

METHODS FOR MODULATING UBE3A-ATS**Sequence Listing**

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL0480SEQ.xml, created on October 28, 2024, which is 478 KB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field

Provided are methods of administering IONIS 1273062/ION582 for reducing the amount or activity of UBE3A-ATS, the endogenous antisense transcript of ubiquitin protein ligase E3A (UBE3A) in a cell or subject, and in certain instances increasing the expression of paternal UBE3A and the amount of UBE3A protein in a cell or subject. Such methods are useful to ameliorate at least one symptom or hallmark of a neurogenetic disorder, such as Angelman syndrome. Such symptoms and hallmarks include developmental delays, ataxia, speech impairment, sleep problems, seizures, and EEG abnormalities.

Background

Angelman syndrome (AS) is a developmental disorder that affects ~1/15,000 live births and is caused by a deficiency of ubiquitin protein ligase E3A (UBE3A). Of the two copies of the UBE3A gene in neurons, the maternal gene is typically expressed, while the paternal gene is subject to genetic imprinting and silencing. Angelman syndrome is caused when a functional copy of the UBE3A gene is not inherited from the mother, either because of a mutation, a deletion, paternal uniparental disomy of chromosome 15, or an imprinting defect. See, Buiting, et al., “Angelman syndrome – insights into a rare neurogenetic disorder,” *Nature Rev. Neuro.*, 2016, 12:584-593.

Angelman syndrome patients experience developmental delays and speech impairment, and commonly experience sleep problems, seizures, and EEG abnormalities. The disorder is usually diagnosed in the first few years of life and the diagnosis can be confirmed by genetic testing. However, therapies for Angelman syndrome remain limited and focus mainly on symptomatic management. See, Williams, C.A. et al., *Genet. Med.*, 12: 385–395, 2010.

Recently, topoisomerase inhibitors currently used in cancer treatment were found to “unsilence” paternal UBE3A expression in both a neuronal culture system and mice. See, Huang, H.S. et al., *Nature*, 481: 185–189, 2012. However, topoisomerase inhibitors are fraught with safety concerns because they are known to be non-specific and capable of inducing DNA damage, such as single and double-strand breaks.

Currently there is a lack of acceptable options for treating neurogenetic disorders such as AS. It is therefore an object herein to provide compounds, methods, and pharmaceutical compositions for the treatment of such diseases.

Summary

Provided are methods of administering ION582 for reducing the amount or activity of UBE3A-ATS, the endogenous antisense transcript of ubiquitin protein ligase E3A (UBE3A) in a cell or subject, and in certain instances increasing the expression of paternal UBE3A and the amount of UBE3A protein in the cell or subject. In certain embodiments, the subject has Angelman syndrome (AS).

Also provided are methods useful for ameliorating at least one symptom or hallmark of a neurogenetic disorder such as Angelman syndrome. In certain embodiments, the symptom or hallmark includes developmental delays, ataxia, speech impairment, sleep problems, seizures, and/or EEG abnormalities.

5 Brief Description of the Drawings

Various aspects of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings below.

10 Figs. 1A-1E illustrate improvement observed in the medium dose (40 mg ION582) and high dose (80 mg ION582) as compared to the low dose (20 mg) on Bayley-4 assessments of cognition (Fig. 1A), receptive communication (Fig. 1B), expressive communication (Fig. 1C), gross motor skills (Fig. 1D), and fine motor skills (Fig. 1E) at 4 months. GSV, Growth scale values.

15 Figs. 2A-2B illustrate improvement observed in receptive communication as measured by Bayley-4 (Fig. 2A) and Vineland-3 (Fig. 2B) for pooled medium and high doses of ION582 compared to natural history (NH) at 6 months. GSV, Growth scale values; SEM, Standard error mean.

Fig. 3 illustrates improvement observed in receptive communication as measured by Bayley-4 in participants with deletion and mutation genotypes for pooled medium and high doses of ION582 at 6 months compared to natural history (NH). GSV, Growth scale values; SEM, Standard error mean.

20 Figs. 4A-4C illustrate improvement observed in expressive communication as measured by Bayley-4 (Fig. 4A), Vineland-3 (Fig. 4B), and SAS-CGI-C (Fig. 4C) for pooled medium and high doses of ION582 compared to natural history (NH).

25 Figs. 5A-5B illustrate improvement observed in Bayley-4 and Vineland-3 measures of receptive communication (Fig. 5A) and expressive communication (Fig. 5B) for pooled medium and high doses of ION582 at 6 months.

Fig. 6 illustrates improvement observed on the ORCA measure of communication for pooled medium and high doses of ION582 at 6 months compared to natural history (NH).

30 Figs. 7A-7B illustrates the correlation between the ORCA measure of communication and the Bayley-4 measure for change in receptive communication (Fig. 7A) and change in expressive communication (Fig. 7B) for pooled medium and high doses of ION582 at 6 months.

Figs. 8A-8B illustrate improvement observed across measures of cognition on Bayley-4 (Fig. 8A) and on SAS-CGI-C (Fig. 8B). GSV, Growth scale values; SEM, Standard error mean; SAS-CGI-C, Symptoms of Angelman Syndrome–Clinician Global Impression-Change.

35 Figs. 9A-9C illustrate improvement observed in fine motor function for pooled medium and high dose ION582 groups at 6 months as measured on Bayley-4 (Fig. 9A), Vineland-3 (Fig. 9B), and SAS-CGI-C (Fig. 9C). GSV, Growth scale values; SEM, Standard error mean; SAS-CGI-C, Symptoms of Angelman Syndrome–Clinician Global Impression-Change.

Figs. 10A-10C illustrate improvement observed in gross motor function for pooled medium and high dose ION582 groups at 6 months as measured on Bayley-4 (Fig. 10A), Vineland-3 (Fig. 10B), and SAS-CGI-C (Fig. 10C).

GSV, Growth scale values; SEM, Standard error mean; SAS-CGI-C. Symptoms of Angelman Syndrome–Clinician Global Impression–Change.

Fig. 11 illustrates the clinically meaningful improvement in participants in overall AS symptom change for patients treated with ION582 (Fig. 11).

5 Detailed Description

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

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

DEFINITIONS

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

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

As used herein, “2′-deoxyribonucleoside” means a nucleoside comprising a 2′-H(H) deoxyribosyl sugar moiety. In certain embodiments, a 2′-deoxyribonucleoside is a 2′-β-D deoxyribonucleoside and comprises a 2′-β-D-deoxyribosyl sugar moiety, which has the β-D configuration as found in naturally occurring deoxyribonucleic acids (DNA). In certain embodiments, a 2′-deoxyribonucleoside may comprise a modified nucleobase or may comprise an RNA nucleobase (uracil).
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As used herein, “2′-MOE” means a 2′-OCH₂CH₂OCH₃ group in place of the 2′-OH group of a ribosyl sugar moiety. A “2′-MOE sugar moiety” is a sugar moiety with a 2′-OCH₂CH₂OCH₃ group in place of the 2′-OH group of a ribosyl sugar moiety. Unless otherwise indicated, a 2′-MOE sugar moiety is in the β-D configuration. “MOE” means O-methoxyethyl.
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As used herein, “2′-MOE nucleoside” means a nucleoside comprising a 2′-MOE sugar moiety.

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

As used herein, “about” means plus or minus 10% of the provided value.

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

As used herein, “ameliorate” in reference to a treatment means improvement in at least one symptom or hallmark relative to the same symptom or hallmark in the absence of the treatment. In certain embodiments,

amelioration is the reduction in the severity or frequency of a symptom or hallmark, or the delayed onset or slowing of progression in the severity or frequency of a symptom or hallmark.

As used herein, “dose” means a quantity of a pharmaceutical agent administered.

As used herein, a “dosing interval” means the approximate amount of time between administration of two consecutive doses. Intervals may vary by a few days for patient convenience, scheduling, and the like and still be considered within the stated dosing interval.

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

As used herein, “loading dose” means a therapeutically effective amount of a pharmaceutical agent administered during an initial dosing phase during which steady state concentration of the pharmaceutical agent is achieved. “Initial loading dose” means the first loading dose administered. “Last loading dose” means the loading dose administered most recently prior to administering a first maintenance dose.

As used herein, “maintenance dose” means a therapeutically effective amount of a pharmaceutical agent administered during a dosing phase after steady state concentration of the pharmaceutical agent has been achieved.

As used herein, the terms “ION582” and “1273062” are interchangeable.

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

As used herein, “nucleoside” means a compound comprising a nucleobase and a sugar moiety. The nucleobase and sugar moiety are each, independently, unmodified or modified. As used herein, “modified nucleoside” means a nucleoside comprising a modified nucleobase and/or a modified sugar moiety. “Linked nucleosides” are nucleosides that are connected in a contiguous sequence (i.e., no additional nucleosides are presented between those that are linked). As used herein, “oligonucleotide” means a strand of linked nucleosides connected via internucleoside linkages, wherein each nucleoside and internucleoside linkage may be modified or unmodified. Unless otherwise indicated, oligonucleotides consist of 8-50 linked nucleosides. As used herein, “modified oligonucleotide” means an oligonucleotide, wherein at least one nucleoside or internucleoside linkage is modified.

As used herein, “pharmaceutical agent” is an oligomeric compound or modified oligonucleotide such as ION582.

As used herein, “pharmaceutically acceptable diluent” means any substance suitable for use in administering to a human subject. In certain embodiments, a pharmaceutically acceptable diluent is sterile water, sterile saline, sterile buffer solution, or sterile artificial cerebrospinal fluid (aCSF).

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

As used herein, “potassium salt” means a salt of a modified oligonucleotide, wherein the cation of the salt is potassium.

As used herein, “RNA” means any RNA transcript, including endogenous antisense transcripts that do not encode a protein (e.g., UBE3A-ATS), and also includes pre-mRNA and mature mRNA unless otherwise specified.

5 As used herein, “sodium salt” means a salt of a modified oligonucleotide, wherein the cation of the salt is sodium.

As used herein, “subject” means a human or non-human animal. In certain embodiments, the subject is a human subject. A “subject in need thereof,” is a subject who would benefit from administration of a modified oligonucleotide disclosed herein. In certain embodiments, the subject in need thereof has Angelman syndrome.

10 As used herein, “sugar moiety” means an unmodified sugar moiety or a modified sugar moiety. “Unmodified sugar moiety” means a 2'-OH(H) β -D ribosyl moiety, as found in RNA (an “unmodified RNA sugar moiety”), or a 2'-H(H) β -D deoxyribosyl moiety, as found in DNA (an “unmodified DNA sugar moiety”). Unmodified sugar moieties have one hydrogen at each of the 1', 3', and 4' positions, an oxygen at the 3' position, and two hydrogens at the 5' position. “Modified sugar moiety” or “modified sugar” means a modified furanosyl sugar moiety or a sugar surrogate.

15 As used herein, “symptom or hallmark” means any physical feature or test result that indicates the existence or extent of a disease or disorder. In certain embodiments, a symptom is apparent to a subject or to a medical professional examining or testing said subject. In certain embodiments, a hallmark is apparent upon invasive diagnostic testing, including, but not limited to, post-mortem tests. In certain embodiments, a symptom or hallmark is measured by EEG. In certain embodiments, the symptom or hallmark is developmental delays, ataxia, speech impairment, sleep problems, seizures, and EEG abnormalities.

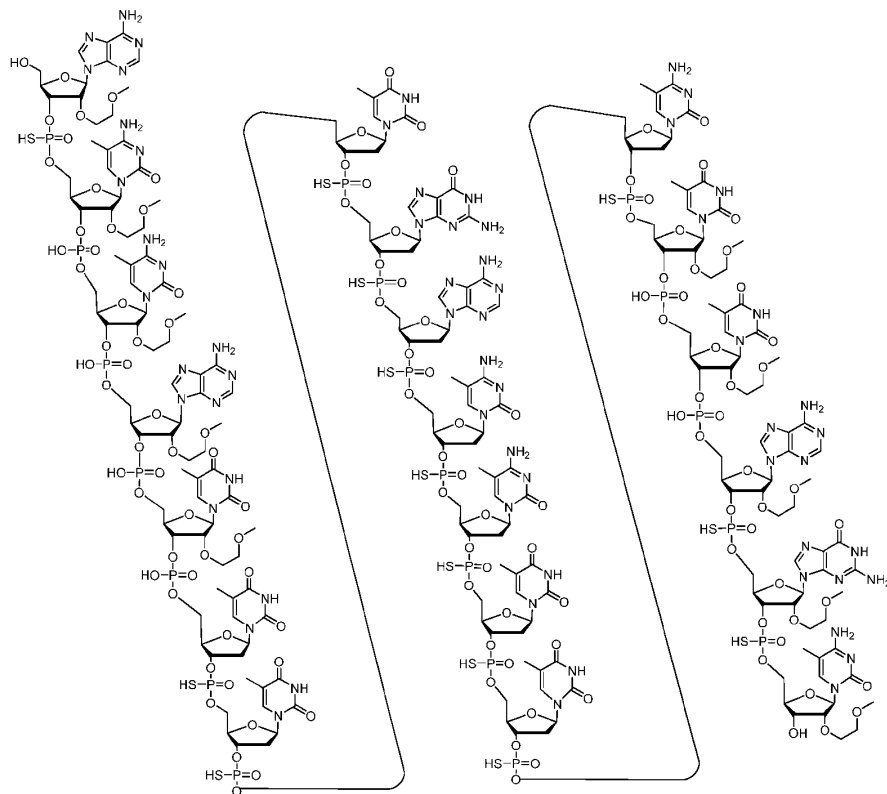
20 As used herein, “therapeutically effective amount” means an amount of a pharmaceutical agent that provides a therapeutic benefit to a human subject. For example, a therapeutically effective amount improves a symptom or hallmark of a disease or disorder.

25 As used herein, “trough concentration” means the concentration of an analyte (e.g., UBE3A protein in a biological sample taken from a dosed human subject immediately prior to the human subject receiving a subsequent dose or the concentration of an analyte on the last study day.

As used herein, “week” means 7 days.

CERTAIN EMBODIMENTS

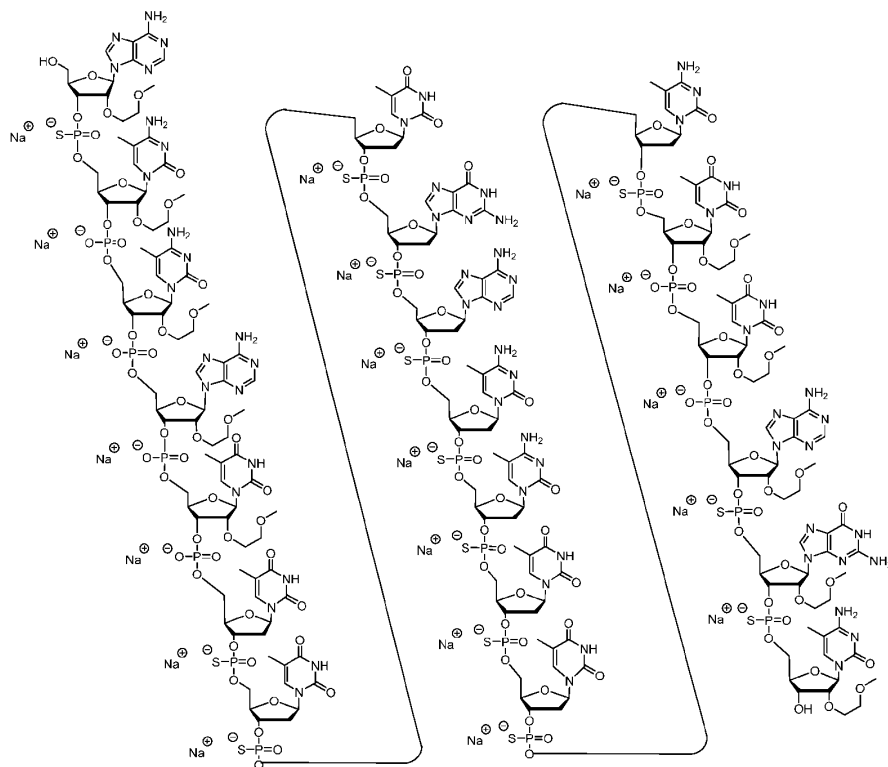
Embodiment 1. A method comprising administering to a human subject a therapeutically effective amount of a modified oligonucleotide according to the following chemical structure:



5 (SEQ ID NO: 5), or a pharmaceutically acceptable salt thereof.

Embodiment 2. The method of embodiment 1, wherein the modified oligonucleotide is the sodium salt or the potassium salt.

Embodiment 3. A method comprising administering to a human subject a therapeutically effective amount of a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 5).

- 5 Embodiment 4. A method comprising administering to a human subject a therapeutically effective amount of a modified oligonucleotide consisting of 19-20 linked nucleosides, wherein the modified oligonucleotide comprises at least 19 contiguous nucleosides of the following chemical notation (5' to 3'):

A_{es}^mC_{eo}^mC_{eo}A_{eo}T_{eo}T_{ds}T_{ds}T_{ds}G_{ds}A_{ds}^mC_{ds}^mC_{ds}T_{ds}T_{ds}^mC_{ds}T_{eo}T_{eo}A_{es}G_{es}^mC_e (SEQ ID NO: 5), wherein:

- 10 A = an adenine nucleobase,
 mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribose sugar moiety,
 15 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

Embodiment 5. The method of any of embodiments 1-4, wherein the modified oligonucleotide is formulated as a pharmaceutical composition comprising a pharmaceutically acceptable diluent.

- Embodiment 6. The method of embodiment 5, wherein the pharmaceutically acceptable diluent is artificial
 20 cerebrospinal fluid (aCSF).

Embodiment 7. The method of embodiment 5, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS).

Embodiment 8. The method of any of embodiments 1-7, wherein the therapeutically effective amount is any of 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, or 150 mg.

Embodiment 9. The method of any of embodiments 1-8, wherein the therapeutically effective amount is any of 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, and 25 mg.

Embodiment 10. The method of any of embodiments 1-8, wherein the therapeutically effective amount is any of 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, and 30 mg.

Embodiment 11. The method of any of embodiments 1-8, wherein the therapeutically effective amount is any of 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg, 38 mg, 39 mg, 40 mg, 41 mg, 42 mg, 43 mg, 44 mg, 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, and 50 mg.

Embodiment 12. The method of any of embodiments 1-8, wherein the therapeutically effective amount is any of 51 mg, 52 mg, 53 mg, 54 mg, 55 mg, 56 mg, 57 mg, 58 mg, 59 mg, 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, and 70 mg.

Embodiment 13. The method of any of embodiments 1-8, wherein the therapeutically effective amount is any of 71 mg, 72 mg, 73 mg, 74 mg, 75 mg, 76 mg, 77 mg, 78 mg, 79 mg, 80 mg, 81 mg, 82 mg, 83 mg, 84 mg, 85 mg, 86 mg, 87 mg, 88 mg, 89 mg, and 90 mg.

Embodiment 14. The method of any of embodiments 1-8, wherein the therapeutically effective amount is any of 91 mg, 92 mg, 93 mg, 94 mg, 95 mg, 96 mg, 97 mg, 98 mg, 99 mg, 100 mg, 101 mg, 102 mg, 103 mg, 104 mg, 105 mg, 106 mg, 107 mg, 108 mg, 109 mg, and 110 mg.

Embodiment 15. The method of any of embodiments 1-7, wherein the therapeutically effective amount is any of from 5 mg to 120 mg, from 5 mg to 115 mg, from 5 mg to 110 mg, from 5 mg to 105 mg, from 5 mg to 100 mg, from 5 mg to 95 mg, from 5 mg to 90 mg, from 5 mg to 85 mg, from 5 mg to 80 mg, from 5 mg to 75 mg, from 5 mg to 70 mg, from 5 mg to 65 mg, from 5 mg to 60 mg, from 5 mg to 55 mg, from 5 mg to 50 mg, from 5 mg to 45 mg, from 5 mg to 40 mg, from 5 mg to 35 mg, from 5 mg to 30 mg, from 5 mg to 25 mg, from 5 mg to 20 mg, from 5 mg to 15 mg, from 5 mg to 10 mg, from 10 mg to 120 mg, from 10 mg to 115 mg, from 10 mg to 110 mg, from 10 mg to 105 mg, from 10 mg to 100 mg, from 10 mg to 95 mg, from 10 mg to 90 mg, from 10 mg to 85 mg, from 10 mg to 80 mg, from 10 mg to 75 mg, from 10 mg to 70 mg, from 10 mg to 65 mg, from 10 mg to 60 mg, from 10 mg to 55 mg, from 10 mg to 50 mg, from 10 mg to 45 mg, from 10 mg to 40 mg, from 10 mg to 35 mg, from 10 mg to 30 mg, from 10 mg to 25 mg, from 10 mg to 20 mg, from 10 mg to 15 mg, from 15 mg to 120 mg, from 15 mg to 115 mg, from 15 mg to 110 mg, from 15 mg to 105 mg, from 15 mg to 100 mg, from 15 mg to 95 mg, from 15 mg to 90 mg, from 15 mg to 85 mg, from 15 mg to 80 mg, from 15 mg to 75 mg, from 15 mg to 70 mg, from 15 mg to 65 mg, from 15 mg to 60 mg, from 15 mg to 55 mg, from 15 mg to 50 mg, from 15 mg to 45 mg, from 15 mg to 40 mg, from 15 mg to 35 mg, from 15 mg to 30 mg, from 15 mg to 25 mg, from 15 mg to 20 mg, from 20 mg to 120 mg, from 20 mg to 115 mg, from 20 mg to 110 mg, from 20 mg to 105 mg, from 20 mg to 100 mg, from 20 mg to 95 mg, from 20 mg to 90 mg, from 20 mg to 85 mg, from 20 mg to 80 mg, from 20 mg to 75 mg, from 20 mg to 70 mg, from 20 mg to 65 mg, from 20 mg to 60 mg, from 20 mg to 55 mg,

from 20 mg to 50 mg, from 20 mg to 45 mg, from 20 mg to 40 mg, from 20 mg to 35 mg, from 20 mg to 30 mg, from 20 mg to 25 mg, from 25 mg to 120 mg, from 25 mg to 115 mg, from 25 mg to 110 mg, from 25 mg to 105 mg, from 25 mg to 100 mg, from 25 mg to 95 mg, from 25 mg to 90 mg, from 25 mg to 85 mg, from 25 mg to 80 mg, from 25 mg to 75 mg, from 25 mg to 70 mg, from 25 mg to 65 mg, from 25 mg to 60 mg, from 25 mg to 55 mg, from 25 mg to 50 mg,

5 from 25 mg to 45 mg, from 25 mg to 40 mg, from 25 mg to 35 mg, from 25 mg to 30 mg, from 30 mg to 120 mg, from 30 mg to 115 mg, from 30 mg to 110 mg, from 30 mg to 105 mg, from 30 mg to 100 mg, from 30 mg to 95 mg, from 30 mg to 90 mg, from 30 mg to 85 mg, from 30 mg to 80 mg, from 30 mg to 75 mg, from 30 mg to 70 mg, from 30 mg to 65 mg, from 30 mg to 60 mg, from 30 mg to 55 mg, from 30 mg to 50 mg, from 30 mg to 45 mg, from 30 mg to 40 mg, from 30 mg to 35 mg, from 35 mg to 120 mg, from 35 mg to 115 mg, from 35 mg to 110 mg, from 35 mg to 105 mg,

10 from 35 mg to 100 mg, from 35 mg to 95 mg, from 35 mg to 90 mg, from 35 mg to 85 mg, from 35 mg to 80 mg, from 35 mg to 75 mg, from 35 mg to 70 mg, from 35 mg to 65 mg, from 35 mg to 60 mg, from 35 mg to 55 mg, from 35 mg to 50 mg, from 35 mg to 45 mg, from 35 mg to 40 mg, from 40 mg to 120 mg, from 40 mg to 115 mg, from 40 mg to 110 mg, from 40 mg to 105 mg, from 40 mg to 100 mg, from 40 mg to 95 mg, from 40 mg to 90 mg, from 40 mg to 85 mg, from 40 mg to 80 mg, from 40 mg to 75 mg, from 40 mg to 70 mg, from 40 mg to 65 mg, from 40 mg to 60 mg,

15 from 40 mg to 55 mg, from 40 mg to 50 mg, from 40 mg to 45 mg, from 45 mg to 120 mg, from 45 mg to 115 mg, from 45 mg to 110 mg, from 45 mg to 105 mg, from 45 mg to 100 mg, from 45 mg to 95 mg, from 45 mg to 90 mg, from 45 mg to 85 mg, from 45 mg to 80 mg, from 45 mg to 75 mg, from 45 mg to 70 mg, from 45 mg to 65 mg, from 45 mg to 60 mg, from 45 mg to 55 mg, from 45 mg to 50 mg, from 50 mg to 120 mg, from 50 mg to 115 mg, from 50 mg to 110 mg, from 50 mg to 105 mg, from 50 mg to 100 mg, from 50 mg to 95 mg, from 50 mg to 90 mg, from 50 mg to 85 mg,

20 from 50 mg to 80 mg, from 50 mg to 75 mg, from 50 mg to 70 mg, from 50 mg to 65 mg, from 50 mg to 60 mg, from 50 mg to 55 mg, from 55 mg to 120 mg, from 55 mg to 115 mg, from 55 mg to 110 mg, from 55 mg to 105 mg, from 55 mg to 100 mg, from 55 mg to 95 mg, from 55 mg to 90 mg, from 55 mg to 85 mg, from 55 mg to 80 mg, from 55 mg to 75 mg, from 55 mg to 70 mg, from 55 mg to 65 mg, from 55 mg to 60 mg, from 60 mg to 120 mg, from 60 mg to 115 mg, from 60 mg to 110 mg, from 60 mg to 105 mg, from 60 mg to 100 mg, from 60 mg to 95 mg, from 60 mg to 90 mg, from 60 mg to 85 mg,

25 from 60 mg to 80 mg, from 60 mg to 75 mg, from 60 mg to 70 mg, from 65 mg to 120 mg, from 65 mg to 115 mg, from 65 mg to 110 mg, from 65 mg to 105 mg, from 65 mg to 100 mg, from 65 mg to 95 mg, from 65 mg to 90 mg, from 65 mg to 85 mg, from 65 mg to 80 mg, from 65 mg to 75 mg, from 65 mg to 70 mg, from 70 mg to 120 mg, from 70 mg to 115 mg, from 70 mg to 110 mg, from 70 mg to 105 mg, from 70 mg to 100 mg, from 70 mg to 95 mg, from 70 mg to 90 mg, from 70 mg to 85 mg, from 70 mg to 80 mg, from 75 mg to 120 mg, from 75 mg to 115 mg, from 75 mg to 110 mg,

30 from 75 mg to 105 mg, from 75 mg to 100 mg, from 75 mg to 95 mg, from 75 mg to 90 mg, from 75 mg to 85 mg, from 75 mg to 80 mg, from 80 mg to 120 mg, from 80 mg to 115 mg, from 80 mg to 110 mg, from 80 mg to 105 mg, from 80 mg to 100 mg, from 80 mg to 95 mg, from 80 mg to 90 mg, from 85 mg to 120 mg, from 85 mg to 115 mg, from 85 mg to 110 mg, from 85 mg to 105 mg, from 85 mg to 100 mg, from 85 mg to 95 mg, from 85 mg to 90 mg, from 90 mg to 120 mg, from 90 mg to 115 mg, from 90 mg to 110 mg, from 90 mg to 105 mg, from 90 mg to 100 mg, from 95 mg to 120 mg, from 95 mg to 115 mg, from 95 mg to 110 mg, from 95 mg to 105 mg, from 95 mg to 100 mg, from 100 mg to 120 mg, from 100 mg to 115 mg, from 100 mg to 110 mg, from 100 mg to 105 mg, from 105 mg to 120 mg, from 105 mg to 115 mg, from 105 mg to 110 mg, from 110 mg to 120 mg, from 110 mg to 115 mg, and from 115 mg to 120 mg.

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Embodiment 16. The method of any of embodiments 1-7 or 15, wherein the therapeutically effective amount is any of 15 mg to 25 mg, from 18 mg to 25 mg, from 19 mg to 25 mg, from 18 mg to 23 mg, from 19 mg to 23 mg, from 18 mg to 22 mg, from 19 mg to 22 mg, from 18 mg to 21 mg, or from 19 mg to 21 mg.

Embodiment 17. The method of any of embodiments 1-7 or 15, wherein the therapeutically effective amount is any of 35 mg to 45 mg, from 38 mg to 45 mg, from 39 mg to 45 mg, from 38 mg to 43 mg, from 39 mg to 43 mg, from 38 mg to 42 mg, from 39 mg to 42 mg, from 38 mg to 41 mg, or from 39 mg to 41 mg.

