAA TTAAGGAAAA CCGTGAGGCT AATCTAGCTG CTATTATTGA ACGTCTGCAG GAAAAGGAGA GGCATGCTGC GGAGGTGCGC AGGAACAAGG AACTCCAGGT TGAACTGTCT GGCTGA

(SEQ ID NO: 1437)

[00201] In various embodiments, the full length STMN2 protein comprises an amino acid sequence with accession number XP_005251199, identified below as SEQ ID NO: 1438.

MAYKEKMKEL SMLSLICSCF YPEPRNINIY TYDDMEVKQI NKRASGQAFE LILKPPSPIS EAPRTLASPK KKDLSLEEIQ KKLEAAEERR KSQEAQVLKQ LAEKREHERE VLQKALEENN NFSKMAEEKL ILKMEQIKEN REANLAAIIE RLQEKERHAA EVRRNKELQV ELSG

(SEQ ID NO: 1438)

STMN2 Transcript with a Cryptic Exon

[00202] In one embodiment, a STMN2 transcript with a cryptic exon can comprise the sequence provided as SEQ ID NO: 944.

ACTTGTAATATACAGGTATCCCTCCTGGTAAGCTCTGGTATTATGTCTTAACATTTTTA
AATCTATGGTAATCTTTACAAAATATTTTACTTCCGAACTCATATACCTGGGGATTTT
ATTACTCTGGGAATTATGTGTTCTGCCCCATCACTCTCTCTTAATTGGATTTTTAAAAT
TATATTCATATTGCAGGACTCGGCAGAAGACCTTCGAGAGAAAGGTAGAAAATAAGA
ATTTGGCTCTCTGTGTGAGCATGTGTGCGTGTGTGCGAGAGAGAGAGACAGACAGCC
TGCCTAAGAAGAAATGAATGTGAATGCGGCTTGTGGCACAGTTGACAAGGATGATAA
ATCAATAATGCAAGCTTACTATCATTTATGAATAGCAATACTGAAGAAATTAAAACA
AAAGATTGCTGTCTCAATATATCTTATATTTATTATTTACCAAATTATTCTAAGAGTAT
TTCTTCC

(SEQ ID NO: 944)

[00203] In one embodiment, a STMN2 transcript with a cryptic exon can comprise a pre-mRNA STMN2 transcript. In one embodiment, a STMN2 transcript with a cryptic exon can comprise the sequence provided as SEQ ID NO: 1391.

AGCTCCTAGGAAGCTTCAGGGCTTAAAGCTCCACTCTACTTGGACTGTACTATCAGGC
CCCCAAAATGGGGGGAGCCGACAGGGAAGGACTGATTTCCATTTCAAACTGCATTCT
GGTACTTTGTACTCCAGCACCATTGGCCGATCAATATTTAATGCTTGGAGATTCTGAC
TCTGCGGGAGTCATGTCAGGGGACCTTGGGAGCCAATCTGCTTGAGCTTCTGAGTGA
TAATTATTCATGGGCTCCTGCCTCTTGCTCTTTCTCTAGCACGGTCCCACTCTGCAGAC
TCAGTGCCTTATTCAGTCTTCTCTCTCGCTCTCTCCGCTGCTGTAGCCGGACCCTTTGC
CTTCGCCACTGCTCAGCGTCTGCACATCCCTACAATGGCTAAAACAGCAATGGTAAG
GCACTGCGCCTCGTTCTCCGTCGGCTCTACCTGGAGCCCACCTCTCACCTCCTCTCTTG
AGCTCTAGAAGCATTCAGAGATATTTTATAAAGAAAAAGATGTTAATGGTAACACAG
GACCAGGAAGGACAGGGCAGTTCTGGGGGAGGTGGGAGGGCAGAGAAGAGGTCTAT
GGAAATCTAAAGCGAAGAATTTCTTTTAAAAGGTAGAAGCGGGTAAGTTGCCCTCCT
ATGGGTAGAGAATTTATTCTGTTTCCATATTTAAAATTAGGACTCAATCGTGAGGGGA
GGAAGCTACCTTAACTGTTTGCCTTAAATGGGCTTAAGGGACATTTTGGAAAGTGCTT
TATAACGACCTTTTTTTTTTTTATTTCTTCTCTAGTTTAAGAAGAAAATAGGAAAGGG
GTAAAGGGAAGGTGGGAGAAAGGAAAAAGAAAATTGCAAAGTCAAAGCGGTCCCAT
CCCGCTGTTTGAAAGATGGGTGGAGACGGGGGGAGGGGATGGAGAGAACTGGGCAC
ATTTTACGGTATTGTCTCGTCGAAGAAACCGCTAGTCCTGGGGTGCGGTGCAGGGAG
GTAAGACGGCGGGGGACAGGGTGGGGGTAGGACCTCCGCTCCTTTGTTTTAGGGCAA
GGGAGGGGAAGGAGAGAGGAAGTCGCGGAGGGCGTGGAGGGCGCGGGTGGGCAGC
TGCAGGGGCGGGGAAGCGCGCGGCAGGGAGGGGTGGAGGGACAGCGGCTTCGAAG
GCGCTGGGGTGGGGTTTCTTTGTGTGCGGACCAGCGGTCCCGGGGGGAGGCACCTGC
AGCGCTGGGCGCACAATGCGGACAGCCCCACCCAGTGCGGAACCGCGCAGCCCCGC
CCCCCCGCCCGGTGCTGCATCTTCATTCGAAAGGGGGTCGGGTGGGGAGCGCAGCGT
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CACACAACTCACTCCTGACCCCTTTTTTATATTGCAAGTGCATAGTCATTAGTAAAAA
GAAGGATTTTTGATGATACTGACCTCATCTTGAATTTAATTAGGCTCATATGACAGAA
TTCCATAGATGGAATTGACATCCTAGGTCATATAGTCCAAGTCCTTGTTTATATTTGA
TACCTAGTGAGATTAAAGGGACATTAAAAAGTAAAGAAAGGAAAGACCTCATATTTC
TTACCTTCCAGTAGAGAAATCTTTCTATGAAATCAGAGGAAAGAATTAGAGGACCAG
AATTTTTCCTAAAATCAACTTTCATACATCTTTTTTCATATAAAAGGCATAGCTGCAT
ACAATGCTAAAATATTGTATTACATTTCCTTTATATTGATGGGAGGAAGGGGGTAAAT
TGCAGAAAACATTGTAAATTTAGATATGCTTGGGCCTCTGACAGTGCCTAGCAAATA
TCAGGAGATCAATAATGAAATAAATATTATCAAAGAGTAGTCTTCTTGATGAACCTT
CTCTGAGTATCACAACTGCTTTAGGAACCTCTAGATTCAAGGTCTAGTAATTGCAAAC
AGTGAGCTGATAAGAAAAACAGACTGTATGGGAAATTACATGCTTCCTGCATGACTG
CCTTTTGTTCTCCCACATTTTGATATAAAGTCACATTAACAGTTCATGAGTAAATATTC
GATAATGTGAACGTAAAGTGTTCAAATAATAGAGTGACTAAAATGCCTGAAAACAAA
TAATTTTTAATTAGAAACTCATAATCATTTATTTTCTCTTTTTCCACATTATCTCAAGC
TCACAAATTATATTTATTCTTTCCTATGGCAAAATCCATTTTGTTAACACTAATTTTGA
GTTTAACAAGAAGTGTACTCCAAAGTAGCCTAATAATACTAATTATAATGTTTCCTGC
TATGTTATCAGTTTGAATTTATATGAATCTTTAGACTTGAGGCTTCTTTTTCCTAGCAT
AGTGATGGTCTGGGCTTTTTCTCAATTTTTGCCAGAGCTCAGCTCTCACTAATTAGTTT
CTTTCTGCATGAGAAAAAGATTTTGCTTCATCTTTTTCCTTATAATAGCAGAACAAAA
AGAAGAATCAGCTGCATCCATGCTAATTTCCCCTGTGACATTTCCAAACAGGATTTGA
TTTCTCTATGCATGCCTCTTTCCTTCTCTTCATGGTTTTTGAACATATACAAAAGCTCA
TTTAAACCAATTAAATAAAATTGTTTTTAATCTCTTTCTCTAGAGTCAACTTCCTGCTT
ACTCCAACTCTGTATCTTTGAAGGAAGTATAGGGTGGTCTATGCCTTTTTTCTCCCAG
AATCTACACTTGAAAAGACACATTTTTCCATGCAACTATAAAATGTTCTCCTCACTCA
ACATTGAAATTGTATAGCAGTGATTAAGAGAGTGAGCTGTAGAGCCAGGTTCCCTGG
GTTTAAATCCCACTTGTTAGTATCATGAAGATGGGCAAGTTACTTACCCTTCCTGTGT
TTCAGTTTCTTCATCTGCAAAATGGGGACAATAATAGAATGTCCACTATAAGATTATT
GTGAGGATTAAGGGAATTAATACAGGTAAAACGTGTACTGATGCAGGTCTGGTACAC
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CCTTGAGATTAATAGAGTTTAACGATAAGTTTTACTTTATAGCTGGTCAAGTTTATTT
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TCTTAAAATTTCAATTCAATGAACATTTATTTAGCGCCTATGATATATGCAAGACAGT
TTGATTTTAGTCATCTGATGTATAGCCACATACTAAAAAATACTGATTTTAGTCATCT
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AGTTCCCAATCCCAGGCTAGTACCTTGGTTCCTTATGTAAATAAACATCCACCAATTA
CATGCTATCTGCAAAGCACTCTGCTAGGCCCTGCAAATGGAAAAAAAAATGATAAAA
CATAGTCCAGGCCCTCAATGAGCTTACAGTCAAATATAATAGAGGAGACAAGAACAG
AGAGGCTCATAATACAACTAGAATAAAATGACTGCCGAATAAAAGGAAAGATTTAT
GCAGGTGTTCAAATGGAAAGTGAGATAAGTTTGCAGGTTAGTCTTTGCAGTCTCATA

AAAATCTTTATGGAGAAAAGGACAATGGTCATAGGGCTTAAAGAGTAAGTTTATAAT
CCTGACCAGTGGAGATGAAAGACTAGCATTGAAAATTGCATGACAAGACAATTCCAT
TAAACTGAAACATCAAGTGTGTGTAGGAAAAGATGGGGGTTATGACTGGAAACGTCA
CTTGGACTGCAATTATGAAGGGCCTTGACAAACAGGTCAAGAGTTTAAGAAGCAGTA
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CTTAAAATATTAGTCAAAAGGAACGACATCATTAGAAATGATAGAGAAACAATAATG
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AATAACATGAACTTTTGGTCATAGTTTTAAACAAAAACAGTGTTAAATATATTTTTTA
AAACACAGTAAGTCTTGTAAGATCTTTTCTAACATGACATTTTGCAGGGCCCATATTT
TCCTTCTGAAATGGGAAAAATTCATAAAAGTAGACACCAAACTGGGTTACTTCTAGT
CAAGCGCATGGTACGCAAAGGACCAGACAAAAAGGGCCTGTGACATTTCTTCTTCCT
TTTGTGTTTTTTAGGAGAGGCATGCTGCGGAGGTGCGCAGGAACAAGGAACTCCAGG
TTGAACTGTCTGGCTGAAGCAAGGGAGGGTCTGGCACGCCCCACCAATAGTAAATCC
CCCTGCCTATATTATAATGGATCATGCGATATCAGGATGGGGAATGTATGACATGGTT
TAAAAAGAACTCATTATAAAAAAAAAAAAACAAAAAAAATCAAAAATTAAAAAAAA
TCAATGCGGTCTCTTTGCAGAATGTTTTGCTTGATGTTTAAAAAATACCTTGGATCTT
ATTTTGTAAATACTTACATTTTTGTTAAAAAATACAAGTATTGCATTATGCAAGTTAT
TTCATAATCTTACATGTCCTGTAACAGGCTTTTGATGTTGTGTCTTTCCACTCAAATGA
ATTTGCTAGGTCTGTTCTTTTTGAAGCTCCCCATGTCTAACTCCATTCCAAAAGAAAA
ATGAGGTCAGTAGACAGTCTATGGTGCTAGAAACCCACCATTGCCTAATGACCTAGA
AGGCTTTGTTGTCTCTGAGCTTGACTAAGACCATACCTAGATCACAGGTATTATGACT
CCACATGAACCTTCACATTTGTTCGCTCATAATCTACTTACTGCCTAAAAACTACAAA
ACCAGGCTAAGAAATACCACCAGTCATAGCATTTACTTCTGCTTCTCCTGGATTATGT
GCTACAAATGTGCTTTGGCTTTAGAAAGGGATGGATGAGAAGACAGACCTGAGACCA
ATCTGGGTAGAAGCAAAAAGTTGAACCTTTTAAAGTGCTGAACACAAATCCAAATTC
GAATGGTTCAAGCAGCCGTGAAATCGCTCTTCATAAAGTGGGCTTAATTCTCTAGTTT
AAGTTCTTTTGATGGAATGAATTAATTAATGTGTCAGGTGGCTTATTTGTGGATGCCA
TGATTGATGATGTTCATTTTAAGCTCTTACCTATAGTACAAGTACATGATGCTACTGA
ATATTTTTCCACTTGGAAACTGTGAGCTGGTTGTTGCATTAAAACACACATACAAACA
AAATCAAAAACACTGCGGACTTTCACTCAAGCTGGTCTTTCTTCCCCAGTGTAAGGCA
ATCCTGCCTACTAACAACACCAACAACAAAACACTCCATCTGTGAAGCTGACGCAGT
TAAGGGGGCTAGGCAGGGCATTTGTGCCAACTAAGAATCACCAGATACCCACCATAA
GTACCTATCGCAGTTTTGAAGTCGTTTCTCCCCAACTCCCAACTCCTGAAGGTTGCTG
CCTGCATATTTACTCTTCATTAGTGCTATTTTCCTGTATGTCATTGTGAGCAAGCTGTG
ATTAATAAAGAATTGGAGTTCTGTGAACTAATAAAGGTTTGGTCTGTT

(SEQ ID NO: 1391)

[00204] A STMN2 cryptic exon sequence within the STMN2 transcript is provided as SEQ ID NO: 447.

GACTCGGCAGAAGACCTTCGAGAGAAAGGTAGAAAATAAGAATTTGGCTCTCTGTGT
GAGCATGTGTGCGTGTGTGCGAGAGAGAGAGACAGACAGCCTGCCTAAGAAGAAAT
GAATGTGAATGCGGCTTGTGGCACAGTTGACAAGGATGATAAATCAATAATGCAAGC
TTACTATCATTTATGAATAGCAATACTGAAGAAATTAAAACAAAAGATTGCTGTCTC

(SEQ ID NO: 447) (Source: NCBI Reference Sequence: NC_000008.11).

[00205] In various embodiments, the STMN2 transcript with a cryptic exon shares between 90-100% identity with SEQ ID NO: 944. In various embodiments, the STMN2 transcript with a cryptic exon shares at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity with SEQ ID NO: 944.

STMN2 Antisense Oligonucleotides Targeting Portions of the STMN2 Transcript

[00206] In various embodiments, STMN2 AON disclosed herein target specific portions of STMN2 transcripts that include a cryptic exon. SEQ ID NO: 944, shown above, describes one example of a STMN2 transcript that includes a cryptic exon. In some embodiments, a STMN2 transcript that includes a cryptic exon may share at least 80%, 85%, 90%, 95%, or 100% identity with the nucleobase sequence of SEQ ID NO: 944.

[00207] In some embodiments, an STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript having a length of 10 nucleobases. In some embodiments, an STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript having a length of 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleobases in length.

[00208] In some embodiments, an STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript comprising any one of positions 121-144, 144-168, 146-170, 150-170, 150-172, 150-174, 169-193, 169-189, 169-191, 170-190, 170-192, 171-191, 171-193, 172-192, 172-194, 170-194, 171-195, 172-196, 173-197, 185-209, 197-221, 237-261, 249-273, 252-276, or 276-300 of SEQ ID NO: 944. In some embodiments, an STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript comprising any one of positions 144-164, 144-166, 145-167, 146-166, 146-168, 147-165, or 148-168 of SEQ ID NO: 944. In some embodiments, an STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript comprising any one of positions 173-191, 173-193, 173-195, 173-197, 175-195, 175-197, 177-197, or 179-197 of SEQ ID NO: 944. In some embodiments, an STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript comprising any one of positions 185-205, 187-209, 189-209, 185-207, 197-217, 197-219, or 191-209 of SEQ ID NO: 944. In some embodiments, an STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript comprising any one of positions 237-255, 237-257, 237-

259, 239-259, 239-261, 241-261, 237-257, 249-269, 249-271, 252-272, 252-274, or 243-261 of SEQ ID NO: 944.

[00209] In some embodiments, an STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript consisting of any one of positions 121-144, 144-168, 146-170, 150-170, 150-172, 150-174, 169-193, 169-189, 169-191, 170-190, 170-192, 171-191, 171-193, 172-192, 172-194, 170-194, 171-195, 172-196, 173-197, 185-209, 197-221, 237-261, 249-273, 252-276, or 276-300 of SEQ ID NO: 944. In some embodiments, an STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript consisting of any one of positions 144-164, 144-166, 145-167, 146-166, 146-168, 147-165, or 148-168 of SEQ ID NO: 944. In some embodiments, an STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript consisting of any one of positions 173-191, 173-193, 173-195, 173-197, 175-195, 175-197, 177-197, or 179-197 of SEQ ID NO: 944. In some embodiments, an STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript consisting of any one of positions 185-205, 187-209, 189-209, 185-207, 197-217, 197-219, or 191-209 of SEQ ID NO: 944. In some embodiments, an STMN2 AON targets a specific portion of the STMN2 transcript, the specific portion of the STMN2 transcript consisting of any one of positions 237-255, 237-257, 237-259, 239-259, 239-261, 241-261, 237-257, 249-269, 249-271, 252-272, 252-274, or 243-261 of SEQ ID NO: 944.

[00210] In various embodiments, the STMN2 AON comprises a nucleobase sequence that comprises a portion of at least 10 contiguous nucleobases that is complementary to an equal length portion of nucleobases within any one of positions 144-164, 144-166, 145-167, 146-166, 146-168, 147-165, 148-168, 173-191, 173-193, 173-195, 173-197, 175-195, 175-197, 177-197, 179-197, 185-205, 185-207, 197-217, 197-219, 187-209, 189-209, 191-209, 237-255, 237-257, 237-259, 239-259, 239-261, 241-261, 237-257, 249-269, 249-271, 252-272, 252-274, or 243-261 of SEQ ID NO: 944. In various embodiments, the STMN2 AON comprises a nucleobase sequence that comprises a portion of at least 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleobases that is complementary to an equal length portion of nucleobases within any one of positions 144-164, 144-166, 145-167, 146-166, 146-168, 147-165, 148-168, 173-191, 173-193, 173-195, 173-197, 175-195, 175-197, 177-197, 179-197, 185-205, 185-207,

197-217, 197-219, 187-209, 189-209, 191-209, 237-255, 237-257, 237-259, 239-259, 239-261, 241-261, 237-257, 249-269, 249-271, 252-272, 252-274, or 243-261 of SEQ ID NO: 944.

[00211] In various embodiments, the oligonucleotide comprises linked nucleosides with at least a 19 contiguous nucleobase sequence that is at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) complementary to an equal length portion of a transcript with at least 90% identity (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity) to SEQ ID NO: 944, or to a contiguous 19 to 50 nucleobase portion of SEQ ID NO: 944, wherein at least one nucleoside linkage of the linked nucleosides is a non-natural linkage. In various embodiments, the oligonucleotide comprises linked nucleosides with at least a 19, 20, 21, 22, 23, 24, or 25 contiguous nucleobase sequence that is at least 90% complementary (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary) to an equal length portion of a transcript with at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to SEQ ID NO: 944, or to a contiguous 19 to 50 nucleobase portion of SEQ ID NO: 944, wherein at least one nucleoside linkage of the linked nucleosides is a non-natural linkage.

[00212] In various embodiments, the oligonucleotide comprises linked nucleosides with at least a 19 contiguous nucleobase sequence that comprises a portion of at least 10 contiguous nucleobases that shares at least 90% identity (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity) with an equal length portion of any one of SEQ ID NOs: 1-446, SEQ ID NOs: 894-918, SEQ ID NOs: 945-1390, or SEQ ID NOs: 1392-1432. In various embodiments, the oligonucleotide comprises linked nucleosides with at least a 19 contiguous nucleobase sequence that comprises a portion of at least 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleobases that shares at least 90% identity (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity) with an equal length portion of any one of SEQ ID NOs: 1-446, SEQ ID NOs: 894-918, SEQ ID NOs: 945-1390, or SEQ ID NOs: 1392-1432.

[00213] In various embodiments, the oligonucleotide comprises linked nucleosides with at least a 19 contiguous nucleobase sequence that comprises a portion of at least 10 contiguous nucleobases that shares at least 90% identity (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity) with an equal length portion of any one of SEQ ID NOs: 31, 36, 41, 46, 55, 144, 146, 150, 169, 170, 171, 172, 173, 177, 181, 185, 197, 203, 209, 215, 237, 244, 249, 252, 380, 385, 390, 395, 400, 975, 980, 985, 999, 1088, 1090, 1094, 1113, 1114, 1115, 1116,

1117, 1121, 1125, 1129, 1141, 1147, 1153, 1159, 1181, 1188, 1193, 1196, 1324, 1329, 1334, 1339, or 1344, wherein at least one nucleoside linkage of the linked nucleosides is a non-natural linkage. In various embodiments, the oligonucleotide comprises linked nucleosides with at least a 19 contiguous nucleobase sequence that comprises a portion of at least 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleobases that shares at least 90% identity (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity) with an equal length portion of any one of SEQ ID NOs: 31, 36, 41, 46, 55, 144, 146, 150, 169, 170, 171, 172, 173, 177, 181, 185, 197, 203, 209, 215, 237, 244, 249, 252, 380, 385, 390, 395, 400, 975, 980, 985, 999, 1088, 1090, 1094, 1113, 1114, 1115, 1116, 1117, 1121, 1125, 1129, 1141, 1147, 1153, 1159, 1181, 1188, 1193, 1196, 1324, 1329, 1334, 1339, or 1344, wherein at least one nucleoside linkage of the linked nucleosides is a non-natural linkage.

[00214] In various embodiments, the oligonucleotide comprises linked nucleosides with at least a 19 contiguous nucleobase sequence, wherein the nucleobase sequence comprises a portion of at least 10 contiguous nucleobases that shares at least 90% identity (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity) to an equal length portion of any one of SEQ ID NOs: 894-918 or SEQ ID NOs: 1392-1432. In various embodiments, the oligonucleotide comprises linked nucleosides with at least a 20, 21, 22, 23, 24, or 25 contiguous nucleobase sequence, wherein the nucleobase sequence comprises a portion of at least 10 contiguous nucleobases that shares at least 90% identity (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity) to an equal length portion of any one of SEQ ID NOs: 894-918 or SEQ ID NOs: 1392-1432.

[00215] In various embodiments, the oligonucleotide comprises linked nucleosides with at least a 19 contiguous nucleobase sequence, wherein the nucleobase sequence comprises a portion of at least 10 contiguous nucleobases that shares at least 90% identity (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity) to an equal length portion of any one of SEQ ID NOs: 894-918 or SEQ ID NOs: 1392-1432. In various embodiments, the oligonucleotide comprises linked nucleosides with at least a 20, 21, 22, 23, 24, or 25 contiguous nucleobase sequence, wherein the nucleobase sequence comprises a portion of at least 10 contiguous nucleobases that shares at least 90% identity (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,

98%, 99%, or 100% identity) to an equal length portion of any one of SEQ ID NOs: 894-918 or SEQ ID NOs: 1392-1432.

