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(54) **Titre : PROCÉDES DE TRAITEMENT POUR DYSTROPHIE MUSCULAIRE**
(54) **Title: TREATMENT METHODS FOR MUSCULAR DYSTROPHY**

(57) **Abrégé/Abstract:**

New dosing regimens for treating muscular dystrophy in a patient suffering from Duchenne muscular dystrophy (DMD) with an antisense oligonucleotide conjugate that causes skipping of an exon in the human dystrophin gene are described. Also described is a method of treating a patient with an antisense oligomer CPP conjugate and a magnesium supplement.



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(57) Abstract: New dosing regimens for treating muscular dystrophy in a patient suffering from Duchenne muscular dystrophy (DMD) with an antisense oligonucleotide conjugate that causes skipping of an exon in the human dystrophin gene are described. Also described is a method of treating a patient with an antisense oligomer CPP conjugate and a magnesium supplement.



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TREATMENT METHODS FOR MUSCULAR DYSTROPHY

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Number 63/182,327, filed on April 30, 2021 and U.S. Provisional Application Number 63/249,721, filed on September 29, 2021. The entire teachings of the above-referenced applications are incorporated by reference in their entirety.

REFERENCE TO A SEQUENCE LISTING SUBMITTED ELECTRONICALLY VIA EFS-WEB

[0002] The content of the electronically submitted sequence listing in ASCII text file (Name: 4140_0510002_Seqlisting_ST25; Size: 223,634 bytes; and Date of Creation: April 12, 2022) is herein incorporated by reference in its entirety.

FIELD OF THE DISCLOSURE

[0003] The present disclosure relates to new dosing regimens for treating muscular dystrophy in a patient suffering from Duchenne muscular dystrophy (DMD) with an antisense oligonucleotide conjugate that causes skipping of an exon in the human dystrophin gene. It also provides methods for reducing toxicity associated with the treatments involving antisense oligonucleotide CPP conjugates.

BACKGROUND OF THE DISCLOSURE

[0004] Dystrophin is a critical structural protein that protects muscle from repeated strain-induced injury, affecting skeletal, diaphragmatic, and cardiac muscles. Duchenne muscular dystrophy is a rare, serious, life-threatening, X-linked recessive degenerative neuromuscular disease caused by mutations in the dystrophin gene. These mutations disrupt the reading frame of dystrophin messenger ribonucleic acid (mRNA), preventing the translation of functional dystrophin protein. Any exonic mutation that changes the reading frame of the

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exon, or introduces a stop codon, or is characterized by removal of an entire out of frame exon or exons, or duplications of one or more exons, has the potential to disrupt production of functional dystrophin, resulting in DMD. The absence of dystrophin protein is the direct cause of the disease and patients follow a predictable disease course with a relentlessly progressive deterioration of skeletal muscle function from early childhood leading to premature death, usually before 30 years of age.

[0005] Duchenne muscular dystrophy (DMD) is caused by a defect in the expression of the protein dystrophin. The gene encoding the protein contains 79 exons spread out over more than 2 million nucleotides of DNA. Any exonic mutation that changes the reading frame of the exon, or introduces a stop codon, or is characterized by removal of an entire out of frame exon or exons, or duplications of one or more exons, has the potential to disrupt production of functional dystrophin, resulting in DMD.

[0006] A less severe form of muscular dystrophy, Becker muscular dystrophy (BMD) has been found to arise where a mutation, typically a deletion of one or more exons, results in a correct reading frame along the entire dystrophin transcript, such that translation of mRNA into protein is not prematurely terminated. If the joining of the upstream and downstream exons in the processing of a mutated dystrophin pre-mRNA maintains the correct reading frame of the gene, the result is an mRNA coding for a protein with a short internal deletion that retains some activity, resulting in a BMD phenotype.

[0007] For many years it has been known that deletions of an exon or exons which do not alter the reading frame of a dystrophin protein would give rise to a BMD phenotype, whereas an exon deletion that causes a frame-shift will give rise to DMD (Monaco, Bertelson et al. 1988). In general, dystrophin mutations including point mutations and exon deletions that change the reading frame and thus interrupt proper protein translation result in DMD. It should also be noted that some BMD and DMD patients have exon deletions covering multiple exons.

[0008] Antisense oligonucleotides, e.g., splice switching oligonucleotides (SSOs), have been successfully used for the treatment of DMD to induce alternative splicing of pre-mRNAs by steric blockade of the spliceosome. SSOs have been specifically designed to target specific regions of the pre-mRNA, typically exons to induce the skipping of a mutation of the DMD

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gene thereby restoring these out-of-frame mutations in-frame to enable the production of internally shortened, yet functional dystrophin protein. Such antisense oligomers have been known to target completely within the exon (so called exon internal sequences) or at a splice donor or splice acceptor junction that crosses from the exon into a portion of the intron.

[0009] For example, eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to skip exon 51 of the human dystrophin gene in patients with DMD who are amenable to exon 51 skipping to restore the read frame and produce a functional shorter form of the dystrophin protein. The United States Food and Drug Administration (FDA) approved in 2016 Exondys 51[®] (eteplirsen) for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. For another example, golodirsen (Vyondys 53[®]), also an antisense oligonucleotide of the PMO subclass, has been recently approved for the treatment of DMD in patients with a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.

[0010] The discovery and development of antisense oligomers conjugated to cell-penetrating peptides (e.g., PPMOs) for DMD has also been an area of research (*see, e.g.*, U.S. Patent No. 10,888,578; U.S. Application No. 16/469,104; U.S. Application No. 16/001,310). Cell-penetrating peptides (CPP), for example, an arginine-rich peptide transport moiety, have been shown to be effective in enhancing penetration of antisense oligomers into a cell and to cause exon skipping in different muscle groups in animal models. To date, however, the relationship between human systemic exposure to dose levels of antisense oligomer conjugates (e.g., PPMOs) has not been established.

[0011] Magnesium deficiency (or hypomagnesemia) is an electrolyte disturbance in which there is a low level of magnesium in the body. Causes of hypomagnesemia can include exposure to certain drugs. Hypomagnesemia can result in multiple symptoms. Symptoms include tremor, poor coordination, muscle spasms, loss of appetite, personality changes, and nystagmus. Complications may include seizures or cardiac arrest such as from torsade de pointes. Those with low magnesium often have low potassium.

[0012] The diagnosis of hypomagnesemia is typically based on finding low blood magnesium levels. Normal magnesium levels can fluctuate between about 0.6 to about 1.1 mmol/L (about 1.5 to about 2.7 mg/dL) with levels less than about 0.6 mmol/L

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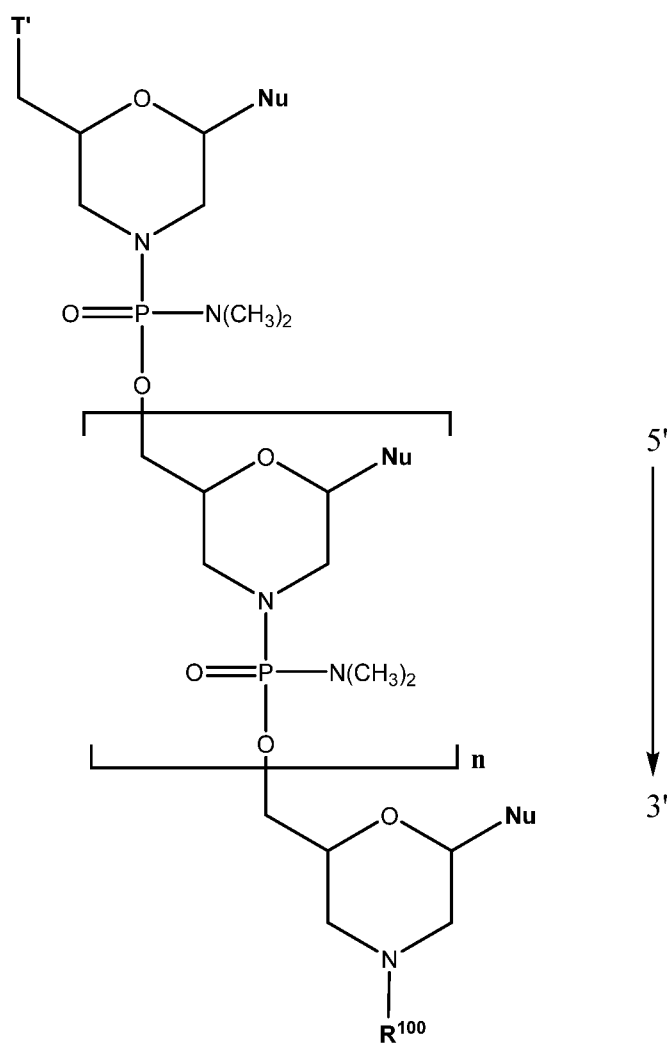
(about 1.5 mg/dL) usually defining hypomagnesemia. The effects of antisense oligomer conjugates, such as PPMOs, on magnesium levels of patients, including DMD patients, receiving PPMO therapy is not known.

[0013] Thus, despite the successes achieved in pre-clinical models with antisense oligomers conjugated to cell-penetrating peptides, the need remains for a safe and effective dosing paradigm for treating DMD and BMD with such conjugates in human patients.

SUMMARY OF THE DISCLOSURE

[0014] In some aspects, the disclosure relates to a method of treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation that is amenable to exon skipping, comprising administering to the patient an antisense oligomer conjugate of Formula (I):

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(I),

or a pharmaceutically acceptable salt thereof,

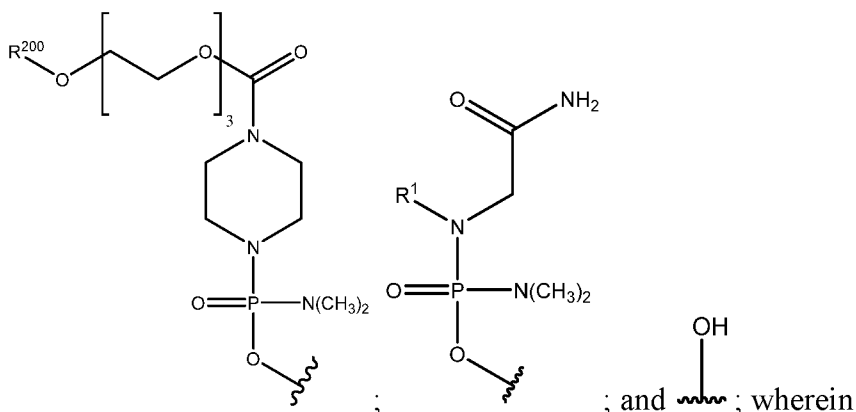
wherein:

n is 1-40;

each Nu is a nucleobase, which, taken together, form a targeting sequence complementary to an exon annealing site in the dystrophin pre-mRNA;

T' is a moiety selected from:

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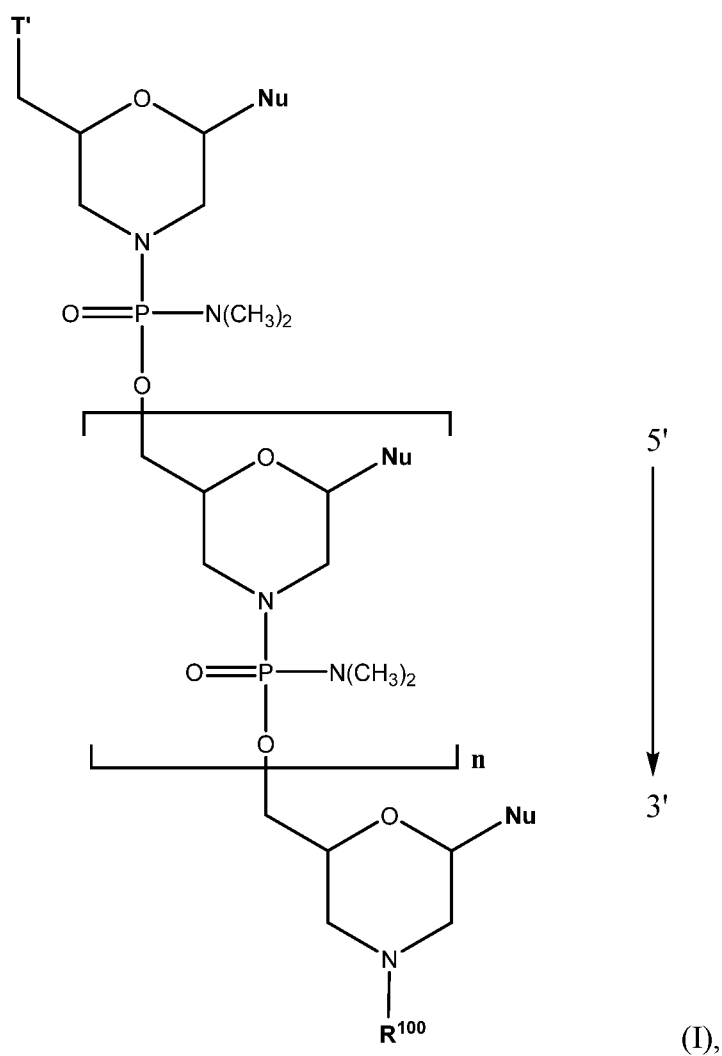
[0015] R^{100} a cell-penetrating peptide, R^{200} is hydrogen, and R^1 is C_1 - C_6 alkyl,

[0016] and wherein the conjugate is administered in a dose effective to provide a mean area under the curve (AUC) of the conjugate, or the pharmaceutically acceptable salt thereof between about 100 and about 200 $\mu\text{g}\cdot\text{h/mL}$, between about 120 and about 240 $\mu\text{g}\cdot\text{h/mL}$, or between about 200 and about 500 $\mu\text{g}\cdot\text{h/mL}$.

[0017] In some aspects, R^{100} is a CPP, wherein the CPP is attached to the 3'-end of the oligomer by an amide bond at the CPP carboxy terminus. In other aspects, R^{100} is a substituent "Z," defined as the combination of a CPP and a linker that bridges the CPP at its carboxy terminus to the 3'-end of the oligonucleotide.

[0018] In some aspects, the present disclosure relates to a method of treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation that is amenable to exon 51 skipping, comprising administering to the patient an antisense oligomer conjugate of Formula (I):

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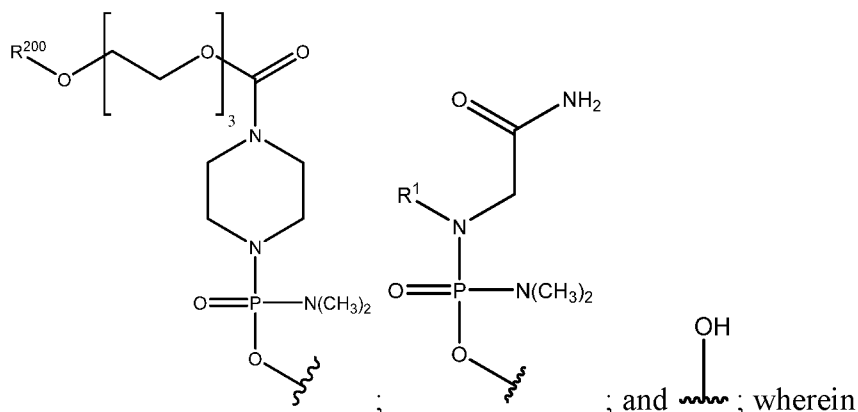
[0019] or a pharmaceutically acceptable salt thereof, wherein:

[0020] n is 1-40;

[0021] each **Nu** is a nucleobase, which, taken together, form a targeting sequence complementary to an exon annealing site in the dystrophin pre-mRNA;

[0022] **T'** is a moiety selected from:

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[0023] R^{100} a cell-penetrating peptide, R^{200} is hydrogen, and R^1 is C_1 - C_6 alkyl,

[0024] wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 1500 mg of the $\cdot 6HCl$ salt of the conjugate once every four weeks, to achieve a mean AUC of between about 100 and about 200 $ug \cdot h/mL$, between about 120 and about 240 $ug \cdot h/mL$, or between about 200 and about 500 $ug \cdot h/mL$.

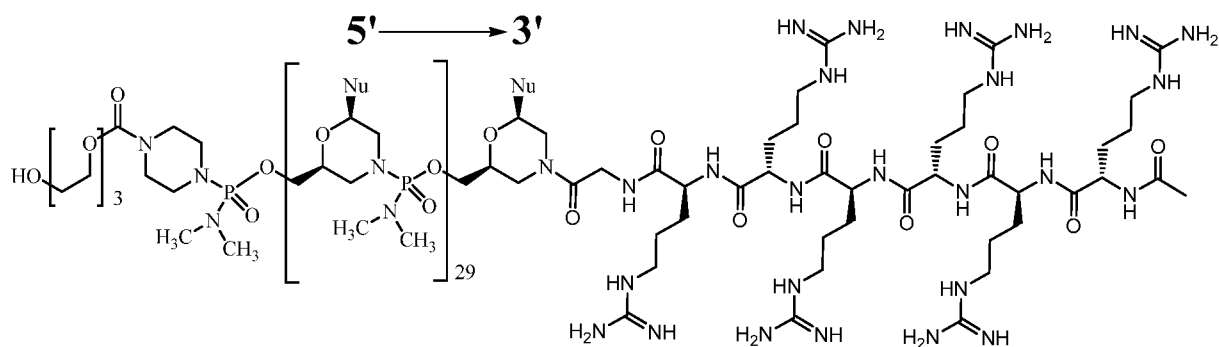
[0025] In some aspects, the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 1200 mg, about 300 mg to about 1000 mg, about 300 mg to about 750 mg, about 300 mg to about 500 mg, about 400 mg to about 1400 mg, about 400 mg to about 1100 mg, about 400 mg to about 900 mg, about 400 mg to about 600 mg, about 500 mg to about 1500 mg, about 500 mg to about 1300 mg, about 500 mg to about 1000 mg, about 500 mg to about 950 mg, about 500 mg to about 850 mg, about 500 mg to about 750 mg, about 500 mg to about 650 mg, about 600 mg to about 1400 mg, about 600 mg to about 1300 mg, about 600 mg to about 1200 mg, about 600 mg to about 1000, or about 600 mg to about 900 mg of the $\cdot 6HCl$ salt of the conjugate. In some aspects, the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a mean AUC of between about 100 and about 200 $ug \cdot h/mL$. In some aspects, the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a mean AUC of between about 120 and about 240 $ug \cdot h/mL$.

[0026] In certain aspects, the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a mean AUC of between about 200 and about 500 $ug \cdot h/mL$.

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- [0027] In certain aspects, the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, or about 900 mg of the $\cdot 6\text{HCl}$ salt of the conjugate.
- [0028] In some aspects, the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, or about 1500 mg of the $\cdot 6\text{HCl}$ salt of the conjugate.
- [0029] In some aspects, the cell-penetrating peptide is chosen from RXRRXRRXRRXR- (SEQ ID NO: 18), RFFRFFRFFR- (SEQ ID NO: 19), RXRRXRRXRRXRXB- (SEQ ID NO: 20), RFFRFFRFFRG- (SEQ ID NO: 21), RRRRRRG- (SEQ ID NO: 22), RRRRRR- (SEQ ID NO: 23), RRRRRG- (SEQ ID NO: 24), or RRRRR- (SEQ ID NO: 25), wherein R is arginine, X is 6-aminohexanoic acid, B is β -alanine, F is phenylalanine, and G is glycine.
- [0030] In other aspects, the cell-penetrating peptide is chosen from RRRRRRG- (SEQ ID NO: 22), RRRRRR- (SEQ ID NO: 23), RRRRRG- (SEQ ID NO: 24), or RRRRR- (SEQ ID NO: 25), wherein R is arginine and G is glycine. In one aspect, the cell-penetrating peptide is RRRRRRG- (SEQ ID NO: 22), wherein R is arginine and G is glycine.
- [0031] In some aspects, the antisense oligomer of the antisense oligomer conjugate has $n+2$ base pairs, where n in formula (I) is 1 to 40, optionally 13-38, optionally 13-28, optionally 13-23 or optionally 13-18. In other words, the oligomer is 15-40, 15-35, 15-30, 15-25, or 15-20 nucleotides in length.
- [0032] In some aspects, the antisense oligomer conjugate causes skipping of an exon in the human dystrophin gene. In some aspects, the exon is chosen from exon 44, 45, 50, 51, 52, or 53. In certain aspects, the exon is chosen from exon 45, 51, or 53.
- [0033] In certain aspects, the present disclosure provides a method of treating a patient with DMD in need thereof who has a mutation that is amenable to exon skipping, comprising administering to the patient an antisense oligomer conjugate of Formula (III):

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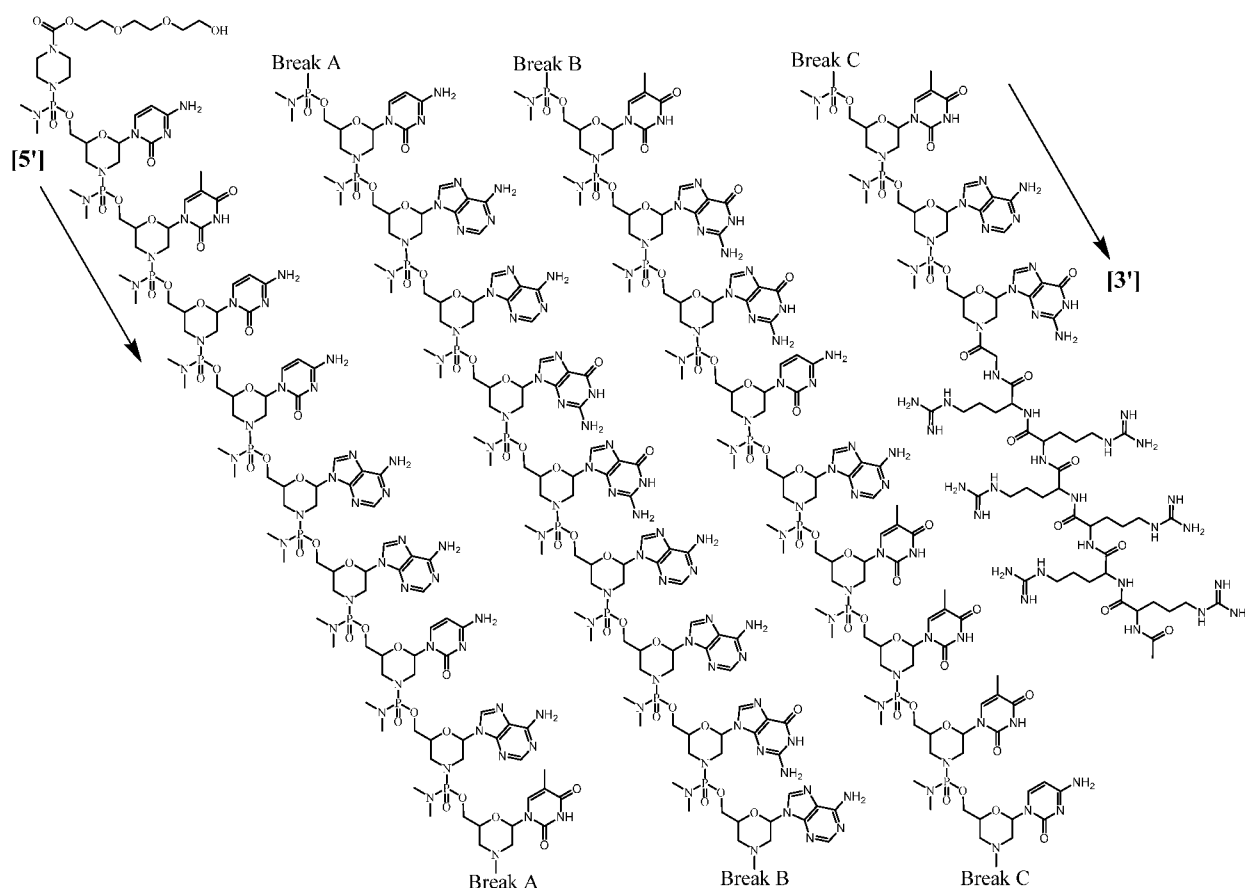


(III),

or a pharmaceutically acceptable salt thereof,

[0034] wherein each Nu is a nucleobase, which, taken together, form a targeting sequence that is complementary to an exon annealing site in the dystrophin pre-mRNA.

[0035] In some embodiments, the present disclosure provides a method of treating a patient with DMD in need thereof who has a mutation that is amenable to exon 51 skipping, comprising administering to the patient an antisense oligomer conjugate has Formula (IV):

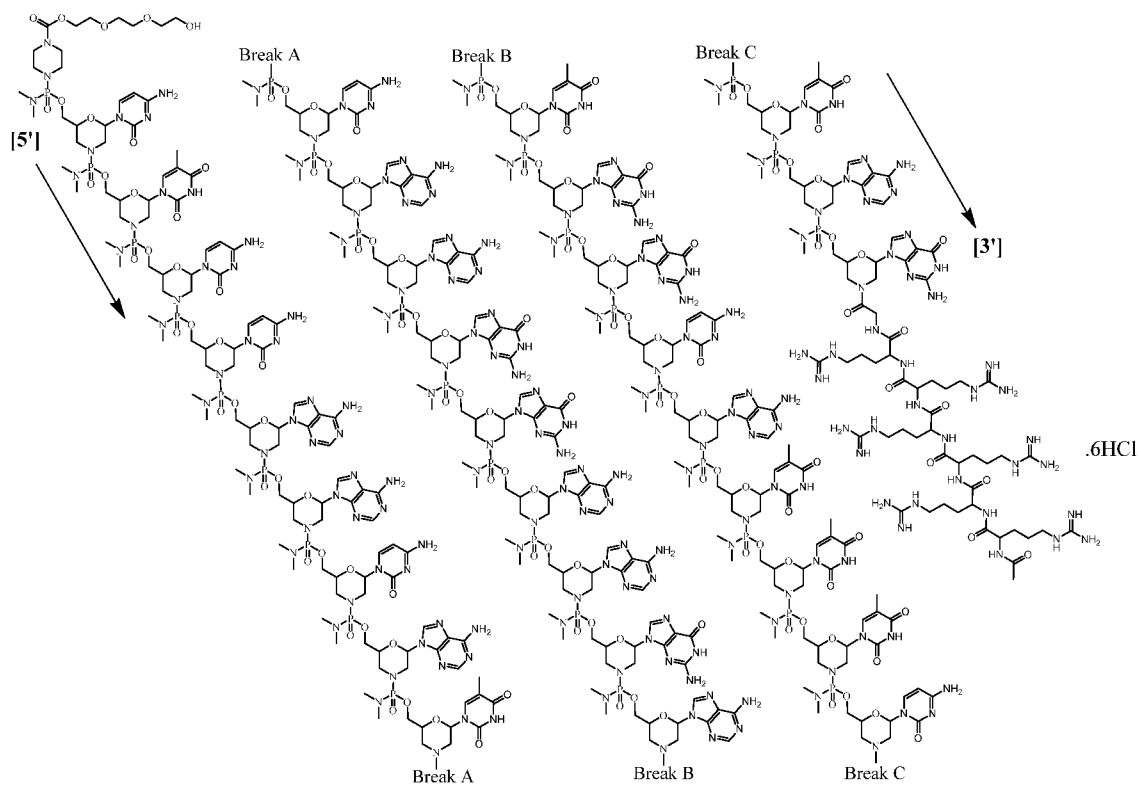


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(IV)

or a pharmaceutically acceptable salt thereof.

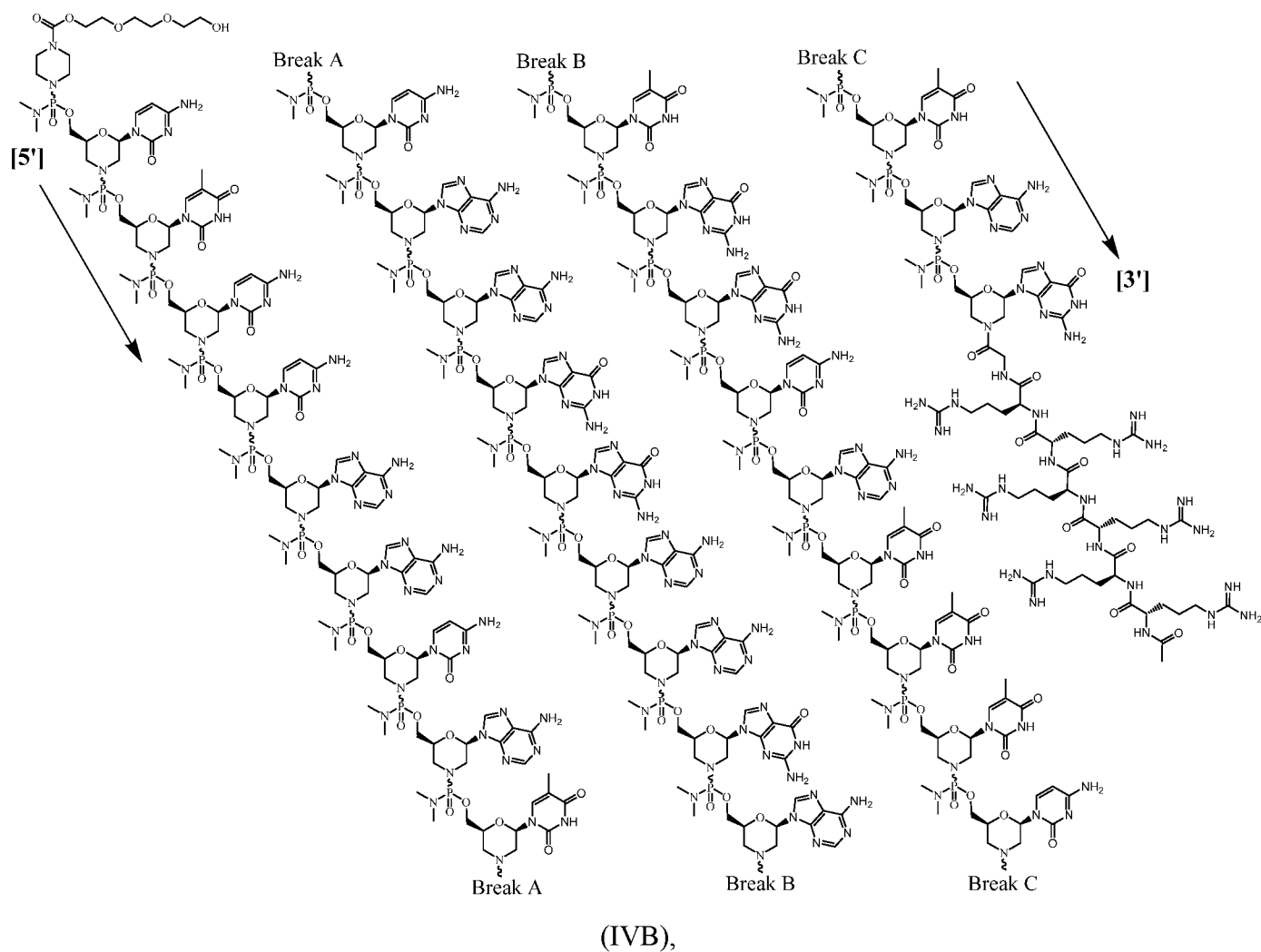
[0036] In other aspects, the antisense oligomer conjugate has Formula (IVA):



(IVA).

[0037] In some aspects, the antisense oligomer conjugate has Formula (IVB):

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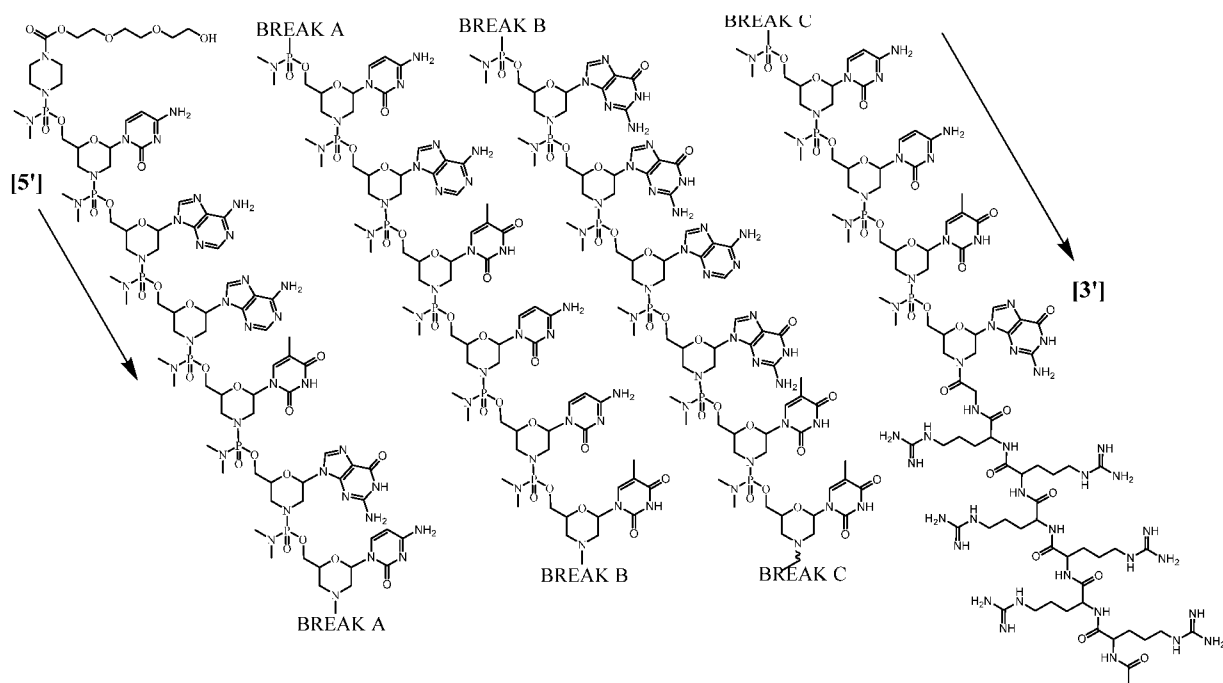


or a pharmaceutically acceptable salt thereof.

[0038] In some embodiments, an antisense oligomer conjugate of Formula (IVB) is an HCl (hydrochloric acid) salt thereof. In certain embodiments, the HCl salt is a $\cdot 6\text{HCl}$ salt.

[0039] Yet in other embodiments, the present disclosure provides a method of treating a patient with DMD in need thereof who has a mutation that is amenable to exon 45 skipping, comprising administering to the patient an antisense oligomer conjugate has Formula (VI):

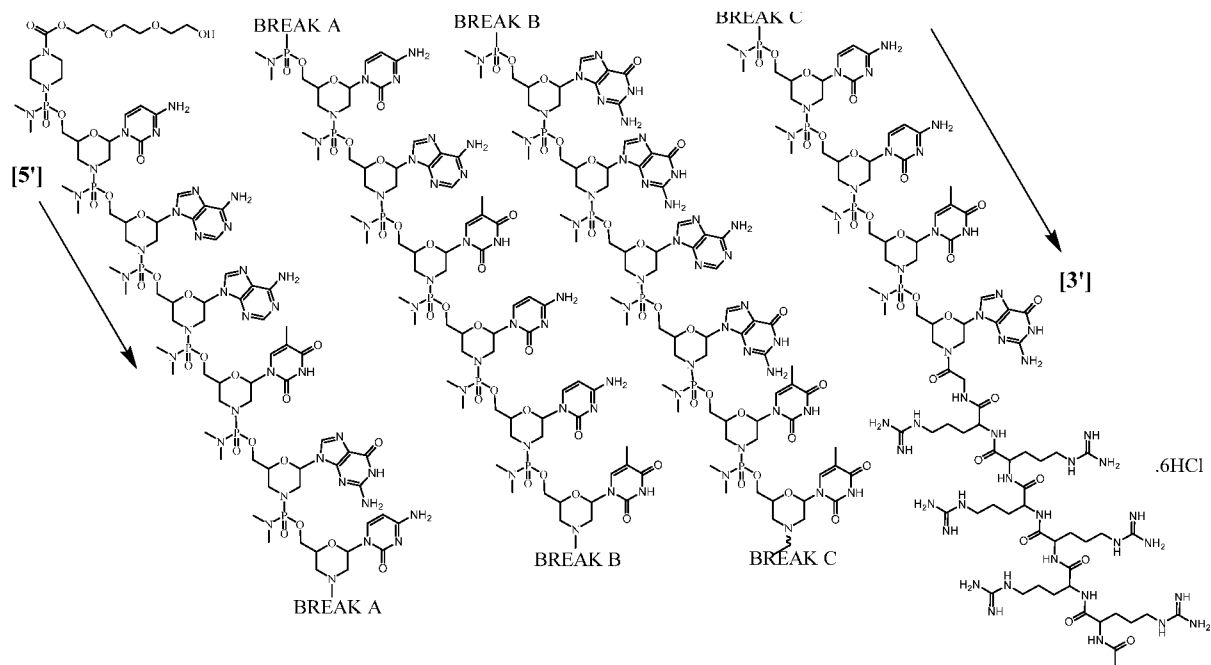
- 13 -



(VI),

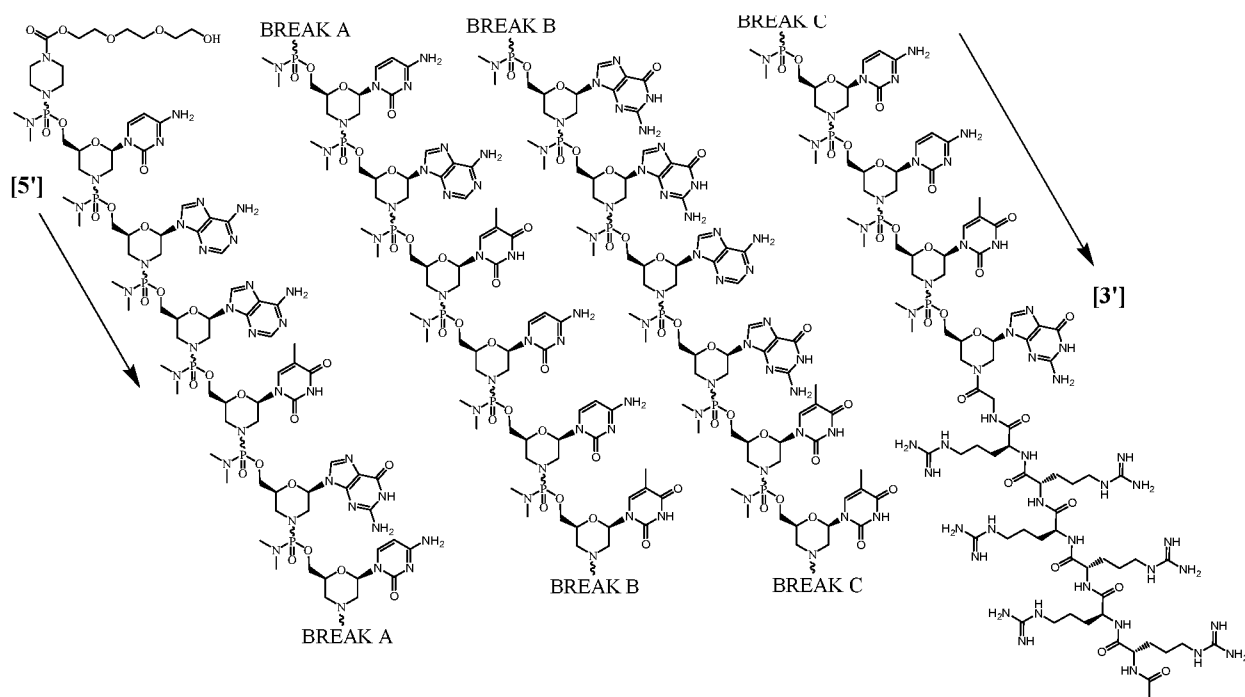
or a pharmaceutically acceptable salt thereof.

[0040] In some aspects, the antisense oligomer conjugate has Formula (VIA):



[0041] In some aspects, the antisense oligomer conjugate is according to Formula (VIB):

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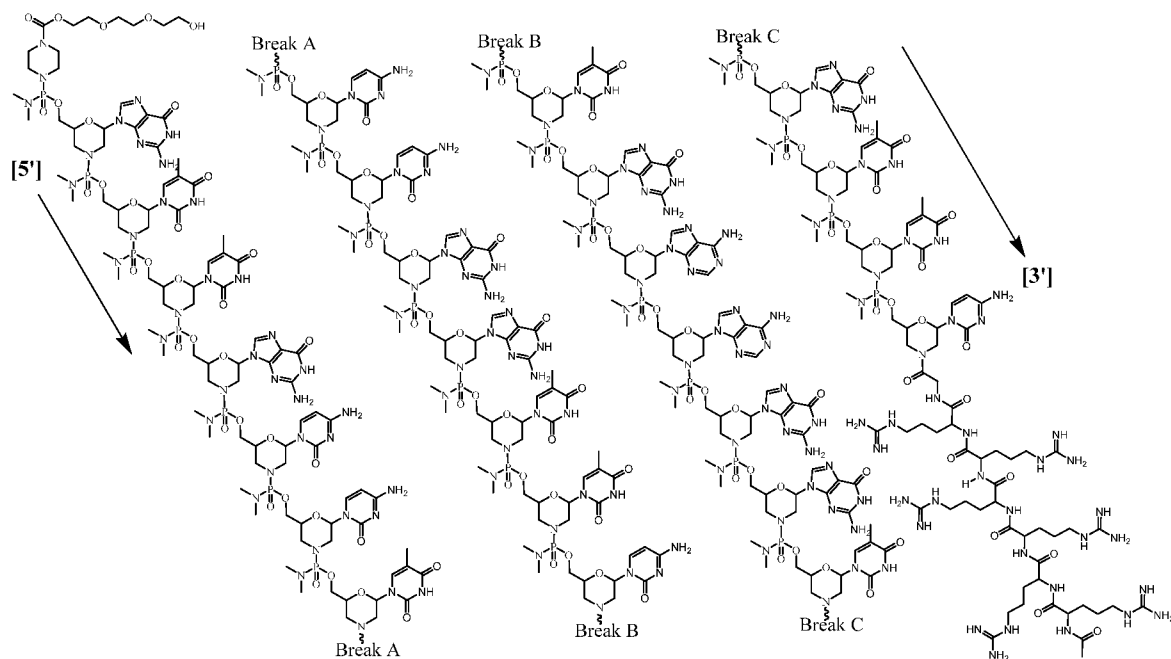
(VIB),

or a pharmaceutically acceptable salt thereof.

[0042] In some aspects, an antisense oligomer conjugate of Formula (VIB) is an HCl (hydrochloric acid) salt thereof. In certain embodiments, the HCl salt is a $\cdot 6\text{HCl}$ salt.