Embodiment 18. The method of any of embodiments 1-7 or 15, wherein the therapeutically effective amount is any of from 55 mg to 65 mg, from 58 mg to 65 mg, from 59 mg to 65 mg, from 58 mg to 63 mg, from 59 mg to 63 mg, from 58 mg to 62 mg, from 59 mg to 62 mg, from 58 mg to 61 mg, or from 59 mg to 61 mg.

Embodiment 19. The method of any of embodiments 1-7 or 15, wherein the therapeutically effective amount is any of from 75 mg to 85 mg, from 78 mg to 85 mg, from 79 mg to 85 mg, from 78 mg to 83 mg, from 79 mg to 83 mg, from 78 mg to 82 mg, from 79 mg to 82 mg, from 78 mg to 81 mg, or from 79 mg to 81 mg.

Embodiment 20. The method of any of embodiments 1-7, wherein the therapeutically effective amount is any of less than 150 mg, less than 145 mg, less than 140 mg, less than 135 mg, less than 130 mg, less than 125 mg, less than 120 mg, less than 115 mg, less than 110 mg, less than 105 mg, less than 100 mg, less than 95 mg, less than 90 mg, less than 85 mg, less than 80 mg, less than 75 mg, less than 70 mg, less than 65 mg, less than 60 mg, less than 55 mg, less than 50 mg, less than 45 mg, less than 40 mg, less than 35 mg, less than 30 mg, less than 25 mg, less than 20 mg, less than 15 mg, less than 10 mg, and less than 5 mg.

Embodiment 21. The method of any of embodiments 1-7 or 20, wherein the therapeutically effective amount is any of less than 85 mg, less than 80 mg, less than 75 mg, less than 70 mg, less than 65 mg, less than 60 mg, less than 55 mg, less than 50 mg, less than 45 mg, less than 40 mg, less than 35 mg, less than 30 mg, less than 25 mg, less than 20 mg, less than 15 mg, and less than 10 mg.

Embodiment 22. The method of any of embodiments 1-7, wherein the therapeutically effective amount is any of at least 5 mg, at least 10 mg, at least 15 mg, at least 20 mg, at least 25 mg, at least 30 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 55 mg, at least 60 mg, at least 65 mg, at least 70 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, at least about 100 mg, at least 105 mg, at least 115 mg, at least 120 mg, at least 125 mg, at least 130 mg, at least 135 mg, at least 140 mg, and at least 145 mg.

Embodiment 23. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 5 mg.

Embodiment 24. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 10 mg.

Embodiment 25. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 20 mg.

Embodiment 26. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 30 mg.

Embodiment 27. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 40 mg.

Embodiment 28. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 50 mg.

Embodiment 29. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 60 mg.

Embodiment 30. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 70 mg.

Embodiment 31. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 80 mg.

Embodiment 32. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 90 mg.

Embodiment 33. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 100 mg.

Embodiment 34. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 110 mg.

- Embodiment 35. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 120 mg.
- Embodiment 36. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 4-6 mg.
- Embodiment 37. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 9-11 mg.
- Embodiment 38. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 19-21 mg.
- 5 Embodiment 39. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 29-31 mg.
- Embodiment 40. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 39-41 mg.
- Embodiment 41. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 48-52 mg.
- Embodiment 42. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 58-62 mg.
- Embodiment 43. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 68-72 mg.
- 10 Embodiment 44. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 78-82 mg.
- Embodiment 45. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 88-92 mg.
- Embodiment 46. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 98-102 mg.
- Embodiment 47. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 108-112 mg.
- Embodiment 48. The method of any of embodiments 1-7, wherein the therapeutically effective amount is 118-122 mg.
- 15 Embodiment 49. The method of any of embodiments 1-48, wherein the therapeutically effective amount is administered as a single dose.
- Embodiment 50. The method of embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once every 28 days.
- Embodiment 51. The method of embodiment 49, wherein the method comprises administering a dose of any of the
- 20 therapeutically effective amounts of embodiments 1-48 once every 56 days.
- Embodiment 52. The method of embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once every 84 days.
- Embodiment 53. The method of embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once every 4, 8, 10, 12, 16, 18, 20, 24, 28, or 32 weeks.
- 25 Embodiment 54. The method of embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once every 4 weeks.
- Embodiment 55. The method of embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once every 8 weeks.
- Embodiment 56. The method of embodiment 49, wherein the method comprises administering a dose of any of the
- 30 therapeutically effective amounts of embodiments 1-48 once every 12 weeks.
- Embodiment 57. The method of embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once every 16 weeks.
- Embodiment 58. The method of embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once every 20 weeks.
- 35 Embodiment 59. The method of embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once every 24 weeks.
- Embodiment 60. The method of embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once monthly.

- Embodiment 61. The method embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once every two months.
- Embodiment 62. The method embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once every four months.
- 5 Embodiment 63. The method embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once every five months.
- Embodiment 64. The method of embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once every six months.
- Embodiment 65. The method of embodiment 49, wherein the method comprises administering a dose of any of the
10 therapeutically effective amounts of embodiments 1-48 once every 6 months, once every 7 months, once every 8 months, once every 9 months, once every 10 months, once every 11 months, or once every 12 months.
- Embodiment 66. The method embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once quarterly.
- Embodiment 67. The method embodiment 49, wherein the method comprises administering a dose of any of the
15 therapeutically effective amounts of embodiments 1-48 once triannually.
- Embodiment 68. The method of embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once semiannually.
- Embodiment 69. The method of embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 once annually.
- 20 Embodiment 70. The method of embodiment 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of embodiments 1-48 any of once every 1 week, once every 2 weeks, once every 3 weeks, 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, once every 12 weeks, once every 13 weeks, once every 14 weeks, once every 15 weeks, once every 16 weeks, once every 17 weeks, once every 18 weeks, once every 19 weeks,
25 once every 20 weeks, once every 21 weeks, once every 22 weeks, once every 23 weeks, once every 24 weeks, once every month, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 7 months, once every 8 months, once every 9 months, once every 10 months, once every 11 months, or once every year.
- Embodiment 71. The method of any of embodiments 1-70, wherein the method comprises administering to the human
30 subject a dose of 10 mg of the modified oligonucleotide once every four weeks.
- Embodiment 72. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 20 mg of the modified oligonucleotide once every four weeks.
- Embodiment 73. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 30 mg of the modified oligonucleotide once every four weeks.
- 35 Embodiment 74. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide once every four weeks.
- Embodiment 75. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 50 mg of the modified oligonucleotide once every four weeks.

- Embodiment 76. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 60 mg of the modified oligonucleotide once every four weeks.
- Embodiment 77. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 70 mg of the modified oligonucleotide once every four weeks.
- 5 Embodiment 78. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide once every four weeks.
- Embodiment 79. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 90 mg of the modified oligonucleotide once every four weeks.
- Embodiment 80. The method of any of embodiments 1-70, wherein the method comprises administering to the human
10 subject a dose of 10 mg of the modified oligonucleotide once every eight weeks.
- Embodiment 81. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 20 mg of the modified oligonucleotide once every eight weeks.
- Embodiment 82. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 30 mg of the modified oligonucleotide once every eight weeks.
- 15 Embodiment 83. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide once every eight weeks.
- Embodiment 84. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 50 mg of the modified oligonucleotide once every eight weeks.
- Embodiment 85. The method of any of embodiments 1-70, wherein the method comprises administering to the human
20 subject a dose of 60 mg of the modified oligonucleotide once every eight weeks.
- Embodiment 86. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 70 mg of the modified oligonucleotide once every eight weeks.
- Embodiment 87. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide once every eight weeks.
- 25 Embodiment 88. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 90 mg of the modified oligonucleotide once every eight weeks.
- Embodiment 89. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 10 mg of the modified oligonucleotide once every twelve weeks.
- Embodiment 90. The method of any of embodiments 1-70, wherein the method comprises administering to the human
30 subject a dose of 20 mg of the modified oligonucleotide once every twelve weeks.
- Embodiment 91. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 30 mg of the modified oligonucleotide once every twelve weeks.
- Embodiment 92. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide once every twelve weeks.
- 35 Embodiment 93. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 50 mg of the modified oligonucleotide once every twelve weeks.
- Embodiment 94. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 60 mg of the modified oligonucleotide once every twelve weeks.

Embodiment 95. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 70 mg of the modified oligonucleotide once every twelve weeks.

Embodiment 96. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide once every twelve weeks.

5 Embodiment 97. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 90 mg of the modified oligonucleotide once every twelve weeks.

Embodiment 98. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 20 mg of the modified oligonucleotide once every quarter.

10 Embodiment 99. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 30 mg of the modified oligonucleotide once every quarter.

Embodiment 100. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide once every quarter.

Embodiment 101. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 50 mg of the modified oligonucleotide once every quarter.

15 Embodiment 102. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 60 mg of the modified oligonucleotide once every quarter.

Embodiment 103. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 70 mg of the modified oligonucleotide once every quarter.

20 Embodiment 104. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide once every quarter.

Embodiment 105. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 90 mg of the modified oligonucleotide once every quarter.

25 Embodiment 106. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 10 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

30 Embodiment 107. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 20 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

Embodiment 108. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 30 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

35 Embodiment 109. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

Embodiment 110. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide every 12 to 13 weeks or quarterly or four times a year.

Embodiment 111. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 50 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year. The method of any of embodiments 1-69, wherein the method comprises administering to the human subject a dose of 60 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

Embodiment 112. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 60 mg of the modified oligonucleotide every 12 to 13 weeks or quarterly or four times a year.

Embodiment 113. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 70 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

Embodiment 114. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

Embodiment 115. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide every 12 to 13 weeks or quarterly or four times a year.

Embodiment 116. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 90 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

Embodiment 117. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 10 mg of the modified oligonucleotide once every 28 days.

Embodiment 118. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 20 mg of the modified oligonucleotide once every 28 days.

Embodiment 119. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 30 mg of the modified oligonucleotide once every 28 days.

Embodiment 120. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide once every 28 days.

Embodiment 121. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 50 mg of the modified oligonucleotide once every 28 days.

Embodiment 122. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 60 mg of the modified oligonucleotide once every 28 days.

- Embodiment 123. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 70 mg of the modified oligonucleotide once every 28 days.
- Embodiment 124. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide once every 28 days.
- 5 Embodiment 125. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 90 mg of the modified oligonucleotide once every 28 days.
- Embodiment 126. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 10 mg of the modified oligonucleotide once every 56 days.
- Embodiment 127. The method of any of embodiments 1-70, wherein the method comprises administering to the human
10 subject a dose of 20 mg of the modified oligonucleotide once every 56 days.
- Embodiment 128. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 30 mg of the modified oligonucleotide once every 56 days.
- Embodiment 129. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide once every 56 days.
- 15 Embodiment 130. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 50 mg of the modified oligonucleotide once every 56 days.
- Embodiment 131. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 60 mg of the modified oligonucleotide once every 56 days.
- Embodiment 132. The method of any of embodiments 1-70, wherein the method comprises administering to the human
20 subject a dose of 70 mg of the modified oligonucleotide once every 56 days.
- Embodiment 133. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide once every 56 days.
- Embodiment 134. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 90 mg of the modified oligonucleotide once every 56 days.
- 25 Embodiment 135. The method of any of embodiments 1-134, wherein four doses of the modified oligonucleotide are administered.
- Embodiment 136. The method of any of embodiments 1-134, wherein three doses of the modified oligonucleotide are administered.
- Embodiment 137. The method of any of embodiments 1-134, wherein two doses of the modified oligonucleotide are
30 administered.
- Embodiment 138. The method of any of embodiments 1-134, wherein the method comprises administering to the human subject a dose of 20 mg of the modified oligonucleotide on day 1, day 29, and day 85 for a total of 3 doses, then administering a dose of up to 40 mg every 12 weeks for up to 5 doses.
- Embodiment 139. The method of any of embodiments 1-70, wherein the method comprises administering to the human
35 subject a dose of 40 mg of the modified oligonucleotide on day 1, day 29, and day 85, then administering a dose of up to 40 mg every 12 weeks for up to 5 doses.
- Embodiment 140. The method of any of embodiments 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide on day 1, day 29, and day 85, then administering a dose of up to 80 mg every 12 weeks for up to 5 doses.

Embodiment 141. The method of any of embodiments 1-70, wherein the modified oligonucleotide is administered to the human subject at a total dose per month of from 5 mg to 100 mg, from 5 mg to 80 mg, from 5 mg to 60 mg, from 5 mg to 40 mg, from 5 mg to 20 mg, from 10 mg to 100 mg, from 10 mg to 80 mg, from 10 mg to 60 mg, from 10 mg to 40 mg, from 10 mg to 20 mg, from 20 mg to 100 mg, from 20 mg to 80 mg, from 20 mg to 60 mg, from 20 mg to 40 mg, from 40 mg to 100 mg, from 40 mg to 80 mg, from 40 mg to 60 mg, or from 80 mg to 100 mg.

Embodiment 142. The method of any of embodiments 1-70, wherein the modified oligonucleotide is administered to the human subject at a total dose per 3 months of from 15 mg to 300 mg, from 15 mg to 180 mg, from 15 mg to 150 mg, from 15 mg to 100 mg, from 15 mg to 80 mg, from 15 mg to 50 mg, from 40 mg to 300 mg, from 40 mg to 180 mg, from 40 mg to 150 mg, from 40 mg to 100 mg, from 40 mg to 80 mg, from 80 mg to 300 mg, from 80 mg to 180 mg, from 80 mg to 150 mg, from 80 mg to 100 mg, from 100 mg to 300 mg, from 100 mg to 180 mg, from 100 mg to 150 mg, or from 150 to 300 mg.

Embodiment 143. The method of any of embodiments 1-70, wherein the modified oligonucleotide is administered to the human subject at a total dose per 4 months of from 20 mg to 400 mg, from 20 mg to 350 mg, from 20 mg to 300 mg, from 20 mg to 250 mg, from 20 mg to 200 mg, from 20 mg to 150 mg, from 20 mg to 100 mg, from 50 mg to 400 mg, from 50 mg to 350 mg, from 50 mg to 300 mg, from 50 mg to 250 mg, from 50 mg to 200 mg, from 50 mg to 150 mg, from 50 mg to 100 mg, from 100 mg to 400 mg, from 100 mg to 350 mg, from 100 mg to 300 mg, from 100 mg to 250 mg, from 100 mg to 200 mg, from 100 mg to 150 mg, from 200 mg to 400 mg, from 200 mg to 350 mg, from 200 mg to 300 mg, from 200 mg to 250 mg, from 300 mg to 400 mg, or from 300 mg to 350 mg.

Embodiment 144. The method of any of embodiments 1-70, wherein the modified oligonucleotide is administered to the human subject at a total dose per 6 month of from 30 mg to 600 mg, from 30 mg to 500 mg, from 30 mg to 400 mg, from 30 mg to 300 mg, from 30 mg to 200 mg, from 30 mg to 100 mg, from 50 mg to 600 mg, from 50 mg to 500 mg, from 50 mg to 400 mg, from 50 mg to 300 mg, from 50 mg to 200 mg, from 50 mg to 100 mg, from 100 mg to 600 mg, from 100 mg to 500 mg, from 100 mg to 400 mg, from 100 mg to 300 mg, from 100 mg to 200 mg, from 200 mg to 600 mg, from 200 mg to 500 mg, from 200 mg to 400 mg, from 200 mg to 300 mg, from 300 mg to 600 mg, from 300 mg to 500 mg, from 300 mg to 400 mg, from 400 mg to 600 mg, from 400 mg to 500 mg, or from 500 mg to 600 mg.

Embodiment 145. The method of any of embodiments 1-70, wherein the modified oligonucleotide is administered to the human subject at a total dose per year of from 60 mg to 1200 mg, from 60 mg to 1100 mg, from 60 mg to 1000 mg, from 60 mg to 900 mg, from 60 mg to 800 mg, from 60 mg to 700 mg, from 60 mg to 600 mg, from 60 mg to 500 mg, from 60 mg to 400 mg, from 60 mg to 300 mg, from 60 mg to 200 mg, from 60 mg to 100 mg, from 100 mg to 1200 mg, from 100 mg to 1100 mg, from 100 mg to 1000 mg, from 100 mg to 900 mg, from 100 mg to 800 mg, from 100 mg to 700 mg, from 100 mg to 600 mg, from 100 mg to 500 mg, from 100 mg to 400 mg, from 100 mg to 300 mg, from 100 mg to 200 mg, from 200 mg to 1200 mg, from 200 mg to 1100 mg, from 200 mg to 1000 mg, from 200 mg to 900 mg, from 200 mg to 800 mg, from 200 mg to 700 mg, from 200 mg to 600 mg, from 200 mg to 500 mg, from 200 mg to 400 mg, from 200 mg to 300 mg, from 300 mg to 1200 mg, from 300 mg to 1100 mg, from 300 mg to 1000 mg, from 300 mg to 900 mg, from 300 mg to 800 mg, from 300 mg to 700 mg, from 300 mg to 600 mg, from 300 mg to 500 mg, from 300 mg to 400 mg, from 400 mg to 1200 mg, from 400 mg to 1100 mg, from 400 mg to 1000 mg, from 400 mg to 900 mg, from 400 mg to 800 mg, from 400 mg to 700 mg, from 400 mg to 600 mg, from 400 mg to 500 mg, from 500 mg to 1200 mg, from 500 mg to 1100 mg, from 500 mg to 1000 mg, from 500 mg to 900 mg, from 500 mg to 800 mg, from 500 mg to 700 mg, from 500 mg to 600 mg, from 600 mg to 1200 mg, from 600 mg to 1100 mg, from 600 mg to 1000

mg, from 600 mg to 900 mg, from 600 mg to 800 mg, from 600 mg to 700 mg, from 700 mg to 1200 mg, from 700 mg to 1100 mg, from 700 mg to 1000 mg, from 700 mg to 900 mg, from 700 mg to 800 mg, from 800 mg to 1200 mg, from 800 mg to 1100 mg, from 800 mg to 1000 mg, from 800 mg to 900 mg, from 900 mg to 1200 mg, from 900 mg to 1100 mg, from 900 mg to 1000 mg, from 1000 mg to 1200 mg, from 1000 mg to 1100mg, or from 1100 mg to 1200 mg.

5 Embodiment 146. The method of embodiment 145, wherein the modified oligonucleotide is administered every month, every 2 months, every 3 months, every 4 months, every 6 months, or once per year.

Embodiment 147. The method of embodiment 145, wherein each administration is at an interval independently selected from 2 weeks, 4 weeks, one month, two months, 3 months, 4 months, and 6 months.

Embodiment 148. The method of any of embodiments 141-145, wherein the administration is at varying dosing intervals.

10 Embodiment 149. The method of any of embodiments 1-148, wherein the method comprises administering to the human subject a loading dose of the modified oligonucleotide.

Embodiment 150. The method of any of embodiments 1-148, wherein the method does not comprise administering to the human subject a loading dose of the modified oligonucleotide.

15 Embodiment 151. The method of any of embodiments 1-150, wherein the method comprises administering to the human subject a maintenance dose of the modified oligonucleotide, optionally 1, 2, 3, 4, or 5 maintenance doses.

Embodiment 152. The method of any of embodiments 1-151, wherein the dose is administered by intrathecal administration.

Embodiment 153. The method of any of embodiments 1-152, wherein the dose is administered by bolus intrathecal administration.

20 Embodiment 154. The method of any of embodiments 1-153, wherein the size of Delta wave in the human subject is reduced.

Embodiment 155. The method of any of embodiments 1-154, wherein the human subject has a decrease in Delta activity compared to the Delta activity of the subject prior to administering the modified oligonucleotide.

25 Embodiment 156. The method of any of embodiments 1-155, wherein the human subject has a faster frequency rhythms (theta) compared to the frequency rhythms of the subject prior to administering the modified oligonucleotide.

Embodiment 157. The method of any of embodiments 1-156, wherein the human subject has an improvement in total Bayley score compared to the Bayley score of the subject prior to administering the modified oligonucleotide.

30 Embodiment 158. The method of any of embodiments 1-157, wherein the human subject is less than 18 years of age, less than 15 years of age, less than 13 years of age, less than 10 years of age, less than 8 years of age, or less than 5 years of age.

Embodiment 159. The method of any of embodiments 1-157, wherein the human subject is from 2 years of age up to 5 years of age, from 4 years of age up to 17 years of age, or from 1 years of age up to 17 years of age.

Embodiment 160. The method of any of embodiments 1-157, wherein the human subject is 13 years of age or older, or 18 years of age or older.

35 Embodiment 161. The method of any of embodiments 1-157, wherein the human subject is from 18 years of age to 50 years of age.

Embodiment 162. The method of any of embodiments 1-157, wherein the human subject is 18 years of age or older.

Embodiment 163. The method of any of embodiments 1-157, wherein the human subject is 17 years of age or younger.

Embodiment 164. The method of any of the preceding embodiments, wherein a disease or disorder associated with UBE3A is ameliorated in the human subject in need thereof.

Embodiment 165. The method of any of the preceding embodiments, wherein UBE3A-ATS RNA is reduced in the human subject in need thereof.

5 Embodiment 166. The method of any of the preceding embodiments, wherein UBE3A protein is increased.

Embodiment 167. The method of any of embodiments 1-166, wherein the disease or disorder associated with UBE3A is a developmental disorder.

Embodiment 168. The method of any of embodiments 1-167, wherein the disease or disorder associated with UBE3A is Angelman syndrome.

10 Embodiment 169. The method of any of embodiments 1-168, wherein at least one symptom or hallmark of the disease or disorder associated with UBE3A is ameliorated.

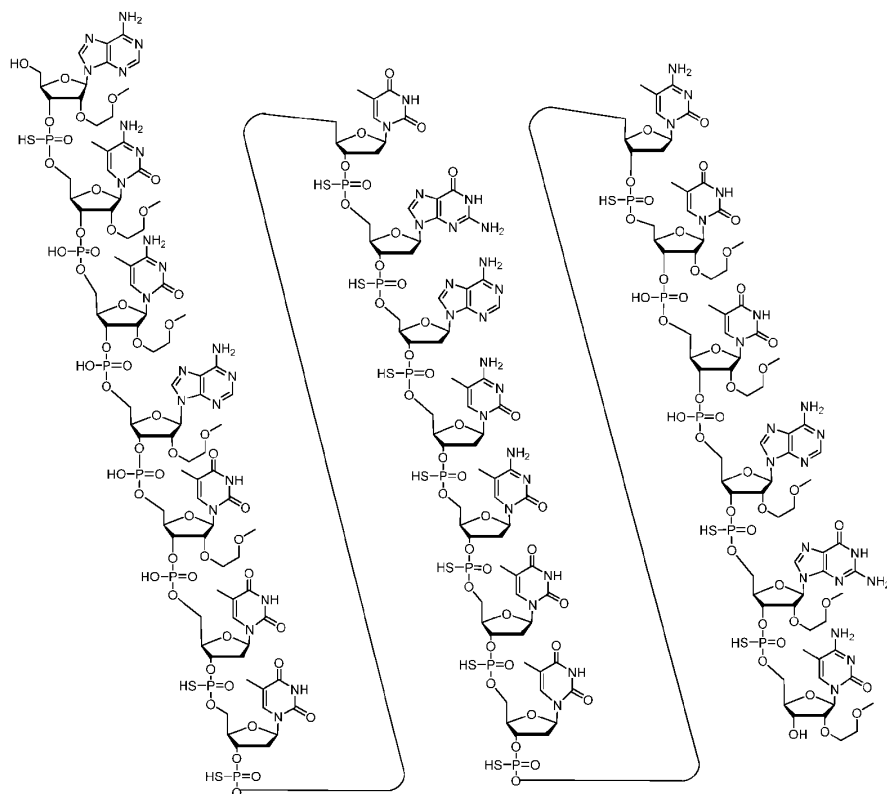
Embodiment 170. The method of any of embodiments 1-169, wherein the at least one symptom or hallmark is selected from developmental delays, ataxia, cognitive impairment, impairments in fine and/or gross motor skills, speech impairment, impairment in receptive communication and/or expressive communication, impairment in daily living skills, impaired socialization skills sleep problems, seizures, and EEG abnormalities.

15

Embodiment 171. The method of embodiment 169, wherein the at least one symptom or hallmark is developmental delays, ataxia, speech impairment, sleep problems, seizures, or EEG abnormalities.

Embodiment 172. A method of treating a patient having Angelman syndrome, comprising

- 20
- a) at a first time assessing the patient for sleep, seizures, communication, motor function, and/or ability to perform activities of daily living;
 - b) administering to the human subject a therapeutically effective amount of a modified oligonucleotide according to the following chemical structure:

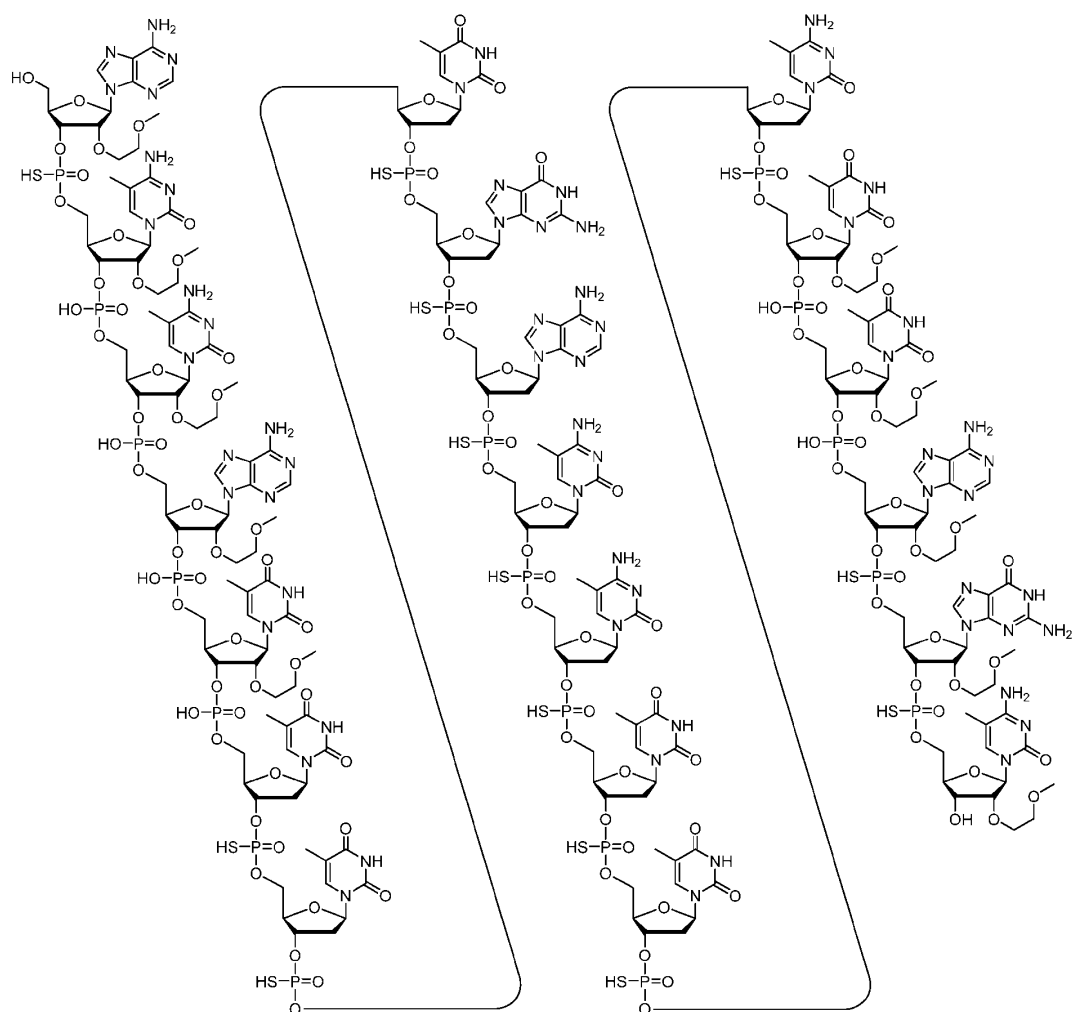


(SEQ ID NO: 5), or a pharmaceutically acceptable salt thereof.

- c) at a second time wherein the second time is after administering the modified oligonucleotide, reassessing the patient for sleep, seizures, communication, motor function, and/or ability to perform activities of daily living; and
- d) if there is no improvement or insufficient improvement between the assessments at the first time and the second time, increasing the amount of the next administered dose.