[00216] In various embodiments, the oligonucleotide comprises linked nucleosides with at least a 19 contiguous nucleobase sequence, the nucleobase sequence comprising a portion of at least 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleobases that shares at least 90% identity (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity) to of any one of SEQ ID NOs: 894-918 or SEQ ID NOs: 1392-1432.

[00217] In various embodiments, the nucleobase sequence comprises a portion of at least 10 contiguous nucleobases that is at least 90% complementary (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary) to an equal length portion of nucleobases within any one of positions 121-144, 144-168, 146-170, 150-170, 150-172, 150-174, 169-193, 169-189, 169-191, 170-190, 170-192, 171-191, 171-193, 172-192, 172-194, 170-194, 171-195, 172-196, 173-197, 185-209, 197-221, 237-261, 249-273, 252-276, or 276-300 of SEQ ID NO: 944. In various embodiments, the nucleobase sequence comprises a portion of at least 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleobases that is at least 90% complementary (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary) to an equal length portion of nucleobases within any one of positions 121-144, 144-168, 146-170, 150-170, 150-172, 150-174, 169-193, 169-189, 169-191, 170-190, 170-192, 171-191, 171-193, 172-192, 172-194, 170-194, 171-195, 172-196, 173-197, 185-209, 197-221, 237-261, 249-273, 252-276, or 276-300 of SEQ ID NO: 944.

[00218] In various embodiments, the nucleobase sequence comprises a portion of at least 10 contiguous nucleobases that is at least 90% complementary (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary) to an equal length portion of nucleobases within any one of positions 121-144, 144-168, 146-170, 150-170, 150-172, 150-174, 169-193, 169-189, 169-191, 170-190, 170-192, 171-191, 171-193, 172-192, 172-194, 170-194, 171-195, 172-196, 173-197, 185-209, 197-221, 237-261, 249-273, 252-276, or 276-300 of SEQ ID NO: 944. In various embodiments, the nucleobase sequence comprises a portion of at least 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleobases that is at least 90% complementary (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary) to an equal length portion of nucleobases within any one of positions 121-144, 144-168, 146-170, 150-170, 150-172, 150-174, 169-193, 169-189, 169-191, 170-190, 170-192,

171-191, 171-193, 172-192, 172-194, 170-194, 171-195, 172-196, 173-197, 185-209, 197-221, 237-261, 249-273, 252-276, or 276-300 of SEQ ID NO: 944.

[00219] In various embodiments, the portion of the nucleobase sequence is 100% complementary to an equal length portion of nucleobases within any one of positions 121-144, 144-168, 146-170, 150-170, 150-172, 150-174, 169-193, 169-189, 169-191, 170-190, 170-192, 171-191, 171-193, 172-192, 172-194, 170-194, 171-195, 172-196, 173-197, 185-209, 197-221, 237-261, 249-273, 252-276, or 276-300 of SEQ ID NO: 944. In various embodiments, the portion of the nucleobase sequence is 100% complementary to an equal length portion of nucleobases within any one of positions 144-164, 144-166, 145-167, 146-166, 146-168, 147-165, or 148-168 of SEQ ID NO: 944. In various embodiments, the portion of the nucleobase sequence is 100% complementary to an equal length portion of nucleobases within any one of positions 173-191, 173-193, 173-195, 173-197, 175-195, 175-197, 177-197, or 179-197 of SEQ ID NO: 944. In various embodiments, the portion of the nucleobase sequence is 100% complementary to an equal length portion of nucleobases within any one of positions 185-205, 187-209, 189-209, 185-207, 197-217, 197-219, or 191-209 of SEQ ID NO: 944. In various embodiments, the portion of the nucleobase sequence is 100% complementary to an equal length portion of nucleobases within any one of positions 237-255, 237-257, 237-259, 239-259, 239-261, 241-261, 237-257, 249-269, 249-271, 252-272, 252-274, or 243-261 of SEQ ID NO: 944.

STMN2 Antisense Oligonucleotide Variants

[00220] In various embodiments, STMN2 AONs include different variants, hereafter referred to as STMN2 AON variants. A STMN2 AON variant may be an oligonucleotide sequence of 5 to 100 nucleotides in length, for example, 10 to 40 nucleotides in length, for example, 14 to 40 nucleotides in length, 10 to 30 nucleotides in length, for example, 14 to 30 nucleotides in length, for example, 16 to 28 nucleotides in length, for example, 19 to 23 nucleotides in length, for example, 21 to 23 nucleotides in length, for example, or 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. A STMN2 AON variant may be an oligonucleotide sequence complementary to a portion of a STMN2 pre-mRNA sequence or a STMN2 gene sequence.

[00221] In various embodiments, a STMN2 AON variant represents a modified version of a corresponding STMN2 AON that includes a nucleobase sequence selected from any one of SEQ ID NOs: 1-446 or SEQ ID NOs: 945-1390. In some embodiments, a STMN2 AON variant includes a nucleobase sequence that represents a shortened version of a nucleobase sequence of a

STMN2 AON selected from any one of SEQ ID NOs: 1-446 OR SEQ ID NOs: 945-1390. As one example, if a STMN2 AON includes a 25mer (*e.g.*, 25 nucleotides in length) a variant (*e.g.*, a STMN2 variant) may include a shorter version (*e.g.*, 15mer, 16mer, 17mer, 18mer, 19mer, 20mer, 21mer, 22mer, 23mer, or 24mer) of the 25mer STMN2 AON. In one embodiment, a nucleobase sequence of a STMN2 AON variant differs from a corresponding nucleobase sequence of a STMN2 AON in that 1, 2, 3, 4, 5, or 6 nucleotides are removed from one or both of the 3' and 5' ends of the nucleobase sequence of the STMN2 AON. In one embodiment, the corresponding STMN2 AON variant may include a 23mer where two nucleotides were removed from one of the 3' or 5' end of a 25mer included in the STMN2 AON. In one embodiment, the corresponding STMN2 AON variant may include a 23mer where one nucleotide is removed from each of the 3' and 5' ends of the 25mer included in the STMN2 AON. In one embodiment, the corresponding STMN2 AON variant may include a 21mer where two nucleotides are removed from each of the 3' and 5' ends of the 25mer included in the STMN2 AON. In one embodiment, the corresponding STMN2 AON variant may include a 21mer where four nucleotides are removed from either the 3' or 5' end of the 25mer included in the STMN2 AON. In one embodiment, the corresponding STMN2 AON variant may include a 19mer where three nucleotides are removed from each of the 3' and 5' ends of the 25mer included in the STMN2 AON. In one embodiment, the corresponding STMN2 AON variant may include a 19mer where six nucleotides are removed from either the 3' or 5' end of the 25mer included in the STMN2 AON.

[00222] Example sequences of STMN2 AON variants are shown below in Table 3. The example STMN2 AON variants are each associated with an identifier that describes the differences between the STMN2 AON variant and the corresponding STMN2 AON. As an example, a STMN2 AON variant includes SEQ ID NO: 894 and is identified using identifier: QSN-144-1/5-1/3. This first portion of the identifier "QSN-144" indicates that the STMN2 AON variant is a modified version of the QSN-144 STMN2 AON which includes SEQ ID NO: 144. Additionally, the second portion of the identifier which includes the numerical indicators of "1/5-1/3" indicate that one nucleotide is removed from each of the 5' end and the 3' end of the nucleobase sequence included in the QSN-144 STMN2 AON (*e.g.*, 1 nucleotide removed from each of 3' and 5' end of SEQ ID NO: 144). To provide another example, a STMN2 AON variant includes SEQ ID NO: 895 and is identified as QSN-144-2/3. This STMN2 AON variant is a modified version of the QSN-144 STMN2 AON. The numerical indicators of "2/3" indicate that two nucleotides are removed from the 3' end of the nucleobase sequence of the QSN-144 STMN2 AON (*e.g.*, 2 bases removed from 3' end of SEQ ID NO: 144).

[00223] In some embodiments, a STMN2 AON variant differs from a corresponding STMN2 AON in that one or more internucleoside linkages of the STMN2 AON variant are phosphodiester bonds. In such embodiments, the length of the STMN2 AON variant may be the same length as the corresponding STMN2 AON (*e.g.*, 25 nucleotides in length). In some embodiments, the phosphodiester internucleoside linkages connect two, three, four, five, six, seven, eight, nine, or ten contiguous nucleotides.

[00224] In some embodiments, the phosphodiester internucleoside linkages connect nucleotides located at one or both of the 3' or 5' ends. For example, two, three, four, five, six, seven, eight, nine, or ten contiguous nucleotides at one or both of the 3' or 5' ends are connected via phosphodiester internucleoside linkages.

[00225] In some embodiments, the phosphodiester internucleoside linkages connect nucleotides located within the nucleobase sequence. For example, within a 25mer STMN2 AON variant, contiguous nucleotides between positions 6-15 may be connected through phosphodiester internucleoside linkages. In some embodiments, contiguous nucleotides between any one of positions 7-15, 8-14, or 9-13 are connected through phosphodiester internucleoside linkages.

[00226] Table 5 below identifies variants of STMN2 AON sequences:

Table 5. STMN2 Antisense Oligonucleotide Variant Sequences

SEQ ID NO:	Identifier	AON Sequence* (5' →3')	SEQ ID NO:	Target Sequence (5' →3')
894	QSN-144-1/5-1/3	ATCCAATTAAGAGAGAGTGATGG	919	CCATCACTCTCTCTTAATTGGAT
895	QSN-144-2/3	AATCCAATTAAGAGAGAGTGATG	920	CATCACTCTCTCTTAATTGGATT
896	QSN-144-2/5	TCCAATTAAGAGAGAGTGATGGG	921	CCCATCACTCTCTCTTAATTGGA
897	QSN-144-2/5-2/3	TCCAATTAAGAGAGAGTGATG	922	CATCACTCTCTCTTAATTGGA
898	QSN-144-3/5-3/3	CCAATTAAGAGAGAGTGAT	923	ATCACTCTCTCTTAATTGG
899	QSN-144-4/3	AATCCAATTAAGAGAGAGTGA	924	TCACTCTCTCTTAATTGGATT
900	QSN-144-4/5	CAATTAAGAGAGAGTGATGGG	925	CCCATCACTCTCTCTTAATTG
901	QSN-173-2/3	GAGTCCTGCAATATGAATATAAT	926	ATTATATTCATATTGCAGGACTC

902	QSN-173-2/5	GTCCTGCAATATGAATATAATTT	927	AAATTATATTCATATTGCAGGAC
903	QSN-173-2/5-2/3	GTCCTGCAATATGAATATAAT	928	ATTATATTCATATTGCAGGAC
904	QSN-173-4/3	GAGTCCTGCAATATGAATATA	929	TATATTCATATTGCAGGACTC
905	QSN-173-4/5	CCTGCAATATGAATATAATTT	930	AAATTATATTCATATTGCAGG
906	QSN-173-6/3	GAGTCCTGCAATATGAATA	931	TATTCATATTGCAGGACTC
907	QSN-173-6/5	TGCAATATGAATATAATTT	932	AAATTATATTCATATTGCA
908	QSN-185-2/5	GTCTTCTGCCGAGTCCTGCAATA	933	TATTGCAGGACTCGGCAGAAGAC
909	QSN-185-4/3	AGGTCTTCTGCCGAGTCCTGC	934	GCAGGACTCGGCAGAAGACCT
910	QSN-185-4/5	CTTCTGCCGAGTCCTGCAATA	935	TATTGCAGGACTCGGCAGAAG
911	QSN-185-6/5	TCTGCCGAGTCCTGCAATA	936	TATTGCAGGACTCGGCAGA
912	QSN-237-2/3	GCACACATGCTCACACAGAGAGC	937	GCTCTCTGTGTGAGCATGTGTGC
913	QSN-237-2/5	ACACATGCTCACACAGAGAGCCA	938	TGGCTCTCTGTGTGAGCATGTGT
914	QSN-237-2/5-2/3	ACACATGCTCACACAGAGAGC	939	GCTCTCTGTGTGAGCATGTGT
915	QSN-237-4/3	GCACACATGCTCACACAGAGA	940	TCTCTGTGTGAGCATGTGTGC
916	QSN-237-4/5	ACATGCTCACACAGAGAGCCA	941	TGGCTCTCTGTGTGAGCATGT
917	QSN-237-6/3	GCACACATGCTCACACAGA	942	TCTGTGTGAGCATGTGTGC
918	QSN-237-6/5	ATGCTCACACAGAGAGCCA	943	TGGCTCTCTGTGTGAGCAT
1417	QSN-173-po3	G-A-G-TCCTGCAATATGAATATAA-T-T-T[1]	620	AAATTATATTCATATTGCAGGACTC
1418	QSN-173-po5	GAGTCCTG-C-A-A-T-A-TGAATATAATTT[1]	620	AAATTATATTCATATTGCAGGACTC
1419	QSN-144-po3	A-A-T-CCAATTAAGAGAGAGTGAT-G-G-G[1]	591	CCCATCACTCTCTCTTAATTGGATT
1420	QSN-144-po5	AATCCAAT-T-A-A-G-A-GAGAGTGATGGG[1]	591	CCCATCACTCTCTCTTAATTGGATT
1421	QSN-185-po3	A-G-G-TCTTCTGCCGAGTCCTGCA-A-T-A[1]	633	ATTGCAGGACTCGGCAGAAGACCTT
1422	QSN-185-po5	AGGTCTTC-T-G-C-C-G-AGTCCTGCAATA[1]	633	ATTGCAGGACTCGGCAGAAGACCTT
1423	QSN-237-po3	G-C-A-CACATGCTCACACAGAGAG-C-C-A[1]	684	TGGCTCTCTGTGTGAGCATGTGTGC
1424	QSN-237-po5	GCACACAT-G-C-T-C-A-CACAGAGAGCCA[1]	684	TGGCTCTCTGTGTGAGCATGTGTGC

* Except where noted to the contrary (*e.g.*, in SEQ ID NOs: 1417, 1418, 1419, 1420, 1421, 1422, 1423, and 1424 in Table 5), at least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a

methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothiate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3'amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage. In some embodiments, except where noted to the contrary (*e.g.*, in SEQ ID NOs: 1417, 1418, 1419, 1420, 1421, 1422, 1423, and 1424 in Table 5), every nucleoside linkage is a phosphorothioate linkage.

[1] The notation "-" indicates the presence of a phosphodiester linkage in SEQ ID NOs: 1417, 1418, 1419, 1420, 1421, 1422, 1423, and 1424 in Table 5.

[00227] Table 6 below identifies additional variants of STMN2 AON sequences:

Table 6. Additional STMN2 Antisense Oligonucleotide Variant Sequences

SEQ ID NO:	Identifier	AON Sequence* (5' → 3')
1392	QSN-144-1/5-1/3	AUCCAAUUAAGAGAGAGUGAUGG
1393	QSN-144-2/3	AAUCCAAUUAAGAGAGAGUGAUG
1394	QSN-144-2/5	UCCAAUUAAGAGAGAGUGAUGGG
1395	QSN-144-2/5-2/3	UCCAAUUAAGAGAGAGUGAUG
1396	QSN-144-3/5-3/3	CCAAUUAAGAGAGAGUGAU
1397	QSN-144-4/3	AAUCCAAUUAAGAGAGAGUGA
1398	QSN-144-4/5	CAAUUAAGAGAGAGUGAUGGG
1399	QSN-173-2/3	GAGUCCUGCAAUAUGAAUAUAAU
1400	QSN-173-2/5	GUCCUGCAAUAUGAAUAUAAUUU
1401	QSN-173-2/5-2/3	GUCCUGCAAUAUGAAUAUAAU
1402	QSN-173-4/3	GAGUCCUGCAAUAUGAAUAUA
1403	QSN-173-4/5	CCUGCAAUAUGAAUAUAAUUU
1404	QSN-173-6/3	GAGUCCUGCAAUAUGAAUA
1405	QSN-173-6/5	UGCAAUAUGAAUAUAAUUU
1406	QSN-185-2/5	GUCUUCUGCCGAGUCCUGCAAUA
1407	QSN-185-4/3	AGGUCUUCUGCCGAGUCCUGC
1408	QSN-185-4/5	CUUCUGCCGAGUCCUGCAAUA
1409	QSN-185-6/5	UCUGCCGAGUCCUGCAAUA
1410	QSN-237-2/3	GCACACAUGCUCACACAGAGAGC
1411	QSN-237-2/5	ACACAUGCUCACACAGAGAGCCA
1412	QSN-237-2/5-2/3	ACACAUGCUCACACAGAGAGC

1413	QSN-237-4/3	GCACACAUGCUCACACAGAGA
1414	QSN-237-4/5	ACAUGCUCACACAGAGAGCCA
1415	QSN-237-6/3	GCACACAUGCUCACACAGA
1416	QSN-237-6/5	AUGCUCACACAGAGAGCCA
1425	QSN-173-po3	G-A-G-UCCUGCAAUAUGAAUAUAA-U-U-U[1]
1426	QSN-173-po5	GAGUCCUG-C-A-A-U-A-UGAAUAUAAUUU[1]
1427	QSN-144-po3	A-A-U-CCAAUUAAGAGAGAGUGAU-G-G-G[1]
1428	QSN-144-po5	AAUCCAAU-U-A-A-G-A-GAGAGUGAUGGG[1]
1429	QSN-185-po3	A-G-G-UCUUCUGCCGAGUCCUGCA-A-U-A[1]
1430	QSN-185-po5	AGGUCUUC-U-G-C-C-G-AGUCCUGCAAUA[1]
1431	QSN-237-po3	G-C-A-CACAUGCUCACACAGAGAG-C-C-A[1]
1432	QSN-237-po5	GCACACAU-G-C-U-C-A-CACAGAGAGCCA[1]

* Except where noted to the contrary (*e.g.*, in SEQ ID NOs: 1425, 1426, 1427, 1428, 1429, 1430, 1431, and 1432 in Table 6), at least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothiate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage. In some embodiments, except where noted to the contrary (*e.g.*, in SEQ ID NOs: 1425, 1426, 1427, 1428, 1429, 1430, 1431, and 1432 in Table 6), every nucleoside linkage is a phosphorothioate linkage.

[1] The notation "-" indicates the presence of a phosphodiester linkage in SEQ ID NOs: 1425, 1426, 1427, 1428, 1429, 1430, 1431, and 1432 in Table 6.

Performance of STMN2 Antisense Oligonucleotides and Variants

[00228] Generally, STMN2 AON and STMN2 AON variants can target STMN2 transcripts with a cryptic exon in order to increase, restore, rescue, or stabilize levels of expression of STMN2 mRNA that is capable of translation to produce a functional STMN2 protein (*e.g.*, full length STMN2). In various embodiments, STMN2 AON and STMN2 AON variants can exhibit at least a 60%, 70%, 80%, or 90% increase of full length STMN2 protein. In various embodiments, STMN2 AON and STMN2 AON variants can exhibit at least a 100%, 200%, 300%, or 400% increase of full length STMN2 protein. In some embodiments, the percent

increase of the full length STMN2 protein is an increase in comparison to a reduced level of full length STMN2 protein achieved using a TDP43 antisense oligonucleotide. For example, a TDP43 antisense oligonucleotide can be used to deplete full length STMN2 protein followed by increase of the full length STMN2 protein using a STMN2 AON or STMN2 AON variant.

[00229] In some embodiments, STMN2 AON and STMN2 AON variants reduce levels of STMN2 transcript with a cryptic exon. In various embodiments, STMN2 AON and STMN2 AON variants can exhibit at least a 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% reduction of the STMN2 transcript with the cryptic exon. In some embodiments, the percent reduction of cryptic exon levels is a decrease in comparison to an increased level of cryptic exon achieved using a TDP43 antisense oligonucleotide. For example, a TDP43 antisense oligonucleotide can be used to increase cryptic exon levels followed by a reduction of cryptic exon levels using a STMN2 AON or STMN2 AON variant.

[00230] In some embodiments, STMN2 AON and STMN2 AON variants can exhibit at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length STMN2 protein. In some embodiments, the percent rescue of full length STMN2 refers to the % of full length STMN2 following depletion using a TDP43 antisense oligonucleotide and a treatment using STMN2 AON or STMN2 AON variant in comparison to a negative control (*e.g.*, cells that did not undergo depletion or treatment or cells that were treated with a vehicle solution).

[00231] In some embodiments, STMN2 AON and AON variants exhibit between 50% to 100% rescue of full length STMN2. In some embodiments, STMN2 AON and AON variants exhibit between 60% to 100% rescue of full length STMN2. In some embodiments, STMN2 AON and AON variants exhibit between 70% to 100% rescue of full length STMN2. In some embodiments, STMN2 AON and AON variants exhibit between 80% to 100% rescue of full length STMN2. In some embodiments, STMN2 AON and AON variants exhibit between 90% to 100% rescue of full length STMN2. In some embodiments, STMN2 AON and AON variants exhibit between 60% to 90% rescue of full length STMN2. In some embodiments, STMN2 AON and AON variants exhibit between 50% to 80% rescue of full length STMN2. In some embodiments, STMN2 AON and AON variants exhibit between 60% to 80% rescue of full length STMN2.

[00232] In particular embodiments, QSN-31 STMN2 AON (SEQ ID NO: 31) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-31 STMN2 AON (SEQ ID NO: 31) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-31 STMN2 AON (SEQ ID NO: 31) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-31 STMN2

AON (SEQ ID NO: 31) oligonucleotide are phosphorothioate linkages, each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and each "C" is replaced with a 5-MeC.

[00233] In particular embodiments, QSN-36 STMN2 AON (SEQ ID NO: 36) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-36 STMN2 AON (SEQ ID NO: 36) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-36 STMN2 AON (SEQ ID NO: 36) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-36 STMN2 AON (SEQ ID NO: 36) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-36 STMN2 AON (SEQ ID NO: 36) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC.

[00234] In particular embodiments, QSN-41 STMN2 AON (SEQ ID NO: 41) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-41 STMN2 AON (SEQ ID NO: 41) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-41 STMN2 AON (SEQ ID NO: 41) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-41 STMN2 AON (SEQ ID NO: 41) oligonucleotide are phosphorothioate linkages, each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and each "C" is replaced with a 5-MeC.

[00235] In particular embodiments, QSN-46 STMN2 AON (SEQ ID NO: 46) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-46 STMN2 AON (SEQ ID NO: 46) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-46 STMN2 AON (SEQ ID NO: 46) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-46 STMN2 AON (SEQ ID NO: 46) oligonucleotide are phosphorothioate linkages, each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and each "C" is replaced with a 5-MeC.

[00236] In particular embodiments, QSN-55 STMN2 AON (SEQ ID NO: 55) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-55 STMN2 AON (SEQ ID NO: 55) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-55 STMN2 AON (SEQ ID NO: 55) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-55 STMN2 AON (SEQ ID NO: 55) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-55 STMN2 AON (SEQ ID NO: 55) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC.

[00237] In particular embodiments, QSN-144 STMN2 AON (SEQ ID NO: 144) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-144 STMN2 AON (SEQ ID NO: 144) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-144 STMN2 AON (SEQ ID NO: 144) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-144 STMN2 AON (SEQ ID NO: 144) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-144 STMN2 AON (SEQ ID NO: 144) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC.