[0043] In some aspects, the present disclosure provides a method of treating a patient with DMD in need thereof who has a mutation that is amenable to exon 53 skipping, comprising administering to the patient an antisense oligomer conjugate has Formula (VIII):

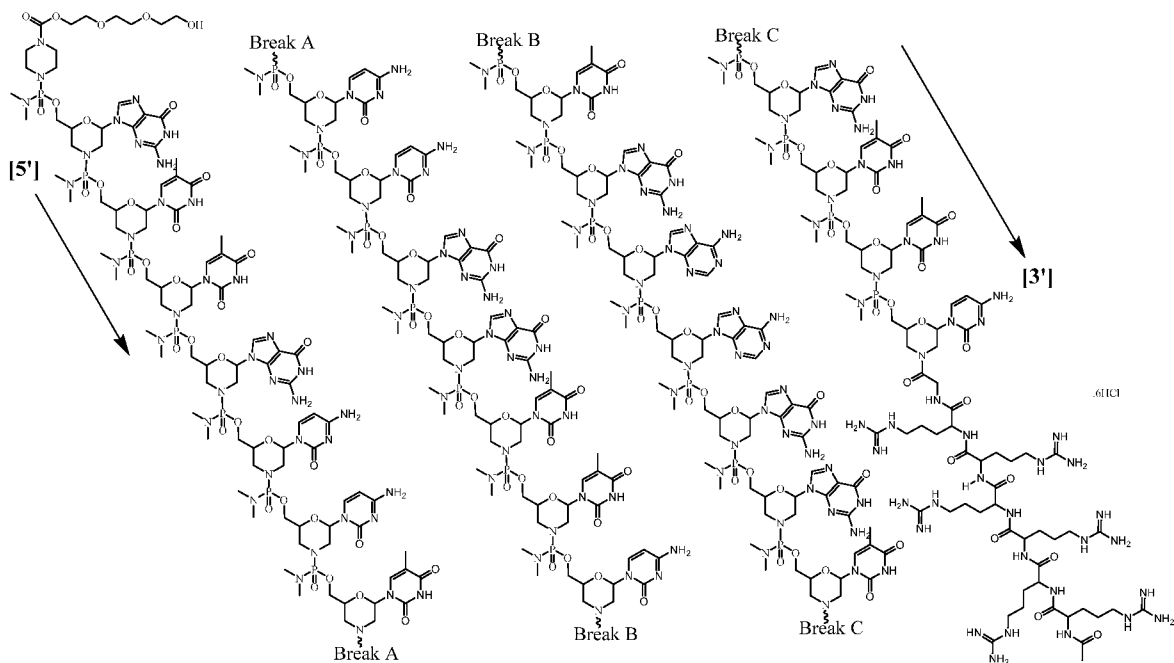
- 15 -



(VIII),

or a pharmaceutically acceptable salt thereof.

[0044] In other aspects, the antisense oligomer conjugate has Formula (VIII A):

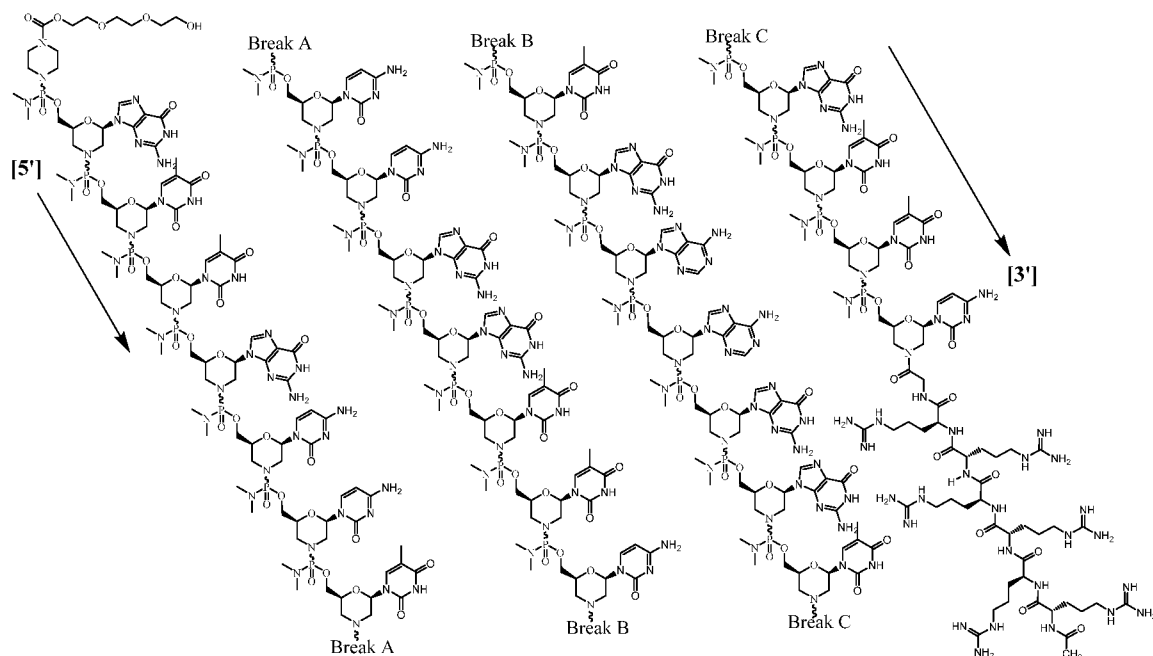


[0045]

(VIII A).

[0046] In other aspects, the antisense oligomer conjugate has Formula (VIII B):

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(VIIIB),

or a pharmaceutically acceptable salt thereof.

[0047] In some embodiments, an antisense oligomer conjugate of Formula (VIIIB) is an HCl (hydrochloric acid) salt thereof. In certain embodiments, the HCl salt is a $\cdot 6\text{HCl}$ salt.

[0048] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 700 mg of the $\cdot 6\text{HCl}$ salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.

[0049] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 600 mg of the $\cdot 6\text{HCl}$ salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.

[0050] In other aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 900 mg to about 1200 mg of the $\cdot 6\text{HCl}$ salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.

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- [0051] In one aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1100 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.
- [0052] In other aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 750 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs greater than or equal to about 18 kg to less than about 50 kg.
- [0053] In other aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1250 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs greater than or equal to about 18 kg to less than about 50 kg.
- [0054] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof is administered at a dose equivalent to about 600 mg to about 800 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
- [0055] In one aspect, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 650 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
- [0056] In other aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1000 mg of the ·6HCl salt of the conjugate to about 1300 mg once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
- [0057] In one aspect, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1200 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
- [0058] In other aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 600 mg to about 900 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.

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- [0059] In another aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 700 mg to about 900 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
- [0060] In one aspect, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 750 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
- [0061] In yet other aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1200 mg to about 1600 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
- [0062] In one aspect, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1400 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
- [0063] In yet other aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 850 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs greater than or equal to about 50 kg.
- [0064] In yet other aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1350 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs greater than or equal to about 50 kg.
- [0065] In other aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 600 mg to about 900 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 65 kg to about 150 kg.
- [0066] In another aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 700 mg to about 900 mg of the

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·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 65 kg to about 150 kg.

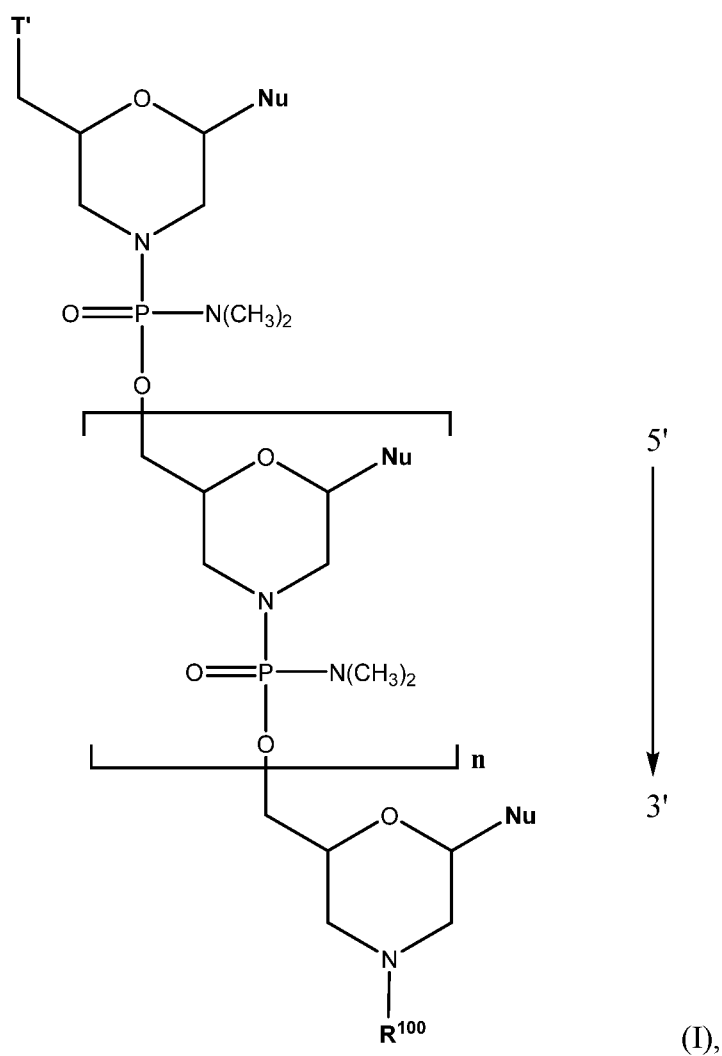
[0067] In one aspect, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 750 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 65 kg to about 150 kg.

[0068] In yet other aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1200 mg to about 1600 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 65 kg to about 150 kg.

[0069] In one aspect, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1400 mg of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 65 kg to about 150 kg.

[0070] The present disclosure also provides a method of treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation that is amenable to exon 51 skipping, comprising administering to the patient an antisense oligomer conjugate of Formula (I):

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or a pharmaceutically acceptable salt thereof,

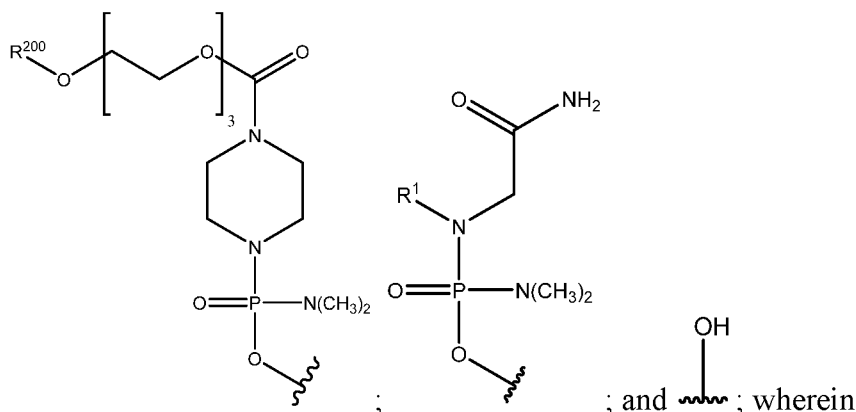
wherein:

n is 1-40;

each **Nu** is a nucleobase, which, taken together, form a targeting sequence complementary to an exon annealing site in the dystrophin pre-mRNA;

T' is a moiety selected from:

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[0071] **R¹⁰⁰** a cell-penetrating peptide, **R²⁰⁰** is hydrogen, and **R¹** is C₁-C₆ alkyl,

[0072] at a dose equivalent to the dose of the ·6HCl salt of the conjugate according to the following schedule:

- i) about 300 mg to about 700 mg, or about 900 mg to about 1200 mg, once every four weeks for a patient that weighs from about 10 kg to about 25 kg;
 - ii) about 600 mg to about 800 mg, or about 1000 mg to about 1300 mg, once every four weeks for a patient that weighs from about 25 kg to about 50 kg; or
 - iii) about 700 mg to about 900 mg, or about 1200 mg to about 1500 mg, once every four weeks for a patient that weighs from about 50 kg to about 100 kg;
- to achieve a mean AUC between about 100 and about 200 ug·h/mL, or is between about 200 and about 500 ug·h/mL, respectively.

[0073] In some embodiments, the conjugate is administered at a dose equivalent to the dose of the ·6HCl salt of the conjugate according to the following schedule:

- iv) about 300 mg to about 700 mg, or about 900 mg to about 1200 mg, once every four weeks for a patient that weighs from about 10 kg to about 25 kg;
 - v) about 500 mg to about 800 mg, or about 1000 mg to about 1300 mg, once every four weeks for a patient that weighs from about 25 kg to about 50 kg; or
 - vi) about 700 mg to about 900 mg, or about 1200 mg to about 1500 mg, once every four weeks for a patient that weighs from about 50 kg to about 100 kg;
- to achieve a mean AUC between about 100 and about 200 ug·h/mL, or is between about 200 and about 500 ug·h/mL, respectively.

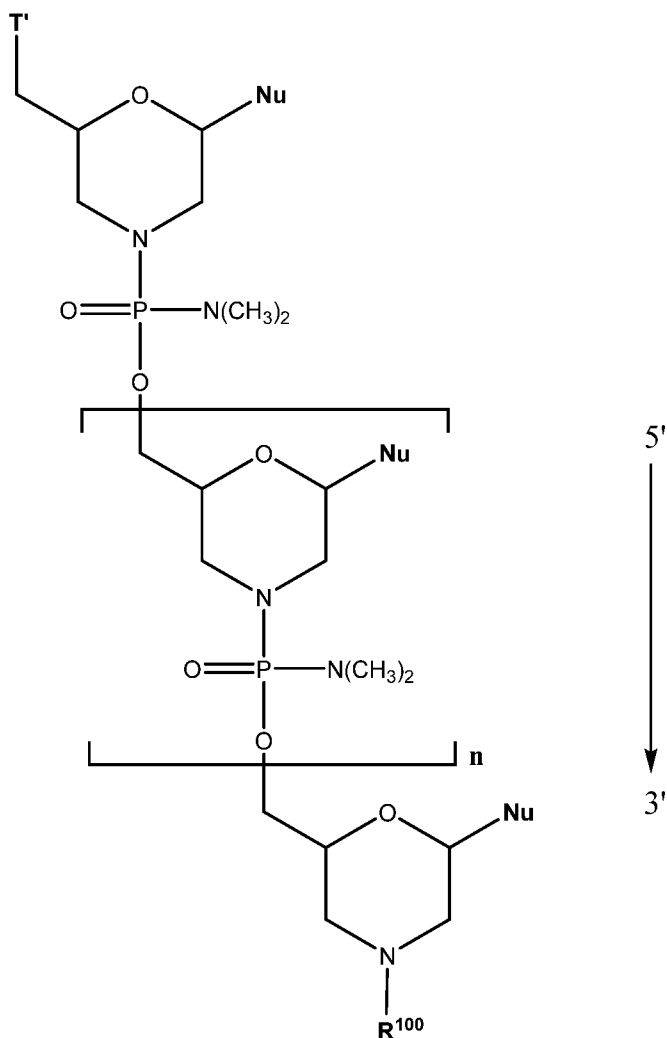
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- [0074] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 600 mg, or about 1100 mg, of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.
- [0075] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 750 mg, or about 1250 mg, of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 18 kg to about 50 kg.
- [0076] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 650 mg, or about 1200 mg, of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
- [0077] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 750 mg, or about 1400 mg, of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
- [0078] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 850 mg, or about 1350 mg, of the ·6HCl salt of the conjugate once every four weeks to a patient that weighs greater than or equal to 50 kg.
- [0079] In one aspect, the present disclosure provides a method of treating a patient in need thereof, comprising administering to the patient an antisense oligomer conjugate, and further comprising administering a magnesium supplement to the patient.
- [0080] In one particular aspect, the present disclosure also provides a method of treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation that is amenable to exon skipping, comprising administering to the patient an antisense oligomer conjugate of Formula (I), as described herein, and further comprising administering a magnesium supplement to the patient.

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[0081] The present disclosure also provides a method of treating a patient with Duchenne muscular dystrophy (DMD) with an antisense oligomer conjugate, comprising administering to the patient:

i) an antisense oligomer conjugate of Formula (I):



or a pharmaceutically acceptable salt thereof,

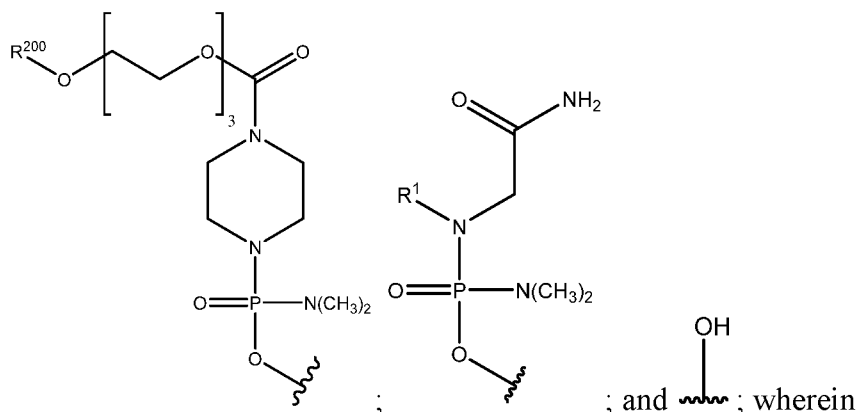
wherein:

n is 1-40;

each **Nu** is a nucleobase, which, taken together, form a targeting sequence complementary to an exon annealing site in the dystrophin pre-mRNA;

T' is a moiety selected from:

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R^{100} a cell-penetrating peptide, R^{200} is hydrogen, and R^1 is C₁-C₆ alkyl; and

ii) a magnesium supplement.

[0082] In some aspects, the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 1200 mg, about 300 mg to about 1000 mg, about 300 mg to about 750 mg, about 300 mg to about 500 mg, about 400 mg to about 1400 mg, about 400 mg to about 1100 mg, about 400 mg to about 900 mg, about 400 mg to about 600 mg, about 500 mg to about 1500 mg, about 500 mg to about 1300 mg, about 500 mg to about 1000 mg, about 500 mg to about 950 mg, about 500 mg to about 850 mg, about 500 mg to about 750 mg, about 500 mg to about 650 mg, about 600 mg to about 1400 mg, about 600 mg to about 1200 mg, about 600 mg to about 1200 mg, about 600 mg to about 1000, or about 600 mg to about 900 mg of the $\cdot 6\text{HCl}$ salt of the conjugate.

[0083] In some aspects, the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, or about 900 mg of the $\cdot 6\text{HCl}$ salt of the conjugate.

[0084] In some aspects, the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, or about 1500 mg of the $\cdot 6\text{HCl}$ salt of the conjugate.

[0085] In certain aspects, the cell-penetrating peptide is chosen from RRRRXXRRRXXR (SEQ ID NO: 18), RFFRFFRFFR (SEQ ID NO: 19), RXRRXXRRXXRXB (SEQ ID NO: 20), RFFRFFRFFRG (SEQ ID NO: 21), RRRRRRG (SEQ ID NO: 22), RRRRRR (SEQ ID

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NO: 23), RRRRRRG (SEQ ID NO: 24), or RRRRRR (SEQ ID NO: 25), wherein R is arginine, X is 6-aminohexanoic acid, B is β -alanine, F is phenylalanine, and G is glycine. In certain other aspects, the cell-penetrating peptide is chosen from RRRRRRG (SEQ ID NO: 22), RRRRRR (SEQ ID NO: 23), RRRRRG (SEQ ID NO: 24), or RRRRR (SEQ ID NO: 25), wherein R is arginine and G is glycine. In one particular aspect, the cell-penetrating peptide is RRRRRRG (SEQ ID NO: 22), wherein R is arginine and G is glycine.

[0086] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, causes skipping of an exon in the human dystrophin gene. In some aspects, the exon is chosen from exon 44, 45, 50, 51, 52, or 53. In certain aspects, the exon is chosen from exon 45, 51, or 53.

[0087] In some aspects, the magnesium supplement is administered in an amount effective to provide a normal serum magnesium level. In certain aspects, the magnesium supplement is administered at a dose equivalent to about 100 to about 2400 mg magnesium oxide per day. In other aspects, the magnesium supplement is administered at a dose equivalent to about 400 to about 2400 mg magnesium oxide per day.

[0088] In some aspects, the method of the present disclosure further comprises measuring serum magnesium level of said patient at two or more weeks from said administration. In some additional aspects, the method of the present disclosure comprises administering a second dose of magnesium supplement, at a dose based upon the measured serum magnesium level.

[0089] In some aspects, the magnesium supplement is chosen from magnesium oxide, magnesium citrate, magnesium carbonate, magnesium hydrogen phosphate, magnesium glycerophosphate, magnesium trisilicate, magnesium hydroxide, magnesium hydroxide carbonate, magnesium acetate, magnesium citrate, magnesium lactate, magnesium gluconate, magnesium chloride, magnesium aspartate, magnesium caprilate, magnesium ascorbate; magnesium taurate, magnesium malate, and magnesium diglycinate, magnesium pidulate, or magnesium sulfate. In one aspect, the magnesium supplement is from magnesium oxide.

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BRIEF DESCRIPTION OF THE FIGURES

- [0090] **FIG. 1** demonstrates the difference in initial body weights of animals in two 12-week non-human primate (NHP) studies.
- [0091] **FIG. 2** depicts plasma exposure versus body weight in NHPs after administration of PPMO-1.
- [0092] **FIG 3** depicts area under the curve (AUC) and plasma peak concentration ($C_{\max}$) versus body weight in NHPs after administration of PPMO-1. Higher body weight is associated with higher AUC and $C_{\max}$.
- [0093] **FIG. 4** is a graph depicting plasma peak concentration ($C_{\max}$) of PPMO-1 at 20 and 30 mg/kg in human DMD patients.
- [0094] **FIG. 5** depicts the correlation between plasma peak concentration ($C_{\max}$) and body weight of DMD patients that were administered either 20 mg/kg PPMO-1 (bottom) or 30 mg/kg PPMO-1 (top).

DETAILED DESCRIPTION

- [0095] The present disclosure relates to novel dosing methods for treating muscular dystrophy, such as DMD and BMD, by administering an antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, specifically designed to induce exon skipping in the human dystrophin gene.
- [0096] The present disclosure also provides therapeutically effective dosing regimens that minimize unwanted side-effects associated with administration of an antisense oligomer conjugate. Specifically, the disclosure provides methods for reducing the frequency and severity of hypomagnesemia in a patient that is being treated with administering an antisense oligomer conjugate.

Definitions

- [0097] By "about" is meant a quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length that varies by as much as 30, 25, 20, 15, 10, 9, 8,

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7, 6, 5, 4, 3, 2 or 1% to a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length.

[0098] The term "alkyl," as used herein, unless otherwise specified, refers to a saturated straight or branched hydrocarbon. In certain embodiments, the alkyl group is a primary, secondary, or tertiary hydrocarbon. In certain embodiments, the alkyl group includes one to ten carbon atoms, i.e., C₁ to C₁₀ alkyl. In certain embodiments, the alkyl group includes one to six carbon atoms, i.e., C₁ to C₆ alkyl. In certain embodiments, the alkyl group is selected from the group consisting of methyl, CF₃, CCl₃, CFC1₂, CF₂Cl, ethyl, CH₂CF₃, CF₂CF₃, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl. The term includes both substituted and unsubstituted alkyl groups, including halogenated alkyl groups. In certain embodiments, the alkyl group is a fluorinated alkyl group. Non-limiting examples of moieties with which the alkyl group can be substituted are selected from the group consisting of halogen (fluoro, chloro, bromo, or iodo), hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., *Protective Groups in Organic Synthesis*, John Wiley and Sons, Second Edition, 1991, hereby incorporated by reference.

[0099] "Amenable to exon skipping" as used herein with regard to a subject or patient is intended to include subjects and patients having one or more mutations in the dystrophin gene which, absent the skipping of the particular exon of the dystrophin pre-mRNA, causes the reading frame to be out-of-frame thereby disrupting translation of the pre-mRNA leading to an inability of the subject or patient to produce functional or semi-functional dystrophin. Determining whether a patient has a mutation in the dystrophin gene that is amenable to exon skipping is well within the purview of one of skill in the art (see, e.g., Aartsma-Rus et al. (2009) *Hum Mutat.* 30:293-299; Gurvich et al., *Hum Mutat.* 2009; 30(4) 633-640; and Fletcher et al. (2010) *Molecular Therapy* 18(6) 1218-1223.).

[0100] The terms "oligomer" and "oligonucleotide" are used interchangeably and refer to a sequence of subunits connected by intersubunit linkages. In certain instances, the term "oligomer" is used in reference to an "antisense oligomer." For "antisense oligomers," each

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subunit consists of: (i) a ribose sugar or a derivative thereof; and (ii) a nucleobase bound thereto, such that the order of the base-pairing moieties forms a base sequence that is complementary to a target sequence in a nucleic acid (typically an RNA) by Watson-Crick base pairing, to form a nucleic acid:oligomer heteroduplex within the target sequence with the proviso that either the subunit, the intersubunit linkage, or both are not naturally occurring. In certain embodiments, the antisense oligomer is a PMO.

[0101] The terms "complementary" and "complementarity" refer to two or more oligomers (i.e., each comprising a nucleobase sequence) that are related with one another by Watson-Crick base-pairing rules. For example, the nucleobase sequence "T-G-A (5' → 3')," is complementary to the nucleobase sequence "A-C-T (3' → 5')." Complementarity may be "partial," in which less than all of the nucleobases of a given nucleobase sequence are matched to the other nucleobase sequence according to base pairing rules. For example, in some embodiments, complementarity between a given nucleobase sequence and the other nucleobase sequence may be about 70%, about 75%, about 80%, about 85%, about 90% or about 95%. Or, there may be "complete" or "perfect" (100%) complementarity between a given nucleobase sequence and the other nucleobase sequence to continue the example. The degree of complementarity between nucleobase sequences has significant effects on the efficiency and strength of hybridization between the sequences.

[0102] The terms "effective amount" and "therapeutically effective amount" are used interchangeably herein and refer to an amount of therapeutic compound, such as an antisense oligomer conjugate, administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect. For an antisense oligomer conjugate, this effect is typically brought about by inhibiting translation or natural splice-processing of a selected target sequence, or producing a clinically meaningful amount of dystrophin (statistical significance).

[0103] By "enhance" or "enhancing," or "increase" or "increasing," or "stimulate" or "stimulating," refers generally to the ability of one or more antisense oligomer conjugates or pharmaceutical compositions to produce or cause a greater physiological response (i.e., downstream effects) in a cell or a subject, as compared to the response caused by either no antisense oligomer conjugate or a control compound. A greater physiological response may

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include increased expression of a functional form of a dystrophin protein, or increased dystrophin-related biological activity in muscle tissue, among other responses apparent from the understanding in the art and the description herein. Increased muscle function can also be measured, including increases or improvements in muscle function by about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. The percentage of muscle fibers that express a functional dystrophin can also be measured, including increased dystrophin expression in about 1%, 2%, 5%, 15%, 16%, 17%, 18%, 19%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of muscle fibers. For instance, it has been shown that around 40% of muscle function improvement can occur if 25-30% of fibers express dystrophin (see, e.g., DelloRusso et al, Proc Natl Acad Sci USA 99: 12979-12984, 2002). An "increased" or "enhanced" amount is typically a "statistically significant" amount, and may include an increase that is 1.1, 1.2, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50 or more times (e.g., 500, 1000 times, including all integers and decimal points in between and above 1), e.g., 1.5, 1.6, 1.7, 1.8, etc.) the amount produced by no antisense oligomer conjugate (the absence of an agent) or a control compound.

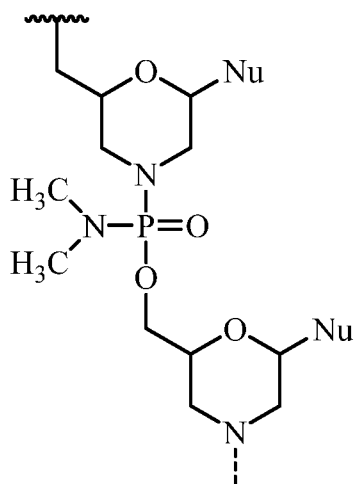
[0104] As used herein, the terms "function" and "functional" and the like refer to a biological, enzymatic, or therapeutic function.

[0105] A "functional" dystrophin protein refers generally to a dystrophin protein having sufficient biological activity to reduce the progressive degradation of muscle tissue that is otherwise characteristic of muscular dystrophy, typically as compared to the altered or "defective" form of dystrophin protein that is present in certain subjects with DMD or BMD. In certain embodiments, a functional dystrophin protein may have about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% (including all integers in between) of the *in vivo* biological activity of wild-type dystrophin, as measured according to routine techniques in the art. Included are truncated forms of dystrophin, such as those forms that are produced following the administration of certain of the exon-skipping antisense oligomer conjugates of the present disclosure.

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[0106] The terms “mismatch” or “mismatches” refer to one or more nucleobases (whether contiguous or separate) in an oligomer nucleobase sequence that are not matched to a target pre-mRNA according to base pairing rules. While perfect complementarity is often desired, some embodiments can include one or more but preferably 6, 5, 4, 3, 2, or 1 mismatches with respect to the target pre-mRNA. Variations at any location within the oligomer are included. In certain embodiments, antisense oligomer conjugates of the disclosure include variations in nucleobase sequence near the termini variations in the interior, and if present are typically within about 6, 5, 4, 3, 2, or 1 subunits of the 5' and/or 3' terminus.

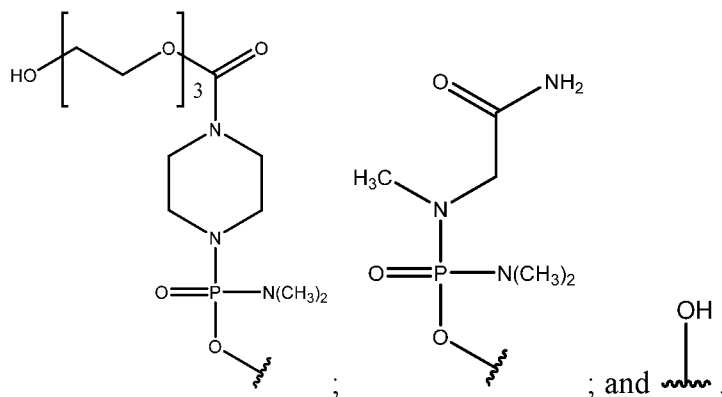
[0107] The terms “morpholino,” “morpholino oligomer,” and “PMO” refer to a phosphorodiamidate morpholino oligomer of the following general structure:



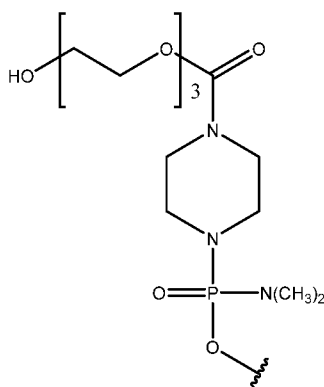
and as described in Figure 2 of Summerton, J., et al., *Antisense & Nucleic Acid Drug Development*, 7: 187-195 (1997). Morpholinos as described herein include all stereoisomers and tautomers of the foregoing general structure. The synthesis, structures, and binding characteristics of morpholino oligomers are detailed in U.S. Patent Nos.: 5,698,685; 5,217,866; 5,142,047; 5,034,506; 5,166,315; 5,521,063; 5,506,337; 8,076,476; and 8,299,206; all of which are incorporated herein by reference.

[0108] In some aspects, a morpholino oligo (PMO) is conjugated at the 5' or 3' end of the oligomer with a “tail” moiety to increase its stability and/or solubility. Exemplary tails include:

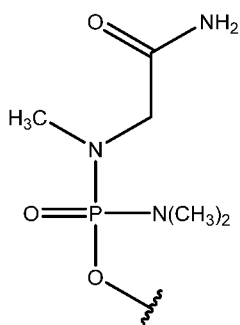
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[0109] Of the above exemplary tail moieties, “TEG” or “EG3” refers to the following tail moiety:



[0110] Of the above exemplary tail moieties, “GT” refers to the following tail moiety:



[0111] Useful morpholino oligomers are described in more detail below.

[0112] The terms “antisense oligomer CPP conjugate,” “antisense oligomer conjugate,” and “PPMO” refer to a conjugate where a PMO has been conjugated to a cell-penetrating peptide. CPPs are described more fully hereinbelow.

[0113] As seen in the table below, non-limiting examples of CPP’s for use herein include $-(\text{RXR})_4-\text{R}^a$, $-\text{R}-(\text{FFR})_3-\text{R}^a$, $-\text{B}-\text{X}-(\text{RXR})_4-\text{R}^a$, $-\text{B}-\text{X}-\text{R}-(\text{FFR})_3-\text{R}^a$, $-\text{GLY}-\text{R}-(\text{FFR})_3-$

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R^a , -GLY- R_5 - R^a and - R_5 - R^a , -GLY- R_6 - R^a and - R_6 - R^a , wherein R^a is selected from H, acyl, acetyl, benzoyl, and stearoyl, and wherein R is arginine, X is 6-aminohexanoic acid, B is β -alanine, F is phenylalanine and GLY (or G) is glycine. The CPP “ R_6 ” is meant to indicate a peptide of six (6) arginine residues linked together via amide bonds (and not a single substituent *e.g.* R^6). In some embodiments, R^a is H or acyl. In some embodiments, R^a is acetyl. Exemplary CPPs are provided in Table 1, below.

[0114] In one aspect, the CPP is chosen from one of the following sequences:

Name	Sequence
(RXR) ₄	RXRRXRRXRRXR (SEQ ID NO: 18)
(RFF) ₃ R	RFFRFFRFFR (SEQ ID NO: 19)
(RXR) ₄ XB	RXRRXRRXRRXRXB (SEQ ID NO: 20)
(RFF) ₃ RXB	RFFRFFRFFRXB (SEQ ID NO: 26)
(RFF) ₃ RG	RFFRFFRFFRG (SEQ ID NO: 21)
R_6 G	RRRRRRG (SEQ ID NO: 22)
R_6	RRRRRR (SEQ ID NO: 23)
R_5 G	RRRRRG (SEQ ID NO: 24)
R_5	RRRRR (SEQ ID NO: 25)

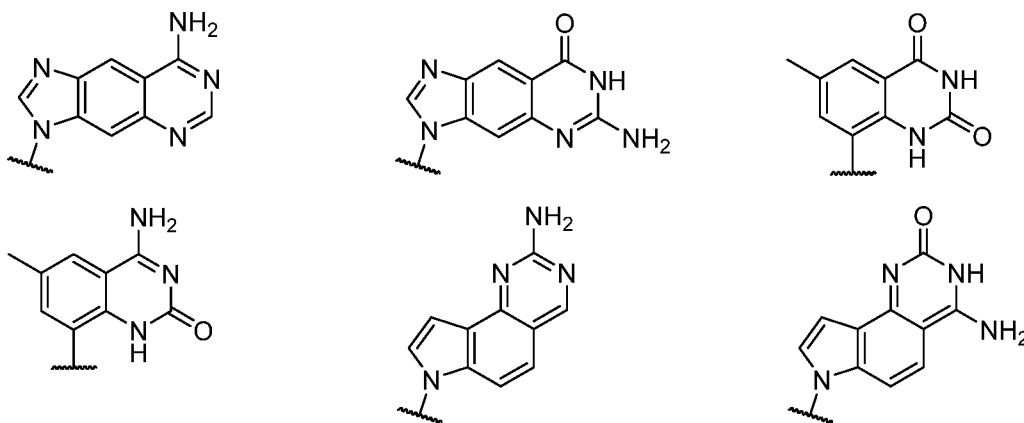
[0115] CPPs, their synthesis, and methods of conjugating to an oligomer are further described in U.S. Patent Nos. 9,161,948 and 10,888,578, U.S. Application Publication No. 2012/0289457, and International Patent Application Publication Nos. WO 2004/097017, WO 2009/005793, and WO 2012/150960, the disclosures of which are incorporated herein by reference in their entirety. A more comprehensive list of CPPs is provided below.

[0116] The terms “nucleobase” (Nu), “base pairing moiety” or “base” are used interchangeably to refer to a purine or pyrimidine base found in naturally occurring, or “native” DNA or RNA (*e.g.*, uracil, thymine, adenine, cytosine, and guanine), as well as analogs of these naturally occurring purines and pyrimidines. These analogs may confer improved properties, such as binding affinity, to the oligomer. Exemplary analogs include hypoxanthine (the base component of inosine); 2,6-diaminopurine; 5-methyl cytosine; C5-propynyl-modified pyrimidines; 10-(9-(aminoethoxy)phenoxazinyl) (G-clamp) and the like.

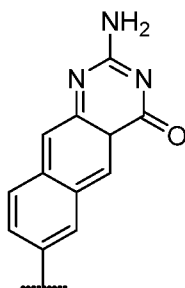
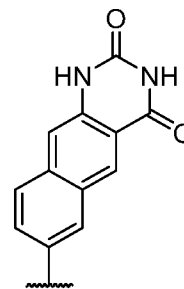
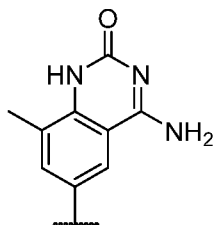
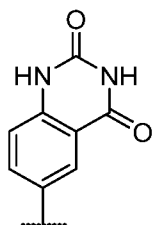
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[0117] Further examples of base pairing moieties include, but are not limited to, uracil, thymine, adenine, cytosine, guanine and hypoxanthine (inosine) having their respective amino groups protected by acyl protecting groups, 2-fluorouracil, 2-fluorocytosine, 5-bromouracil, 5-iodouracil, 2,6-diaminopurine, azacytosine, pyrimidine analogs such as pseudoisocytosine and pseudouracil and other modified nucleobases such as 8-substituted purines, xanthine, or hypoxanthine (the latter two being the natural degradation products). The modified nucleobases disclosed in: Chiu and Rana, RNA, 2003, 9, 1034-1048; Limbach *et al.* Nucleic Acids Research, 1994, 22, 2183-2196; and Revankar and Rao, Comprehensive Natural Products Chemistry, vol. 7, 313; are also contemplated, the contents of which are incorporated herein by reference.

[0118] Further examples of base pairing moieties include, but are not limited to, expanded-size nucleobases in which one or more benzene rings has been added. Nucleic acid base replacements described in: the Glen Research catalog (www.glenresearch.com); Krueger AT *et al.*, Acc. Chem. Res., 2007, 40, 141-150; Kool, ET, Acc. Chem. Res., 2002, 35, 936-943; Benner S.A., *et al.*, Nat. Rev. Genet., 2005, 6, 553-543; Romesberg, F.E., *et al.*, Curr. Opin. Chem. Biol., 2003, 7, 723-733; and Hirao, I., Curr. Opin. Chem. Biol., 2006, 10, 622-627; the contents of which are incorporated herein by reference, are contemplated as useful in the antisense oligomer conjugates described herein. Examples of expanded-size nucleobases include those shown below, as well as tautomeric forms thereof.



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[0119] The term “exposure” refers to dose (PPMO input to the body) and various measures of acute or integrated PPMO concentrations in plasma and other biological fluid (e.g., C_{max}, C_{min}, C_{ss}, AUC). The term “response” refers to a direct measure of the pharmacologic effect of the drug. Response includes a broad range of endpoints or biomarkers ranging from a potential or accepted surrogate (e.g., effects on blood pressure, magnesium levels, or cardiac output) to the full range of short-term or longterm clinical effects related to efficacy and safety.

[0120] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

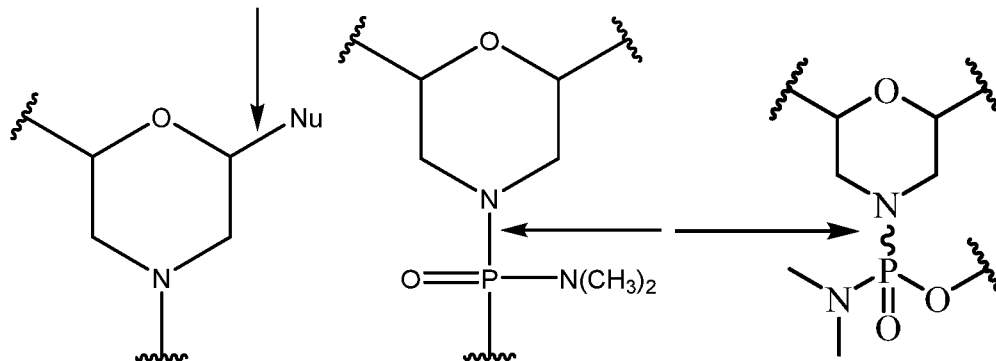
[0121] For clarity, structures of the disclosure are continuous from 5' to 3', and, for the convenience of depicting the entire structure in a compact form, various illustration breaks labeled “BREAK A,” “BREAK B,” and “BREAK C” have been included. As would be understood by the skilled artisan, for example, each indication of “BREAK A” shows a continuation of the illustration of the structure at these points. The skilled artisan understands

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that the same is true for each instance of “BREAK B” and for “BREAK C” in the structures above. None of the illustration breaks, however, are intended to indicate, nor would the skilled artisan understand them to mean, an actual discontinuation of the structure above.

[0122] As used herein, a set of brackets used within a structural formula indicate that the structural feature between the brackets is repeated. In some embodiments, the brackets used can be “[” and “],” and in certain embodiments, brackets used to indicate repeating structural features can be “(” and “).” In some embodiments, the number of repeat iterations of the structural feature between the brackets is the number indicated outside the brackets such as 2, 3, 4, 5, 6, 7, and so forth. In various embodiments, the number of repeat iterations of the structural feature between the brackets is indicated by a variable indicated outside the brackets such as “n”.

[0123] As used herein, a straight bond or a squiggly bond drawn to a chiral carbon or phosphorous atom within a structural formula indicates that the stereochemistry of the chiral carbon or phosphorous is undefined and is intended to include all forms of the chiral center. Examples of such illustrations are depicted below.



Management of Hypomagnesemia

[0124] The present description provides methods for reducing the severity and frequency of hypomagnesemia in DMD patients. The incidence rate of hypomagnesemia in DMD patients is generally no greater than that in healthy individuals. Unexpectedly, the present inventors have observed that patients treated with an antisense oligomer CPP conjugate (e.g., PPMO), higher exposure (AUC values) correlates with the severity and frequency of

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hypomagnesemia (magnesium deficiency). Thus, the methods described herein can result in decreased toxicity associated with abnormal magnesium levels associated with administration of with an antisense oligomer CPP conjugate (e.g., PPMO) in a human patient.

[0125] In some aspects, the present disclosure provides methods for treating hypomagnesemia associated with administering an antisense oligomer CPP conjugate (e.g., PPMO) to a patient to effect exon skipping by administering a magnesium supplement to a patient being treated with an antisense oligomer CPP conjugate. In some aspects, the patient is a DMD patient. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula (I) or a pharmaceutically acceptable salt thereof. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula (IVB) or a pharmaceutically acceptable salt thereof. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula (VIB) or a pharmaceutically acceptable salt thereof. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula (VIII B) or a pharmaceutically acceptable salt thereof.

[0126] In some aspects, the present disclosure provides methods for preventing hypomagnesemia associated with administering an antisense oligomer CPP conjugate (e.g., PPMO) to a patient to effect exon skipping by administering a magnesium supplement to a patient being treated with an antisense oligomer CPP conjugate. In some aspects, the patient is a DMD patient. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula (I) or a pharmaceutically acceptable salt thereof. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula (IVB) or a pharmaceutically acceptable salt thereof. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula (VIB) or a pharmaceutically acceptable salt thereof. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula (VIII B) or a pharmaceutically acceptable salt thereof.

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[0127] In some aspects the present disclosure provides methods for maintaining normal serum magnesium levels in a patient to whom an antisense oligomer conjugate (e.g., PPMO) is being administered, by administering a magnesium supplement to a patient being treated with an antisense oligomer CPP conjugate. In some aspects, the patient is a DMD patient. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula (I) or a pharmaceutically acceptable salt thereof. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula (IVB) or a pharmaceutically acceptable salt thereof. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula (VIB) or a pharmaceutically acceptable salt thereof. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula (VIIIB) or a pharmaceutically acceptable salt thereof.

