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 examples, 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 examples, the oligonucleotide inhibitors are antisense oligonucleotides. In various examples, the oligonucleotide inhibitors target a Stathmin-2 (STMN2) transcript. In some examples, the STMN2 transcript includes a cryptic exon, such as the cryptic exon with a sequence identified below in SEQ ID NO: 447.

[014a] In one aspect of the present disclosure, there is provided a compound comprising an oligonucleotide comprising linked nucleosides with at least a 19 contiguous nucleobase sequence that is at least 90% complementary to an equal length portion of a transcript with at least 90% 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.

[014b] In another aspect of the present disclosure, there is provided an oligonucleotide comprising linked nucleosides with at least a 19 contiguous nucleobase sequence that is at least 90% complementary to an equal length portion of a transcript with at least 90% 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.

[014c] In a further aspect of the present disclosure, there is provided 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% identity to an equal length portion of any one of SEQ ID NOs: 894-918 or SEQ ID NOs: 1392-1432.

[014d] In another aspect of the present disclosure, there is provided 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% identity to an equal length portion of any one of SEQ ID NOs: 894-918 or SEQ ID NOs: 1392-1432.

[014e] In a further aspect of the present disclosure, there is provided 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% 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.

[014f] In another aspect of the present disclosure, there is provided 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% 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.

[014g] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising one or more of the oligonucleotides disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[014h] In another aspect of the present disclosure, there is provided a use of an oligonucleotide disclosed herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a neurological disease and/or a neuropathy in a patient in need thereof.

[014i] In another aspect of the present disclosure, there is provided a use of an oligonucleotide disclosed herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for restoring axonal outgrowth and/or regeneration of a motor neuron, wherein the motor neuron is to be exposed to the medicament.

[014j] In another aspect of the present disclosure, there is provided a use of an oligonucleotide disclosed herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for increasing, promoting, stabilizing, or maintaining STMN2 expression and/or function in a neuron, wherein the neuron is to be exposed to the medicament.

[014k] In another aspect of the present disclosure, there is provided a use of an oligonucleotide disclosed herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for the treatment of neurological disease or a neuropathy.

[014l] In another aspect of the present disclosure, there is provided an oligonucleotide disclosed herein, or a pharmaceutically acceptable salt thereof, for use as a medicament in the treatment of a neurological disease or a neuropathy.

[014m] In another aspect of the present disclosure, there is provided an oligonucleotide disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of a neurological disease or a neuropathy.

[014n] In another aspect of the present disclosure, there is provided an 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 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).

[014o] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the oligonucleotide of the previous aspect, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[014p] In another aspect of the present disclosure, there is provided an oligonucleotide disclosed herein 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 suffering from 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.

[014q] In another aspect of the present disclosure, there is provided the oligonucleotide disclosed herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, 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 use in therapy.

[014r] In another aspect of the present disclosure, there is provided a use of an oligonucleotide disclosed herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, 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), in the manufacture of a medicament for treating a neurological disease and/or a neuropathy in a patient in need thereof.

[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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, the oligonucleotide is 19 and 40 nucleosides in length. In various examples, 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 examples, at least two, three, or four internucleoside linkages of the oligonucleotide are phosphodiester internucleoside linkages. In various examples, the oligonucleotide comprises at least two, three, or four modified internucleoside linkages.

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

[0024] In various examples, the oligonucleotide comprises at least one modified sugar moiety. In various examples, 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 examples, 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 examples, the oligonucleotide comprises one or more 2'-*O*-(2-methoxyethyl) nucleosides that are linked through phosphorothioate internucleoside linkages. In some examples, all cytosine nucleosides in a STMN2 antisense oligonucleotide of the present disclosure comprise modified sugar moiety comprising 2'-MOE, all nucleosides comprise modified nucleobase 5-methyl cytosine, and all internucleoside linkages are phosphorothioate linkage. In various examples, 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 examples, the oligonucleotide comprises five linked nucleosides that are linked through phosphodiester internucleoside linkages. In various examples, the each of the five linked nucleosides are 2'-*O*-(2-methoxyethyl) (2'MOE) nucleosides. In various examples, each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'MOE) nucleosides.