[00238] In particular embodiments, QSN-146 STMN2 AON (SEQ ID NO: 146) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-146 STMN2 AON (SEQ ID NO: 146) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-146 STMN2 AON (SEQ ID NO: 146) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-146 STMN2 AON (SEQ ID NO: 146) oligonucleotide are phosphorothioate linkages, each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and each "C" is replaced with a 5-MeC.

[00239] In particular embodiments, QSN-150 STMN2 AON (SEQ ID NO: 150) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-150 STMN2

AON (SEQ ID NO: 150) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-150 STMN2 AON (SEQ ID NO: 150) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-150 STMN2 AON (SEQ ID NO: 150) oligonucleotide are phosphorothioate linkages, each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and each "C" is replaced with a 5-MeC.

[00240] In particular embodiments, QSN-169 STMN2 AON (SEQ ID NO: 169) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-169 STMN2 AON (SEQ ID NO: 169) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-169 STMN2 AON (SEQ ID NO: 169) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-169 STMN2 AON (SEQ ID NO: 169) oligonucleotide are phosphorothioate linkages, each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and each "C" is replaced with a 5-MeC.

[00241] In particular embodiments, QSN-170 STMN2 AON (SEQ ID NO: 170) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-170 STMN2 AON (SEQ ID NO: 170) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-170 STMN2 AON (SEQ ID NO: 170) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-170 STMN2 AON (SEQ ID NO: 170) oligonucleotide are phosphorothioate linkages, each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and each "C" is replaced with a 5-MeC.

[00242] In particular embodiments, QSN-171 STMN2 AON (SEQ ID NO: 171) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-171 STMN2 AON (SEQ ID NO: 171) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-171 STMN2 AON (SEQ ID NO: 171) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-171 STMN2 AON (SEQ ID NO: 171) oligonucleotide are phosphorothioate linkages, each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and each "C" is replaced with a 5-MeC.

[00243] In particular embodiments, QSN-172 STMN2 AON (SEQ ID NO: 172) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-172 STMN2 AON (SEQ ID NO: 172) exhibits between 60 to 90% rescue of full length STMN2. In particular

embodiments, QSN-172 STMN2 AON (SEQ ID NO: 172) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-172 STMN2 AON (SEQ ID NO: 172) oligonucleotide are phosphorothioate linkages, each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and each "C" is replaced with a 5-MeC.

[00244] In particular embodiments, QSN-173 STMN2 AON (SEQ ID NO: 173) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-173 STMN2 AON (SEQ ID NO: 173) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-173 STMN2 AON (SEQ ID NO: 173) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-173 STMN2 AON (SEQ ID NO: 173) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-O-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-173 STMN2 AON (SEQ ID NO: 173) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC.

[00245] In particular embodiments, QSN-177 STMN2 AON (SEQ ID NO: 177) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-177 STMN2 AON (SEQ ID NO: 177) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-177 STMN2 AON (SEQ ID NO: 177) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-177 STMN2 AON (SEQ ID NO: 177) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-177 STMN2 AON (SEQ ID NO: 177) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-O-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In particular embodiments, QSN-181 STMN2 AON (SEQ ID NO: 181) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-181 STMN2 AON (SEQ ID NO: 181) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-181 STMN2 AON (SEQ ID NO: 181) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-181 STMN2 AON (SEQ ID NO: 181) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-O-(2-methoxyethyl) (2'-MOE) nucleosides. In some

embodiments, all internucleoside linkages of the QSN-181 STMN2 AON (SEQ ID NO: 181) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC.

[00246] In particular embodiments, QSN-185 STMN2 AON (SEQ ID NO: 185) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-185 STMN2 AON (SEQ ID NO: 185) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-185 STMN2 AON (SEQ ID NO: 185) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-185 STMN2 AON (SEQ ID NO: 185) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In some embodiments, all internucleoside linkages of the QSN-185 STMN2 AON (SEQ ID NO: 185) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-O-(2-methoxyethyl) (2'-MOE) nucleosides. In particular embodiments, QSN-197 STMN2 AON (SEQ ID NO: 197) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-197 STMN2 AON (SEQ ID NO: 197) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-197 STMN2 AON (SEQ ID NO: 197) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-197 STMN2 AON (SEQ ID NO: 197) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-197 STMN2 AON (SEQ ID NO: 197) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC.

[00247] In particular embodiments, QSN-203 STMN2 AON (SEQ ID NO: 203) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-203 STMN2 AON (SEQ ID NO: 203) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-203 STMN2 AON (SEQ ID NO: 203) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-203 STMN2 AON (SEQ ID NO: 203) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-203 STMN2 AON (SEQ ID NO: 203) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the

oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In particular embodiments, QSN-209 STMN2 AON (SEQ ID NO: 209) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-209 STMN2 AON (SEQ ID NO: 209) exhibits between 60 to 90% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-209 STMN2 AON (SEQ ID NO: 209) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In particular embodiments, QSN-209 STMN2 AON (SEQ ID NO: 209) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-209 STMN2 AON (SEQ ID NO: 209) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC.

[00248] In particular embodiments, QSN-215 STMN2 AON (SEQ ID NO: 215) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-215 STMN2 AON (SEQ ID NO: 215) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-215 STMN2 AON (SEQ ID NO: 215) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-215 STMN2 AON (SEQ ID NO: 215) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-215 STMN2 AON (SEQ ID NO: 215) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In particular embodiments, QSN-237 STMN2 AON (SEQ ID NO: 237) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-237 STMN2 AON (SEQ ID NO: 237) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-237 STMN2 AON (SEQ ID NO: 237) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-237 STMN2 AON (SEQ ID NO: 237) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-237 STMN2 AON (SEQ ID NO: 237) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC.

[00249] In particular embodiments, QSN-244 STMN2 AON (SEQ ID NO: 244) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-244 STMN2 AON (SEQ ID NO: 244) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-244 STMN2 AON (SEQ ID NO: 244) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-244 STMN2 AON (SEQ ID NO: 244) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-244 STMN2 AON (SEQ ID NO: 244) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC.

[00250] In particular embodiments, QSN-249 STMN2 AON (SEQ ID NO: 249) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-249 STMN2 AON (SEQ ID NO: 249) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-249 STMN2 AON (SEQ ID NO: 249) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-249 STMN2 AON (SEQ ID NO: 249) oligonucleotide are phosphorothioate linkages, each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides, and each "C" is replaced with a 5-MeC.

[00251] In particular embodiments, QSN-252 STMN2 AON (SEQ ID NO: 252) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-252 STMN2 AON (SEQ ID NO: 252) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-252 STMN2 AON (SEQ ID NO: 252) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-252 STMN2 AON (SEQ ID NO: 252) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-252 STMN2 AON (SEQ ID NO: 252) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC.

[00252] In particular embodiments, QSN-380 STMN2 AON (SEQ ID NO: 380) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-380 STMN2 AON (SEQ ID NO: 380) exhibits between 60 to 90% rescue of full length STMN2. In particular

embodiments, QSN-380 STMN2 AON (SEQ ID NO: 380) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-380 STMN2 AON (SEQ ID NO: 380) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-380 STMN2 AON (SEQ ID NO: 380) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In particular embodiments, QSN-385 STMN2 AON (SEQ ID NO: 385) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-385 STMN2 AON (SEQ ID NO: 385) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-385 STMN2 AON (SEQ ID NO: 385) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-385 STMN2 AON (SEQ ID NO: 385) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-385 STMN2 AON (SEQ ID NO: 385) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC.

[00253] In particular embodiments, QSN-390 STMN2 AON (SEQ ID NO: 390) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-390 STMN2 AON (SEQ ID NO: 390) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-390 STMN2 AON (SEQ ID NO: 390) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-390 STMN2 AON (SEQ ID NO: 390) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-390 STMN2 AON (SEQ ID NO: 390) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In particular embodiments, QSN-395 STMN2 AON (SEQ ID NO: 395) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-395 STMN2 AON (SEQ ID NO: 395) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-395 STMN2 AON (SEQ ID NO: 395) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-395 STMN2

AON (SEQ ID NO: 395) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-395 STMN2 AON (SEQ ID NO: 395) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC. In particular embodiments, QSN-400 STMN2 AON (SEQ ID NO: 400) exhibits between 50 to 80% rescue of full length STMN2. In particular embodiments, QSN-400 STMN2 AON (SEQ ID NO: 400) exhibits between 60 to 90% rescue of full length STMN2. In particular embodiments, QSN-400 STMN2 AON (SEQ ID NO: 400) exhibits between 70 to 100% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-400 STMN2 AON (SEQ ID NO: 400) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides. In some embodiments, all internucleoside linkages of the QSN-400 STMN2 AON (SEQ ID NO: 400) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides and each "C" is replaced with a 5-MeC.

[00254] In particular embodiments, QSN-144-1/5-1/3 (SEQ ID NO: 894) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-144-1/5-1/3 (SEQ ID NO: 894) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-144-1/5-1/3 (SEQ ID NO: 894) exhibits between 50 to 60% rescue of full length STMN2. In particular embodiments, QSN-144-2/3 (SEQ ID NO: 895) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-144-2/3 (SEQ ID NO: 895) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-144-2/3 (SEQ ID NO: 895) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-144-2/3 STMN2 AON (SEQ ID NO: 895) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00255] In particular embodiments, QSN-144-2/5 (SEQ ID NO: 896) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-144-2/5 (SEQ ID NO: 896) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-144-2/5 (SEQ ID NO: 896) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-144-2/5 (SEQ ID NO: 896) oligonucleotide

are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00256] In particular embodiments, QSN-144-2/5-2/3 (SEQ ID NO: 897) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-144-2/5-2/3 (SEQ ID NO: 897) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-144-2/5-2/3 (SEQ ID NO: 897) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-144-2/5-2/3 STMN2 AON (SEQ ID NO: 897) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00257] In particular embodiments, QSN-144-3/5-3/3 (SEQ ID NO: 898) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-144-3/5-3/3 (SEQ ID NO: 898) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-144-3/5-3/3 (SEQ ID NO: 898) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-144-3/5-3/3 (SEQ ID NO: 898) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00258] In particular embodiments, QSN-144-4/3 (SEQ ID NO: 899) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-144-4/3 (SEQ ID NO: 899) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-144-4/3 (SEQ ID NO: 899) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-144-4/3 STMN2 AON (SEQ ID NO: 899) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00259] In particular embodiments, QSN-144-4/5 (SEQ ID NO: 900) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-144-4/5 (SEQ ID NO: 900) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-144-4/5 (SEQ ID NO: 900) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-144-4/5 (SEQ ID NO: 900) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00260] In particular embodiments, QSN-173-2/3 (SEQ ID NO: 901) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-173-2/3 (SEQ ID NO: 901) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-173-

2/3 (SEQ ID NO: 901) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-173-2/3 STMN2 AON (SEQ ID NO: 901) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00261] In particular embodiments, QSN-173-2/5 (SEQ ID NO: 902) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-173-2/5 (SEQ ID NO: 902) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-173-2/5 (SEQ ID NO: 902) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-173-2/5 (SEQ ID NO: 902) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00262] In particular embodiments, QSN-173-2/5-2/3 (SEQ ID NO: 903) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-173-2/5-2/3 (SEQ ID NO: 903) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-173-2/5-2/3 (SEQ ID NO: 903) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-173-2/5-2/3 (SEQ ID NO: 903) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00263] In particular embodiments, QSN-173-4/3 (SEQ ID NO: 904) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-173-4/3 (SEQ ID NO: 904) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-173-4/3 (SEQ ID NO: 904) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-173-4/3 (SEQ ID NO: 904) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00264] In particular embodiments, QSN-173-4/5 (SEQ ID NO: 905) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-173-4/5 (SEQ ID NO: 905) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-173-4/5 (SEQ ID NO: 905) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-173-4/5 (SEQ ID NO: 905) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00265] In particular embodiments, QSN-173-6/3 (SEQ ID NO: 906) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-173-6/3 (SEQ ID NO: 906) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-173-6/3 (SEQ ID NO: 906) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-173-6/3 (SEQ ID NO: 906) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00266] In particular embodiments, QSN-173-6/5 (SEQ ID NO: 907) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-173-6/5 (SEQ ID NO: 907) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-173-6/5 (SEQ ID NO: 907) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-173-6/5 (SEQ ID NO: 907) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00267] In particular embodiments, QSN-185-2/5 (SEQ ID NO: 908) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-185-2/5 (SEQ ID NO: 908) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-185-2/5 (SEQ ID NO: 908) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-185-2/5 (SEQ ID NO: 908) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00268] In particular embodiments, QSN-185-4/3 (SEQ ID NO: 909) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-185-4/3 (SEQ ID NO: 909) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-185-4/3 (SEQ ID NO: 909) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-185-4/3 (SEQ ID NO: 909) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00269] In particular embodiments, QSN-185-4/5 (SEQ ID NO: 910) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-185-4/5 (SEQ ID NO: 910) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-185-4/5 (SEQ ID NO: 910) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-185-4/5 (SEQ ID NO: 910) oligonucleotide

are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

[00270] In particular embodiments, QSN-185-6/5 (SEQ ID NO: 911) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-185-6/5 (SEQ ID NO: 911) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-185-6/5 (SEQ ID NO: 911) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-185-6/5 (SEQ ID NO: 911) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-O-(2-methoxyethyl) (2'-MOE) nucleosides.

[00271] In particular embodiments, QSN-237-2/3 (SEQ ID NO: 912) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-237-2/3 (SEQ ID NO: 912) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-237-2/3 (SEQ ID NO: 912) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-237-2/3 (SEQ ID NO: 912) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-O-(2-methoxyethyl) (2'-MOE) nucleosides.

[00272] In particular embodiments, QSN-237-2/5 (SEQ ID NO: 913) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-237-2/5 (SEQ ID NO: 913) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-237-2/5 (SEQ ID NO: 913) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-237-2/5 (SEQ ID NO: 913) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-O-(2-methoxyethyl) (2'-MOE) nucleosides.

[00273] In particular embodiments, QSN-237-2/5-2/3 (SEQ ID NO: 914) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-237-2/5-2/3 (SEQ ID NO: 914) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-237-2/5-2/3 (SEQ ID NO: 914) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-237-2/5-2/3 (SEQ ID NO: 914) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-O-(2-methoxyethyl) (2'-MOE) nucleosides.

[00274] In particular embodiments, QSN-237-4/3 (SEQ ID NO: 915) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-237-4/3 (SEQ ID NO: 915) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-237-

4/3 (SEQ ID NO: 915) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-237-4/3 (SEQ ID NO: 915) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-O-(2-methoxyethyl) (2'-MOE) nucleosides.

[00275] In particular embodiments, QSN-237-4/5 (SEQ ID NO: 916) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-237-4/5 (SEQ ID NO: 916) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-237-4/5 (SEQ ID NO: 916) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-237-4/5 (SEQ ID NO: 916) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-O-(2-methoxyethyl) (2'-MOE) nucleosides.

[00276] In particular embodiments, QSN-237-6/3 (SEQ ID NO: 917) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-237-6/3 (SEQ ID NO: 917) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-237-6/3 (SEQ ID NO: 917) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of the QSN-237-6/3 (SEQ ID NO: 917) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-O-(2-methoxyethyl) (2'-MOE) nucleosides.

[00277] In particular embodiments, QSN-237-6/5 (SEQ ID NO: 918) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-237-6/5 (SEQ ID NO: 918) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-237-6/5 (SEQ ID NO: 918) exhibits between 50 to 60% rescue of full length STMN2. In some embodiments, all internucleoside linkages of QSN-237-6/5 (SEQ ID NO: 918) oligonucleotide are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2'-O-(2-methoxyethyl) (2'-MOE) nucleosides.

[00278] In particular embodiments, QSN-173-po3 (SEQ ID NO: 1417) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-173-po3 (SEQ ID NO: 1417) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-173-po3 (SEQ ID NO: 1417) exhibits between 50 to 60% rescue of full length STMN2. In particular embodiments, QSN-173-po5 (SEQ ID NO: 1418) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-173-po5 (SEQ ID NO: 1418) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-173-po5 (SEQ ID NO: 1418) exhibits between 50 to 60% rescue of full length STMN2.

[00279] In particular embodiments, QSN-144-po3 (SEQ ID NO: 1419) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-144-po3 (SEQ ID NO: 1419) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-144-po3 (SEQ ID NO: 1419) exhibits between 50 to 60% rescue of full length STMN2. In particular embodiments, QSN-144-po5 (SEQ ID NO: 1420) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-144-po5 (SEQ ID NO: 1420) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-144-po5 (SEQ ID NO: 1420) exhibits between 50 to 60% rescue of full length STMN2.

[00280] In particular embodiments, QSN-185-po3 (SEQ ID NO: 1421) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-185-po3 (SEQ ID NO: 1421) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-185-po3 (SEQ ID NO: 1421) exhibits between 50 to 60% rescue of full length STMN2. In particular embodiments, QSN-185-po5 (SEQ ID NO: 1422) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-185-po5 (SEQ ID NO: 1422) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-185-po5 (SEQ ID NO: 1422) exhibits between 50 to 60% rescue of full length STMN2.

[00281] In particular embodiments, QSN-237-po3 (SEQ ID NO: 1423) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-237-po3 (SEQ ID NO: 1423) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-237-po3 (SEQ ID NO: 1423) exhibits between 50 to 60% rescue of full length STMN2. In particular embodiments, QSN-237-po5 (SEQ ID NO: 1424) exhibits between 30 to 100% rescue of full length STMN2. In particular embodiments, QSN-237-po5 (SEQ ID NO: 1424) exhibits between 40 to 80% rescue of full length STMN2. In particular embodiments, QSN-237-po5 (SEQ ID NO: 1424) exhibits between 50 to 60% rescue of full length STMN2.

Additional Chemically Modified STMN2 Antisense Oligonucleotides

[00282] STMN2 AONs described herein, can include chemically modified nucleosides, including modified ribonucleosides and modified deoxyribonucleosides. Chemically modified nucleosides include, but are not limited to, uracil, uracine, uridine, 2'-O-(2-methoxyethyl) modifications, for example, 2'-O-(2-methoxyethyl)guanosine, 2'-O-(2-methoxyethyl)adenosine, 2'-O-(2-methoxyethyl)cytosine, and 2'-O-(2-methoxyethyl)thymidine. In certain embodiments, mixed modalities, *e.g.*, a combination of a STMN2 peptide nucleic acid (PNA) and a STMN2 locked nucleic acid (LNA). Chemically modified nucleosides also include, but are not limited to,

locked nucleic acids (LNAs), 2'-MOE, 2'-O-methyl, 2'-fluoro, and 2'-fluoro-β-D-arabinonucleotide (FANA), and Fluoro Cyclohexenyl nucleic acid (F-CeNA) modifications. Chemically modified nucleosides that can be included in STMN2 AONs described herein are described in Johannes and Lucchino, (2018) "Current Challenges in Delivery and Cytosolic Translocation of Therapeutic RNAs" *Nucleic Acid Ther.* 28(3): 178–93; Rettig and Behlke, (2012) "Progress toward in vivo use of siRNAs-II" *Mol Ther* 20:483–512; and Khvorova and Watts, (2017) "The chemical evolution of oligonucleotide therapies of clinical utility" *Nat Biotechnol.*, 35(3):238-48, the contents of each of which are incorporated by reference herein.

[00283] STMN2 AONs described herein can include chemical modifications that promote stabilization of an oligonucleotide's terminal 5'-phosphate and phosphatase-resistant analogs of 5′-phosphate. Chemical modifications that promote oligonucleotide terminal 5'-phosphate stabilization or which are phosphatase-resistant analogs of 5′-phosphate include, but are not limited to, 5′-methyl phosphonate, 5′-methylenephosphonate, 5′-methylenephosphonate analogs, 5′-*E*-vinyl phosphonate (5′-*E*-VP), 5′-phosphorothioate, and 5′-*C*-methyl analogs. Chemical modifications that promote AON terminal 5'-phosphate stabilization and phosphatase-resistant analogues of 5′-phosphate are described in Khvorova and Watts, (2017) "The chemical evolution of oligonucleotide therapies of clinical utility" *Nat Biotechnol.*, 35(3):238-48, the contents of which are incorporated by reference herein.

[00284] In some embodiments described herein, STMN2 AONs described herein can include chemically modified nucleosides, for example, 2' O-methyl ribonucleosides, for example, 2' O-methyl cytidine, 2' O-methyl guanosine, 2' O-methyl uridine, and/or 2' O-methyl adenosine. STMN2 AONs described herein can include one or more chemically modified bases, including a 5-methylpyrimidine, for example, 5-methyl cytosine, and/or a 5-methylpurine, for example, 5-methylguanine. Chemically modified bases can further include pseudo-uridine or 5'methoxyuridine. STMN2 AONs described herein can include any of the following chemically modified nucleosides: 5-methyl-2'-O-methylcytidine, 5-methyl-2'-O-methylthymidine, 5-methylcytidine, 5-methyluridine, and/or 5-methyl 2'-deoxycytidine.

[00285] STMN2 AONs described herein can include a phosphate backbone where one or more of the oligonucleoside linkages is a phosphate linkage. STMN2 AONs described herein may include a modified oligonucleotide backbone, where one or more of the nucleoside linkages of the nucleobase sequence is selected from the group consisting of a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate

linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothiate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3'amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage. In some embodiments of STMN2 AONs described herein, at least one internucleoside linkage of the nucleobase sequence is a phosphorothioate linkage. For example, in some embodiments of STMN2 AONs described herein, one, two, three, or more internucleoside linkages of the nucleobase sequence is a phosphorothioate linkage. In preferred embodiments of STMN2 AONs described herein, all internucleoside linkages of the nucleobase sequence are phosphorothioate linkages. Thus, in some embodiments, all of the nucleotide linkages of a STMN2 AON of any of SEQ ID NOs: 1-446, SEQ ID NOs: 894-918, SEQ ID NOs: 945-1390, or SEQ ID NOs: 1392-1432 are phosphorothioate linkages. In some embodiments, one or more of the nucleotide linkages of a STMN2 AON of any of SEQ ID NOs: SEQ ID NOs: 1-446, SEQ ID NOs: 894-918, SEQ ID NOs: 945-1390, or SEQ ID NOs: 1392-1432 are phosphorothioate linkages.

[00286] It is contemplated that in some embodiments, a disclosed STMN2 AON may optionally have at least one modified nucleobase, *e.g.*, 5-methyl cytosine, and/or at least one methylphosphonate nucleotide, which is placed, for example, either at only one of the 5′ or 3′ ends or at both 5′ and 3′ ends or along the oligonucleotide sequence. In some embodiments, all internucleoside linkages of a STMN2 AON oligonucleotide of the present disclosure are phosphorothioate linkages, and each of the linked nucleosides of the oligonucleotide are 2’-O-(2-methoxyethyl) (2’-MOE) nucleosides and each “C” is replaced with a 5-MeC.