[0128] Hypomagnesemia in a patient (e.g., a DMD patient) can be diagnosed by a physical exam, symptoms, medical history, and a laboratory test to test the magnesium body content. Generally speaking, the means for detecting the magnesium body contents include the detection of blood levels of magnesium, in the patient's plasma or in the serum (whose anomalies generally indicate a disorder in magnesium metabolism and are, normally, the starting point for a set of further specific tests); the detection of magnesium levels in the urine (which gives a measure of the elimination of magnesium via urine, and is normally associated with protein intake, being the Mg/urea ratio in the urine quite constant); the detection of magnesium levels in the spinal fluid; the detection of erythrocytic magnesium (which shows the amount of Mg contained in the bone marrow when erythropoiesis occurs and allows, therefore, an indirect medullary exploration as concerns magnesium); the detection of lymphocytic magnesium; nuclear magnetic resonance with ²⁵Mg (which evidences any modifications in the subcellular distribution of magnesium and in the different chemical-physical structures); and, the detection of magnesium contents in the patient's bones, muscles or any other tissue or organ of interest.

[0129] Hypomagnesemia is defined according to the CTCAE (Common Terminology Criteria for Adverse Events) or magnesium reduction level:

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
<LLN – 1.2 mg/dL; <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL; <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL; <0.4 – 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death

[0130] Severe hypomagnesemia usually results in concentrations of <0.9 mg/dL (< 0.4 mmol/L).

[0131] An aspect of the present disclosure includes treating a patient diagnosed with hypomagnesemia by administering to the patient a magnesium supplement. Herein throughout, in the context of magnesium-containing products, magnesium supplements, magnesium formulations and/or magnesium therapy, the term "magnesium" refers to Mg^{+2} ions, either in a form of free ions in a salt or in a form of a complex.

[0132] In certain aspects, magnesium supplement is administered prophylactically, without first testing for hypomagnesemia. An aspect of the present disclosure includes treating a patient with Duchenne muscular dystrophy (DMD) with an antisense oligomer CPP conjugate, comprising administering to the patient: (i) an antisense oligonucleotide CPP conjugate that includes a morpholino phosphorodiamidate antisense oligomer that is: (a) 100% complementary to a portion of an exon of the human dystrophin pre-mRNA, and (b) 15 to 50 nucleotides in length, wherein the antisense oligonucleotide is administered intravenously; and a magnesium supplement. In another aspect, the oligomer is 15-40, 15-35, 15-30, 15-25, or 15-20 nucleotides in length. In some aspects, the oligo is 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, or 15 nucleotides in length. In one aspect, the oligo is 30 nucleotides in length. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula (I) or a pharmaceutically acceptable salt thereof. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula (IVB) or a pharmaceutically acceptable salt thereof. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula

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(VIB) or a pharmaceutically acceptable salt thereof. In some aspects, the antisense oligomer CPP conjugate is an antisense oligomer CPP conjugate of Formula (VIIIB) or a pharmaceutically acceptable salt thereof.

[0133] In some aspects, magnesium supplement is administered to a patient orally. Magnesium-containing products for oral administration include, for example, magnesium oxide, magnesium citrate, magnesium carbonate, magnesium hydrogen phosphate, magnesium glycerophosphate, magnesium trisilicate, magnesium hydroxide, magnesium hydroxide carbonate, magnesium acetate, magnesium citrate, magnesium lactate, magnesium gluconate, magnesium chloride, magnesium aspartate, magnesium caprilate, magnesium ascorbate; magnesium taurate, magnesium malate, and magnesium diglycinate, magnesium pidulate or magnesium sulfate. In some aspects, the magnesium supplement is magnesium oxide.

[0134] In some aspects, magnesium supplement is administered to a patient intravenously. Intravenously administered magnesium includes, for example, magnesium sulfate.

[0135] Like many metal-containing complexes, the different magnesium compounds have different mechanisms of uptake *in vivo*. Additionally, upon administration, including ingestion, the transition metal complexes may undergo any number of reactions *in vivo* that affect the bioavailability and resulting therapeutic effect. By way of example, magnesium citrate is soluble in gastric fluid and thus is readily available for passive absorption in the upper gastrointestinal tract. Magnesium acetate, magnesium ascorbate and magnesium lactate are soluble in gastric fluid and share the upper gastrointestinal passive absorption potential of magnesium citrate. The ascorbate radical serves as a source of vitamin C by conversion to ascorbic acid upon exposure to hydrochloric acid in the gastric fluid, whereas the magnesium ion is converted to soluble magnesium chloride. The satisfactory water solubility of magnesium acetate, magnesium ascorbate, magnesium citrate and magnesium lactate provide for a diffusional gradient of magnesium in the upper small intestine where some passive absorption of magnesium occurs. Magnesium oxide is converted to magnesium chloride in the stomach, and offers the advantage of a high ionic magnesium content, since 60% by weight of the magnesium oxide molecule is elemental magnesium. Magnesium diglycinate represents a form of magnesium that is absorbed in part as an intact dipeptide in the proximal

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small intestine via a dipeptide transport pathway and therefore provides a third absorptive mechanism for magnesium.

[0136] A variety of dosages, in amount of magnesium, are contemplated by the present disclosure. Unless expressly provided otherwise, the dose amounts referred to herein refer to the amount equivalent to the amount of magnesium oxide. The dose may range from about 5 mg to about 1000 mg or more. In some aspects, the dose may range from about 5 mg to about 900 mg, about 850 mg, about 800 mg, about 750 mg, about 700 mg, about 650 mg, about 600 mg, about 550 mg, about 500 mg, about 450 mg, about 400 mg, about 350 mg, about 300 mg, about 250 mg, about 200 mg, about 150 mg, about 100 mg, or to about 50 mg. In some aspects, the dose may range from about 15 mg to about 900 mg, about 850 mg, about 800 mg, about 750 mg, about 700 mg, about 650 mg, about 600 mg, about 550 mg, about 500 mg, about 450 mg, about 400 mg, about 350 mg, about 300 mg, about 250 mg, about 200 mg, about 150 mg, about 100 mg, or to about 50 mg. In some aspects, the dose may range from about 30 mg to about 900 mg, about 850 mg, about 800 mg, about 750 mg, about 700 mg, about 650 mg, about 600 mg, about 550 mg, about 500 mg, about 450 mg, about 400 mg, about 350 mg, about 300 mg, about 250 mg, about 200 mg, about 150 mg, about 100 mg, or to about 50 mg. In some aspects, the dose may range from about 60 mg to about 900 mg, about 850 mg, about 800 mg, about 750 mg, about 700 mg, about 650 mg, about 600 mg, about 550 mg, about 500 mg, about 450 mg, about 400 mg, about 350 mg, about 300 mg, about 250 mg, about 200 mg, about 150 mg, about 100 mg, or to about 50 mg. In some aspects, the dose may range from about 100 mg to about 900 mg, about 850 mg, about 800 mg, about 750 mg, about 700 mg, about 650 mg, about 600 mg, about 550 mg, about 500 mg, about 450 mg, about 400 mg, about 350 mg, about 300 mg, about 250 mg, or about 200 mg. In some aspects, the dose may range from about 200 mg to about 900 mg, about 850 mg, about 800 mg, about 750 mg, about 700 mg, about 650 mg, about 600 mg, about 550 mg, about 500 mg, about 450 mg, about 400 mg, about 350 mg, about 300 mg, to about 250 mg. In some aspects, the dose may range from about 300 mg to about 900 mg, about 850 mg, about 800 mg, about 750 mg, about 700 mg, about 650 mg, about 600 mg, about 550 mg, about 500 mg, about 450 mg, about 400 mg, or to about 350 mg. In some aspects, the dose may range from about 400 mg to about 900 mg, about 850 mg, about 800 mg, about 750 mg,

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about 700 mg, about 650 mg, about 600 mg, about 550 mg, about 500 mg, or to about 450 mg.

[0137] Specific dosages of the magnesium supplement include about 5 mg, about 10 mg, about 15mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 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, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, 770 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 805 mg, about 810 mg, about 815 mg, about 820 mg, about 825 mg, about 830 mg, about 835 mg, about 840 mg, about 845 mg, 850 mg, about 855 mg, about 860 mg, about 865 mg, 880 mg, about 885

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mg, about 890 mg, about 895 mg, about 900, about 905 mg, about 910 mg, about 915 mg, about 920 mg, about 925 mg, about 930 mg, about 935 mg, about 940 mg, about 945 mg, 950 mg, about 955 mg, 960 mg, about 965 mg, about 970 mg, about 975 mg, about 980 mg, about 985 mg, about 990 mg, about 995 mg, or about 1000 mg.

[0138] In some aspects, the present disclosure provides methods for treating or preventing hypomagnesemia associated with administering an antisense oligomer CPP conjugate of Formulas (IVB), or a pharmaceutically acceptable salt thereof to a patient to effect exon skipping by administering a magnesium supplement to a patient being treated with an antisense oligomer CPP conjugate, wherein the magnesium supplement dose is about 400 mg to 900 mg.

[0139] In some aspects, the present disclosure provides methods for treating or preventing hypomagnesemia associated with administering an antisense oligomer CPP conjugate of Formulas (VIB), or a pharmaceutically acceptable salt thereof to a patient to effect exon skipping by administering a magnesium supplement to a patient being treated with an antisense oligomer CPP conjugate, wherein the magnesium supplement dose is about 400 mg to 900 mg.

[0140] In some aspects, the present disclosure provides methods for treating or preventing hypomagnesemia associated with administering an antisense oligomer CPP conjugate of Formulas (VIIB), or a pharmaceutically acceptable salt thereof to a patient to effect exon skipping by administering a magnesium supplement to a patient being treated with an antisense oligomer CPP conjugate, wherein the magnesium supplement dose is about 400 mg to 900 mg.

[0141] In an aspect, a dose of a magnesium supplement is equivalent to about 400 mg of magnesium oxide. In another aspect, a dose of a magnesium supplement is equivalent to about 800 mg of magnesium oxide.

[0142] Higher doses of magnesium are also contemplated. For example, the dose may range from about 1000 mg to about 2400 mg, about 1000 mg to about 2000 mg, about 1000 mg to about 1500 mg, about 1050 mg to about 2400 mg, about 1050 mg to about 2000 mg, about 1050 mg to about 1500 mg, 1100 mg to about 2400 mg, about 1100 mg to about 2000 mg, about 1100 mg to about 1500 mg, 1200 mg to about 2400 mg, about 1200 mg to about 2000

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mg, about 12 mg to about 1500 mg, 1500 mg to about 2400 mg, or about 1500 mg to about 2000 mg. Specific doses of magnesium can include about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1900 mg, about 1950 mg, about 2000 mg, about 2050 mg, about 2100 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, or about 2400 mg.

[0143] Higher dosages, may be used as short-term regimes (e.g. less than about one month) and may taper into dosages in the lower end of the ranges. In many such instances it will be advantageous to not to fall below about 40 to 100 mg per day of magnesium when tapering the dose. Alternatively, the appropriate dose of magnesium may be based on the condition of any subject, as assessed by a number of variables of import. Alternatively, the dosages may depend on the mode of administration. Alternatively, magnesium dose may vary with the amounts of an antisense oligomer CPP conjugate. Appropriate dosages may depend on numerous factors, and may be readily determined by one of skill in the art.

[0144] In some aspects, a magnesium supplement is administered once daily. In other aspect, the magnesium supplement is administered twice daily. In yet other aspects, the magnesium supplement is administered three times a day. More frequent daily administration of the magnesium supplement, as determined by a treating physician, is also contemplated by the present disclosure.

[0145] A magnesium supplement and an antisense oligomer CPP conjugate can be administered to an individual in any order. In one aspect, a magnesium supplement and an antisense oligomer CPP conjugate are administered simultaneously. For example, a magnesium supplement and an antisense oligomer CPP conjugate can be administered within the same hour of each other. In some aspects, a magnesium supplement and an antisense oligomer CPP conjugate can also be administered within about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, about 20 hours, about 21 hours, about 22 hours, about 23 hours, or about 24 hours of each other.

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[0146] In other aspects, an antisense oligomer CPP conjugate can be administered once every 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 days, or every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 weeks, while a magnesium supplement is administered once, twice, three time, four times, or more daily. In other aspects, an antisense oligomer CPP conjugate can be administered once every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months, while a magnesium supplement is administered once, twice, three time, four times, or more daily.

[0147] Magnesium supplementation can also begin prior to initiation of a treatment regimen with an antisense oligomer CPP conjugate. For example, a patient can begin magnesium supplementation 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, or more days prior to the first treatment with an antisense oligomer CPP conjugate. Alternatively, Magnesium supplementation can also begin after initiation of a treatment regimen with an antisense oligomer CPP conjugate. For example, a patient can begin magnesium supplementation 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, or more days after the first treatment with an antisense oligomer CPP conjugate.

[0148] In another aspect, any of these magnesium supplement aspects can be combined with one of the PPMO dosing aspects described below.

[0149] Serum magnesium level of a patient should be measured regularly during treatment with an antisense oligomer CPP conjugate. In some aspects, serum magnesium level of a patient is measured prior to administering an antisense oligomer CPP conjugate. In some aspects, serum magnesium level of the patient is measured at two or more weeks from the administration of the conjugate. Depending on patient's serum magnesium level at a given measurement, the dose of the magnesium supplement can be adjusted up or down to maintain a normal serum magnesium level. As such, administering a second dose of magnesium supplement, at a dose based upon the measured serum magnesium level, is also contemplated by the present disclosure.

Dosing of Antisense Oligomer CPP Conjugates (PPMOs)

[0150] In previous clinical settings involving splice-switching oligomers (SSOs) for treatment of DMD (*e.g.*, PPMOs, such as eteplirsen, golodirsen), weight based (mg/kg)

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approaches have been used. It has now been unexpectedly discovered that both dystrophin expression and safety (hypomagnesemia) are related to exposure (dose) of PPMO.

[0151] It has been discovered that using weight-based (mg/kg) PPMO dosing approach, higher body weight (BW) is associated with higher drug exposure, resulting in a risk of underdose for lighter patients and risk of overdose for heavier patients. As such, it has been discovered that a weight-based dosing approach leads to sub-optimal dystrophin expression in lighter patients, and potential hypomagnesemia in heavier patients.

[0152] The present disclosure provides novel dosing regimens developed to optimize dystrophin expression and minimize hypomagnesemia concerns in human patients.

[0153] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a targeted mean AUC so as to maximize dystrophin expression and minimize hypomagnesemia in a patient.

[0154] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC of between about 100 and about 200 ug·h/mL, between about 100 and about 190 ug·h/mL, between about 100 and about 180 ug·h/mL, between about 100 and about 170 ug·h/mL, between about 100 and about 160 ug·h/mL, between about 100 and about 150 ug·h/mL, between about 100 and about 140 ug·h/mL, between about 100 and about 130 ug·h/mL, between about 100 and about 120 ug·h/mL, or between about 100 and about 110 ug·h/mL.

[0155] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 110 and about 200 ug·h/mL, between about 120 and about 200 ug·h/mL, between about 130 and about 200 ug·h/mL, between about 140 and about 200 ug·h/mL, between about 150 and about 200 ug·h/mL, between about 160 and about 200 ug·h/mL, between about 170 and about 200 ug·h/mL, between about 180 and about 200 ug·h/mL, or between about 190 and about 200 ug·h/mL.

[0156] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 110 and about 190 ug·h/mL, between about 120 and about 190 ug·h/mL, between about 130 and about 190 ug·h/mL, between about 140 and about 190 ug·h/mL, between about 150 and about

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190 ug·h/mL, between about 160 and about 190 ug·h/mL, between about 170 and about 190 ug·h/mL, or between about 180 and about 190 ug·h/mL.

[0157] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 110 and about 180 ug·h/mL, between about 120 and about 180 ug·h/mL, between about 130 and about 180 ug·h/mL, between about 140 and about 180 ug·h/mL, between about 150 and about 180 ug·h/mL, between about 160 and about 180 ug·h/mL, or between about 170 and about 180 ug·h/mL.

[0158] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 110 and about 170 ug·h/mL, between about 120 and about 170 ug·h/mL, between about 130 and about 170 ug·h/mL, between about 140 and about 170 ug·h/mL, between about 150 and about 170 ug·h/mL, or between about 160 and about 170 ug·h/mL.

[0159] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 110 and about 160 ug·h/mL, between about 120 and about 160 ug·h/mL, between about 130 and about 160 ug·h/mL, between about 140 and about 160 ug·h/mL, or between about 150 and about 160 ug·h/mL.

[0160] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 110 and about 150 ug·h/mL, between about 120 and about 150 ug·h/mL, between about 130 and about 150 ug·h/mL, or between about 140 and about 150 ug·h/mL.

[0161] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 120 and about 240 ug·h/mL, between about 120 and about 230 ug·h/mL, between about 120 and about 220 ug·h/mL, between about 120 and about 210 ug·h/mL, between about 120 and about 200 ug·h/mL, between about 120 and about 190 ug·h/mL, between about 120 and about 180 ug·h/mL, between about 120 and about 170 ug·h/mL, between about 120 and about 160 ug·h/mL, between about 120 and about 150 ug·h/mL, between about 120 and about 140 ug·h/mL, or between about 120 and about 130 ug·h/mL.

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- [0162]** In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 130 and about 200 ug·h/mL, between about 130 and about 190 ug·h/mL, between about 130 and about 180 ug·h/mL, between about 130 and about 170 ug·h/mL, between about 130 and about 160 ug·h/mL, between about 130 and about 150 ug·h/mL, or between about 130 and about 140 ug·h/mL.
- [0163]** In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 140 and about 200 ug·h/mL, between about 140 and about 190 ug·h/mL, between about 140 and about 180 ug·h/mL, between about 140 and about 170 ug·h/mL, between about 140 and about 160 ug·h/mL, or between about 140 and about 150 ug·h/mL.
- [0164]** In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 150 and about 200 ug·h/mL, between about 150 and about 190 ug·h/mL, between about 150 and about 180 ug·h/mL, between about 150 and about 170 ug·h/mL, or between about 150 and about 160 ug·h/mL.
- [0165]** In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 160 and about 200 ug·h/mL, between about 160 and about 190 ug·h/mL, between about 160 and about 180 ug·h/mL, or between about 160 and about 170 ug·h/mL.
- [0166]** In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 170 and about 200 ug·h/mL, between about 170 and about 190 ug·h/mL, or between about 170 and about 180 ug·h/mL.
- [0167]** In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 130 and about 240 ug·h/mL, between about 140 and about 240 ug·h/mL, between about 150 and about 240 ug·h/mL, between about 160 and about 240 ug·h/mL, between about 170 and about 240 ug·h/mL, between about 180 and about 240 ug·h/mL, between about 190 and about 240 ug·h/mL, between about 200 and about 240 ug·h/mL, between about 210 and about 240

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ug·h/mL, between about 220 and about 240 ug·h/mL, or between about 230 and about 240 ug·h/mL.

[0168] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 130 and about 230 ug·h/mL, between about 140 and about 230 ug·h/mL, between about 150 and about 230 ug·h/mL, between about 160 and about 230 ug·h/mL, between about 170 and about 230 ug·h/mL, between about 180 and about 230 ug·h/mL, between about 190 and about 230 ug·h/mL, between about 200 and about 230 ug·h/mL, between about 210 and about 230 ug·h/mL, or between about 220 and about 230 ug·h/mL.

[0169] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 130 and about 220 ug·h/mL, between about 140 and about 220 ug·h/mL, between about 150 and about 220 ug·h/mL, between about 160 and about 220 ug·h/mL, between about 170 and about 220 ug·h/mL, between about 180 and about 220 ug·h/mL, or between about 190 and about 220 ug·h/mL, between about 200 and about 220 ug·h/mL, or between about 210 and about 220 ug·h/mL.

[0170] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 130 and about 210 ug·h/mL, between about 140 and about 210 ug·h/mL, between about 150 and about 210 ug·h/mL, between about 160 and about 210 ug·h/mL, between about 170 and about 210 ug·h/mL, between about 180 and about 210 ug·h/mL, between about 190 and about 210 ug·h/mL, or between about 200 and about 210 ug·h/mL.

[0171] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 130 and about 200 ug·h/mL, between about 140 and about 200 ug·h/mL, between about 150 and about 200 ug·h/mL, between about 160 and about 200 ug·h/mL, between about 170 and about 200 ug·h/mL, between about 180 and about 200 ug·h/mL, or between about 190 and about 200 ug·h/mL.

[0172] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 130

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and about 190 ug·h/mL, between about 140 and about 190 ug·h/mL, between about 150 and about 190 ug·h/mL, or between about 160 and about 190 ug·h/mL, between about 170 and about 190 ug·h/mL, or between about 180 and about 190 ug·h/mL.

[0173] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 130 and about 180 ug·h/mL, between about 140 and about 180 ug·h/mL, between about 150 and about 180 ug·h/mL, between about 160 and about 180 ug·h/mL, or between about 170 and about 180 ug·h/mL.

[0174] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 130 and about 170 ug·h/mL, between about 140 and about 170 ug·h/mL, between about 150 and about 170 ug·h/mL, or between about 160 and about 170 ug·h/mL.

[0175] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 130 and about 160 ug·h/mL, between about 140 and about 160 ug·h/mL, or between about 150 and about 160 ug·h/mL.

[0176] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 130 and about 150 ug·h/mL, or between about 140 and about 150 ug·h/mL.

[0177] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 140 and about 240 ug·h/mL, between about 140 and about 230 ug·h/mL, between about 140 and about 220 ug·h/mL, between about 140 and about 210 ug·h/mL, between about 140 and about 200 ug·h/mL, between about 140 and about 190 ug·h/mL, between about 140 and about 180 ug·h/mL, between about 140 and about 170 ug·h/mL, between about 140 and about 160 ug·h/mL, or between about 140 and about 150 ug·h/mL.

[0178] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 150 and about 240 ug·h/mL, between about 150 and about 230 ug·h/mL, between about 150 and about 220 ug·h/mL, between about 150 and about 210 ug·h/mL, between about 150 and about

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200 ug·h/mL, between about 150 and about 190 ug·h/mL, between about 150 and about 180 ug·h/mL, between about 150 and about 170 ug·h/mL, or between about 150 and about 160 ug·h/mL.

[0179] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 160 and about 240 ug·h/mL, between about 160 and about 230 ug·h/mL, between about 160 and about 220 ug·h/mL, between about 160 and about 210 ug·h/mL, between about 160 and about 200 ug·h/mL, between about 160 and about 200 ug·h/mL, between about 160 and about 180 ug·h/mL, or between about 160 and about 170 ug·h/mL.

[0180] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 170 and about 240 ug·h/mL, between about 170 and about 230 ug·h/mL, between about 170 and about 220 ug·h/mL, between about 170 and about 210 ug·h/mL, between about 170 and about 200 ug·h/mL, between about 170 and about 190 ug·h/mL, or between about 170 and about 180 ug·h/mL.

[0181] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 180 and about 240 ug·h/mL, between about 180 and about 230 ug·h/mL, between about 180 and about 220 ug·h/mL, or between about 180 and about 210 ug·h/mL, between about 180 and about 200 ug·h/mL, or between about 180 and about 190 ug·h/mL.

[0182] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 190 and about 240 ug·h/mL, between about 190 and about 230 ug·h/mL, between about 190 and about 220 ug·h/mL, between about 190 and about 210 ug·h/mL, or between about 190 and about 200 ug·h/mL.

[0183] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 200 and about 240 ug·h/mL, between about 200 and about 230 ug·h/mL, between about 200 and about 220 ug·h/mL, or between about 200 and about 210 ug·h/mL.

[0184] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable

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salt thereof, is administered at a dose effective to provide the mean AUC is between about 210 and about 240 ug·h/mL, between about 210 and about 230 ug·h/mL, or between about 210 and about 220 ug·h/mL.

[0185] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 200 and about 500 ug·h/mL, between about 200 and about 490 ug·h/mL, between about 200 and about 480 ug·h/mL, between about 200 and about 470 ug·h/mL, between about 200 and about 460 ug·h/mL, between about 200 and about 450 ug·h/mL, between about 200 and about 440 ug·h/mL, between about 200 and about 430 ug·h/mL, between about 200 and about 420 ug·h/mL, between about 200 and about 410 ug·h/mL, between about 200 and about 400 ug·h/mL, between about 200 and about 390 ug·h/mL, between about 200 and about 380 ug·h/mL, between about 200 and about 370 ug·h/mL, between about 200 and about 360 ug·h/mL, between about 200 and about 350 ug·h/mL, between about 200 and about 340 ug·h/mL, between about 200 and about 330 ug·h/mL, between about 200 and about 320 ug·h/mL, between about 200 and about 310 ug·h/mL, between about 200 and about 300 ug·h/mL, between about 200 and about 290 ug·h/mL, between about 200 and about 280 ug·h/mL, between about 200 and about 270 ug·h/mL, between about 200 and about 260 ug·h/mL, between about 200 and about 250 ug·h/mL, between about 200 and about 240 ug·h/mL, between about 200 and about 230 ug·h/mL, between about 200 and about 220 ug·h/mL, or between about 200 and about 210 ug·h/mL.

[0186] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC is between about 210 and about 500 ug·h/mL, between about 210 and about 490 ug·h/mL, between about 210 and about 480 ug·h/mL, between about 210 and about 470 ug·h/mL, between about 210 and about 460 ug·h/mL, between about 210 and about 450 ug·h/mL, between about 210 and about 440 ug·h/mL, between about 210 and about 430 ug·h/mL, between about 210 and about 420 ug·h/mL, between about 210 and about 410 ug·h/mL, between about 210 and about 400 ug·h/mL, between about 210 and about 390 ug·h/mL, between about 210 and about 380 ug·h/mL, between about 210 and about 370 ug·h/mL, between about 210 and about 360 ug·h/mL, between about 210 and about 350 ug·h/mL, between about 210 and about 340

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ug·h/mL, between about 210 and about 330 ug·h/mL, between about 210 and about 320 ug·h/mL, between about 210 and about 310 ug·h/mL, between about 210 and about 300 ug·h/mL, between about 210 and about 290 ug·h/mL, between about 210 and about 280 ug·h/mL, between about 210 and about 270 ug·h/mL, between about 210 and about 260 ug·h/mL, between about 210 and about 250 ug·h/mL, between about 210 and about 240 ug·h/mL, between about 210 and about 230 ug·h/mL, or between about 210 and about 220 ug·h/mL.

[0187] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC of between about 220 and about 500 ug·h/mL, between about 220 and about 490 ug·h/mL, between about 220 and about 480 ug·h/mL, between about 220 and about 470 ug·h/mL, between about 220 and about 460 ug·h/mL, between about 220 and about 450 ug·h/mL, between about 220 and about 440 ug·h/mL, between about 220 and about 430 ug·h/mL, between about 220 and about 420 ug·h/mL, between about 220 and about 410 ug·h/mL, between about 220 and about 400 ug·h/mL, between about 220 and about 390 ug·h/mL, between about 220 and about 380 ug·h/mL, between about 220 and about 370 ug·h/mL, between about 220 and about 360 ug·h/mL, between about 220 and about 350 ug·h/mL, between about 220 and about 340 ug·h/mL, between about 220 and about 330 ug·h/mL, between about 220 and about 320 ug·h/mL, between about 220 and about 310 ug·h/mL, between about 220 and about 300 ug·h/mL, between about 220 and about 290 ug·h/mL, between about 220 and about 280 ug·h/mL, between about 220 and about 270 ug·h/mL, between about 220 and about 260 ug·h/mL, between about 220 and about 250 ug·h/mL, between about 220 and about 240 ug·h/mL, or between about 220 and about 230 ug·h/mL.

[0188] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC of between about 230 and about 500 ug·h/mL, between about 230 and about 490 ug·h/mL, between about 230 and about 480 ug·h/mL, between about 230 and about 470 ug·h/mL, between about 230 and about 460 ug·h/mL, between about 230 and about 450 ug·h/mL, between about 230 and about 440 ug·h/mL, between about 230 and about 430 ug·h/mL, between about 230 and about 420 ug·h/mL, between about 230 and about 410 ug·h/mL, between about 230 and about 400

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ug·h/mL, between about 230 and about 390 ug·h/mL, between about 230 and about 380 ug·h/mL, between about 230 and about 370 ug·h/mL, between about 230 and about 360 ug·h/mL, between about 230 and about 350 ug·h/mL, between about 230 and about 340 ug·h/mL, between about 230 and about 330 ug·h/mL, between about 230 and about 320 ug·h/mL, between about 230 and about 310 ug·h/mL, between about 230 and about 300 ug·h/mL, between about 230 and about 290 ug·h/mL, between about 230 and about 280 ug·h/mL, between about 230 and about 270 ug·h/mL, between about 230 and about 260 ug·h/mL, between about 230 and about 250 ug·h/mL, or between about 230 and about 240 ug·h/mL.

[0189] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC of between about 240 and about 500 ug·h/mL, between about 240 and about 490 ug·h/mL, between about 240 and about 480 ug·h/mL, between about 240 and about 470 ug·h/mL, between about 240 and about 460 ug·h/mL, between about 240 and about 450 ug·h/mL, between about 240 and about 440 ug·h/mL, between about 240 and about 430 ug·h/mL, between about 240 and about 420 ug·h/mL, between about 240 and about 410 ug·h/mL, between about 240 and about 400 ug·h/mL, between about 240 and about 390 ug·h/mL, between about 240 and about 380 ug·h/mL, between about 240 and about 370 ug·h/mL, between about 240 and about 360 ug·h/mL, between about 240 and about 350 ug·h/mL, between about 240 and about 340 ug·h/mL, between about 240 and about 330 ug·h/mL, between about 240 and about 320 ug·h/mL, between about 240 and about 310 ug·h/mL, between about 240 and about 300 ug·h/mL, between about 240 and about 290 ug·h/mL, between about 240 and about 280 ug·h/mL, between about 240 and about 270 ug·h/mL, between about 240 and about 260 ug·h/mL, or between about 240 and about 250 ug·h/mL.

[0190] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC of between about 300 and about 500 ug·h/mL, between about 300 and about 490 ug·h/mL, between about 300 and about 480 ug·h/mL, between about 300 and about 470 ug·h/mL, between about 300 and about 460 ug·h/mL, between about 300 and about 450 ug·h/mL, between about 300 and about 440 ug·h/mL, between about 300 and about 430 ug·h/mL, between about 300 and about 420

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ug·h/mL, between about 300 and about 410 ug·h/mL, between about 300 and about 400 ug·h/mL, between about 300 and about 390 ug·h/mL, between about 300 and about 380 ug·h/mL, between about 300 and about 370 ug·h/mL, between about 300 and about 360 ug·h/mL, between about 300 and about 350 ug·h/mL, between about 300 and about 340 ug·h/mL, between about 300 and about 330 ug·h/mL, between about 300 and about 320 ug·h/mL, or between about 300 and about 310 ug·h/mL.

[0191] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC of between about 325 and about 500 ug·h/mL, between about 325 and about 490 ug·h/mL, between about 325 and about 480 ug·h/mL, between about 325 and about 470 ug·h/mL, between about 325 and about 460 ug·h/mL, between about 325 and about 450 ug·h/mL, between about 325 and about 440 ug·h/mL, between about 325 and about 430 ug·h/mL, between about 325 and about 420 ug·h/mL, between about 325 and about 410 ug·h/mL, between about 325 and about 400 ug·h/mL, between about 325 and about 390 ug·h/mL, between about 325 and about 380 ug·h/mL, between about 325 and about 370 ug·h/mL, between about 325 and about 360 ug·h/mL, between about 325 and about 350 ug·h/mL, between about 325 and about 340 ug·h/mL, or between about 325 and about 330 ug·h/mL.

[0192] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC of between about 330 and about 500 ug·h/mL, between about 330 and about 490 ug·h/mL, between about 330 and about 480 ug·h/mL, between about 330 and about 470 ug·h/mL, between about 330 and about 460 ug·h/mL, between about 330 and about 450 ug·h/mL, between about 330 and about 440 ug·h/mL, between about 330 and about 430 ug·h/mL, between about 330 and about 420 ug·h/mL, between about 330 and about 410 ug·h/mL, between about 330 and about 400 ug·h/mL, between about 330 and about 390 ug·h/mL, between about 330 and about 380 ug·h/mL, between about 330 and about 370 ug·h/mL, between about 330 and about 360 ug·h/mL, between about 330 and about 350 ug·h/mL, or between about 330 and about 340 ug·h/mL.

[0193] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC of between about 335

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and about 500 ug·h/mL, between about 335 and about 490 ug·h/mL, between about 335 and about 480 ug·h/mL, between about 335 and about 470 ug·h/mL, between about 335 and about 460 ug·h/mL, between about 335 and about 450 ug·h/mL, between about 335 and about 440 ug·h/mL, between about 335 and about 430 ug·h/mL, between about 335 and about 420 ug·h/mL, between about 335 and about 410 ug·h/mL, between about 335 and about 400 ug·h/mL, between about 335 and about 390 ug·h/mL, between about 335 and about 380 ug·h/mL, between about 335 and about 370 ug·h/mL, between about 335 and about 360 ug·h/mL, between about 335 and about 350 ug·h/mL, or between about 335 and about 340 ug·h/mL.

[0194] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean AUC of between about 340 and about 500 ug·h/mL, between about 340 and about 490 ug·h/mL, between about 340 and about 480 ug·h/mL, between about 340 and about 470 ug·h/mL, between about 340 and about 460 ug·h/mL, between about 340 and about 450 ug·h/mL, between about 340 and about 440 ug·h/mL, between about 340 and about 430 ug·h/mL, between about 340 and about 420 ug·h/mL, between about 340 and about 410 ug·h/mL, between about 340 and about 400 ug·h/mL, between about 340 and about 390 ug·h/mL, between about 340 and about 380 ug·h/mL, between about 340 and about 370 ug·h/mL, between about 340 and about 360 ug·h/mL, or between about 340 and about 350 ug·h/mL.

[0195] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a mean AUC of about 100 ug·h/mL, about 110 ug·h/mL, about 120 ug·h/mL, about 130 ug·h/mL, about 140 ug·h/mL, about 150 ug·h/mL, about 160 ug·h/mL, about 170 ug·h/mL, about 171 ug·h/mL, about 175 ug·h/mL, about 178 ug·h/mL, about 180 ug·h/mL, about 190 ug·h/mL, about 200 ug·h/mL, about 210 ug·h/mL, about 220 ug·h/mL, about 230 ug·h/mL, about 240 ug·h/mL, about 250 ug·h/mL, about 260 ug·h/mL, about 270 ug·h/mL, about 280 ug·h/mL, about 290 ug·h/mL, about 296 ug·h/mL, about 298 ug·h/mL, about 300 ug·h/mL, about 310 ug·h/mL, about 320 ug·h/mL, about 330 ug·h/mL, about 340 ug·h/mL, about 350 ug·h/mL, about 360 ug·h/mL, about 370 ug·h/mL, about 380 ug·h/mL, about 390 ug·h/mL, about 400 ug·h/mL, about 410 ug·h/mL, about 420 ug·h/mL, about 430 ug·h/mL, about 450 ug·h/mL, about 460 ug·h/mL, about 470

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ug·h/mL, about 480 ug·h/mL, about 490 ug·h/mL, or about 500 ug·h/mL.

[0196] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a targeted mean $C_{\max}$ of the conjugate, or a pharmaceutically acceptable salt thereof, so as to maximize dystrophin expression and minimize hypomagnesemia in a patient.

[0197] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean $C_{\max}$ of the conjugate, or a pharmaceutically acceptable salt thereof, of between about 70 and about 150 ug/ml, between about 70 and about 140 ug/ml, between about 70 and about 130 ug/ml, between about 70 and about 120 ug/ml, between about 70 and about 110 ug/ml, between about 70 and about 100 ug/ml, between about 70 and about 90 ug/ml, or between about 70 and about 80 ug/ml.

[0198] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean $C_{\max}$ of the conjugate, or a pharmaceutically acceptable salt thereof, of between about 75 and about 150 ug/ml, between about 75 and about 140 ug/ml, between about 75 and about 130 ug/ml, between about 75 and about 120 ug/ml, between about 75 and about 110 ug/ml, between about 75 and about 100 ug/ml, between about 75 and about 90 ug/ml, or between about 75 and about 80 ug/ml.

[0199] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean $C_{\max}$ of the conjugate, or a pharmaceutically acceptable salt thereof, of between about 80 and about 150 ug/ml, between about 80 and about 140 ug/ml, between about 80 and about 130 ug/ml, between about 80 and about 120 ug/ml, between about 80 and about 110 ug/ml, between about 80 and about 100 ug/ml, or between about 80 and about 90 ug/ml.

[0200] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean $C_{\max}$ of the conjugate, or a pharmaceutically acceptable salt thereof, of between about 85 and about 150 ug/ml, between about 85 and about 140 ug/ml, between about 85 and about 130 ug/ml, between about 85 and about 120 ug/ml, between about 85 and about 110 ug/ml, between about 85 and about 100 ug/ml, or between about 85 and about 90 ug/ml.

[0201] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable

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salt thereof, is administered at a dose effective to provide the mean $C_{\max}$ of the conjugate, or a pharmaceutically acceptable salt thereof, of between about 90 and about 150 ug/ml, between about 90 and about 140 ug/ml, between about 90 and about 130 ug/ml, between about 90 and about 120 ug/ml, between about 90 and about 110 ug/ml, or between about 90 and about 100 ug/ml.

[0202] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean $C_{\max}$ of the conjugate, or a pharmaceutically acceptable salt thereof, of between about 95 and about 150 ug/ml, between about 95 and about 140 ug/ml, between about 95 and about 130 ug/ml, between about 95 and about 120 ug/ml, between about 95 and about 110 ug/ml, or between about 95 and about 100 ug/ml.

[0203] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean $C_{\max}$ of the conjugate, or a pharmaceutically acceptable salt thereof, of between about 100 and about 150 ug/ml, between about 100 and about 140 ug/ml, between about 100 and about 130 ug/ml, between about 100 and about 120 ug/ml, or between about 100 and about 110 ug/ml.

[0204] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean $C_{\max}$ of the conjugate, or a pharmaceutically acceptable salt thereof, of between about 130 and about 250 ug/ml, between about 140 and about 250 ug/ml, between about 150 and about 250 ug/ml, between about 160 and about 250 ug/ml, between about 170 and about 250 ug/ml, between about 180 and about 250 ug/ml, between about 190 and about 250 ug/ml, between about 200 and about 250 ug/ml, between about 210 and about 250 ug/ml, between about 220 and about 250 ug/ml, between about 230 and about 250 ug/ml, or between about 240 and about 250 ug/ml.

[0205] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean $C_{\max}$ of the conjugate, or a pharmaceutically acceptable salt thereof, of between about 130 and about 200 ug/ml, between about 140 and about 200 ug/ml, between about 150 and about 200 ug/ml, between about 160 and about 200 ug/ml, between about 170 and about 200 ug/ml, between about 180 and about 200 ug/ml, or between about 190 and about 200 ug/ml.

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[0206] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean $C_{\max}$ of the conjugate, or a pharmaceutically acceptable salt thereof, of between about 130 and about 190 ug/ml, between about 140 and about 190 ug/ml, between about 150 and about 190 ug/ml, between about 160 and about 190 ug/ml, between about 170 and about 190 ug/ml, or between about 180 and about 190 ug/ml.

[0207] In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean $C_{\max}$ of the conjugate, or a pharmaceutically acceptable salt thereof, of between about 130 and about 180 ug/ml, between about 140 and about 180 ug/ml, between about 150 and about 180 ug/ml, between about 160 and about 180 ug/ml, or between about 170 and about 180 ug/ml. In some aspects, the antisense oligomer CPP conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean $C_{\max}$ of the conjugate, or a pharmaceutically acceptable salt thereof, of between about 130 and about 170 ug/ml, between about 140 and about 170 ug/ml, between about 150 and about 170 ug/ml, or between about 160 and about 170 ug/ml.

[0208] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide the mean $C_{\max}$ of the conjugate, or a pharmaceutically acceptable salt thereof, of about 80 ug/ml, about 85 ug/ml, about 90 ug/ml, about 95 ug/ml, about 100 ug/ml, about 105 ug/ml, about 110 ug/ml, about 115 ug/ml, about 120 ug/ml, about 125 ug/ml, about 130 ug/ml, about 135 ug/ml, about 140 ug/ml, about 145 ug/ml, about 150 ug/ml, about 155 ug/ml, about 160 ug/ml, about 165 ug/ml, about 170 ug/ml, about 175 ug/ml, about 180 ug/ml, about 185 ug/ml, about 190 ug/ml, about 195 ug/ml, about 200 ug/ml, about 205 ug/ml, about 210 ug/ml, about 215 ug/ml, about 220 ug/ml, about 225 ug/ml, about 230 ug/ml, about 235 ug/ml, about 240 ug/ml, about 245 ug/ml, or about 250 ug/ml.

[0209] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose of about 300 mg to about 900 mg, about 300 mg to about 850 mg, about 300 mg to about 800 mg, about 300 mg to about 850 mg, about 300 mg to about 800 mg, about 300 mg to about 750 mg, about 300 mg to about 700 mg, about 300 mg to about 650 mg, about 300 mg to about 600 mg, about 300 mg to about 550 mg, about 300 mg to about 500 mg, about 300 mg to about 450 mg, about 300 mg to about 400 mg, or about 300 mg.

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- [0210]** In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 300 mg to about 900 mg, about 300 mg to about 850 mg, about 300 mg to about 800 mg, about 300 mg to about 850 mg, about 300 mg to about 800 mg, about 300 mg to about 750 mg, about 300 mg to about 700 mg, about 300 mg to about 650 mg, about 300 mg to about 600 mg, about 300 mg to about 550 mg, about 300 mg to about 500 mg, about 300 mg to about 450 mg, about 300 mg to about 400 mg, or about 300 mg to about 350 mg.
- [0211]** In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 350 mg to about 900 mg, about 400 mg to about 900 mg, about 500 mg to about 900 mg, about 550 mg to about 900 mg, about 600 mg to about 800 mg, about 650 mg to about 900 mg, about 700 mg to about 900 mg, about 750 mg to about 900 mg, about 800 mg to about 900 mg, or about 850 mg to about 900 mg.
- [0212]** In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 350 mg to about 850 mg, about 400 mg to about 850 mg, about 500 mg to about 850 mg, about 550 mg to about 850 mg, about 600 mg to about 800 mg, about 650 mg to about 850 mg, about 700 mg to about 850 mg, about 750 mg to about 850 mg, or about 800 mg to about 850 mg.
- [0213]** In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 350 mg to about 800 mg, about 400 mg to about 800 mg, about 500 mg to about 800 mg, about 550 mg to about 800 mg, about 600 mg to about 800 mg, about 650 mg to about 800 mg, about 700 mg to about 800 mg, or about 750 mg to about 800 mg.
- [0214]** In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 350 mg to about 750 mg, about 400 mg to about 750 mg, about 500 mg to about 750 mg, about 550 mg to about 750 mg, about 600 mg to about 750 mg, about 650 mg to about 750 mg, or about 700 mg to about 750 mg.