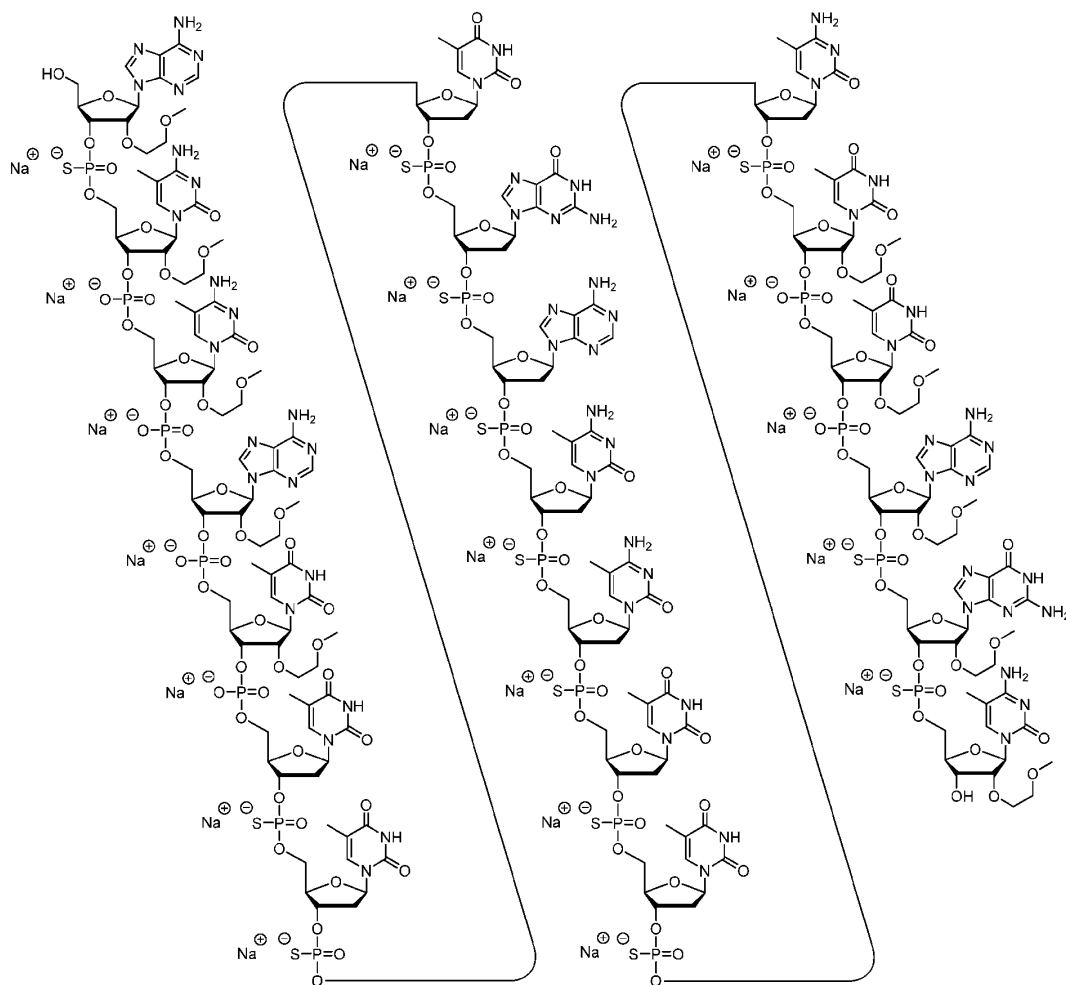
Embodiment 173. Use of a modified oligonucleotide in the manufacture of a medicament for treating Angelman syndrome, wherein the modified oligonucleotide is:

a. a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 5), or a pharmaceutically acceptable salt thereof;

b.a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 5), or

- c. a modified oligonucleotide consisting of 19-20 linked nucleosides, wherein the modified oligonucleotide comprises at least 19 contiguous nucleosides of the following chemical notation (5' to 3'):

$A_{es}^m C_{eo}^m C_{eo}^m A_{eo} T_{ds} T_{ds} T_{ds} G_{ds} A_{cs}^m C_{ds}^m C_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds} A_{es} G_{es}^m C_e$ (SEQ ID NO: 5), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribsyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

wherein the treatment of Angelman syndrome comprises administering a therapeutically effective amount of the modified oligonucleotide and the therapeutically effective amount is 5-150 mg.

Embodiment 174. The use of embodiment 173, wherein the therapeutically effective amount is any of 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, or 150 mg.

Embodiment 175. The use of embodiment 173, wherein the therapeutically effective amount is any of from 5 mg to 120 mg, from 5 mg to 115 mg, from 5 mg to 110 mg, from 5 mg to 105 mg, from 5 mg to 100 mg, from 5 mg to 95 mg, from 5 mg to 90 mg, from 5 mg to 85 mg, from 5 mg to 80 mg, from 5 mg to 75 mg, from 5 mg to 70 mg, from 5 mg to 65 mg, from 5 mg to 60 mg, from 5 mg to 55 mg, from 5 mg to 50 mg, from 5 mg to 45 mg, from 5 mg to 40 mg, from 5 mg to 35 mg, from 5 mg to 30 mg, from 5 mg to 25 mg, from 5 mg to 20 mg, from 5 mg to 15 mg, from 5 mg to 10 mg, from 10 mg to 120 mg, from 10 mg to 115 mg, from 10 mg to 110 mg, from 10 mg to 105 mg, from 10 mg to 100 mg, from 10 mg to 95 mg, from 10 mg to 90 mg, from 10 mg to 85 mg, from 10 mg to 80 mg, from 10 mg to 75 mg, from 10 mg to 70 mg, from 10 mg to 65 mg, from 10 mg to 60 mg, from 10 mg to 55 mg, from 10 mg to 50 mg, from 10 mg to 45 mg, from 10 mg to 40 mg, from 10 mg to 35 mg, from 10 mg to 30 mg, from 10 mg to 25 mg, from 10 mg to 20 mg, from 10 mg to 15 mg, from 15 mg to 120 mg, from 15 mg to 115 mg, from 15 mg to 110 mg, from 15 mg to 105 mg, from 15 mg to 100 mg, from 15 mg to 95 mg, from 15 mg to 90 mg, from 15 mg to 85 mg, from 15 mg to 80 mg, from 15 mg to 75 mg, from 15 mg to 70 mg, from 15 mg to 65 mg, from 15 mg to 60 mg, from 15 mg to 55 mg, from 15 mg to 50 mg, from 15 mg to 45 mg, from 15 mg to 40 mg, from 15 mg to 35 mg, from 15 mg to 30 mg, from 15 mg to 25 mg, from 15 mg to 20 mg, from 20 mg to 120 mg, from 20 mg to 115 mg, from 20 mg to 110 mg, from 20 mg to 105 mg, from 20 mg to 100 mg, from 20 mg to 95 mg, from 20 mg to 90 mg, from 20 mg to 85 mg, from 20 mg to 80 mg, from 20 mg to 75 mg, from 20 mg to 70 mg, from 20 mg to 65 mg, from 20 mg to 60 mg, from 20 mg to 55 mg, from 20 mg to 50 mg, from 20 mg to 45 mg, from 20 mg to 40 mg, from 20 mg to 35 mg, from 20 mg to 30 mg, from 20 mg to 25 mg, from 25 mg to 120 mg, from 25 mg to 115 mg, from 25 mg to 110 mg, from 25 mg to 105 mg, from 25 mg to 100 mg, from 25 mg to 95 mg, from 25 mg to 90 mg, from 25 mg to 85 mg, from 25 mg to 80 mg, from 25 mg to 75 mg, from 25 mg to 70 mg, from 25 mg to 65 mg, from 25 mg to 60 mg, from 25 mg to 55 mg, from 25 mg to 50 mg, from 25 mg to 45 mg, from 25 mg to 40 mg, from 25 mg to 35 mg, from 25 mg to 30 mg, from 30 mg to 120 mg, from 30 mg to 115 mg, from 30 mg to 110 mg, from 30 mg to 105 mg, from 30 mg to 100 mg, from 30 mg to 95 mg, from 30 mg to 90 mg, from 30 mg to 85 mg, from 30 mg to 80 mg, from 30 mg to 75 mg, from 30 mg to 70 mg, from 30 mg to 65 mg, from 30 mg to 60 mg, from 30 mg to 55 mg, from 30 mg to 50 mg, from 30 mg to 45 mg, from 30 mg to 40 mg, from 30 mg to 35 mg, from 35 mg to 120 mg, from 35 mg to 115 mg, from 35 mg to 110 mg, from 35 mg to 105 mg, from 35 mg to 100 mg, from 35 mg to 95 mg, from 35 mg to 90 mg, from 35 mg to 85 mg, from 35 mg to 80 mg, from 35 mg to 75 mg, from 35 mg to 70 mg, from 35 mg to 65 mg, from 35 mg to 60 mg, from 35 mg to 55 mg, from 35 mg to 50 mg, from 35 mg to 45 mg, from 35 mg to 40 mg, from 40 mg to 120 mg, from 40 mg to 115 mg, from 40 mg to 110 mg, from 40 mg to 105 mg, from 40 mg to 100 mg, from 40 mg to 95 mg, from 40 mg to 90 mg, from 40 mg to 85 mg, from 40 mg to 80 mg, from 40 mg to 75 mg, from 40 mg to 70 mg, from 40 mg to 65 mg, from 40 mg to 60 mg, from 40 mg to 55 mg, from 40 mg to 50 mg, from 40 mg to 45 mg, from 45 mg to 120 mg, from 45 mg to 115 mg, from 45 mg to 110 mg, from 45 mg to 105 mg, from 45 mg to 100 mg, from 45 mg to 95 mg, from 45 mg to 90 mg, from 45 mg to 85 mg, from 45 mg to 80 mg, from 45 mg to 75 mg, from 45 mg to 70 mg, from 45 mg to 65 mg, from 45 mg to 60 mg.

- from 45 mg to 55 mg, from 45 mg to 50 mg, from 50 mg to 120 mg, from 50 mg to 115 mg, from 50 mg to 110 mg, from 50 mg to 105 mg, from 50 mg to 100 mg, from 50 mg to 95 mg, from 50 mg to 90 mg, from 50 mg to 85 mg, from 50 mg to 80 mg, from 50 mg to 75 mg, from 50 mg to 70 mg, from 50 mg to 65 mg, from 50 mg to 60 mg, from 50 mg to 120 mg, from 55 mg to 115 mg, from 55 mg to 110 mg, from 55 mg to 105 mg, from 55 mg to 100 mg, from 55 mg to 95 mg, from 55 mg to 90 mg, from 55 mg to 85 mg, from 55 mg to 80 mg, from 55 mg to 75 mg, from 55 mg to 70 mg, from 55 mg to 65 mg, from 55 mg to 60 mg, from 60 mg to 120 mg, from 60 mg to 115 mg, from 60 mg to 110 mg, from 60 mg to 105 mg, from 60 mg to 100 mg, from 60 mg to 95 mg, from 60 mg to 90 mg, from 60 mg to 85 mg, from 60 mg to 80 mg, from 60 mg to 75 mg, from 60 mg to 70 mg, from 65 mg to 120 mg, from 65 mg to 115 mg, from 65 mg to 110 mg, from 65 mg to 105 mg, from 65 mg to 100 mg, from 65 mg to 95 mg, from 65 mg to 90 mg, from 65 mg to 85 mg, from 65 mg to 80 mg, from 65 mg to 75 mg, from 65 mg to 70 mg, from 70 mg to 120 mg, from 70 mg to 115 mg, from 70 mg to 110 mg, from 70 mg to 105 mg, from 70 mg to 100 mg, from 70 mg to 95 mg, from 70 mg to 90 mg, from 70 mg to 85 mg, from 70 mg to 80 mg, from 75 mg to 120 mg, from 75 mg to 115 mg, from 75 mg to 110 mg, from 75 mg to 105 mg, from 75 mg to 100 mg, from 75 mg to 95 mg, from 75 mg to 90 mg, from 75 mg to 85 mg, from 75 mg to 80 mg, from 80 mg to 120 mg, from 80 mg to 115 mg, from 80 mg to 110 mg, from 80 mg to 105 mg, from 80 mg to 100 mg, from 80 mg to 95 mg, from 80 mg to 90 mg, from 85 mg to 120 mg, from 85 mg to 115 mg, from 85 mg to 110 mg, from 85 mg to 105 mg, from 85 mg to 100 mg, from 85 mg to 95 mg, from 85 mg to 90 mg, from 90 mg to 120 mg, from 90 mg to 115 mg, from 90 mg to 110 mg, from 90 mg to 105 mg, from 90 mg to 100 mg, from 95 mg to 120 mg, from 95 mg to 115 mg, from 95 mg to 110 mg, from 95 mg to 105 mg, from 95 mg to 100 mg, from 100 mg to 120 mg, from 100 mg to 115 mg, from 100 mg to 110 mg, from 100 mg to 105 mg, from 105 mg to 120 mg, from 105 mg to 115 mg, from 105 mg to 110 mg, from 110 mg to 120 mg, from 110 mg to 115 mg, and from 115 mg to 120 mg.
- Embodiment 176. The use of embodiment 173, wherein the therapeutically effective amount is any of 15 mg to 25 mg, from 18 mg to 25 mg, from 19 mg to 25 mg, from 18 mg to 23 mg, from 19 mg to 23 mg, from 18 mg to 22 mg, from 19 mg to 22 mg, from 18 mg to 21 mg, or from 19 mg to 21 mg.
- Embodiment 177. The use of embodiment 173, wherein the therapeutically effective amount is any of 35 mg to 45 mg, from 38 mg to 45 mg, from 39 mg to 45 mg, from 38 mg to 43 mg, from 39 mg to 43 mg, from 38 mg to 42 mg, from 39 mg to 42 mg, from 38 mg to 41 mg, or from 39 mg to 41 mg.
- Embodiment 178. The use of embodiment 173, wherein the therapeutically effective amount is any of from 55 mg to 65 mg, from 58 mg to 65 mg, from 59 mg to 65 mg, from 58 mg to 63 mg, from 59 mg to 63 mg, from 58 mg to 62 mg, from 59 mg to 62 mg, from 58 mg to 61 mg, or from 59 mg to 61 mg.
- Embodiment 179. The use of embodiment 173, wherein the therapeutically effective amount is any of from 75 mg to 85 mg, from 78 mg to 85 mg, from 79 mg to 85 mg, from 78 mg to 83 mg, from 79 mg to 83 mg, from 78 mg to 82 mg, from 79 mg to 82 mg, from 78 mg to 81 mg, or from 79 mg to 81 mg.
- Embodiment 180. The use of embodiment 173, wherein the therapeutically effective amount is about 5 mg.
- Embodiment 181. The use of embodiment 173, wherein the therapeutically effective amount is about 10 mg.
- Embodiment 182. The use of embodiment 173, wherein the therapeutically effective amount is about 20 mg.
- Embodiment 183. The use of embodiment 173, wherein the therapeutically effective amount is about 30 mg.
- Embodiment 184. The use of embodiment 173, wherein the therapeutically effective amount is about 40 mg.
- Embodiment 185. The use of embodiment 173, wherein the therapeutically effective amount is about 50 mg.
- Embodiment 186. The use of embodiment 173, wherein the therapeutically effective amount is about 60 mg.

- Embodiment 187. The use of embodiment 173, wherein the therapeutically effective amount is about 70 mg.
- Embodiment 188. The use of embodiment 173, wherein the therapeutically effective amount is about 80 mg.
- Embodiment 189. The use of embodiment 173, wherein the therapeutically effective amount is about 90 mg.
- Embodiment 190. The use of embodiment 173, wherein the therapeutically effective amount is about 100 mg.
- 5 Embodiment 191. The use of embodiment 173, wherein the therapeutically effective amount is about 110 mg.
- Embodiment 192. The use of embodiment 173, wherein the therapeutically effective amount is about 120 mg.
- Embodiment 193. The use of embodiment 173, wherein the therapeutically effective amount is 4-6 mg.
- Embodiment 194. The use of embodiment 173, wherein the therapeutically effective amount is 9-11 mg.
- Embodiment 195. The use of embodiment 173, wherein the therapeutically effective amount is 19-21 mg.
- 10 Embodiment 196. The use of embodiment 173, wherein the therapeutically effective amount is 29-31 mg.
- Embodiment 197. The use of embodiment 173, wherein the therapeutically effective amount is 39-41 mg.
- Embodiment 198. The use of embodiment 173, wherein the therapeutically effective amount is 48-52 mg.
- Embodiment 199. The use of embodiment 173, wherein the therapeutically effective amount is 58-62 mg.
- Embodiment 200. The use of embodiment 173, wherein the therapeutically effective amount is 68-72 mg.
- 15 Embodiment 201. The use of embodiment 173, wherein the therapeutically effective amount is 78-82 mg.
- Embodiment 202. The use of embodiment 173, wherein the therapeutically effective amount is 88-92 mg.
- Embodiment 203. The use of embodiment 173, wherein the therapeutically effective amount is 98-102 mg.
- Embodiment 204. The use of embodiment 173, wherein the therapeutically effective amount is 108-112 mg.
- Embodiment 205. The use of embodiment 173, wherein the therapeutically effective amount is 118-122 mg.
- 20 Embodiment 206. The use of any of embodiments 173-205, wherein the medicament is formulated for administration once every 28 days.
- Embodiment 207. The use of any of embodiments 173-205, wherein the medicament is formulated for administration once every 56 days.
- Embodiment 208. The use of any of embodiments 173-205, wherein the wherein the medicament is formulated for
- 25 administration once every 84 days.
- Embodiment 209. The use of any of embodiments 173-205, wherein the medicament is formulated for administration once every 4, 8, 10, 12, 16, 18, 20, 24, 28, or 32 weeks.
- Embodiment 210. The use of any of embodiments 173-205, wherein the medicament is formulated for administration once every 4 weeks.
- 30 Embodiment 211. The use of any of embodiments 173-205, wherein the medicament is formulated for administration once every 8 weeks.
- Embodiment 212. The use of any of embodiments 173-205, wherein the medicament is formulated for administration once every 12 weeks.
- Embodiment 213. The use of any of embodiments 173-205, wherein the medicament is formulated for administration
- 35 once every 16 weeks.
- Embodiment 214. The use of any of embodiments 173-205, wherein the medicament is formulated for administration once every 20 weeks.
- Embodiment 215. The use of any of embodiments 173-205, wherein the medicament is formulated for administration once every 24 weeks.

Embodiment 216. The use of any of embodiments 173-205, wherein the medicament is formulated for administration once monthly.

Embodiment 217. The use of any of embodiments 173-205, wherein the medicament is formulated for administration once every two months.

- 5 Embodiment 218. The use of any of 173-205, wherein the medicament is formulated for administration once every four months.

Embodiment 219. The use of any of embodiments 173-205, wherein the medicament is formulated for administration once every five months.

- 10 Embodiment 220. The use of any of embodiments 173-205, wherein the medicament is formulated for administration once every six months.

Embodiment 221. The use of any of embodiments 173-205, wherein the medicament is formulated for administration once quarterly.

Embodiment 222. The use of any of embodiments 173-205, wherein the medicament is formulated for administration once triannually.

- 15 Embodiment 223. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 20 mg of the modified oligonucleotide and the medicament is formulated for administration once every four weeks.

Embodiment 224. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 40 mg of the modified oligonucleotide and the medicament is formulated for administration once every four weeks.

- 20 Embodiment 225. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 60 mg of the modified oligonucleotide and the medicament is formulated for administration once every four weeks.

Embodiment 226. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 80 mg of the modified oligonucleotide and the medicament is formulated for administration once every four weeks.

Embodiment 227. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 20 mg of the modified oligonucleotide and the medicament is formulated for administration once every eight weeks.

- 25 Embodiment 228. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 40 mg of the modified oligonucleotide and the medicament is formulated for administration once every eight weeks.

Embodiment 229. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 60 mg of the modified oligonucleotide and the medicament is formulated for administration once every eight weeks.

- 30 Embodiment 230. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 80 mg of the modified oligonucleotide and the medicament is formulated for administration once every eight weeks.

Embodiment 231. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 20 mg of the modified oligonucleotide and the medicament is formulated for administration once every twelve weeks.

Embodiment 232. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 40 mg of the modified oligonucleotide and the medicament is formulated for administration once every twelve weeks.

- 35 Embodiment 233. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 60 mg of the modified oligonucleotide and the medicament is formulated for administration once every twelve weeks.

Embodiment 234. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 80 mg of the modified oligonucleotide and the medicament is formulated for administration once every twelve weeks.

Embodiment 235. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 20 mg of the modified oligonucleotide and the medicament is formulated for administration once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

- 5 Embodiment 236. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 40 mg of the modified oligonucleotide and the medicament is formulated for administration once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

- 10 Embodiment 237. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 60 mg of the modified oligonucleotide and the medicament is formulated for administration once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

- 15 Embodiment 238. The use of any of embodiments 173-205, wherein the therapeutically effect amount is 80 mg of the modified oligonucleotide and the medicament is formulated for administration once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

Embodiment 239. The use of any of embodiments 173-227, wherein the medicament is formulated for intrathecal administration.

- 20 Embodiment 240. The use of any of embodiments 173-228, wherein the medicament is formulated for administration to a human subject less than 18 years of age, less than 15 years of age, less than 13 years of age, less than 10 years of age, less than 8 years of age, or less than 5 years of age.

Embodiment 241. The use of embodiment 240, wherein the human subject is from 2 years of age up to 5 years of age, from 4 years of age up to 17 years of age, or from 1 years of age up to 17 years of age.

- 25 Embodiment 242. The use of embodiment 240, wherein the human subject is 13 years of age or older, or 18 years of age or older.

Embodiment 243. The use of embodiment 240, wherein the human subject is from 18 years of age to 50 years of age.

Embodiment 244. The use of any of embodiments 1-146, wherein the human subject is 18 years of age or older.

Embodiment 245. The use of embodiment 240, wherein the human subject is 17 years of age or younger.

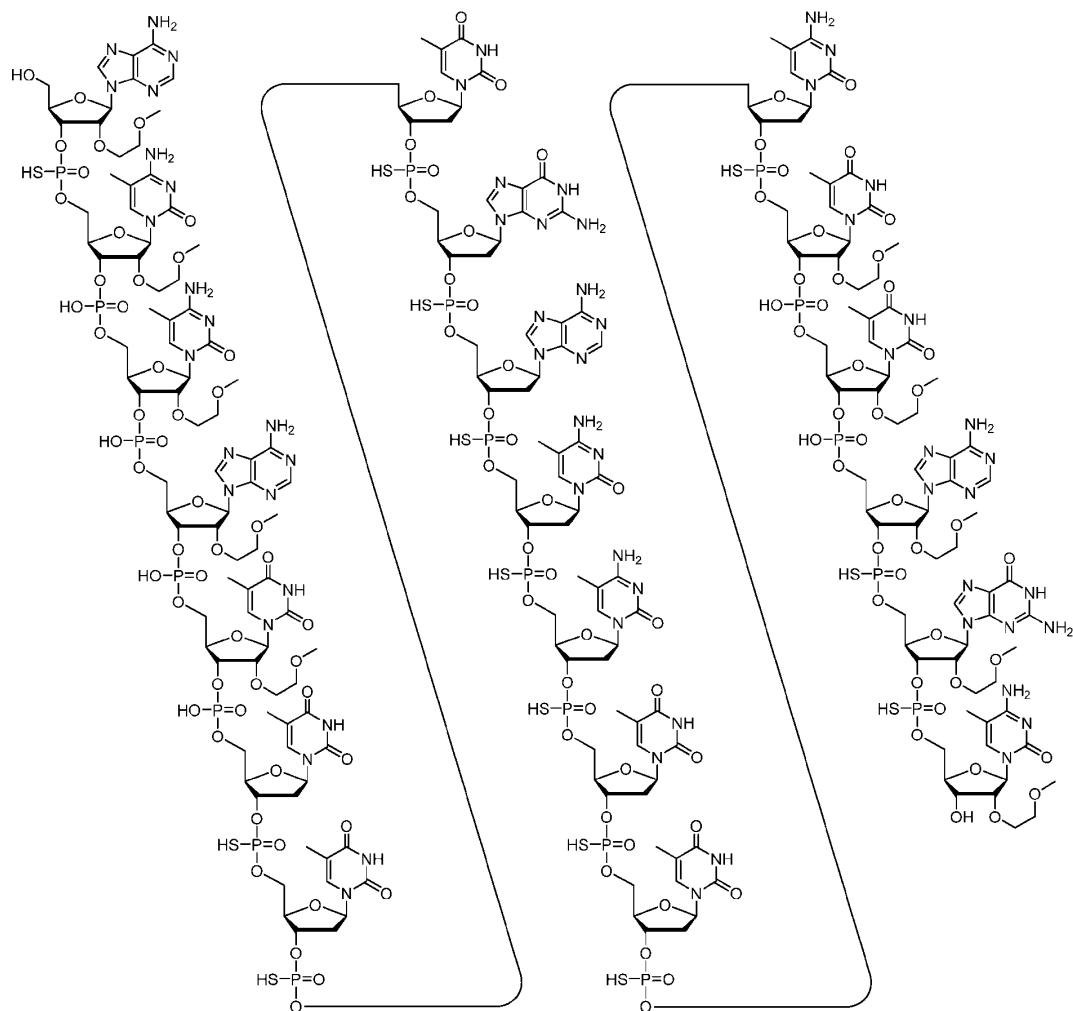
- 30 Embodiment 246. The use of any of embodiments 173-245, wherein the modified oligonucleotide is formulated as a pharmaceutical composition comprising a pharmaceutically acceptable diluent.

Embodiment 247. The use of embodiment 246, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF).

Embodiment 248. The use of embodiment 246, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS).