[00287] Contemplated STMN2 AONs may optionally include at least one modified sugar. For example, the sugar moiety of at least one nucleotide constituting the oligonucleotide is a ribose in which the 2′-OH group may be replaced by any one selected from the group consisting of OR, R, R′OR, SH, SR, NH_2, NR_2, N_3, CN, F, Cl, Br, and I (wherein R is an alkyl or aryl and R′ is an alkylene). Examples of a modified sugar moiety include a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2’-O-(2-methoxyethyl) (2’MOE), 2'-deoxy-2'-fluoro nucleoside, 2’-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2’-4’-bridged nucleic acid (cEt), *S*-cEt, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

[00288] In some embodiments, STMN2 AONs comprise 2'OMe (*e.g.*, an STMN2 AON comprising one or more 2'OMe modified sugar), MOE (*e.g.*, an STMN2 AON comprising one or more MOE modified sugar (*e.g.*, 2'-MOE)), PNA (*e.g.*, a STMN2 AON comprising one or more *N*-(2-aminoethyl)-glycine units linked by amide bonds or carbonyl methylene linkage as repeating units in place of a sugar-phosphate backbone), LNA (*e.g.*, a STMN2 AON comprising one or more locked ribose, and can be a mixture of 2'-deoxy nucleotides or 2'OMe nucleotides), c-ET (*e.g.*, a STMN2 AON comprising one or more cET sugar), cMOE (*e.g.*, a STMN2 AON comprising one or more cMOE sugar), morpholino oligomer (*e.g.*, a STMN2 AON comprising a backbone comprising one or more PMO), deoxy-2'-fluoro nucleoside (*e.g.*, a STMN2 AON comprising one or more 2'-fluoro-β-D-arabinonucleoside), ENA (*e.g.*, a STMN2 AON comprising one or more ENA modified sugar), HNA (*e.g.*, a STMN2 AON comprising one or more HNA modified sugar), or tcDNA (*e.g.*, a STMN2 AON comprising one or more tcDNA modified sugar). In some embodiments, a STMN2 AON comprises one or more phosphorothioate linkage, phosphodiester linkage, phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, morpholino linkage, PNA linkage, or any combination of phosphorothioate linkage, phosphodiester linkage, a phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, morpholino linkage, and PNA linkage. In some embodiments, a STMN2 AON comprises one or more phosphorothioate linkage, phosphodiester linkage, or a combination of phosphorothioate and phosphodiester linkages.

Motor Neuron Diseases

[00289] Motor neuron diseases are a group of diseases characterized by loss of function of motor neurons that coordinate voluntary movement of muscles by the brain. Motor neuron diseases may affect upper and/or lower motor neurons, and may have sporadic or familial origins. Motor neuron diseases include amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), progressive bulbar palsy, pseudobulbar palsy, progressive muscular atrophy, primary lateral sclerosis, spinal muscular atrophy, post-polio syndrome, and ALS with frontotemporal dementia.

[00290] Symptoms of motor neuron diseases include muscle decay or weakening, muscle pain, spasms, slurred speech, difficulty swallowing, loss of muscle control, joint pain, stiff limbs, difficulty breathing, drooling, and complete loss of muscle control, including over basic functions such as breathing, swallowing, eating, speaking, and limb movement. These symptoms are also sometimes accompanied by depression, loss of memory, difficulty with planning, language

deficits, altered behavior, and difficulty assessing spatial relationships and/or changes in personality.

[00291] Motor neuron diseases can be assessed and diagnosed by a clinician of skill, for example, a neurologist, using various tools and tests. For example, the presence or risk of developing a motor neuron disease can be assessed or diagnosed using blood and urine tests (for example, tests that assay for the presence of creatinine kinase), magnetic resonance imaging (MRI), electromyography (EMG), nerve conduction study (NCS), spinal tap, lumbar puncture, and/or muscle biopsy. Motor neuron diseases can be diagnosed with the aid of a physical exam and/or a neurological exam to assess motor and sensory skills, nerve function, hearing and speech, vision, coordination and balance, mental status, and changes in mood or behavior.

Amyotrophic Lateral Sclerosis

[00292] ALS is a progressive motor neuron disease that disrupts signals to all voluntary muscles. ALS results in atrophy of both upper and lower motor neurons. Symptoms of ALS include weakening and wasting of the bulbar muscles, general and bilateral loss of strength, spasticity, muscle spasms, muscle cramps, fasciculations, slurred speech, and difficulty breathing or loss of ability to breathe. Some individuals with ALS also suffer from cognitive decline. At the molecular level, ALS is characterized by protein and RNA aggregates in the cytoplasm of motor neurons, including aggregates of the RNA-binding protein TDP43.

[00293] ALS is most common in males above 40 years of age, although it can also occur in women and children. Risk of ALS is also heightened in individuals who smoke, are exposed to chemicals such as lead, or who have served in the military. Most instances of ALS are sporadic, while only about 10% of cases are familial. Causes of ALS include sporadic or inherited genetic mutations, high levels of glutamate, protein mishandling. Genetic mutations associated with ALS include mutations in the genes SOD1, C9orf72, TARDBP, FUS, ANG, ATXN2, CHCHD10, CHMP2B, DCTN1, ErbB4, FIG4, HNRPA1, MATR3, NEFH, OPTN, PFN1, PRPH, SETX, SIGMAR1, SMN1, SPG11, SQSTM1, TBK1, TRPM7, TUBA4A, UBQLN2, VAPB, and VCP.

Frontotemporal Dementia

[00294] Frontotemporal dementia (FTD) is a form of dementia that affects the frontal and temporal lobes of the brain. It has an earlier average age of onset than Alzheimer's disease – 40 years of age. Symptoms of FTD include extreme changes in behavior and personality, speech and

language problems, and movement-related symptoms such as tremor, rigidity, muscle spasm, weakness, and difficulty swallowing. Subtypes of FTD include behavior variant frontotemporal dementia (bvFTD), characterized by changes in personality and behavior, and primary progressive aphasia (PPA), which affects language skills, speaking, writing and comprehension. FTD is associated with tau protein accumulation (Pick bodies) and altered TDP43 function. About 30% of cases of FTD are familial, and no other risk factors other than family history of the disease are known. Genetic mutations associated with FTD include mutations in the genes C9orf72, Progranulin (GRN), microtubule-associated protein tau (MAPT), UBQLN2, VPC, CHMP2B, TARDBP, FUS, ITM2B, CHCHD10, SQSTM1, PSEN1, PSEN2, CTSF, CYP27A1, TBK1 and TBP.

Amyotrophic lateral sclerosis with frontotemporal dementia

[00295] Amyotrophic lateral sclerosis with frontotemporal dementia (ALS with FTD) is a clinical syndrome in which FTD and ALS occur in the same individual. Interestingly, mutations in C9orf72 are the most common cause of familial forms of ALS and/or FTD. Additionally, mutations in TBK1, VCP, SQSTMI, UBQLN2 and CHMP2B are also associated with ALS with FTD. Symptoms of ALS with FTD include dramatic changes in personality, as well as muscle weakness, muscle atrophy, fasciculations, spasticity, dysarthria, dysphagia, and degeneration of the spinal cord, motor neurons, and frontal and temporal lobes of the brain. At the molecular level, ALS with FTD is characterized by the accumulation of TDP-43 and/or FUS proteins in the cytoplasm. TBK1 mutations are associated with ALS, FTD, and ALS with FTD.

Methods of Treatment

[00296] The disclosure contemplates, in part, treating neurological diseases (for example, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD) and/or neuropathies such a chemotherapy induced neuropathy in a patient in need thereof comprising administering a disclosed inhibitor of STMN2 transcripts that include a cryptic exon, for example, a STMN2 AON. In some embodiments, provided herein are methods for treatment of a neurological disease in a patient in need thereof, comprising administering a disclosed STMN2 AON. In some embodiments of the disclosure, an effective amount of a disclosed inhibitor of STMN2 transcripts that include a cryptic exon may be administered to a patient in

need thereof to treat a neurological disease, and/or to increase, restore, or stabilize expression of STMN2 mRNA that is capable of translation to produce a functional STMN2 protein, thereby increase, restore, or stabilize STMN2 activity and/or function.

[00297] In some embodiments, treating a neurological disease comprises at least ameliorating or reducing one symptom associated with the neurological disease (for example, reducing muscle weakness in a patient with ALS). Methods of treating a neurological disease (for example, ALS, FTD, or ALS with FTD) in a patient suffering therefrom are provided, that include administering a disclosed inhibitor of STMN2 transcripts that include a cryptic exon, for example, a STMN2 AON. In some embodiments, methods of slowing the progression of a neurological disease, for example, a motor neuron disease, are provided.

[00298] Provided herein are methods of treating, reducing the risk of developing, or delaying the onset of a neurological disease in a subject in need thereof comprising administering a disclosed inhibitor of STMN2 transcripts that include a cryptic exon, for example, a STMN2 AON. The methods include for example, treating a subject at risk of developing a neurological disease; *e.g.*, administering to the subject an effective amount of a disclosed STMN2 AON. Neurological diseases that can be treated in this manner include motor neuron diseases, ALS, FTD, ALS with FTD, progressive bulbar palsy, pseudobulbar palsy, progressive muscular atrophy, primary lateral sclerosis, spinal muscular atrophy, and post-polio syndrome.

[00299] Methods of preventing or treating neurological diseases (for example, PD, ALS, FTD, and ALS with FTD) form part of this disclosure. Such methods may comprise administering to a patient in need thereof or a patient at risk, a pharmaceutical preparation comprising a STMN2 AON such as a STMN2 AON disclosed herein. For example, a method of preventing or treating a neurological disease is provided comprising administering to a patient in need thereof a STMN2 AON disclosed herein.

[00300] Patients treated using an above method may experience an increase, restoration of, or stabilization of STMN2 mRNA expression, which is capable of translation to produce a functional STMN2 protein, of at least about 5%, 10%, 20%, 30%, 40% or even 50%, thereby increase, restore, or stabilize STMN2 activity and/or function in a target cell (for example, a motor neuron) after administering an inhibitor of STMN2 transcripts that include a cryptic exon, after *e.g.* 1 day, 2 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 1 month, 2 months, 3, months, 4 months, 5, months, or 6 months or more. Administering such inhibitor of

STMN2 transcripts that include a cryptic exon may be on, *e.g.*, at least a daily basis. The inhibitor of STMN2 transcripts that include a cryptic exon may be administered orally. In some embodiments, the inhibitor of STMN2 transcripts that include a cryptic exon is administered intrathecally or intracisternally. For example, in an embodiment described herein, an inhibitor of STMN2 transcripts that include a cryptic exon is administered intrathecally or intracisternally about every 3 months. The delay or amelioration of clinical manifestation of a neurological disease in a patient as a consequence of administering an inhibitor of STMN2 transcripts that include a cryptic exon disclosed here may be at least *e.g.*, 6 months, 1 year, 18 months or even 2 years or more as compared to a patient who is not administered an inhibitor of STMN2 transcripts that include a cryptic exon, such as one disclosed herein.

[00301] The inhibitors of STMN2 transcripts that include a cryptic exon, for example STMN2 AONs, of the invention can be used alone or in combination with each other whereby at least two inhibitors of STMN2 transcripts that include a cryptic exon of the invention are used together in a single composition or as part of a treatment regimen. STMN2 oligonucleotides can be used alone or in combination with each other whereby at least two STMN2 oligonucleotides are used together in a single composition or as part of a treatment regimen. The inhibitors of STMN2 transcripts that include a cryptic exon of the invention may also be used in combination with other drugs for treating neurological diseases or conditions.

Treatment and Evaluation

[00302] A patient, as described herein, refers to any animal at risk for, suffering from or diagnosed with a neurological disease, including, but not limited to, mammals, primates, and humans. In certain embodiments, the patient may be a non-human mammal such as, for example, a cat, a dog, or a horse. In certain embodiments, the patient is a human. A patient may be an individual diagnosed with a high risk of developing a neurological disease, someone who has been diagnosed with a neurological disease, someone who previously suffered from a neurological disease, or an individual evaluated for symptoms or indications of a neurological disease, for example, any of the signs or symptoms associated with neurological diseases such as amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD) and/or neuropathies such a chemotherapy induced neuropathy.

[00303] "A patient in need," as used herein, refers to a patient suffering from any of the symptoms or manifestations of a neurological disease, a patient who may suffer from any of the symptoms or manifestations of a neurological disease, or any patient who might benefit from a method of the disclosure for treating a neurological disease. A patient in need may include a patient who is diagnosed with a risk of developing a neurological disease, a patient who has suffered from a neurological disease in the past, or a patient who has previously been treated for a neurological disease.

[00304] "Effective amount," as used herein, refers to the amount of an agent that is sufficient to at least partially treat a condition when administered to a patient. The therapeutically effective amount will vary depending on the severity of the condition, the route of administration of the component, and the age, weight, etc. of the patient being treated. Accordingly, an effective amount of a disclosed inhibitor of STMN2 transcripts that include a cryptic exon is the amount of the inhibitor of STMN2 transcripts that include a cryptic exon necessary to treat a neurological disease in a patient such that administration of the agent prevents a neurological disease from occurring in a subject, prevents neurological disease progression (*e.g.*, prevents the onset or increased severity of symptoms of the neurological such as muscle weakening, spasms, or fasciculation), or relieves or completely ameliorates all associated symptoms of a neurological disease, *i.e.* causes regression of the disease.

[00305] Efficacy of treatment may be evaluated by means of evaluation of gross symptoms associated with a neurological disease, analysis of tissue histology, biochemical assay, imaging methods such as, for example, magnetic resonance imaging, or other known methods. For instance, efficacy of treatment may be evaluated by analyzing gross symptoms of the disease such as changes in muscle strength and control or other aspects of gross pathology associated with a neurological disease following administration of a disclosed inhibitor of STMN2 transcripts that include a cryptic exon to a patient suffering from a neurological disease.

[00306] Efficacy of treatment may also be evaluated at the tissue or cellular level, for example, by means of obtaining a tissue biopsy (*e.g.*, a brain, spinal, muscle, or motor neuron tissue biopsy) and evaluating gross tissue or cell morphology or staining properties. Biochemical assays that examine protein or RNA expression may also be used to evaluate efficacy of treatment. For instance, one may evaluate levels of a protein or gene product indicative of a neurological disease, in dissociated cells or non-dissociated tissue via immunocytochemical, immunohistochemical, Western blotting, or Northern blotting methods, or methods useful for evaluating RNA levels such

as quantitative or semi-quantitative polymerase chain (*e.g.*, digital PCR (DigitalPCR, dPCR, or dePCR), qPCR etc.) reaction. One may also evaluate the presence or level of expression of useful biomarkers (*e.g.*, neurofilament light (NEFL), neurofilament heavy (NEFH), TDP-43 or p75 extracellular domain ($p75^{ECD}$)) found in spinal cord fluid, cerebrospinal fluid, extracellular vesicles (for example, exosome-like cerebrospinal fluid extracellular vesicles ("CSF exosomes"), such as those described in Welton *et al.*, (2017) "Cerebrospinal fluid extracellular vesicle enrichment for protein biomarker discovery in neurological disease; multiple sclerosis" *J Extracell Vesicles.*, 6(1):1-10; and Street *et al.*, (2012) "Identification and proteomic profiling of exosomes in human cerebrospinal fluid" *J Transl. Med.*, 10:5), urine, fecal matter, lymphatic fluid, blood, plasma, or serum to evaluate disease state and efficacy of treatment. One may also evaluate the presence or level of expression of useful biomarkers found in the plasma, neuronal extracellular vesicles/exosomes. Additional measurements of efficacy may include strength duration time constant (SDTC), short interval cortical inhibition (SICI), dynamometry, accurate test of limb isometric strength (ATLIS), compound muscle action potential (bio), and ALSFRS-R. In certain embodiments, urinary neurotrophin receptor p75 extracellular domain ($p75^{ECD}$) is a disease progression and prognostic biomarker in amyotrophic lateral sclerosis (ALS). Phosphorylated neurofilament heavy chain (pNFH) in cerebrospinal fluid (CSF) predict disease status and survival in *C9ORF72*-associated amyotrophic lateral sclerosis (c9ALS) patients. CSF pNFH as a prognostic biomarker for clinical trials, which will increase the likelihood of successfully developing a treatment for c9ALS.

[00307] In evaluating efficacy of treatment, suitable controls may be chosen to ensure a valid assessment. For instance, one can compare symptoms evaluated in a patient with a neurological disease following administration of a disclosed inhibitor of STMN2 transcripts that include a cryptic exon to those symptoms in the same patient prior to treatment or at an earlier point in the course of treatment or in another patient not diagnosed with the neurological disease. Alternatively, one may compare the results of biochemical or histological analysis of tissue following administration of a disclosed inhibitor of STMN2 transcripts that include a cryptic exon with those of tissue from the same patient or from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the inhibitor of STMN2 transcripts that include a cryptic exon. Additionally, one may compare blood, plasma, serum, cell, urine, lymphatic fluid, spinal cord fluid, cerebrospinal fluid, or fecal samples following administration of the inhibitor of STMN2 transcripts that include a cryptic exon with comparable samples from an individual not diagnosed with the neurological disease or from the same patient

prior to administration of the inhibitor of STMN2 transcripts that include a cryptic exon. In some embodiments one may compare extracellular vesicles (for example CSF exosomes), following administration of the inhibitor of STMN2 transcripts that include a cryptic exon with extracellular vesicles from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the inhibitor of STMN2 transcripts that include a cryptic exon.

[00308] Validation of inhibition of STMN2 transcripts that include a cryptic exon may be determined by direct or indirect assessment of STMN2 expression levels or activity. For instance, biochemical assays that measure STMN2 protein or RNA expression may be used to evaluate overall inhibition of STMN2 transcripts that include a cryptic exon. For instance, one may measure STMN2 protein levels in cells or tissue by Western blot to evaluate overall STMN2 levels. One may also measure STMN2 mRNA levels by means of Northern blot or quantitative polymerase chain reaction to determine overall inhibition of STMN2 transcripts that include a cryptic exon. One may also evaluate STMN2 protein levels or levels of another protein indicative of STMN2 signaling activity in dissociated cells, non-dissociated tissue, extracellular vesicles (for example, CSF exosomes), blood, serum, or fecal matter via immunocytochemical or immunohistochemical methods.

[00309] Modulation of splicing of STMN2 transcripts that include a cryptic exon may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of useful biomarkers (*e.g.*, neurofilament light (NEFL), neurofilament heavy (NEFH), TDP-43, or $p75^{ECD}$ found in plasma, spinal cord fluid, cerebrospinal fluid, extracellular vesicles (for example, CSF exosomes), blood, urine, lymphatic fluid, fecal matter, or tissue to evaluate efficacy of inhibition of STMN2 transcripts that include a cryptic exon. Inhibition of STMN2 transcripts that include a cryptic exon may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of physiological biomarkers such as compound muscle action potential (bio). Additional measurements may include strength duration time constant (SDTC), short interval cortical inhibition (SICI), dynamometry, accurate test of limb isometric strength (ATLIS), compound muscle action potential, and ALSFRS-R. In certain embodiments, urinary neurotrophin receptor p75 extracellular domain ($p75^{ECD}$) is a disease progression and prognostic biomarker in amyotrophic lateral sclerosis (ALS). Phosphorylated neurofilament heavy chain (pNFH) in cerebrospinal fluid (CSF) predict disease status and

survival in c9ALS patients. CSF pNFH as a prognostic biomarker for clinical trials, which will increase the likelihood of successfully developing a treatment for c9ALS.

[00310] In some embodiments, the present disclosure provides methods of correcting splicing of a STMN2 transcript with a cryptic exon, and thereby restoring full length STMN2 protein expression in cells of a patient suffering from a neurological disease. Splicing of a STMN2 transcript may be corrected in any cell in which STMN2 expression or activity occurs, including cells of the nervous system (including the central nervous system, the peripheral nervous system, motor neurons, the brain, the brain stem, the frontal lobes, the temporal lobes, the spinal cord), the musculoskeletal system, spinal fluid, and cerebrospinal fluid. Cells of the musculoskeletal system include skeletal muscle cells (*e.g.*, myocytes). Motor neurons include upper motor neurons and lower motor neurons.

Pharmaceutical Compositions and Routes of Administration

[00311] The present disclosure also provides methods for treating a neurological disease via administration of a pharmaceutical composition comprising a disclosed inhibitor of STMN2 transcripts that include a cryptic exon. In another aspect, the disclosure provides a pharmaceutical composition for use in treating a neurological disease. The pharmaceutical composition may be comprised of a disclosed antisense oligonucleotide that targets STMN2 transcripts that include a cryptic exon, and a pharmaceutically acceptable carrier. As used herein the term "pharmaceutical composition" means, for example, a mixture containing a specified amount of a therapeutic compound, *e.g.*, a therapeutically effective amount, of a therapeutic compound in a pharmaceutically acceptable carrier to be administered to a mammal, *e.g.*, a human, in order to treat a neurological disease. In some embodiments, contemplated herein are pharmaceutical compositions comprising a disclosed inhibitor of STMN2 transcripts that include a cryptic exon, and a pharmaceutically acceptable carrier. In another aspect, the disclosure provides use of a disclosed inhibitor of STMN2 transcripts that include a cryptic exon in the manufacture of a medicament for treating a neurological disease. "Medicament," as used herein, has essentially the same meaning as the term "pharmaceutical composition."

[00312] As used herein, "pharmaceutically acceptable carrier" means buffers, carriers, and excipients suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. The carrier(s) should be "acceptable" in the sense of being

compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers include buffers, solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art. In one embodiment the pharmaceutical composition is administered orally and includes an enteric coating suitable for regulating the site of absorption of the encapsulated substances within the digestive system or gut. For example, an enteric coating can include an ethylacrylate-methacrylic acid copolymer.

[00313] In one embodiment, a disclosed inhibitor of STMN2 transcripts that include a cryptic exon and any pharmaceutical composition thereof may be administered by one or several routes, including topically, intrathecally, intracisternally, parenterally (*e.g.*, subcutaneous, intramuscular, intradermal, intraduodenal, or intravenous), intralesionally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, or intraduodenally. The term parenteral as used herein includes subcutaneous injections, intrapancreatic administration, intravenous, intracisternal, intrathecal, intramuscular, intraperitoneal, intrasternal injection or infusion techniques. For example, a disclosed inhibitor of STMN2 transcripts that include a cryptic exon may be administered subcutaneously to a subject. In another example, a disclosed inhibitor of STMN2 transcripts that include a cryptic exon may be administered orally to a subject. In another example, a disclosed inhibitor of STMN2 transcripts that include a cryptic exon may be administered directly to the nervous system, or specific regions or cells of the nervous system (*e.g.*, the brain, brain stem, lower motor neurons, spinal cord, upper motor neurons) via parenteral administration, for example, a disclosed inhibitor of STMN2 transcripts that include a cryptic exon may be administered intrathecally or intracisternally.

[00314] In some embodiments, an inhibitor of STMN2 transcripts that include a cryptic exon, for example a STMN2 AON, can be encapsulated in a nanoparticle coating. It is believed that nanoparticle encapsulation prevents AON degradation and enhances cellular uptake. For example, in some embodiments an inhibitor of STMN2 transcripts that include a cryptic exon is encapsulated in a coating of a cationic polymer, for example, a synthetic polymer (*e.g.*, poly-L-lysine, polyamidoamine, a poly(β-amino ester), and polyethyleneimine) or a naturally occurring polymer (*e.g.*, chitosan and a protamine). In some embodiments, an inhibitor of STMN2 transcripts that include a cryptic exon is encapsulated in a lipid or lipid-like material, for example, a cationic lipid, a cationic lipid-like material, or an ionizable lipid that is positively charged only

at an acidic pH. For example, in some embodiments, an inhibitor of STMN2 transcripts that include a cryptic exon is encapsulated in a lipid nanoparticle that includes hydrophobic moieties, *e.g.*, cholesterol and/or a polyethylene glycol (PEG) lipid.

[00315] In some embodiments, an inhibitor of STMN2 transcripts that include a cryptic exon, for example, a STMN2 AON, is conjugated to a bioactive ligand. For example, in some embodiments described herein, an inhibitor of STMN2 transcripts that include a cryptic exon such as a STMN2 AON is conjugated to a peptide, a lipid, N-acetylgalactosamine (GalNAc), cholesterol, vitamin E, an antibody, or a cell-penetrating peptide (for example, transactivator of transcription (TAT) and penetratine).