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- [0215] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the ·6HCl salt of the conjugate of about 350 mg to about 700 mg, about 400 mg to about 700 mg, about 500 mg to about 700 mg, about 550 mg to about 700 mg, about 600 mg to about 700 mg, or about 650 mg to about 700 mg.
- [0216] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the ·6HCl salt of the conjugate of about 400 mg to about 900 mg, about 400 mg to about 850 mg, about 400 mg to about 800 mg, about 400 mg to about 750 mg, about 400 mg to about 700 mg, about 400 mg to about 650 mg, about 400 mg to about 600 mg, about 400 mg to about 550 mg, about 400 mg to about 500 mg, or about 400 mg to about 450 mg.
- [0217] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the ·6HCl salt of the conjugate of about 950 mg to about 1500 mg, about 900 mg to about 1500 mg, about 850 mg to about 1500 mg, or about 800 mg to about 1500 mg.
- [0218] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the ·6HCl salt of the conjugate of about 950 mg to about 1450 mg, about 900 mg to about 1450 mg, about 850 mg to about 1450 mg, or about 800 mg to about 1450 mg.
- [0219] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the ·6HCl salt of the conjugate of about 950 mg to about 1400 mg, about 900 mg to about 1400 mg, about 850 mg to about 1400 mg, or about 800 mg to about 1400 mg.
- [0220] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the ·6HCl salt of the conjugate of about 950 mg to about 1350 mg, about 900 mg to about 1350 mg, about 850 mg to about 1350 mg, or about 800 mg to about 1350 mg.
- [0221] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the ·6HCl salt of the conjugate of

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about 950 mg to about 1300 mg, about 900 mg to about 1300 mg, about 850 mg to about 1300 mg, or about 800 mg to about 1300 mg.

[0222] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 950 mg to about 1250 mg, about 900 mg to about 1250 mg, about 850 mg to about 1250 mg, or about 800 mg to about 1250 mg.

[0223] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 950 mg to about 1200 mg, about 900 mg to about 1200 mg, about 850 mg to about 1200 mg, about 800 mg to about 1200 mg, about 900 mg to about 1100 mg, about 900 mg to about 1000 mg, about 800 mg to about 1100 mg, about 800 mg to about 1000 mg.

[0224] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 1000 mg to about 1500 mg, about 1000 mg to about 1450 mg, about 1000 mg to about 1400 mg, about 1000 mg to about 1350 mg, about 1000 mg to about 1300 mg, about 1000 mg to about 1250 mg, about 1000 mg to about 1200 mg, about 1000 mg to about 1150 mg, or about 1000 mg to about 1100 mg.

[0225] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, or about 900 mg of the $\cdot 6\text{HCl}$ salt of the conjugate.

[0226] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, or about 1500 mg of the $\cdot 6\text{HCl}$ salt of the conjugate.

[0227] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered according to patient weight. The following weight bands are contemplated by the present disclosure: from about 5 kg to about 25 kg, from about 10 kg to about 25 kg, from about 15 kg to about 25 kg, from about 20 kg to about 25 kg, from about 18 kg

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to about 50kg, from about 25 kg to about 50 kg, from about 30 kg to about 50 kg, from about 35 kg to about 50 kg, from about 40 kg to about 50 kg, from about 50 kg to about 100 kg, from about 55 kg to about 100 kg, from about 60 kg to about 100 kg, from about 65 kg to about 100 kg, from about 70 kg to about 100 kg, from about 75 kg to about 100 kg, from about 80 kg to about 100 kg, from about 85 kg to about 100 kg, from about 90 kg to about 100 kg, from about 50 kg to about 90 kg, from about 55 kg to about 90 kg, from about 60 kg to about 90 kg, from about 65 kg to about 90 kg, from about 70 kg to about 90 kg, from about 75 kg to about 90 kg, from about 80 kg to about 90 kg, or from about 85 kg to about 90 kg.

[0228] The following weight bands are also contemplated by the present disclosure: from greater than or equal to 5 kg to less than 25 kg, from greater than or equal to 10 kg to less than 25 kg, from greater than or equal to 15 kg to less than 25 kg, from greater than or equal to 20 kg to less than 25 kg, from greater than or equal to 18 kg to less than 50 kg, from greater than or equal to 25 kg to less than 50 kg, from greater than or equal to 30 kg to less than 50 kg, from greater than or equal to 35 kg to less than 50 kg, from greater than or equal to 40 kg to less than 50 kg, greater than or equal to 50 kg, from greater than or equal to 50 kg to less than 100 kg, from greater than or equal to 55 kg to less than 100 kg, from greater than or equal to 60 kg to less than 100 kg, from greater than or equal to 65 kg to less than 100 kg, from greater than or equal to 70 kg to less than 100 kg, from greater than or equal to 75 kg to less than 100 kg, from greater than or equal to 80 kg to less than 100 kg, from greater than or equal to 85 kg to less than 100 kg, from greater than or equal to 90 kg to less than 100 kg, from greater than or equal to 50 kg to less than 90 kg, from greater than or equal to 55 kg to less than 90 kg, from greater than or equal to 60 kg to less than 90 kg, from greater than or equal to 65 kg to less than 90 kg, from greater than or equal to 70 kg to less than 90 kg, from greater than or equal to 75 kg to less than 90 kg, from greater than or equal to 80 kg to less than 90 kg, or from greater than or equal to 85 kg to less than 90 kg.

[0229] The following weight bands are also contemplated by the present disclosure: from about 5 kg to about 20 kg, from about 10 kg to about 20 kg, from about 15 kg to about 20 kg, from about 25 kg to about 40 kg, from about 30 kg to about 40 kg, from about 35 kg to about 40 kg, from about 18 kg to about 50 kg, from about 50 kg to about 90 kg, from about 55 kg to about 90 kg, from about 60 kg to about 90 kg, from about 65 kg to about 90 kg, from about 70 kg to about

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90 kg, from about 75 kg to about 90 kg, from about 80 kg to about 90 kg, or from about 85 kg to about 90 kg.

[0230] The following weight bands are also contemplated by the present disclosure: from greater than or equal to 5 kg to less than 20 kg, from greater than or equal to 10 kg to less than 20 kg, from greater than or equal to 15 kg to less than 20 kg, from greater than or equal to 25 kg to less than 40 kg, from greater than or equal to 30 kg to less than 40 kg, from greater than or equal to 35 kg to less than 40 kg, from greater than or equal to 50 kg to less than 90 kg, from greater than or equal to 55 kg to less than 90 kg, from greater than or equal to 60 kg to less than 90 kg, from greater than or equal to 65 kg to less than 90 kg, from greater than or equal to 70 kg to less than 90 kg, from greater than or equal to 75 kg to less than 90 kg, from greater than or equal to 80 kg to less than 90 kg, or from greater than or equal to 85 kg to less than 90 kg.

[0231] The following weight bands are also contemplated by the present disclosure: from about 5 kg to about 15 kg, from about 10 kg to about 15 kg, from about 25 kg to about 30 kg, from about 30 kg to about 35 kg, from about 30 kg to about 45 kg, from about 50 kg to about 85 kg, from about 55 kg to about 85 kg, from about 60 kg to about 85 kg, from about 65 kg to about 85 kg, from about 70 kg to about 85 kg, from about 75 kg to about 85 kg, from about 50 kg to about 75 kg, from about 55 kg to about 75 kg, from about 60 kg to about 75 kg, from about 65 kg to about 75 kg, from about 70 kg to about 75 kg or from about 80 kg to about 85 kg.

[0232] The following weight bands are also contemplated by the present disclosure: from greater than or equal to 5 kg to less than 15 kg, from greater than or equal to 10 kg to less than 15 kg, from greater than or equal to 25 kg to less than 30 kg, from greater than or equal to 30 kg to less than 35 kg, from greater than or equal to 30 kg to less than 45 kg, from greater than or equal to 50 kg to less than 85 kg, from greater than or equal to 55 kg to less than 85 kg, from greater than or equal to 60 kg to less than 85 kg, from greater than or equal to 65 kg to less than 85 kg, from greater than or equal to 70 kg to less than 85 kg, from greater than or equal to 75 kg to less than 85 kg, from greater than or equal to 50 kg to less than 75 kg, from greater than or equal to 55 kg to less than 75 kg, from greater than or equal to 60 kg to less than 75 kg, from greater than or equal to 65 kg to less than 75 kg, from greater than or equal to 70 kg to less than 75 kg or from greater than or equal to 80 kg to less than 85 kg.

[0233] The following weight bands are also contemplated by the present disclosure: from about

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10 kg to about 50 kg, from about 10 kg to about 45 kg, from about 10 kg to about 40 kg, from about 10 kg to about 35 kg, from about 15 kg to about 50 kg, from about 15 kg to about 45 kg, from about 15 kg to about 40 kg, from about 15 kg to about 35 kg, from about 20 kg to about 50 kg, from about 20 kg to about 45 kg, from about 20 kg to about 40 kg, from about 20 kg to about 35 kg, from about 25 kg to about 50 kg, from about 25 kg to about 45 kg, from about 25 kg to about 40 kg, or from about 25 kg to about 35 kg.

[0234] The following weight bands are also contemplated by the present disclosure: from greater than or equal to 10 kg to less than 50 kg, from greater than or equal to 10 kg to less than 45 kg, from greater than or equal to 10 kg to less than 40 kg, from greater than or equal to 10 kg to less than 35 kg, from greater than or equal to 15 kg to less than 50 kg, from greater than or equal to 15 kg to less than 45 kg, from greater than or equal to 15 kg to less than 40 kg, from greater than or equal to 15 kg to less than 35 kg, from greater than or equal to 20 kg to less than 50 kg, from greater than or equal to 20 kg to less than 45 kg, from greater than or equal to 20 kg to less than 40 kg, from greater than or equal to 20 kg to less than 35 kg, from greater than or equal to 25 kg to less than 50 kg, from greater than or equal to 25 kg to less than 45 kg, from greater than or equal to 25 kg to less than 40 kg, or from greater than or equal to 25 kg to less than 35 kg.

[0235] The following weight bands are also contemplated by the present disclosure: from about 20 kg to about 110 kg, from about 30 kg to about 110 kg, from about 40 kg to about 110 kg, from about 50 kg to about 110 kg, from about 60 kg to about 110 kg, from about 20 kg to about 100 kg, from about 30 kg to about 100 kg, from about 40 kg to about 100 kg, from about 50 kg to about 100 kg, from about 60 kg to about 100 kg, from about 20 kg to about 90 kg, from about 30 kg to about 90 kg, from about 40 kg to about 90 kg, from about 50 kg to about 90 kg, or from about 60 kg to about 90 kg.

[0236] The following weight bands are also contemplated by the present disclosure: from greater than or equal to 20 kg to less than 110 kg, from greater than or equal to 30 kg to less than 110 kg, from greater than or equal to 40 kg to less than 110 kg, from greater than or equal to 50 kg to less than 110 kg, from greater than or equal to 60 kg to less than 110 kg, from greater than or equal to 20 kg to less than 100 kg, from greater than or equal to 30 kg to less than 100 kg, from greater than or equal to 40 kg to less than 100 kg, from greater than or equal to 50 kg to less than 100 kg, from greater than or equal to 60 kg to less than 100 kg, from greater than or equal to 20 kg to less

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than 90 kg, from greater than or equal to 30 kg to less than 90 kg, from greater than or equal to 40 kg to less than 90 kg, from greater than or equal to 50 kg to less than 90 kg, or from greater than or equal to 60 kg to less than 90 kg.

[0237] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered according to the weight bands at a dose effective to achieve a mean AUC of between about 100 and about 200 ug·h/mL in a patient within a particular weight band. In other aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered according to the weight bands at a dose effective to achieve a mean AUC of between about 120 and about 240 ug·h/mL in a patient within a particular weight band. In other aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered according to the weight bands at a dose effective to achieve a mean AUC of between about 200 and about 500 ug·h/mL in a patient within a particular weight band.

[0238] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the ·6HCl salt of the conjugate according to the following schedule:

vii) about 300 mg to about 700 mg, or about 900 mg to about 1200 mg, once every four weeks for a patient that weighs from about 10 kg to about 25 kg;

viii) about 600 mg to about 800 mg, or about 1000 mg to about 1300 mg, once every four weeks for a patient that weighs from about 25 kg to about 50 kg; or

ix) about 700 mg to about 900 mg, or about 1200 mg to about 1500 mg, once every four weeks for a patient that weighs from about 50 kg to about 100 kg;

to achieve a mean AUC between about 100 and about 200 ug·h/mL, or is between about 200 and about 500 ug·h/mL.

[0239] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the ·6HCl salt of the conjugate according to the following schedule:

x) about 500 mg to about 700 mg, or about 1000 mg to about 1200 mg, once every four weeks for a patient that weighs from about 15 kg to about 40 kg; or

xi) about 600 mg to about 800 mg, or about 1100 mg to about 1400 mg, once every four weeks for a patient that weighs from about 40 kg to about 100 kg;

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to achieve a mean AUC between about 100 and about 200 ug·h/mL, or is between about 200 and about 500 ug·h/mL.

[0240] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the ·6HCl salt of the conjugate according to the following schedule:

- xii) about 750 mg to about 1250 mg, once every four weeks for a patient that weighs greater than or equal to about 18 kg to less than about 50 kg; or
- xiii) about 850 mg to about 1350 mg, once every four weeks for a patient that weighs greater than or equal to about 50 kg;

to achieve a mean AUC between about 120 and about 240 ug·h/mL, or between about 200 and about 500 ug·h/mL.

[0241] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from about 5 kg to about 25 kg, from about 10 kg to about 25 kg, from about 15 kg to about 25 kg, from about 20 kg to about 25 kg, 5 kg to about 20 kg, from about 10 kg to about 20 kg, or from about 15 kg to about 20 kg at a dose equivalent to the dose of the ·6HCl salt of the conjugate of from about 300 mg to about 750 mg, about 350 mg to about 750 mg, about 400 mg to about 750 mg, about 450 mg to about 750 mg, about 400 mg to about 750 mg, about 450 mg to about 750 mg, about 500 mg to about 750 mg, about 550 mg to about 750 mg, about 600 mg to about 750 mg, about 650 mg to about 750 mg, 300 mg to about 700 mg, about 350 mg to about 700 mg, about 400 mg to about 700 mg, about 450 mg to about 700 mg, about 400 mg to about 700 mg, about 450 mg to about 700 mg, about 500 mg to about 700 mg, about 550 mg to about 700 mg, about 600 mg to about 700 mg, about 650 mg to about 700 mg, about 300 mg to about 650 mg, about 350 mg to about 650 mg, about 400 mg to about 650 mg, about 450 mg to about 650 mg, about 500 mg to about 650 mg, about 550 mg to about 650 mg, or about 600 mg to about 650 mg.

[0242] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from about 25 kg to about 50 kg, from about 30 kg to about 50 kg, from about 35 kg to about 50 kg, from about 40 kg to about 50 kg, from about 25 kg to about 40 kg, from about 30 kg to about 40 kg, from about 35 kg to about 40 kg, from about 25 kg to about 30 kg, from about 30 kg to about 45 kg, from about 35 kg to about 45 kg,

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from about 40 kg to about 45 kg, from about 30 kg to about 35 kg, from about 35 kg to about 45 kg, from about 25 kg to about 45 kg, from about 25 kg to about 35 kg, or from about 35 kg to about 45 kg at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of from about 600 mg to about 800 mg, about 650 mg to about 800 mg, about 700 mg to about 800 mg, about 750 mg to about 800 mg, about 600 mg to about 750 mg, about 650 mg to about 750 mg, about 700 mg to about 750 mg, 600 mg to about 700 mg, or about 650 mg to about 700 mg.

[0243] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs greater than or equal to about 18 kg to less than about 50 kg at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of from about 750 mg to about 1250 mg. In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs greater than about 50 kg, at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of from about 850 mg to about 1350 mg.

[0244] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from about 50 kg to about 100 kg, from about 55 kg to about 100 kg, from about 60 kg to about 100 kg, from about 65 kg to about 100 kg, from about 70 kg to about 100 kg, from about 75 kg to about 100 kg, from about 80 kg to about 100 kg, from about 85 kg to about 100 kg, or from about 90 kg to about 100 kg, from about 50 kg to about 90 kg, from about 55 kg to about 90 kg, from about 60 kg to about 90 kg, from about 65 kg to about 90 kg, from about 70 kg to about 90 kg, from about 75 kg to about 90 kg, from about 80 kg to about 90 kg, or from about 85 kg to about 90 kg at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of from about 700 mg to about 900 mg, about 750 mg to about 900 mg, about 800 mg to about 900 mg, or about 850 mg to about 900 mg, about 700 mg to about 850 mg, about 750 mg to about 850 mg, or about 800 mg to about 850 mg, about 700 mg to about 750 mg, about 750 mg to about 800 mg, about 750 mg to about 900 mg, or about 800 mg to about 900 mg.

[0245] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from about 5 kg to about 25 kg, from about 10 kg to about 25 kg, from about 15 kg to about 25 kg, from about 20 kg to about 25 kg, 5 kg to about 20 kg, from about 10 kg to about 20 kg, or from about 15 kg to about 20 kg at a dose

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equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of from about 900 mg to about 1200 mg, about 850 mg to about 1200 mg, about 800 mg to about 1200 mg, about 900 mg to about 1100 mg, about 900 mg to about 1000 mg, about 800 mg to about 1100 mg, or about 800 mg to about 1000 mg.

[0246] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from about 25 kg to about 50 kg, from about 30 kg to about 50 kg, from about 35 kg to about 50 kg, from about 40 kg to about 50 kg, from about 25 kg to about 40 kg, from about 30 kg to about 40 kg, from about 35 kg to about 40 kg, from about 25 kg to about 30 kg, from about 30 kg to about 45 kg, from about 35 kg to about 45 kg, from about 40 kg to about 45 kg, from about 30 kg to about 35 kg, from about 35 kg to about 45 kg, from about 25 kg to about 45 kg, from about 25 kg to about 35 kg, or from about 35 kg to about 45 kg at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of from about 1000 mg to about 1300 mg, about 1000 mg to about 1250 mg, about 1000 mg to about 1200 mg, about 1000 mg to about 1150 mg, about 1050 mg to about 1100 mg, about 1050 mg to about 1300 mg, about 1050 mg to about 1250 mg, about 1050 mg to about 1200 mg, about 1050 mg to about 1150 mg, about 1050 mg to about 1100 mg, about 1050 mg to about 1250, about 1100 mg to about 1250, about 1150 mg to about 1250, about 1200 mg to about 1250, or about 1250 mg to about 1300.

[0247] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from about 50 kg to about 100 kg, from about 55 kg to about 100 kg, from about 60 kg to about 100 kg, from about 65 kg to about 100 kg, from about 70 kg to about 100 kg, from about 75 kg to about 100 kg, from about 80 kg to about 100 kg, from about 85 kg to about 100 kg, or from about 90 kg to about 100 kg, from about 50 kg to about 90 kg, from about 55 kg to about 90 kg, from about 60 kg to about 90 kg, from about 65 kg to about 90 kg, from about 70 kg to about 90 kg, from about 75 kg to about 90 kg, from about 80 kg to about 90 kg, or from about 85 kg to about 90 kg at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of from about 1200 mg to about 1500 mg, 1000 mg to about 1500 mg, about 1000 mg to about 1450 mg, about 1000 mg to about 1400 mg, about 1000 mg to about 1350 mg, about 1000 mg to about 1300 mg, about 1000 mg to about 1250 mg, about 1200 mg to about 1450 mg, about 1200 mg to about 1400 mg, about 1200 mg to about 1350 mg, about 1200

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mg to about 1300 mg, or about 1200 mg to about 1250 mg.

[0248] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from about 5 kg to about 25 kg, from about 10 kg to about 25 kg, from about 15 kg to about 25 kg, from about 20 kg to about 25 kg, 5 kg to about 20 kg, from about 10 kg to about 20 kg, or from about 15 kg to about 20 kg at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 550 mg, 600 mg, about 650 mg, or about 700 mg.

[0249] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from about 5 kg to about 25 kg, from about 10 kg to about 25 kg, from about 15 kg to about 25 kg, from about 20 kg to about 25 kg, 5 kg to about 20 kg, from about 10 kg to about 20 kg, or from about 15 kg to about 20 kg at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 1050 mg, 1100 mg, 1150 mg, or about 1200 mg.

[0250] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from about 25 kg to about 50 kg, from about 30 kg to about 50 kg, from about 35 kg to about 50 kg, from about 40 kg to about 50 kg, from about 25 kg to about 40 kg, from about 30 kg to about 40 kg, from about 35 kg to about 40 kg, from about 25 kg to about 30 kg, from about 30 kg to about 45 kg, from about 35 kg to about 45 kg, from about 40 kg to about 45 kg, from about 30 kg to about 35 kg, from about 35 kg to about 45 kg, from about 25 kg to about 45 kg, from about 25 kg to about 35 kg, or from about 35 kg to about 45 kg at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 600 mg, about 650 mg, about 700 mg, or about 700 mg.

[0251] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from about 25 kg to about 50 kg, from about 30 kg to about 50 kg, from about 35 kg to about 50 kg, from about 40 kg to about 50 kg, from about 25 kg to about 40 kg, from about 30 kg to about 40 kg, from about 35 kg to about 40 kg, from about 25 kg to about 30 kg, from about 30 kg to about 45 kg, from about 35 kg to about 45 kg, from about 40 kg to about 45 kg, from about 30 kg to about 35 kg, from about 35 kg to about 45 kg, from about 25 kg to about 45 kg, from about 25 kg to about 35 kg, or from about 35 kg to about 45 kg at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of

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the conjugate of about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, or about 1300 mg.

[0252] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from about 50 kg to about 100 kg, from about 55 kg to about 100 kg, from about 60 kg to about 100 kg, from about 65 kg to about 100 kg, from about 70 kg to about 100 kg, from about 75 kg to about 100 kg, from about 80 kg to about 100 kg, from about 85 kg to about 100 kg, or from about 90 kg to about 100 kg, from about 50 kg to about 90 kg, from about 55 kg to about 90 kg, from about 60 kg to about 90 kg, from about 65 kg to about 90 kg, from about 70 kg to about 90 kg, from about 75 kg to about 90 kg, from about 80 kg to about 90 kg, or from about 85 kg to about 90 kg at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 700 mg, about 750 mg, about 800 mg, or about 850 mg.

[0253] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from about 50 kg to about 100 kg, from about 55 kg to about 100 kg, from about 60 kg to about 100 kg, from about 65 kg to about 100 kg, from about 70 kg to about 100 kg, from about 75 kg to about 100 kg, from about 80 kg to about 100 kg, from about 85 kg to about 100 kg, or from about 90 kg to about 100 kg, from about 50 kg to about 90 kg, from about 55 kg to about 90 kg, from about 60 kg to about 90 kg, from about 65 kg to about 90 kg, from about 70 kg to about 90 kg, from about 75 kg to about 90 kg, from about 80 kg to about 90 kg, or from about 85 kg to about 90 kg at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, or about 1550 mg.

[0254] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from about 80 kg to about 100 kg, from about 85 kg to about 100 kg, from about 90 kg to about 100 kg, from about 95 kg to about 100 kg, from about 80 kg to about 90 kg, from about 75 kg to about 90 kg, from about 75 kg to about 95 kg, from about 75 kg to about 80 kg, or from about 80 kg to about 90 kg, at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1100 mg.

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- [0255] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from about 80 kg to about 100 kg, from about 85 kg to about 100 kg, from about 90 kg to about 100 kg, from about 95 kg to about 100 kg, from about 80 kg to about 90 kg, from about 75 kg to about 90 kg, from about 75 kg to about 95 kg, from about 75 kg to about 80 kg, or from about 80 kg to about 90 kg, at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, or about 1400 mg.
- [0256] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from more than about 45 kg, about 50 kg, about 55 kg, about 60 kg, or about 65 kg, at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg.
- [0257] In some aspects, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered to a patient that weighs from more than about 45 kg, about 50 kg, about 55 kg, about 60 kg, or about 65 kg, at a dose equivalent to the dose of the $\cdot 6\text{HCl}$ salt of the conjugate of about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, or about 1450 mg.
- [0258] If desired, the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain situations, dosing is one administration per day. In certain embodiments, dosing is one or more administration per every 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 days, or every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 weeks, or every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months, as needed, to maintain the desired expression of a functional dystrophin protein. In certain embodiments, dosing is one or more administrations once every two weeks. In some embodiments, dosing is one administration once every two weeks. In various embodiments, dosing is one or more administrations every month. In certain embodiments, dosing is one administration every month.

Cell Penetrating Peptides (CPPs)

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[0259] As described, cell-penetrating peptides (CPP), for example, an arginine-rich peptide transport moiety, have been shown to be effective in enhancing penetration of antisense oligomers into a cell and to cause exon skipping in different muscle groups in animal models.

[0260] Exemplary CPPs are provided in Table 1.

Table 1.

Exemplary Carrier Peptide Sequences	
Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
(RFF) ₃ ; CP0407	RFFRFFRFF-aa (SEQ ID NO: 89)
RTR	RTRTRFLRRT-aa (SEQ ID NO: 90)
RFFR	RFFRFFRFFR-aa (SEQ ID NO: 91)
KTR	KTRTKFLKKT-aa (SEQ ID NO: 92)
KFF	KFFKFFKFF-aa (SEQ ID NO: 93)
KFFK	KFFKFFKFFK-aa (SEQ ID NO: 94)
(RFF) ₂	RFFRFF-aa (SEQ ID NO: 95)
(RFF) ₂ R	RFFRFFR-aa (SEQ ID NO: 96)
RX	RXXRXXR-aa (SEQ ID NO: 97)
(RXR) ₄ ; P007	RXRRXRRXRRXR-aa (SEQ ID NO: 98)
Tat ₄₇₋₅₈	YGRKKRRQRRR-aa (SEQ ID NO: 99)
Tat ₄₈₋₅₈	GRKKRRQRRR-aa (SEQ ID NO: 100)
Tat ₄₉₋₅₈	RKKRRQRRR-aa (SEQ ID NO: 101)
Penetratin	RQIKIWFQNRRMKWKKGG-aa (SEQ ID NO: 102)
Transportan	GWTLNSAGYLLGKINLKALAALAKKIL-aa (SEQ ID NO: 103)
2XHph-1	YARVRRRGPRGYARVRRRGPRR-aa (SEQ ID NO: 104)
Hph-1	YARVRRRGPRR-aa (SEQ ID NO: 105)
Sim-2	AKAARQAAR-aa (SEQ ID NO: 106)
HSV1 VP22	DAATATRGRSAASRPTERPRAPARSASRPRRPVE-aa (SEQ ID NO: 107)
Pep-1	KETWWETWWTEWSQPKKKRKV-aa (SEQ ID NO: 108)
Pep-2	KETWFETWFTEWSQPKKKRKV-aa (SEQ ID NO: 109)

Exemplary Carrier Peptide Sequences	
Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
ANTP	RQIKIWFQNRRMKWKK-aa (SEQ ID NO: 110)
R ₆ Pen	RRRRRR-RQIKIWFQNRRMKWKKGG-aa (SEQ ID NO: 111)
rTat	RRRQRRKKRC-aa (SEQ ID NO: 112)
pTat	CYGRKKRRQRRR-aa (SEQ ID NO: 113)
R ₉ F ₂	RRRRRRRRRFFC-aa (SEQ ID NO: 114)
R ₉ CF ₂ , RRRRRRRRRCFF	RRRRRRRRRCFF-aa (SEQ ID NO: 115)
R ₈ CF ₂ R	RRRRRRRRRCFFR-aa (SEQ ID NO: 116)
R ₆ CF ₂ R ₃	RRRRRRRCFFRRR-aa (SEQ ID NO: 117)
R ₅ FCFR ₄	RRRRRRCFFRRRR-aa (SEQ ID NO: 118)
R ₅ F ₂ R ₄	RRRRRFFRRRR-aa (SEQ ID NO: 119)
R ₄ CF ₂ R ₅	RRRRCFFRRRRR-aa (SEQ ID NO: 120)
R ₂ CF ₂ R ₇	RRCFFRRRRRRR-aa (SEQ ID NO: 121)
CF ₂ R ₉	CFFRRRRRRRRR-aa (SEQ ID NO: 122)
CR ₉ F ₂	CRRRRRRRRRFF-aa (SEQ ID NO: 123)
F ₂ R ₉	FFRRRRRRRRR-aa (SEQ ID NO: 124)
R ₅ F ₂ CF ₂ R ₄	RRRRRFFCFFRRRR-aa (SEQ ID NO: 125)
R ₉ I ₂	RRRRRRRRRII-aa (SEQ ID NO: 126)
R ₈ F ₃	RRRRRRRRFFF-aa (SEQ ID NO: 127)
R ₉ F ₄	RRRRRRRRRFFFF-aa (SEQ ID NO: 128)
R ₅ F ₂	RRRRRRRRFF-aa (SEQ ID NO: 129)
R ₆ F ₂	RRRRRRFF-aa (SEQ ID NO: 130)
R ₅ F ₂	RRRRRFF-aa (SEQ ID NO: 131)
(RRX) ₃ RR	RRXRRXRRXR-aa (SEQ ID NO: 132)
(RXR) ₄	RXRRXRRXRRXR-aa (SEQ ID NO: 98)
(XRR) ₄	XRRXRRXRRXR-aa (SEQ ID NO: 134)
(RX) ₅ RR	RXRXRXRXRXR-aa (SEQ ID NO: 135)

Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
(RXR) ₃	RXRRXRRX-aa (SEQ ID NO: 136)
(RXR) ₂ R	RXRRXRR-aa (SEQ ID NO: 137)
(RXR) ₂	RXRRX-aa (SEQ ID NO: 138)
(RKX) ₃ RK	RKXRKXRKXRK-aa (SEQ ID NO: 139)
(RHX) ₃ RH	RHXRHXRHXRH-aa (SEQ ID NO: 140)
R ₈ CF ₂ R	RRRRRRRRCFFR-aa (SEQ ID NO: 116)
(RRX) ₃ RR	RRXRRXRRXRR-aa (SEQ ID NO: 132)
(RXR) ₄ ; P007	RXRRXRRXRRX-aa (SEQ ID NO: 98)
(XRR) ₄	XRRXRRXRRXRR-aa (SEQ ID NO: 134)
(RX) ₅ R	RXRXRXRXRX-aa (SEQ ID NO: 135)
(RX) ₇ R	RXRXRXRXRXRX-aa (SEQ ID NO: 146)
(RXR) ₅	RXRRXRRXRRXRR-aa (SEQ ID NO: 147)
(RXRRBR) ₂ ; B	RXRRBRXRRBR-aa (SEQ ID NO: 148)
(RXR) ₃ RBR	RXRRXRRXRRBR-aa (SEQ ID NO: 149)
(RB) ₅ RXRBR	RBRBRBRBRXRBR-aa (SEQ ID NO: 150)
RBRBRBRXRBRBR	RBRBRBRXRBRBR-aa (SEQ ID NO: 151)
BR	
X(RB) ₃ RX(RB) ₃ R-X	XRBRBRBRXRBRBRBR-aa (SEQ ID NO: 152)
(RBRX) ₄	RBRXRBRXRBRXRBR-aa (SEQ ID NO: 153)
(RB) ₄ (RX) ₃ R	RBRBRBRBRXRXR-aa (SEQ ID NO: 154)
RX(RB) ₂ RX(RB) ₃ R	RXRBRBRXRBRBRBR-aa (SEQ ID NO: 155)
(RB) ₇ R	RBRBRBRBRBRBRBR-aa (SEQ ID NO: 156)
R ₄	tg-RRRR-aa (SEQ ID NO: 157)
R ₅	tg-RRRRR-aa (SEQ ID NO: 158)
R ₆	tg-RRRRRR-aa (SEQ ID NO: 159)
R ₇	tg-RRRRRRR-aa (SEQ ID NO: 160)
R ₈	tg-RRRRRRRR-aa (SEQ ID NO: 161)
R ₅ GR ₄	tg-RRRRRGRRRR-aa (SEQ ID NO: 162)

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Exemplary Carrier Peptide Sequences	
Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
R ₅ F ₂ R ₄	tg-RRRRRFFRRRR-aa (SEQ ID NO: 163)
Tat	tg-RKKRRQRRR-aa (SEQ ID NO: 164)
rTat	tg-RRRQRRKKR-aa (SEQ ID NO: 165)
	RXRRXR-aa (SEQ ID NO: 138)
	RBRRBR-aa (SEQ ID NO: 167)
	RXRRBR-aa (SEQ ID NO: 168)
	RBRRXR-aa (SEQ ID NO: 169)
	RXRY ^b RXR-aa (SEQ ID NO: 170)
	RBRY ^b RBR-aa (SEQ ID NO: 171)
	RXRY ^b RBR-aa (SEQ ID NO: 172)
	RBRY ^b RXR-aa (SEQ ID NO: 173)
	RXRILFQYRXR-aa (SEQ ID NO: 174)
	RBRIILFQYRBR-aa (SEQ ID NO: 175)
	RXRILFQYRBR-aa (SEQ ID NO: 176)
	RBRIILFQYRXR-aa (SEQ ID NO: 177)
	RXRRXRRXR-aa (SEQ ID NO: 136)
	RBRRBRRBR-aa (SEQ ID NO: 179)
	RXRRBRRXR-aa (SEQ ID NO: 180)
	RXRRBRRBR-aa (SEQ ID NO: 181)
	RXRRXRRBR-aa (SEQ ID NO: 182)
	RBRRXRRBR-aa (SEQ ID NO: 183)
	RBRRXRRXR-aa (SEQ ID NO: 184)
	RBRRBRRXR-aa (SEQ ID NO: 185)
	RXRY ^b RXRRXR-aa (SEQ ID NO: 186)
	RXRRXRY ^b RXR-aa (SEQ ID NO: 187)
	RXRILFQYRXRRXR-aa (SEQ ID NO: 188)
	RXRRXRILFQYRXR-aa (SEQ ID NO: 189)
	RXRY ^b RXRY ^b RXR-aa (SEQ ID NO: 190)

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Exemplary Carrier Peptide Sequences	
Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	RXRILFQYRXRILFQYRXXR-aa (SEQ ID NO: 191)
	RXRILFQYRXRY ^b RXR-aa (SEQ ID NO: 192)
	RXRY ^b RXRILFQYRXXR-aa (SEQ ID NO: 193)
	RBRY ^b RBRRBR-aa (SEQ ID NO: 194)
	RBRRBRY ^b RBR-aa (SEQ ID NO: 195)
	RBRILFQYRBRRBR-aa (SEQ ID NO: 196)
	RBRRBRILFQYRBR-aa (SEQ ID NO: 197)
	RBRYRBRY ^b RBR-aa (SEQ ID NO: 198)
	RBRILFQYRBILFQYRBR-aa (SEQ ID NO: 199)
	RBRY ^b RBRILFQYRBR-aa (SEQ ID NO: 200)
	RBRILFQYRBRY ^b RBR-aa (SEQ ID NO: 201)
	RXRY ^b RBRRXR-aa (SEQ ID NO: 202)
	RXRRBRY ^b RXR-aa (SEQ ID NO: 203)
	RXRILFQYRBRRXR-aa (SEQ ID NO: 204)
	RXRRBRILFQYRXXR-aa (SEQ ID NO: 205)
	RXRY ^b RBRY ^b RXR-aa (SEQ ID NO: 206)
	RXRILFQYRBILFQYRXXR-aa (SEQ ID NO: 207)
	RXRY ^b RBRILFQYRXXR-aa (SEQ ID NO: 208)
	RXRILFQYRBRY ^b RXR-aa (SEQ ID NO: 209)
	RXRY ^b RBRRBR-aa (SEQ ID NO: 210)
	RXRRBRY ^b RBR-aa (SEQ ID NO: 211)
	RXRILFQYRBRRBR-aa (SEQ ID NO: 212)
	RXRRBRILFQYRBR-aa (SEQ ID NO: 213)
	RXRY ^b RBRY ^b RBR-aa (SEQ ID NO: 214)
	RXRILFQYRBILFQYRBR-aa (SEQ ID NO: 215)
	RXRY ^b RBRILFQYRBR-aa (SEQ ID NO: 216)
	RXRILFQYRBRY ^b RBR-aa (SEQ ID NO: 217)
	RXRY ^b RXRRBR-aa (SEQ ID NO: 218)

Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	RXRRXRY ^b RBR-aa (SEQ ID NO: 219)
	RXRILFQYRXRRBR-aa (SEQ ID NO: 220)
	RXRRXRILFQYRBR-aa (SEQ ID NO: 221)
	RXRY ^b RXRY ^b RBR-aa (SEQ ID NO: 222)
	RXRILFQYRXRILFQYRBR-aa (SEQ ID NO: 223)
	RXRY ^b RXRILFQYRBR-aa (SEQ ID NO: 224)
	RXRILFQYRXRY ^b RBR-aa (SEQ ID NO: 225)
	RBRY ^b RXRRBR-aa (SEQ ID NO: 226)
	RBRXRY ^b RBR-aa (SEQ ID NO: 227)
	RBRILFQYRXRRBR-aa (SEQ ID NO: 228)
	RBRXRILFQYRBR-aa (SEQ ID NO: 229)
	RBRY ^b RXRY ^b RBR-aa (SEQ ID NO: 230)
	RBRILFQYRXRILFQYRBR-aa (SEQ ID NO: 231)
	RBRY ^b RXRILFQYRBR-aa (SEQ ID NO: 232)
	RBRILFQYRXRY ^b RBR-aa (SEQ ID NO: 233)
	RBRY ^b RXRRXR-aa (SEQ ID NO: 234)
	RBRXRY ^b RXR-aa (SEQ ID NO: 235)
	RBRILFQYRXRRXR-aa (SEQ ID NO: 236)
	RBRXRILFQYRXR-aa (SEQ ID NO: 237)
	RBRY ^b RXRY ^b RXR-aa (SEQ ID NO: 238)
	RBRILFQYRXRILFQYRXR-aa (SEQ ID NO: 239)
	RBRY ^b RXRILFQYRXR-aa (SEQ ID NO: 240)
	RBRILFQYRXRY ^b RXR-aa (SEQ ID NO: 241)
	RBRY ^b RBRRXR-aa (SEQ ID NO: 242)
	RBRRBRY ^b RXR-aa (SEQ ID NO: 243)
	RBRILFQYRBRRXR-aa (SEQ ID NO: 244)
	RBRRBRILFQYRXR-aa (SEQ ID NO: 245)
	RBRY ^b RBRY ^b RXR-aa (SEQ ID NO: 246)

Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	RBRILFQYRBRILFQYRXXR-aa (SEQ ID NO: 247)
	RBRY ^b RBRILFQYRXXR-aa (SEQ ID NO: 248)
	RBRILFQYRBRY ^b RXXR-aa (SEQ ID NO: 249)
	RXRRXRRXRRXXR-aa (SEQ ID NO: 98)
	RXRRBRRXRILFQYRXXRBRXXR-aa (SEQ ID NO: 251)
	RXRRBRRXRRBR-aa (SEQ ID NO: 148)
	YGRKKRRQRRRP-aa (SEQ ID NO: 253)
	RXRRXRRXRRXRXBASSLNIAXC-aa (SEQ ID NO: 254)
	RXRRBRRXRILFQYRXXRBRXRBASSLNIAXC-aa (SEQ ID NO: 255)
	RXRRBRRXRASSLNIA RXXRBRXRBC-aa (SEQ ID NO: 256)
	RXRRBRRXRRBRXBASSLNIA-aa (SEQ ID NO: 257)
	THRPPMWSPVWP-aa (SEQ ID NO: 258)
	HRPPMWSPVWP-aa (SEQ ID NO: 259)
	THRPPMWSPV-aa (SEQ ID NO: 260)
	THRPPMWSP-aa (SEQ ID NO: 261)
	THRPPMWSPVFP-aa (SEQ ID NO: 262)
	THRPPMWSPVYP-aa (SEQ ID NO: 263)
	THRPPMWSPA WP-aa (SEQ ID NO: 264)
	THRPPMWSPLWP-aa (SEQ ID NO: 265)
	THRPPMWSP IWP-aa (SEQ ID NO: 266)
	THRPPMWTPVVWP-aa (SEQ ID NO: 267)
	THRPPMFSPVWP-aa (SEQ ID NO: 268)
	THRPPMWS-aa (SEQ ID NO: 269)
	HRPPMWSPVW-aa (SEQ ID NO: 270)
	THRPPMYSPVWP-aa (SEQ ID NO: 271)

Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	THRPPnleWSPVWP-aa (nle = norleucine) (SEQ ID NO: 272)
	THKPPMWSPVWP-aa (SEQ ID NO: 273)
	SHRPPMWSPVWP-aa (SEQ ID NO: 274)
	STFTHPR-aa (SEQ ID NO: 275)
	YDIDNRR-aa (SEQ ID NO: 276)
	AYKPVGR-aa (SEQ ID NO: 277)
	HAIYPRH-aa (SEQ ID NO: 278)
	HTPNSTH-aa (SEQ ID NO: 279)
	ASSPVHR-aa (SEQ ID NO: 280)
	SSLPLRK-aa (SEQ ID NO: 281)
	KKRS-aa (SEQ ID NO: 282)
	KRSK-aa (SEQ ID NO: 283)
	KKRSK-aa (SEQ ID NO: 284)
	KSRK-aa (SEQ ID NO: 285)
	SRKR-aa (SEQ ID NO: 286)
	RKRK-aa (SEQ ID NO: 287)
	KSRKR-aa (SEQ ID NO: 288)
	QHPPWRV-aa (SEQ ID NO: 289)
	THPPTTH-aa (SEQ ID NO: 290)
	YKHTPTT-aa (SEQ ID NO: 291)
	QGMHRGT-aa (SEQ ID NO: 292)
	SRKRK-aa (SEQ ID NO: 293)
	KSRKRK-aa (SEQ ID NO: 294)
	PKKKRKV-aa (SEQ ID NO: 295)
	GKKRSKV-aa (SEQ ID NO: 296)
	KSRKRKL-aa (SEQ ID NO: 297)
	HSPSKIP-aa (SEQ ID NO: 298)

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Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	HMATFHY-aa (SEQ ID NO: 299)
	AQPNKFK-aa (SEQ ID NO: 300)
	NLTRLHT-aa (SEQ ID NO: 301)
	KKKR-aa (SEQ ID NO: 302)
	KKRK-aa (SEQ ID NO: 303)
	KKKRK-aa (SEQ ID NO: 304)
	RRRRRRQIKIWFQNRRMKWKKGGC-aa (SEQ ID NO: 305)
	RRRRRRRQIKIWFQNRRMKWKKGGC-aa (SEQ ID NO: 306)
	RQIKIWFQNRRMKWKKGGC-aa (SEQ ID NO: 307)
	RRRRRRRQIKIWFQNRRMKWKKC-aa (SEQ ID NO: 308)
	RXRRXRRXRRQIKIWFQNRRMKWKKGGC-aa (SEQ ID NO: 309)
	RRRRRRRQIKILFQNRXRXRXRC-aa (SEQ ID NO: 310)
	RXRRXRRXRXRC-aa (SEQ ID NO: 311)
	RXRRXRRXRXRC-aa (SEQ ID NO: 312)
	RXRRXRRXRIKILFQNRRMKWKKGGC-aa (SEQ ID NO: 313)
	RXRRXRRXRIKILFQNRRMKWKKC-aa (SEQ ID NO: 314)
	RXRRXRRXRIKILFQNRMKWKKC-aa (SEQ ID NO: 315)
	RXRRXRRXRIKILFQNXRMKWKKC-aa (SEQ ID NO: 316)
	RXRRXRRXRIKILFQNHRMKWKKC-aa (SEQ ID NO: 317)

Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	RXRRXRRXRIKILFQNXXRMKWKKC-aa (SEQ ID NO: 316)
	RXRRXRRXRIKILFQNXXRMKWKKC-aa (SEQ ID NO: 316)
	RXRRXRRXRIKILFQNXXRMKWKAC-aa (SEQ ID NO: 320)
	RXRRXRRXRIKILFQNXXRMKWHKAC-aa (SEQ ID NO: 321)
	RXRRXRRXRIKILFQNXXRMKWHRC-aa (SEQ ID NO: 322)
	RXXRXRRXRIKILFQNRRMKWKKC-aa (SEQ ID NO: 323)
	RARARARARIKILFQNRRMKWKKC-aa (SEQ ID NO: 324)
	RXRRXRRXRILFQNXXRMKWHKAC-aa (SEQ ID NO: 3253)
	RXRRXRRXRIHILFQNXXRMKWHKAC-aa (SEQ ID NO: 326)
	RXRRXRRXRIRILFQNXXRMKWHKAC-aa (SEQ ID NO: 327)
	RXRRXRRXRILFQYXXRMKWHKAC-aa (SEQ ID NO: 328)
	RXRRXRRXRLYSPLSFQXXRMKWHKAC-aa (SEQ ID NO: 329)
	RXRRXRRXRISILFQYXXRMKWHKAC-aa (SEQ ID NO: 330)
	RXRRXRRXRILFQYXXRMKWHKAC-aa (SEQ ID NO: 331)

Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	RXRRXRILFQYXRMKWHKAC-aa (SEQ ID NO: 332)
	RXRRARRXRIHILFQYXRMKWHKAC-aa (SEQ ID NO: 333)
	RARRXRRARIHILFQYXRMKWHKAC-aa (SEQ ID NO: 334)
	RXRRXRRXRIHILFQYXRMKWHKAC-aa (SEQ ID NO: 335)
	RXRRXRRXRILFQNXRMKWHKAC-aa (SEQ ID NO: 325)
	RXRRXRRXRIHILFQNXRMKWHKAC-aa (SEQ ID NO: 326)
	RXRRXRRXRIKILFQNRMKWHK-aa (SEQ ID NO: 338)
	RXRRXRRXRIKILFQNXRMKWHK-aa (SEQ ID NO: 339)
	RXRRXRRXRILFQNRMKWHK-aa (SEQ ID NO: 340)
	RXRRXRRXRILFQNXRMKWHK-aa (SEQ ID NO: 341)
	RXRRXRRXRIHILFQNRMKWHK-aa (SEQ ID NO: 342)
	RXRRXRRXRIHILFQNXRMKWHK-aa (SEQ ID NO: 343)
	RXRRXRRXRIRILFQNRMKWHK-aa (SEQ ID NO: 344)
	RXRRXRRXRIRILFQNXRMKWHK-aa (SEQ ID NO: 345)
	RXRRXRRXRIILFQNRMKWHK-aa (SEQ ID NO: 346)
	RXRRXRRXRIILFQNXRMKWHK-aa (SEQ ID NO: 347)
	RXRRXRRXRKILFQNRMKWHK-aa (SEQ ID NO: 348)
	RXRRXRRXRKILFQNXRMKWHK-aa (SEQ ID NO: 349)
	RXRRXRRRXILFQNRMKWHK-aa (SEQ ID NO: 350)
	RXRRXRRRXILFQNXRMKWHK-aa (SEQ ID NO: 351)
	RXRRXRRXRHILFQNRMKWHK-aa (SEQ ID NO: 352)
	RXRRXRRXRHILFQNXRMKWHK-aa (SEQ ID NO: 353)
	RXRRXRRXRILFQNRMKWHK-aa (SEQ ID NO: 354)

Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	RXRRXRRXRILFQNXRMKWHK-aa (SEQ ID NO: 355)
	RXRRXRRXRILFQNRRMKWHK-aa (SEQ ID NO: 356)
	RXRRXRRXRILFQNXRMKWHK-aa (SEQ ID NO: 357)
	RXRRXRRXRIKILFYRRMKWHK-aa (SEQ ID NO: 358)
	RXRRXRRXRIKILFYXRMKWHK-aa (SEQ ID NO: 359)
	RXRRXRRXRILFYRRMKWHK-aa (SEQ ID NO: 360)
	RXRRXRRXRILFYXRMKWHK-aa (SEQ ID NO: 361)
	RXRRXRRXRIHILFYRRMKWHK-aa (SEQ ID NO: 362)
	RXRRXRRXRIHILFYXRMKWHK-aa (SEQ ID NO: 363)
	RXRRXRRXRILFYRRMKWHK-aa (SEQ ID NO: 364)
	RXRRXRRXRILFYXRMKWHK-aa (SEQ ID NO: 365)
	RXRRXRRXRILFYRRMKWHK-aa (SEQ ID NO: 366)
	RXRRXRRXRILFYXRMKWHK-aa (SEQ ID NO: 367)
	RXRRXRRXRKILFYRRMKWHK-aa (SEQ ID NO: 368)
	RXRRXRRXRKILFYXRMKWHK-aa (SEQ ID NO: 369)
	RXRRXRRXRILFYRRMKWHK-aa (SEQ ID NO: 370)
	RXRRXRRXRILFYXRMKWHK-aa (SEQ ID NO: 371)
	RXRRXRRXRHILFYRRMKWHK-aa (SEQ ID NO: 372)
	RXRRXRRXRHILFYXRMKWHK-aa (SEQ ID NO: 373)
	RXRRXRRXRILFYRRMKWHK-aa (SEQ ID NO: 374)
	RXRRXRRXRILFYXRMKWHK-aa (SEQ ID NO: 375)
	RXRRXRRXRILFYRRMKWHK-aa (SEQ ID NO: 376)
	RXRRXRRXRILFYXRMKWHK-aa (SEQ ID NO: 377)
	RXRRXRRXR-aa (SEQ ID NO: 136)
	RXRRXRRXR-aa (SEQ ID NO: 98)
	RARRAR-aa (SEQ ID NO: 380)
	RARRARRAR-aa (SEQ ID NO: 381)
	RARRARRARRAR-aa (SEQ ID NO: 382)

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Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	RXRRXRI-aa (SEQ ID NO: 383)
	RXRRARRXR-aa (SEQ ID NO: 384)
	RARRXRRAR-aa (SEQ ID NO: 385)
	RRRRR-aa (SEQ ID NO: 386)
	RRRRRR-aa (SEQ ID NO: 387)
	RRRRRRR-aa (SEQ ID NO: 388)
	RXRRXRRXRRXRC-aa (SEQ ID NO: 311)
	RXRRXRRXRRXRC-aa (SEQ ID NO: 312)
	RXRRXRRXRIKILFQNRRMKWKKGGC-aa (SEQ ID NO: 313)
	RXRRXRRXRIKILFQNRRMKWKKC-aa (SEQ ID NO: 314)
	RXRRXRRXRIKILFQNRMKWKKC-aa (SEQ ID NO: 315)
	RXRRXRRXRIKILFQNXRMKWKKC-aa (SEQ ID NO: 316)
	RXRRXRRXRIKILFQNHRMKWKKC-aa (SEQ ID NO: 317)
	RXRRXRRXRIKILFQNXRMKWKKC-aa (SEQ ID NO: 316)
	RXRRXRRXRIKILFQNXRMKWKKC-aa (SEQ ID NO: 316)
	RXRRXRRXRIKILFQNXRMKWKAC-aa (SEQ ID NO: 320)
	RXRRXRRXRIKILFQNXRMKWHKAC-aa (SEQ ID NO: 321)
	RXRRXRRXRIKILFQNXRMKWHRC-aa (SEQ ID NO: 322)

Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	RXRRXRRXRIKILFQNRRMKWKKC-aa (SEQ ID NO: 323)
	RARARARARIKILFQNRRMKWKKC-aa (SEQ ID NO: 324)
	RXRRXRRXRIXILFQNXRMKWHKAC-aa (SEQ ID NO: 325)
	RXRRXRRXRIHILFQNXRMKWHKAC-aa (SEQ ID NO: 326)
	RXRRXRRXRIRILFQNXRMKWHKAC-aa (SEQ ID NO: 327)
	RXRRXRRXRIXILFYXRMKWHKAC-aa (SEQ ID NO: 328)
	RXRRXRRXRLYSPLSFQXRMKWHKAC-aa (SEQ ID NO: 329)
	RRMKWHK-aa (SEQ ID NO: 408)
	XRMKWHK-aa (SEQ ID NO: 409)
	XXXXXXXXXXXXXXXXXILFQXXRMKWHK-aa (SEQ ID NO: 410)
	XXXXXXXXXXXXXXXXXILFQXXRMKWHK-aa (SEQ ID NO: 410)
	RRRRRRRQIKILFQNPKKRKRKVGGC-aa (SEQ ID NO: 412)
	HHFFRRRRRRRRRFFC-aa (SEQ ID NO: 413)
	HHHHHHRRRRRRRRRFFC-aa (SEQ ID NO: 414)
	HHHHHHFFRRRRRRRRRFFC-aa (SEQ ID NO: 415)
	HHHHHXXRRRRRRRRRFFC-aa (SEQ ID NO: 416)
	HHHHHHXXFFRRRRRRRRRFFC-aa (SEQ ID NO: 417)
	HHHXRRRRRRRRRFFXHHHC-aa (SEQ ID NO: 418)

Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	XRMKWHK-aa (SEQ ID NO: 409)
	XRWKWHK-aa (SEQ ID NO: 420)
	RXRARXR-aa (SEQ ID NO: 421)
	RXRXRXR-aa (SEQ ID NO: 422)
	RARXRAR-aa (SEQ ID NO: 423)
	RXRAR-aa (SEQ ID NO: 424)
	XXXXXXXXXXXXXXXXXILFQXXHMKWHK-aa (SEQ ID NO: 425)
	XXXXXXXXXXXXXXXXXILFQXXRWKWHK-aa (SEQ ID NO: 426)
	XXXXXXXXXXXXXXXXXILFQXXHWKWHK-aa (SEQ ID NO: 427)
	XXXXXXXXXXXXXXXXXILFQXXR XRARXR-aa (SEQ ID NO: 428)
	XXXXXXXXXXXXXXXXXILFQXXR XRXRXR-aa (SEQ ID NO: 429)
	XXXXXXXXXXXXXXXXXILFQXXR RRRXR-aa (SEQ ID NO: 430)
	XXXXXXXXXXXXXXXXXILFQXRARXRAR-aa (SEQ ID NO: 431)
	XXXXXXXXXXXXXXXXXILFQXXR XRARXR-aa (SEQ ID NO: 428)
	XXXXXXXXXXXXXXXXXILFQXXR XRAR-aa (SEQ ID NO: 433)
	XXXXXXXXXXXXXXXXXILIQXXRMKWHK-aa (SEQ ID NO: 434)
	XXXXXXXXXXXXXXXXXILIQXXHMKWHK-aa (SEQ ID NO: 435)

Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	XXXXXXXXXXXXXXXXXILIQXXRWKWHK-aa (SEQ ID NO: 436)
	XXXXXXXXXXXXXXXXXILIQXXHWKWHK-aa (SEQ ID NO: 437)
	XXXXXXXXXXXXXXXXXILIQXXRXXRXXR-aa (SEQ ID NO: 438)
	XXXXXXXXXXXXXXXXXILIQXXRXXRXXR-aa (SEQ ID NO: 439)
	XXXXXXXXXXXXXXXXXILIQXXRXXRXXR-aa (SEQ ID NO: 440)
	XXXXXXXXXXXXXXXXXILIQXXRXXRXXR-aa (SEQ ID NO: 441)
	XXXXXXXXXXXXXXXXXILIQXXRXXRXXR-aa (SEQ ID NO: 438)
	XXXXXXXXXXXXXXXXXILIQXXRXXRXXR-aa (SEQ ID NO: 443)
	XXXXXXXXXXXXXXXXXILFQXXHMKWHK-aa (SEQ ID NO: 425)
	XXXXXXXXXXXXXXXXXILFQXXRWKWHK-aa (SEQ ID NO: 426)
	XXXXXXXXXXXXXXXXXILFQXXHWKWHK-aa (SEQ ID NO: 427)
	XXXXXXXXXXXXXXXXXILFQXXRXXRXXR-aa (SEQ ID NO: 428)
	XXXXXXXXXXXXXXXXXILFQXXRXXRXXR-aa (SEQ ID NO: 429)
	XXXXXXXXXXXXXXXXXILFQXXRXXRXXR-aa (SEQ ID NO: 430)

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Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	XXXXXXXXXXXXXXXXXILFQXRARXRAR-aa (SEQ ID NO: 431)
	XXXXXXXXXXXXXXXXXILFQXRXRARXR-aa (SEQ ID NO: 428)
	XXXXXXXXXXXXXXXXXILFQXRXRAR-aa (SEQ ID NO: 433)
	XXXXXXXXXXXXXXXXXILIQXXRMKWHK-aa (SEQ ID NO: 434)
	XXXXXXXXXXXXXXXXXILIQXXHMKWHK-aa (SEQ ID NO: 435)
	XXXXXXXXXXXXXXXXXILIQXXRWKWHK-aa (SEQ ID NO: 436)
	XXXXXXXXXXXXXXXXXILIQXXHWKWHK-aa (SEQ ID NO: 437)
	XXXXXXXXXXXXXXXXXILIQXRXRARXR-aa (SEQ ID NO: 438)
	XXXXXXXXXXXXXXXXXILIQXRXRXRXR-aa (SEQ ID NO: 439)
	XXXXXXXXXXXXXXXXXILIQXRRRXR-aa (SEQ ID NO: 440)
	XXXXXXXXXXXXXXXXXILIQXRARXRAR-aa (SEQ ID NO: 441)
	XXXXXXXXXXXXXXXXXILIQXRXRARXR-aa (SEQ ID NO: 438)
	XXXXXXXXXXXXXXXXXILIQXRXRAR-aa (SEQ ID NO: 443)
	RXRRARRXRARXA-aa (SEQ ID NO: 463)

Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	RXRRARRXRILFQYXHMKWHKAC-aa (SEQ ID NO: 464)
	RXRRARRXRILFQYXRMKWHKAC-aa (SEQ ID NO: 465)
	RXRRARRXRILFQYXRWKWHKAC-aa (SEQ ID NO: 466)
	RXRRXRRXRRXRC-aa (SEQ ID NO: 311)
	RXRRXRRXRILFQNXRMKWHKAC-aa (SEQ ID NO: 325)
	RXRRXRRXRIHILFQNXRMKWHKAC-aa (SEQ ID NO: 326)
	RXRRXRRXRILFQYXRMKWHKAC-aa (SEQ ID NO: 328)
	RXRRXRRXRLYSPLSFQXRMKWHKAC-aa (SEQ ID NO: 329)
	RXRRXRRXRILFQYXRMKWHKAC-aa (SEQ ID NO: 331)
	RXRRXRILFQYXRMKWHKAC-aa (SEQ ID NO: 332)
	RARRXRRARILFQYXRMKWHKAC-aa (SEQ ID NO: 474)
	RXRRARRXRILFQYXRMKWHKAC-aa (SEQ ID NO: 465)
	RARRXRRARILFQYXRMKWHKAC-aa (SEQ ID NO: 474)
	RXRRARRXRILFQYXRMKWHKAC-aa (SEQ ID NO: 465)
	RXRRARRXRILFQYXHMKWHKAC-aa (SEQ ID NO: 464)

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Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	RXRRARRXRILFQYXRMKWHKAC-aa (SEQ ID NO: 465)
	RXRRARRXRILFQYXRWKWHKAC-aa (SEQ ID NO: 466)
	RXRRARRXRILFQYXHWKWHKAC-aa (SEQ ID NO: 481)
	RXRRARRXRILFQYRXRAXRAC-aa (SEQ ID NO: 482)
	RXRRARRXRILFQYRXRXRXRAC-aa (SEQ ID NO: 483)
	RXRRARRXRILIQYXRMKWHKAC-aa (SEQ ID NO: 484)
	RXRRXRILFQYRXRXRXRC-aa (SEQ ID NO: 485)
	RXRRARRXRILFQYRXRAXRAC-aa (SEQ ID NO: 482)
	RXRRARRXRILFQYRXRXRXRAC-aa (SEQ ID NO: 483)
	RXRRARRXRILIQYXRMKWHKAC-aa (SEQ ID NO: 484)
	RXRRXRILFQYRXRXRXRCYS-aa (SEQ ID NO: 489)
	RARRXRRARILFQYRARXRARAC-aa (SEQ ID NO: 490)
	RARRXRRARILFQYRXRAXRAC-aa (SEQ ID NO: 491)
	RARRXRRARILFQYRXRXRXRAC-aa (SEQ ID NO: 492)
	RARRXRRARILFQYRXRAXAC-aa (SEQ ID NO: 493)
	RXRRARRXRILFQYRXRXRXRAC-aa (SEQ ID NO: 494)
	RXRRARRXRILFQYRXRAXAC-aa (SEQ ID NO: 495)
	RXRRARRXRIHILFQNXXRMKWHKAC-aa (SEQ ID NO: 496)
	RXRRARRXRRARXAC-aa (SEQ ID NO: 497)
	RXRRARRXRILFQYXHMKWHK-aa (SEQ ID NO: 498)
	RXRRARRXRILFQYXRMKWHK-aa (SEQ ID NO: 499)
	RXRRARRXRILFQYXRWKWHK-aa (SEQ ID NO: 500)

Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	RXRRARRXRILFQYXRMKWHK-aa (SEQ ID NO: 499)
	RXRRARRXRILFQYRXRARXR-aa (SEQ ID NO: 502)
	RXRRARRXRILFQYRXXRXXR-aa (SEQ ID NO: 503)
	RXRRARRXRILFQYRXRRXR-aa (SEQ ID NO: 504)
	RXRRARRXRILFQYRARXRAR-aa (SEQ ID NO: 505)
	RXRRARRXRILFQYRXRAR-aa (SEQ ID NO: 506)
	RXRRARRXRILIQYXHMKWHK-aa (SEQ ID NO: 507)
	RXRRARRXRILIQYXRMKWHK-aa (SEQ ID NO: 508)
	RXRRARRXRILIQYXRWKWHK-aa (SEQ ID NO: 509)
	RXRRARRXRILIQYXRMKWHK-aa (SEQ ID NO: 508)
	RXRRARRXRILIQYRXRARXR-aa (SEQ ID NO: 511)
	RXRRARRXRILIQYRXXRXXR-aa (SEQ ID NO: 512)
	RXRRARRXRILIQYRXXRXXR-aa (SEQ ID NO: 513)
	RXRRARRXRILIQYRARXRAR-aa (SEQ ID NO: 514)
	RXRRARRXRILIQYRXRAR-aa (SEQ ID NO: 515)
	RARRXRRARILFQYXHMKWHK-aa (SEQ ID NO: 516)
	RARRXRRARILFQYXRMKWHK-aa (SEQ ID NO: 517)
	RARRXRRARILFQYXRWKWHK-aa (SEQ ID NO: 518)
	RARRXRRARILFQYXRMKWHK-aa (SEQ ID NO: 517)
	RARRXRRARILFQYRXRARXR-aa (SEQ ID NO: 520)
	RARRXRRARILFQYRXXRXXR-aa (SEQ ID NO: 521)
	RARRXRRARILFQYRXRRXR-aa (SEQ ID NO: 522)
	RARRXRRARILFQYRARXRAR-aa (SEQ ID NO: 523)
	RARRXRRARILFQYRXRAR-aa (SEQ ID NO: 524)
	RARRXRRARILIQYXHMKWHK-aa (SEQ ID NO: 525)
	RARRXRRARILIQYXRMKWHK-aa (SEQ ID NO: 526)
	RARRXRRARILIQYXRWKWHK-aa (SEQ ID NO: 527)
	RARRXRRARILIQYXRMKWHK-aa (SEQ ID NO: 526)

Exemplary Carrier Peptide Sequences

Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	RARRXRRARILIQYRXRARXR-aa (SEQ ID NO: 529)
	RARRXRRARILIQYRXRXRXR-aa (SEQ ID NO: 530)
	RARRXRRARILIQYRXRRXR-aa (SEQ ID NO: 531)
	RARRXRRARILIQYRARXRAR-aa (SEQ ID NO: 532)
	RARRXRRARILIQYRXRAR-aa (SEQ ID NO: 533)
	RXRRXRILFQYXHKWHK-aa (SEQ ID NO: 534)
	RXRRXRILFQYXRMKWHK-aa (SEQ ID NO: 535)
	RXRRXRILFQYXRWKWHK-aa (SEQ ID NO: 536)
	RXRRXRILFQYXRMKWHK-aa (SEQ ID NO: 535)
	RXRRXRILFQYRXRARXR-aa (SEQ ID NO: 538)
	RXRRXRILFQYRXRXRXR-aa (SEQ ID NO: 539)
	RXRRXRILFQYRXRRXR-aa (SEQ ID NO: 540)
	RXRRXRILFQYRARXRAR-aa (SEQ ID NO: 541)
	RXRRXRILFQYRXRAR-aa (SEQ ID NO: 542)
	RXRRXRILIQYXHKWHK-aa (SEQ ID NO: 543)
	RXRRXRILIQYXRMKWHK-aa (SEQ ID NO: 544)
	RXRRXRILIQYXRWKWHK-aa (SEQ ID NO: 545)
	RXRRXRILIQYXRMKWHK-aa (SEQ ID NO: 544)
	RXRRXRILIQYRXRARXR-aa (SEQ ID NO: 547)
	RXRRXRILIQYRXRXRXR-aa (SEQ ID NO: 548)
	RXRRXRILIQYRXRRXR-aa (SEQ ID NO: 549)
	RXRRXRILIQYRARXRAR-aa (SEQ ID NO: 550)
	RXRRXRILIQYRXRAR-aa (SEQ ID NO: 551)
	PRPXXXXXXXXXXXXPRG-aa (SEQ ID NO: 552)
	RRRRRRRR-aa (SEQ ID NO: 553)
	RRMKWKK-aa (SEQ ID NO: 554)
	PKKKRKV-aa (SEQ ID NO: 295)

Exemplary Carrier Peptide Sequences	
Name	Sequence (Amino to Carboxy Terminus or 5' to 3')
	CKDEPQRRSARLSAKPAPPKPEPKPKKAPAKK-aa (SEQ ID NO: 556)
	RKKRRQRRR-aa (SEQ ID NO: 101)
	RKKRRQRR-aa (SEQ ID NO: 558)
	RKKRRQR-aa (SEQ ID NO: 559)
	KKRRQRRR-aa (SEQ ID NO: 560)
	KKRRQRRR-aa (SEQ ID NO: 560)
	AKKRRQRRR-aa (SEQ ID NO: 562)
	RAKRRQRRR-aa (SEQ ID NO: 563)
	RKARRQRRR-aa (SEQ ID NO: 564)
	RKKARQRRR-aa (SEQ ID NO: 565)
	CRWRWKCKK-aa (SEQ ID NO: 566)

aa = glycine or proline; B = 3-alanine; X = 6-aminohexanoic acid; tg. = unmodified amino terminus, or the amino terminal capped with an acetyl, benzoyl or stearoyl group (i.e., an acetyl amide, benzoyl amide or stearoyl amide) and Y^b is:

NH- (CHR)-C(O) - wherein n is 2 to 7 and each R is independently, at each occurrence, hydrogen or methyl. For simplicity, not all sequences are noted with a terminal tg group; however, each of the above sequences may comprise an unmodified amino terminus or an amino terminus capped with an acetyl, benzoyl or stearoyl group.

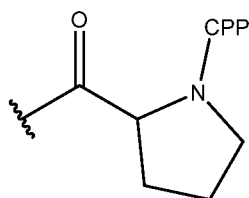
[0261] In some embodiments, an antisense oligonucleotide comprises a substituent “Z,” defined as the combination of a CPP and a linker. The linker bridges the CPP at its carboxy terminus to the 3'-end and/or the 5'-end of the oligonucleotide. In various embodiments, an antisense oligonucleotide may comprise only one CPP linked to the 3' end of the oligomer. In other embodiments, an antisense oligonucleotide may comprise only one CPP linked to the 5' end of the oligomer.

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[0262] The linker within Z may comprise, for example, 1, 2, 3, 4, or 5 amino acids. For example, the linker may comprise 1, 2, 3, 4, or 5 of a glycine moiety, wherein the CPP is attached to the glycine moiety by an amide bond at the CPP carboxy terminus. In one aspect, the linker comprises one glycine moiety.

[0263] In particular embodiments, Z is selected from:

-C(O)(CH₂)₅NH-CPP;
 -C(O)(CH₂)₂NH-CPP;
 -C(O)(CH₂)₂NHC(O)(CH₂)₅NH-CPP;
 -C(O)CH₂NH-CPP; and the formula:

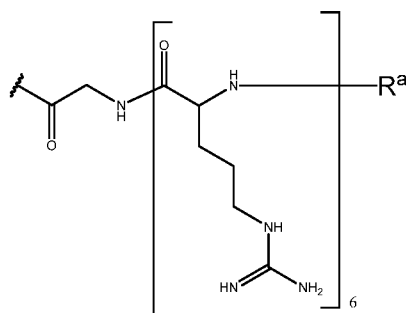


wherein the CPP is attached to the linker moiety by an amide bond at the CPP carboxy terminus.

[0264] In various embodiments, the CPP is an arginine-rich peptide as defined above and seen in Table 1. In certain embodiments, the arginine-rich CPP is -R₆-R^a, (*i.e.*, six arginine residues), wherein R^a is selected from H, acyl, acetyl, benzoyl, and stearoyl. In certain embodiments, R^a is acetyl.

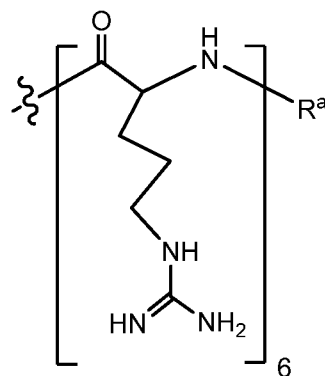
[0265] In certain embodiments, Z is -C(O)CH₂NH-R₆-R^a covalently bonded to an antisense oligomer of the disclosure at the 5' and/or 3' end of the oligomer, wherein R^a is H, acyl, acetyl, benzoyl, or stearoyl to cap the amino terminus of the R₆. In certain embodiments, R^a is acetyl. In these non-limiting examples, the CPP is -R₆-R^a and the linker is -C(O)CH₂NH-, (*i.e.* GLY). This particular example of Z = -C(O)CH₂NH-R₆-R^a is also exemplified by the following structure:

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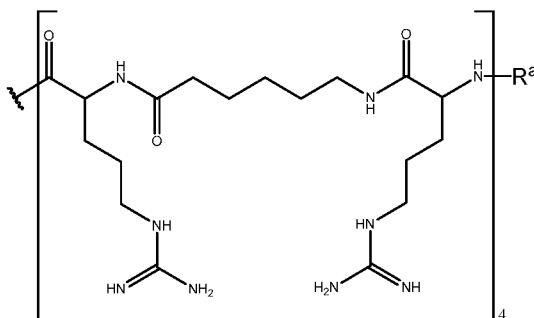
wherein R^a is selected from H, acyl, acetyl, benzoyl, and stearoyl. In some embodiments, R^a is H or acyl. In some embodiments, R^a is acetyl.

[0266] In various embodiments, the CPP is $-R_6-R^a$, also exemplified as the following formula:



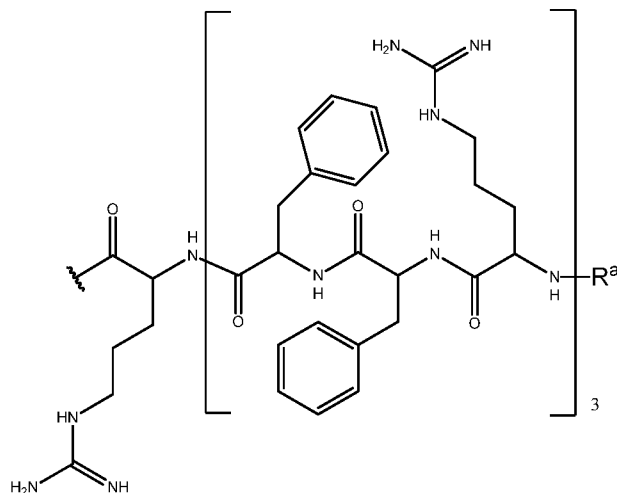
wherein R^a is selected from H, acyl, acetyl, benzoyl, and stearoyl. In certain embodiments, the CPP is SEQ ID NO: 128. In some embodiments, R^a is H or acyl. In some embodiments, R^a is acetyl.

[0267] In some embodiments, the CPP is $-(RXR)_4-R^a$, also exemplified as the following formula:



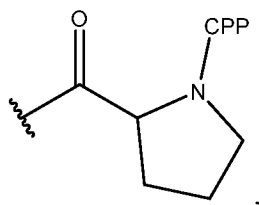
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[0268] In various embodiments, the CPP is $-R-(FFR)_3-R^a$, also exemplified as the following formula:



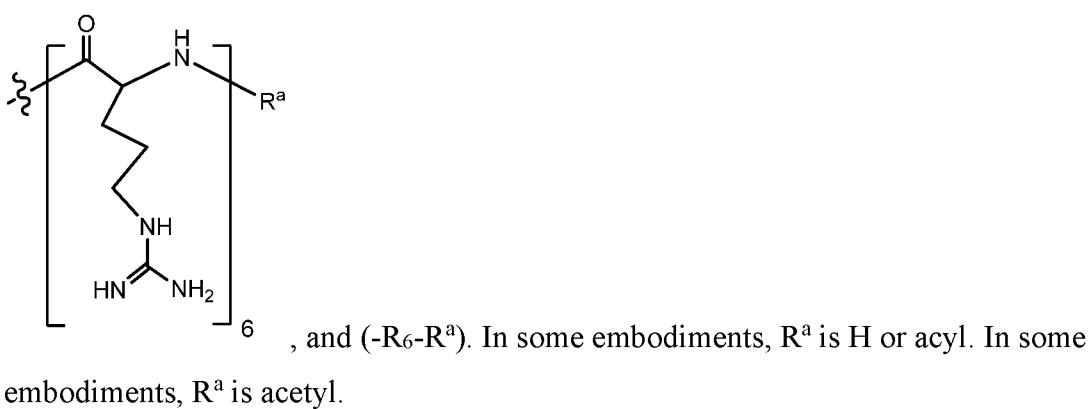
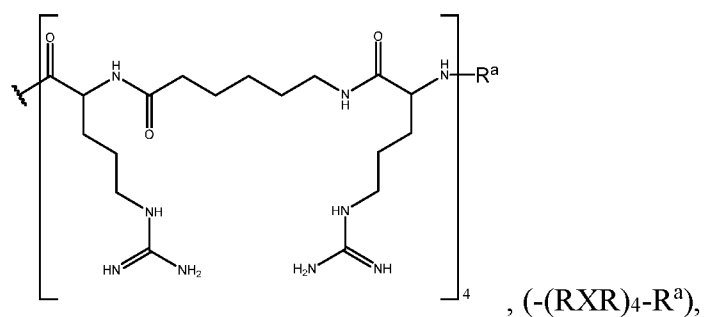
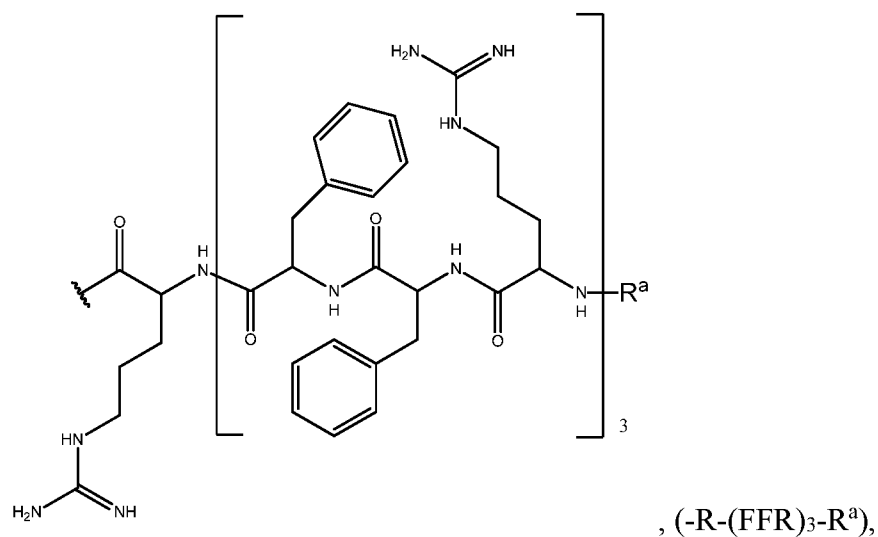
[0269] In various embodiments, Z is selected from:

- C(O)(CH₂)₅NH-CPP;
- C(O)(CH₂)₂NH-CPP;
- C(O)(CH₂)₂NHC(O)(CH₂)₅NH-CPP;
- C(O)CH₂NH-CPP, and the formula:



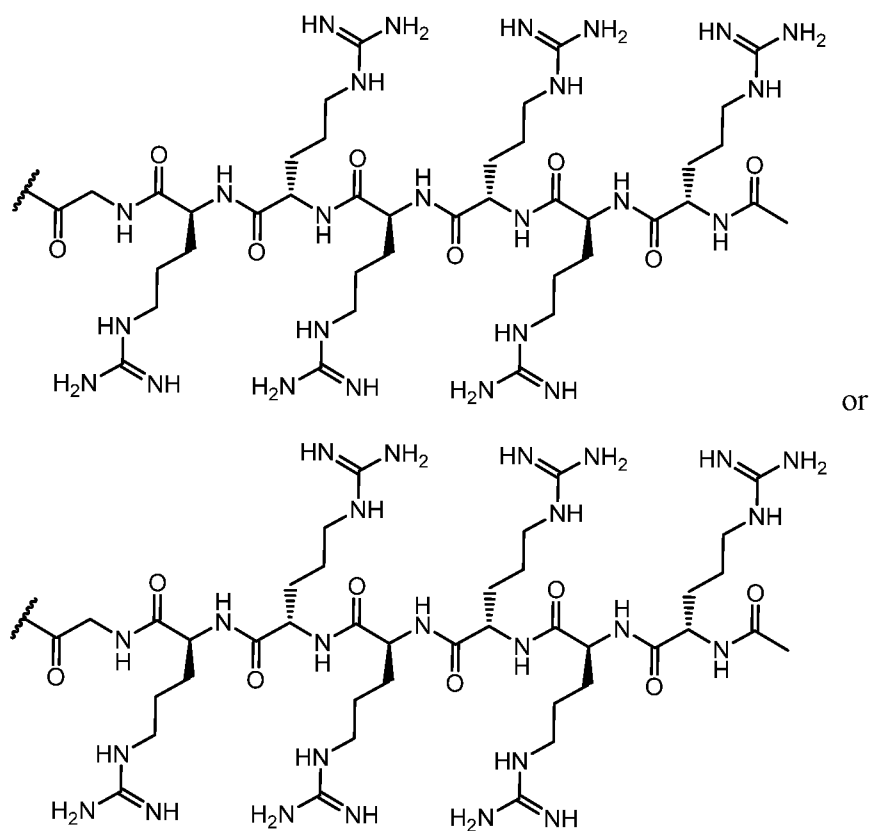
wherein the CPP is attached to the linker moiety by an amide bond at the CPP carboxy terminus, and wherein the CPP is selected from:

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[0270] In some embodiments, “-G-R₆” or “-G-R₆-Ac” is conjugated to the 3’ end of an antisense oligomer of the disclosure and is of the following formula:

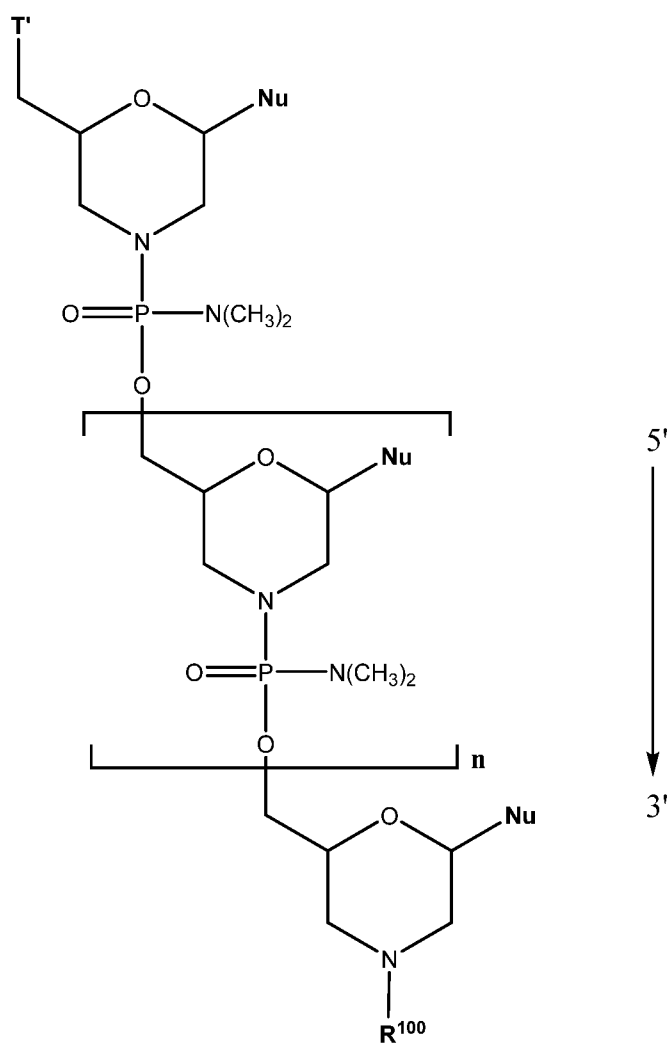
- 98 -



Antisense Oligomer CPP Conjugates

[0271] In various aspects, the disclosure provides antisense oligomers according to Formula (I):

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(I)

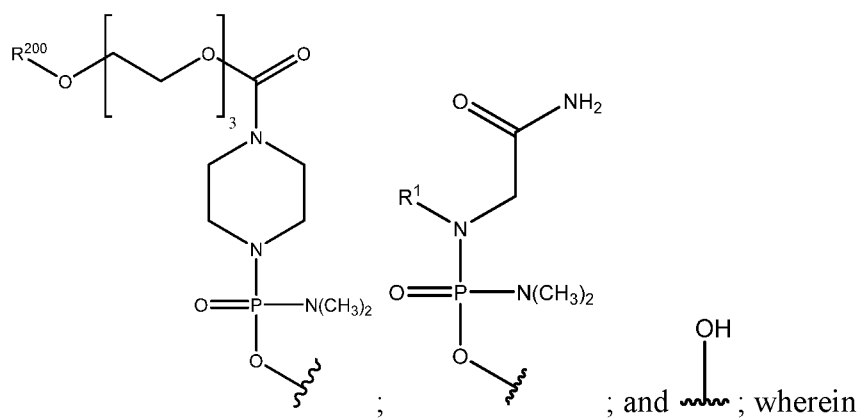
or a pharmaceutically acceptable salt thereof, wherein:

n is 1-40;

each Nu is a nucleobase, which, taken together form a targeting sequence that is complementary to an exon annealing site in the dystrophin pre-mRNA;

T' is a moiety selected from:

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R^{100} a cell-penetrating peptide,

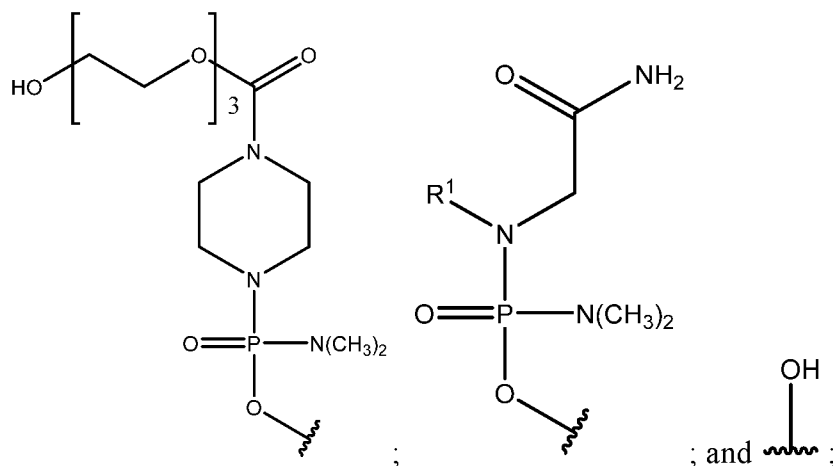
R^{200} is hydrogen, and

R^1 is $\text{C}_1\text{-C}_6$ alkyl.

[0272] In various aspects, an antisense oligomer conjugate of the disclosure is according to Formula (II):

T is a moiety selected from:

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R^1 is C_1 - C_6 alkyl;

wherein the targeting sequence is complementary to an annealing site in the dystrophin pre-mRNA.

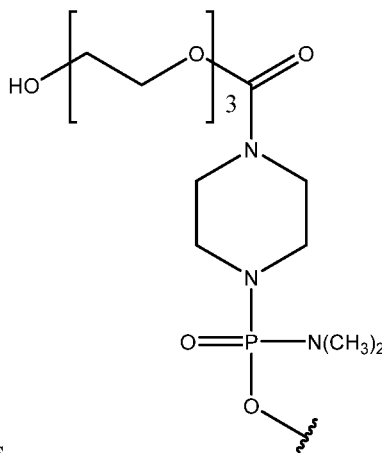
[0273] In some aspects, the antisense oligonucleotide conjugate in the composition comprises a sequence that is complementary to 15 to 35 nucleobases of an exon 44, exon 45, exon 50, exon 51, exon 52, or exon 53 target region of the dystrophin pre-mRNA. Oligonucleotide sequences designed to target and skip these dystrophin exons have been described in the art. See for example, the following PCT published applications and issued US patents: WO2018/129384, WO2019/060775, WO2020/219820 WO2018/007475, WO2018/091544, WO2020/089325, WO2004/048570, WO2020/028832, WO2017/062862, US Pat. No. 10,683,322, US Pat. No. 8,969,551, US Pat. No. 10,781,448, US Pat. No. 9,988,629, US Pat. No. 9,840,706, US Pat. No. 10,851,373, WO2020/004675, and WO2020/0158792, the sequence disclosure of which is incorporated herein.

[0274] A number of exemplary targeting sequences are described below. These sequences can be provided as morpholino targeting sequences and incorporated into the antisense oligonucleotide conjugates of Formula I.

[0275] In some aspects, the targeting sequence is complementary to an exon 51 annealing site in the dystrophin pre-mRNA. In some aspects, the site is designated as H51A(+66+95). In some aspects, the targeting sequence is complementary to an exon 45 annealing site in the dystrophin pre-mRNA. In some aspects, the site is designated as H45A(-03+19). In some

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aspects, the targeting sequence is complementary to an exon 53 annealing site in the dystrophin pre-mRNA. In some aspects, the site is designated as H53A(+36+60).