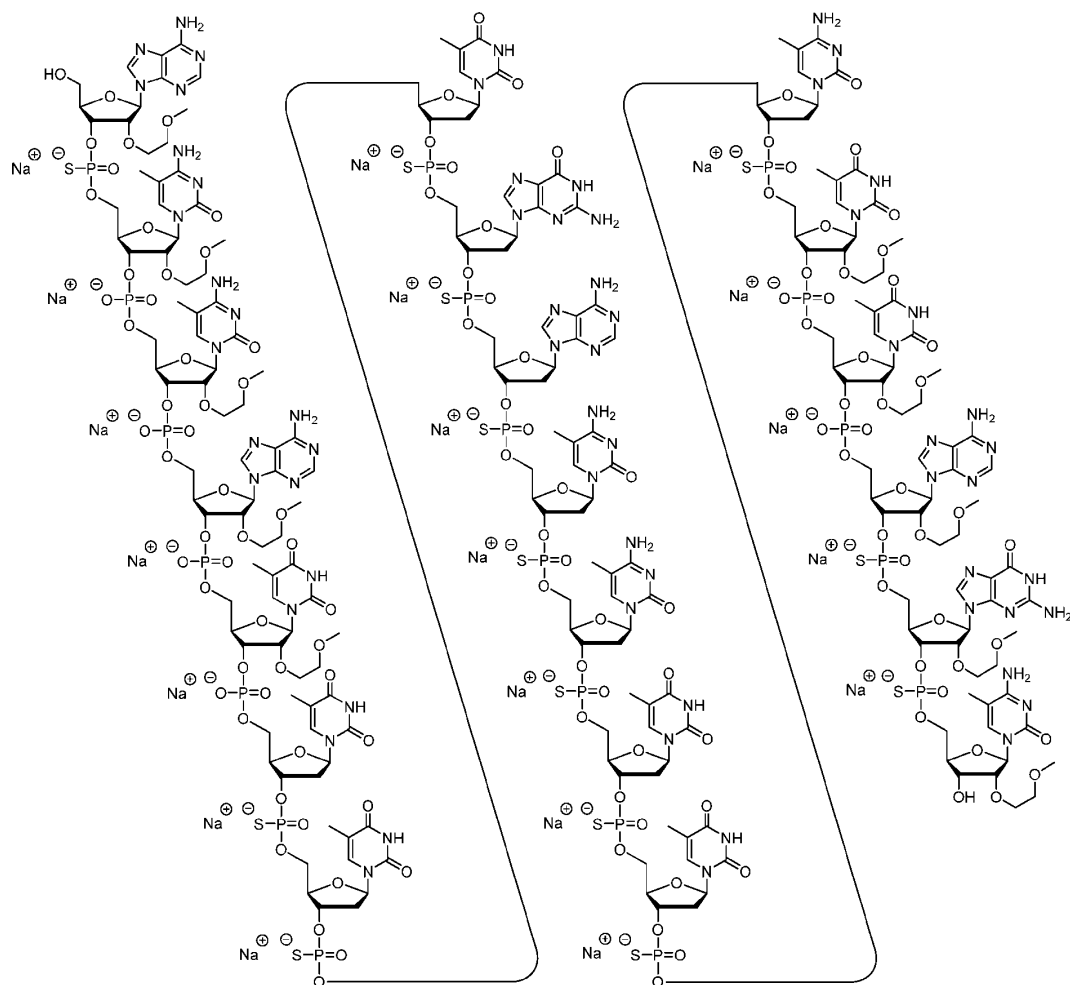
Embodiment 249. A method for treating Angelman syndrome comprising administering to a human having Angelman syndrome a therapeutically effective amount of a modified oligonucleotide, wherein the modified oligonucleotide is:

- a. a modified oligonucleotide according to the following chemical structure:



5 (SEQ ID NO: 5), or a pharmaceutically acceptable salt thereof;

b. a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 5), or

c. a modified oligonucleotide consisting of 19-20 linked nucleosides, wherein the modified oligonucleotide comprises at least 19 contiguous nucleosides of the following chemical notation (5' to 3'):

$A_{es}^mC_{eo}^mC_{eo}A_{eo}T_{ds}T_{ds}T_{ds}G_{ds}A_{cds}^mC_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ds}A_{es}G_{es}^mC_e$ (SEQ ID NO: 5), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribose sugar moiety,

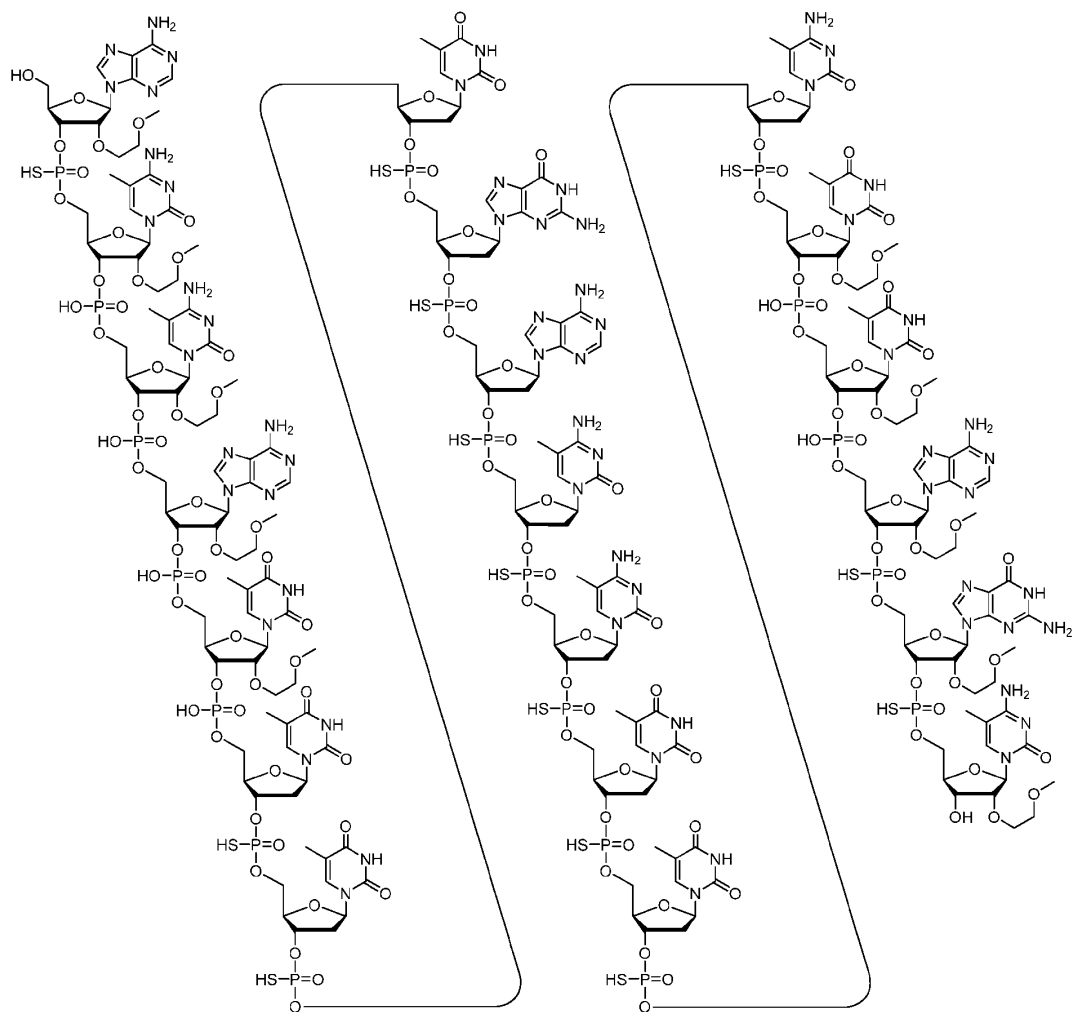
s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

wherein the therapeutically effective amount is 40 mg and the therapeutically effective amount is administered quarterly.

Embodiment 250. A method for treating Angelman syndrome comprising administering to a human having Angelman syndrome a therapeutically effective amount of a modified oligonucleotide, wherein the modified oligonucleotide is:

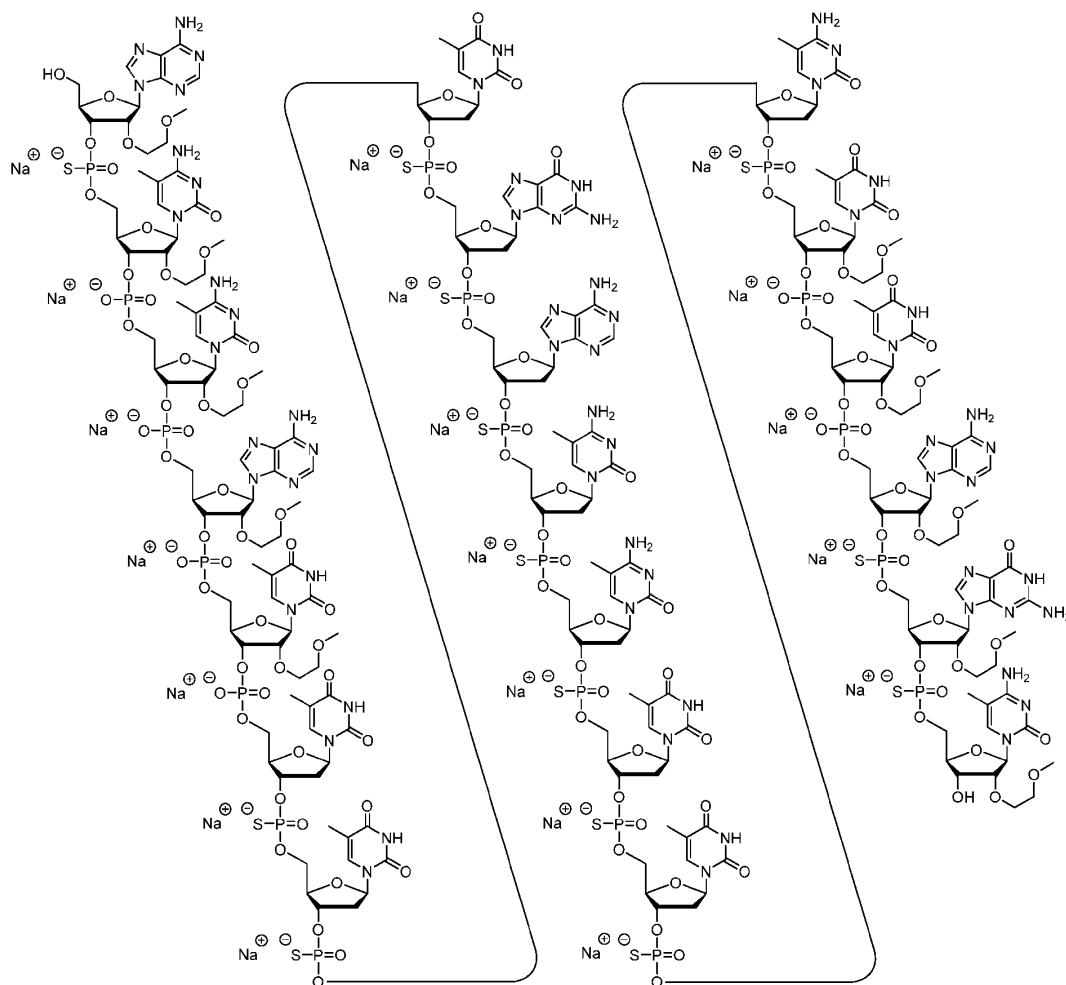
a) a modified oligonucleotide according to the following chemical structure:



5

(SEQ ID NO: 5), or a pharmaceutically acceptable salt thereof;

b) a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 5), or

c) a modified oligonucleotide consisting of 19-20 linked nucleosides, wherein the modified oligonucleotide comprises at least 19 contiguous nucleosides of the following chemical notation (5' to 3'):

$A_{es}^m C_{eo}^m C_{eo} A_{eo} T_{ds} T_{ds} T_{ds} G_{ds} A_{ds}^m C_{ds}^m C_{ds} T_{ds} T_{ds}^m C_{ds} T_{eo} T_{eo} A_{es} G_{es}^m C_e$ (SEQ ID NO: 5), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribose sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

wherein the therapeutically effective amount is 80 mg and the therapeutically effective amount is administered quarterly.

Embodiment 251. The method of embodiment 249 or 250, wherein at least one symptom or hallmark of Angelman syndrome is ameliorated.

Embodiment 252. The method of embodiment 251, wherein at least one symptom or hallmark is selected from
 5 developmental delays, ataxia, cognitive impairment, impairments in fine and/or gross motor skills, speech impairment, impairment in receptive communication and/or expressive communication, impairment in daily living skills, impaired socialization skills, sleep problems, seizures, and EEG abnormalities.

Embodiment 253. The method of embodiment 251, wherein the symptom or hallmark is developmental delays, ataxia, speech impairment, sleep problems, seizures, or EEG abnormalities.

10 Embodiment 254. The method of embodiment 251 wherein the at least one symptom or hallmark is cognitive impairment.

Embodiment 255. The method of embodiment 251 wherein the at least one symptom or hallmark is fine motor skills.

Embodiment 256. The method of embodiment 251 wherein the at least one symptom or hallmark is gross motor skills.

Embodiment 257. The method of embodiment 251 wherein the at least one symptom or hallmark is receptive
 15 communication.

Embodiment 258. The method of embodiment 251 wherein the at least one symptom or hallmark is expressive communication.

Embodiment 259. The method of embodiment 251 wherein the at least one symptom or hallmark is impairment in daily living skills.

20 Embodiment 260. The method of embodiment 251 wherein the at least one symptom or hallmark is impairment in socialization skills.

Embodiment 261. The method of embodiment 251 wherein the at least one symptom or hallmark is sleep problems.

UBE3A-ATS

25 In certain embodiments, oligomeric compounds comprise or consist of a modified oligonucleotide, such as ION582, that is complementary to a target nucleic acid, wherein the target nucleic acid is UBE3A-ATS. In certain embodiments, UBE3A-ATS nucleic acid has the sequence set forth in SEQ ID NO: 1 (GENBANK Accession No: NC_000015.10_TRUNC_24821647_25441028), SEQ ID NO: 2 (Ensemble Gene ID ENSG00000224078), or SEQ ID NO: 3 (the cDNA of Ensemble transcript ENST00000554726.2, Ensembl Release 110 (July 2023)).

30 In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2, or SEQ ID NO: 3 is capable of reducing UBE3A-ATS in a cell. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1 is capable of increasing UBE3A RNA or protein in a cell. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2, or SEQ ID NO: 3 is capable of increasing paternal UBE3A RNA or protein in a cell. In certain embodiments, the cell is in a subject. In certain embodiments, the oligomeric
 35 compound consists of a modified oligonucleotide. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2, or SEQ ID NO: 3 is capable of ameliorating one or more symptom or hallmark of a neurogenetic disorder when administered to a subject. In certain embodiments, the neurogenetic disorder is AS. In certain embodiments, the symptoms or hallmarks are selected from developmental delays, ataxia, cognitive impairment, impairments in fine and/or gross motor skills, speech impairment, impairment in receptive communication and/or

expressive communication, impairment in daily living skills, impaired socialization skills sleep problems, seizures, and EEG abnormalities. In certain embodiments, the symptoms or hallmarks are selected from developmental delays, ataxia, speech impairment, sleep problems, seizures, and EEG abnormalities.

5 **Certain Target Nucleic Acids in Certain Tissues**

In certain embodiments, oligomeric compounds comprise or consist of a modified oligonucleotide, such as ION582 that is complementary to a target nucleic acid, wherein the target nucleic acid is expressed in a pharmacologically relevant tissue. In certain embodiments, the pharmacologically relevant tissues are the cells and tissues that comprise the central nervous system. Such tissues include the cortex, hippocampus, and spinal cord.

10 **Compound No. 1273062/ION582**

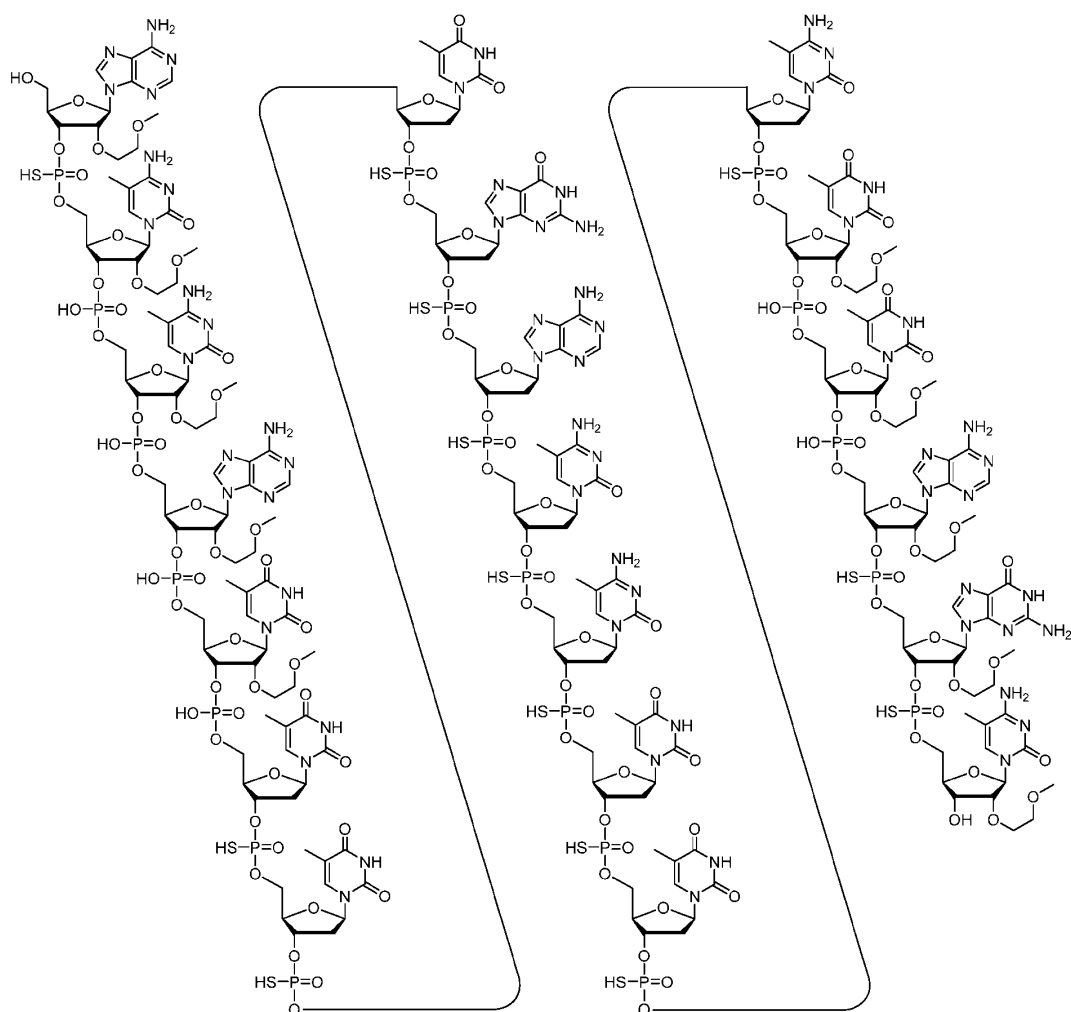
In certain embodiments, Compound No. 1273062 is characterized as a 5-10-5 MOE gapmer of linked nucleosides having a nucleobase sequence (from 5' to 3') of ACCATTTTGACCTTCTTAGC (SEQ ID NO: 4), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1273062 is represented by the following chemical notation:

$A_{es}^m C_{eo}^m C_{eo} A_{eo} T_{ds} T_{ds} T_{ds} G_{ds} A_{ds}^m C_{ds}^m C_{ds}^m T_{ds} T_{ds}^m C_{ds} T_{eo} T_{eo} A_{es} G_{es}^m C_e$ (SEQ ID NO: 5), wherein:

- 20 A = an adenine nucleobase,
 $^m C$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 25 d = a 2'-β-D-deoxyribose sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

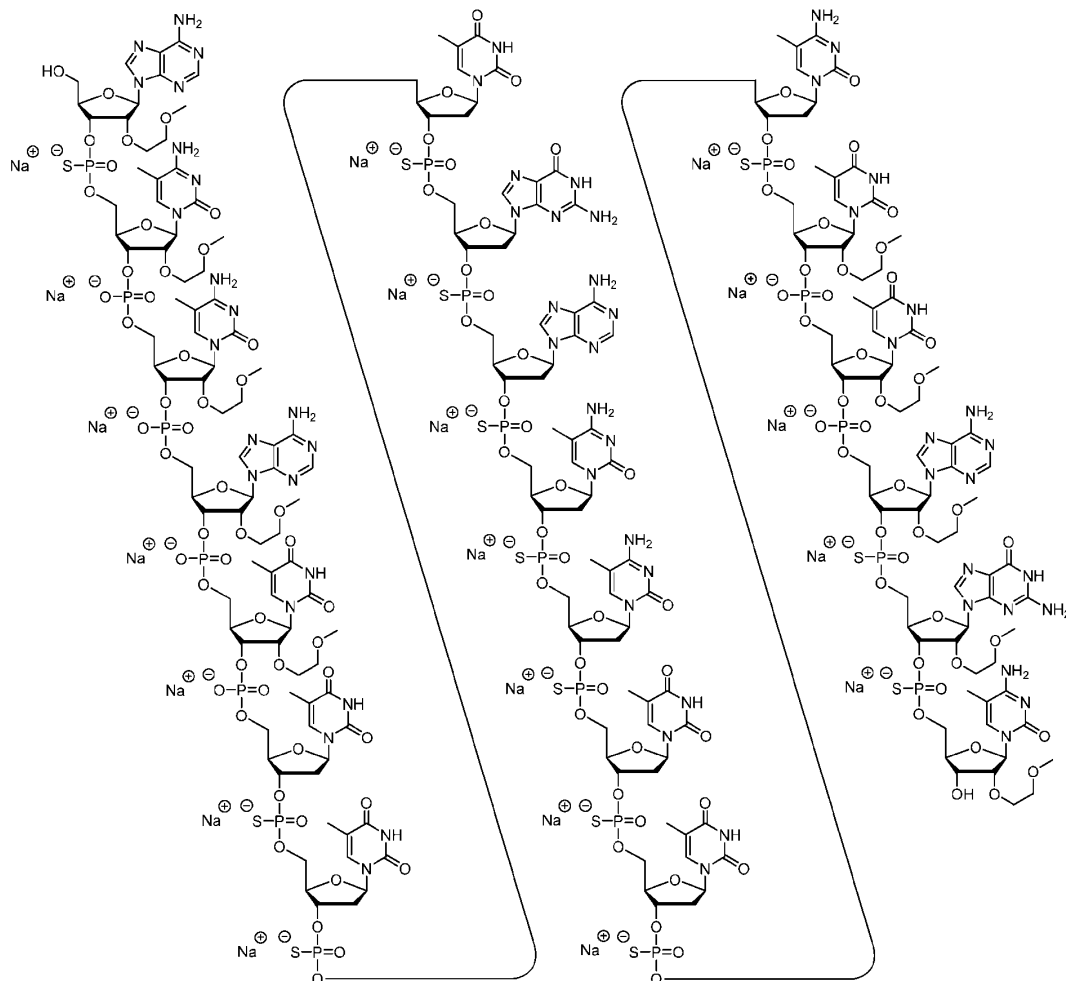
In certain embodiments, Compound No. 1273062 is represented by the following chemical structure:



(SEQ ID NO: 5).

Structure 11. Compound No. 1273062

In certain embodiments, the sodium salt of Compound No. 1273062 is represented by the following chemical structure:



(SEQ ID NO: 5).

5 **Structure 12. The sodium salt of Compound No. 1273062**

Compound 1273062 is described in WO 2020/205463, the entire content of which is hereby incorporated by reference.

I. Certain Pharmaceutical Compositions

In certain embodiments, described herein are methods of administering to a subject a pharmaceutical composition comprising the modified oligonucleotide 1273062. In certain embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable diluent. In certain embodiments, the pharmaceutical composition comprises or consists essentially of a sterile saline solution and the modified oligonucleotide 1273062. In certain
 10 embodiments, the sterile saline is pharmaceutical grade saline. In certain embodiments, the pharmaceutical composition comprises or consists essentially of sterile water and the modified oligonucleotide 1273062. In certain embodiments, the sterile water is pharmaceutical grade water. In certain embodiments, the pharmaceutical composition comprises or
 15 consists essentially of artificial cerebrospinal fluid (aCSF) and the modified oligonucleotide 1273062. In certain

embodiments, the artificial cerebrospinal fluid is pharmaceutical grade. In certain embodiments, the pharmaceutical composition comprises a certain concentration of modified oligonucleotide 1273062 in aCSF, and is diluted in aCSF diluent to achieve the intended clinical dose. In certain embodiments, 1273062 is formulated in aCSF at 30 mg/mL and is diluted in aCSF diluent to achieve the intended clinical dose. In certain embodiments, 1273062 is formulated in aCSF at 20 mg/mL and is diluted in aCSF diluent to achieve the intended clinical dose.

In certain embodiments, pharmaceutical compositions comprise one or more excipients and the modified oligonucleotide 1273062. In certain embodiments, excipients are selected from water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, and polyvinylpyrrolidone.

In certain embodiments, pharmaceutical compositions comprising the modified oligonucleotide 1273062 encompass any pharmaceutically acceptable salt of the modified oligonucleotide 1273062, esters of the modified oligonucleotide 1273062, or salts of such esters. In certain embodiments, pharmaceutical compositions comprising the modified oligonucleotide 1273062 are capable of providing (directly or indirectly) the biologically active metabolite or residue thereof upon administration to a human subject. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of the modified oligonucleotide 1273062, prodrugs of the modified oligonucleotide 1273062, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts.

In certain embodiments, pharmaceutical compositions comprise one or more lipid moieties and the modified oligonucleotide 1273062. In certain embodiments, lipid moieties are used to increase distribution of 1273062 to a particular cell or tissue. In certain such methods, the modified oligonucleotide 1273062 is introduced into preformed liposomes or lipoplexes made of mixtures of cationic lipids and neutral lipids. In certain methods, DNA complexes with mono- or poly-cationic lipids are formed without the presence of a neutral lipid.

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

In certain embodiments, pharmaceutical compositions comprise one or more tissue-specific delivery molecules designed to deliver modified oligonucleotides described herein to specific tissues or cell types. For example, in certain embodiments, pharmaceutical compositions include liposomes coated with a tissue-specific antibody.

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

In certain embodiments, a pharmaceutical composition is prepared for administration by injection (*e.g.*, intravenous, subcutaneous, intramuscular, intrathecal (IT), intracerebroventricular (ICV)). In certain embodiments the administration by injection is intrathecal. In certain of such embodiments, a pharmaceutical composition comprises a carrier and is formulated in aqueous solution, such as aCSF, water, or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (*e.g.*, ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid carriers, suspending agents and the like. Certain pharmaceutical compositions for injection are presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers. Certain pharmaceutical compositions for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in pharmaceutical compositions for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes.

Under certain conditions, the modified oligonucleotide 1273062 acts as an acid. Although 1273062 may be drawn or described in protonated (free acid) form, or ionized and in association with a cation (salt) form, aqueous solutions of 1273062 exist in equilibrium among such forms. For example, a phosphate linkage of 1273062 in aqueous solution exists in equilibrium among free acid, anion, and salt forms. Unless otherwise indicated, the term, "1273062," is intended to include all such forms. Moreover, 1273062 has several such linkages, each of which is in equilibrium. Thus, 1273062 exists in solution in an ensemble of forms at multiple positions all at equilibrium. The term "1273062" is intended to include all such forms. Drawn structures necessarily depict a single form. Nevertheless, unless otherwise indicated, such drawings are likewise intended to include corresponding forms. Herein, a structure depicting the free acid of 1273062 followed by the term "or a salt thereof" expressly includes all such forms that may be fully or partially protonated/de-protonated/in association with a cation. In certain instances, one or more specific cation is identified.

In certain embodiments, 1273062 is in aqueous solution with sodium. In certain embodiments, 1273062 is in aqueous solution with potassium. In certain embodiments, 1273062 is in PBS. In certain embodiments, 1273062 is in water. In certain such embodiments, the pH of the solution is adjusted with NaOH and/or HCl to achieve a desired pH.

Herein, certain specific doses are described. For clarity, a dose of 1273062 in milligrams indicates the mass of the free acid form of 1273062. As described above, in aqueous solution, the free acid is in equilibrium with anionic and salt forms. However, for the purpose of calculating dose, it is assumed that 1273062 exists as a solvent-free, sodium-acetate free, anhydrous, free acid. For example, where 1273062 is in solution comprising sodium (*e.g.*, saline), 1273062 may be partially or fully de-protonated and in association with Na⁺ ions. However, the mass of the protons is nevertheless counted toward the weight of the dose, and the mass of the Na⁺ ions are not counted toward the weight of the dose. Thus, for example, a dose of 10 mg of 1273062 equals the number of fully protonated molecules that weighs 10 mg. This would be equivalent to 10.59 mg of solvent-free, sodium-acetate free, anhydrous sodiated 1273062.

Certain Dosage Amounts

In certain embodiments, described herein are methods of administering to a subject a therapeutically effective amount of the modified oligonucleotide 1273062. In certain embodiments, the therapeutically effective amount is 20 mg. In certain embodiments, the therapeutically effective amount is 40 mg. In certain embodiments, the therapeutically effective amount is 60 mg. In certain embodiments, the therapeutically effective amount is 80 mg.

In certain embodiments, described herein are methods of administering to a subject aged 2-5 years a therapeutically effective amount of the modified oligonucleotide 1273062. In certain embodiments, the therapeutically effective amount is 20 mg. In certain embodiments, the therapeutically effective amount is 40 mg. In certain embodiments, the therapeutically effective amount is 60 mg. In certain embodiments, the therapeutically effective amount is 80 mg.

In certain embodiments, described herein are methods of administering to a subject aged 4-17 years a therapeutically effective amount of the modified oligonucleotide 1273062. In certain embodiments, the therapeutically effective amount is 20 mg. In certain embodiments, the therapeutically effective amount is 40 mg. In certain embodiments, the therapeutically effective amount is 60 mg. In certain embodiments, the therapeutically effective amount is 80 mg.

In certain embodiments, described herein are methods of administering to a subject aged 18-50 years a therapeutically effective amount of the modified oligonucleotide 1273062. In certain embodiments, the therapeutically effective amount is 20 mg. In certain embodiments, the therapeutically effective amount is 40 mg. In certain embodiments, the therapeutically effective amount is 60 mg. In certain embodiments, the therapeutically effective amount is 80 mg.

In certain embodiments, described herein are methods of administering to a subject a therapeutically effective amount of the modified oligonucleotide 1273062. In certain embodiments, the therapeutically effective amount is 20 mg. In certain embodiments, the therapeutically effective amount is 40 mg. In certain embodiments, the therapeutically effective amount is 60 mg. In certain embodiments, the therapeutically effective amount is 80 mg.

In certain embodiments, described herein are methods of administering to a subject aged over 18 years a therapeutically effective amount of the modified oligonucleotide 1273062. In certain embodiments, the therapeutically effective amount is 20 mg. In certain embodiments, the therapeutically effective amount is 40 mg. In certain embodiments, the therapeutically effective amount is 60 mg. In certain embodiments, the therapeutically effective amount is 80 mg.

In certain embodiments, the therapeutically effective amount is any of 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, or 150 mg.

In certain embodiments, the therapeutically effective amount is any of about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, or about 150 mg.