[00316] Pharmaceutical compositions containing a disclosed inhibitor of STMN2 transcripts that include a cryptic exon, such as those disclosed herein, can be presented in a dosage unit form and can be prepared by any suitable method. A pharmaceutical composition should be formulated to be compatible with its intended route of administration. Useful formulations can be prepared by methods well known in the pharmaceutical art. For example, see *Remington's Pharmaceutical Sciences*, 18th ed. (Mack Publishing Company, 1990).

[00317] Pharmaceutical formulations, in some embodiments, are sterile. Sterilization can be accomplished, for example, by filtration through sterile filtration membranes. Where the composition is lyophilized, filter sterilization can be conducted prior to or following lyophilization and reconstitution.

Parenteral Administration

[00318] The pharmaceutical compositions of the disclosure can be formulated for parenteral administration, *e.g.*, formulated for injection via the intravenous, intracisternal, intramuscular, subcutaneous, intrathecal, intralesional, or intraperitoneal routes. The preparation of an aqueous composition, such as an aqueous pharmaceutical composition containing a disclosed inhibitor of STMN2 transcripts that include a cryptic exon, will be known to those of skill in the art in light of the present disclosure. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for use in preparing solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified.

[00319] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including normal saline, phosphate buffer saline, artificial cerebrospinal fluid, sesame oil, peanut oil or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

[00320] Solutions of active compounds as free base or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables. The sterile injectable preparation may also be a sterile injectable solution, suspension, or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. In one embodiment, a disclosed STMN2 antisense oligonucleotide may be suspended in a carrier fluid comprising 1% (w/v) sodium carboxymethylcellulose and 0.1% (v/v) TWEEN™ 80. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[00321] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. Sterile injectable solutions of the disclosure may be prepared by incorporating a disclosed STMN2 antisense oligonucleotide (*e.g.*, inhibitor of STMN2 transcripts that include a cryptic exon) in the required amount of the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a

previously sterile-filtered solution thereof. The injectable formulations can be sterilized, for example, by filtration through a bacteria-retaining filter.

[00322] The preparation of more, or highly concentrated solutions for intramuscular injection is also contemplated. In this regard, the use of DMSO as solvent is preferred as this will result in extremely rapid penetration, delivering high concentrations of the disclosed inhibitor of STMN2 transcripts that include a cryptic exon to a small area.

[00323] Suitable preservatives for use in such a solution include benzalkonium chloride, benzethonium chloride, chlorobutanol, thimerosal and the like. Suitable buffers include boric acid, sodium and potassium bicarbonate, sodium and potassium borates, sodium and potassium carbonate, sodium acetate, sodium biphosphate and the like, in amounts sufficient to maintain the pH at between about pH 6 and pH 8, and for example, between about pH 7 and pH 7.5. Suitable tonicity agents are dextran 40, dextran 70, dextrose, glycerin, potassium chloride, propylene glycol, sodium chloride, and the like, such that the sodium chloride equivalent of the solution is in the range 0.9 plus or minus 0.2%. Suitable antioxidants and stabilizers include sodium bisulfite, sodium metabisulfite, sodium thiosulfite, thiourea and the like. Suitable wetting and clarifying agents include polysorbate 80, polysorbate 20, poloxamer 282 and tyloxapol. Suitable viscosity-increasing agents include dextran 40, dextran 70, gelatin, glycerin, hydroxyethylcellulose, hydroxymethylpropylcellulose, lanolin, methylcellulose , petrolatum, polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose and the like.

Oral Administration

[00324] In some embodiments, contemplated herein are compositions suitable for oral delivery of a disclosed inhibitor of STMN2 transcripts that include a cryptic exon, *e.g.*, tablets that include an enteric coating, *e.g.*, a gastro-resistant coating, such that the compositions may deliver an inhibitor of STMN2 transcripts that include a cryptic exon to, *e.g.*, the gastrointestinal tract of a patient.

[00325] For example, a tablet for oral administration is provided that comprises granules (*e.g.*, is at least partially formed from granules) that include a disclosed inhibitor of STMN2 transcripts that include a cryptic exon, *e.g.*, a STMN2 antisense oligonucleotide, *e.g.*, a STMN2 antisense oligonucleotide represented by any of SEQ ID NOs: 1-446, SEQ ID NOs: 894-918, SEQ ID NOs: 945-1390, or SEQ ID NOs: 1392-1432, and pharmaceutically acceptable excipients. Such a tablet

may be coated with an enteric coating. Contemplated tablets may include pharmaceutically acceptable excipients such as fillers, binders, disintegrants, and/or lubricants, as well as coloring agents, release agents, coating agents, sweetening, flavoring such as wintergreen, orange, xylitol, sorbitol, fructose, and maltodextrin, and perfuming agents, preservatives and/or antioxidants.

[00326] In some embodiments, contemplated pharmaceutical formulations include an intra-granular phase that includes a disclosed inhibitor of STMN2 transcripts that include a cryptic exon, *e.g.* a STMN2 antisense oligonucleotide, *e.g.*, a STMN2 antisense oligonucleotide represented by any of SEQ ID NOs: 1-446, SEQ ID NOs: 894-918, SEQ ID NOs: 945-1390, or SEQ ID NOs: 1392-1432, and a pharmaceutically acceptable salt, *e.g.*, a STMN2 antisense oligonucleotide, *e.g.*, an antisense oligonucleotide represented by any of SEQ ID NOs: 1-446, SEQ ID NOs: 894-918, SEQ ID NOs: 945-1390, or SEQ ID NOs: 1392-1432, and a pharmaceutically acceptable filler. For example, a disclosed inhibitor of STMN2 transcripts that include a cryptic exon and a filler may be blended together, optionally, with other excipients, and formed into granules. In some embodiments, the intragranular phase may be formed using wet granulation, *e.g.*, a liquid (*e.g.*, water) is added to the blended inhibitor of STMN2 transcripts that include a cryptic exon compound and filler, and then the combination is dried, milled and/or sieved to produce granules. One of skill in the art would understand that other processes may be used to achieve an intragranular phase.

[00327] In some embodiments, contemplated formulations include an extra-granular phase, which may include one or more pharmaceutically acceptable excipients, and which may be blended with the intragranular phase to form a disclosed formulation.

[00328] A disclosed formulation may include an intragranular phase that includes a filler. Exemplary fillers include, but are not limited to, cellulose, gelatin, calcium phosphate, lactose, sucrose, glucose, mannitol, sorbitol, microcrystalline cellulose, pectin, polyacrylates, dextrose, cellulose acetate, hydroxypropylmethyl cellulose, partially pre-gelatinized starch, calcium carbonate, and others including combinations thereof.

[00329] In some embodiments, a disclosed formulation may include an intragranular phase and/or an extragranular phase that includes a binder, which may generally function to hold the ingredients of the pharmaceutical formulation together. Exemplary binders of the disclosure may include, but are not limited to, the following: starches, sugars, cellulose or modified cellulose such as hydroxypropyl cellulose, lactose, pre-gelatinized maize starch, polyvinyl pyrrolidone,

hydroxypropyl cellulose, hydroxypropylmethyl cellulose, low substituted hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl cellulose, sugar alcohols and others including combinations thereof.

[00330] Contemplated formulations, *e.g.*, that include an intragranular phase and/or an extragranular phase, may include a disintegrant such as, but not limited to, starch, cellulose, crosslinked polyvinyl pyrrolidone, sodium starch glycolate, sodium carboxymethyl cellulose, alginates, corn starch, crosmellose sodium, crosslinked carboxymethyl cellulose, low substituted hydroxypropyl cellulose, acacia, and others including combinations thereof. For example, an intragranular phase and/or an extragranular phase may include a disintegrant.

[00331] In some embodiments, a contemplated formulation includes an intra-granular phase comprising a disclosed inhibitor of STMN2 transcripts that include a cryptic exon and excipients chosen from: mannitol, microcrystalline cellulose, hydroxypropylmethyl cellulose, and sodium starch glycolate or combinations thereof, and an extra-granular phase comprising one or more of: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate or mixtures thereof.

[00332] In some embodiments, a contemplated formulation may include a lubricant, *e.g.* an extra-granular phase may contain a lubricant. Lubricants include but are not limited to talc, silica, fats, stearin, magnesium stearate, calcium phosphate, silicone dioxide, calcium silicate, calcium phosphate, colloidal silicon dioxide, metallic stearates, hydrogenated vegetable oil, partially hydrogenated vegetable oil, corn starch, sodium benzoate, polyethylene glycols, sodium acetate, calcium stearate, sodium lauryl sulfate, sodium chloride, magnesium lauryl sulfate, talc, and stearic acid.

[00333] In some embodiments, the pharmaceutical formulation comprises an enteric coating. Generally, enteric coatings create a barrier for the oral medication that controls the location at which the drug is absorbed along the digestive track. Enteric coatings may include a polymer that disintegrates at different rates according to pH. Enteric coatings may include for example, cellulose acetate phthalate, methyl acrylate-methacrylic acid copolymers, cellulose acetate succinate, hydroxylpropylmethyl cellulose phthalate, methyl methacrylate-methacrylic acid copolymers, ethylacrylate-methacrylic acid copolymers, methacrylic acid copolymer type C, polyvinyl acetate-phthalate, and cellulose acetate phthalate.

[00334] Exemplary enteric coatings include Opadry® AMB, Acryl-EZE®, Eudragit® grades. In some embodiments, an enteric coating may comprise about 5% to about 10%, about 5% to about 20%, 8% to about 15%, about 8% to about 20%, about 10% to about 20%, or about 12 to about 20%, or about 18% of a contemplated tablet by weight. For example, enteric coatings may include an ethylacrylate-methacrylic acid copolymer.

[00335] For example, in a contemplated embodiment, a tablet is provided that comprises or consists essentially of about 0.5% to about 70%, *e.g.*, about 0.5% to about 10%, or about 1% to about 20%, by weight of a disclosed STMN2 antisense oligonucleotide or a pharmaceutically acceptable salt thereof. Such a tablet may include for example, about 0.5% to about 60% by weight of mannitol, *e.g.*, about 30% to about 50% by weight mannitol, *e.g.*, about 40% by weight mannitol; and/or about 20% to about 40% by weight of microcrystalline cellulose, or about 10% to about 30% by weight of microcrystalline cellulose. For example, a disclosed tablet may comprise an intragranular phase that includes about 30% to about 60%, *e.g.* about 45% to about 65% by weight, or alternatively, about 5 to about 10% by weight of a disclosed STMN2 antisense oligonucleotide, about 30% to about 50%, or alternatively, about 5% to about 15% by weight mannitol, about 5% to about 15% microcrystalline cellulose, about 0% to about 4%, or about 1% to about 7% hydroxypropylmethylcellulose, and about 0% to about 4%, *e.g.*, about 2% to about 4% sodium starch glycolate by weight.

[00336] In another contemplated embodiment, a pharmaceutical tablet formulation for oral administration of a disclosed inhibitor of STMN2 transcripts that include a cryptic exon comprises an intra-granular phase, wherein the intra-granular phase includes a disclosed STMN2 AON or a pharmaceutically acceptable salt thereof (such as a sodium salt), and a pharmaceutically acceptable filler, and which may also include an extra-granular phase, that may include a pharmaceutically acceptable excipient such as a disintegrant. The extra-granular phase may include components chosen from microcrystalline cellulose, magnesium stearate, and mixtures thereof. The pharmaceutical composition may also include an enteric coating of about 12% to 20% by weight of the tablet. For example, a pharmaceutically acceptable tablet for oral use may comprise about .5% to 10% by weight of a disclosed STMN2 AON, *e.g.*, a disclosed STMN2 AON or a pharmaceutically acceptable salt thereof, about 30% to 50% by weight mannitol, about 10% to 30% by weight microcrystalline cellulose, and an enteric coating comprising an ethylacrylate-methacrylic acid copolymer.

[00337] In another example, a pharmaceutically acceptable tablet for oral use may comprise an intra-granular phase, comprising about 5 to about 10% by weight of a disclosed STMN2 AON, *e.g.*, a disclosed STMN2 AON or a pharmaceutically acceptable salt thereof, about 40% by weight mannitol, about 8% by weight microcrystalline cellulose, about 5% by weight hydroxypropylmethyl cellulose, and about 2% by weight sodium starch glycolate; an extra-granular phase comprising about 17% by weight microcrystalline cellulose, about 2% by weight sodium starch glycolate, about 0.4% by weight magnesium stearate; and an enteric coating over the tablet comprising an ethylacrylate-methacrylic acid copolymer.

[00338] In some embodiments the pharmaceutical composition may contain an enteric coating comprising about 13% or about 15%, 16%, 17% or 18% by weight, *e.g.*, AcyrlEZE® (*see, e.g.*, PCT Publication No. WO 2010/054826, which is hereby incorporated by reference in its entirety).

[00339] The rate at which the coating dissolves and the active ingredient is released is its dissolution rate. In an embodiment, a contemplated tablet may have a dissolution profile, *e.g.* when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in a phosphate buffer with a pH of 7.2, of about 50% to about 100% of the inhibitor of STMN2 transcripts that include a cryptic exon releasing after about 120 minutes to about 240 minutes, for example after 180 minutes. In another embodiment, a contemplated tablet may have a dissolution profile, *e.g.* when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in diluted HCl with a pH of 1.0, where substantially none of the inhibitor of STMN2 transcripts that include a cryptic exon is released after 120 minutes. A contemplated tablet, in another embodiment, may have a dissolution profile, *e.g.* when tested in USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in a phosphate buffer with a pH of 6.6, of about 10% to about 30%, or not more than about 50%, of the inhibitor of STMN2 transcripts that include a cryptic exon releasing after 30 minutes.

[00340] In some embodiments, methods provided herein may further include administering at least one other agent that is directed to treatment of diseases and disorders disclosed herein. In one embodiment, contemplated other agents may be co-administered (*e.g.*, sequentially or simultaneously).

Dosage and Frequency of Administration

[00341] The dosage or amounts described below refer either to the oligonucleotide or a pharmaceutically acceptable salt thereof.

[00342] In some embodiments, formulations include dosage forms that include at least 1 μg, at least 5 μg, at least 10 μg, at least 20 μg, at least 30 μg, at least 40 μg, at least 50 μg, at least 60 μg, at least 70 μg, at least 80 μg, at least 90 μg, or at least 100 μg of an inhibitor, for example, a STMN2 antisense oligonucleotide, of STMN2 transcripts that include a cryptic exon. In some embodiments, formulations include dosage forms that include from 10 mg to 500 mg, from 1 mg to 10 mg, from 10 mg to 20 mg, from 20 mg to 30 mg, from 30 mg to 40 mg, from 40 mg to 50 mg, from 50 mg to 60 mg, from 60 mg to 70 mg, from 70 mg to 80 mg, from 80 mg to 90 mg, from 90 mg to 100 mg, from 100 mg to 150 mg, from 150 mg to 200 mg, from 200 mg to 250 mg, from 250 mg to 300 mg, from 300 mg to 350 mg, from 350 mg to 400 mg, from 400 mg to 450 mg, from 450 mg to 500 mg, from 500 mg to 600 mg, from 600 mg to 700 mg, from 700 mg to 800 mg, from 800 mg to 900 mg, from 900 mg to 1 g, from 1 mg to 50 mg, from 20 mg to 40 mg, or from 1 mg to 500 mg of a STMN2 antisense oligonucleotide.

[00343] In some embodiments, formulations include dosage forms that include or consist essentially of about 10 mg to about 500 mg of an inhibitor of STMN2 transcripts that include a cryptic exon, for example, a STMN2 AON. For example, formulations that include about 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1 g, 1.5 g, 2.0 g, 2.5 g, 3.0 g, 3.5 g, 4.0 g, 4.5 g, or 5.0 g of a disclosed inhibitor of STMN2 transcripts that include a cryptic exon are contemplated herein. In some embodiments, a formulation may include about 40 mg, 80 mg, or 160 mg of a disclosed inhibitor of STMN2 transcripts that include a cryptic exon. In some embodiments, a formulation may include at least 100 μg of a disclosed inhibitor of STMN2 transcripts that include a cryptic exon. For example, formulations may include about 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg of a disclosed inhibitor of STMN2 transcripts that include a cryptic exon. The amount administered will depend on variables such as the type and extent of disease or indication to be treated, the overall health and size of the patient, the *in vivo* potency of the inhibitor of STMN2 transcripts that include a cryptic exon, the pharmaceutical formulation, and the route of administration. The initial dosage can be increased beyond the upper level in order to rapidly achieve the desired blood-level or tissue level. Alternatively, the initial dosage can be smaller than the optimum, and the dosage may be progressively increased during the course of treatment. Human dosage can be optimized, *e.g.*, in a conventional Phase I dose escalation study. Dosing frequency can vary, depending on factors such as route of administration, dosage amount and the disease being

treated. Exemplary dosing frequencies are once per day, once per week and once every two weeks. In some embodiments, dosing is once per day for 7 days. In some embodiments, dosing is once every 4 weeks, once every 5 weeks, once every 6 weeks, once every 7 weeks, once every 8 weeks, once every 9 weeks, once every 10 weeks, once every 11 weeks, or once every 12 weeks. In some embodiments, dosing is once a month to every three months.

Combination Therapies

[00344] In various embodiments, a STMN2 AON as disclosed herein can be administered in combination with one or more additional therapies. The combination therapy of the disclosed oligonucleotide and the one or more additional therapies can, in some embodiments, be synergistic in treating any of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD) and/or neuropathies such a chemotherapy induced neuropathy.

[00345] Example additional therapies include any of Riluzole (Rilutek), Edaravone (Radicava), rivastigmine, donepezil, galantamine, selective serotonin reuptake inhibitor, antipsychotic agents, cholinesterase inhibitors, memantine, benzodiazepine antianxiety drugs, AMX0035 (ELYBRIO), ZILUCOPLAN (RA101495), dual AON intrathecal administration (*e.g.*, BIIB067, BIIB078), BIIB100, levodopa/carbidopa, dopaminergic agents (*e.g.*, ropinirole, pramipexole, rotigotine), medroxyprogesterone, KCNQ2/KCNQ3 openers, anticonvulsants and psychostimulant agents. Additional therapies can further include breathing care, physical therapy, occupational therapy, speech therapy, and nutritional support. In various embodiments, an additional therapy can be a second antisense oligonucleotide. As an example, the second antisense oligonucleotide may target a STMN2 transcript (*e.g.*, STMN2 pre-mRNA, mature STMN2 mRNA) to modulate the expression levels of full length STMN2 protein.

[00346] In various embodiments, the disclosed oligonucleotide and the one or more additional therapies can be conjugated to one another and provided in a conjugated form. Further description regarding conjugates involving the disclosed oligonucleotide is described below. In various embodiments, the disclosed oligonucleotide and one or more additional therapies are provided concurrently. In various embodiments, the disclosed oligonucleotide and one or more

additional therapies are provided simultaneously. In various embodiments, the disclosed oligonucleotide and one or more additional therapies are provided sequentially.

Conjugates

[00347] In certain embodiments, provided herein are oligomeric compounds, which comprise an oligonucleotide (*e.g.*, STMN2 oligonucleotide) and optionally one or more conjugate groups and/or terminal groups. Conjugate groups include one or more conjugate moiety and a conjugate linker which links the conjugate moiety to the oligonucleotide. Conjugate groups may be attached to either or both ends of an oligonucleotide and/or at any internal position. In certain embodiments, conjugate groups are attached to the 2'-position of a nucleoside of a modified oligonucleotide. In certain embodiments, conjugate groups that are attached to either or both ends of an oligonucleotide are terminal groups. In certain such embodiments, conjugate groups or terminal groups are attached at the 3' and/or 5'-end of oligonucleotides. In certain such embodiments, conjugate groups (or terminal groups) are attached at the 3'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 3'-end of oligonucleotides. In certain embodiments, conjugate groups (or terminal groups) are attached at the 5'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 5'-end of oligonucleotides.

[00348] Examples of terminal groups include but are not limited to conjugate groups, capping groups, phosphate moieties, protecting groups, modified or unmodified nucleosides, and two or more nucleosides that are independently modified or unmodified.

Conjugate Groups

[00349] In certain embodiments, a STMN2 AON is covalently attached to one or more conjugate groups. In certain embodiments, conjugate groups modify one or more properties of the attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge and clearance. In particular embodiments, conjugate groups modify the circulation time (*e.g.*, increase) of the oligonucleotides in the bloodstream such that increased concentrations of the oligonucleotides are delivered to the brain. In particular embodiments, conjugate groups modify the residence time (*e.g.*, increase residence time) of the oligonucleotides in a target organ (*e.g.*, brain) such that increased residence time of the oligonucleotides improves their performance (*e.g.*, efficacy). In particular embodiments, conjugate groups increase the delivery of the

oligonucleotide to the brain through the blood brain barrier and/or brain parenchyma (*e.g.*, through receptor mediated transcytosis). In particular embodiments, conjugate groups enable the oligonucleotide to target a specific organ (*e.g.*, the brain). In certain embodiments, conjugate groups impart a new property on the attached oligonucleotide, *e.g.*, fluorophores or reporter groups that enable detection of the oligonucleotide. Certain conjugate groups and conjugate moieties have been described previously, for example: cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., Bioorg. Med. Chem. Lett., 1994, 4, 1053-1060), a thioether, *e.g.*, hexyl-S-tritylthiol (Manoharan et al., Ann. NY. Acad. Sci., 1992, 660, 306-309; Manoharan et al., Bioorg. Med. Chem. Lett., 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533-538), an aliphatic chain, *e.g.*, do-decan-diol or undecyl residues (Saison-Behmoaras et al., EMBO J, 1991, 10, 1111-1118; Kabanov et al., FEBS Lett., 1990, 259, 327-330; Svinarchuk et al., Biochimie, 1993, 75, 49-54), a phospholipid, *e.g.*, di-hexadecyl-rac -glycerol or triethyl -ammonium l,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654; Shea et al., Nucl. Acids Res., 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14, 969-973), or adamantane acetic acid a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264, 229-237), an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277, 923-937), a tocopherol group (Nishina *et al.*, Molecular Therapy Nucleic Acids, 2015, 4, e220; and Nishina *et al.*, Molecular Therapy, 2008, 16, 734-740), or a GalNAc cluster (*e.g.*, WO2014/179620).

Conjugate Moieties

[00350] Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides, peptides, carbohydrates, vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterols, thiocholesterols, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins, fluorophores, and dyes. In particular embodiments, conjugate moieties are selected from a peptide, a lipid, N-acetylgalactosamine (GalNAc), cholesterol, vitamin E, lipoic acid, panthothenic acid, polyethylene glycol, an antibody (*e.g.*, an antibody for crossing the blood brain barrier such as anti-transferrin receptor antibody), or a cell-penetrating peptide (*e.g.*, transactivator of transcription (TAT) and penetratine).

[00351] In certain embodiments, a conjugate moiety comprises an active drug substance, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fen-bufen, ketoprofen, (*S*)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, fingolimod, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indomethacin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.

Conjugate Linkers

[00352] Conjugate moieties are attached to a STMN2 AON through conjugate linkers. In certain oligomeric compounds, the conjugate linker is a single chemical bond (i.e., the conjugate moiety is attached directly to an oligonucleotide through a single bond). In certain embodiments, the conjugate linker comprises a chain structure, an oligomer of repeating units such as ethylene glycol, nucleosides, or amino acid units.