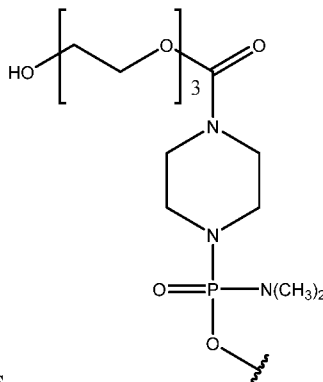
[0276] In various embodiments, T is

[0277] In various embodiments, R¹ is methyl, CF₃, CCl₃, CFCl₂, CF₂Cl, ethyl, CH₂CF₃, CF₂CF₃, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, 3-methylpentyl, 2,2-dimethylbutyl, or 2,3-dimethylbutyl.

[0278] In some embodiments, an antisense oligomer conjugate of Formula (I) is an HCl (hydrochloric acid) salt thereof. In certain embodiments, the HCl salt is a ·6HCl salt.

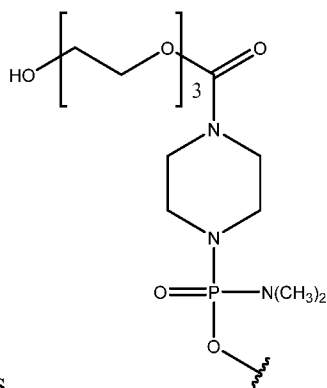
[0279] In some embodiments, each Nu is independently selected from cytosine (C), guanine (G), thymine (T), adenine (A), 5-methylcytosine (5mC), uracil (U), and hypoxanthine (I).

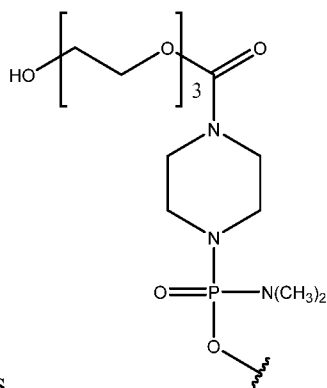
[0280] In some embodiments, the targeting sequence is 5'-CTCCAACATCAAGGAAGATGGCATTCTAG-3', wherein each thymine (T) is optionally uracil (U) (SEQ ID NO: 31).



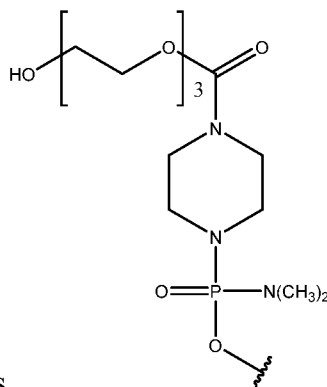
[0281] In various embodiments, T is , and the targeting sequence is 5'-CTCCAACATCAAGGAAGATGGCATTCTAG-3', wherein each thymine (T) is optionally uracil (U) (SEQ ID NO: 31).

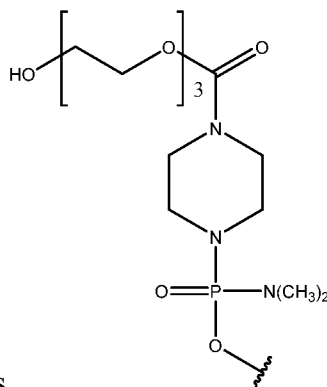
- 104 -

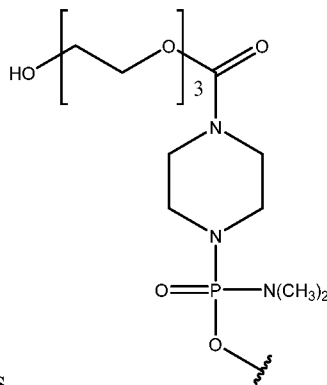


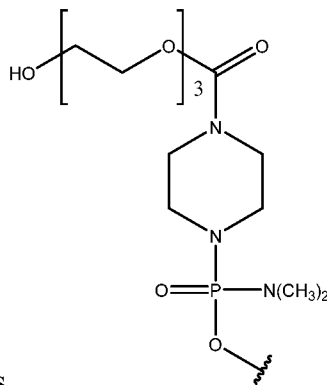
[0282] In various embodiments, T is , and the targeting sequence is 5'-CTCCAACATCAAGGAAGATGGCATTCTAG-3' (SEQ ID NO: 32).

[0283] In some embodiments, the targeting sequence is 5'-CAATGCCATCCTGGAGTTCCTG-3', wherein each thymine (T) is optionally uracil (U) (SEQ ID NO: 28).



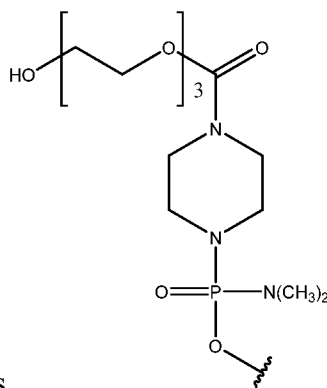
[0284] In various embodiments, T is , and the targeting sequence is 5'-CAATGCCATCCTGGAGTTCCTG-3', wherein each thymine (T) is optionally uracil (U) (SEQ ID NO: 28).



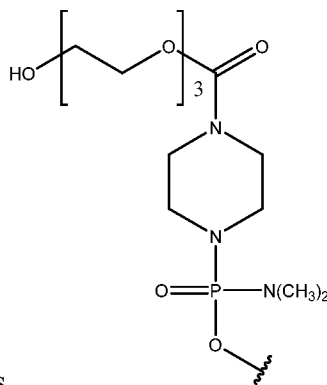
[0285] In various embodiments, T is , and the targeting sequence is 5'-CAATGCCATCCTGGAGTTCCTG-3' (SEQ ID NO: 27).

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[0286] In some embodiments, the targeting sequence is 5'-GTTGCCTCCGGTTCTGAAGGTGTTC-3', wherein each thymine (T) is optionally uracil (U) (SEQ ID NO: 30).

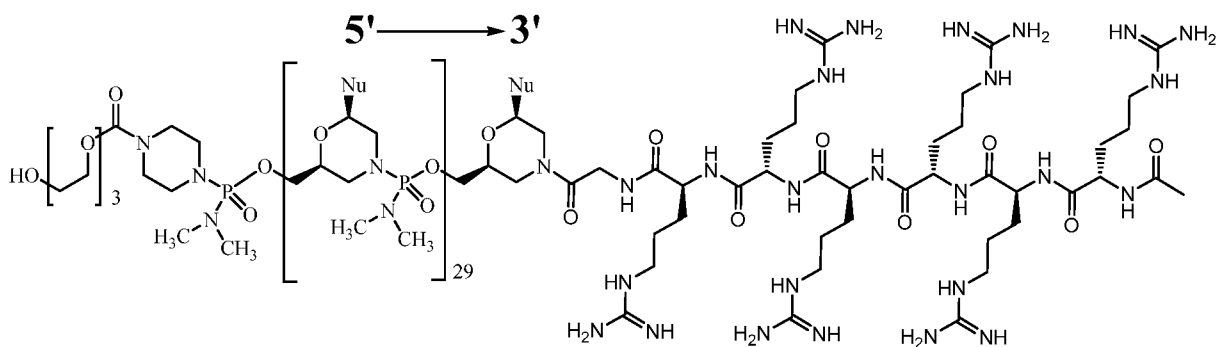


[0287] In various embodiments, T is , and the targeting sequence is 5'-GTTGCCTCCGGTTCTGAAGGTGTTC-3', wherein each thymine (T) is optionally uracil (U) (SEQ ID NO: 30).



[0288] In various embodiments, T is , and the targeting sequence is 5'-GTTGCCTCCGGTTCTGAAGGTGTTC-3' (SEQ ID NO: 29).

[0289] In some embodiments, including, for example, some embodiments of Formula (I), an antisense oligomer conjugate of the disclosure is according to Formula (III):



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(III)

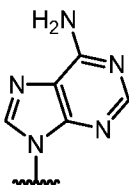
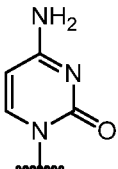
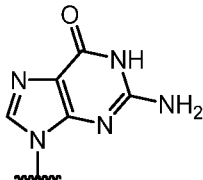
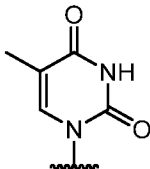
or a pharmaceutically acceptable salt thereof, wherein:

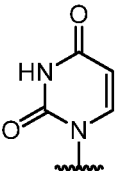
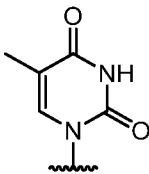
each Nu is a nucleobase which taken together to form a targeting sequence that is complementary to an exon 51 annealing site in the dystrophin pre-mRNA designated as H51A(+66+95).

[0290] In some embodiments, each Nu is independently selected from cytosine (C), guanine (G), thymine (T), adenine (A), 5-methylcytosine (5mC), uracil (U), and hypoxanthine (I).

[0291] In various embodiments, each Nu from 1 to 30 and 5' to 3' is:

Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu
1	C	6	A	11	A	16	A	21	G	26	X
2	X	7	C	12	A	17	G	22	C	27	C
3	C	8	A	13	G	18	A	23	A	28	X
4	C	9	X	14	G	19	X	24	X	29	A
5	A	10	C	15	A	20	G	25	X	30	G

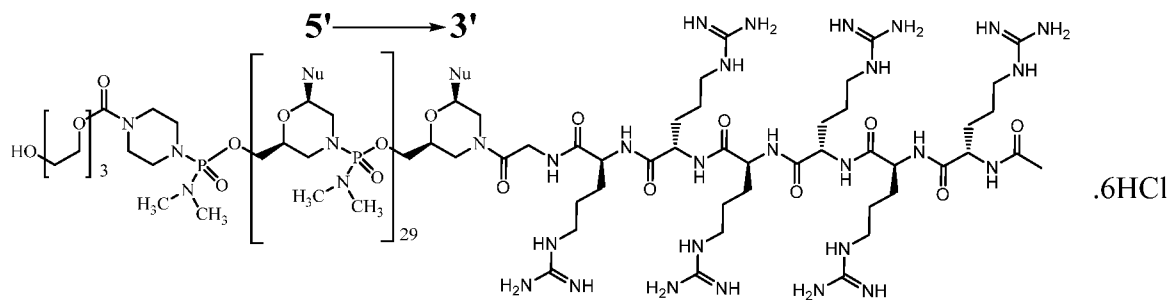
wherein A is , C is , G is , and X is  or

. In certain embodiments, each X is independently .

[0292] In some embodiments, an antisense oligomer conjugate of Formula (III) is an HCl (hydrochloric acid) salt thereof. In certain embodiments, the HCl salt is a ·6HCl salt.

[0293] In some embodiments, including, for example, some embodiments of Formula (III), an antisense oligomer conjugate of the disclosure is according to Formula (IIIA):

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IIIA,

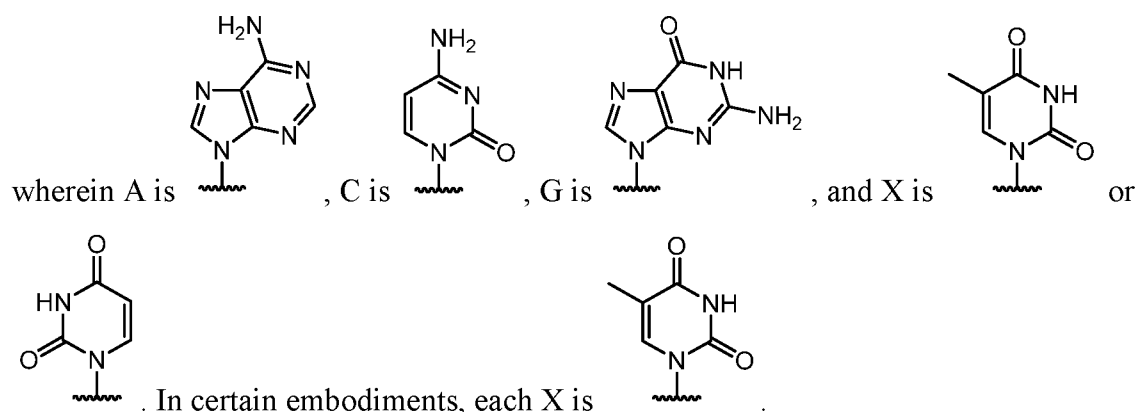
wherein each Nu is a nucleobase which taken together to form a targeting sequence that is complementary to an exon 51 annealing site in the dystrophin pre-mRNA designated as H51A(+66+95).

[0294] In some embodiments, each Nu is independently selected from cytosine (C), guanine (G), thymine (T), adenine (A), 5-methylcytosine (5mC), uracil (U), and hypoxanthine (I).

In various embodiments, each Nu from 1 to 30 and 5' to 3' is:

Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu
1	C	6	A	11	A	16	A	21	G	26	X
2	X	7	C	12	A	17	G	22	C	27	C
3	C	8	A	13	G	18	A	23	A	28	X
4	C	9	X	14	G	19	X	24	X	29	A
5	A	10	C	15	A	20	G	25	X	30	G

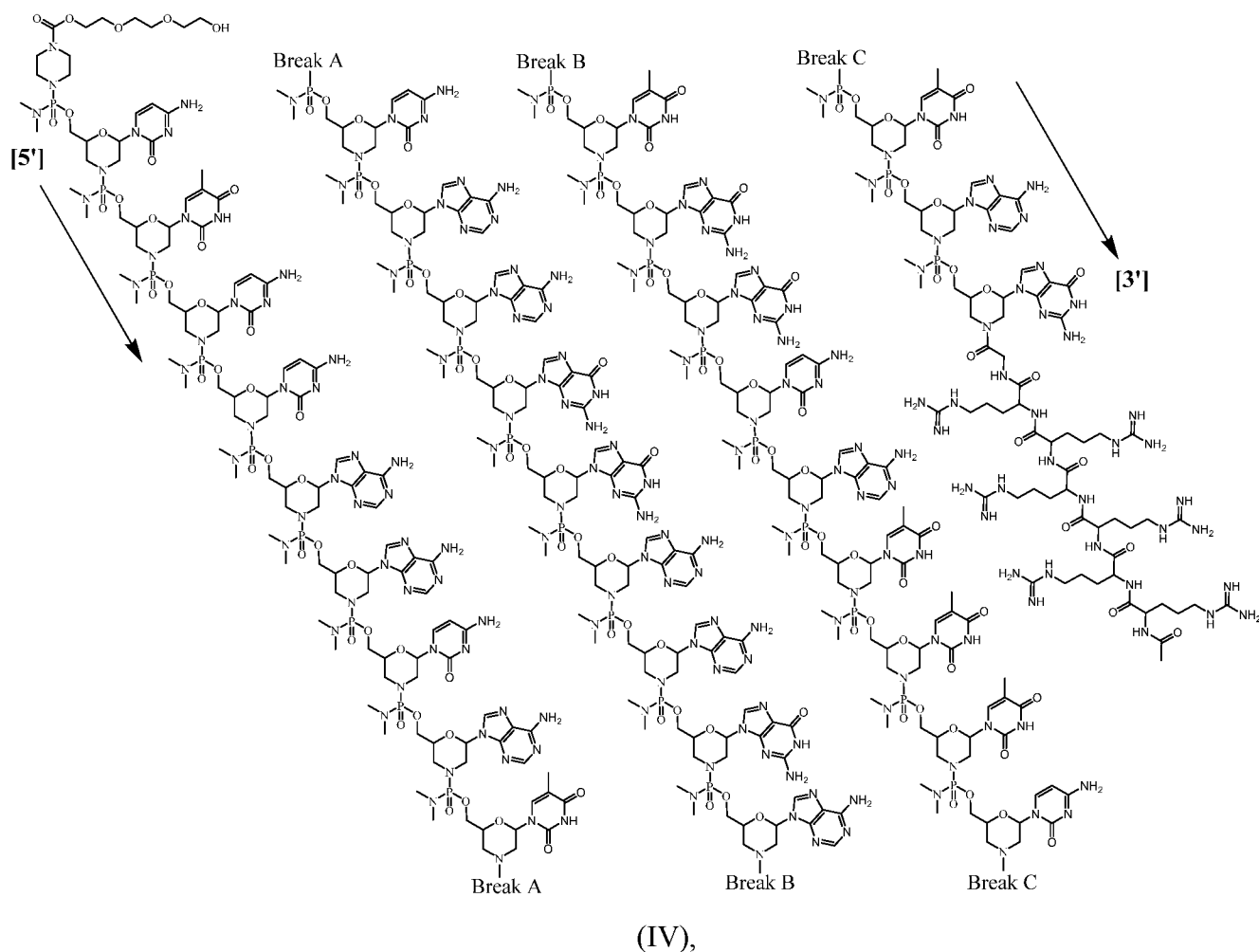
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[0295] In some embodiments including, for example, embodiments of antisense oligomer conjugates of Formula (III) and Formula (IIIA), the targeting sequence is 5'-CTCCAACATCAAGGAAGATGGCATTCTAG-3' wherein each thymine (T) is optionally uracil (U) (SEQ ID NO: 31). In various embodiments including, for example, embodiments of antisense oligomer conjugates of Formula (III) and Formula (IIIA), the targeting sequence is 5'-CTCCAACATCAAGGAAGATGGCATTCTAG-3' (SEQ ID NO: 32).

[0296] In some embodiments, including, for example, embodiments of antisense oligomer conjugates of Formula (I), an antisense oligomer conjugate of the disclosure is according to Formula (IV):

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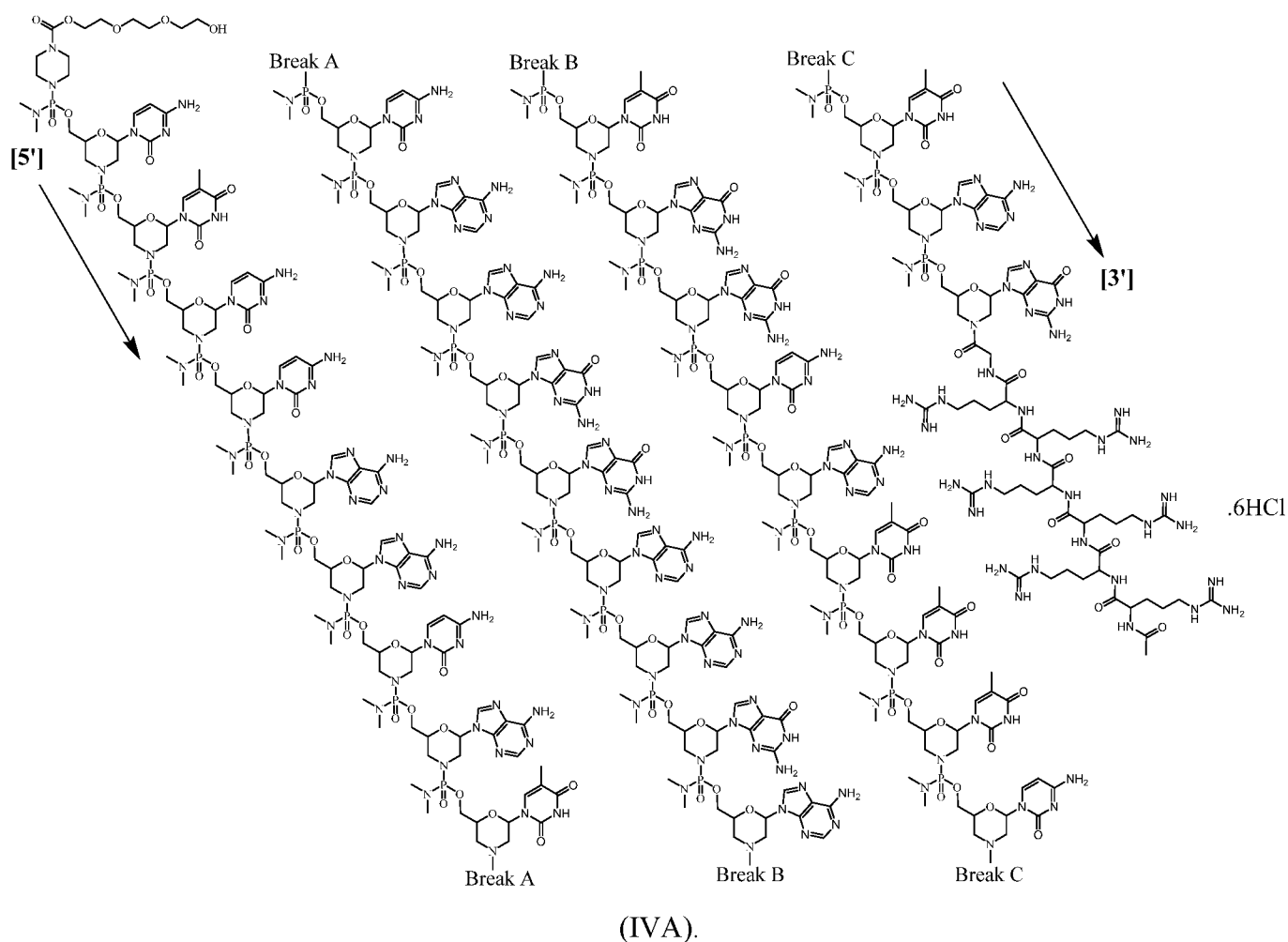


or a pharmaceutically acceptable salt thereof.

[0297] In some embodiments, an antisense oligomer conjugate of Formula (IV) is an HCl (hydrochloric acid) salt thereof. In certain embodiments, the HCl salt is a $\cdot 6\text{HCl}$ salt.

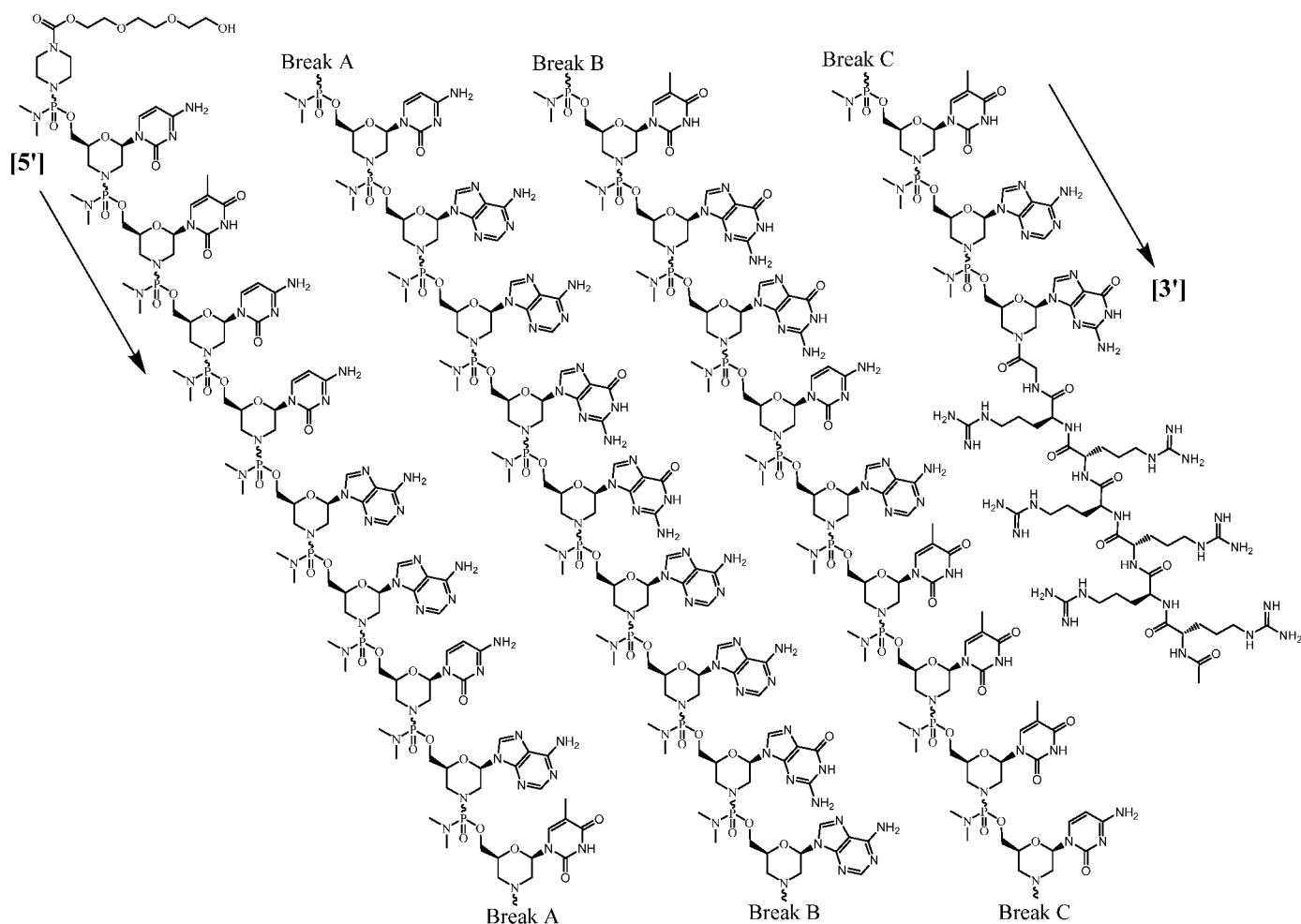
[0298] In some embodiments, including, for example, embodiments of antisense oligomer conjugates of Formula (IV), an antisense oligomer conjugate of the disclosure is according to Formula (IVA):

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[0299] In some embodiments of the disclosure, including some embodiments of antisense oligomer conjugates of Formula (I) and embodiments of antisense oligomer conjugates of Formula (IV), the antisense oligomer conjugate is according to Formula (IVB):

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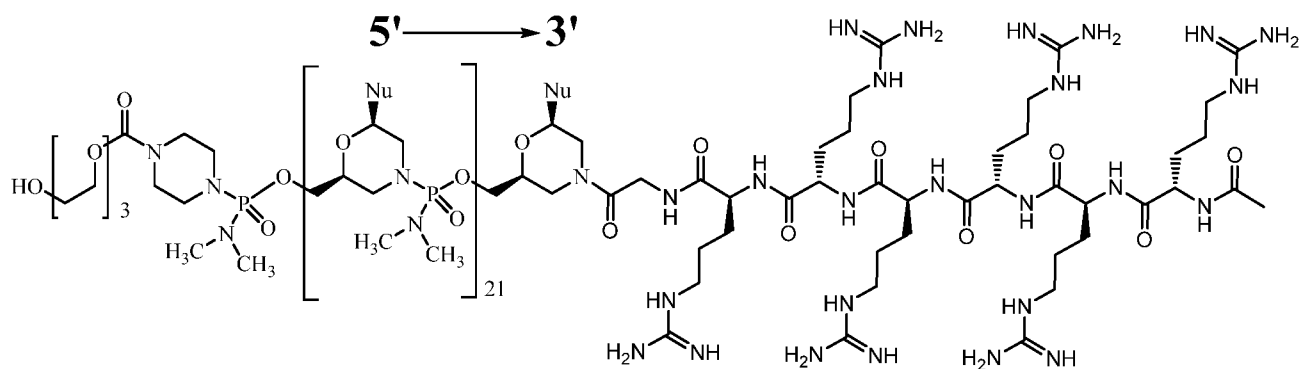
(IVB),

or a pharmaceutically acceptable salt thereof.

[0300] In some embodiments, an antisense oligomer conjugate of Formula (IVB) is an HCl (hydrochloric acid) salt thereof. In certain embodiments, the HCl salt is a $\cdot 6\text{HCl}$ salt.

[0301] In some embodiments, including, for example, embodiments of antisense oligomer conjugates of Formula (IVB), an antisense oligomer conjugate of the disclosure is according to Formula (IVC):

[0302] In some embodiments, including, for example, some embodiments of Formula (I), an antisense oligomer conjugate of the disclosure is according to Formula (V):



or a pharmaceutically acceptable salt thereof, wherein:

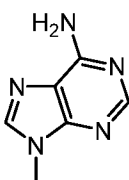
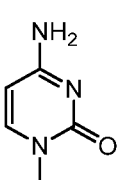
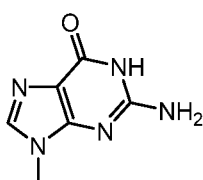
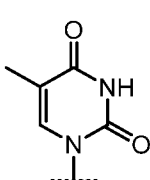
- 113 -

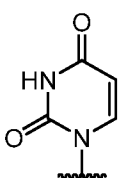
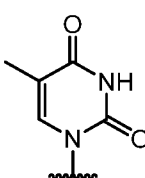
each Nu is a nucleobase which taken together form a targeting sequence that is complementary to an exon 45 annealing site in the dystrophin pre-mRNA designated as H45A(-03+19).

[0303] In some embodiments, each Nu is independently selected from cytosine (C), guanine (G), thymine (T), adenine (A), 5-methylcytosine (5mC), uracil (U), and hypoxanthine (I).

In various embodiments, each Nu from 1 to 22 and 5' to 3' is:

Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu
1	C	6	A	11	A	16	A	21	G	26	X
2	X	7	C	12	A	17	G	22	C	27	C
3	C	8	A	13	G	18	A	23	A	28	X
4	C	9	X	14	G	19	X	24	X	29	A
5	A	10	C	15	A	20	G	25	X	30	G

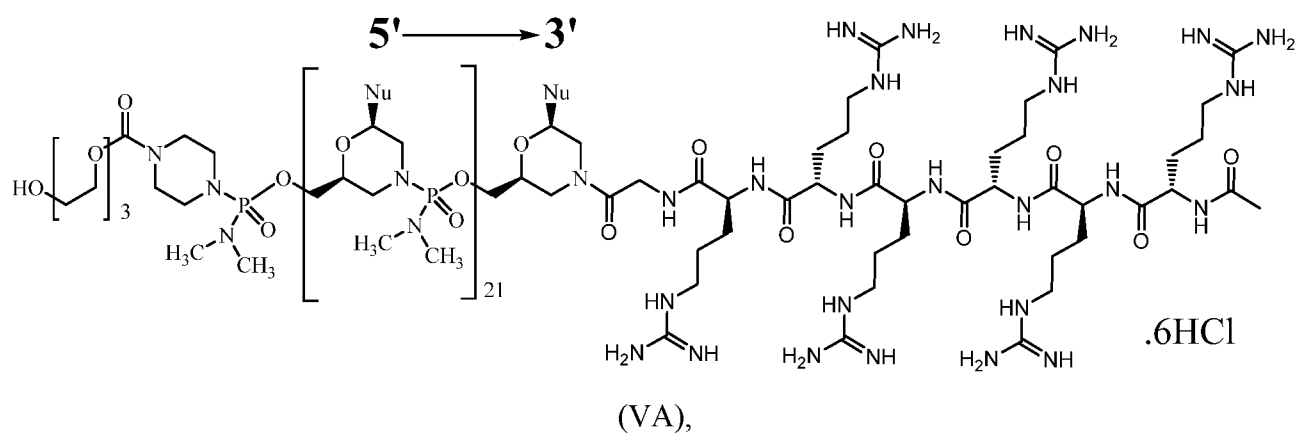
wherein A is , C is , G is , and X is  or

. In certain embodiments, each X is independently .

[0304] In Some embodiments, an antisense oligomer conjugate of Formula (V) is an HCl (hydrochloric acid) salt thereof. In certain embodiments, the HCl salt is a ·6HCl salt.

[0305] In some embodiments, including, for example, some embodiments of Formula (V), an antisense oligomer conjugate of the disclosure is according to Formula (VA):

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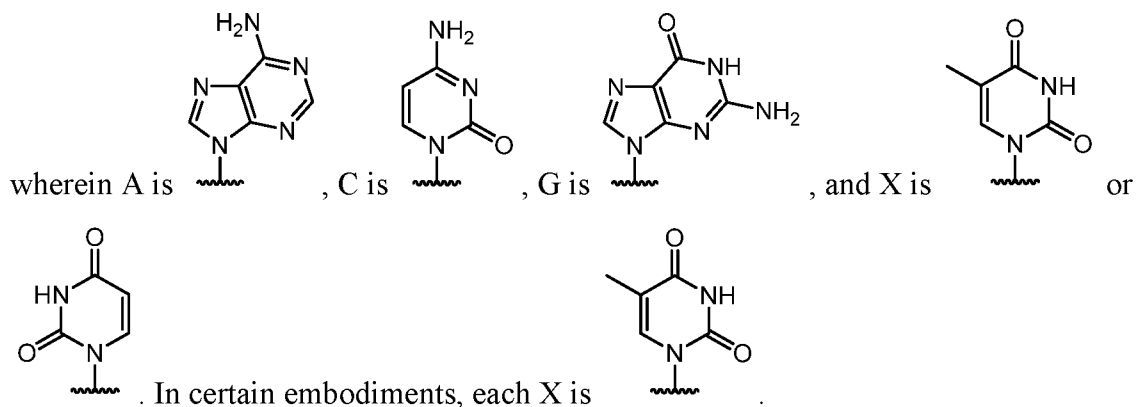
wherein each Nu is a nucleobase which taken together form a targeting sequence that is complementary to an exon 45 annealing site in the dystrophin pre-mRNA designated as H45A(-03+19).

[0306] In some embodiments, each Nu is independently selected from cytosine (C), guanine (G), thymine (T), adenine (A), 5-methylcytosine (5mC), uracil (U), and hypoxanthine (I).

In various embodiments, each Nu from 1 to 30 and 5' to 3' is:

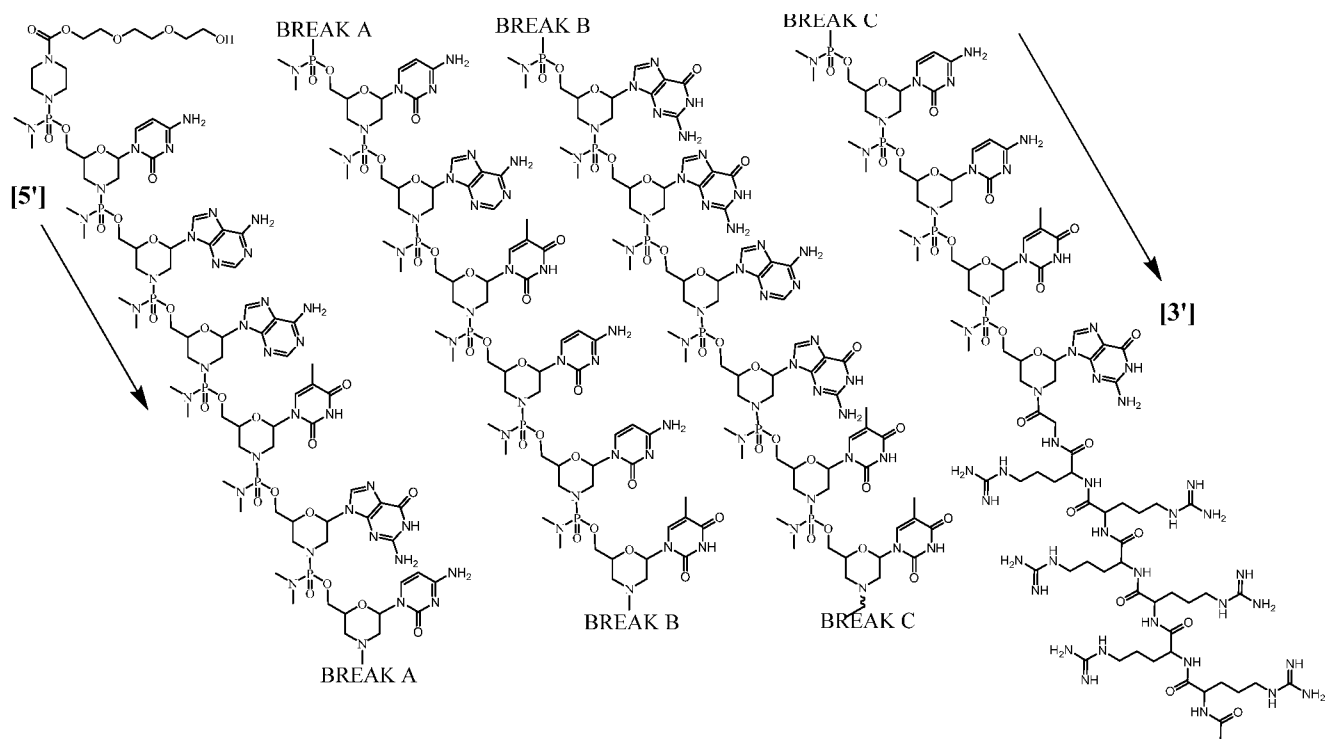
Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu
1	C	6	C	11	C	16	G	21	X
2	A	7	C	12	X	17	X	22	G
3	A	8	A	13	G	18	X		
4	X	9	X	14	G	19	C		
5	G	10	C	15	A	20	C		

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[0307] In some embodiments including, for example, embodiments of antisense oligomer conjugates of Formula (V) and Formula (VA), the targeting sequence is 5'-CAATGCCATCCTGGAGTTCCTG-3' wherein each thymine (T) is optionally uracil (U) (SEQ ID NO: 28). In various embodiments including, for example, embodiments of antisense oligomer conjugates of Formula (V) and Formula (VA), the targeting sequence is 5'-CAATGCCATCCTGGAGTTCCTG-3' (SEQ ID NO: 27).

[0308] In some embodiments, including, for example, embodiments of antisense oligomer conjugates of Formula (I), an antisense oligomer conjugate of the disclosure is according to Formula (VI):



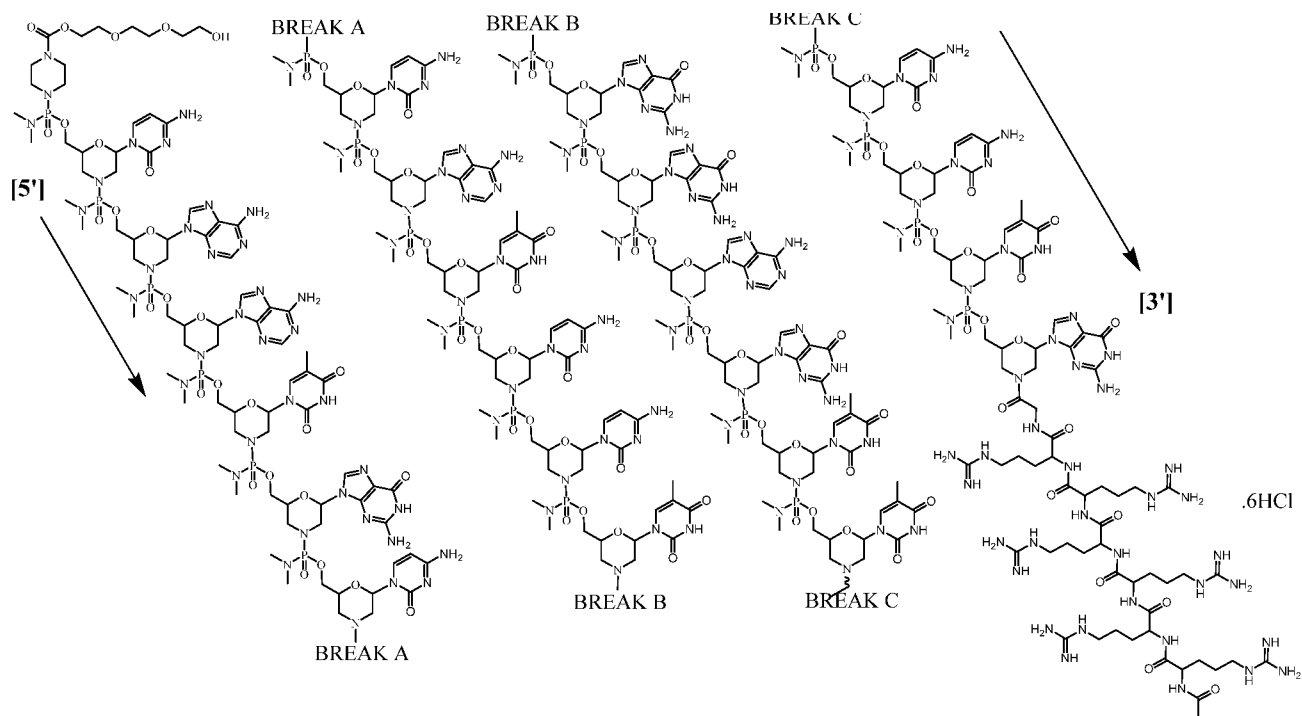
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(VI),

or a pharmaceutically acceptable salt thereof.

[0309] In some embodiments, an antisense oligomer conjugate of Formula (VI) is an HCl (hydrochloric acid) salt thereof. In certain embodiments, the HCl salt is a $\cdot 6\text{HCl}$ salt.

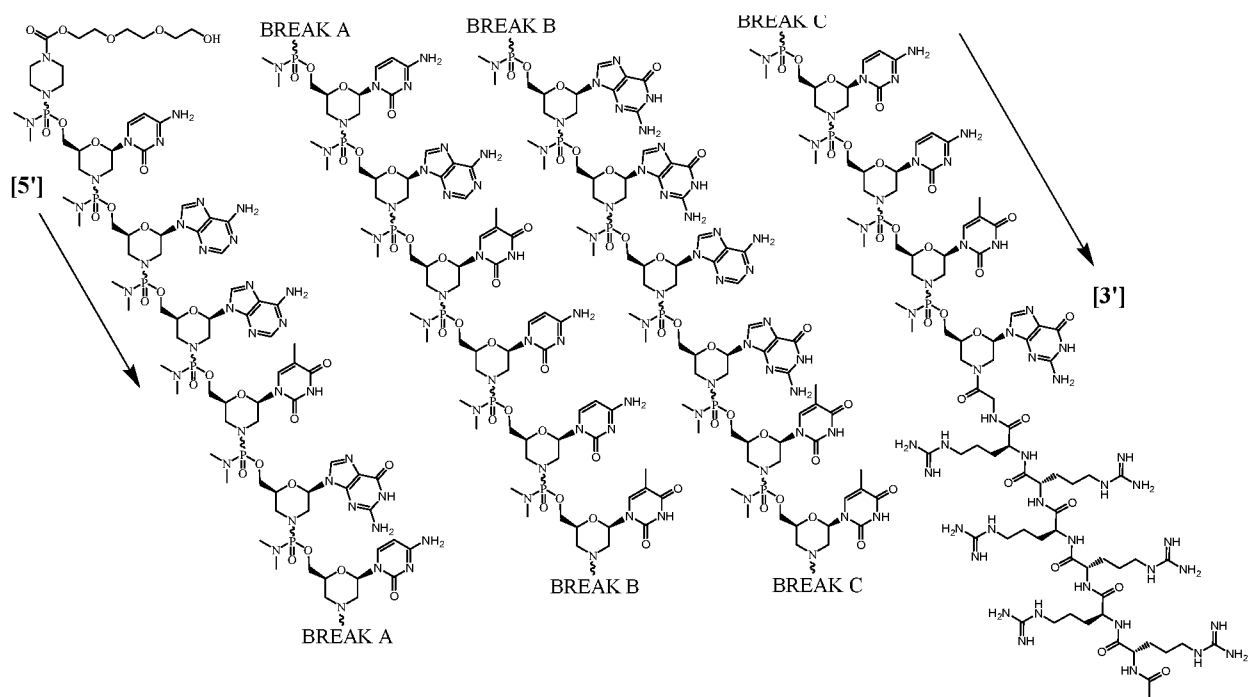
[0310] In some embodiments, including, for example, embodiments of antisense oligomer conjugates of Formula (VI), an antisense oligomer conjugate of the disclosure is according to Formula (VIA):



(VIA).