[0026] In various examples, 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 examples, the oligonucleotide exhibits at least a 100% increase of full length STMN2 transcript or STMN2 protein. In various examples, the oligonucleotide exhibits at least a 200% increase of full length STMN2 transcript or STMN2 protein. In various examples, the oligonucleotide exhibits at least a 300% increase of full length STMN2 transcript or STMN2 protein. In various examples, the oligonucleotide exhibits at least a 400% increase of full length STMN2 transcript or STMN2 protein. In various examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, the neuron is a neuron of a patient in need of treatment of a neurological disease and/or a neuropathy. In various examples, 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 examples, the neuropathy is chemotherapy induced neuropathy.

[0030] In various examples, the exposing is performed *in vivo* or *ex vivo*. In various examples, the exposing comprises administering a STMN2 oligonucleotide (STMN2 AON) disclosed herein or a pharmaceutical composition thereof to a patient in need thereof. In various examples, 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 examples, a STMN2 oligonucleotide or a pharmaceutical composition thereof is administered

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

[0031] In various examples, the patient is a human. In various examples, 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 examples, 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 examples, 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 examples, 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 examples, the neuropathy is chemotherapy induced neuropathy. In various examples, 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 examples, the pharmaceutical composition is administered intrathecally or intracisternally. In various examples, a therapeutically effective amount of a STMN2 oligonucleotide or a pharmaceutical composition thereof is administered intrathecally or intracisternally. In various examples, 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 examples, 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 examples, 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 examples, 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 examples, at least one internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. In various examples, 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 examples, the oligonucleotide comprises one or more 2'-O-(2-methoxyethyl) nucleosides that are linked through phosphorothioate internucleoside linkages. In various

examples, the oligonucleotide comprises five linked nucleosides that are linked through phosphodiester internucleoside linkages. In various examples, each of the five linked nucleosides are 2'-*O*-(2-methoxyethyl) (2'MOE) nucleosides. In various examples, each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'MOE) nucleosides. In various examples, 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 examples, wherein the oligonucleotide comprises one or more chiral centers and/or double bonds. In various examples, 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 examples, 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 examples, 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

CLAIMS

WHAT IS CLAIMED IS:

1. A compound comprising an oligonucleotide comprising linked nucleosides with at least a 19 contiguous nucleobase sequence that is at least 90% complementary to an equal length portion of a transcript with at least 90% 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.

2. An oligonucleotide comprising linked nucleosides with at least a 19 contiguous nucleobase sequence that is at least 90% complementary to an equal length portion of a transcript with at least 90% 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.

3. The oligonucleotide of claim 1 or 2, wherein the nucleobase sequence comprises a portion of at least 10 contiguous nucleobases 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.

4. The oligonucleotide of any one of claims 1-3, wherein 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% 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.

5. The oligonucleotide of any one of claims 1-3, wherein the nucleobase sequence comprises a portion of at least 10 contiguous nucleobases 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,.

6. The oligonucleotide of any one of claims 1-5, wherein 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% 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.

7. 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% identity to an equal length portion of any one of SEQ ID NOs: 894-918 or SEQ ID NOs: 1392-1432.

8. 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% identity to an equal length portion of any one of SEQ ID NOs: 894-918 or SEQ ID NOs: 1392-1432.

9. The oligonucleotide of claim 7 or 8, wherein 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% identity to of any one of SEQ ID NOs: 894-918 or SEQ ID NOs: 1392-1432.

10. 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% 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.

11. 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% 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.

12. The oligonucleotide of claim 10 or 11, wherein 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.

13. The oligonucleotide of claim 12, wherein 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.

14. The oligonucleotide of claim 12, wherein 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.

15. The oligonucleotide of claim 12, wherein 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.

16. The oligonucleotide of claim 12, wherein 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.

17. The oligonucleotide of claim 10 or 11, wherein 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.

18. The oligonucleotide of claim 10 or 11, wherein 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.

19. The oligonucleotide of any one of claims 1-18, wherein the oligonucleotide is 19 and 40 nucleosides in length.

20. The oligonucleotide of any one of the above claims, 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 (*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.

21. The oligonucleotide of any one of the above claims, wherein at least two, three, or four internucleoside linkages of the oligonucleotide are phosphodiester internucleoside linkages.

22. The oligonucleotide of any one of claims 1-20, wherein the oligonucleotide comprises at least two, three, or four modified internucleoside linkages.

23. The oligonucleotide of claim 22, wherein each of the modified internucleoside linkage of the oligonucleotide is independently selected from a phosphorothioate linkage, a phosphoramidate linkage, a phosphoramidothiate linkage, a phosphorodiamidate.