[00353] In certain embodiments, a conjugate linker comprises one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether, and hydroxylamino. In certain such embodiments, the conjugate linker comprises groups selected from alkyl, amino, oxo, amide and ether groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and amide groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and ether groups. In certain embodiments, the conjugate linker comprises at least one phosphorus moiety. In certain embodiments, the conjugate linker comprises at least one phosphate group. In certain embodiments, the conjugate linker includes at least one neutral linking group.

[00354] In certain embodiments, conjugate linkers, including the conjugate linkers described above, are bifunctional linking moieties, *e.g.*, those known in the art to be useful for attaching conjugate groups to parent compounds, such as the oligonucleotides provided herein. In general, a bifunctional linking moiety comprises at least two functional groups. One of the functional groups is selected to bind to a particular site on a parent compound and the other is selected to bind to a conjugate group. Examples of functional groups used in a bifunctional linking moiety include but are not limited to electrophiles for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In certain embodiments, bifunctional linking moieties comprise one or more groups selected from amino, hydroxyl, carboxylic acid, thiol, alkyl, alkenyl, and alkynyl.

[00355] Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane- l-carboxylate

(SMCC) and 6-aminohexanoic acid (AHEX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C_1-C_{10} alkyl, substituted or unsubstituted C_2-C_{10} alkenyl or substituted or unsubstituted C_2-C_{10} alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

[00356] In certain embodiments, conjugate linkers comprise 1-10 linker-nucleosides. In certain embodiments, conjugate linkers comprise 2-5 linker-nucleosides. In certain embodiments, conjugate linkers comprise 3 linker-nucleosides.

[00357] In certain embodiments, such linker-nucleosides are modified nucleosides. In certain embodiments such linker-nucleosides comprise a modified sugar moiety. In certain embodiments, linker-nucleosides are unmodified. In certain embodiments, linker-nucleosides comprise an optionally protected heterocyclic base selected from a purine, substituted purine, pyrimidine or substituted pyrimidine. In certain embodiments, a cleavable moiety is a nucleoside selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methyl cytosine, 4-N -benzoyl-5 -methyl cytosine, adenine, 6-N-benzoyladenine, guanine and 2-N-isobutyrylguanine. It is typically desirable for linker-nucleosides to be cleaved from the oligomeric compound after it reaches a target tissue. Accordingly, linker-nucleosides are typically linked to one another and to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are phosphodiester bonds.

[00358] Herein, linker-nucleosides are not considered to be part of the oligonucleotide. Accordingly, in embodiments in which an oligomeric compound comprises an oligonucleotide consisting of a specified number or range of linked nucleosides and/or a specified percent complementarity to a reference nucleic acid and the oligomeric compound also comprises a conjugate group comprising a conjugate linker comprising linker-nucleosides, those linker-nucleosides are not counted toward the length of the oligonucleotide and are not used in determining the percent complementarity of the oligonucleotide for the reference nucleic acid.

[00359] In certain embodiments, it is desirable for a conjugate group to be cleaved from the STMN2 AON. For example, in certain circumstances oligomeric compounds comprising a particular conjugate moiety are better taken up by a particular cell type, but once the oligomeric compound has been taken up, it is desirable that the conjugate group be cleaved to release the unconjugated or parent oligonucleotide. Thus, certain conjugate linkers may comprise one or

more cleavable moieties. In certain embodiments, a cleavable moiety is a cleavable bond. In certain embodiments, a cleavable moiety is a group of atoms comprising at least one cleavable bond. In certain embodiments, a cleavable moiety comprises a group of atoms having one, two, three, four, or more than four cleavable bonds. In certain embodiments, a cleavable moiety is selectively cleaved inside a cell or subcellular compartment, such as a lysosome. In certain embodiments, a cleavable moiety is selectively cleaved by endogenous enzymes, such as nucleases.

[00360] In certain embodiments, a cleavable bond is selected from among: an amide, an ester, an ether, one or both esters of a phosphodiester, a phosphate ester, a carbamate, or a disulfide. In certain embodiments, a cleavable bond is one or both of the esters of a phosphodiester. In certain embodiments, a cleavable moiety comprises a phosphate or phosphodiester. In certain embodiments, the cleavable moiety is a phosphate linkage between an oligonucleotide and a conjugate moiety or conjugate group.

[00361] In certain embodiments, a cleavable moiety comprises or consists of one or more linker-nucleosides. In certain such embodiments, the one or more linker-nucleosides are linked to one another and/or to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are unmodified phosphodiester bonds. In certain embodiments, a cleavable moiety is 2'-deoxy nucleoside that is attached to either the 3' or 5'-terminal nucleoside of an oligonucleotide by a phosphate internucleoside linkage and covalently attached to the remainder of the conjugate linker or conjugate moiety by a phosphate or phosphorothioate linkage. In certain such embodiments, the cleavable moiety is 2'-deoxy adenosine.

Terminal Groups

[00362] In certain embodiments, oligomeric compounds comprise one or more terminal groups. In certain such embodiments, oligomeric compounds comprise a stabilized 5'-phosphate. Stabilized 5'-phosphates include, but are not limited to 5'-phosphonates, including, but not limited to 5'-vinylphosphonates. In certain embodiments, terminal groups comprise one or more abasic nucleosides and/or inverted nucleosides. In certain embodiments, terminal groups comprise one or more 2'-linked nucleosides. In certain such embodiments, the 2'-linked nucleoside is an abasic nucleoside.

Diagnostic Methods

[00363] The disclosure also provides a method of diagnosing a patient with a neurological disease that relies upon detecting levels of STMN2 expression signal in one or more biological samples of a patient. As used herein, the term "STMN2 expression signal" can refer to any indication of STMN2 gene expression, or gene or gene product activity. STMN2 gene products include RNA (*e.g.*, mRNA), peptides, and proteins. Indices of STMN2 gene expression that can be assessed include, but are not limited to, STMN2 gene or chromatin state, STMN2 gene interaction with cellular components that regulate gene expression, STMN2 gene product expression levels (*e.g.*, expression levels of STMN2 transcripts that include a cryptic exon, STMN2 protein expression levels), or interaction of STMN2 RNA or protein with transcriptional, translational, or post-translational processing machinery.

[00364] Detection of STMN2 expression signal may be accomplished through *in vivo*, *in vitro*, or *ex vivo* methods. In a preferred embodiment, methods of the disclosure may be carried out *in vitro*. Methods of detecting may involve detection in blood, serum, fecal matter, tissue, cerebrospinal fluid, spinal fluid, extracellular vesicles (for example, CSF exosomes), or cells of a patient. Detection may be achieved by measuring expression signal of STMN2 transcripts that include a cryptic exon in whole tissue, tissue explants, cell cultures, dissociated cells, cell extract, extracellular vesicles (for example, CSF exosomes), or body fluids, including blood, spinal fluid, cerebrospinal fluid, urine, lymphatic fluid, or serum. Contemplated methods of detection include assays that measure levels of STMN2 gene product expression such as Western blotting, FACS, ELISA, other quantitative binding assays, cell or tissue growth assays, Northern blots, quantitative or semi-quantitative polymerase chain reaction, dPCR, Quanterix SR-X™ Ultra-Sensitive Biomarker Detection System powered by Simoa® bead technology, medical imaging methods (*e.g.*, MRI), or immunostaining methods (*e.g.*, immunohistochemistry or immunocytochemistry).

Additional Embodiments

[00365] Disclosed herein is a compound comprising an oligonucleotide comprising a nucleobase sequence at least 90% complementary to at least 10 contiguous nucleobases of a transcript comprising a sequence at least 90% identity to SEQ ID NO: 1391 or SEQ ID NO: 944, or a contiguous 15 to 50 nucleobase portion of SEQ ID NO: 1391 or SEQ ID NO: 944, wherein at least one nucleoside linkage of the nucleobase sequence is a non-natural linkage. Additionally

disclosed herein is an oligonucleotide comprising a nucleobase sequence at least 90% complementary to at least 10 contiguous nucleobases of a transcript comprising a sequence at least 90% identity to SEQ ID NO: 1391 or SEQ ID NO: 944, or a contiguous 15 to 50 nucleobase portion of SEQ ID NO: 1391 or SEQ ID NO: 944, wherein at least one nucleoside linkage of the nucleobase sequence is a non-natural linkage.

[00366] In one aspect, the oligonucleotide comprises at least a contiguous 10 nucleobase sequence that shares 90% identity with an equal length portion of any one of SEQ ID NOs: 1-446, SEQ ID NOs: 894-918, SEQ ID NOs: 945-1390, or SEQ ID NOs: 1392-1432. In one aspect, the oligonucleotide comprises at least a contiguous 11, 12, 13, 14, 15, 16, or 17 nucleobase sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-446, SEQ ID NOs: 894-918, SEQ ID NOs: 945-1390, or SEQ ID NOs: 1392-1432. In one aspect, the oligonucleotide comprises at least a contiguous 10 nucleobase sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 31, 36, 41, 46, 55, 144, 146, 150, 169, 170, 171, 172, 173, 177, 181, 185, 197, 203, 209, 215, 237, 244, 249, 252, 380, 385, 390, 395, 400, 975, 980, 985, 999, 1088, 1090, 1094, 1113, 1114, 1115, 1116, 1117, 1121, 1125, 1129, 1141, 1147, 1153, 1159, 1181, 1188, 1193, 1196, 1324, 1329, 1334, 1339, or 1344, 1339, or 1344, wherein at least one nucleoside linkage of the nucleobase sequence is a non-natural linkage. In one aspect, the oligonucleotide comprises at least a contiguous 11, 12, 13, 14, 15, 16, or 17 nucleobase sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 31, 36, 41, 46, 55, 144, 146, 150, 169, 170, 171, 172, 173, 177, 181, 185, 197, 203, 209, 215, 237, 244, 249, 252, 380, 385, 390, 395, 400, 975, 980, 985, 999, 1088, 1090, 1094, 1113, 1114, 1115, 1116, 1117, 1121, 1125, 1129, 1141, 1147, 1153, 1159, 1181, 1188, 1193, 1196, 1324, 1329, 1334, 1339, or 1344.

[00367] Additionally disclosed herein is an oligonucleotide comprising a nucleobase sequence at least 90% complementary to at least a contiguous 10 nucleobase sequence of a transcript comprising at least 90% identity to SEQ ID NO: 944, or a contiguous 20 to 50 nucleobase portion thereof, wherein at least one nucleoside linkage of the nucleobase sequence is a non-natural linkage. In one aspect, the oligonucleotide comprises at least a contiguous 10 nucleobase sequence that shares 90% identity with an equal length portion of any one of SEQ ID NOs: 1-446 or SEQ ID NOs: 894-918. In one aspect, the oligonucleotide comprises at least a contiguous 11, 12, 13, 14, 15, 16, or 17 nucleobase sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-446 or SEQ ID NOs: 894-918. In one aspect, the

oligonucleotide comprises at least a contiguous 10 nucleobase sequence that shares at least 90% identity with an equal length portion of any one of one of SEQ ID NOs: 31, 36, 41, 46, 55, 144, 146, 150, 169, 170, 171, 172, 173, 177, 181, 185, 197, 203, 209, 215, 237, 244, 249, 252, 380, 385, 390, 395, 400, 975, 980, 985, 999, 1088, 1090, 1094, 1113, 1114, 1115, 1116, 1117, 1121, 1125, 1129, 1141, 1147, 1153, 1159, 1181, 1188, 1193, 1196, 1324, 1329, 1334, 1339, or 1344, wherein at least one nucleoside linkage of the nucleobase sequence is a non-natural linkage. In one aspect, the oligonucleotide comprises at least a contiguous 11, 12, 13, 14, 15, 16, or 17 nucleobase sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 31, 36, 41, 46, 55, 144, 146, 150, 169, 170, 171, 172, 173, 177, 181, 185, 197, 203, 209, 215, 237, 244, 249, 252, 380, 385, 390, 395, 400, 975, 980, 985, 999, 1088, 1090, 1094, 1113, 1114, 1115, 1116, 1117, 1121, 1125, 1129, 1141, 1147, 1153, 1159, 1181, 1188, 1193, 1196, 1324, 1329, 1334, 1339, or 1344.

[00368] Additionally disclosed herein is a stathmin-2 (STMN2) antisense oligonucleotide comprising a nucleic acid sequence that is at least 90% complementary with a continuous 10 nucleobase sequence of an STMN2 transcript comprising a cryptic exon comprising a nucleotide sequence at least 90% identical to SEQ ID NO: 447 or a continuous 20 to 50 nucleobase portion thereof, wherein at least one nucleoside linkage of the nucleotide sequence is a non-natural linkage. Additionally disclosed herein is a stathmin-2 (STMN2) antisense oligonucleotide comprising a nucleic acid sequence that shares at least 90% identity with a continuous 10 nucleobase sequence of any one of SEQ ID NOs: 1-446, wherein at least one nucleoside linkage of the nucleotide sequence is a non-natural linkage. In one aspect, the nucleic acid sequence shares at least 90% identity with a continuous 11, 12, 13, 14, 15, 16, or 17 nucleobase sequence of any one of SEQ ID NOs: 1-446.

[00369] Additionally disclosed herein is a stathmin-2 (STMN2) antisense oligonucleotide comprising a nucleic acid sequence that shares at least 90% identity with a continuous 10 nucleobase sequence of any one of SEQ ID NOs: 31, 36, 41, 46, 55, 144, 146, 150, 169, 170, 171, 172, 173, 177, 181, 185, 197, 203, 209, 215, 237, 244, 249, 252, 380, 385, 390, 395, 400, 975, 980, 985, 999, 1088, 1090, 1094, 1113, 1114, 1115, 1116, 1117, 1121, 1125, 1129, 1141, 1147, 1153, 1159, 1181, 1188, 1193, 1196, 1324, 1329, 1334, 1339, or 1344, wherein at least one nucleoside linkage of the nucleotide sequence is a non-natural linkage. In one aspect, the nucleic acid sequence shares at least 90% identity with a continuous 11, 12, 13, 14, 15, 16, or 17 nucleobase sequence of any one of SEQ ID NOs: 31, 36, 41, 46, 55, 144, 146, 150, 169, 170, 171,

172, 173, 177, 181, 185, 197, 203, 209, 215, 237, 244, 249, 252, 380, 385, 390, 395, 400, 975, 980, 985, 999, 1088, 1090, 1094, 1113, 1114, 1115, 1116, 1117, 1121, 1125, 1129, 1141, 1147, 1153, 1159, 1181, 1188, 1193, 1196, 1324, 1329, 1334, 1339, or 1344.

Modifications in General

[0001] While certain compounds, compositions and methods described herein have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds described herein and are not intended to limit the same. Each of the references, GenBank accession numbers, and the like recited in the present application is incorporated herein by reference in its entirety.

[0002] Although the sequence listing accompanying this filing identifies each sequence as either "RNA" or "DNA" as required, in reality, those sequences may be modified with any combination of chemical modifications. One of skill in the art will readily appreciate that such designation as "RNA" or "DNA" to describe modified oligonucleotides is, in certain instances, arbitrary. For example, an oligonucleotide comprising a nucleoside comprising a 2'-OH sugar moiety and a thymine base could be described as a DNA having a modified sugar (2'-OH in place of one 2'-H of DNA) or as an RNA having a modified base (thymine (methylated uracil) in place of a uracil of RNA). Accordingly, nucleic acid sequences provided herein, including, but not limited to those in the sequence listing, are intended to encompass nucleic acids containing any combination of natural or modified RNA and/or DNA, including, but not limited to such nucleic acids having modified nucleobases. By way of further example and without limitation, an oligomeric compound having the nucleobase sequence "ATCGATCG" encompasses any oligomeric compounds having such nucleobase sequence, whether modified or unmodified, including, but not limited to, such compounds comprising RNA bases, such as those having sequence "AUCGAUCG" and those having some DNA bases and some RNA bases such as "AUCGATCG" and oligomeric compounds having other modified nucleobases, such as "AT^{m}CGAUCG," wherein ^{m}C indicates a cytosine base comprising a methyl group at the 5-position.

[0003] Certain compounds described herein (*e.g.*, modified oligonucleotides) have one or more asymmetric center and thus give rise to enantiomers, diastereomers, and other stereoisomeric configurations that may be defined, in terms of absolute stereochemistry, as (R) or (S), as α or β such as for sugar anomers, or as (D) or (L), such as for amino acids, etc. Compounds provided herein that are drawn or described as having certain stereoisomeric configurations include only

the indicated compounds. Compounds provided herein that are drawn or described with undefined stereochemistry included all such possible isomers, including their stereorandom and optically pure forms, unless specified otherwise. Likewise, all tautomeric forms of the compounds herein are also included unless otherwise indicated. Unless otherwise indicated, compounds described herein are intended to include corresponding salt forms.

[0004] The compounds described herein include variations in which one or more atoms are replaced with a non-radioactive isotope or radioactive isotope of the indicated element. For example, compounds herein that comprise hydrogen atoms encompass all possible deuterium substitutions for each of the ^{1}H hydrogen atoms. Isotopic substitutions encompassed by the compounds herein include but are not limited to: ^{2}H or ^{3}H in place of ^{1}H, ^{13}C or ^{14}C in place of ^{12}C, ^{15}N in place of ^{14}N, ^{17}O or ^{18}O in place of ^{16}O, and ^{33}S, ^{34}S, ^{35}S, or ^{36}S in place of ^{32}S. In certain embodiments, non-radioactive isotopic substitutions may impart new properties on the oligomeric compound that are beneficial for use as a therapeutic or research tool.

EXAMPLES

[00370] The disclosure is further illustrated by the following examples. The examples are provided for illustrative purposes only, and are not to be construed as limiting the scope or content of the disclosure in any way.

Example 1: Initial Design and Selection of STMN2 Antisense Oligonucleotides

[00371] Antisense oligonucleotides complementary to STMN2 RNA were designed and tested to identify STMN2 antisense oligonucleotides (AONs) capable of acting as inhibitors of STMN2 transcripts that include a cryptic exon.

[00372] FIGs. 1A-1C depict portions of the STMN2 transcript and STMN2 antisense oligonucleotides that are designed to target certain portions of the STMN2 transcript. Specifically, regions of the STMN2 transcript include branch points (*e.g.*, branch point 1, 2, and 3) a 3' splice acceptor region, an ESE binding region, TDP43 binding sites, and a Poly A region. STMN2 antisense oligonucleotides, are identified according to the position of the STMN2 transcript that the STMN2 antisense oligonucleotide corresponds to. For example, FIG. 1A depicts a STMN2 antisense oligonucleotide that targets positions 36 to 60 of the STMN2 transcript, which includes a branch point 1. Similarly, a different STMN2 antisense oligonucleotide targets positions 144 to 178 of the STMN2 transcript, which includes a branch

point 3. Other STMN2 antisense oligonucleotides can be designed using any of the sequences disclosed above (*e.g.*, SEQ ID NOs: 1-446, 894-918, 945-1390, or 1392-1432).

[00373] Generally, the length of the STMN2 antisense oligonucleotides are 25 nucleotides in length. However, variants of the STMN2 antisense oligonucleotides were also designed with varying lengths (*e.g.*, 23mers, 21mers, or 19mers). Specific STMN2 AONs and AON variants that were designed and developed for testing are shown in below in Table 7.

Table 7: Identifying information of STMN2 AONs and AON variants including sequence and chemistry information.

STMN2 AON	SEQ ID NO:	Sequence (5'-3')	Internucleoside Linkages	Sugar Moeity
QSN-36	36	TTAAAAATGTTAAGACATAATACCA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-31	31	AATGTTAAGACATAATACCAGAGCT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-41	41	TAGATTTAAAAATGTTAAGACATAA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-46	46	TACCATAGATTTAAAAATGTTAAGA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-55	55	TGTAAAGATTACCATAGATTTAAAA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-144	144	AATCCAATTAAGAGAGAGTGATGGG	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-146	146	AAAATCCAATTAAGAGAGAGTGATG	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-150	150	TTTAAAAATCCAATTAAGAGAGAGT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-169	169	CCTGCAATATGAATATAATTTTAAA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-170	170	TCCTGCAATATGAATATAATTTTAA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-171	171	GTCCTGCAATATGAATATAATTTTA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-172	172	AGTCCTGCAATATGAATATAATTTT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC

QSN-173	173	GAGTCCTGCAATATGAATATAATTT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-177	177	TGCCGAGTCCTGCAATATGAATATA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-181	181	CTTCTGCCGAGTCCTGCAATATGAA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-185	185	AGGTCTTCTGCCGAGTCCTGCAATA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-197	197	CCTTTCTCTCGAAGGTCTTCTGCCG	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-203	203	TTTCTACCTTTCTCTCGAAGGTCTT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-209	209	TCTTATTTTCTACCTTTCTCTCGAA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-215	215	CCAAAATTCTTATTTTCTACCTTTCT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-237	237	GCACACATGCTCACACAGAGAGCCA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-244	244	CACACACGCACACATGCTCACACAG	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-249	249	TCTCGCACACACGCACACATGCTCA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-252	252	CTCTCTCGCACACACGCACACATGC	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-380	380	TGTTTTAATTTCTTCAGTATTGCTA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-385	385	TCTTTTGTTTTAATTTCTTCAGTAT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC

QSN-390	390	AGCAATCTTTTGTTTTAATTTCTTC	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-395	395	GAGACAGCAATCTTTTGTTTTAATT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-400	400	ATATTGAGACAGCAATCTTTTGTTT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-434	434	CTTAGAATAATTTGGTAAATAATAA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-436	436	CTCTTAGAATAATTTGGTAAATAAT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-438	438	TACTCTTAGAATAATTTGGTAAATA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-440	440	AATACTCTTAGAATAATTTGGTAAA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-442	442	GAAATACTCTTAGAATAATTTGGTA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-445	445	GAAGAAATACTCTTAGAATAATTTG	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-446	446	GGAAGAAATACTCTTAGAATAATTT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-144-1/5-1/3	894	ATCCAATTAAGAGAGAGTGATGG	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-144-2/3	895	AATCCAATTAAGAGAGAGTGATG	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-144-2/5	896	TCCAATTAAGAGAGAGTGATGGG	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-144-2/5-2/3	897	TCCAATTAAGAGAGAGTGATG	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC

QSN-144-3/5-3/3	898	CCAATTAAGAGAGAGTGAT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-144-4/3	899	AATCCAATTAAGAGAGAGTGA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-144-4/5	900	CAATTAAGAGAGAGTGATGGG	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-144-p03	1419	A-A-T-CCAATTAAGAGAGAGTGAT-G-G-G	Phosphorothioate linkages except for linkages indicated with "-", which are phosphodiester linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-144-p05	1420	AATCCAAT-T-A-A-G-A-GAGAGTGATGGG	Phosphorothioate linkages except for linkages indicated with "-", which are phosphodiester linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-173-2/3	901	GAGTCCTGCAATATGAATATAAT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-173-2/5	902	GTCCTGCAATATGAATATAATTT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-173-2/5-2/3	903	GTCCTGCAATATGAATATAAT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-173-4/3	904	GAGTCCTGCAATATGAATATA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-173-4/5	905	CCTGCAATATGAATATAATTT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-173-6/3	906	GAGTCCTGCAATATGAATA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-173-6/5	907	TGCAATATGAATATAATTT	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-173-po3	1417	G-A-G-TCCTGCAATATGAATATAA-T-T-T	Phosphorothioate linkages except for linkages indicated with "-", which are phosphodiester linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC

QSN-173-po5	1418	GAGTCCTG-C-A-A-T-A-TGAATATAAATTT	Phosphorothioate linkages except for linkages indicated with "-", which are phosphodiester linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-185-2/5	908	GTCTTCTGCCGAGTCCTGCAATA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-185-4/3	909	AGGTCTTCTGCCGAGTCCTGC	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-185-4/5	910	CTTCTGCCGAGTCCTGCAATA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-185-6/5	911	TCTGCCGAGTCCTGCAATA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-185-po3	1421	A-G-G-TCTTCTGCCGAGTCCTGCA-A-T-A	Phosphorothioate linkages except for linkages indicated with "-", which are phosphodiester linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-185-po5	1422	AGGTCTTC-T-G-C-C-G-AGTCCTGCAATA	Phosphorothioate linkages except for linkages indicated with "-", which are phosphodiester linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-237-2-3p	912	GCACACATGCTCACACAGAGAGC	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-237-2-5p	912	ACACATGCTCACACAGAGAGCCA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-237-2-5p-2-3p	914	ACACATGCTCACACAGAGAGC	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-237-4-3p	915	GCACACATGCTCACACAGAGA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-237-4-5p	916	ACATGCTCACACAGAGAGCCA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-237-6-3p	917	GCACACATGCTCACACAGA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC
QSN-237-6-5p	918	ATGCTCACACAGAGAGCCA	All phosphorothioate linkages	All nucleosides have 2'MOE sugar moeity; each "C" is 5-MeC

QSN-237-po3	1423	G-C-A-CACATGCTCACACAGAGAG-C-C-A	Phosphorothioate linkages except for linkages indicated with "-", which are phosphodiester linkages	All nucleosides have 2'MOE sugar moiety; each "C" is 5-MeC
QSN-237-p05	1424	GCACACAT-G-C-T-C-A-CACAGAGAGCCA	Phosphorothioate linkages except for linkages indicated with "-", which are phosphodiester linkages	All nucleosides have 2'MOE sugar moiety; each "C" is 5-MeC

Example 2: Methods for Evaluating STMN2 Antisense Oligonucleotides

[00374] STMN2 antisense oligonucleotides were evaluated in SY5Y cells and human motor neurons. Specifically, Examples 3, 4, and 5 below describe results generated from evaluation of STMN2 antisense oligonucleotides in SY5Y cells. Example 6 and 7 below describe results generated from evaluation of STMN2 antisense oligonucleotides in human motor neurons.