[0311] In some embodiments of the disclosure, including some embodiments of antisense oligomer conjugates of Formula (I) and embodiments of antisense oligomer conjugates of Formula (VI), the antisense oligomer conjugate is according to Formula (VIB):

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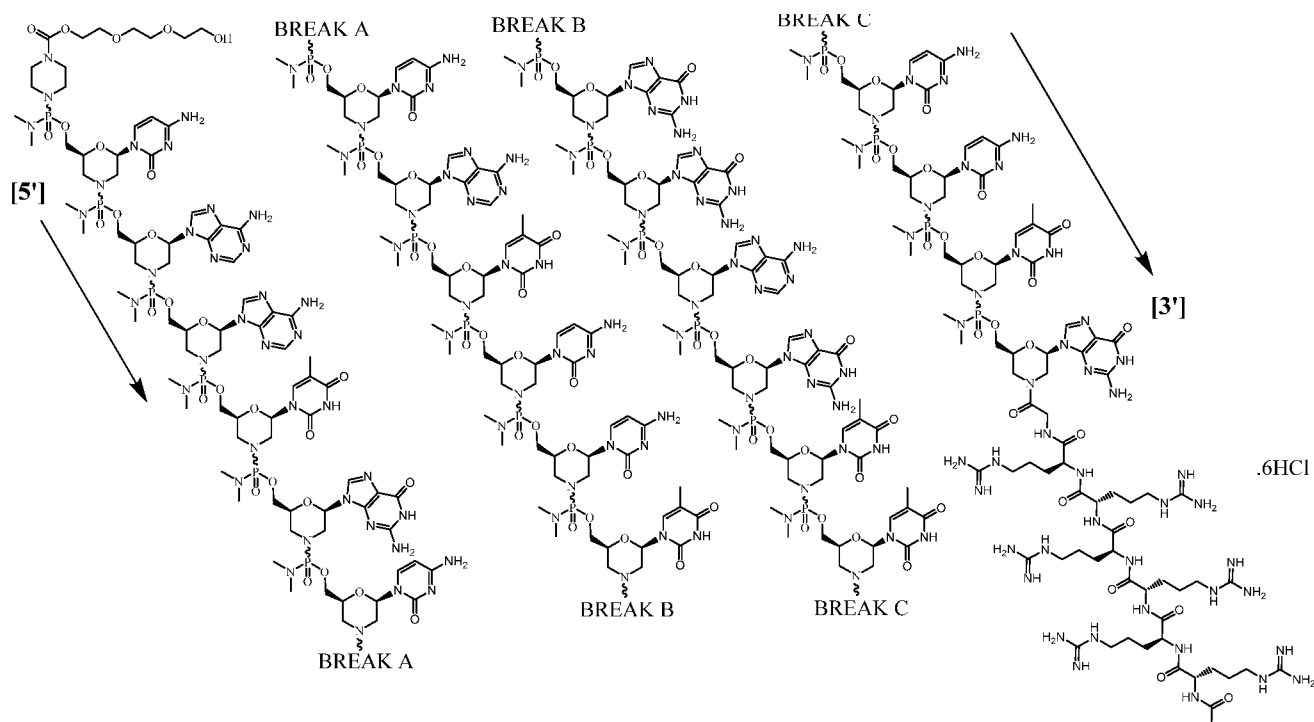
(VIB),

or a pharmaceutically acceptable salt thereof.

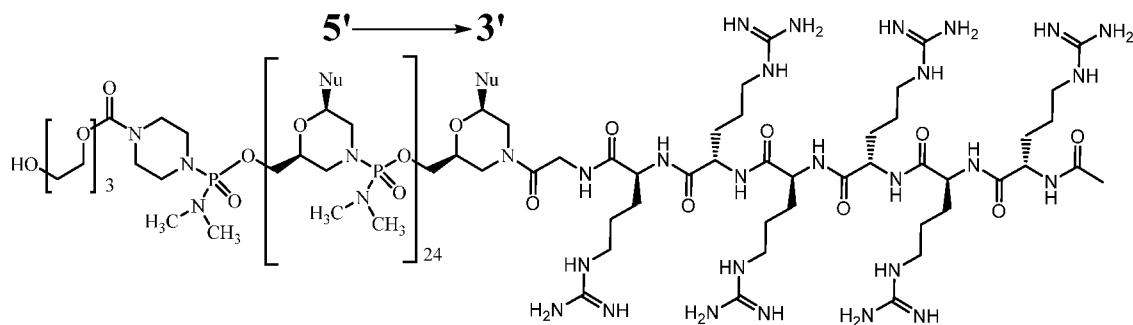
[0312] In some embodiments, an antisense oligomer conjugate of Formula (VIB) is an HCl (hydrochloric acid) salt thereof. In certain embodiments, the HCl salt is a $\cdot 6\text{HCl}$ salt.

[0313] In some embodiments, including, for example, embodiments of antisense oligomer conjugates of Formula (VIB), an antisense oligomer conjugate of the disclosure is according to Formula (VIC):

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[0314] In some embodiments, including, for example, some embodiments of Formula (I), an antisense oligomer conjugate of the disclosure is according to Formula (VII):



or a pharmaceutically acceptable salt thereof, wherein:

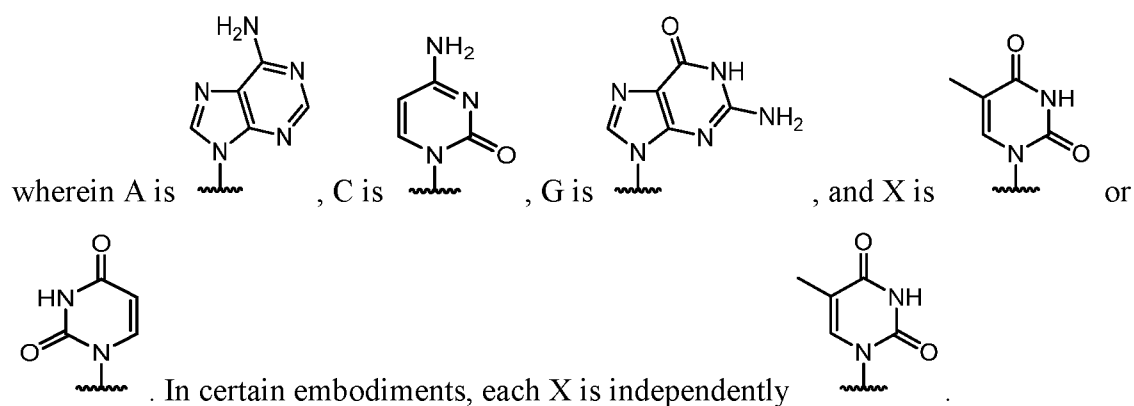
each Nu is a nucleobase which taken together form a targeting sequence that is complementary to an exon 53 annealing site in the dystrophin pre-mRNA designated as H53A(+36+60).

[0315] In some embodiments, each Nu is independently selected from cytosine (C), guanine (G), thymine (T), adenine (A), 5-methylcytosine (5mC), uracil (U), and hypoxanthine (I).

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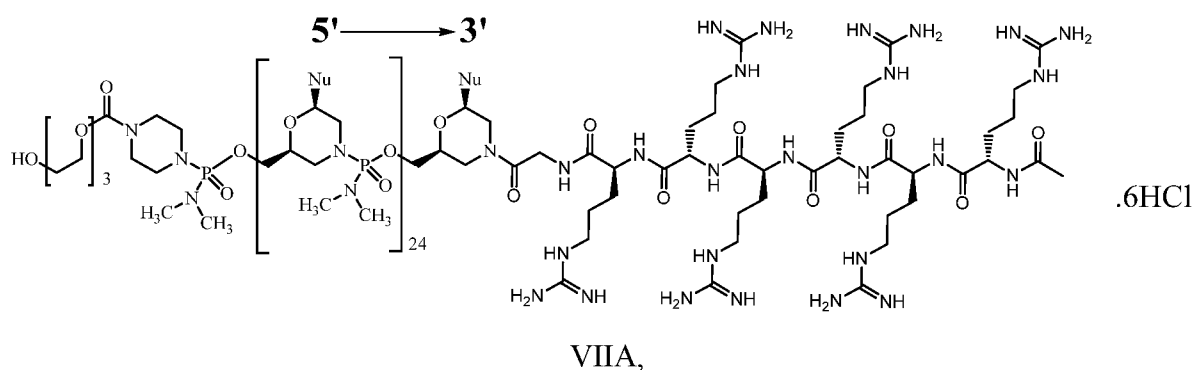
In various embodiments, each Nu from 1 to 25 and 5' to 3' is:

Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu
1	G	6	C	11	G	16	G	21	X
2	X	7	X	12	X	17	A	22	G
3	X	8	C	13	X	18	A	23	X
4	G	9	C	14	C	19	G	24	X
5	C	10	G	15	X	20	G	25	C



In Some embodiments, an antisense oligomer conjugate of Formula (VII) is an HCl (hydrochloric acid) salt thereof. In certain embodiments, the HCl salt is a $\cdot 6\text{HCl}$ salt.

In some embodiments, including, for example, some embodiments of Formula (VII), an antisense oligomer conjugate of the disclosure is according to Formula (VIIA):



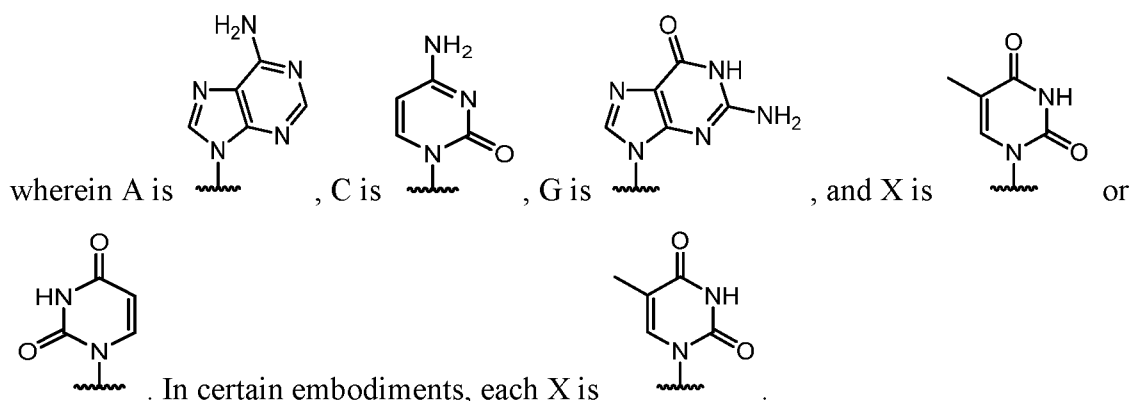
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wherein each Nu is a nucleobase which taken together form a targeting sequence that is complementary to an exon 53 annealing site in the dystrophin pre-mRNA designated as H53A(+36+60).

[0316] In some embodiments, each Nu is independently selected from cytosine (C), guanine (G), thymine (T), adenine (A), 5-methylcytosine (5mC), uracil (U), and hypoxanthine (I).

In various embodiments, each Nu from 1 to 25 and 5' to 3' is:

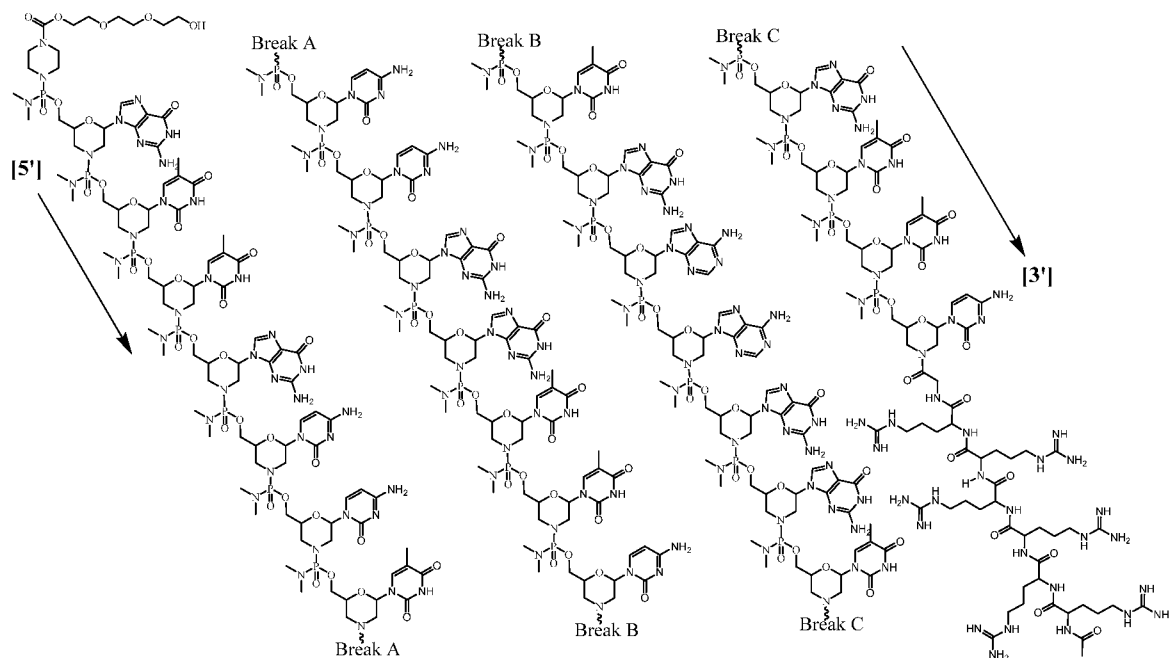
Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu	Position No. 5' to 3'	Nu
1	G	6	C	11	G	16	G	21	X
2	X	7	X	12	X	17	A	22	G
3	X	8	C	13	X	18	A	23	X
4	G	9	C	14	C	19	G	24	X
5	C	10	G	15	X	20	G	25	C



[0317] In some embodiments including, for example, embodiments of antisense oligomer conjugates of Formula (VII) and Formula (VIIA), the targeting sequence is 5'-GTTGCCTCCGGTTCTGAAGGTGTTC-3' wherein each thymine (T) is optionally uracil (U) (SEQ ID NO: 30). In various embodiments including, for example, embodiments of antisense oligomer conjugates of Formula (VII) and Formula (VIIA), the targeting sequence is 5'-GTTGCCTCCGGTTCTGAAGGTGTTC-3' (SEQ ID NO: 29).

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[0318] In some embodiments, including, for example, embodiments of antisense oligomer conjugates of Formula (I), an antisense oligomer conjugate of the disclosure is according to Formula (VIII):

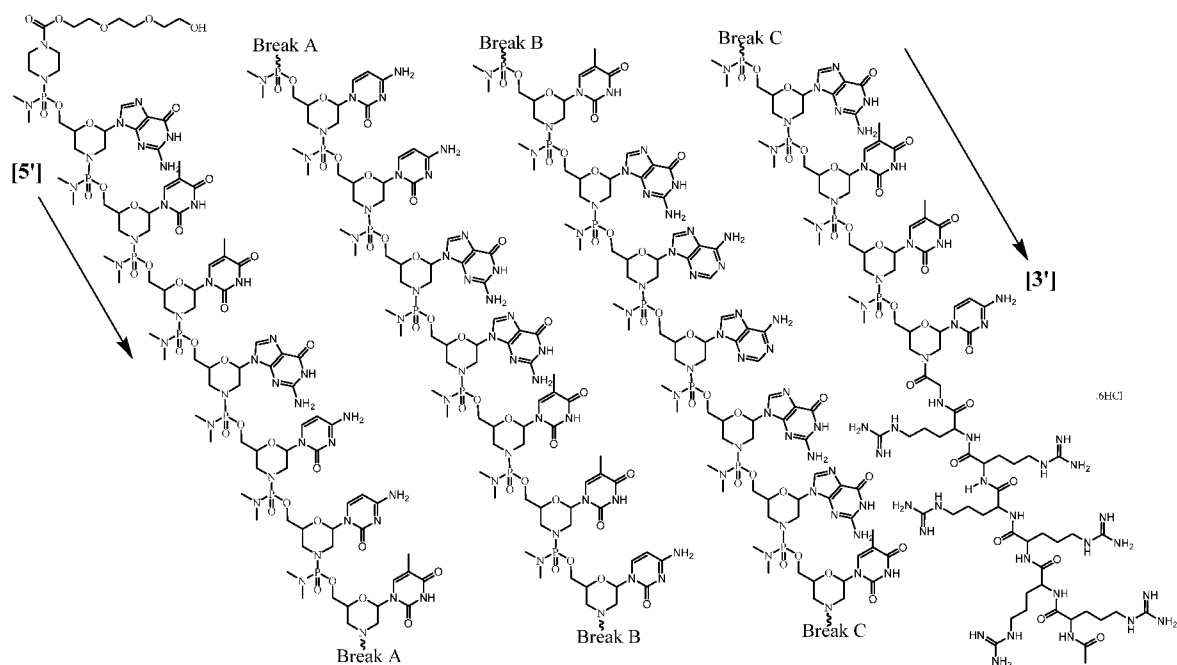


VIII,

or a pharmaceutically acceptable salt thereof.

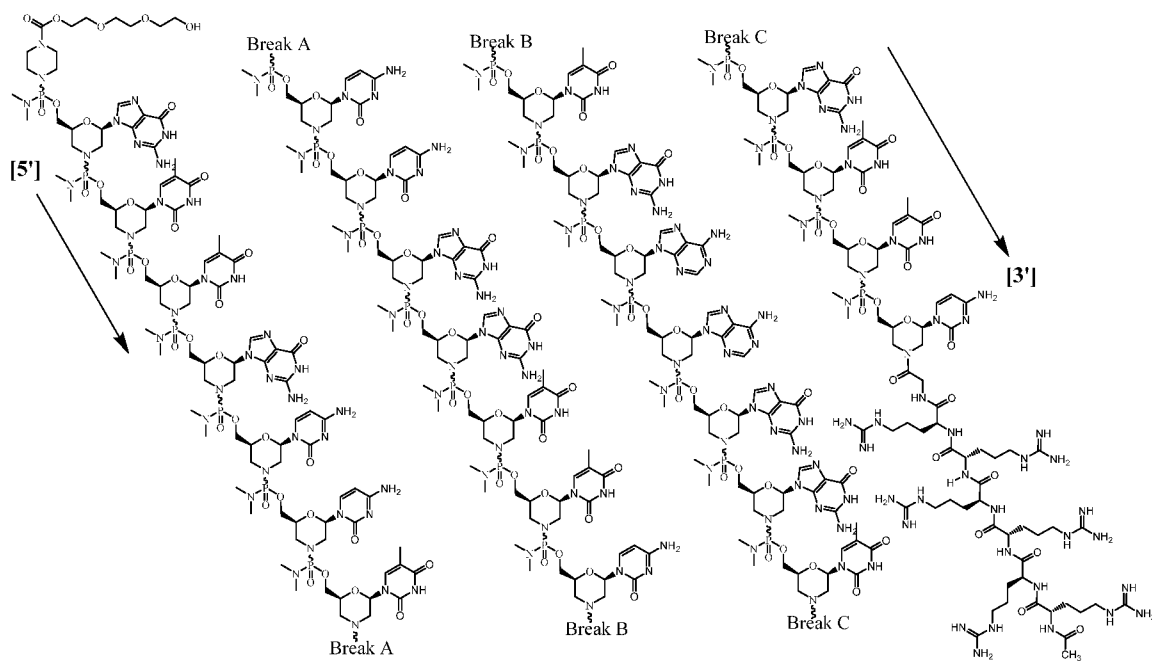
[0319] In some embodiments, an antisense oligomer conjugate of Formula (VIII) is an HCl (hydrochloric acid) salt thereof. In certain embodiments, the HCl salt is a $\cdot 6\text{HCl}$ salt. In some embodiments, including, for example, embodiments of antisense oligomer conjugates of Formula (VIII), an antisense oligomer conjugate of the disclosure is according to Formula (VIIIa):

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(VIII A).

[0320] In some embodiments of the disclosure, including some embodiments of antisense oligomer conjugates of Formula (I) and embodiments of antisense oligomer conjugates of Formula (VIII), the antisense oligomer conjugate is according to Formula (VIII B):

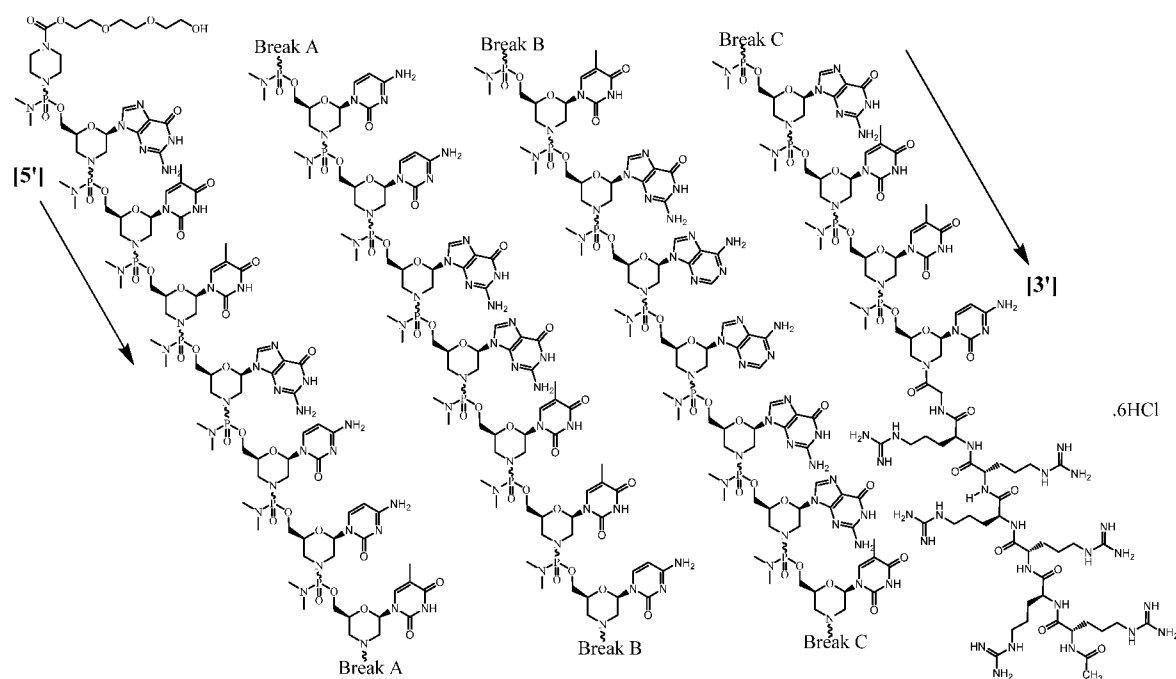


(VIII B).

- 123 -

or a pharmaceutically acceptable salt thereof.

[0321] In some embodiments, an antisense oligomer conjugate of Formula (VIIB) is an HCl (hydrochloric acid) salt thereof. In certain embodiments, the HCl salt is a $\cdot 6\text{HCl}$ salt. In some embodiments, including, for example, embodiments of antisense oligomer conjugates of Formula (VIIB), an antisense oligomer conjugate of the disclosure is according to Formula (VIIC):



VIIC.

[0322] In one aspect, the disclosure provides an antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, capable of binding a selected target to induce exon skipping in the human dystrophin gene, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, comprises a sequence of bases that is complementary to an exon 51 target region of the dystrophin pre-mRNA designated as an annealing site; wherein the base sequence and annealing site are selected from one of the following:

Annealing Site	Base Sequence [5' to 3']
H51D(+16-07)	CTC ATA CCT TCT GCT TGA TGA TC (SEQ ID NO: 567)

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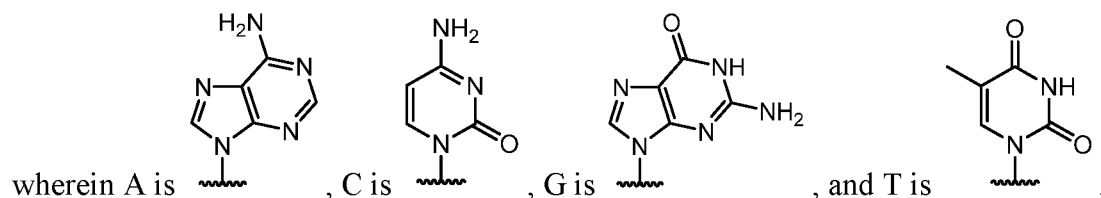
Annealing Site	Base Sequence [5' to 3']
H50D(+103+127)	GGG ATC CAG TAT ACT TAC AGG CTC C (SEQ ID NO: 568)
H51A(+61+82)	GAA GAT GGC ATT TCT AGT TTG G (SEQ ID NO: 569)
H51A(+61+83)	GGA AGA TGG CAT TTC TAG TTT GG (SEQ ID NO: 570)
H51A(+61+89)	CAT CAA GGA AGA TGG CAT TTC TAG TTT GG (SEQ ID NO: 571)
H51A(+66+89)	CAT CAA GGA AGA TGG CAT TTC TAG (SEQ ID NO: 572)
H51A(+66+93)	CCA ACA TCA AGG AAG ATG GCA TTT CTA G (SEQ ID NO: 573)
H51A(+69+92)	CAA CAT CAA GGA AGA TGG CAT TTC (SEQ ID NO: 574)
H51A(+69+96)	CCT CCA ACA TCA AGG AAG ATG GCA TTT C (SEQ ID NO: 575)
H51A(+74+96)	CCT CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 576)
H51A(+74+99)	GTA CCT CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 577)
H51A(+74+100)	GGT ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 578)
H51A(+74+102)	CAG GTA CCT CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 579)
H51A(+74+103)	GCA GGT ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 580)
H51A(+75+96)	CCT CCA ACA TCA AGG AAG ATG G (SEQ ID NO: 581)
H51A(+75+99)	GTA CCT CCA ACA TCA AGG AAG ATG G (SEQ ID NO: 582)
H51A(+76+99)	GTA CCT CCA ACA TCA AGG AAG ATG (SEQ ID NO: 583)
H51A(+76+105)	GAG CAG GTA CCT CCA ACA TCA AGG AAG ATG (SEQ ID NO: 584)
H51A(+80+103)	GCA GGT ACC TCC AAC ATC AAG GAA G (SEQ ID NO: 585)
H51A(+80+105)	GAG CAG GTA CCT CCA ACA TCA AGG AAG (SEQ ID NO: 586)
H51A(+80+107)	CAG AGC AGG TAC CTC CAA CAT CAA GGA AG (SEQ ID NO: 587)
H51A(+80+108)	CCA GAG CAG GTA CCT CCA ACA TCA AGG AAG (SEQ ID NO: 588)
H51A(+83+103)	GCA GGT ACC TCC AAC ATC AAG G (SEQ ID NO: 589)
H51A(+83+105)	GAG CAG GTA CCT CCA ACA TCA AGG (SEQ ID NO: 590)
H51A(+83+107)	CAG AGC AGG TAC CTC CAA CAT CAA GG (SEQ ID NO: 591)
H51A(+83+109)	GCC AGA GCA GGT ACC TCC AAC ATC AAG G (SEQ ID NO: 592)
H51A(+84+107)	CAG AGC AGG TAC CTC CAA CAT CAA G (SEQ ID NO: 593)
H51A(+84+111)	CTG CCA GAG CAG GTA CCT CCA ACA TCA AG (SEQ ID NO: 594)
H51A(+84+105)	GAG CAG GTA CCT CCA ACA TCA AG (SEQ ID NO: 595)
H51A(+87+109)	GCC AGA GCA GGT ACC TCC AAC ATC (SEQ ID NO: 596)
H51A(+93+116)	GAA ATC TGC CAG AGC AGG TAC CTC (SEQ ID NO: 597)
H51A(+75+100)	GGT ACC TCC AAC ATC AAG GAA GAT GG (SEQ ID NO: 598)
H51A(+74+101)	AGG TAC CTC CAA CAT CAA GGA AGA TGG C (SEQ ID NO: 599)
H51A(+74+98)	TAC CTC CAA CAT CAA GGA AGA TGG C (SEQ ID NO: 600)
H51A(+74+97)	ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 601)
H51A(+74+94)	TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 602)
H51A(+74+93)	CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 603)
H51A(+74+92)	CAA CAT CAA GGA AGA TGG C (SEQ ID NO: 604)
H51A(+69+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TTT C (SEQ ID NO: 605)
H51A(+70+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TTT (SEQ ID NO: 606)
H51A(+71+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TT (SEQ ID NO: 607)

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Annealing Site	Base Sequence [5' to 3']
H51A(+72+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA T (SEQ ID NO: 608)
H51A(+73+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA (SEQ ID NO: 609)
H51A(+77+99)	GTA CCT CCA ACA TCA AGG AAG AT (SEQ ID NO: 610)
H51A(+78+99)	GTA CCT CCA ACA TCA AGG AAG A (SEQ ID NO: 611)
H51A(+79+99)	GTA CCT CCA ACA TCA AGG AAG
H51.SA.(-60-36)	GAA GAA AAA GAA AAA TTA GAA ACA C (SEQ ID NO: 613)
H51.SA.(-50-26)	AAG GAA AAA AGA AGA AAA AGA AAA A (SEQ ID NO: 614)
H51.SA.(-45-21)	GCA AAA AGG AAA AAA GAA GAA AAA G (SEQ ID NO: 615)
H51.SA.(-40-16)	TTT TTG CAA AAA GGA AAA AAG AAG A (SEQ ID NO: 616)
H51.SA.(-35-11)	TTG GGT TTT TGC AAA AAG GAA AAA A (SEQ ID NO: 617)
H51.SA.(-30-6)	ATA TTT TGG GTT TTT GCA AAA AGG A (SEQ ID NO: 618)
H51.SA.(-25-1)	CTA AAA TAT TTT GGG TTT TTG CAA A (SEQ ID NO: 619)
H51.SA.(-20+5)	AGG AGC TAA AAT ATT TTG GGT TTT T (SEQ ID NO: 620)
H51.SA.(-15+10)	TGA GTA GGA GCT AAA ATA TTT TGG G (SEQ ID NO: 621)
H51.SA.(-10+15)	CAG TCT GAG TAG GAG CTA AAA TAT T (SEQ ID NO: 622)
H51.SA.(-5+20)	AGT AAC AGT CTG AGT AGG AGC TAA A (SEQ ID NO: 623)
H51.SA.(-1+24)	CCA GAG TAA CAG TCT GAG TAG GAG C (SEQ ID NO: 624)
H51.SA.(-65-41)	AAA AGA AAA ATT AGA AAC ACA AGC T (SEQ ID NO: 625)
H51.SA.(-70-46)	AAA AAT TAG AAA CAC AAG CTA AAG A (SEQ ID NO: 626)
H51.SA.(-75-51)	TTA GAA ACA CAA GCT AAA GAG CCA A (SEQ ID NO: 627)
H51.SA.(-80-56)	AAC ACA AGC TAA AGA GCC AAT TTC A (SEQ ID NO: 628)
H51.SA.(-85-61)	AAG CTA AAG AGC CAA TTT CAA TAA C (SEQ ID NO: 629)
H51.SA.(-90-66)	AAA GAG CCA ATT TCA ATA ACA ATA A (SEQ ID NO: 630)
H51.SA.(-95-71)	GCC AAT TTC AAT AAC AAT AAG TCA A (SEQ ID NO: 631)
H51.SA.(-100-76)	TTT CAA TAA CAA TAA GTC AAA TTT A (SEQ ID NO: 632)
H51A(+1+30)	GTG TCA CCA GAG TAA CAG TCT GAG TAG GAG (SEQ ID NO: 633)
H51A(+10+39)	CCA CAG GTT GTG TCA CCA GAG TAA CAG TCT (SEQ ID NO: 634)
H51A(+6+35)	AG GTT GTG TCA CCA GA GTA ACA GTC TGA GT (SEQ ID NO: 635)
H51A(+49+78)	ATG GCA TTT CTA GTT TGG AGA TGG CAG TTT (SEQ ID NO: 636)
H51A(+1+25)	ACC AGA GTA ACA GTC TGA GTA GGA G (SEQ ID NO: 637)
H51A(+4+28)	GTC ACC AGA GTA ACA GTC TGA GTA G (SEQ ID NO: 638)
H51A(+16+40)	ACC ACA GGT TGT GTC ACC AGA GTA A (SEQ ID NO: 639)
H51A(+21+45)	TAG TAA CCA CAG GTT GTG TCA CCA G (SEQ ID NO: 640)
H51A(+26+50)	TTC CTT AGT AAC CAC AGG TTG TGT C (SEQ ID NO: 641)
H51A(+31+55)	GCA GTT TCC TTA GTA ACC ACA GGT T (SEQ ID NO: 642)
H51A(+36+60)	AGA TGG CAG TTT CCT TAG TAA CCA C (SEQ ID NO: 643)
H51A(+41+65)	TTT GGA GAT GGC AGT TTC CTT AGT A (SEQ ID NO: 644)
H51A(+86+110)	TGC CAG AGC AGG TAC CTC CAA CAT C (SEQ ID NO: 645)
H51A(+91+115)	AAA TCT GCC AGA GCA GGT ACC TCC A (SEQ ID NO: 646)
H51A(+96+120)	GGT TGA AAT CTG CCA GAG CAG GTA C (SEQ ID NO: 647)

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Annealing Site	Base Sequence [5' to 3']
H51A(+101+125)	AGC CCG GTT GAA ATC TGC CAG AGC A (SEQ ID NO: 648)
H51A(+106+130)	GTC CAA GCC CGG TTG AAA TCT GCC A (SEQ ID NO: 649)
H51A(+111+135)	GTT CTG TCC AAG CCC GGT TGA AAT C (SEQ ID NO: 650)
H51A(+116+140)	GGT AAG TTC TGT CCA AGC CCG GTT G (SEQ ID NO: 651)
H51A(+121+145)	CAG TCG GTA AGT TCT GTC CAA GCC C (SEQ ID NO: 652)
H51A(+126+150)	AAA GCC AGT CGG TAA GTT CTG TCC A (SEQ ID NO: 653)
H51A(+131+155)	CAG AGA AAG CCA GTC GGT AAG TTC T (SEQ ID NO: 654)
H51A(+136+160)	TCA AGC AGA GAA AGC CAG TCG GTA A (SEQ ID NO: 655)
H51A(+141+165)	CTT GAT CAA GCA GAG AAA GCC AGT C (SEQ ID NO: 656)
H51A(+146+170)	TAT AAC TTG ATC AAG CAG AGA AAG C (SEQ ID NO: 657)
H51A(+151+175)	GAT TTT ATA ACT TGA TCA AGC AGA G (SEQ ID NO: 658)
H51A(+156+180)	TCT GTG ATT TTA TAA CTT GAT CAA G (SEQ ID NO: 659)
H51A(+161+185)	CAC CCT CTG TGA TTT TAT AAC TTG A (SEQ ID NO: 660)
H51A(+166+190)	ACC ATC ACC CTC TGT GAT TTT ATA A (SEQ ID NO: 661)
H51A(+171+195)	CAC CCA CCA TCA CCC TCT GTG ATT T (SEQ ID NO: 662)
H51A(+176+200)	AAG GTC ACC CAC CAT CAC CCT CTG T (SEQ ID NO: 663)
H51A(+181+205)	TCC TCA AGG TCA CCC ACC ATC ACC C (SEQ ID NO: 664)
H51A(+186+210)	TGA TAT CCT CAA GGT CAC CCA CCA T (SEQ ID NO: 665)
H51A(+191+215)	CTC GTT GAT ATC CTC AAG GTC ACC C (SEQ ID NO: 666)
H51A(+196+220)	ATC ATC TCG TTG ATA TCC TCA AGG T (SEQ ID NO: 667)
H51A(+201+225)	TGA TGA TCA TCT CGT TGA TAT CCT C (SEQ ID NO: 668)
H51A(+206+230)	CTG CTT GAT GAT CAT CTC GTT GAT A (SEQ ID NO: 669)
H51D(+211-02)	ACC TTC TGC TTG ATG ATC ATC TCG T (SEQ ID NO: 670)
H51D(+214-05)	CAT ACC TTC TGC TTG ATG ATC ATC T (SEQ ID NO: 671)
H51D(+217-08)	TCT CAT ACC TTC TGC TTG ATG ATC A (SEQ ID NO: 672)
H51D(+220-11)	TTT TCT CAT ACC TTC TGC TTG ATG A (SEQ ID NO: 673)
H51D(+223-14)	ATT TTT TCT CAT ACC TTC TGC TTG A (SEQ ID NO: 674)
H51D(+226-17)	ATC ATT TTT TCT CAT ACC TTC TGC T (SEQ ID NO: 675)
H51D(+229-20)	TTT ATC ATT TTT TCT CAT ACC TTC T (SEQ ID NO: 676)
H51D(+232-23)	ACT TTT ATC ATT TTT TCT CAT ACC T (SEQ ID NO: 677)
H51D(-02-26)	CCA ACT TTT ATC ATT TTT TCT CAT A (SEQ ID NO: 678)
H51A(+1+30)	GTG TCA CCA GAG TAA CAG TCT GAG TAG GAG (SEQ ID NO: 633)



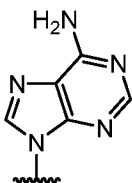
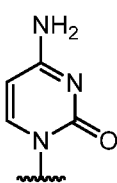
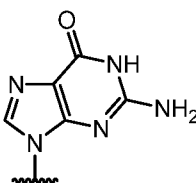
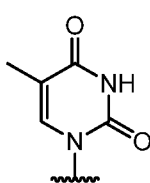
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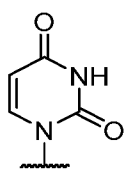
[0323] In one aspect, the base sequence and annealing site are selected from one of the following:

Annealing Site	Base Sequence [5' to 3']
H51A(+66+95)	CTC CAA CAT CAA GGA AGA TGG CAT TTC TAG (SEQ ID NO: 679)
H51A(+74+97)	ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 601)
H51A(+70+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TTT (SEQ ID NO: 606)
H51A(+72+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA T (SEQ ID NO: 608)
H51A(+68+87)	TCA AGG AAG ATG GCA TTT CT (SEQ ID NO: 680)
H51A(+68+87)	UCA AGG AmAGm AmUGm GmCA UUU CU (SEQ ID NO: 681)
H53A(+36+60)	GTT GCC TCC GGT TCT GAA GGT GTT C (SEQ ID NO: 682)
H53A(+36+60)	GTT G5mC5mC T5mC5mC GGT T5mC T GAA GGT GTT 5Mc (SEQ ID NO: 683)
H53A(+36+56)	CCT CCG GTT CTG AAG GTG TTC (SEQ ID NO: 684)
H53A(+23+47)	CTG AAG GTG TTC TTG TAC TTC ATC C (SEQ ID NO: 34)
H53A(+32+56)	CCT CCG GTT CTG AAG GTG TTC TTG T (SEQ ID NO: 685)
H53A(+33+60)	GTT GCC TCC GGT TCT GAA GGT GTT CTT G (SEQ ID NO: 686)
H53A(+30+59)	TTG CCT CCG GTT CTG AAG GTG TTC TTG TAC (SEQ ID NO: 687)
H53A(+39+62)	CTG TTG CCT CCG GTT CTG AAG GTG (SEQ ID NO: 688)
H53A(+36+69)	CAT TCA ACT GTT GCC TCC GGT TCT GAA GGT G (SEQ ID NO: 689)
H53A(+45+62)	CTG TTG CCT CCG GTT CTG (SEQ ID NO: 690)
H45A(-03+19)	CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 691)
H45A(-09+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA T (SEQ ID NO: 692)
H45A(-03+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 693)
H45A(-06+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA A (SEQ ID NO: 694)
H45A(-12+19)	CAA TGC CAT CCT GGA GTT CCT GTA AGA TAC C (SEQ ID NO: 695)
H45A(-09+19)	CAA TGC CAT CCT GGA GTT CCT GTA AGA T (SEQ ID NO: 696)
H45A(-12+16)	TGC CAT CCT GGA GTT CCT GTA AGA TAC C (SEQ ID NO: 697)
H45A(-14+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA TAC CAA (SEQ ID NO: 698)
H45A(-08+19)	CAA TGC CAT CCT GGA GTT CCT GTA AGA (SEQ ID NO: 699)
HM45A(-07+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA AG (SEQ ID NO: 700)
H45A(-12+22)	GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA TAC C (SEQ ID NO: 701)
H45A(-09+22)	GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA T (SEQ ID NO: 702)
H45A(-09+30)	TTG CCG CTG CCC AAT GCC ATC CTG GAG TTC CTG TAA GAT (SEQ ID NO: 703)
H45A(-06+22)	GCC CAA TGC CAT CCT GGA GTT CCT GTA A (SEQ ID NO: 704)
H45A(-06+28)	GCC GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA A (SEQ ID NO: 705)

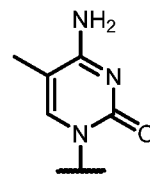
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Annealing Site	Base Sequence [5' to 3']
H45A(-03+22)	GCC CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 706)
H45A(-03+28)	GCC GCT GCC CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 707)
H45A(+9+26)	m5C-G-m5C-T-G-C-m5C-m5C-A-A-T-G-m5C-m5C-A-U-m5C-m5C (SEQ ID NO: 708)
H44A(-10+15)	GAT CTG TCA AAT CGC CTG CAG GTA A (SEQ ID NO: 709)
H44A(-07+15)	GAT CTG TCA AAT CGC CTG CAG G (SEQ ID NO: 710)
H44M(-07+17)	CAG ATC TGT CAA ATC GCC TGC AGG (SEQ ID NO: 711)
H44A(-08+15)	GAT CTG TCA AAT CGC CTG CAG GT (SEQ ID NO: 712)
H44A(-06+15)	GAT CTG TCA AAT CGC CTG CAG (SEQ ID NO: 713)
H44A(-08+17)	CAG ATC TGT CAA ATC GCC TGC AGG T (SEQ ID NO: 714)
H44A(-06+17)	CAG ATC TGT CAA ATC GCC TGC AG (SEQ ID NO: 715)
H50D(+04-18)	GGG ATC CAG TAT ACT TAC AGG C (SEQ ID NO: 716)
H50D(+07-18)	GGG ATC CAG TAT ACT TAC AGG CTC C (SEQ ID NO: 568)
H50D(+07-16)	GAT CCA GTA TAC TTA CAG GCT CC (SEQ ID NO: 717)
H50D(+07-17)	GGA TCC AGT ATA CTT ACA GGC TCC (SEQ ID NO: 718)
H50A(-19+07)	ACT TCC TCT TTA ACA GAA AAG CAT AC (SEQ ID NO: 719)
H50D(+07-15)	ATC CAG TAT ACT TAC AGG CTC C (SEQ ID NO: 720)
H50A(-02+23)	GAG CTC AGA TCT TCT AAC TTC CTC T (SEQ ID NO: 721)
H50D(+06-18)	GGG ATC CAG TAT ACT TAC AGG CTC (SEQ ID NO: 722)
H50D(+07-20)	ATG GGA TCC AGT ATA CTT ACA GGC TCC (SEQ ID NO: 723)
H52A(-01+24)	CTG TTC CAA ATC CTG CAT TGT TGC C (SEQ ID NO: 724)