In certain embodiments, the therapeutically effective amount is any of 10 mg to 200 mg, 10 mg to 100 mg, 20 mg to 80 mg, 40 mg to 200 mg, 40 mg to 190 mg, 40 mg to 180 mg, 40 mg to 170 mg, from 40 mg to 160 mg, 40 mg to 150 mg, 40 mg to 140 mg, 40 mg to 120 mg, 40 mg to 110 mg, 40 mg to 100 mg, 40 mg to 80 mg, 40 mg to 70 mg, 40 mg to 60 mg, 40 mg to 50 mg, 50 mg to 200 mg, 50 mg to 190 mg, 50 mg to 180 mg, 50 mg to 170 mg, 50 mg to 160 mg, 50 mg to 150 mg, 50 mg to 140 mg, 50 mg to 120 mg, 50 mg to 110 mg, 50 mg to 100 mg, 50 mg to 80 mg, 50 mg to 70 mg, 50 mg to 60 mg, 60 mg to 200 mg, 60 mg to 190 mg, 60 mg to 180 mg, 60 mg to 170 mg, 60 mg to 160 mg, 60 mg to 150 mg, 60 mg to 140 mg, 60 mg to 120 mg, 60 mg to 115 mg, 60 mg to 110 mg, 60 mg to 100 mg, 60 mg to

80 mg, 60 mg to 70 mg, 70 mg to 200 mg, 70 mg to 190 mg, 70 mg to 180 mg, 70 mg to 170 mg, 70 mg to 160 mg, 70 mg to 150 mg, 70 mg to 140 mg, 70 mg to 120 mg, 70 mg to 110 mg, 70 mg to 100 mg, 70 mg to 80 mg, 80 mg to 200 mg, 80 mg to 190 mg, 80 mg to 180 mg, 80 mg to 170 mg, 80 mg to 160 mg, 80 mg to 150 mg, 80 mg to 140 mg, 80 mg to 120 mg, 80 mg to 110 mg, 80 mg to 100 mg, 80 mg to 90 mg, 90 mg to 200 mg, 90 mg to 190 mg, 90 mg to 180 mg, 90 mg to 170 mg, 90 mg to 160 mg, 90 mg to 150 mg, 90 mg to 140 mg, 90 mg to 120 mg, 90 mg to 110 mg, 90 mg to 100 mg, 100 mg to 200 mg, 100 mg to 190 mg, 100 mg to 180 mg, 100 mg to 170 mg, 100 mg to 160 mg, 100 mg to 150 mg, 100 mg to 140 mg, 100 mg to 120 mg, 100 mg to 110 mg, 110 mg to 200 mg, 110 mg to 190 mg, 110 mg to 180 mg, 110 mg to 170 mg, 110 mg to 160 mg, 110 mg to 150 mg, 110 mg to 140 mg, 110 mg to 130 mg, 110 mg to 120 mg, 120 mg to 200 mg, 120 mg to 190 mg, 120 mg to 180 mg, 120 mg to 170 mg, 120 mg to 160 mg, 120 mg to 150 mg, 120 mg to 140 mg, 120 mg to 130 mg, 130 mg to 200 mg, 130 mg to 190 mg, 130 mg to 180 mg, 130 mg to 170 mg, 130 mg to 160 mg, 130 mg to 150 mg, 130 mg to 140 mg, 140 mg to 200 mg, 140 mg to 190 mg, 140 mg to 180 mg, 140 mg to 170 mg, 140 mg to 160 mg, 140 mg to 150 mg, 150 mg to 200 mg, 150 mg to 190 mg, 150 mg to 180 mg, 150 mg to 170 mg, 150 mg to 160 mg, 160 mg to 200 mg, 160 mg to 190 mg, 160 mg to 180 mg, 160 mg to 170 mg, 180 mg to 200 mg, 180 mg to 190 mg, 190 mg to 200 mg, 105 mg to 135 mg, 105 mg to 130 mg, 105 mg to 125 mg, 105 mg to 120 mg, 110 mg to 135 mg, 110 mg to 130 mg, 110 mg to 125 mg, 110 mg to 120 mg, 115 mg to 135 mg, 115 mg to 130 mg, 115 mg to 125 mg, 115 mg to 120 mg, 115 mg to 125 mg, 115 mg to 120 mg, 120 mg to 135 mg, 120 mg to 125 mg, 125 mg to 140 mg, 125 mg to 130 mg, 130 mg to 135 mg, 135 mg to 140 mg, 120 mg to 129 mg, 120 mg to 128 mg, 120 mg to 127 mg, 120 mg to 86 mg, 120 mg to 124 mg, 120 mg to 123 mg, 120 mg to 122 mg, 120 mg to 121 mg, 121 mg to 130 mg, 122 mg to 129 mg, 122 mg to 128 mg, 122 mg to 127 mg, 122 mg to 126 mg, 122 mg to 125 mg, 122 mg to 124 mg, 122 mg to 123 mg, 123 mg to 130 mg, 123 mg to 129 mg, 123 mg to 128 mg, 123 mg to 127 mg, 123 mg to 126 mg, 123 mg to 125 mg, 123 mg to 124 mg, 124 mg to 130 mg, 124 mg to 129 mg, 124 mg to 128 mg, 124 mg to 127 mg, 124 mg to 126 mg, 124 mg to 125 mg, 125 mg to 129 mg, 125 mg to 128 mg, 125 mg to 127 mg, 125 mg to 126 mg, 126 mg to 130 mg, 126 mg to 129 mg, 126 mg to 128 mg, 126 mg to 127 mg, 127 mg to 130 mg, 127 mg to 129 mg, 127 mg to 128 mg, 128 mg to 130 mg, 128 mg to 129 mg, and 129 mg to 130 mg.

In certain embodiments, the therapeutically effective amount is any of less than 150 mg, less than 145 mg, less than 140 mg, less than 135 mg, less than 130 mg, less than 125 mg, less than 120 mg, less than 115 mg, less than 110 mg, less than 105 mg, less than 100 mg, less than 95 mg, less than 90 mg, less than 85 mg, less than 80 mg, less than 75 mg, less than 70 mg, less than 65 mg, less than 60 mg, less than 55 mg, less than 50 mg, less than 45 mg, less than 40 mg, less than 35 mg, less than 30 mg, less than 25 mg, less than 20 mg, less than 15 mg, less than 10 mg, and less than 5 mg.

In certain embodiments, the therapeutically effective amount is any of less than about 150 mg, less than about 145 mg, less than about 140 mg, less than about 135 mg, less than about 130 mg, less than about 125 mg, less than about 120 mg, less than about 115 mg, less than about 110 mg, less than about 105 mg, less than about 100 mg, less than about 95 mg, less than about 90 mg, less than about 85 mg, less than about 80 mg, less than about 75 mg, less than about 70 mg, less than about 65 mg, less than about 60 mg, less than about 55 mg, less than about 50 mg, less than about 45 mg, less than about 40 mg, less than about 35 mg, less than about 30 mg, less than about 25 mg, less than about 20 mg, less than about 15 mg, less than about 10 mg, and less than about 5 mg.

In certain embodiments, the therapeutically effective amount is any of at least 5 mg, at least 10 mg, at least 15 mg, at least 20 mg, at least 25 mg, at least 30 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 55 mg, at least 60 mg, at least 65 mg, at least 70 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, at least 100 mg, at least 105 mg, at least 115 mg, at least 120 mg, at least 125 mg, at least 130 mg, at least 135 mg, at least 140 mg, at least 145 mg, at least 150 mg.

In certain embodiments, the therapeutically effective amount is any of at least about 5 mg, at least about 10 mg, at least about 15 mg, at least about 20 mg, at least about 25 mg, at least about 30 mg, at least about 35 mg, at least about 40 mg, at least about 45 mg, at least about 50 mg, at least about 55 mg, at least about 60 mg, at least about 65 mg, at least about 70 mg, at least about 75 mg, at least about 80 mg, at least about 85 mg, at least about 90 mg, at least about 95 mg, at least about 100 mg, at least about 105 mg, at least about 115 mg, at least about 120 mg, at least about 125 mg, at least about 130 mg, at least about 135 mg, at least about 140 mg, at least about 145 mg, or at least about 150 mg, at least about 155 mg, at least about 160 mg, at least about 165 mg, at least about 170 mg, at least about 175 mg, at least about 180 mg, at least about 185, at least about 190 mg, at least about 195 mg, and at least about 200 mg.

In certain embodiments, the therapeutically effective amount is 4-6 mg. In certain embodiments, the therapeutically effective amount is 9-11 mg. In certain embodiments, the therapeutically effective amount is 19-21 mg. In certain embodiments, the therapeutically effective amount is 29-31 mg. In certain embodiments, the therapeutically effective amount is 39-41 mg. In certain embodiments, the therapeutically effective amount is 48-52 mg. In certain embodiments, the therapeutically effective amount is 58-62 mg. In certain embodiments, the therapeutically effective amount is 68-72 mg. In certain embodiments, the therapeutically effective amount is 78-82 mg. In certain embodiments, the therapeutically effective amount is 88-92 mg. In certain embodiments, the therapeutically effective amount is 98-102 mg. In certain embodiments, the therapeutically effective amount is 108-112 mg. In certain embodiments, the therapeutically effective amount is 118-122 mg.

Certain Dosing Intervals

In certain embodiments, described herein are methods of administering to a subject a therapeutically effective amount of the modified oligonucleotide 1273062 one or more times. The skilled artisan will recognize that the intervals may vary by a few days or weeks, that is, a monthly interval may include administrations that are not exactly at one month but may vary by a few days with each administration. Similarly, a quarterly dosing interval indicates dosing 4 times per year and includes dosing schedules that are not exactly at 3 months but may vary by a few days or a week.

In certain embodiments, methods comprise administering the therapeutically effective amount at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 times. In certain embodiments, methods comprise administering the therapeutically effective amount once every 4 weeks. In certain embodiments, methods comprise administering the therapeutically effective amount once every 6 weeks. In certain embodiments, methods comprise administering the therapeutically effective amount once every 8 weeks. In certain embodiments, methods comprise administering the therapeutically effective amount once every 12 weeks. In certain embodiments, methods comprise administering the therapeutically effective amount once every 16 weeks. In certain embodiments, methods comprise administering the therapeutically effective amount once every 20 weeks. In certain embodiments, methods comprise administering the therapeutically effective amount once every 24 weeks. In certain embodiments, methods comprise administering the

therapeutically effective amount once every 6 months. In certain embodiments, methods comprise administering the therapeutically effective amount monthly. In certain embodiments, methods comprise administering the therapeutically effective amount once every two months. In certain embodiments, methods comprise administering the therapeutically effective amount once every three months. In certain embodiments, methods comprise administering the therapeutically effective amount quarterly. In certain embodiments, methods comprise administering the therapeutically effective amount semiannually. In certain embodiments, methods comprise administering the therapeutically effective amount annually. In certain embodiments, methods comprise administering the therapeutically effective amount once every two years.

In certain embodiments, methods comprise administering the therapeutically effective amount about every 1 week, about every 2 weeks, about every 3 weeks, about every 4 weeks, about every 5 weeks, about every 6 weeks, about every 7 weeks, about every 8 weeks, about every 9 weeks, about every 10 weeks, about every 11 weeks, about every 12 weeks, about every 13 weeks, about every 14 weeks, about every 15 weeks, about every 16 weeks, about every 17 weeks, about every 18 weeks, about every 19 weeks, about every 20 weeks, about every 21 weeks, about every 22 weeks, about every 23 weeks, about every 24 weeks, or about every 6 months. In certain embodiments, methods comprise administering the therapeutically effective amount about monthly. In certain embodiments, methods comprise administering the therapeutically effective amount once about every two months. In certain embodiments, methods comprise administering the therapeutically effective amount once about every three months. In certain embodiments, methods comprise administering the therapeutically effective amount about quarterly. In certain embodiments, methods comprise administering the therapeutically effective amount about semiannually. In certain embodiments, methods comprise administering the therapeutically effective amount about annually. In certain embodiments, methods comprise administering the therapeutically effective amount once about every two years.

In certain embodiments, methods comprise administering the therapeutically effective amount for at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, or at least about 12 months.

Loading and Maintenance Doses

In certain embodiment, the therapeutically effective amount is administered as a loading dose and/or a maintenance dose. In certain embodiments, methods comprise administering a loading dose or doses and subsequently administering a maintenance dose or doses. In certain embodiments, methods comprise administering a loading dose once about every 4 weeks, and subsequently administering a maintenance dose once about every 4 weeks, about every 8 weeks, about every 12 weeks, about every 16 weeks, about 20 weeks, about 24 weeks, or about 6 months. In certain embodiments, methods comprise administering a loading dose once about every 4 weeks, and subsequently administering a maintenance dose once about every 6 months. In certain embodiments, methods comprise administering a loading dose once about every 12 weeks, and subsequently administering a maintenance dose once about every 6 months.

In certain embodiments, methods comprise administering at least 2 loading doses, at least 3 loading doses, at least 4 loading doses, at least 5 loading doses, or at least 6 loading doses. In certain embodiments, methods comprise administering 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 loading doses. In certain embodiments, methods comprise administering a loading dose or doses about every 1 week, about every 2 weeks, about every 3 weeks, about every 4

weeks, about every 5 weeks, about every 6 weeks, about every 7 weeks, about every 8 weeks, about every 9 weeks, about every 10 weeks, about every 11 weeks, or about every 12 weeks. In certain embodiments, methods comprise administering an initial loading dose and administering a second loading dose about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, or about 12 weeks after administering the initial loading dose.

In certain embodiments, methods comprise administering at least 2 maintenance doses, at least 3 maintenance doses, at least 4 maintenance doses, at least 5 maintenance doses, or at least 6 maintenance doses. In certain embodiments, methods comprise administering 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 maintenance doses. In some instances, methods comprise administering a maintenance dose or doses about every 4 weeks, about every 5 weeks, about every 6 weeks, about every 7 weeks, about every 8 weeks, about every 9 weeks, about every 10 weeks, about every 11 weeks, about every 12 weeks, about every 13 weeks, about every 14 weeks, about every 15 weeks, about every 16 weeks, about every 17 weeks, about every 18 weeks, about every 19 weeks, about every 20 weeks, about every 21 weeks, about every 22 weeks, about every 23 weeks, about every 24 weeks, or about every 6 months. In certain embodiments, methods comprise administering a first maintenance dose and administering a second maintenance dose about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, about 21 weeks, about 22 weeks, about 23 weeks, about 24 weeks, or about 6 months after administering the first maintenance dose.

In certain embodiments, methods comprise administering a first maintenance dose or doses about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, about 21 weeks, about 22 weeks, about 23 weeks, or about 24 weeks after administering the last loading dose.

Certain Total Doses Amounts

In certain embodiments, described herein are methods of administering to a subject a total dose of the modified oligonucleotide 1273062. As used herein, “total dose” refers to the calculated total amount of a modified oligonucleotide per a unit of time. For example, a total dose of 100 mg per month, includes methods where 100 mg is administered over the course of one month in individual doses less than 100 mg (e.g., 25 mg every week or 50 mg every 2 weeks), or methods where a single dose of 100 mg is administered each month, or methods where a dose of more than 100 mg is administered less frequently than once per month (e.g., a single dose of 200 mg every 2 months, or 300 mg every 3 months, and so on).

In some embodiments, the modified oligonucleotide is administered to the human subject at a total dose per month of from 5 mg to 100 mg, from 5 mg to 80 mg, from 5 mg to 60 mg, from 5 mg to 40 mg, from 5 mg to 20 mg, from 10 mg to 100 mg, from 10 mg to 80 mg, from 10 mg to 60 mg, from 10 mg to 40 mg, from 10 mg to 20 mg, from 20 mg to 100 mg, from 20 mg to 80 mg, from 20 mg to 60 mg, from 20 mg to 40 mg, from 40 mg to 100 mg, from 40 mg to 80 mg, from 40 mg to 60 mg, or from 80 mg to 100 mg. In certain such embodiments, doses are administered once per month, once per quarter, every 6 months, or once per year.

In some embodiments, the modified oligonucleotide is administered to the human subject at a total dose per 3 months of from 15 mg to 300 mg, from 15 mg to 180 mg, from 15 mg to 150 mg, from 15 mg to 100 mg, from 15 mg to 80 mg, from 15 mg to 50 mg, from 40 mg to 300 mg, from 40 mg to 180 mg, from 40 mg to 150 mg, from 40 mg to 100 mg, from 40 mg to 80 mg, from 80 mg to 300 mg, from 80 mg to 180 mg, from 80 mg to 150 mg, from 80 mg to 100 mg, from 100 mg to 300 mg, from 100 mg to 180 mg, from 100 mg to 150 mg, or from 150 to 300 mg. In certain such
5 embodiments, doses are administered once per month, once per quarter, every 6 months, or once per year.

In some embodiments, the modified oligonucleotide is administered to the human subject at a total dose per 4 months of from 20 mg to 400 mg, from 20 mg to 350 mg, from 20 mg to 300 mg, from 20 mg to 250 mg, from 20 mg to 200 mg, from 20 mg to 150 mg, from 20 mg to 100 mg, from 50 mg to 400 mg, from 50 mg to 350 mg, from 50 mg to 300 mg, from 50 mg to 250 mg, from 50 mg to 200 mg, from 50 mg to 150 mg, from 50 mg to 100 mg, from 100 mg to 400 mg, from 100 mg to 350 mg, from 100 mg to 300 mg, from 100 mg to 250 mg, from 100 mg to 200 mg, from 100 mg to 150 mg, from 200 mg to 400 mg, from 200 mg to 350 mg, from 200 mg to 300 mg, from 200 mg to 250 mg, from 300 mg to 400 mg, or from 300 mg to 350 mg. In certain such embodiments, doses are administered once per month, once per quarter, every 6 months, or once per year.

15 In some embodiments, the modified oligonucleotide is administered to the human subject at a total dose per 6 month of from 30 mg to 600 mg, from 30 mg to 500 mg, from 30 mg to 400 mg, from 30 mg to 300 mg, from 30 mg to 200 mg, from 30 mg to 100 mg, from 50 mg to 600 mg, from 50 mg to 500 mg, from 50 mg to 400 mg, from 50 mg to 300 mg, from 50 mg to 200 mg, from 50 mg to 100 mg, from 100 mg to 600 mg, from 100 mg to 500 mg, from 100 mg to 400 mg, from 100 mg to 300 mg, from 100 mg to 200 mg, from 200 mg to 600 mg, from 200 mg to 500 mg, from 200 mg to 400 mg, from 200 mg to 300 mg, from 300 mg to 600 mg, from 300 mg to 500 mg, from 300 mg to 400 mg, from 400 mg to 600 mg, from 400 mg to 500 mg, or from 500 mg to 600 mg. In certain such embodiments, doses are
20 administered once per month, once per quarter, every 6 months, or once per year.

In some embodiments, the modified oligonucleotide is administered to the human subject at a total dose per year of from 60 mg to 1200 mg, from 60 mg to 1100 mg, from 60 mg to 1000 mg, from 60 mg to 900 mg, from 60 mg to 800 mg, from 60 mg to 700 mg, from 60 mg to 600 mg, from 60 mg to 500 mg, from 60 mg to 400 mg, from 60 mg to 300 mg, from 60 mg to 200 mg, from 60 mg to 100 mg, from 100 mg to 1200 mg, from 100 mg to 1100 mg, from 100 mg to 1000 mg, from 100 mg to 900 mg, from 100 mg to 800 mg, from 100 mg to 700 mg, from 100 mg to 600 mg, from 100 mg to 500 mg, from 100 mg to 400 mg, from 100 mg to 300 mg, from 100 mg to 200 mg, from 200 mg to 1200 mg, from 200 mg to 1100 mg, from 200 mg to 1000 mg, from 200 mg to 900 mg, from 200 mg to 800 mg, from 200 mg to 700 mg, from 200 mg to 600 mg, from 200 mg to 500 mg, from 200 mg to 400 mg, from 200 mg to 300 mg, from 300 mg to 1200 mg, from 300 mg to 1100 mg, from 300 mg to 1000 mg, from 300 mg to 900 mg, from 300 mg to 800 mg, from 300 mg to 700 mg, from 300 mg to 600 mg, from 300 mg to 500 mg, from 300 mg to 400 mg, from 400 mg to 1200 mg, from 400 mg to 1100 mg, from 400 mg to 1000 mg, from 400 mg to 900 mg, from 400 mg to 800 mg, from 400 mg to 700 mg, from 400 mg to 600 mg, from 400 mg to 500 mg, from 500 mg to 1200 mg, from 500 mg to 1100 mg, from 500 mg to 1000 mg, from 500 mg to 900 mg, from 500 mg to 800 mg, from 500 mg to 700 mg, from 500 mg to 600 mg, from 600 mg to 1200 mg, from 600 mg to 1100 mg, from 600 mg to 1000 mg, from 600 mg to 900 mg, from 600 mg to 800 mg, from 600 mg to 700 mg, from 700 mg to 1200 mg, from 700 mg to 1100 mg, from 700 mg to
25 30 35

1000 mg, from 700 mg to 900 mg, from 700 mg to 800 mg, from 800 mg to 1200 mg, from 800 mg to 1100 mg, from 800 mg to 1000 mg, from 800 mg to 900 mg, from 900 mg to 1200 mg, from 900 mg to 1100 mg, from 900 mg to 1000 mg, from 1000 mg to 1200 mg, from 1000 mg to 1100mg, or from 1100 mg to 1200 mg. In certain such embodiments, doses are administered once per month, once per quarter, every 6 months, or once per year.

- 5 In any of the above embodiments, the total dose may be administered in one dose of the entire dose or more than one separate doses, which separate doses together are the total dose. In any of the above embodiments the administration is at varying intervals.

Clinical Assessment Methods

- 10 In some embodiments, patients are assessed using the Bayley Scales of Infant and Toddler Development®, Fourth Edition (BSID-IV). The BSID-IV is the most extensively used measure of infant and toddler development in clinical and research practice. The BSID has been used extensively worldwide since then to assess the development of infants. The BSID was standardized in 1,700 infants, toddlers, and preschoolers between 1 and 42 months of age. The normed scores derived from the BSID-IV are used in clinical practice to detect infants with developmental delays, as well as to evaluate developmental progress and the impact of therapeutic interventions. In addition, the generated T-
- 15 scores and percentiles for developmental achievement allow direct clinical comparison of any stabilization of decline or improvement against normally developing children. The developmental skills included in the Bayley Scales are considered to broadly encompass those demonstrated by AS patients. The BSID consists of a core battery of 5 scales. Sixteen (16) standardized sub-domain scores and 5 standardized domain scores are generated: Cognitive, Language, Motor, Social-Emotional, and Adaptive Behavior. Standardized scores range from 1 to 19. Higher scores are indicative
- 20 of higher levels of development. Total raw scores are also available for subtests in the record form for Cognition, Communication (receptive and expressive), Motor (fine and gross motor skills). The Social Emotional and Adaptive Behavior scales will not be administered in this study. For each subtest, these are counts of the total number of items for which child received credit (i.e., up to 2 points for each item).

- 25 In some embodiments, patients are assessed using Electroencephalograph (EEG). Abnormal EEG activity is robust and widely observed in AS patients, particularly in slow 1-4Hz “delta” rhythms and 8-12Hz “alpha” rhythms, hypersynchronicity, seizures and decreased sleep spindle frequency and duration.

- 30 In some embodiments, patients are assessed by the Symptoms of Angelman Syndrome - Clinical Global Impression of Change (SAS-CGI-Change). The SAS-CGI-Change is a clinician-rated measure, assessing the clinician’s impression about changes in the patient’s condition, in this case AS (no other conditions or co-morbidities), compared with baseline, considering aspects of severity, frequency, and impact on day-to-day activities in specific functional domains, including cognition, expressive communication, gross motor skills, fine motor skills daily living skills, sleep, and behavior. The SAS-CGI-Change utilizes a 7-point response scale, ranging from “very much improved” (1) to “very much worse” (7). Clinicians make a judgment on any changes from baseline based on the totality of information available to them (e.g., insights from patient and/or caregiver, information captured during the completion of other
- 35 assessments).

In some embodiments, patients are assessed with the Vineland Adaptive Behavior Scales (third edition) assessment (Vineland-3). The Vineland-3 is an instrument that measures communication, daily living skills, socialization, and maladaptive behavior. The Comprehensive Interview Form (i.e., a semi structured interview) will be administered to the patient's caregiver. The investigator or a designee will ask the caregiver open-ended questions relating to the patient's activities and behavior. Standardized domain scores will be obtained for the individual domains of socialization, communication, daily living skills, and motor skills. An adaptive behavior composite score will also be generated. Standardized scores on the domains and composite score range from 20 to 160, with higher scores indicating better functioning.

In some embodiments, patients are assessed with the Observer-Reported Communication Ability (ORCA) measure. The ORCA measure is a questionnaire built to assess the communication ability of individuals that have a neurodevelopmental disorder associated with a significant impact on communication. The ORCA measure was originally designed for individuals with AS aged 2 years or older. The measure is designed to observe the overall communication ability of the patient from the perspective of their primary caregiver and consists of 84 questions with 70 behavior items within 22 concepts. The assessment considers the heterogeneity of communication modalities and assesses the individual's unique methods of communicating. The total ORCA score reflects the primary caregiver's assessment of the patient's ability to perform behaviors frequently and consistently, indicating the patient's total communication ability.

Example 1: Phase 1-2a Human Clinical Trial with Compound ION582 for treatment of Angelman Syndrome – MAD study (HALOS, part 1)

Compound ION582 was formulated for administration as a sterile solution of the compound in aCSF at a concentration of 20mg/mL. ION582 is provided as a 5mL fill volume in a 6mL clear glass vial. Compound ION582 was assessed in a randomized phase 1-2a Multiple Ascending Dose (MAD) trial, where the compound was administered intrathecally into the cerebral spinal fluid of Angelman syndrome (AS) patients with a lumbar puncture. The participants included a minimum of 51 males and females ranging from ages 2-34 years with both UBE3A deletion and UBE3A mutation phenotypes represented. All patients had a confirmed genetic diagnosis of Angelman syndrome with the characteristic phenotype of seizures, motor deficits, little to no language abilities, and decreased sleep.

Patients were enrolled in 3 ascending dose levels in 7 cohorts to allow for the evaluation of treatment at different ION582 dose levels and age groups. ION582 was administered 3 times throughout the treatment period on Day 1, Day 29, and Day 85. Subjects were between ages 2 and 50 years old and were assigned to the following 7 cohorts:

Cohort A: 20 mg ION582 (patients ranging from 4 to 17 years of age);

Cohort B: 40 mg ION582 (patients ranging from 4 to 17 years of age);

Cohort C: 80 mg ION582 (patients ranging from 4 to 17 years of age);

Cohort D1: 20 mg ION582 (patients ranging from 2 to 5 years of age);

Cohort D2: 40 mg ION582 (patients ranging from 2 to 5 years of age);

Cohort D3: 80 mg ION582 (patients ranging from 2 to 5 years of age); and

Cohort E: 80 mg ION582 (patients ranging from 18 to 50 years of age).

Patients were evaluated over a 12-week Post-Treatment Follow-Up Period where they returned to the Study Centers for a visit on Study Days 113 and 169.

- 5 98% of enrolled participants completed Part 1 MAD. The disposition of the patient population is described in the table below:

	Low Dose (20mg) (n=11)	Medium Dose (40mg) (n=13)	High Dose (80mg) (n=27)
Mean age at screening, years (min, max)	5.7 (2.1, 11)	7.6 (4.4, 17.5)	12.1 (2.7, 34.3)
Genotype, n (%) • Mutation • Deletion	1 (9) 10 (91)	3 (23) 10 (77)	4 (15) 23 (85)
Completed treatment, n (%)	11 (100)	12 (92)	27 (100)
Discontinued treatment, n	0	1*	0

*Not deemed related to study drug

- 10 Compound ION582 was found to be well-tolerated at all dose levels. No concerning safety trends were observed by the Independent Safety Monitoring Committee which reviewed all data on an on-going basis. The majority of the adverse events (AEs) reported were consistent with the patient's medical histories, diagnosis of Angelman syndrome, and/or the finding related to the lumbar punctures. No trends were observed in safety labs including CSF (cell counts, protein, glucose), blood, or urine. There were no reports of lower limb weakness, ataxia, or radiculopathy.

Events in >10% of Participants			
	Events (n)	Participants (n)	Participants (% , N = 51)
Pyrexia	13	10	19.6%
Vomiting	11	10	19.6%
Upper Respiratory Tract Infection	10	9	17.6%

Assessment at Day 113 (4 weeks after the last MAD dose)

- 15 Electroencephalogram (EEG) patterns were recorded and read over the course of the MAD study. 20 electrodes were secured to the scalp while the individual was awake in order to evaluate brain function. EEGs are commonly used to detect brain activity associated with seizures or to look for evidence of damage to the brain caused by tumors or stroke. AS patients are known to have increased slow brain wave (delta wave) activity in their brains compared to the

control population and the size of delta wave predicts clinical severity in AS patients. For example, reduced delta waves would indicate improved brain function. Approximately 70% of the subjects showed a reduction in slow-wave delta activity compared with baseline one month after last dose. The decreased delta activity suggested that EEG activity was improved in these subjects. Further, the magnitude of the delta wave was also observed to be reduced. Additionally, over
5 80% of subjects showed an increase in faster frequency rhythms (theta) compared with baseline one month after the last dose, which also suggested that EEG activity was improved.