[00375] STMN2 antisense oligonucleotides were evaluated in SY5Y cells. The cells were plated in 6-well or 96-well plates and cultured to 80% confluency. Antisense oligonucleotide (AON) to TDP43 was transfected with RNAiMax (Thermo Fisher Scientific, Waltham, MA, USA) to express the cryptic exon, thus preventing transcription of full-length STMN2 (STMN2-FL) product. Vehicle was treated with RNAiMax alone. Positive controls included cells that were treated with TDP43 siRNA alone ("siRNA TDP43") and/or TDP43 AON alone ("AON TDP43" or "TDP43 AON"). siRNA TDP43 was purchased as ON-TARGETplus Human TARDBP (23435) siRNA – SMARTpool (#L-012394-00-0005) from Horizon/Dharmacon. TARDBP (23435) siRNA includes four individual siRNAs that targets four separate sequences:

1) Target sequence 1: GCUCAAGCAUGGAUUCUAA (SEQ ID NO: 1439)
2) Target sequence 2: CAAUCAAGGUAGUAAUAUG (SEQ ID NO: 1440)
3) Target sequence 3: GGGCUUCGCUACAGGAAUC (SEQ ID NO: 1441)
4) Target sequence 4: CAGGGUGGAUUUGGUAAUA (SEQ ID NO: 1442)

[00376] TDP43 AON is a gapmer oligonucleotide and has the following sequence and chemistry:

5' A*A*G*G*C*T*T*C*A*T*A*T*T*G*T*A*C*T*T*T 3' (SEQ ID NO: 1443)

where * = phosphorothioate, underlined = DNA, other=2'MOE RNA; each "C" is 5-MeC.

[00377] To evaluate STMN2 AON ability to restore STMN2-FL, antisense oligonucleotides to STMN2 were co-incubated with TDP43 AON in RNAiMax. After 96 hours, transcript levels (*e.g.*, STMN2 full length transcript, STMN2 transcript with cryptic exon, or TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher TaqMan Gene Expression Assay Hs03929097_g1. RT-qPCR was performed for detecting STMN2 transcripts with cryptic exon using the following primer sequences: 1) Forward primer: 5' - CTCAGTGCCTTATTCAGTCTTCTC - 3' (SEQ ID NO: 1444), 2) Reverse primer: 5' – TCTTCTGCCGAGTCCCATTT-3' (SEQ ID NO: 1445) and 3) Probe: 5' - /56-FAM/ TCAGCGTCTGCACATCCCTACAAT /3BHQ_1/ -3' (SEQ ID NO: 1446). RT-qPCR was performed for detecting full length STMN2 transcripts using the following primer sequences: 1) Forward primer: 5' – CCACGAACTTTAGCTTCTCCA – 3' (SEQ ID NO:

1447), 2) Reverse primer: 5' – GCCAATTGTTTCAGCACCTG – 3' (SEQ ID NO: 1448), and 3) Probe: 5' -/56-FAM/ ACTTTCTTCTTTCCTCTGCAGCCTCC /3BHQ_1/ - 3' (SEQ ID NO: 1449).

[00378] RT-qPCR was performed on Applied Biosystems ® 7500 Real-time PCR systems. One cycle of reverse transcription was performed at a temperature of 50° C for 5 min. One cycle of RT inactivation/initial denaturation was performed at a temperature of 95° C for 20 seconds. Forty five cycles of amplification were performed at a temperature of 95° C for 1 second followed by 60° C for 20 seconds.

[00379] STMN2-FL or STMN2 cryptic signal (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (*e.g.*, % increase of STMN-FL), the normalized STMN2-FL signal was further normalized to the vehicle (treated with RNAiMax alone, deltadeltaCt). Relative quantity of transcript level was calculated using the equation $RQ=2^{-deltadeltaCt}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0).

[00380] Percent decrease of STMN2 with cryptic exon expression was calculated using the equation of:

$$100 - \left(\frac{\text{Mean relative quantity of STMN2 with cryptic exon in response to STMN2 AON}}{\text{Mean relative quantity of STMN2 with cryptic exon in response to TDP43 AON}} * 100\right)$$

The percent increase of full length STMN2 mRNA transcript was calculated using the equation of:

$$\left(\frac{\text{Mean relative quantity of FL STMN2 transcript in response to STMN2 AON}}{\text{Mean relative quantity of FL STMN2 transcript in response to TDP43 AON}}\right) * 100$$

[00381] STMN2 antisense oligonucleotides were also evaluated in human motor neurons for potency in reducing cryptic exon and increasing STMN2 full length transcript. iCell human motor neurons (Cellular Dynamics International) were plated at 15 x 10^3 cells/well in a 96-well plate for RT-qPCR RNA quantification or 3 x 10^5 cells/well in a 6-well plate for western blot protein quantification according to manufacturer's instructions. Neurons were transfected with TDP43 AON and/or STMN2 AON using endoporter (GeneTools, LLC.) or treated with endoporter alone. Treatment conditions were tested in biological triplicate (qRT-PCR) or duplicate (western blot) wells. The same TDP43 AON described above is used here for evaluating human motor neurons. TDP43 AON is a gapmer oligonucleotide and has the following sequence and chemistry:

5' A*A*G*G*C*T*T*C*A*T*A*T*T*G*T*A*C*T*T*T 3' (SEQ ID NO: 1443)

where * = phosphorothioate, underlined = DNA, other=2'MOE RNA; each "C" is 5-MeC.

[00382] After 72 hours, antisense oligonucleotides and endoporter were washed out and replaced with fresh media. After 72 additional hours, RNA was collected from the 96-well plates

for RT-qPCR or protein collected from the 6-well plates for western blot. RNA was isolated, cDNA generated and multiplexed RT-qPCR assay performed with taqman probes for STMN2 cryptic exon, STMN2 full length transcript and reference GAPDH quantification. The same primers for detecting GAPDH, STMN2 transcript with cryptic exon, and full length STMN2, as described above in reference to SY5Y cells, were applied here for conducting RT-qPCR for human motor neurons. For protein quantification, the soluble portion of the protein collection was denatured and separated by SDS-PAGE, transferred to polyvinylidene difluoride membranes and probed with antibodies against GAPDH (Proteintech, 60004-1-1g), TDP-43 (Proteintech, 10782-2-AP), and Stathmin-2 (ThermoFisher, PA5-23049).

[00383] STMN2 antisense oligonucleotides were tested for their ability to increase or restore full-length STMN2 mRNA (*i.e.*, mRNA from which full-length STMN2 is translated) levels in TDP43 silenced cells (*e.g.*, SY5Y cells and human motor neurons). In some cases, STMN2 antisense oligonucleotides were tested for their ability to reduce STMN2 transcripts with cryptic exon. As described further below, the quantified percentage increase/restoration of STMN2-FL and/or percentage reduction of STMN2 transcripts with cryptic exon is described in reference to levels of STMN-FL and/or STMN2 transcripts with cryptic exon in a control group (*e.g.*, cells treated with 500 nM TDP43 AON).

Example 3: STMN2 Antisense Oligonucleotides Restore Full Length STMN2 and Reduce STMN2 Transcripts with Cryptic Exon in SY5Y cells

[00384] FIGs. 1B and 1C demonstrate the effectiveness of STMN2 AONs targeting different regions of the STMN2 transcript with cryptic exon. In particular, FIG. 1B depicts STMN2 AONs that were designed and evaluated in SY5Y cells. FIG. 1C depicts STMN2 AONs that were designed and evaluated in human motor neurons. STMN2 AONs represented by a solid line resulted in cells with increased STMN2-FL mRNA expression by greater than 50% over TDP43 AON treated alone. STMN2 AONs represented by a dotted line resulted in cells with increased STMN2-FL (full length) mRNA by less than 50% over TDP43 AON treated alone.

[00385] Referring to FIG. 2, TDP43 transcript was decreased by around 52% and STMN2-FL was decreased by around 57% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 36 increased TDP43 levels by 25% and increased STMN-FL levels by 55% (rescued to 67%). A 50 nM and a 500 nM treatment of a STMN2 AON with SEQ ID NO: 177 increased STMN-FL levels by 58% (rescued to 68%) and 53% (rescued to 66%) respectively. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 203 increased TDP43

levels by 15% and STMN-FL levels by 72% (rescued to 74%). A 50 nM and a 500 nM treatment of a STMN2 AON with SEQ ID NO: 395 increased STMN-FL levels by 49% (rescued to 64%) and 37% (rescued to 59%) respectively. Dotted line represents level of expression of FL-STMN2 in response to 500 nM TDP43 AON.

[00386] Referring to FIG. 3, the quantity of STMN2 transcript with cryptic exon was increased more than 20-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 173 reduced STMN2 transcript with cryptic exon levels by 68%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 181 reduced STMN2 transcript with cryptic exon levels by 65%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 197 reduced STMN2 transcript with cryptic exon levels by 39%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 215 reduced STMN2 transcript with cryptic exon levels by 31%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 385 reduced STMN2 transcript with cryptic exon levels by 53%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 400 reduced STMN2 transcript with cryptic exon levels by 74%. Dotted line represents level of expression of STMN2 with cryptic exon in response to 500 nM TDP43 AON.

[00387] Referring to FIG. 4, STMN2-FL was decreased by around 59% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 173 increased STMN-FL levels to 166% (rescued to 68%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 197 increased STMN-FL levels to 146% (rescued to 60%). Dotted line represents level of expression of FL-STMN2 in response to 500 nM TDP43 AON.

[00388] Referring to FIG. 5A, the quantity of STMN2 transcript with cryptic exon was increased more than 36-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 185 reduced STMN2 transcript with cryptic exon levels by 58%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 87%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 380 reduced STMN2 transcript with cryptic exon levels by 70%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 390 reduced STMN2 transcript with cryptic exon levels by 58%. Dotted line represents level of expression of STMN2 with cryptic exon in response to 500 nM TDP43 AON.

[00389] Referring to FIG. 5B, STMN2-FL was decreased by 66% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 185 increased STMN-FL levels to 209% (rescued to 71%). A 500 nM treatment of a STMN2 AON with SEQ ID NO:

237 increased STMN-FL levels to 347% (rescued to 118%). Dotted line represents level of expression of FL-STMN2 in response to 500 nM TDP43 AON.

[00390] Referring to FIG. 6A, the quantity of STMN2 transcript with cryptic exon was increased more than 20-fold when treated with 500 nM TDP43 AON (two different syntheses). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 144 reduced STMN2 transcript with cryptic exon levels by 83 to 88%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 92 to 93%. Dotted line represents level of expression of STMN2 with cryptic exon in response to 500 nM TDP43 AON.

[00391] Referring to FIG. 6B, STMN2-FL was decreased by about 80% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 144 increased STMN-FL levels to between 376% and 429% (rescued to between 79% to 90%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 237 increased STMN-FL levels to between 490% and 538% (rescued to 103% to 113%). Dotted line represents level of expression of FL-STMN2 in response to 500 nM TDP43 AON.

[00392] Referring to FIG. 7A, the quantity of STMN2 transcript with cryptic exon was increased more than 23-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 173 reduced STMN2 transcript with cryptic exon levels by 83%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 177 reduced STMN2 transcript with cryptic exon levels by 83%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 181 reduced STMN2 transcript with cryptic exon levels by 72%. Dotted line represents level of expression of STMN2 with cryptic exon in response to 500 nM TDP43 AON.

[00393] Referring to FIG. 7B, STMN2-FL was decreased by about 58% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 173 increased STMN-FL levels to 219% (rescued to 92%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 181 increased STMN-FL levels to 188% (rescued to 79%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 185 increased STMN-FL levels to 174% (rescued to 73%). Dotted line represents level of expression of FL-STMN2 in response to 500 nM TDP43 AON.

[00394] Referring to FIG. 8A, the quantity of STMN2 transcript with cryptic exon was increased more than 20-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 197 reduced STMN2 transcript with cryptic exon levels by 65%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 237 reduced STMN2 transcript with

cryptic exon levels by 94%. Dotted line represents level of expression of STMN2 with cryptic exon in response to 500 nM TDP43 AON.

[00395] Referring to FIG. 8B, STMN2-FL was decreased by 59% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 197 increased STMN-FL levels to 185% (rescued to 76%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 237 increased STMN-FL levels to 227% (rescued to 93%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 380 increased STMN-FL levels to 171% (rescued to 70%). Dotted line represents level of expression of FL-STMN2 in response to 500 nM TDP43 AON.

[00396] Referring to FIG. 9A, the quantity of STMN2 transcript with cryptic exon was increased more than 50-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 144 reduced STMN2 transcript with cryptic exon levels by 92%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 173 reduced STMN2 transcript with cryptic exon levels by 82%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 96%. Dotted line represents level of expression of STMN2 with cryptic exon in response to 500 nM TDP43 AON.

[00397] Referring to FIG. 9B, STMN2-FL was decreased by 67% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 144 increased STMN-FL levels to 235% (rescued to 87%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 173 increased STMN-FL levels to 232% (rescued to 86%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 237 increased STMN-FL levels to 243% (rescued to 90%). Dotted line represents level of expression of FL-STMN2 in response to 500 nM TDP43 AON.

[00398] Referring to FIG. 10A, the quantity of STMN2 transcript with cryptic exon was increased more than 65-fold when treated with 500 nM TDP43 AON. A 200 nM treatment of a STMN2 AON with SEQ ID NO: 181 reduced STMN2 transcript with cryptic exon levels by 50%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 181 reduced STMN2 transcript with cryptic exon levels by 73%. Referring to FIG. 10B, STMN2-FL was decreased by 67% when treated with 500 nM TDP43 AON. A 50 nM treatment of a STMN2 AON with SEQ ID NO: 181 increased STMN-FL levels to 215% (rescued to 71%). A 200 nM treatment of a STMN2 AON with SEQ ID NO: 181 increased STMN-FL levels to 197% (rescued to 65%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 181 increased STMN-FL levels to 194% (rescued to 64%).

[00399] Referring to FIG. 11A, the quantity of STMN2 transcript with cryptic exon was increased more than 26-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 185 reduced STMN2 transcript with cryptic exon levels by 47%. Referring to FIG. 11B, STMN2-FL was decreased by 74% when treated with 500 nM TDP43 AON. A 50 nM treatment of a STMN2 AON with SEQ ID NO: 185 increased STMN-FL levels to 173% (rescued to 45%). A 200 nM treatment of a STMN2 AON with SEQ ID NO: 185 increased STMN-FL levels to 346% (rescued to 90%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 185 increased STMN-FL levels to 265% (rescued to 69%).

[00400] Referring to FIG. 12A, the quantity of STMN2 transcript with cryptic exon was increased more than 41-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 197 reduced STMN2 transcript with cryptic exon levels by 51%. Referring to FIG. 12B, STMN2-FL was decreased by 65% when treated with 500 nM TDP43 AON. A 20 nM treatment of a STMN2 AON with SEQ ID NO: 197 increased STMN-FL levels to 186% (rescued to 65%). A 50 nM treatment of a STMN2 AON with SEQ ID NO: 197 increased STMN-FL levels to 231% (rescued to 81%). A 200 nM treatment of a STMN2 AON with SEQ ID NO: 197 increased STMN-FL levels to 254% (rescued to 89%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 197 increased STMN-FL levels to 269% (rescued to 94%).

[00401] Referring to FIG. 13A, the quantity of STMN2 transcript with cryptic exon was increased more than 41-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 144 reduced STMN2 transcript with cryptic exon levels by 93%. Referring to FIG. 13B, STMN2-FL was decreased by 84% when treated with 500 nM TDP43 AON. A 50 nM treatment of a STMN2 AON with SEQ ID NO: 144 increased STMN-FL levels to 175% (rescued to 28%). A 200 nM treatment of a STMN2 AON with SEQ ID NO: 144 increased STMN-FL levels to 360% (rescued to 57%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 144 increased STMN-FL levels to 544% (rescued to 87%).

[00402] Referring to FIG. 14A, the quantity of STMN2 transcript with cryptic exon was increased more than 70-fold when treated with 500 nM TDP43 AON. A 200 nM treatment of a STMN2 AON with SEQ ID NO: 173 reduced STMN2 transcript with cryptic exon levels by 59%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 173 reduced STMN2 transcript with cryptic exon levels by 70%. Referring to FIG. 14B, STMN2-FL was decreased by 62% when treated with 500 nM TDP43 AON. A 200 nM treatment of a STMN2 AON with SEQ ID NO:

173 increased STMN-FL levels by 100% (rescued to 76%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 173 increased STMN-FL levels by 158% (rescued to 98%).

[00403] Referring to FIG. 15A, the quantity of STMN2 transcript with cryptic exon was increased more than 70-fold when treated with 500 nM TDP43 AON. A 200 nM treatment of a STMN2 AON with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 78%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 92%. Referring to FIG. 15B, STMN2-FL was decreased by 77% when treated with 500 nM TDP43 AON. A 50 nM treatment of a STMN2 AON with SEQ ID NO: 237 increased STMN-FL levels to 187% (rescued to 43%). A 200 nM treatment of a STMN2 AON with SEQ ID NO: 237 increased STMN-FL levels to 235% (rescued to 54%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 237 increased STMN-FL levels to 309% (rescued to 71%).

[00404] Referring to FIG. 16, STMN2-FL was decreased by 44% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 173 increased STMN-FL levels to 152%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 237 increased STMN-FL levels to 134%.

[00405] Referring to FIG. 17A, the quantity of STMN2 transcript with cryptic exon was increased more than 30-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 96%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 912 reduced STMN2 transcript with cryptic exon levels by 97%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 913 reduced STMN2 transcript with cryptic exon levels by 97%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 916 reduced STMN2 transcript with cryptic exon levels by 71%.

[00406] Referring to FIG. 17B, STMN2-FL was decreased by 76% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 237 increased STMN-FL levels to 338% (rescued to 81%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 912 increased STMN-FL levels to 163% (rescued to 39%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 915 increased STMN-FL levels to 196% (rescued to 47%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 916 increased STMN-FL levels to 225% (rescued to 54%).

[00407] Referring to FIG. 18A, the quantity of STMN2 transcript with cryptic exon was increased more than 19-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 185 reduced STMN2 transcript with cryptic exon levels by 83%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 908 reduced STMN2 transcript with cryptic exon levels by 85%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 910 reduced STMN2 transcript with cryptic exon levels by 78%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 911 reduced STMN2 transcript with cryptic exon levels by 78%.

[00408] Referring to FIG. 18B, STMN2-FL was decreased by 82% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 185 increased STMN-FL levels to 261% (rescued to 47%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 908 increased STMN-FL levels to 244% (rescued to 44%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 909 increased STMN-FL levels to 228% (rescued to 41%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 910 increased STMN-FL levels to 244% (rescued to 44%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 911 increased STMN-FL levels to 283% (rescued to 51%).

[00409] Referring to FIG. 19A, the quantity of STMN2 transcript with cryptic exon was increased more than 23-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 173 reduced STMN2 transcript with cryptic exon levels by 81%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 901 reduced STMN2 transcript with cryptic exon levels by 86%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 904 reduced STMN2 transcript with cryptic exon levels by 81%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 906 reduced STMN2 transcript with cryptic exon levels by 75%.

[00410] Referring to FIG. 19B, STMN2-FL was decreased by 83 % when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 173 increased STMN-FL levels to 365% (rescued to 62%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 901 increased STMN-FL levels to 306% (rescued to 52%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 904 increased STMN-FL levels to 312% (rescued to 53%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 905 increased STMN-FL levels to 188% (rescued to 32%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 906 increased STMN-FL levels to 288% (rescued to 49%).

[00411] Referring to FIG. 20A, the quantity of STMN2 transcript with cryptic exon was increased more than 35-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a

STMN2 AON with SEQ ID NO: 237 reduced STMN2 transcript with cryptic exon levels by 91%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 912 reduced STMN2 transcript with cryptic exon levels by 94%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 913 reduced STMN2 transcript with cryptic exon levels by 96%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 917 reduced STMN2 transcript with cryptic exon levels by 82%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 918 reduced STMN2 transcript with cryptic exon levels by 38%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 914 reduced STMN2 transcript with cryptic exon levels by 33%.

[00412] Referring to FIG. 20B, STMN2-FL was decreased by 80% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 237 increased STMN-FL levels to 425% (rescued to 85%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 912 increased STMN-FL levels to 450% (rescued to 90%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 918 increased STMN-FL levels to 205% (rescued to 41%).

[00413] Referring to FIG. 21A, the quantity of STMN2 transcript with cryptic exon was increased more than 11-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 173 reduced STMN2 transcript with cryptic exon levels by 72%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 902 reduced STMN2 transcript with cryptic exon levels by 85%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 903 reduced STMN2 transcript with cryptic exon levels by 55%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 1417 reduced STMN2 transcript with cryptic exon levels by 49%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 1418 reduced STMN2 transcript with cryptic exon levels by 57%.

[00414] Referring to FIG. 21B, STMN2-FL was decreased by 73% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 173 increased STMN-FL levels by 85% (rescued to 50%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 903 increased STMN-FL levels by 85% (rescued to 50%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 1417 increased STMN-FL levels by 74% (rescued to 47%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 1418 increased STMN-FL levels by 89% (rescued to 51%).

[00415] Referring to FIG. 22A, the quantity of STMN2 transcript with cryptic exon was increased more than 13-fold when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 144 reduced STMN2 transcript with cryptic exon levels by 91%.