24. The oligonucleotide of claim 22 or 23, wherein all internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

25. The oligonucleotide of claim 23, wherein the phosphorothioate internucleoside linkage is in one of a *R*p configuration or a *S*p configuration.

26. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified nucleobase.

27. The oligonucleotide of claim 26, wherein the at least one modified nucleobase is 5-methyl cytosine, pseudouridine, or 5-methoxyuridine.

28. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified sugar moiety.

29. The modified oligonucleotide of claim 28, wherein the modified sugar moiety is one of a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-O-(2-methoxyethyl) (2'MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

30. The oligonucleotide of any one of claims 1-23, 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.

31. The oligonucleotide of any one of claims 1-20 and 22-29, wherein the oligonucleotide comprises one or more 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides that are linked through phosphorothioate internucleoside linkages, optionally wherein all nucleosides in the oligonucleotide comprise modified sugar moiety comprising 2'-MOE; further optionally wherein all cytosine nucleosides in the oligonucleotide comprise modified nucleobase 5-methyl cytosine; and further optionally wherein all internucleoside linkages are phosphorothioate linkages.

32. The oligonucleotide of any one of claims 1-23 and 25-29, wherein 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.

33. The oligonucleotide of claim 32, wherein the oligonucleotide comprises five linked nucleosides that are linked through phosphodiester internucleoside linkages.

34. The oligonucleotide of claim 33, wherein the each of the five linked nucleosides are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

35. The oligonucleotide of claim 33 or 34, wherein each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

36. The oligonucleotide of any one of claims 1-35, wherein the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length STMN2 transcript or STMN2 protein, optionally wherein the increase is in comparison to a level prior to exposing a neuron to the oligonucleotide.

37. The oligonucleotide of any one of claims 1-36, wherein the oligonucleotide exhibits at least a 100% increase of full length STMN2 transcript or STMN2 protein, optionally wherein the increase is in comparison to a level prior to exposing a neuron to the oligonucleotide.

38. The oligonucleotide of any one of claims 1-37, wherein the oligonucleotide exhibits at least a 200% increase of full length STMN2 transcript or STMN2 protein, optionally wherein the increase is in comparison to a level prior to exposing a neuron to the oligonucleotide.

39. The oligonucleotide of any one of claims 1-38, wherein the oligonucleotide exhibits at least a 300% increase of full length STMN2 transcript or STMN2 protein, optionally wherein the increase is in comparison to a level prior to exposing a neuron to the oligonucleotide.

40. The oligonucleotide of any one of claims 1-39, wherein the oligonucleotide exhibits at least a 400% increase of full length STMN2 transcript or STMN2 protein, optionally wherein the increase is in comparison to a level prior to exposing a neuron to the oligonucleotide.

41. The oligonucleotide of any one of claims 36-40, wherein 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.

42. The oligonucleotide of any one of claims 1-35, wherein 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, optionally wherein the increase is in comparison to a level prior to exposing a neuron to the oligonucleotide.

43. The oligonucleotide of any one of claims 1-35 and 42, wherein the oligonucleotide exhibits at least a 50%, 60%, 70%, 80%, or 90% reduction of the STMN2 transcript with the cryptic exon.

44. A pharmaceutical composition comprising one or more of the oligonucleotides of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

45. Use of an oligonucleotide of any one of claims 1-43 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, in the manufacture of a medicament for treating a neurological disease and/or a neuropathy in a patient in need thereof.

46. The use of claim 45, wherein 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).

47. The use of claim 45, wherein the neuropathy is chemotherapy induced neuropathy.

48. Use of an oligonucleotide of any one of claims 1-43 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, in the manufacture of a medicament for restoring axonal outgrowth and/or regeneration of a motor neuron, wherein the motor neuron is to be exposed to the medicament.

49. Use of an oligonucleotide of any one of claims 1-43 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, in the manufacture of a medicament for increasing, promoting, stabilizing, or maintaining STMN2 expression and/or function in a neuron, wherein the neuron is to be exposed to the medicament.

50. The use of claim 48 or 49, wherein the neuron is a neuron of a patient in need of treatment of a neurological disease and/or a neuropathy.

51. The use of claim 50, wherein 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).

52. The use of claim 50, wherein the neuropathy is chemotherapy induced neuropathy.

53. The use of any one of claims 48-52, wherein the exposing is to be performed *in vivo* or *ex vivo*.

54. The use of any one of claims 48-52, wherein the exposing comprises the oligonucleotide which is to be administered to a patient determined to have a transcript comprising a cryptic exon sequence of SEQ ID NO: 447.