Functional outcome assessments were also carried out. Clinical evaluators carried out Symptoms of Angelman Syndrome-Clinical Global Improvement-Change (SAS-CGI-C) where a subjective assessment of clinical functioning was carried out on a 7-point scale where nine key areas of functioning including cognitive impairment, expressive
10 communication, fine motor skills, gross motor skills, maladaptive behaviors, activities of daily living, seizures, sleep and overall AS were measured. The majority of the patients demonstrated some level of improvement in overall functioning as rated by the clinician on the SAS-CGI-C scale. In addition, Bayley Scales of Infant and Toddler Development-4 (Bayley-4) were measured. This is a direct assessment of clinical functioning that measures general cognitive
15 functioning, gross motor skills, fine motor skills, expressive and receptive language. The majority of the patients also showed some level of improvement in the total Bayley score beyond that observed in natural history studies conducted over the same time period. Greater improvements were observed in the medium dose (40mg ION582) and high dose (80mg ION582) as compared to the low dose (20mg) on Bayley-4 assessments at 4 months (Figs. 1A-1E). There was an imbalance in numbers of participants by age and genotype across dose groups; the number individuals for each age and genotype in each dosage group is provided above.

20 **Assessment at Day 169 (12 weeks after last MAD dose; ~6 months from first dose)**

Study participants were assessed at day 169 (12 weeks after the last dose of the MAD study; ~6 months from first dose). This 6-month assessment enabled the comparison to data collected in the long-running, NIH-sponsored natural history study which followed individuals with Angelman syndrome over many years in order to characterize the natural course of the disorder ("natural history"), which shows minimal changes over 12 months. Analyses from each of
25 the Bayley-4, Vineland-3, ORCA, and SAS-CGI-C measures in the medium dose (40mg ION582) and high dose (80mg ION582) groups were pooled; pooling increased sample size and enabled a more robust comparison to age- and genotype-matched natural history data. The low dose (20mg ION582) group established minimal safety and efficacy and was not assessed at 6 months.

Improvement was observed in receptive communication, which is the ability to receive and understand
30 information, as measured by Bayley-4 (Fig. 2A) and Vineland-3 (Fig. 2B) for pooled medium and high doses of ION582 compared to natural history at 6 months. Similar improvements were observed in receptive communication as measured by Bayley-4 (Fig. 3) in participants with deletion and mutation genotypes for pooled medium and high doses of ION582 at 6 months compared to natural history.

Improvement was observed in expressive communication, which is the ability to express one's needs, thoughts
35 and feelings, as measured by Bayley-4 (Fig. 4A), Vineland-3 (Fig. 4B), and SAS-CGI-C (Fig. 4C) for pooled medium and high doses of ION582 compared to natural history. Improvements on Bayley-4 and Vineland-3 measures of

expressive communication exceeded natural history, and SAS-CGI-C, which were not compared to natural history, showed clinically meaningful change, with a ≥ 1 point change considered clinically meaningful, out of a maximum improvement of 3 points.

Consistent improvements were observed in Bayley-4 and Vineland-3 measures of receptive communication (Fig. 5A) and expressive communication (Fig. 5B) for pooled medium and high doses of ION582 at 6 months.

Clinically meaningful improvement was observed on the ORCA measure of communication for pooled medium and high doses of ION582 at 6 months compared to natural history (Fig. 6.). The ORCA T-score range was 25.8–83.8, (standardized, mean=50, SD=10). A 3.6-point improvement was achieved with ION582 at 6 months of treatment, with a ≥ 2 -point improvement considered clinically meaningful. Improvement at 6 months for ION582 exceeds natural history.

The ORCA measure of communication correlates well with improvements seen with Bayley-4 for change in receptive communication (Fig. 7A) and expressive communication (Fig. 7B) for pooled medium and high doses of ION582 at 6 months.

Improvement was observed across measures of cognition on Bayley-4, which showed improvement in cognition for ION582 exceeded natural history (Fig. 8A), and on SAS-CGI-C (Fig. 8B), which were not compared to natural history, showed clinically meaningful change, with a ≥ 1 point change considered clinically meaningful, out of a maximum improvement of 3 points.

Improvement was observed in fine motor function for pooled medium and high dose ION582 groups at 6 months as measured on Bayley-4 (Fig. 9A), Vineland-3 (Fig. 9B), and SAS-CGI-C (Fig. 9C), with improvements for ION582 exceeding natural history on Bayley-4 and Vineland-3 and directional improvement seen on SAS-CGI-C.

Improvement was observed in gross motor function for pooled medium and high dose ION582 groups at 6 months as measured on Bayley-4 (Fig. 10A), Vineland-3 (Fig. 10B), and SAS-CGI-C (Fig. 10C), with improvements for ION582 exceeding natural history on Bayley-4 and Vineland-3 and clinically meaningful change seen for ION582 on SAS-CGI-C.

Clinically meaningful improvement was seen in a majority of participants in overall AS symptom change for patients treated with ION582 (Fig. 11). 97% of patients improved in SAS-CGI-C overall AS symptom change, and nearly all patients showed a ≥ 1 change in overall symptom severity at 6 months. Clinically meaningful improvement was observed in a majority of study participants for pooled medium and high dose ION582 groups at 6 months across all domains assessed on AS-specific SAS-CGI-C, as shown in the table below.

Participants with ≥ 1 Point Improvement on SAS-CGI-Change between Baseline and 6 months

Overall Angelman Syndrome Symptoms	Cognitive Impairment	Gross Motor Skills	Expressive Communication	Fine Motor Skills	Sleep problems	Impairment of Activities of Daily Living	Maladaptive Behaviors	Seizures
97%	85%	74%	69%	64%	59%	62%	56%	18%

Improvement exceeding natural history (NH) was observed in a majority of participants in pooled medium and high dose ION582 groups at 6 months across all domains assessed on Vineland-3, as shown in the table below.

Participants with Improvement Beyond NH on Vineland-3 between Baseline and 6 months

Communication		Motor Skills		Daily Living Skills			Socialization		
Receptive Communication	Expressive Communication	Gross Motor	Fine Motor	Personal	Community	Domestic	Inter-personal Relationships	Play and Leisure	Coping Skills
90%	84%	53%	63%	74%	79%	82%	79%	87%	63%

5

A majority of participants demonstrated benefit in nearly all domains assessed in the HALOS study for medium and high dose groups at 6 months. See summary in table below.

Participants with Improvement in Domains Assessed at 6 months

	Bayley-4 ¹	Vineland-3 ¹	ORCA ^{2,3}	SAS-CGI-C ^{4,5}
Cognition	67%	Not in assessment	Not in assessment	85%
Receptive Communication	67%	90%	60%	Not in assessment
Expressive Communication	69%	84%		69%
Gross Motor	46%	53%	Not in assessment	74%
Fine Motor	72%	63%	Not in assessment	64%
Daily Living Skills	Not assessed in HALOS study	74-82% ⁶	Not in assessment	62%
Socialization	Not assessed in HALOS study	63-87% ⁷	Not in assessment	Not in assessment
Sleep	Not in assessment	Not in assessment	Not in assessment	59%
Behavior	Not assessed in HALOS study	Not assessed in HALOS study	Not in assessment	56%

1. Improvement exceeds Natural History. 2. Improvement on ORCA exceeding proposed minimal clinically meaningful difference of ≥ 2 . 3. ORCA T-score range: 25.8–83.8, (standardized, mean=50, SD=10). 4. Improvement on SAS-CGI-C exceeding proposed minimal clinically meaningful difference of ≥ 1 point. 5. SAS-CGI-C response range: Very Much

10

Worse-Very Much Improved. 6. Range across 3 subdomains (personal, community and domestic). 7. Range across 3 subdomains (Coping skills, interpersonal relationships and play and leisure)

Consistent benefit was observed with ION582 treatment in AS patients in the HALOS study. Favorable safety and tolerability were demonstrated at all dose levels. Statistically significant, dose dependent reduction in EEG delta power was observed in children, correlated with improvement in cognition. Evidence of clinical improvement observed across key functional areas, including 97% of participants showed clinically meaningful improvement in overall Angelman syndrome symptoms on SAS-CGI-C (in the medium and high dose groups, with ≥ 1 point (out of a maximum improvement of 3 points) change considered clinically meaningful); improvements in communication, cognition and motor function exceeding natural history on Bayley-4, Vineland-3 and ORCA; and consistent benefit was seen across all ages and genotypes.

Example 2: Phase 1-2a Human Clinical Trial with ION582 for treatment of Angelman Syndrome – LTE study (HALOS, part 2)

A randomized Long-Term Extension (LTE) portion of the Phase 1-2a study will be conducted to evaluate the safety and tolerability of intrathecal bolus (ITB) administrations of ION582 over a longer period of time in patients with Angelman syndrome (AS).

This 49-week Long-Term Extension (LTE) study will be conducted at multiple centers and is comprised of patients from the study described in Example 1 above, who have completed the above study with a 12-week Post-Treatment Follow-Up Period. Patients will receive a maximum of 5 intrathecal bolus (ITB) injections of ION582 across 49 weeks in the LTE Treatment Period. Dosing will occur as frequently as every 12 weeks on Days 1, 85, 169, 253, and 337. Dose-level will be assigned based upon the cohort in which the patient enrolled in as well as safety and tolerability data generated from the study described in Example 1 above. There will be up to 2 dosing groups:

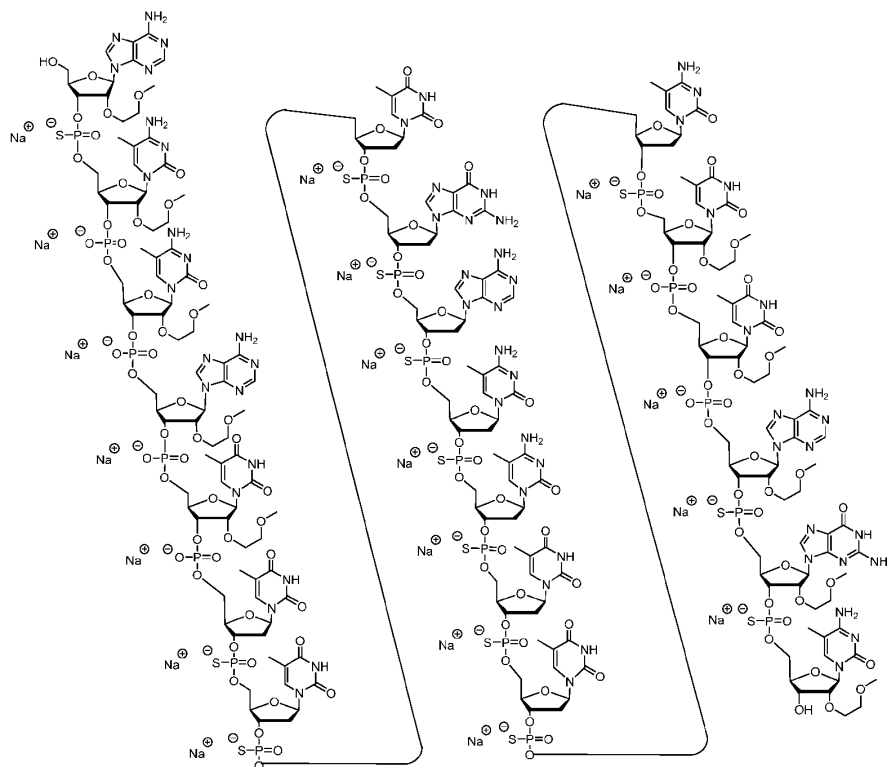
Group 1: Cohorts A, B, D1, D2: Up to 40 mg ION582 ITB injection

Group 2: Cohorts C, D3, and E: Up to 80 mg ION582 ITB injection

Following the LTE Treatment Period, patients will enter a Post-Treatment Follow-Up Period of 32 weeks. Patients will return to the Study Center for a visit on Study Day 421 and a final visit on Study Day 561.

Safety and tolerability of ION582 in patients with Angelman syndrome (AS) will be based on incidence and severity of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), changes in vital signs, and changes in clinical laboratory results. Pharmacokinetics (PK) in cerebrospinal fluid (CSF), plasma and urine of ascending dose-levels of multiple IT bolus administrations of ION582 in patients with AS will also be evaluated. The effects of ION582 on AS biomarkers and clinical features including motor, language, cognitive functioning, sleep, and electroencephalogram (EEG) patterns in patients with AS will also be evaluated.

3. A method comprising administering to a human subject a therapeutically effective amount of a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 5).

4. A method comprising administering to a human subject a therapeutically effective amount of a modified oligonucleotide consisting of 19-20 linked nucleosides, wherein the modified oligonucleotide comprises at least 19 contiguous nucleosides of the following chemical notation (5' to 3'):

A_{es}^mC_{eo}^mC_{eo}A_{eo}T_{eo}T_{ds}T_{ds}G_{ds}A_{ds}^mC_{ds}^mC_{ds}T_{ds}T_{ds}^mC_{ds}T_{eo}T_{eo}A_{es}G_{es}^mC_e (SEQ ID NO: 5), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribose sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

5. The method of any of claims 1-4, wherein the modified oligonucleotide is formulated as a pharmaceutical composition comprising a pharmaceutically acceptable diluent.
6. The method of claim 5, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF).
7. The method of claim 5, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS).

8. The method of any of claims 1-7, wherein the therapeutically effective amount is any of 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, or 150 mg.
9. The method of any of claims 1-8, wherein the therapeutically effective amount is any of 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, and 25 mg.
10. The method of any of claims 1-8, wherein the therapeutically effective amount is any of 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, and 30 mg.
11. The method of any of claims 1-8, wherein the therapeutically effective amount is any of 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg, 38 mg, 39 mg, 40 mg, 41 mg, 42 mg, 43 mg, 44 mg, 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, and 50 mg.
12. The method of any of claims 1-8, wherein the therapeutically effective amount is any of 51 mg, 52 mg, 53 mg, 54 mg, 55 mg, 56 mg, 57 mg, 58 mg, 59 mg, 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, and 70 mg.
13. The method of any of claims 1-8, wherein the therapeutically effective amount is any of 71 mg, 72 mg, 73 mg, 74 mg, 75 mg, 76 mg, 77 mg, 78 mg, 79 mg, 80 mg, 81 mg, 82 mg, 83 mg, 84 mg, 85 mg, 86 mg, 87 mg, 88 mg, 89 mg, and 90 mg.
14. The method of any of claims 1-8, wherein the therapeutically effective amount is any of 91 mg, 92 mg, 93 mg, 94 mg, 95 mg, 96 mg, 97 mg, 98 mg, 99 mg, 100 mg, 101 mg, 102 mg, 103 mg, 104 mg, 105 mg, 106 mg, 107 mg, 108 mg, 109 mg, and 110 mg.
15. The method of any of claims 1-7, wherein the therapeutically effective amount is any of from 5 mg to 120 mg, from 5 mg to 115 mg, from 5 mg to 110 mg, from 5 mg to 105 mg, from 5 mg to 100 mg, from 5 mg to 95 mg, from 5 mg to 90 mg, from 5 mg to 85 mg, from 5 mg to 80 mg, from 5 mg to 75 mg, from 5 mg to 70 mg, from 5 mg to 65 mg, from 5 mg to 60 mg, from 5 mg to 55 mg, from 5 mg to 50 mg, from 5 mg to 45 mg, from 5 mg to 40 mg, from 5 mg to 35 mg, from 5 mg to 30 mg, from 5 mg to 25 mg, from 5 mg to 20 mg, from 5 mg to 15 mg, from 5 mg to 10 mg, from 10 mg to 120 mg, from 10 mg to 115 mg, from 10 mg to 110 mg, from 10 mg to 105 mg, from 10 mg to 100 mg, from 10 mg to 95 mg, from 10 mg to 90 mg, from 10 mg to 85 mg, from 10 mg to 80 mg, from 10 mg to 75 mg, from 10 mg to 70 mg, from 10 mg to 65 mg, from 10 mg to 60 mg, from 10 mg to 55 mg, from 10 mg to 50 mg, from 10 mg to 45 mg, from 10 mg to 40 mg, from 10 mg to 35 mg, from 10 mg to 30 mg, from 10 mg to 25 mg, from 10 mg to 20 mg, from 10 mg to 15 mg, from 15 mg to 120 mg, from 15 mg to 115 mg, from 15 mg to 110 mg, from 15 mg to 105 mg, from 15 mg to 100 mg, from 15 mg to 95 mg, from 15 mg to 90 mg, from 15 mg to 85 mg, from 15 mg to 80 mg, from 15 mg to 75 mg, from 15 mg to 70 mg, from 15 mg to 65 mg, from 15 mg to 60 mg, from 15 mg to 55 mg, from 15 mg to 50 mg, from 15 mg to 45 mg, from 15 mg to 40 mg, from 15 mg to 35 mg, from 15 mg to 30 mg, from 15 mg to 25 mg, from 15 mg to 20 mg, from 20 mg to 120 mg, from 20 mg to 115 mg, from 20 mg to 110 mg, from 20 mg to 105 mg, from 20 mg to 100 mg, from 20 mg to 95 mg, from 20 mg to 90 mg, from 20 mg to 85 mg, from 20 mg to 80 mg, from 20 mg to 75 mg, from 20 mg to 70 mg, from 20 mg to 65 mg, from 20 mg to 60 mg, from 20 mg to 55 mg, from 20 mg to 50 mg, from 20 mg to 45 mg, from 20 mg to 40 mg, from 20 mg to 35 mg, from 20 mg to 30 mg, from 20 mg to 25 mg, from 25 mg to 120 mg, from 25 mg to 115 mg, from 25 mg to 110 mg, from 25 mg to 105 mg, from 25 mg to 100 mg, from 25 mg to 95 mg, from 25 mg to 90 mg, from 25 mg to 85 mg, from 25 mg to 80 mg, from 25 mg to 75 mg, from 25 mg to 70 mg, from 25 mg to 65 mg, from 25 mg to 60 mg, from 25 mg to 55 mg, from 25 mg to 50 mg, from 25 mg to 45 mg, from 25 mg to 40 mg, from 25 mg to 35 mg, from 25 mg to 30 mg, from 25 mg to 25 mg.

100 mg, from 25 mg to 95 mg, from 25 mg to 90 mg, from 25 mg to 85 mg, from 25 mg to 80 mg, from 25 mg to 75 mg, from 25 mg to 70 mg, from 25 mg to 65 mg, from 25 mg to 60 mg, from 25 mg to 55 mg, from 25 mg to 50 mg, from 25 mg to 45 mg, from 25 mg to 40 mg, from 25 mg to 35 mg, from 25 mg to 30 mg, from 30 mg to 120 mg, from 30 mg to 115 mg, from 30 mg to 110 mg, from 30 mg to 105 mg, from 30 mg to 100 mg, from 30 mg to 95 mg, from 30 mg to 90 mg, from 30 mg to 85 mg, from 30 mg to 80 mg, from 30 mg to 75 mg, from 30 mg to 70 mg, from 30 mg to 65 mg, from 30 mg to 60 mg, from 30 mg to 55 mg, from 30 mg to 50 mg, from 30 mg to 45 mg, from 30 mg to 40 mg, from 30 mg to 35 mg, from 35 mg to 120 mg, from 35 mg to 115 mg, from 35 mg to 110 mg, from 35 mg to 105 mg, from 35 mg to 100 mg, from 35 mg to 95 mg, from 35 mg to 90 mg, from 35 mg to 85 mg, from 35 mg to 80 mg, from 35 mg to 75 mg, from 35 mg to 70 mg, from 35 mg to 65 mg, from 35 mg to 60 mg, from 35 mg to 55 mg, from 35 mg to 50 mg, from 35 mg to 45 mg, from 35 mg to 40 mg, from 40 mg to 120 mg, from 40 mg to 115 mg, from 40 mg to 110 mg, from 40 mg to 105 mg, from 40 mg to 100 mg, from 40 mg to 95 mg, from 40 mg to 90 mg, from 40 mg to 85 mg, from 40 mg to 80 mg, from 40 mg to 75 mg, from 40 mg to 70 mg, from 40 mg to 65 mg, from 40 mg to 60 mg, from 40 mg to 55 mg, from 40 mg to 50 mg, from 40 mg to 45 mg, from 45 mg to 120 mg, from 45 mg to 115 mg, from 45 mg to 110 mg, from 45 mg to 105 mg, from 45 mg to 100 mg, from 45 mg to 95 mg, from 45 mg to 90 mg, from 45 mg to 85 mg, from 45 mg to 80 mg, from 45 mg to 75 mg, from 45 mg to 70 mg, from 45 mg to 65 mg, from 45 mg to 60 mg, from 45 mg to 55 mg, from 45 mg to 50 mg, from 50 mg to 120 mg, from 50 mg to 115 mg, from 50 mg to 110 mg, from 50 mg to 105 mg, from 50 mg to 100 mg, from 50 mg to 95 mg, from 50 mg to 90 mg, from 50 mg to 85 mg, from 50 mg to 80 mg, from 50 mg to 75 mg, from 50 mg to 70 mg, from 50 mg to 65 mg, from 50 mg to 60 mg, from 50 mg to 120 mg, from 55 mg to 115 mg, from 55 mg to 110 mg, from 55 mg to 105 mg, from 55 mg to 100 mg, from 55 mg to 95 mg, from 55 mg to 90 mg, from 55 mg to 85 mg, from 55 mg to 80 mg, from 55 mg to 75 mg, from 55 mg to 70 mg, from 55 mg to 65 mg, from 55 mg to 60 mg, from 60 mg to 120 mg, from 60 mg to 115 mg, from 60 mg to 110 mg, from 60 mg to 105 mg, from 60 mg to 100 mg, from 60 mg to 95 mg, from 60 mg to 90 mg, from 60 mg to 85 mg, from 60 mg to 80 mg, from 60 mg to 75 mg, from 60 mg to 70 mg, from 65 mg to 120 mg, from 65 mg to 115 mg, from 65 mg to 110 mg, from 65 mg to 105 mg, from 65 mg to 100 mg, from 65 mg to 95 mg, from 65 mg to 90 mg, from 65 mg to 85 mg, from 65 mg to 80 mg, from 65 mg to 75 mg, from 65 mg to 70 mg, from 70 mg to 120 mg, from 70 mg to 115 mg, from 70 mg to 110 mg, from 70 mg to 105 mg, from 70 mg to 100 mg, from 70 mg to 95 mg, from 70 mg to 90 mg, from 70 mg to 85 mg, from 70 mg to 80 mg, from 75 mg to 120 mg, from 75 mg to 115 mg, from 75 mg to 110 mg, from 75 mg to 105 mg, from 75 mg to 100 mg, from 75 mg to 95 mg, from 75 mg to 90 mg, from 75 mg to 85 mg, from 75 mg to 80 mg, from 80 mg to 120 mg, from 80 mg to 115 mg, from 80 mg to 110 mg, from 80 mg to 105 mg, from 80 mg to 100 mg, from 80 mg to 95 mg, from 80 mg to 90 mg, from 85 mg to 120 mg, from 85 mg to 115 mg, from 85 mg to 110 mg, from 85 mg to 105 mg, from 85 mg to 100 mg, from 85 mg to 95 mg, from 85 mg to 90 mg, from 90 mg to 120 mg, from 90 mg to 115 mg, from 90 mg to 110 mg, from 90 mg to 105 mg, from 90 mg to 100 mg, from 95 mg to 120 mg, from 95 mg to 115 mg, from 95 mg to 110 mg, from 95 mg to 105 mg, from 95 mg to 100 mg, from 100 mg to 120 mg, from 100 mg to 115 mg, from 100 mg to 110 mg, from 100 mg to 105 mg, from 105 mg to 120 mg, from 105 mg to 115 mg, from 105 mg to 110 mg, from 110 mg to 120 mg, from 110 mg to 115 mg, and from 115 mg to 120 mg.

16. The method of any of claims 1-7 or 15, wherein the therapeutically effective amount is any of 15 mg to 25 mg, from 18 mg to 25 mg, from 19 mg to 25 mg, from 18 mg to 23 mg, from 19 mg to 23 mg, from 18 mg to 22 mg, from 19 mg to 22 mg, from 18 mg to 21 mg, or from 19 mg to 21 mg.

17. The method of any of claims 1-7 or 15, wherein the therapeutically effective amount is any of 35 mg to 45 mg, from 38 mg to 45 mg, from 39 mg to 45 mg, from 38 mg to 43 mg, from 39 mg to 43 mg, from 38 mg to 42 mg, from 39 mg to 42 mg, from 38 mg to 41 mg, or from 39 mg to 41 mg.
18. The method of any of claims 1-7 or 15, wherein the therapeutically effective amount is any of from 55 mg to 65 mg, from 58 mg to 65 mg, from 59 mg to 65 mg, from 58 mg to 63 mg, from 59 mg to 63 mg, from 58 mg to 62 mg, from 59 mg to 62 mg, from 58 mg to 61 mg, or from 59 mg to 61 mg.
19. The method of any of claims 1-7 or 15, wherein the therapeutically effective amount is any of from 75 mg to 85 mg, from 78 mg to 85 mg, from 79 mg to 85 mg, from 78 mg to 83 mg, from 79 mg to 83 mg, from 78 mg to 82 mg, from 79 mg to 82 mg, from 78 mg to 81 mg, or from 79 mg to 81 mg.
20. The method of any of claims 1-7, wherein the therapeutically effective amount is any of less than 150 mg, less than 145 mg, less than 140 mg, less than 135 mg, less than 130 mg, less than 125 mg, less than 120 mg, less than 115 mg, less than 110 mg, less than 105 mg, less than 100 mg, less than 95 mg, less than 90 mg, less than 85 mg, less than 80 mg, less than 75 mg, less than 70 mg, less than 65 mg, less than 60 mg, less than 55 mg, less than 50 mg, less than 45 mg, less than 40 mg, less than 35 mg, less than 30 mg, less than 25 mg, less than 20 mg, less than 15 mg, less than 10 mg, and less than 5 mg.
21. The method of any of claims 1-7 or 20, wherein the therapeutically effective amount is any of less than 85 mg, less than 80 mg, less than 75 mg, less than 70 mg, less than 65 mg, less than 60 mg, less than 55 mg, less than 50 mg, less than 45 mg, less than 40 mg, less than 35 mg, less than 30 mg, less than 25 mg, less than 20 mg, less than 15 mg, and less than 10 mg.
22. The method of any of claims 1-7, wherein the therapeutically effective amount is any of at least 5 mg, at least 10 mg, at least 15 mg, at least 20 mg, at least 25 mg, at least 30 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 55 mg, at least 60 mg, at least 65 mg, at least 70 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, at least about 100 mg, at least 105 mg, at least 115 mg, at least 120 mg, at least 125 mg, at least 130 mg, at least 135 mg, at least 140 mg, and at least 145 mg.
23. The method of any of claims 1-7, wherein the therapeutically effective amount is 5 mg.
24. The method of any of claims 1-7, wherein the therapeutically effective amount is 10 mg.
25. The method of any of claims 1-7, wherein the therapeutically effective amount is 20 mg.
26. The method of any of claims 1-7, wherein the therapeutically effective amount is 30 mg.
27. The method of any of claims 1-7, wherein the therapeutically effective amount is 40 mg.
28. The method of any of claims 1-7, wherein the therapeutically effective amount is 50 mg.
29. The method of any of claims 1-7, wherein the therapeutically effective amount is 60 mg.
30. The method of any of claims 1-7, wherein the therapeutically effective amount is 70 mg.
31. The method of any of claims 1-7, wherein the therapeutically effective amount is 80 mg.
32. The method of any of claims 1-7, wherein the therapeutically effective amount is 90 mg.
33. The method of any of claims 1-7, wherein the therapeutically effective amount is 100 mg.
34. The method of any of claims 1-7, wherein the therapeutically effective amount is 110 mg.
35. The method of any of claims 1-7, wherein the therapeutically effective amount is 120 mg.
36. The method of any of claims 1-7, wherein the therapeutically effective amount is 4-6 mg.
37. The method of any of claims 1-7, wherein the therapeutically effective amount is 9-11 mg.