A 500 nM treatment of a STMN2 AON with SEQ ID NO: 896 reduced STMN2 transcript with cryptic exon levels by 80%. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 894 reduced STMN2 transcript with cryptic exon levels by 85%.

[00416] Referring to FIG. 22B, STMN2-FL was decreased by 65% when treated with 500 nM TDP43 AON. A 500 nM treatment of a STMN2 AON with SEQ ID NO: 144 increased STMN-FL levels by 94% (rescued to 68%). A 500 nM treatment of a STMN2 AON with SEQ ID NO: 896 increased STMN-FL levels by 114% (rescued to 75%).

Example 4: Additional Experiments Demonstrating STMN2 Antisense Oligonucleotides Restore Full Length STMN2 and Reduce STMN2 Transcripts with Cryptic Exon in SY5Y cells

[00417] FIG. 25A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different QSN-144 STMN2 AONs and AON variants. FIG. 25B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different QSN-144 STMN2 AONs and AON variants. In particular, the STMN2 AONs and AON variants tested included: QSN-144 (SEQ ID NO: 144), QSN-144-2/3 (SEQ ID NO: 895), QSN-144-4/3 (SEQ ID NO: 899), QSN-144-2/5 (SEQ ID NO: 896), QSN-144-1/5 1/3 (SEQ ID NO: 894), QSN-144-2/5 2/3 (SEQ ID NO: 897), QSN-144-3/5 3/3 (SEQ ID NO: 898), QSN-144-po3 (SEQ ID NO: 1419), and QSN-144-po5 (SEQ ID NO: 1420).

[00418] Treatment with 500 nM TDP43 AON resulted in a 41.7 fold increase of STMN2 transcript with cryptic exon and a decrease of 70% STMN2-FL. The percentage decrease in STMN2 transcript with cryptic exon and the percentage increase in full length STMN2 in response to a 500 nM treatment of each respective STMN2 and AON variant is shown in Table 8.

Table 8: Effects of 500 nM treatment of QSN-144 STMN2 AON and QSN-144 AON variants.

STMN2 AON	SEQ ID NO:	Relative STMN2 Cryptic Exon Quantity	Percentage Decrease in STMN2 transcript with cryptic exon	Relative Full Length STMN2 Quantity ("rescued to")	Percentage Increase in FL STMN2
144-2/3	895	23.4	43.9	0.67	223.3
144-4/3	899	35.7	14.4	0.49	163.3
144-2/5	896	8.4	79.9	0.86	286.7

144-1/5-1/3	894	13.5	67.6	0.52	173.3
144-2/5-2/3	897	42.9	-2.9	0.42	140.0
144-3/5-3/3	898	43.7	-4.8	0.43	143.3
144-PO3	1419	41	1.7	0.32	106.7
144-PO5	1420	46.2	-10.8	0.29	96.7

[00419] FIG. 26A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different QSN-173 STMN2 AONs and AON variants. FIG. 26B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different QSN-173 STMN2 AONs and AON variants. In particular, the STMN2 AONs and AON variants tested included: QSN-173 (SEQ ID NO: 173), QSN-173-2/3 (SEQ ID NO: 901), QSN-173-4/3 (SEQ ID NO: 904), QSN-173-6/3 (SEQ ID NO: 906), QSN-173-4/5 (SEQ ID NO: 905), QSN-173-2/5 (SEQ ID NO: 902), QSN-173-6/5 (SEQ ID NO: 907), QSN-173-2/5 2/3 (SEQ ID NO: 903), QSN-173-po3 (SEQ ID NO: 1417), and QSN-173-po5 (SEQ ID NO: 1418). Treatment with 500 nM TDP43 AON resulted in a 15.4 fold increase of STMN2 transcript with cryptic exon and a decrease of 71% STMN2-FL. The percentage decrease in STMN2 transcript with cryptic exon and the percentage increase in full length STMN2 in response to a 500 nM treatment of each respective STMN2 and AON variant is shown in Table 9.

Table 9: Effects of 500 nM treatment of QSN-173 STMN2 AON and QSN-173 AON variants.

STMN2 AON	SEQ ID NO:	Relative STMN2 Cryptic Exon Quantity	Percentage Decrease in STMN2 transcript with cryptic exon	Relative Full Length STMN2 Quantity ("rescued to")	Percentage Increase in FL STMN2
173-2/3	901	5.8	62.3	0.83	286.2
173-4/3	904	6.5	57.8	0.6	206.9
173-6/3	906	7.6	50.6	0.46	158.6
173-4/5	905	16.4	-6.5	0.3	103.4
173-2/5	902	7.5	51.3	0.6	206.9
173-6/5	907	20.5	-33.1	0.37	127.6
173-2/5-2/3	903	9.3	39.6	0.43	148.3
173-PO3	1417	10.5	31.8	0.45	155.2
173-PO5	1418	9.9	35.7	0.49	169.0

[00420] FIG. 27A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different QSN-185 STMN2 AONs and AON variants. FIG. 27B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different QSN-185 STMN2 AONs and AON variants. In particular, the STMN2 AONs and AON variants tested included: QSN-185 (SEQ ID NO: 185), QSN-185-2/5 (SEQ ID NO: 908), QSN-185-4/5 (SEQ ID NO: 910), QSN-185-6/5 (SEQ ID NO: 911), QSN-185-4/3 (SEQ ID NO: 909), QSN-185-po3 (SEQ ID NO: 1421), and QSN-185-po5 (SEQ ID NO: 1422). Treatment with 500 nM TDP43 AON resulted in a 32.1 fold increase of STMN2 transcript with cryptic exon and a decrease of 71% STMN2-FL. The percentage decrease in STMN2 transcript with cryptic exon and the percentage increase in full length STMN2 in response to a 500 nM treatment of each respective STMN2 and AON variant is shown in Table 10.

Table 10: Effects of 500 nM treatment of QSN-185 STMN2 AON and QSN-185 AON variants.

STMN2 AON	SEQ ID NO:	Relative STMN2 Cryptic Exon Quantity	Percentage Decrease in STMN2 transcript with cryptic exon	Relative Full Length STMN2 Quantity ("rescued to")	Percentage Increase in FL STMN2
185-2/5	908	12.1	62.3	0.72	248.3
185-4/5	910	16.4	48.9	0.52	179.3
185-6/5	911	17.5	45.5	0.46	158.6
185-4/3	909	21.2	34.0	0.36	124.1
185-PO3	1421	27.2	15.3	0.4	137.9
185-PO5	1422	24.6	23.4	0.38	131.0

[00421] FIG. 28A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different QSN-237 STMN2 AONs and AON variants. FIG. 28B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different QSN-237 STMN2 AONs and AON variants. In particular, the STMN2 AONs and AON variants tested included: QSN-237 (SEQ ID NO: 237), QSN-237-2/3 (SEQ ID NO: 912), QSN-237-4/3 (SEQ ID NO: 915), QSN-237-2/5 (SEQ ID NO: 913), QSN-237-4/5 (SEQ ID NO: 916), QSN-237-6/3

(SEQ ID NO: 917), QSN-237-6/5 (SEQ ID NO: 918), QSN-237-2/5 2/3 (SEQ ID NO: 914), QSN-237-po3 (SEQ ID NO: 1423), and QSN-237-po5 (SEQ ID NO: 1424). Treatment with 500 nM TDP43 AON resulted in a 15.7 fold increase of STMN2 transcript with cryptic exon and a decrease of 65% STMN2-FL. The percentage decrease in STMN2 transcript with cryptic exon and the percentage increase in full length STMN2 in response to a 500 nM treatment of each respective STMN2 and AON variant is shown in Table 11.

Table 11: Effects of 500 nM treatment of QSN-237 STMN2 AON and QSN-237 AON variants.

STMN2 AON	SEQ ID NO:	Relative STMN2 Cryptic Exon Quantity	Percentage Decrease in STMN2 transcript with cryptic exon	Relative Full Length STMN2 Quantity ("rescued to")	Percentage Increase of FL STMN2
237-2/3	912	1.9	87.9	0.51	145.7
237-4/3	915	14.6	7.0	0.56	160.0
237-2/5	913	7.7	51.0	0.5	142.9
237-4/5	916	8	49.0	0.49	140.0
237-6/3	917	11.7	25.5	0.4	114.3
237-6/5	918	10.7	31.8	0.62	177.1
237-2/5-2/3	914	13.5	14.0	0.51	145.7
237-PO3	1423	6.7	57.3	0.53	151.4
237-PO5	1424	4.7	70.1	0.59	168.6

[00422] FIG. 29A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels using different STMN2 AONs (QSN-31, QSN-41, and QSN-46). FIG. 29B is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 siRNA and TDP43 antisense, and restoration of the full-length STMN2 transcript using different STMN2 AONs (QSN-31, QSN-41, and QSN-46). In particular, the STMN2 AONs and AON variants tested included: QSN-31 (SEQ ID NO: 31), QSN-41 (SEQ ID NO: 41), and QSN-46 (SEQ ID NO: 46). Treatment with 500 nM TDP43 AON resulted in a 10.4 fold increase of STMN2 transcript with cryptic exon and a decrease of 59% STMN2-FL. The percentage decrease in STMN2 transcript with cryptic exon and the percentage increase in full length STMN2 in response to a 500 nM treatment of each respective STMN2 and AON variant is shown in Table 12.

Table 12: Effects of 500 nM treatment of QSN-31, QSN-41, and QSN-46 STMN2 AONs.

STMN2 AON	SEQ ID NO:	Relative STMN2 Cryptic Exon Quantity	Percentage Decrease in STMN2 transcript with cryptic exon	Relative Full Length STMN2 Quantity ("rescued to")	Percentage Increase of FL STMN2
31	31	2.6	75.0	0.38	108.6
41	41	4.1	60.6	0.46	131.4
46	46	8.7	16.3	0.48	137.1

Example 5: Dose response restoration of full length STMN2 mRNA and STMN2 protein using Stathmin-2 cryptic splicing modulator

[00423] The experiment was performed as previously described in human neuroblastoma SY5Y cells. The cells were plated in 6-well or 96-well plates and cultured to 80% confluency. TDP-43 expression in cells were knocked down using an AON to TDP43 to express the cryptic exon, thus preventing transcription of full-length STMN2 (STMN2-FL) product. Cells were additionally co-transfected with a STMN2 ASO (specifically, QSN-237-2/3 (SEQ ID NO: 912)) at varying doses (5 nM, 50 nM, 100 nM, 200 nM, and 500 nM). RNA and protein were isolated for QPCR and western blot assays.

[00424] FIG. 23 shows the dose response curve illustrating increasing restoration of full length STMN2 transcript with increasing concentrations of STMN2 AON. Generally, increasing concentrations of STMN2 AON increased full length STMN2 mRNA, decreased cryptic exon levels. Specifically, a 5 nM treatment of the STMN2 ASO resulted in ~40% restoration of full length STMN2 transcript. A 500 nM treatment of the STMN2 ASO resulted in nearly 100% restoration of full length STMN2 transcript. Additionally, the 500 nM treatment of the STMN2 ASO resulted in the significant reduction (close to 0%) of cryptic exon.

[00425] FIG. 24A shows a Western blot assay demonstrating the qualitative increase of full length STMN2 protein in response to higher concentrations of STMN2 AON. FIG. 24B shows the quantitated levels of full length STMN2 protein normalized to GAPDH in response to different concentrations of STMN2 AON. Generally, both FIG. 24A and 24B show that increasing concentrations of the STMN2 AON resulted in increasing concentrations of full length STMN2 protein. Specifically, as shown in FIG. 24B, lower concentrations (5nM and 50 nM) of the STMN2 AON resulted in full length STMN2 protein concentrations that were ~60% of the control group (cell only). Notably, the 500 nM treatment of the STMN2 ASO resulted in nearly 100% restoration of the full length STMN2 protein (in comparison to the cell only control group).

Example 6: Chemotherapy induced neuropathy as an indication that can be targeted by a Stathmin-2 cryptic splicing modulator

[00426] Referring to FIG. 30, it illustrates a bar graph showing reversal of cryptic exon induction using QSN-237 STMN2 antisense oligonucleotide (SEQ ID NO: 237) even in view of increasing proteasome inhibition. As a control, cells that were treated with endoporter alone (no AON) and then subsequently treated with MG132 (across all concentrations of MG132) demonstrated high levels of cryptic exon. This is indicative of TDP-43 pathology induced by proteasome inhibition in human motor neurons. MG132 causes TDP43 mislocalization leading to STMN2 mis-splicing and increased cryptic exon expression. The addition of QSN-237 (SEQ ID NO: 237) antisense oligonucleotide reverses cryptic exon induction with high potency (IC50 <5nM). As shown in FIG. 30, increasing concentrations of QSN-237 (ranging from 5 nM up to 500 nM) significantly reduces the cryptic exon relative quantity.

[00427] In totality, this data establishes that the QSN-237 antisense oligonucleotide (SEQ ID NO: 237) protects against proteotoxic stress induction of cryptic exon expression. This is applicable in settings where neurons are to be protected from proteotoxic stress as a result of other therapies such as chemotherapeutics.

Example 7: STMN2 Antisense Oligonucleotides Restore Full Length STMN2 and Reduce STMN2 Transcripts with Cryptic Exon in Human Motor Neurons

[00428] FIG. 31A and FIG. 31B show bar graphs showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels and STMN2 full-length mRNA levels, which demonstrate reduction of the STMN2 transcript with cryptic exon mRNA levels and restoration of the full-length STMN2 transcript using different STMN2 AONs and AON variants. In particular, the STMN2 AONs and AON variants tested included: QSN-36 (SEQ ID NO: 36), QSN-55 (SEQ ID NO: 55), QSN-144 (SEQ ID NO: 144), QSN-144-2/5 (SEQ ID NO: 896), QSN-173 (SEQ ID NO: 173), QSN-173-2/5-2/3 (SEQ ID NO: 903), QSN-237 (SEQ ID NO: 237), QSN-237-2/3 (SEQ ID NO: 912), QSN 185 (SEQ ID NO: 185), QSN-185-2/5 (SEQ ID NO: 908), and QSN-252 (SEQ ID NO: 252).

[00429] Table 13 shows the dose-dependent effect (percentage decrease) of STMN2 AONs on levels of expression of STMN2 with cryptic exon. Additionally, Table 14 shows the dose-dependent effect of STMN2 AONs on restoration of levels of full length STMN2 transcript.

Table 13: Dose dependent effect of STMN2 AONs on expression levels of STMN2 with cryptic exon. Values are shown as percentage decrease of expression levels of STMN2 with cryptic exon relative to corresponding value derived from 500 nM TDP43 AON treated cells.

Dose	QSN-36	QSN-55	QSN-144	QSN-144-2-5p	QSN-173	QSN-173-2-5p-2-3p
5	-6	17	87		85	89
20		35	90	90	91	94
50	3	43	94	92	96	97
200		45	97	94	99	100
500	-37	21	98	97	100	100

Dose	QSN-237	QSN-237-2-3p	QSN-185	QSN-185-2-5p	QSN-252
5	99	98	11	-1	22
20	99	100	28	10	28
50	100	100	28	44	71
200	100	100	42	71	95
500	100	100	66	86	98

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Table 14: Dose dependent effect of STMN2 AONs on expression levels of full length STMN2 transcript.

Dose	QSN-36		QSN-55		QSN-144		QSN-144-2-5p	
	Relative Quantity ("rescued to")	Percent Increase of FL STMN2	Relative Quantity ("rescued to")	Percent Increase of FL STMN2	Relative Quantity ("rescued to")	Percent Increase of FL STMN2	Relative Quantity ("rescued to")	Percent Increase of FL STMN2
5	0.19	69	0.54	136	0.63	524		
20			0.51	129	0.51	423	0.57	477
50	0.33	122	0.60	149	0.60	497	0.64	536
200			0.67	168	0.65	543	0.57	477
500	0.32	119	0.93	234	0.77	639	0.74	616

Dose	QSN-173		QSN-173-2-5p-2-3p		QSN-237		QSN-237-2-3p	
	Relative Quantity ("rescued to")	Percent Increase of FL STMN2	Relative Quantity ("rescued to")	Percent Increase of FL STMN2	Relative Quantity ("rescued to")	Percent Increase of FL STMN2	Relative Quantity ("rescued to")	Percent Increase of FL STMN2
5	0.52	437	0.65	499	0.68	525	0.52	397
20	0.58	483	0.72	556	0.79	606	0.55	426
50	0.74	619	0.88	677	0.83	640	0.76	581
200	1.01	840	1.03	791	0.83	636	0.68	527
500	1.15	954	0.96	736	0.97	743	0.73	560

Dose	QSN-185		QSN-185-2-5p		QSN-252	
	Relative Quantity ("rescued to")	Percent Increase of FL STMN2	Relative Quantity ("rescued to")	Percent Increase of FL STMN2	Relative Quantity ("rescued to")	Percent Increase of FL STMN2
5	0.55	184	0.59	196	0.64	121
20	0.75	252	0.74	248	0.55	104
50	0.83	275	0.86	288	0.77	144
200	1.19	396	1.15	384	1.04	197
500	1.02	340	1.49	498	1.04	197

[00430] FIG 32 is a bar graph showing the results of a western blot analysis of STMN2 protein levels, which demonstrates, which demonstrates restoration of the full-length STMN2 protein using different STMN2 AONs and AON variants. In particular, the STMN2 AONs and AON variants tested included: QSN-144 (SEQ ID NO: 144), QSN-144-2/5 (SEQ ID NO: 896), QSN-173 (SEQ ID NO: 173), QSN-173-2/5-2/3 (SEQ ID NO: 903), QSN-185 (SEQ ID NO: 185), QSN-185-2/5 (SEQ ID NO: 908), QSN-237 (SEQ ID NO: 237), and QSN-237-2/3 (SEQ ID NO: 912).

[00431] Table 15 below shows the expression levels of STMN2 protein in relation to control groups (endoporter and TDP43 ASO). Each of the STMN2 AONs and AON variants increased expression levels of STMN2 protein in relation to TDP43 ASO. In some cases, STMN2 AONs (*e.g.*, QSN-144 and QSN-173) and AON variants (*e.g.*, QSN-173-2/5-2/3) restored expression levels of STMN2 protein to levels above the endoporter control.

Table 15: Full length STMN2 expression of human motor neurons treated with STMN2 AONs or AON variants.

Group	percent of endoporter
Endoporter	100
TDP43 ASO	40
QSN-144	113
QSN-144-2/5	87
QSN-173	206
QSN-173-2/5-2/3	131
QSN-185	82
QSN-185-2/5	71
QSN-237	76
QSN-237-2/3	65

[00432] FIG. 33A is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA expression in human motor neurons in response to treatment using different STMN2 AONs. FIG. 33B is a bar graph showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels in response to treatment using different STMN2 AONs. In particular, the STMN2 AONs tested included: QSN-31 (SEQ ID NO: 31), QSN-41 (SEQ ID NO: 41), and QSN-46 (SEQ ID NO: 46).

[00433] Table 16 shows the dose-dependent effect (percentage decrease) of STMN2 AONs on levels of expression of STMN2 with cryptic exon. Additionally, Table 17 shows the dose-dependent effect of STMN2 AONs on restoration of levels of full length STMN2 transcript.

Table 16: Dose dependent effect of STMN2 AONs on expression levels of STMN2 with cryptic exon. Values are shown as percentage decrease of expression levels of STMN2 with cryptic exon relative to corresponding value derived from 500 nM TDP43 AON treated cells.

Dose	QSN-31	QSN-41	QSN-46
5	-62	-19	27
20	-26	18	57
50	-12	45	57
200	-60	17	44
500	-36	-7	18

Table 17: Dose dependent effect of STMN2 AONs on expression levels of full length STMN2 transcript.

Dose	QSN-31		QSN-41		QSN-46	
	Relative Quantity ("rescued to")	Percent Increase of FL STMN2	Relative Quantity ("rescued to")	Percent Increase of FL STMN2	Relative Quantity ("rescued to")	Percent Increase of FL STMN2
5	0.50	167	0.51	127	0.49	121
20	0.56	187	0.53	132	0.62	156
50	0.57	191	0.60	149	0.69	171
200	0.58	195	0.69	173	0.75	189
500	0.82	274	0.72	180	0.80	201

[00434] FIGs. 34A, 34C, and 34E are bar graphs showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA expression in human motor neurons, which demonstrates reduction of the STMN2 transcript with cryptic exon mRNA levels using different

STMN2 AONs. FIG. 34B, 34D, and 34F are bar graphs showing the results of RT-qPCR analysis of STMN2 full-length mRNA levels, which demonstrates the restoration of the full-length STMN2 transcript using different STMN2 AONs. In particular, the STMN2 AONs tested included: QSN-146 (SEQ ID NO: 146), QSN-150 (SEQ ID NO: 150), QSN-169 (SEQ ID NO: 169), QSN-170 (SEQ ID NO: 170), QSN-171 (SEQ ID NO: 171), QSN-172 (SEQ ID NO: 172), and QSN-249 (SEQ ID NO: 249). The dotted line represents 500 nM TDP43 ASO only level of expression.

[00435] Table 18 shows the dose-dependent effect (percentage decrease) of STMN2 AONs on levels of expression of STMN2 with cryptic exon. Additionally, Table 19 shows the dose-dependent effect of STMN2 AONs on restoration of levels of full length STMN2 transcript.

Table 18: Dose dependent effect of STMN2 AONs on expression levels of STMN2 with cryptic exon. Values are shown as percentage decrease of expression levels of STMN2 with cryptic exon relative to corresponding value derived from 500 nM TDP43 AON treated cells.

Dose	QSN-146	QSN-150	QSN-169	QSN-170	QSN-171	QSN-172	QSN-249
5	2	18	4	8	14	20	-1
20	33	40	50	-10	29	18	19
50	34	62	27	47	20	20	35
200	83	87	77	64	76	71	80
500	66	82	92	53	77	75	92

Table 19: Dose dependent effect of STMN2 AONs on expression levels of full length STMN2 transcript.

Dose	QSN-146		QSN-150		QSN-169		QSN-170	
	Relative Quantity ("rescued to")	Percent Increase of FL STMN2	Relative Quantity ("rescued to")	Percent Increase of FL STMN2	Relative Quantity ("rescued to")	Percent Increase of FL STMN2	Relative Quantity ("rescued to")	Percent Increase of FL STMN2
5	0.37	82	0.51	113	0.52	115	0.52	108
20	0.52	115	0.67	148	0.72	159	0.53	111
50	0.61	136	0.71	157	0.62	139	0.72	149
200	0.92	204	0.94	208	0.95	211	0.85	177
500	0.75	166	0.92	205	1.08	240	0.87	181

Dose	QSN-171		QSN-172		QSN-249	
	Relative Quantity	Percent Increase	Relative Quantity	Percent Increase	Relative Quantity	Percent Increase

	("rescued to")	of FL STMN2	("rescued to")	of FL STMN2	("rescued to")	of FL STMN2
5	0.63	131	0.62	130	0.55	104
20	0.56	116	0.60	126	0.55	104
50	0.61	127	0.55	116	0.58	110
200	1.03	214	1.00	209	0.81	152
500	1.03	214	0.95	198	0.97	183

INCORPORATION BY REFERENCE

[00436] The entire disclosure of each of the patent documents and scientific articles cited herein is incorporated by reference for all purposes.

EQUIVALENTS

[00437] The disclosure can be embodied in other specific forms without departing from the essential characteristics thereof. The foregoing embodiments therefore are to be considered illustrative rather than limiting on the disclosure described herein. The scope of the disclosure is indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.