55. The use of any one of claims 45-54, wherein the oligonucleotide is to be administered topically, parenterally, intrathecally, intracisternally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, intralesionally, transdermally, or intraduodenally.

56. The use of claim 54, wherein the oligonucleotide is to be administered orally.

57. The use of any one of claims 45-54, wherein a therapeutically effective amount of the oligonucleotide is to be administered intrathecally or intracisternally.

58. The use of any one of claims 45-46 or 50-57, wherein the patient is a human.

59. The pharmaceutical composition of claim 44, wherein 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.

60. Use of an oligonucleotide of any one of claims 1-43 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, in the manufacture of a medicament for the treatment of neurological disease or a neuropathy.

61. The use of claim 60, wherein 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).

62. The use of claim 60, wherein the neuropathy is chemotherapy induced neuropathy.

63. The use of any one of claims 60-62, wherein the oligonucleotide or the pharmaceutical composition is to be 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.

64. The use of any one of claims 60-62, wherein the oligonucleotide or the pharmaceutical composition is to be administered intrathecally or intracisternally.

65. The use of any one of claims 60-64, wherein a therapeutically effective amount of the oligonucleotide or the pharmaceutical composition is to be administered intrathecally or intracisternally.

66. The use of any one of claims 1-65, wherein the patient is human.

67. An oligonucleotide of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, for use as a medicament in the treatment of a neurological disease or a neuropathy.

68. An oligonucleotide of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, for use in the treatment of a neurological disease or a neuropathy.

69. The oligonucleotide for use of claim 67 or 68, wherein said 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).

70. The oligonucleotide for use of claim 67 or 68, wherein the neuropathy is chemotherapy induced neuropathy.

71. An 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 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).

72. The oligonucleotide of claim 71, wherein at least one internucleoside linkage of the oligonucleotide is a phosphorothioate linkage.

73. The oligonucleotide of claim 71 or 72, 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.

74. The oligonucleotide of any one of claims 71-73, wherein the oligonucleotide comprises one or more 2'-*O*-(2-methoxyethyl) nucleosides that are linked through phosphorothioate internucleoside linkages.

75. The oligonucleotide of claim 71 or 72, wherein the oligonucleotide comprises five linked nucleosides that are linked through phosphodiester internucleoside linkages.

76. The oligonucleotide of claim 75, wherein each of the five linked nucleosides are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

77. The oligonucleotide of any one of claims 71-76, wherein each of the linked nucleosides of the oligonucleotide are 2'-*O*-(2-methoxyethyl) (2'-MOE) nucleosides.

78. The oligonucleotide of claim 71 or 72, wherein 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, further optionally wherein the oligonucleotide comprises at least one 5-methyl cytosine modified nucleobase.

79. A pharmaceutical composition comprising the oligonucleotide of any one of claims 70-78, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

80. An oligonucleotide of any one of claims 1-43 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 suffering from 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.

81. The oligonucleotide of any one of claims 1-43 comprising one or more chiral centers and/or double bonds.

82. The oligonucleotide of claim 81, wherein the oligonucleotide exist as stereoisomers selected from geometric isomers, enantiomers, and diastereomers.

83. The oligonucleotide of any one of claims 1-43 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, 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 use in therapy.

84. Use of an oligonucleotide of any one of claims 1-43 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, 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), in the manufacture of a medicament for treating a neurological disease and/or a neuropathy in a patient in need thereof.

85. The use of claim 84, wherein 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).

86. The use of claim 84, wherein the neuropathy is chemotherapy induced neuropathy.

87. The use of any one of claims 45-58, 63-66, and 84-86, wherein patient for treatment is identified by measuring the presence or level of expression of neurofilament light (NEFL), neurofilament heavy (NEFH), phosphorylated neurofilament heavy chain (pNFH), TDP-43, or $p75^{ECD}$ in the plasma, the spinal cord fluid, the cerebrospinal fluid, the extracellular vesicles (for example, CSF exosomes), the blood, the urine, the lymphatic fluid, fecal matter, or a tissue of the patient.

88. The use of claim 87, wherein the patient for treatment is identified by measuring phosphorylated neurofilament heavy chain (pNFH) in cerebrospinal fluid (CSF).

89. The use of claim 88, wherein the pNFH in the CSF of the patient is used to predict disease status and survival in *C9ORF72*-associated amyotrophic lateral sclerosis (c9ALS) patients after initial administration and/or during on-going treatment.