38. The method of any of claims 1-7, wherein the therapeutically effective amount is 19-21 mg.
39. The method of any of claims 1-7, wherein the therapeutically effective amount is 29-31 mg.
40. The method of any of claims 1-7, wherein the therapeutically effective amount is 39-41 mg.
41. The method of any of claims 1-7, wherein the therapeutically effective amount is 48-52 mg.
42. The method of any of claims 1-7, wherein the therapeutically effective amount is 58-62 mg.
43. The method of any of claims 1-7, wherein the therapeutically effective amount is 68-72 mg.
44. The method of any of claims 1-7, wherein the therapeutically effective amount is 78-82 mg.
45. The method of any of claims 1-7, wherein the therapeutically effective amount is 88-92 mg.
46. The method of any of claims 1-7, wherein the therapeutically effective amount is 98-102 mg.
47. The method of any of claims 1-7, wherein the therapeutically effective amount is 108-112 mg.
48. The method of any of claims 1-7, wherein the therapeutically effective amount is 118-122 mg.
49. The method of any of claims 1-48, wherein the therapeutically effective amount is administered as a single dose.
50. The method of claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once every 28 days.
51. The method of claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once every 56 days.
52. The method of claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once every 84 days.
53. The method of claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once every 4, 8, 10, 12, 16, 18, 20, 24, 28, or 32 weeks.
54. The method of claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once every 4 weeks.
55. The method of claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once every 8 weeks.
56. The method of claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once every 12 weeks.
57. The method of claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once every 16 weeks.
58. The method of claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once every 20 weeks.
59. The method of claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once every 24 weeks.
60. The method claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once monthly.
61. The method claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once every two months.
62. The method claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once every four months.

63. The method claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once every five months.
64. The method of claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once every six months.
65. The method of claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once every 6 months, once every 7 months, once every 8 months, once every 9 months, once every 10 months, once every 11 months, or once every 12 months.
66. The method claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once quarterly.
67. The method claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once triannually.
68. The method of claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once semiannually.
69. The method of claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 once annually.
70. The method of claim 49, wherein the method comprises administering a dose of any of the therapeutically effective amounts of claims 1-48 any of once every 1 week, once every 2 weeks, once every 3 weeks, 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, once every 12 weeks, once every 13 weeks, once every 14 weeks, once every 15 weeks, once every 16 weeks, once every 17 weeks, once every 18 weeks, once every 19 weeks, once every 20 weeks, once every 21 weeks, once every 22 weeks, once every 23 weeks, once every 24 weeks, once every month, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 7 months, once every 8 months, once every 9 months, once every 10 months, once every 11 months, or once every year.
71. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 10 mg of the modified oligonucleotide once every four weeks.
72. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 20 mg of the modified oligonucleotide once every four weeks.
73. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 30 mg of the modified oligonucleotide once every four weeks.
74. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide once every four weeks.
75. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 50 mg of the modified oligonucleotide once every four weeks.
76. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 60 mg of the modified oligonucleotide once every four weeks.
77. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 70 mg of the modified oligonucleotide once every four weeks.
78. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide once every four weeks.

79. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 90 mg of the modified oligonucleotide once every four weeks.
80. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 10 mg of the modified oligonucleotide once every eight weeks.
81. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 20 mg of the modified oligonucleotide once every eight weeks.
82. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 30 mg of the modified oligonucleotide once every eight weeks.
83. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide once every eight weeks.
84. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 50 mg of the modified oligonucleotide once every eight weeks.
85. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 60 mg of the modified oligonucleotide once every eight weeks.
86. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 70 mg of the modified oligonucleotide once every eight weeks.
87. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide once every eight weeks.
88. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 90 mg of the modified oligonucleotide once every eight weeks.
89. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 10 mg of the modified oligonucleotide once every twelve weeks.
90. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 20 mg of the modified oligonucleotide once every twelve weeks.
91. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 30 mg of the modified oligonucleotide once every twelve weeks.
92. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide once every twelve weeks.
93. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 50 mg of the modified oligonucleotide once every twelve weeks.
94. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 60 mg of the modified oligonucleotide once every twelve weeks.
95. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 70 mg of the modified oligonucleotide once every twelve weeks.
96. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide once every twelve weeks.
97. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 90 mg of the modified oligonucleotide once every twelve weeks.

98. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 20 mg of the modified oligonucleotide once every quarter.
99. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 30 mg of the modified oligonucleotide once every quarter.
100. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide once every quarter.
101. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 50 mg of the modified oligonucleotide once every quarter.
102. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 60 mg of the modified oligonucleotide once every quarter.
103. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 70 mg of the modified oligonucleotide once every quarter.
104. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide once every quarter.
105. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 90 mg of the modified oligonucleotide once every quarter.
106. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 10 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.
107. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 20 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.
108. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 30 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.
109. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.
110. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide every 12 to 13 weeks or quarterly or four times a year.
111. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 50 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year. The method of any of claims 1-69, wherein the method comprises administering to the human subject a dose of 60 mg of the modified oligonucleotide once monthly, once every 2 months,

once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

112. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 60 mg of the modified oligonucleotide every 12 to 13 weeks or quarterly or four times a year.

113. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 70 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

114. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

115. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide every 12 to 13 weeks or quarterly or four times a year.

116. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 90 mg of the modified oligonucleotide once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

117. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 10 mg of the modified oligonucleotide once every 28 days.

118. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 20 mg of the modified oligonucleotide once every 28 days.

119. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 30 mg of the modified oligonucleotide once every 28 days.

120. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide once every 28 days.

121. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 50 mg of the modified oligonucleotide once every 28 days.

122. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 60 mg of the modified oligonucleotide once every 28 days.

123. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 70 mg of the modified oligonucleotide once every 28 days.

124. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide once every 28 days.

125. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 90 mg of the modified oligonucleotide once every 28 days.

126. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 10 mg of the modified oligonucleotide once every 56 days.

127. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 20 mg of the modified oligonucleotide once every 56 days.
128. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 30 mg of the modified oligonucleotide once every 56 days.
129. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide once every 56 days.
130. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 50 mg of the modified oligonucleotide once every 56 days.
131. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 60 mg of the modified oligonucleotide once every 56 days.
132. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 70 mg of the modified oligonucleotide once every 56 days.
133. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide once every 56 days.
134. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 90 mg of the modified oligonucleotide once every 56 days.
135. The method of any of claims 1-134, wherein four doses of the modified oligonucleotide are administered.
136. The method of any of claims 1-134, wherein three doses of the modified oligonucleotide are administered.
137. The method of any of claims 1-134, wherein two doses of the modified oligonucleotide are administered.
138. The method of any of claims 1-134, wherein the method comprises administering to the human subject a dose of 20 mg of the modified oligonucleotide on day 1, day 29, and day 85 for a total of 3 doses, then administering a dose of up to 40 mg every 12 weeks for up to 5 doses.
139. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 40 mg of the modified oligonucleotide on day 1, day 29, and day 85, then administering a dose of up to 40 mg every 12 weeks for up to 5 doses.
140. The method of any of claims 1-70, wherein the method comprises administering to the human subject a dose of 80 mg of the modified oligonucleotide on day 1, day 29, and day 85, then administering a dose of up to 80 mg every 12 weeks for up to 5 doses.
141. The method of any of claims 1-70, wherein the modified oligonucleotide is administered to the human subject at a total dose per month of from 5 mg to 100 mg, from 5 mg to 80 mg, from 5 mg to 60 mg, from 5 mg to 40 mg, from 5 mg to 20 mg, from 10 mg to 100 mg, from 10 mg to 80 mg, from 10 mg to 60 mg, from 10 mg to 40 mg, from 10 mg to 20 mg, from 20 mg to 100 mg, from 20 mg to 80 mg, from 20 mg to 60 mg, from 20 mg to 40 mg, from 40 mg to 100 mg, from 40 mg to 80 mg, from 40 mg to 60 mg, or from 80 mg to 100 mg.
142. The method of any of claims 1-70, wherein the modified oligonucleotide is administered to the human subject at a total dose per 3 months of from 15 mg to 300 mg, from 15 mg to 180 mg, from 15 mg to 150 mg, from 15 mg to 100 mg, from 15 mg to 80 mg, from 15 mg to 50 mg, from 40 mg to 300 mg, from 40 mg to 180 mg, from 40 mg to 150 mg, from 40 mg to 100 mg, from 40 mg to 80 mg, from 80 mg to 300 mg, from 80 mg to 180 mg, from 80 mg to 150 mg, from 80 mg to 100 mg, from 100 mg to 300 mg, from 100 mg to 180 mg, from 100 mg to 150 mg, or from 150 to 300 mg.

143. The method of any of claims 1-70, wherein the modified oligonucleotide is administered to the human subject at a total dose per 4 months of from 20 mg to 400 mg, from 20 mg to 350 mg, from 20 mg to 300 mg, from 20 mg to 250 mg, from 20 mg to 200 mg, from 20 mg to 150 mg, from 20 mg to 100 mg, from 50 mg to 400 mg, from 50 mg to 350 mg, from 50 mg to 300 mg, from 50 mg to 250 mg, from 50 mg to 200 mg, from 50 mg to 150 mg, from 50 mg to 100 mg, from 100 mg to 400 mg, from 100 mg to 350 mg, from 100 mg to 300 mg, from 100 mg to 250 mg, from 100 mg to 200 mg, from 100 mg to 150 mg, from 200 mg to 400 mg, from 200 mg to 350 mg, from 200 mg to 300 mg, from 200 mg to 250 mg, from 300 mg to 400 mg, or from 300 mg to 350 mg.

144. The method of any of claims 1-70, wherein the modified oligonucleotide is administered to the human subject at a total dose per 6 month of from 30 mg to 600 mg, from 30 mg to 500 mg, from 30 mg to 400 mg, from 30 mg to 300 mg, from 30 mg to 200 mg, from 30 mg to 100 mg, from 50 mg to 600 mg, from 50 mg to 500 mg, from 50 mg to 400 mg, from 50 mg to 300 mg, from 50 mg to 200 mg, from 50 mg to 100 mg, from 100 mg to 600 mg, from 100 mg to 500 mg, from 100 mg to 400 mg, from 100 mg to 300 mg, from 100 mg to 200 mg, from 200 mg to 600 mg, from 200 mg to 500 mg, from 200 mg to 400 mg, from 200 mg to 300 mg, from 300 mg to 600 mg, from 300 mg to 500 mg, from 300 mg to 400 mg, from 400 mg to 600 mg, from 400 mg to 500 mg, or from 500 mg to 600 mg.

145. The method of any of claims 1-70, wherein the modified oligonucleotide is administered to the human subject at a total dose per year of from 60 mg to 1200 mg, from 60 mg to 1100 mg, from 60 mg to 1000 mg, from 60 mg to 900 mg, from 60 mg to 800 mg, from 60 mg to 700 mg, from 60 mg to 600 mg, from 60 mg to 500 mg, from 60 mg to 400 mg, from 60 mg to 300 mg, from 60 mg to 200 mg, from 60 mg to 100 mg, from 100 mg to 1200 mg, from 100 mg to 1100 mg, from 100 mg to 1000 mg, from 100 mg to 900 mg, from 100 mg to 800 mg, from 100 mg to 700 mg, from 100 mg to 600 mg, from 100 mg to 500 mg, from 100 mg to 400 mg, from 100 mg to 300 mg, from 100 mg to 200 mg, from 200 mg to 1200 mg, from 200 mg to 1100 mg, from 200 mg to 1000 mg, from 200 mg to 900 mg, from 200 mg to 800 mg, from 200 mg to 700 mg, from 200 mg to 600 mg, from 200 mg to 500 mg, from 200 mg to 400 mg, from 200 mg to 300 mg, from 300 mg to 1200 mg, from 300 mg to 1100 mg, from 300 mg to 1000 mg, from 300 mg to 900 mg, from 300 mg to 800 mg, from 300 mg to 700 mg, from 300 mg to 600 mg, from 300 mg to 500 mg, from 300 mg to 400 mg, from 400 mg to 1200 mg, from 400 mg to 1100 mg, from 400 mg to 1000 mg, from 400 mg to 900 mg, from 400 mg to 800 mg, from 400 mg to 700 mg, from 400 mg to 600 mg, from 400 mg to 500 mg, from 500 mg to 1200 mg, from 500 mg to 1100 mg, from 500 mg to 1000 mg, from 500 mg to 900 mg, from 500 mg to 800 mg, from 500 mg to 700 mg, from 500 mg to 600 mg, from 600 mg to 1200 mg, from 600 mg to 1100 mg, from 600 mg to 1000 mg, from 600 mg to 900 mg, from 600 mg to 800 mg, from 600 mg to 700 mg, from 700 mg to 1200 mg, from 700 mg to 1100 mg, from 700 mg to 1000 mg, from 700 mg to 900 mg, from 700 mg to 800 mg, from 800 mg to 1200 mg, from 800 mg to 1100 mg, from 800 mg to 1000 mg, from 800 mg to 900 mg, from 900 mg to 1200 mg, from 900 mg to 1100 mg, from 900 mg to 1000 mg, from 1000 mg to 1200 mg, from 1000 mg to 1100mg, or from 1100 mg to 1200 mg.

146. The method of claim 145, wherein the modified oligonucleotide is administered every month, every 2 months, every 3 months, every 4 months, every 6 months, or once per year.

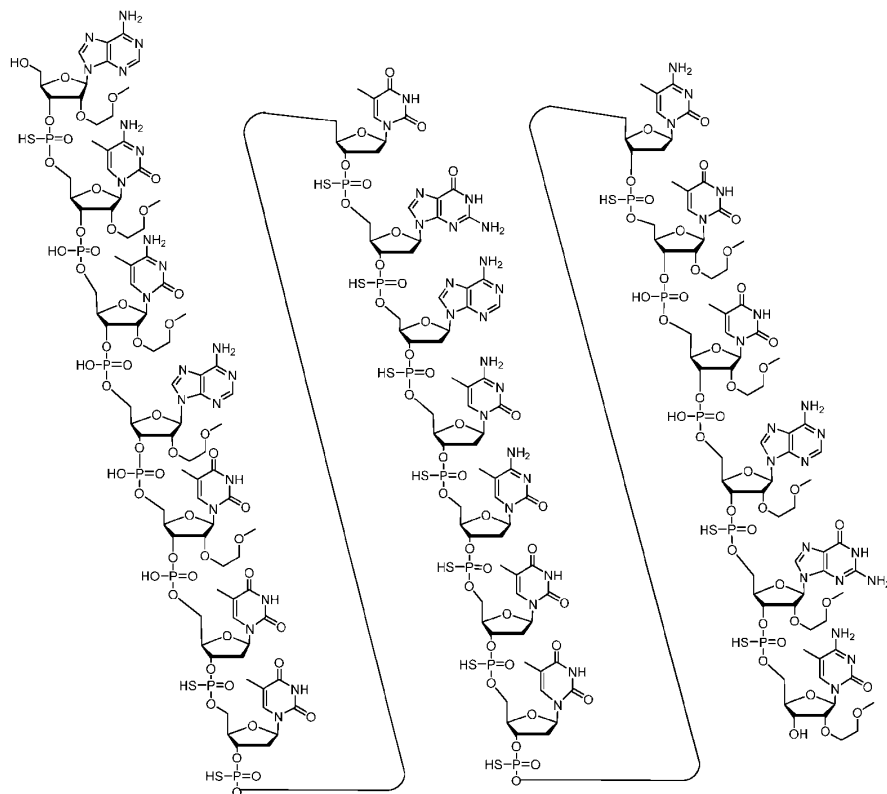
147. The method of claim 145, wherein each administration is at an interval independently selected from 2 weeks, 4 weeks, one month, two months, 3 months, 4 months, and 6 months.

148. The method of any of claims 141-145, wherein the administration is at varying dosing intervals.

149. The method of any of claims 1-148, wherein the method comprises administering to the human subject a loading dose of the modified oligonucleotide.

150. The method of any of claims 1-148, wherein the method does not comprise administering to the human subject a loading dose of the modified oligonucleotide.
151. The method of any of claims 1-150, wherein the method comprises administering to the human subject a maintenance dose of the modified oligonucleotide, optionally 1, 2, 3, 4, or 5 maintenance doses.
152. The method of any of claims 1-151, wherein the dose is administered by intrathecal administration.
153. The method of any of claims 1-152, wherein the dose is administered by bolus intrathecal administration.
154. The method of any of claims 1-153, wherein the size of Delta wave in the human subject is reduced.
155. The method of any of claims 1-154, wherein the human subject has a decrease in Delta activity compared to the Delta activity of the subject prior to administering the modified oligonucleotide.
156. The method of any of claims 1-155, wherein the human subject has a faster frequency rhythms (theta) compared to the frequency rhythms of the subject prior to administering the modified oligonucleotide.
157. The method of any of claims 1-156, wherein the human subject has an improvement in total Bayley score compared to the Bayley score of the subject prior to administering the modified oligonucleotide.
158. The method of any of claims 1-157, wherein the human subject is less than 18 years of age, less than 15 years of age, less than 13 years of age, less than 10 years of age, less than 8 years of age, or less than 5 years of age.
159. The method of any of claims 1-157, wherein the human subject is from 2 years of age up to 5 years of age, from 4 years of age up to 17 years of age, or from 1 years of age up to 17 years of age.
160. The method of any of claims 1-157, wherein the human subject is 13 years of age or older, or 18 years of age or older.
161. The method of any of claims 1-157, wherein the human subject is from 18 years of age to 50 years of age.
162. The method of any of claims 1-157, wherein the human subject is 18 years of age or older.
163. The method of any of claims 1-157, wherein the human subject is 17 years of age or younger.
164. The method of any of the preceding claims, wherein a disease or disorder associated with UBE3A is ameliorated in the human subject in need thereof.
165. The method of any of the preceding claims, wherein UBE3A-ATS RNA is reduced in the human subject in need thereof.
166. The method of any of the preceding claims, wherein UBE3A protein is increased.
167. The method of any of claims 1-166, wherein the disease or disorder associated with UBE3A is a developmental disorder.
168. The method of any of claims 1-167, wherein the disease or disorder associated with UBE3A is Angelman syndrome.
169. The method of any of claims 1-168, wherein at least one symptom or hallmark of the disease or disorder associated with UBE3A is ameliorated.
170. The method of any of claims 1-169, wherein the at least one symptom or hallmark is selected from developmental delays, ataxia, cognitive impairment, impairments in fine and/or gross motor skills, speech impairment, impairment in receptive communication and/or expressive communication, impairment in daily living skills, impaired socialization skills sleep problems, seizures, and EEG abnormalities.
171. The method of claim 169, wherein the at least one symptom or hallmark is developmental delays, ataxia, speech impairment, sleep problems, seizures, or EEG abnormalities.

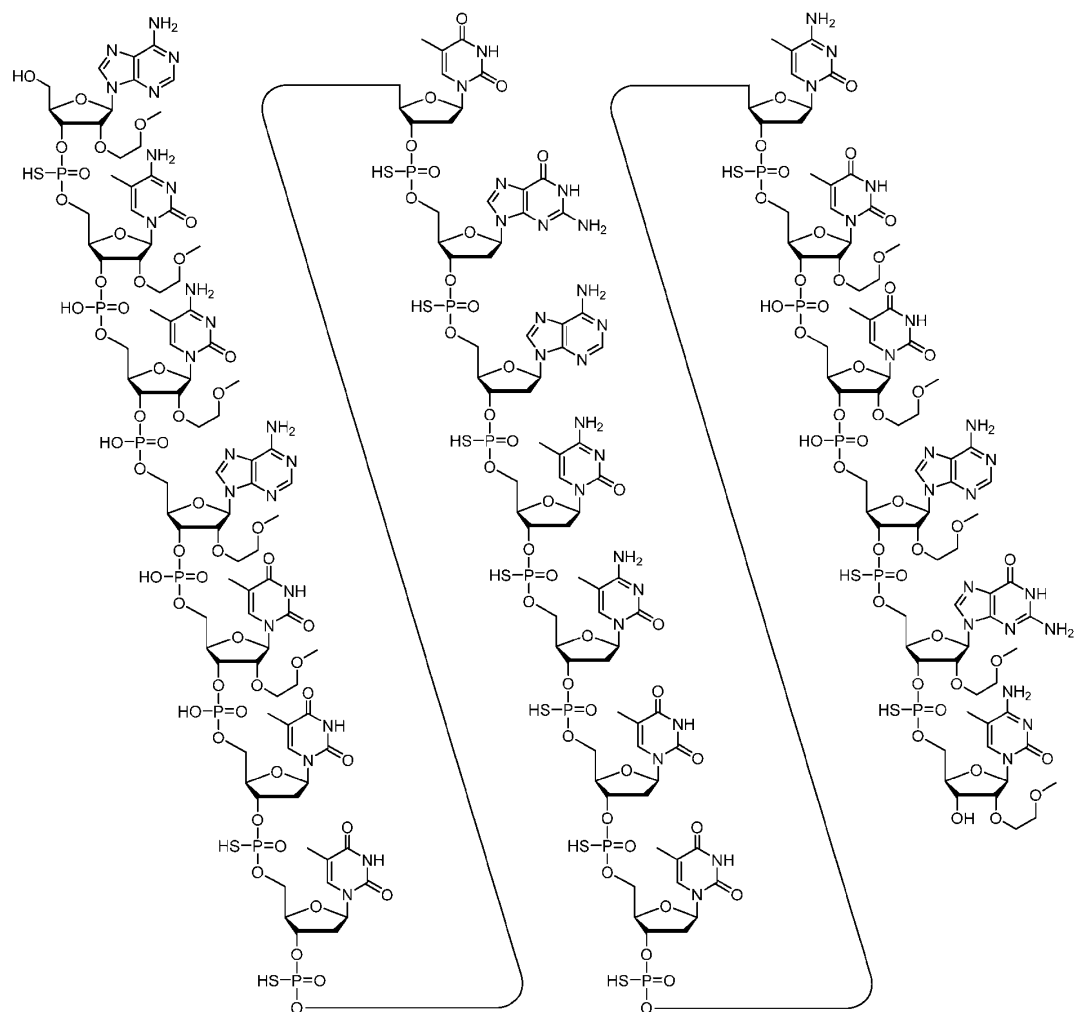
172. A method of treating a patient having Angelman syndrome, comprising
- at a first time assessing the patient for sleep, seizures, communication, motor function, and/or ability to perform activities of daily living;
 - administering to the human subject a therapeutically effective amount of a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 5), or a pharmaceutically acceptable salt thereof,

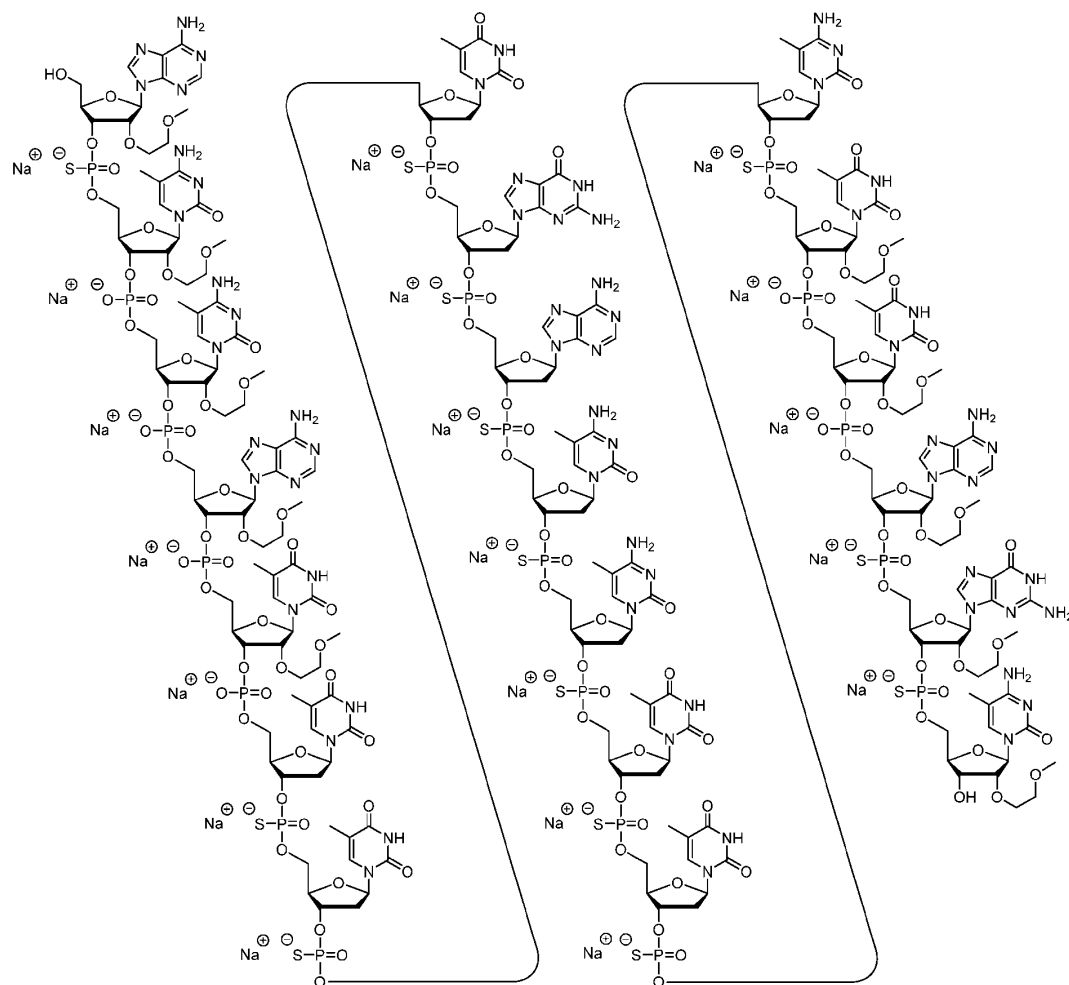
- at a second time wherein the second time is after administering the modified oligonucleotide, reassessing the patient for sleep, seizures, communication, motor function, and/or ability to perform activities of daily living; and
 - if there is no improvement or insufficient improvement between the assessments at the first time and the second time, increasing the amount of the next administered dose.
173. Use of a modified oligonucleotide in the manufacture of a medicament for treating Angelman syndrome, wherein the modified oligonucleotide is:

a. a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 5), or a pharmaceutically acceptable salt thereof;

b. a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 5), or

c. a modified oligonucleotide consisting of 19-20 linked nucleosides, wherein the modified oligonucleotide comprises at least 19 contiguous nucleosides of the following chemical notation (5' to 3'):

$A_{es} mC_{eo} mC_{eo} A_{eo} T_{eo} T_{ds} T_{ds} G_{ds} A_{ds} mC_{ds} mC_{ds} T_{ds} T_{ds} mC_{ds} T_{eo} T_{eo} A_{es} G_{es} mC_e$ (SEQ ID NO: 5), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribose sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage,

wherein the treatment of Angelman syndrome comprises administering a therapeutically effective amount of the modified oligonucleotide and the therapeutically effective amount is 5-150 mg.

174. The use of claim 173, wherein the therapeutically effective amount is any of 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, or 150 mg.

175. The use of claim 173, wherein the therapeutically effective amount is any of from 5 mg to 120 mg, from 5 mg to 115 mg, from 5 mg to 110 mg, from 5 mg to 105 mg, from 5 mg to 100 mg, from 5 mg to 95 mg, from 5 mg to 90 mg, from 5 mg to 85 mg, from 5 mg to 80 mg, from 5 mg to 75 mg, from 5 mg to 70 mg, from 5 mg to 65 mg, from 5 mg to 60 mg, from 5 mg to 55 mg, from 5 mg to 50 mg, from 5 mg to 45 mg, from 5 mg to 40 mg, from 5 mg to 35 mg, from 5 mg to 30 mg, from 5 mg to 25 mg, from 5 mg to 20 mg, from 5 mg to 15 mg, from 5 mg to 10 mg, from 10 mg to 120 mg, from 10 mg to 115 mg, from 10 mg to 110 mg, from 10 mg to 105 mg, from 10 mg to 100 mg, from 10 mg to 95 mg, from 10 mg to 90 mg, from 10 mg to 85 mg, from 10 mg to 80 mg, from 10 mg to 75 mg, from 10 mg to 70 mg, from 10 mg to 65 mg, from 10 mg to 60 mg, from 10 mg to 55 mg, from 10 mg to 50 mg, from 10 mg to 45 mg, from 10 mg to 40 mg, from 10 mg to 35 mg, from 10 mg to 30 mg, from 10 mg to 25 mg, from 10 mg to 20 mg, from 10 mg to 15 mg, from 15 mg to 120 mg, from 15 mg to 115 mg, from 15 mg to 110 mg, from 15 mg to 105 mg, from 15 mg to 100 mg, from 15 mg to 95 mg, from 15 mg to 90 mg, from 15 mg to 85 mg, from 15 mg to 80 mg, from 15 mg to 75 mg, from 15 mg to 70 mg, from 15 mg to 65 mg, from 15 mg to 60 mg, from 15 mg to 55 mg, from 15 mg to 50 mg, from 15 mg to 45 mg, from 15 mg to 40 mg, from 15 mg to 35 mg, from 15 mg to 30 mg, from 15 mg to 25 mg, from 15 mg to 20 mg, from 20 mg to 120 mg, from 20 mg to 115 mg, from 20 mg to 110 mg, from 20 mg to 105 mg, from 20 mg to 100 mg, from 20 mg to 95 mg, from 20 mg to 90 mg, from 20 mg to 85 mg, from 20 mg to 80 mg, from 20 mg to 75 mg, from 20 mg to 70 mg, from 20 mg to 65 mg, from 20 mg to 60 mg, from 20 mg to 55 mg, from 20 mg to 50 mg, from 20 mg to 45 mg, from 20 mg to 40 mg, from 20 mg to 35 mg, from 20 mg to 30 mg, from 20 mg to 25 mg, from 25 mg to 120 mg, from 25 mg to 115 mg, from 25 mg to 110 mg, from 25 mg to 105 mg, from 25 mg to 100 mg, from 25 mg to 95 mg, from 25 mg to 90 mg, from 25 mg to 85 mg, from 25 mg to 80 mg, from 25 mg to 75 mg, from 25 mg to 70 mg, from 25 mg to 65 mg, from 25 mg to 60 mg, from 25 mg to 55 mg, from 25 mg to 50 mg, from 25 mg to 45 mg, from 25 mg to 40 mg, from 25 mg to 35 mg, from 25 mg to 30 mg, from 30 mg to 120 mg, from 30 mg to 115 mg, from 30 mg to 110 mg, from 30 mg to 105 mg, from 30 mg to 100 mg, from 30 mg to 95 mg, from 30 mg to 90 mg, from 30 mg to 85 mg, from 30 mg to 80 mg, from 30 mg to 75 mg, from 30 mg to 70 mg, from 30 mg to 65 mg, from 30 mg to 60 mg, from 30 mg to 55 mg, from 30 mg to 50 mg, from 30 mg to 45 mg, from 30 mg to 40 mg, from 30 mg to 35 mg, from 35 mg to 120 mg, from 35 mg to 115 mg, from 35 mg to 110 mg, from 35 mg to 105 mg, from 35 mg to 100 mg, from 35 mg to 95 mg, from 35 mg to 90 mg, from 35 mg to 85 mg, from 35 mg to 80 mg, from 35 mg to 75 mg, from 35 mg to 70 mg, from 35 mg to 65 mg, from 35 mg to 60 mg, from 35 mg to 55 mg, from 35 mg to 50 mg, from 35 mg to 45 mg, from 35 mg to 40 mg, from 40 mg to 120 mg, from 40 mg to 115 mg, from 40 mg to 110 mg, from 40 mg to 105 mg, from 40 mg to 100 mg, from 40 mg to 95 mg, from 40 mg to 90 mg, from 40 mg to 85 mg, from 40 mg to 80 mg, from 40 mg to 75 mg, from 40 mg to 70 mg, from 40 mg to 65 mg, from 40 mg to 60 mg, from 40 mg to 55 mg, from 40 mg to 50 mg, from 40 mg to 45 mg, from 45 mg to 120 mg, from 45 mg to 115 mg, from 45 mg to 110 mg, from 45 mg to 105 mg, from 45 mg to 100 mg, from 45 mg to 95 mg, from 45 mg to 90 mg, from 45 mg to 85 mg, from 45 mg to 80 mg, from 45 mg to 75 mg, from 45 mg to 70 mg, from 45 mg to 65 mg, from 45 mg to 60 mg, from 45 mg to 55 mg.

from 45 mg to 50 mg, from 50 mg to 120 mg, from 50 mg to 115 mg, from 50 mg to 110 mg, from 50 mg to 105 mg, from 50 mg to 100 mg, from 50 mg to 95 mg, from 50 mg to 90 mg, from 50 mg to 85 mg, from 50 mg to 80 mg, from 50 mg to 75 mg, from 50 mg to 70 mg, from 50 mg to 65 mg, from 50 mg to 60 mg, from 50 mg to 120 mg, from 55 mg to 115 mg, from 55 mg to 110 mg, from 55 mg to 105 mg, from 55 mg to 100 mg, from 55 mg to 95 mg, from 55 mg to 90 mg, from 55 mg to 85 mg, from 55 mg to 80 mg, from 55 mg to 75 mg, from 55 mg to 70 mg, from 55 mg to 65 mg, from 55 mg to 60 mg, from 60 mg to 120 mg, from 60 mg to 115 mg, from 60 mg to 110 mg, from 60 mg to 105 mg, from 60 mg to 100 mg, from 60 mg to 95 mg, from 60 mg to 90 mg, from 60 mg to 85 mg, from 60 mg to 80 mg, from 60 mg to 75 mg, from 60 mg to 70 mg, from 65 mg to 120 mg, from 65 mg to 115 mg, from 65 mg to 110 mg, from 65 mg to 105 mg, from 65 mg to 100 mg, from 65 mg to 95 mg, from 65 mg to 90 mg, from 65 mg to 85 mg, from 65 mg to 80 mg, from 65 mg to 75 mg, from 65 mg to 70 mg, from 70 mg to 120 mg, from 70 mg to 115 mg, from 70 mg to 110 mg, from 70 mg to 105 mg, from 70 mg to 100 mg, from 70 mg to 95 mg, from 70 mg to 90 mg, from 70 mg to 85 mg, from 70 mg to 80 mg, from 75 mg to 120 mg, from 75 mg to 115 mg, from 75 mg to 110 mg, from 75 mg to 105 mg, from 75 mg to 100 mg, from 75 mg to 95 mg, from 75 mg to 90 mg, from 75 mg to 85 mg, from 75 mg to 80 mg, from 80 mg to 120 mg, from 80 mg to 115 mg, from 80 mg to 110 mg, from 80 mg to 105 mg, from 80 mg to 100 mg, from 80 mg to 95 mg, from 80 mg to 90 mg, from 85 mg to 120 mg, from 85 mg to 115 mg, from 85 mg to 110 mg, from 85 mg to 105 mg, from 85 mg to 100 mg, from 85 mg to 95 mg, from 85 mg to 90 mg, from 90 mg to 120 mg, from 90 mg to 115 mg, from 90 mg to 110 mg, from 90 mg to 105 mg, from 90 mg to 100 mg, from 95 mg to 120 mg, from 95 mg to 115 mg, from 95 mg to 110 mg, from 95 mg to 105 mg, from 95 mg to 100 mg, from 100 mg to 120 mg, from 100 mg to 115 mg, from 100 mg to 110 mg, from 100 mg to 105 mg, from 105 mg to 120 mg, from 105 mg to 115 mg, from 105 mg to 110 mg, from 110 mg to 120 mg, from 110 mg to 115 mg, and from 115 mg to 120 mg.

176. The use of claim 173, wherein the therapeutically effective amount is any of 15 mg to 25 mg, from 18 mg to 25 mg, from 19 mg to 25 mg, from 18 mg to 23 mg, from 19 mg to 23 mg, from 18 mg to 22 mg, from 19 mg to 22 mg, from 18 mg to 21 mg, or from 19 mg to 21 mg.

177. The use of claim 173, wherein the therapeutically effective amount is any of 35 mg to 45 mg, from 38 mg to 45 mg, from 39 mg to 45 mg, from 38 mg to 43 mg, from 39 mg to 43 mg, from 38 mg to 42 mg, from 39 mg to 42 mg, from 38 mg to 41 mg, or from 39 mg to 41 mg.

178. The use of claim 173, wherein the therapeutically effective amount is any of from 55 mg to 65 mg, from 58 mg to 65 mg, from 59 mg to 65 mg, from 58 mg to 63 mg, from 59 mg to 63 mg, from 58 mg to 62 mg, from 59 mg to 62 mg, from 58 mg to 61 mg, or from 59 mg to 61 mg.

179. The use of claim 173, wherein the therapeutically effective amount is any of from 75 mg to 85 mg, from 78 mg to 85 mg, from 79 mg to 85 mg, from 78 mg to 83 mg, from 79 mg to 83 mg, from 78 mg to 82 mg, from 79 mg to 82 mg, from 78 mg to 81 mg, or from 79 mg to 81 mg.

180. The use of claim 173, wherein the therapeutically effective amount is about 5 mg.

181. The use of claim 173, wherein the therapeutically effective amount is about 10 mg.

182. The use of claim 173, wherein the therapeutically effective amount is about 20 mg.

183. The use of claim 173, wherein the therapeutically effective amount is about 30 mg.

184. The use of claim 173, wherein the therapeutically effective amount is about 40 mg.

185. The use of claim 173, wherein the therapeutically effective amount is about 50 mg.

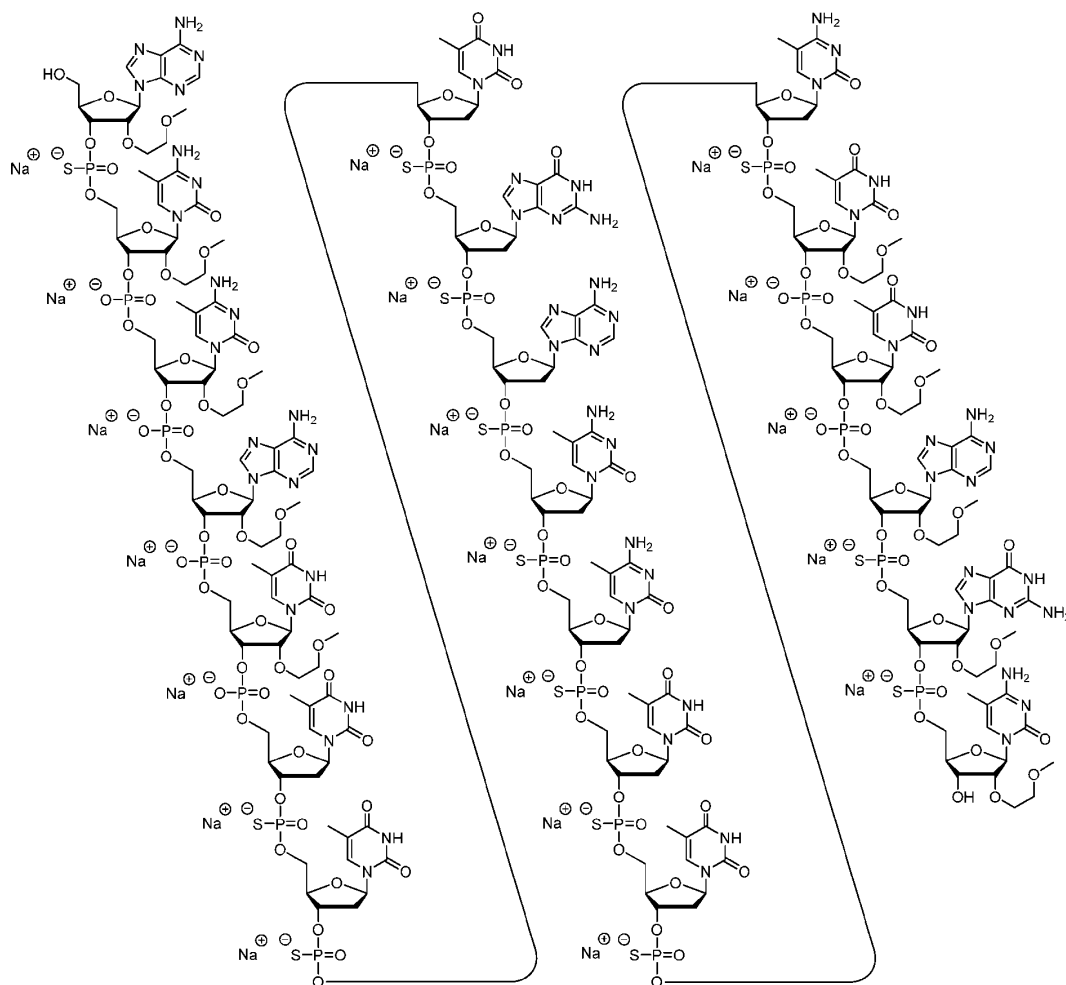
186. The use of claim 173, wherein the therapeutically effective amount is about 60 mg.

187. The use of claim 173, wherein the therapeutically effective amount is about 70 mg.
188. The use of claim 173, wherein the therapeutically effective amount is about 80 mg.
189. The use of claim 173, wherein the therapeutically effective amount is about 90 mg.
190. The use of claim 173, wherein the therapeutically effective amount is about 100 mg.
191. The use of claim 173, wherein the therapeutically effective amount is about 110 mg.
192. The use of claim 173, wherein the therapeutically effective amount is about 120 mg.
193. The use of claim 173, wherein the therapeutically effective amount is 4-6 mg.
194. The use of claim 173, wherein the therapeutically effective amount is 9-11 mg.
195. The use of claim 173, wherein the therapeutically effective amount is 19-21 mg.
196. The use of claim 173, wherein the therapeutically effective amount is 29-31 mg.
197. The use of claim 173, wherein the therapeutically effective amount is 39-41 mg.
198. The use of claim 173, wherein the therapeutically effective amount is 48-52 mg.
199. The use of claim 173, wherein the therapeutically effective amount is 58-62 mg.
200. The use of claim 173, wherein the therapeutically effective amount is 68-72 mg.
201. The use of claim 173, wherein the therapeutically effective amount is 78-82 mg.
202. The use of claim 173, wherein the therapeutically effective amount is 88-92 mg.
203. The use of claim 173, wherein the therapeutically effective amount is 98-102 mg.
204. The use of claim 173, wherein the therapeutically effective amount is 108-112 mg.
205. The use of claim 173, wherein the therapeutically effective amount is 118-122 mg.
206. The use of any of claims 173-205, wherein the medicament is formulated for administration once every 28 days.
207. The use of any of claims 173-205, wherein the medicament is formulated for administration once every 56 days.
208. The use of any of claims 173-205, wherein the wherein the medicament is formulated for administration once every 84 days.
209. The use of any of claims 173-205, wherein the medicament is formulated for administration once every 4, 8, 10, 12, 16, 18, 20, 24, 28, or 32 weeks.
210. The use of any of claims 173-205, wherein the medicament is formulated for administration once every 4 weeks.
211. The use of any of claims 173-205, wherein the medicament is formulated for administration once every 8 weeks.
212. The use of any of claims 173-205, wherein the medicament is formulated for administration once every 12 weeks.
213. The use of any of claims 173-205, wherein the medicament is formulated for administration once every 16 weeks.
214. The use of any of claims 173-205, wherein the medicament is formulated for administration once every 20 weeks.
215. The use of any of claims 173-205, wherein the medicament is formulated for administration once every 24 weeks.

216. The use of any of claims 173-205, wherein the medicament is formulated for administration once monthly.
217. The use of any of claims 173-205, wherein the medicament is formulated for administration once every two months.
218. The use of any of 173-205, wherein the medicament is formulated for administration once every four months.
219. The use of any of claims 173-205, wherein the medicament is formulated for administration once every five months.
220. The use of any of claims 173-205, wherein the medicament is formulated for administration once every six months.
221. The use of any of claims 173-205, wherein the medicament is formulated for administration once quarterly.
222. The use of any of claims 173-205, wherein the medicament is formulated for administration once triannually.
223. The use of any of claims 173-205, wherein the therapeutically effect amount is 20 mg of the modified oligonucleotide and the medicament is formulated for administration once every four weeks.
224. The use of any of claims 173-205, wherein the therapeutically effect amount is 40 mg of the modified oligonucleotide and the medicament is formulated for administration once every four weeks.
225. The use of any of claims 173-205, wherein the therapeutically effect amount is 60 mg of the modified oligonucleotide and the medicament is formulated for administration once every four weeks.
226. The use of any of claims 173-205, wherein the therapeutically effect amount is 80 mg of the modified oligonucleotide and the medicament is formulated for administration once every four weeks.
227. The use of any of claims 173-205, wherein the therapeutically effect amount is 20 mg of the modified oligonucleotide and the medicament is formulated for administration once every eight weeks.
228. The use of any of claims 173-205, wherein the therapeutically effect amount is 40 mg of the modified oligonucleotide and the medicament is formulated for administration once every eight weeks.
229. The use of any of claims 173-205, wherein the therapeutically effect amount is 60 mg of the modified oligonucleotide and the medicament is formulated for administration once every eight weeks.
230. The use of any of claims 173-205, wherein the therapeutically effect amount is 80 mg of the modified oligonucleotide and the medicament is formulated for administration once every eight weeks.
231. The use of any of claims 173-205, wherein the therapeutically effect amount is 20 mg of the modified oligonucleotide and the medicament is formulated for administration once every twelve weeks.
232. The use of any of claims 173-205, wherein the therapeutically effect amount is 40 mg of the modified oligonucleotide and the medicament is formulated for administration once every twelve weeks.
233. The use of any of claims 173-205, wherein the therapeutically effect amount is 60 mg of the modified oligonucleotide and the medicament is formulated for administration once every twelve weeks.
234. The use of any of claims 173-205, wherein the therapeutically effect amount is 80 mg of the modified oligonucleotide and the medicament is formulated for administration once every twelve weeks.
235. The use of any of claims 173-205, wherein the therapeutically effect amount is 20 mg of the modified oligonucleotide and the medicament is formulated for administration once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.

236. The use of any of claims 173-205, wherein the therapeutically effect amount is 40 mg of the modified oligonucleotide and the medicament is formulated for administration once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.
237. The use of any of claims 173-205, wherein the therapeutically effect amount is 60 mg of the modified oligonucleotide and the medicament is formulated for administration once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.
238. The use of any of claims 173-205, wherein the therapeutically effect amount is 80 mg of the modified oligonucleotide and the medicament is formulated for administration once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 8 months, once quarterly, once triannually, once semiannually, once annually, three times a year, or four times a year.
239. The use of any of claims 173-227, wherein the medicament is formulated for intrathecal administration.
240. The use of any of claims 173-228, wherein the medicament is formulated for administration to a human subject less than 18 years of age, less than 15 years of age, less than 13 years of age, less than 10 years of age, less than 8 years of age, or less than 5 years of age.
241. The use of claim 240, wherein the human subject is from 2 years of age up to 5 years of age, from 4 years of age up to 17 years of age, or from 1 years of age up to 17 years of age.
242. The use of claim 240, wherein the human subject is 13 years of age or older, or 18 years of age or older.
243. The use of claim 240, wherein the human subject is from 18 years of age to 50 years of age.
244. The use of any of claims 1-146, wherein the human subject is 18 years of age or older.
245. The use of claim 240, wherein the human subject is 17 years of age or younger.
246. The use of any of claims 173-245, wherein the modified oligonucleotide is formulated as a pharmaceutical composition comprising a pharmaceutically acceptable diluent.
247. The use of claim 246, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF).
248. The use of claim 246, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS).

b. a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 5), or

c. a modified oligonucleotide consisting of 19-20 linked nucleosides, wherein the modified oligonucleotide comprises at least 19 contiguous nucleosides of the following chemical notation (5' to 3'):

$A_{es}^m C_{eo}^m C_{eo}^m A_{eo} T_{es} T_{ds} T_{ds} G_{ds} A_{es}^m C_{ds}^m C_{ds}^m T_{ds}^m C_{ds}^m T_{es} T_{es} A_{es} G_{es}^m C_e$ (SEQ ID NO: 5), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribsyl sugar moiety,

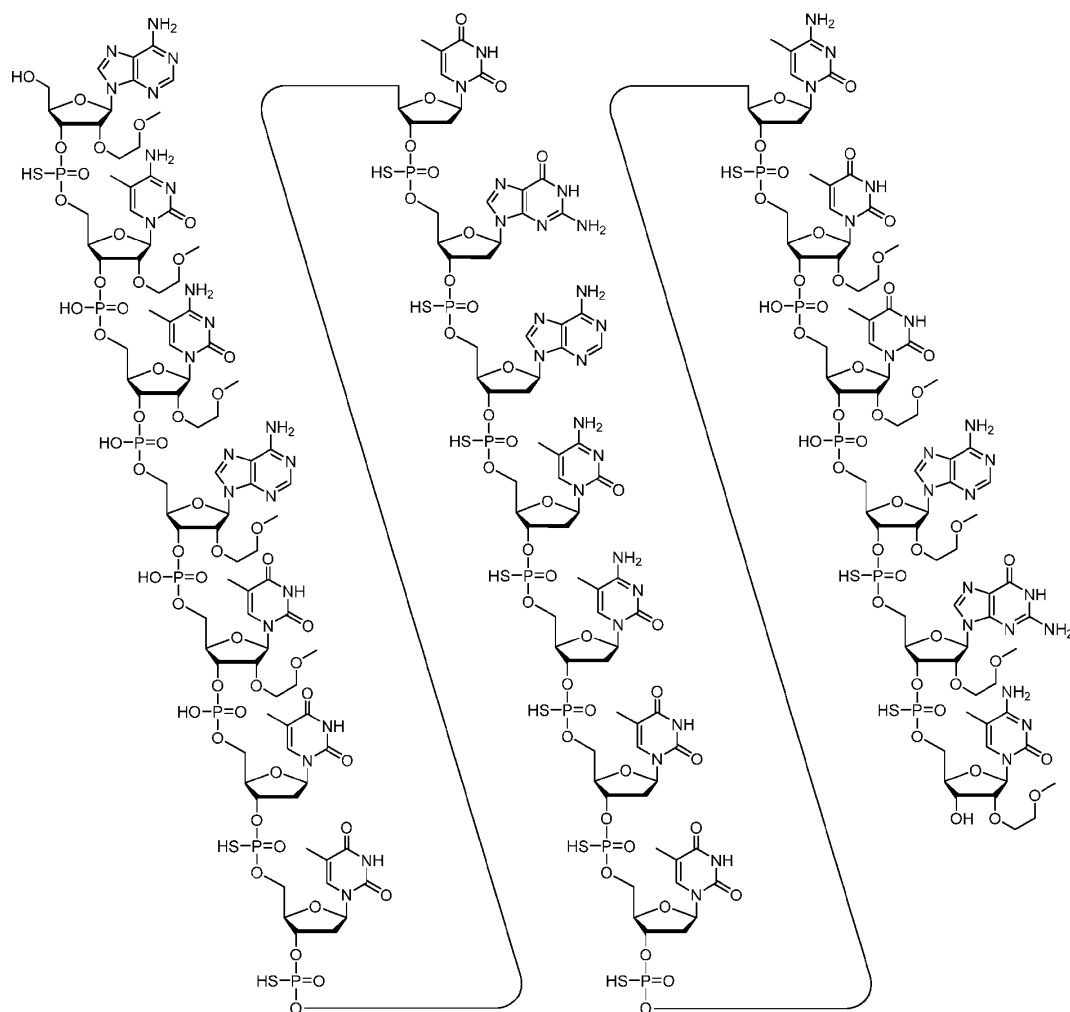
s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage,

wherein the therapeutically effective amount is 40 mg and the therapeutically effective amount is administered quarterly.

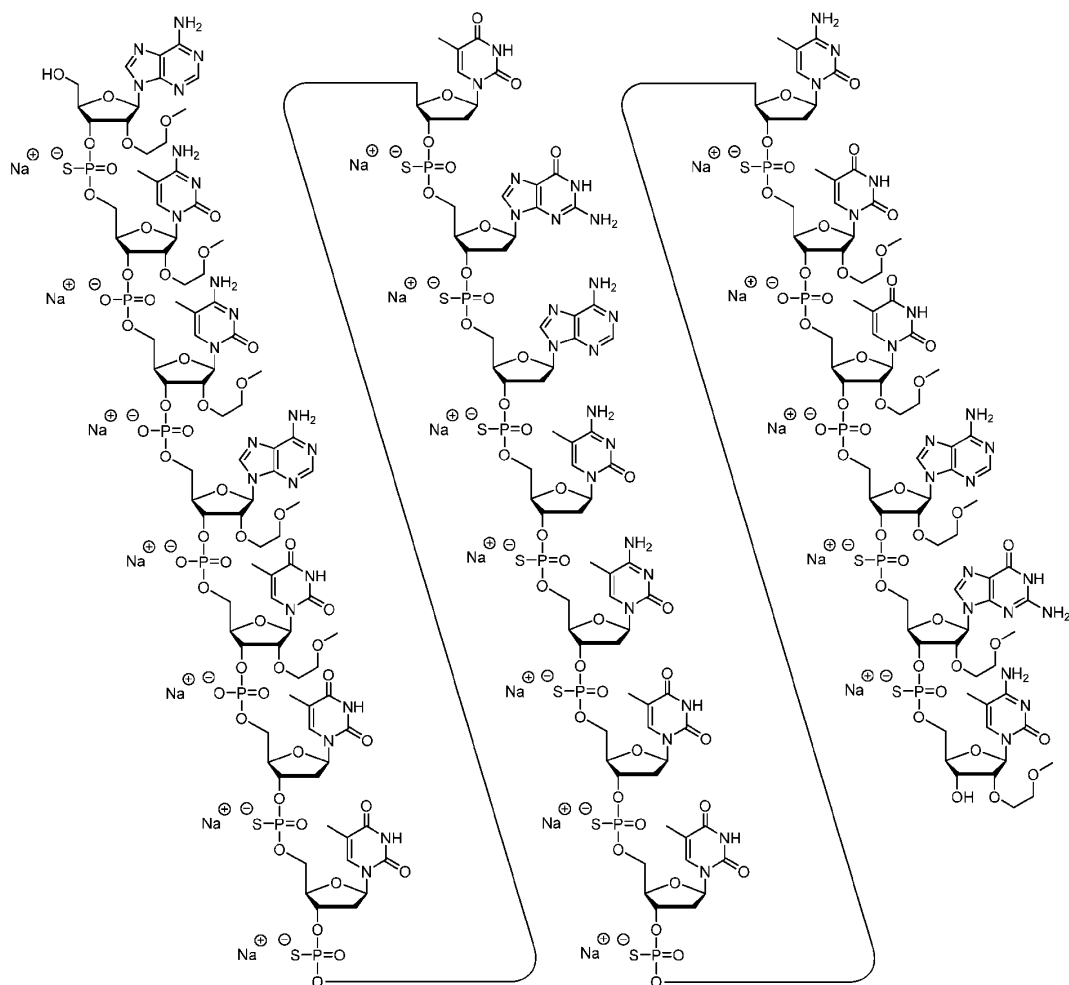
250. A method for treating Angelman syndrome comprising administering to a human having Angelman syndrome a therapeutically effective amount of a modified oligonucleotide, wherein the modified oligonucleotide is:

a) a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 5), or a pharmaceutically acceptable salt thereof.

- b) a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 5), or

- c) a modified oligonucleotide consisting of 19-20 linked nucleosides, wherein the modified oligonucleotide comprises at least 19 contiguous nucleosides of the following chemical notation (5' to 3'):

$A_{es}^m C_{eo}^m C_{eo}^m A_{eo} T_{eo} T_{ds} T_{ds} T_{ds} G_{ds} A_{ds}^m C_{ds}^m C_{ds}^m T_{ds} T_{ds}^m C_{ds} T_{eo} T_{eo} A_{es} G_{es}^m C_e$ (SEQ ID NO: 5), wherein:

A = an adenine nucleobase,

$^m C$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribsyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage,

wherein the therapeutically effective amount is 80 mg and the therapeutically effective amount is administered quarterly.

251. The method of claim 249 or 250, wherein at least one symptom or hallmark of Angelman syndrome is ameliorated.

252. The method of claim 251, wherein at least one symptom or hallmark is selected from developmental delays, ataxia, cognitive impairment, impairments in fine and/or gross motor skills, speech impairment, impairment in receptive communication and/or expressive communication, impairment in daily living skills, impaired socialization skills, sleep problems, seizures, and EEG abnormalities.

253. The method of claim 251, wherein the symptom or hallmark is developmental delays, ataxia, speech impairment, sleep problems, seizures, or EEG abnormalities.

254. The method of claim 251 wherein the at least one symptom or hallmark is cognitive impairment.

255. The method of claim 251 wherein the at least one symptom or hallmark is fine motor skills.

256. The method of claim 251 wherein the at least one symptom or hallmark is gross motor skills.

257. The method of claim 251 wherein the at least one symptom or hallmark is receptive communication.

258. The method of claim 251 wherein the at least one symptom or hallmark is expressive communication.

259. The method of claim 251 wherein the at least one symptom or hallmark is impairment in daily living skills.

260. The method of claim 251 wherein the at least one symptom or hallmark is impairment in socialization skills.

261. The method of claim 251 wherein the at least one symptom or hallmark is sleep problems.