[0324] wherein A is , C is , G is , T is , U is

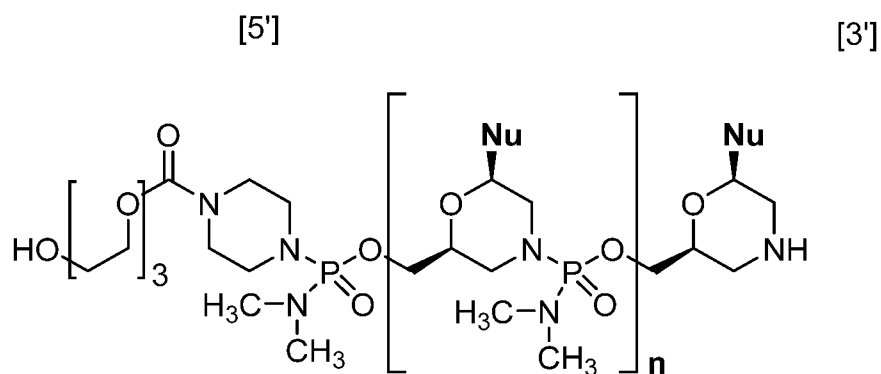


, Gm is methylated guanine, Am is methylated adenine, and m5C is



[0325] In another aspect, the disclosure provides antisense oligomers of Formula (IX):

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IX,

or a pharmaceutically acceptable salt thereof, where each **Nu** from 1 to **n** and 5' to 3' corresponds to the nucleobases in the following sequences:

Annealing Site	Sequence [5' to 3']
H51A(+61+90)	ACA TCA AGG AAG ATG GCA TTT CTA GTT TGG (SEQ ID NO: 725)
H51D(+16-07)	CTC ATA CCT TCT GCT TGA TGA TC (SEQ ID NO: 567)
H50D(+103+127)	GGG ATC CAG TAT ACT TAC AGG CTC C (SEQ ID NO: 568)
H51A(+81+105)	GAG CAG GTA CCT CCA ACA TCA AGG AA (SEQ ID NO: 33)
H51A(+71+100)	GGT ACC TCC AAC ATC AAG GAA GAT GGC ATT (SEQ ID NO: 726)
H51A(+48+73)	ATT TCT AGT TTG GAG ATG GCA GTT TC (SEQ ID NO: 727)
H51A(+59+84)	GGA AGA TGG CAT TTC TAG TTT GGA G (SEQ ID NO: 728)
H51A(+64+88)	CAT CAA GGA AGA TGG CAT TTC TAG TT (SEQ ID NO: 729)
H51A(+89+113)	ATC TGC CAG AGC AGG TAC CTC CAA C (SEQ ID NO: 730)
H51A(+49+68)	TAG TTT GGA GAT GGC AGT TT (SEQ ID NO: 731)
H51A(+64+83)	GGA AGA TGG CAT TTC TAG TT (SEQ ID NO: 732)
H51A(+80+98)	TAC CTC CAA CAT CAA GGA AG (SEQ ID NO: 733)
H51A(+94+113)	ATC TGC CAG AGC AGG TAC CT (SEQ ID NO: 734)
H51A(+109+128)	CCA AGC CCG GTT GAA ATC TG (SEQ ID NO: 735)
H51A(+61+82)	GAA GAT GGC ATT TCT AGT TTG G (SEQ ID NO: 569)
H51A(+61+83)	GGA AGA TGG CAT TTC TAG TTT GG (SEQ ID NO: 570)
H51A(+61+89)	CAT CAA GGA AGA TGG CAT TTC TAG TTT GG (SEQ ID NO: 571)
H51A(+66+89)	CAT CAA GGA AGA TGG CAT TTC TAG (SEQ ID NO: 572)
H51A(+66+93)	CCA ACA TCA AGG AAG ATG GCA TTT CTA G (SEQ ID NO: 573)
H51A(+69+92)	CAA CAT CAA GGA AGA TGG CAT TTC (SEQ ID NO: 574)
H51A(+69+96)	CCT CCA ACA TCA AGG AAG ATG GCA TTT C (SEQ ID NO: 575)
H51A(+74+96)	CCT CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 576)
H51A(+74+99)	GTA CCT CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 577)
H51A(+74+100)	GGT ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 578)
H51A(+74+102)	CAG GTA CCT CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 579)

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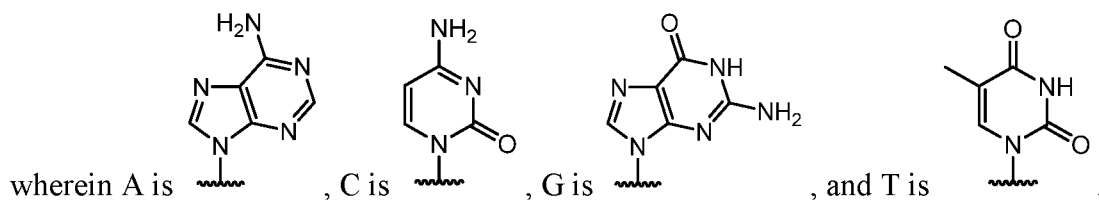
Annealing Site	Sequence [5' to 3']
H51A(+74+103)	GCA GGT ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 580)
H51A(+75+96)	CCT CCA ACA TCA AGG AAG ATG G (SEQ ID NO: 581)
H51A(+75+99)	GTA CCT CCA ACA TCA AGG AAG ATG G (SEQ ID NO: 582)
H51A(+76+99)	GTA CCT CCA ACA TCA AGG AAG ATG (SEQ ID NO: 583)
H51A(+76+105)	GAG CAG GTA CCT CCA ACA TCA AGG AAG ATG (SEQ ID NO: 584)
H51A(+80+103)	GCA GGT ACC TCC AAC ATC AAG GAA G (SEQ ID NO: 585)
H51A(+80+105)	GAG CAG GTA CCT CCA ACA TCA AGG AAG (SEQ ID NO: 586)
H51A(+80+107)	CAG AGC AGG TAC CTC CAA CAT CAA GGA AG (SEQ ID NO: 587)
H51A(+80+108)	CCA GAG CAG GTA CCT CCA ACA TCA AGG AAG (SEQ ID NO: 588)
H51A(+83+103)	GCA GGT ACC TCC AAC ATC AAG G (SEQ ID NO: 589)
H51A(+83+105)	GAG CAG GTA CCT CCA ACA TCA AGG (SEQ ID NO: 590)
H51A(+83+107)	CAG AGC AGG TAC CTC CAA CAT CAA GG (SEQ ID NO: 591)
H51A(+83+109)	GCC AGA GCA GGT ACC TCC AAC ATC AAG G (SEQ ID NO: 592)
H51A(+84+107)	CAG AGC AGG TAC CTC CAA CAT CAA G (SEQ ID NO: 593)
H51A(+84+111)	CTG CCA GAG CAG GTA CCT CCA ACA TCA AG (SEQ ID NO: 594)
H51A(+84+105)	GAG CAG GTA CCT CCA ACA TCA AG (SEQ ID NO: 595)
H51A(+87+109)	GCC AGA GCA GGT ACC TCC AAC ATC (SEQ ID NO: 596)
H51A(+93+116)	GAA ATC TGC CAG AGC AGG TAC CTC (SEQ ID NO: 597)
H51A(+75+100)	GGT ACC TCC AAC ATC AAG GAA GAT GG (SEQ ID NO: 598)
H51A(+74+101)	AGG TAC CTC CAA CAT CAA GGA AGA TGG C (SEQ ID NO: 599)
H51A(+74+98)	TAC CTC CAA CAT CAA GGA AGA TGG C (SEQ ID NO: 600)
H51A(+74+97)	ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 601)
H51A(+74+94)	TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 602)
H51A(+74+93)	CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 603)
H51A(+74+92)	CAA CAT CAA GGA AGA TGG C (SEQ ID NO: 604)
H51A(+69+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TTT C (SEQ ID NO: 605)
H51A(+70+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TTT (SEQ ID NO: 606)
H51A(+71+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TT (SEQ ID NO: 607)
H51A(+72+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA T (SEQ ID NO: 608)
H51A(+73+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA (SEQ ID NO: 609)
H51A(+77+99)	GTA CCT CCA ACA TCA AGG AAG AT (SEQ ID NO: 610)
H51A(+78+99)	GTA CCT CCA ACA TCA AGG AAG A (SEQ ID NO: 611)
H51A(+79+99)	GTA CCT CCA ACA TCA AGG AAG
H51.SA.(-60-36)	GAA GAA AAA GAA AAA TTA GAA ACA C (SEQ ID NO: 613)
H51.SA.(-50-26)	AAG GAA AAA AGA AGA AAA AGA AAA A (SEQ ID NO: 614)
H51.SA.(-45-21)	GCA AAA AGG AAA AAA GAA GAA AAA G (SEQ ID NO: 615)
H51.SA.(-40-16)	TTT TTG CAA AAA GGA AAA AAG AAG A (SEQ ID NO: 616)
H51.SA.(-35-11)	TTG GGT TTT TGC AAA AAG GAA AAA A (SEQ ID NO: 617)
H51.SA.(-30-6)	ATA TTT TGG GTT TTT GCA AAA AGG A (SEQ ID NO: 618)
H51.SA.(-25-1)	CTA AAA TAT TTT GGG TTT TTG CAA A (SEQ ID NO: 619)

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Annealing Site	Sequence [5' to 3']
H51.SA.(-20+5)	AGG AGC TAA AAT ATT TTG GGT TTT T (SEQ ID NO: 620)
H51.SA.(-15+10)	TGA GTA GGA GCT AAA ATA TTT TGG G (SEQ ID NO: 621)
H51.SA.(-10+15)	CAG TCT GAG TAG GAG CTA AAA TAT T (SEQ ID NO: 622)
H51.SA.(-5+20)	AGT AAC AGT CTG AGT AGG AGC TAA A (SEQ ID NO: 623)
H51.SA.(-1+24)	CCA GAG TAA CAG TCT GAG TAG GAG C (SEQ ID NO: 624)
H51.SA.(-65-41)	AAA AGA AAA ATT AGA AAC ACA AGC T (SEQ ID NO: 625)
H51.SA.(-70-46)	AAA AAT TAG AAA CAC AAG CTA AAG A (SEQ ID NO: 626)
H51.SA.(-75-51)	TTA GAA ACA CAA GCT AAA GAG CCA A (SEQ ID NO: 627)
H51.SA.(-80-56)	AAC ACA AGC TAA AGA GCC AAT TTC A (SEQ ID NO: 628)
H51.SA.(-85-61)	AAG CTA AAG AGC CAA TTT CAA TAA C (SEQ ID NO: 629)
H51.SA.(-90-66)	AAA GAG CCA ATT TCA ATA ACA ATA A (SEQ ID NO: 630)
H51.SA.(-95-71)	GCC AAT TTC AAT AAC AAT AAG TCA A (SEQ ID NO: 631)
H51.SA.(-100-76)	TTT CAA TAA CAA TAA GTC AAA TTT A (SEQ ID NO: 632)
H51A(+1+30)	GTG TCA CCA GAG TAA CAG TCT GAG TAG GAG (SEQ ID NO: 633)
H51A(+10+39)	CCA CAG GTT GTG TCA CCA GAG TAA CAG TCT (SEQ ID NO: 634)
H51A(+6+35)	AGG TTG TGT CAC CAG AGT AAC AGT CTG AGT (SEQ ID NO: 736)
H51A(+49+78)	ATG GCA TTT CTA GTT TGG AGA TGG CAG TTT (SEQ ID NO: 636)
H51A(+1+25)	ACC AGA GTA ACA GTC TGA GTA GGA G (SEQ ID NO: 637)
H51A(+4+28)	GTC ACC AGA GTA ACA GTC TGA GTA G (SEQ ID NO: 638)
H51A(+16+40)	ACC ACA GGT TGT GTC ACC AGA GTA A (SEQ ID NO: 639)
H51A(+21+45)	TAG TAA CCA CAG GTT GTG TCA CCA G (SEQ ID NO: 640)
H51A(+26+50)	TTC CTT AGT AAC CAC AGG TTG TGT C (SEQ ID NO: 641)
H51A(+31+55)	GCA GTT TCC TTA GTA ACC ACA GGT T (SEQ ID NO: 642)
H51A(+36+60)	AGA TGG CAG TTT CCT TAG TAA CCA C (SEQ ID NO: 643)
H51A(+41+65)	TTT GGA GAT GGC AGT TTC CTT AGT A (SEQ ID NO: 644)
H51A(+86+110)	TGC CAG AGC AGG TAC CTC CAA CAT C (SEQ ID NO: 645)
H51A(+91+115)	AAA TCT GCC AGA GCA GGT ACC TCC A (SEQ ID NO: 646)
H51A(+96+120)	GGT TGA AAT CTG CCA GAG CAG GTA C (SEQ ID NO: 647)
H51A(+101+125)	AGC CCG GTT GAA ATC TGC CAG AGC A (SEQ ID NO: 648)
H51A(+106+130)	GTC CAA GCC CGG TTG AAA TCT GCC A (SEQ ID NO: 649)
H51A(+111+135)	GTT CTG TCC AAG CCC GGT TGA AAT C (SEQ ID NO: 650)
H51A(+116+140)	GGT AAG TTC TGT CCA AGC CCG GTT G (SEQ ID NO: 651)
H51A(+121+145)	CAG TCG GTA AGT TCT GTC CAA GCC C (SEQ ID NO: 652)
H51A(+126+150)	AAA GCC AGT CGG TAA GTT CTG TCC A (SEQ ID NO: 653)
H51A(+131+155)	CAG AGA AAG CCA GTC GGTA AGT TCT (SEQ ID NO: 737)
H51A(+136+160)	TCA AGC AGA GAA AGC CAG TCG GTA A (SEQ ID NO: 655)
H51A(+141+165)	CTT GAT CAA GCA GAG AAA GCC AGT C (SEQ ID NO: 656)
H51A(+146+170)	TAT AAC TTGA TCA AGC AGA GAA AGC (SEQ ID NO: 738)
H51A(+151+175)	GAT TTT ATA ACT TGA TCA AGC AGA G (SEQ ID NO: 658)
H51A(+156+180)	TCT GTG ATT TTA TAA CTT GAT CAA G (SEQ ID NO: 659)

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Annealing Site	Sequence [5' to 3']
H51A(+161+185)	CAC CCT CTG TGA TTT TAT AAC TTG A (SEQ ID NO: 660)
H51A(+166+190)	ACC ATC ACC CTC TGT GAT TTT ATA A (SEQ ID NO: 661)
H51A(+171+195)	CAC CCA CCA TCA CCC TCT GTG ATT T (SEQ ID NO: 662)
H51A(+176+200)	AAG GTC ACC CAC CAT CAC CCT CTG T (SEQ ID NO: 663)
H51A(+181+205)	TCC TCA AGG TCA CCC ACC ATC ACC C (SEQ ID NO: 664)
H51A(+186+210)	TGA TAT CCT CAA GGT CAC CCA CCA T (SEQ ID NO: 665)
H51A(+191+215)	CTC GTT GAT ATC CTC AAG GTC ACC C (SEQ ID NO: 666)
H51A(+196+220)	ATC ATC TCG TTG ATA TCC TCA AGG T (SEQ ID NO: 667)
H51A(+201+225)	TGA TGA TCA TCT CGT TGA TAT CCT C (SEQ ID NO: 668)
H51A(+206+230)	CTG CTT GAT GAT CAT CTC GTT GAT A (SEQ ID NO: 669)
H51D(+211-02)	ACC TTC TGC TTG ATG ATC ATC TCG T (SEQ ID NO: 670)
H51D(+214-05)	CAT ACC TTC TGC TTG ATG ATC ATC T (SEQ ID NO: 671)
H51D(+217-08)	TCT CAT ACC TTC TGC TTG ATG ATC A (SEQ ID NO: 672)
H51D(+220-11)	TTT TCT CAT ACC TTC TGC TTG ATG A (SEQ ID NO: 673)
H51D(+223-14)	ATT TTT TCT CAT ACC TTC TGC TTG A (SEQ ID NO: 674)
H51D(+226-17)	ATC ATT TTT TCT CAT ACC TTC TGC T (SEQ ID NO: 675)
H51D(+229-20)	TTT ATC ATT TTT TCT CAT ACC TTC T (SEQ ID NO: 676)
H51D(+232-23)	ACT TTT ATC ATT TTT TCT CAT ACC T (SEQ ID NO: 677)
H51D(-02-26)	CCA ACT TTT ATC ATT TTT TCT CAT A (SEQ ID NO: 678)
H51A(+1+30)	GTG TCA CCA GAG TAA CAG TCT GAG TAG GAG (SEQ ID NO: 633)



[0326] In one aspect, the base sequence and annealing site are selected from one of the following:

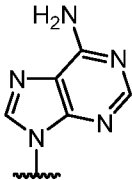
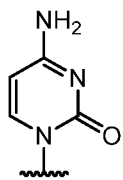
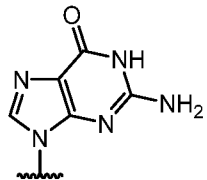
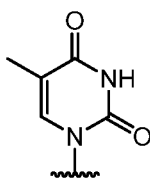
Annealing Site	Base Sequence [5' to 3']
H51A(+66+95)	CTC CAA CAT CAA GGA AGA TGG CAT TTC TAG (SEQ ID NO: 679)
H51A(+74+97)	ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 601)
H51A(+70+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TTT (SEQ ID NO: 606)
H51A(+72+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA T (SEQ ID NO: 608)
H51A(+68+87)	TCA AGG AAG ATG GCA TTT CT (SEQ ID NO: 680)
H51A(+68+87)	UCA AGG AmAGm AmUGm GmCA UUU CU (SEQ ID NO: 681)
H53A(+36+60)	GTT GCC TCC GGT TCT GAA GGT GTT C (SEQ ID NO: 682)

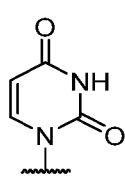
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Annealing Site	Base Sequence [5' to 3']
H53A(+36+60)	GTT G5mC5mC T5mC5mC GGT T5mC T GAA GGT GTT 5mC (SEQ ID NO: 683)
H53A(+36+56)	CCT CCG GTT CTG AAG GTG TTC (SEQ ID NO: 684)
H53A(+23+47)	CTG AAG GTG TTC TTG TAC TTC ATC C (SEQ ID NO: 34)
H53A(+32+56)	CCT CCG GTT CTG AAG GTG TTC TTG T (SEQ ID NO: 685)
H53A(+33+60)	GTT GCC TCC GGT TCT GAA GGT GTT CTT G (SEQ ID NO: 686)
H53A(+30+59)	TTG CCT CCG GTT CTG AAG GTG TTC TTG TAC (SEQ ID NO: 687)
H53A(+39+62)	CTG TTG CCT CCG GTT CTG AAG GTG (SEQ ID NO: 688)
H53A(+36+69)	CAT TCA ACT GTT GCC TCC GGT TCT GAA GGT G (SEQ ID NO: 689)
H53A(+45+62)	CTG TTG CCT CCG GTT CTG (SEQ ID NO: 690)
H45A(-03+19)	CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 691)
H45A(-09+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA T (SEQ ID NO: 692)
H45A(-03+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 693)
H45A(-06+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA A (SEQ ID NO: 694)
H45A(-12+19)	CAA TGC CAT CCT GGA GTT CCT GTA AGA TAC C (SEQ ID NO: 695)
H45A(-09+19)	CAA TGC CAT CCT GGA GTT CCT GTA AGA T (SEQ ID NO: 696)
H45A(-12+16)	TGC CAT CCT GGA GTT CCT GTA AGA TAC C (SEQ ID NO: 697)
H45A(-14+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA TAC CAA (SEQ ID NO: 698)
H45A(-08+19)	CAA TGC CAT CCT GGA GTT CCT GTA AGA (SEQ ID NO: 699)
HM45A(-07+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA AG (SEQ ID NO: 700)
H45A(-12+22)	GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA TAC C (SEQ ID NO: 701)
H45A(-09+22)	GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA T (SEQ ID NO: 702)
H45A(-09+30)	TTG CCG CTG CCC AAT GCC ATC CTG GAG TTC CTG TAA GAT (SEQ ID NO: 703)
H45A(-06+22)	GCC CAA TGC CAT CCT GGA GTT CCT GTA A (SEQ ID NO: 704)
H45A(-06+28)	GCC GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA A (SEQ ID NO: 705)
H45A(-03+22)	GCC CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 706)
H45A(-03+28)	GCC GCT GCC CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 707)
H45A(+9+26)	m5C-G-m5C-T-G-C-m5C-m5C-A-A-T-G-m5C-m5C-A-U-m5C-m5C (SEQ ID NO: 708)
H44A(-10+15)	GAT CTG TCA AAT CGC CTG CAG GTA A (SEQ ID NO: 709)
H44A(-07+15)	GAT CTG TCA AAT CGC CTG CAG G (SEQ ID NO: 710)
H44M(-07+17)	CAG ATC TGT CAA ATC GCC TGC AGG (SEQ ID NO: 711)
H44A(-08+15)	GAT CTG TCA AAT CGC CTG CAG GT (SEQ ID NO: 712)
H44A(-06+15)	GAT CTG TCA AAT CGC CTG CAG (SEQ ID NO: 713)
H44A(-08+17)	CAG ATC TGT CAA ATC GCC TGC AGG T (SEQ ID NO: 714)

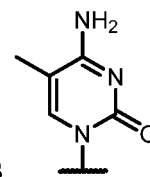
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Annealing Site	Base Sequence [5' to 3']
H44A(-06+17)	CAG ATC TGT CAA ATC GCC TGC AG (SEQ ID NO: 715)
H50D(+04-18)	GGG ATC CAG TAT ACT TAC AGG C (SEQ ID NO: 716)
H50D(+07-18)	GGG ATC CAG TAT ACT TAC AGG CTC C (SEQ ID NO: 568)
H50D(+07-16)	GAT CCA GTA TAC TTA CAG GCT CC (SEQ ID NO: 717)
H50D(+07-17)	GGA TCC AGT ATA CTT ACA GGC TCC (SEQ ID NO: 718)
H50A(-19+07)	ACT TCC TCT TTA ACA GAA AAG CAT AC (SEQ ID NO: 719)
H50D(+07-15)	ATC CAG TAT ACT TAC AGG CTC C (SEQ ID NO: 720)
H50A(-02+23)	GAG CTC AGA TCT TCT AAC TTC CTC T (SEQ ID NO: 721)
H50D(+06-18)	GGG ATC CAG TAT ACT TAC AGG CTC (SEQ ID NO: 722)
H50D(+07-20)	ATG GGA TCC AGT ATA CTT ACA GGC TCC (SEQ ID NO: 723)
H52A(-01+24)	CTG TTC CAA ATC CTG CAT TGT TGC C (SEQ ID NO: 724)

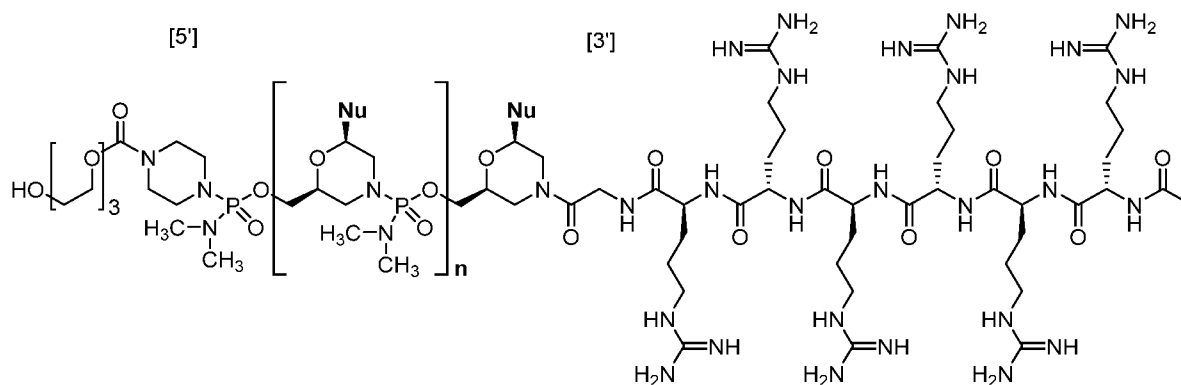
[0327] wherein A is , C is , G is , T is , U is ,



, Gm is methylated guanine, Am is methylated adenine, and m5C is



[0328] In another aspect, the disclosure provides antisense oligomers of Formula (X):



or a pharmaceutically acceptable salt thereof, where each **Nu** from 1 to (n+1) and 5' to 3' corresponds to the nucleobases in the following sequences:

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Annealing Site	Sequence [5' to 3']
H51A(+61+90)	ACA TCA AGG AAG ATG GCA TTT CTA GTT TGG (SEQ ID NO: 725)
H51D(+16-07)	CTC ATA CCT TCT GCT TGA TGA TC (SEQ ID NO: 567)
H50D(+103+127)	GGG ATC CAG TAT ACT TAC AGG CTC C (SEQ ID NO: 568)
H51A(+81+105)	GAG CAG GTA CCT CCA ACA TCA AGG AA (SEQ ID NO: 33)
H51A(+71+100)	GGT ACC TCC AAC ATC AAG GAA GAT GGC ATT (SEQ ID NO: 726)
H51A(+48+73)	ATT TCT AGT TTG GAG ATG GCA GTT TC (SEQ ID NO: 727)
H51A(+59+84)	GGA AGA TGG CAT TTC TAG TTT GGA G (SEQ ID NO: 728)
H51A(+64+88)	CAT CAA GGA AGA TGG CAT TTC TAG TT (SEQ ID NO: 729)
H51A(+89+113)	ATC TGC CAG AGC AGG TAC CTC CAA C (SEQ ID NO: 730)
H51A(+49+68)	TAG TTT GGA GAT GGC AGT TT (SEQ ID NO: 731)
H51A(+64+83)	GGA AGA TGG CAT TTC TAG TT (SEQ ID NO: 732)
H51A(+80+98)	TAC CTC CAA CAT CAA GGA AG (SEQ ID NO: 733)
H51A(+94+113)	ATC TGC CAG AGC AGG TAC CT (SEQ ID NO: 734)
H51A(+109+128)	CCA AGC CCG GTT GAA ATC TG (SEQ ID NO: 735)
H51A(+61+82)	GAA GAT GGC ATT TCT AGT TTG G (SEQ ID NO: 569)
H51A(+61+83)	GGA AGA TGG CAT TTC TAG TTT GG (SEQ ID NO: 570)
H51A(+61+89)	CAT CAA GGA AGA TGG CAT TTC TAG TTT GG (SEQ ID NO: 571)
H51A(+66+89)	CAT CAA GGA AGA TGG CAT TTC TAG (SEQ ID NO: 572)
H51A(+66+93)	CCA ACA TCA AGG AAG ATG GCA TTT CTA G (SEQ ID NO: 573)
H51A(+69+92)	CAA CAT CAA GGA AGA TGG CAT TTC (SEQ ID NO: 574)
H51A(+69+96)	CCT CCA ACA TCA AGG AAG ATG GCA TTT C (SEQ ID NO: 575)
H51A(+74+96)	CCT CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 576)
H51A(+74+99)	GTA CCT CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 577)
H51A(+74+100)	GGT ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 578)
H51A(+74+102)	CAG GTA CCT CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 579)
H51A(+74+103)	GCA GGT ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 580)
H51A(+75+96)	CCT CCA ACA TCA AGG AAG ATG G (SEQ ID NO: 581)
H51A(+75+99)	GTA CCT CCA ACA TCA AGG AAG ATG G (SEQ ID NO: 582)
H51A(+76+99)	GTA CCT CCA ACA TCA AGG AAG ATG (SEQ ID NO: 583)
H51A(+76+105)	GAG CAG GTA CCT CCA ACA TCA AGG AAG ATG (SEQ ID NO: 584)
H51A(+80+103)	GCA GGT ACC TCC AAC ATC AAG GAA G (SEQ ID NO: 585)
H51A(+80+105)	GAG CAG GTA CCT CCA ACA TCA AGG AAG (SEQ ID NO: 586)
H51A(+80+107)	CAG AGC AGG TAC CTC CAA CAT CAA GGA AG (SEQ ID NO: 587)
H51A(+80+108)	CCA GAG CAG GTA CCT CCA ACA TCA AGG AAG (SEQ ID NO: 588)
H51A(+83+103)	GCA GGT ACC TCC AAC ATC AAG G (SEQ ID NO: 589)
H51A(+83+105)	GAG CAG GTA CCT CCA ACA TCA AGG (SEQ ID NO: 590)
H51A(+83+107)	CAG AGC AGG TAC CTC CAA CAT CAA GG (SEQ ID NO: 591)
H51A(+83+109)	GCC AGA GCA GGT ACC TCC AAC ATC AAG G (SEQ ID NO: 592)
H51A(+84+107)	CAG AGC AGG TAC CTC CAA CAT CAA G (SEQ ID NO: 593)
H51A(+84+111)	CTG CCA GAG CAG GTA CCT CCA ACA TCA AG (SEQ ID NO: 594)

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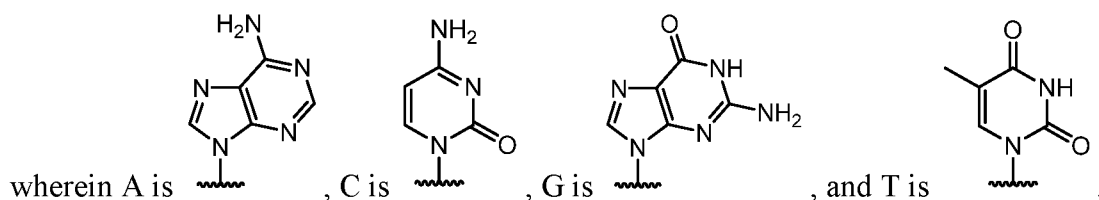
Annealing Site	Sequence [5' to 3']
H51A(+84+105)	GAG CAG GTA CCT CCA ACA TCA AG (SEQ ID NO: 595)
H51A(+87+109)	GCC AGA GCA GGT ACC TCC AAC ATC (SEQ ID NO: 596)
H51A(+93+116)	GAA ATC TGC CAG AGC AGG TAC CTC (SEQ ID NO: 597)
H51A(+75+100)	GGT ACC TCC AAC ATC AAG GAA GAT GG (SEQ ID NO: 598)
H51A(+74+101)	AGG TAC CTC CAA CAT CAA GGA AGA TGG C (SEQ ID NO: 599)
H51A(+74+98)	TAC CTC CAA CAT CAA GGA AGA TGG C (SEQ ID NO: 600)
H51A(+74+97)	ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 601)
H51A(+74+94)	TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 602)
H51A(+74+93)	CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 603)
H51A(+74+92)	CAA CAT CAA GGA AGA TGG C (SEQ ID NO: 604)
H51A(+69+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TTT C (SEQ ID NO: 605)
H51A(+70+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TTT (SEQ ID NO: 606)
H51A(+71+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TT (SEQ ID NO: 607)
H51A(+72+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA T (SEQ ID NO: 608)
H51A(+73+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA (SEQ ID NO: 609)
H51A(+77+99)	GTA CCT CCA ACA TCA AGG AAG AT (SEQ ID NO: 610)
H51A(+78+99)	GTA CCT CCA ACA TCA AGG AAG A (SEQ ID NO: 611)
H51A(+79+99)	GTA CCT CCA ACA TCA AGG AAG
H51.SA.(-60-36)	GAA GAA AAA GAA AAA TTA GAA ACA C (SEQ ID NO: 613)
H51.SA.(-50-26)	AAG GAA AAA AGA AGA AAA AGA AAA A (SEQ ID NO: 614)
H51.SA.(-45-21)	GCA AAA AGG AAA AAA GAA GAA AAA G (SEQ ID NO: 615)
H51.SA.(-40-16)	TTT TTG CAA AAA GGA AAA AAG AAG A (SEQ ID NO: 616)
H51.SA.(-35-11)	TTG GGT TTT TGC AAA AAG GAA AAA A (SEQ ID NO: 617)
H51.SA.(-30-6)	ATA TTT TGG GTT TTT GCA AAA AGG A (SEQ ID NO: 618)
H51.SA.(-25-1)	CTA AAA TAT TTT GGG TTT TTG CAA A (SEQ ID NO: 619)
H51.SA.(-20+5)	AGG AGC TAA AAT ATT TTG GGT TTT T (SEQ ID NO: 620)
H51.SA.(-15+10)	TGA GTA GGA GCT AAA ATA TTT TGG G (SEQ ID NO: 621)
H51.SA.(-10+15)	CAG TCT GAG TAG GAG CTA AAA TAT T (SEQ ID NO: 622)
H51.SA.(-5+20)	AGT AAC AGT CTG AGT AGG AGC TAA A (SEQ ID NO: 623)
H51.SA.(-1+24)	CCA GAG TAA CAG TCT GAG TAG GAG C (SEQ ID NO: 624)
H51.SA.(-65-41)	AAA AGA AAA ATT AGA AAC ACA AGC T (SEQ ID NO: 625)
H51.SA.(-70-46)	AAA AAT TAG AAA CAC AAG CTA AAG A (SEQ ID NO: 626)
H51.SA.(-75-51)	TTA GAA ACA CAA GCT AAA GAG CCA A (SEQ ID NO: 627)
H51.SA.(-80-56)	AAC ACA AGC TAA AGA GCC AAT TTC A (SEQ ID NO: 628)
H51.SA.(-85-61)	AAG CTA AAG AGC CAA TTT CAA TAA C (SEQ ID NO: 629)
H51.SA.(-90-66)	AAA GAG CCA ATT TCA ATA ACA ATA A (SEQ ID NO: 630)
H51.SA.(-95-71)	GCC AAT TTC AAT AAC AAT AAG TCA A (SEQ ID NO: 631)
H51.SA.(-100-76)	TTT CAA TAA CAA TAA GTC AAA TTT A (SEQ ID NO: 632)
H51A(+1+30)	GTG TCA CCA GAG TAA CAG TCT GAG TAG GAG (SEQ ID NO: 633)
H51A(+10+39)	CCA CAG GTT GTG TCA CCA GAG TAA CAG TCT (SEQ ID NO: 634)

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Annealing Site	Sequence [5' to 3']
H51A(+6+35)	AGG TTG TGT CAC CAG AGT AAC AGT CTG AGT (SEQ ID NO: 736)
H51A(+49+78)	ATG GCA TTT CTA GTT TGG AGA TGG CAG TTT (SEQ ID NO: 636)
H51A(+1+25)	ACC AGA GTA ACA GTC TGA GTA GGA G (SEQ ID NO: 637)
H51A(+4+28)	GTC ACC AGA GTA ACA GTC TGA GTA G (SEQ ID NO: 638)
H51A(+16+40)	ACC ACA GGT TGT GTC ACC AGA GTA A (SEQ ID NO: 639)
H51A(+21+45)	TAG TAA CCA CAG GTT GTG TCA CCA G (SEQ ID NO: 640)
H51A(+26+50)	TTC CTT AGT AAC CAC AGG TTG TGT C (SEQ ID NO: 641)
H51A(+31+55)	GCA GTT TCC TTA GTA ACC ACA GGT T (SEQ ID NO: 642)
H51A(+36+60)	AGA TGG CAG TTT CCT TAG TAA CCA C (SEQ ID NO: 643)
H51A(+41+65)	TTT GGA GAT GGC AGT TTC CTT AGT A (SEQ ID NO: 644)
H51A(+86+110)	TGC CAG AGC AGG TAC CTC CAA CAT C (SEQ ID NO: 645)
H51A(+91+115)	AAA TCT GCC AGA GCA GGT ACC TCC A (SEQ ID NO: 646)
H51A(+96+120)	GGT TGA AAT CTG CCA GAG CAG GTA C (SEQ ID NO: 647)
H51A(+101+125)	AGC CCG GTT GAA ATC TGC CAG AGC A (SEQ ID NO: 648)
H51A(+106+130)	GTC CAA GCC CGG TTG AAA TCT GCC A (SEQ ID NO: 649)
H51A(+111+135)	GTT CTG TCC AAG CCC GGT TGA AAT C (SEQ ID NO: 650)
H51A(+116+140)	GGT AAG TTC TGT CCA AGC CCG GTT G (SEQ ID NO: 651)
H51A(+121+145)	CAG TCG GTA AGT TCT GTC CAA GCC C (SEQ ID NO: 652)
H51A(+126+150)	AAA GCC AGT CGG TAA GTT CTG TCC A (SEQ ID NO: 653)
H51A(+131+155)	CAG AGA AAG CCA GTC GGTA AGT TCT (SEQ ID NO: 737)
H51A(+136+160)	TCA AGC AGA GAA AGC CAG TCG GTA A (SEQ ID NO: 655)
H51A(+141+165)	CTT GAT CAA GCA GAG AAA GCC AGT C (SEQ ID NO: 656)
H51A(+146+170)	TAT AAC TTGA TCA AGC AGA GAA AGC (SEQ ID NO: 738)
H51A(+151+175)	GAT TTT ATA ACT TGA TCA AGC AGA G (SEQ ID NO: 658)
H51A(+156+180)	TCT GTG ATT TTA TAA CTT GAT CAA G (SEQ ID NO: 659)
H51A(+161+185)	CAC CCT CTG TGA TTT TAT AAC TTG A (SEQ ID NO: 660)
H51A(+166+190)	ACC ATC ACC CTC TGT GAT TTT ATA A (SEQ ID NO: 661)
H51A(+171+195)	CAC CCA CCA TCA CCC TCT GTG ATT T (SEQ ID NO: 662)
H51A(+176+200)	AAG GTC ACC CAC CAT CAC CCT CTG T (SEQ ID NO: 663)
H51A(+181+205)	TCC TCA AGG TCA CCC ACC ATC ACC C (SEQ ID NO: 664)
H51A(+186+210)	TGA TAT CCT CAA GGT CAC CCA CCA T (SEQ ID NO: 665)
H51A(+191+215)	CTC GTT GAT ATC CTC AAG GTC ACC C (SEQ ID NO: 666)
H51A(+196+220)	ATC ATC TCG TTG ATA TCC TCA AGG T (SEQ ID NO: 667)
H51A(+201+225)	TGA TGA TCA TCT CGT TGA TAT CCT C (SEQ ID NO: 668)
H51A(+206+230)	CTG CTT GAT GAT CAT CTC GTT GAT A (SEQ ID NO: 669)
H51D(+211-02)	ACC TTC TGC TTG ATG ATC ATC TCG T (SEQ ID NO: 670)
H51D(+214-05)	CAT ACC TTC TGC TTG ATG ATC ATC T (SEQ ID NO: 671)
H51D(+217-08)	TCT CAT ACC TTC TGC TTG ATG ATC A (SEQ ID NO: 672)
H51D(+220-11)	TTT TCT CAT ACC TTC TGC TTG ATG A (SEQ ID NO: 673)
H51D(+223-14)	ATT TTT TCT CAT ACC TTC TGC TTG A (SEQ ID NO: 674)

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Annealing Site	Sequence [5' to 3']
H51D(+226-17)	ATC ATT TTT TCT CAT ACC TTC TGC T (SEQ ID NO: 675)
H51D(+229-20)	TTT ATC ATT TTT TCT CAT ACC TTC T (SEQ ID NO: 676)
H51D(+232-23)	ACT TTT ATC ATT TTT TCT CAT ACC T (SEQ ID NO: 677)
H51D(-02-26)	CCA ACT TTT ATC ATT TTT TCT CAT A (SEQ ID NO: 678)
H51A(+1+30)	GTG TCA CCA GAG TAA CAG TCT GAG TAG GAG (SEQ ID NO: 633)



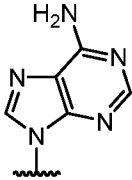
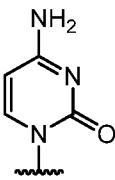
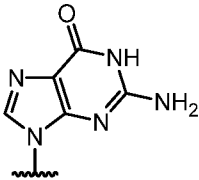
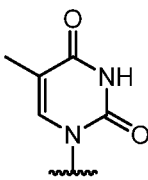
[0329] In one aspect, the base sequence and annealing site are selected from one of the following:

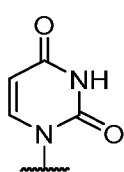
Annealing Site	Base Sequence [5' to 3']
H51A(+66+95)	CTC CAA CAT CAA GGA AGA TGG CAT TTC TAG (SEQ ID NO: 679)
H51A(+74+97)	ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 601)
H51A(+70+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TTT (SEQ ID NO: 606)
H51A(+72+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA T (SEQ ID NO: 608)
H51A(+68+87)	TCA AGG AAG ATG GCA TTT CT (SEQ ID NO: 680)
H51A(+68+87)	UCA AGG AmAGm AmUGm GmCA UUU CU (SEQ ID NO: 681)
H53A(+36+60)	GTT GCC TCC GGT TCT GAA GGT GTT C (SEQ ID NO: 682)
H53A(+36+60)	GTT G5mC5mC T5mC5mC GGT T5mC T GAA GGT GTT 5mC (SEQ ID NO: 683)
H53A(+36+56)	CCT CCG GTT CTG AAG GTG TTC (SEQ ID NO: 684)
H53A(+23+47)	CTG AAG GTG TTC TTG TAC TTC ATC C (SEQ ID NO: 34)
H53A(+32+56)	CCT CCG GTT CTG AAG GTG TTC TTG T (SEQ ID NO: 685)
H53A(+33+60)	GTT GCC TCC GGT TCT GAA GGT GTT CTT G (SEQ ID NO: 686)
H53A(+30+59)	TTG CCT CCG GTT CTG AAG GTG TTC TTG TAC (SEQ ID NO: 687)
H53A(+39+62)	CTG TTG CCT CCG GTT CTG AAG GTG (SEQ ID NO: 688)
H53A(+36+69)	CAT TCA ACT GTT GCC TCC GGT TCT GAA GGT G (SEQ ID NO: 689)
H53A(+45+62)	CTG TTG CCT CCG GTT CTG (SEQ ID NO: 690)
H45A(-03+19)	CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 691)
H45A(-09+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA T (SEQ ID NO: 692)
H45A(-03+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 693)
H45A(-06+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA A (SEQ ID NO: 694)
H45A(-12+19)	CAA TGC CAT CCT GGA GTT CCT GTA AGA TAC C (SEQ ID NO: 695)
H45A(-09+19)	CAA TGC CAT CCT GGA GTT CCT GTA AGA T (SEQ ID NO: 696)

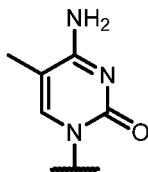
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H45A(-12+16)	TGC CAT CCT GGA GTT CCT GTA AGA TAC C (SEQ ID NO: 697)
H45A(-14+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA TAC CAA (SEQ ID NO: 698)
H45A(-08+19)	CAA TGC CAT CCT GGA GTT CCT GTA AGA (SEQ ID NO: 699)
HM45A(-07+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA AG (SEQ ID NO: 700)
H45A(-12+22)	GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA TAC C (SEQ ID NO: 701)
H45A(-09+22)	GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA T (SEQ ID NO: 702)
H45A(-09+30)	TTG CCG CTG CCC AAT GCC ATC CTG GAG TTC CTG TAA GAT (SEQ ID NO: 703)
H45A(-06+22)	GCC CAA TGC CAT CCT GGA GTT CCT GTA A (SEQ ID NO: 704)
H45A(-06+28)	GCC GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA A (SEQ ID NO: 705)
H45A(-03+22)	GCC CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 706)
H45A(-03+28)	GCC GCT GCC CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 707)
H45A(+9+26)	m5C-G-m5C-T-G-C-m5C-m5C-A-A-T-G-m5C-m5C-A-U-m5C-m5C (SEQ ID NO: 708)
H44A(-10+15)	GAT CTG TCA AAT CGC CTG CAG GTA A (SEQ ID NO: 709)
H44A(-07+15)	GAT CTG TCA AAT CGC CTG CAG G (SEQ ID NO: 710)
H44M(-07+17)	CAG ATC TGT CAA ATC GCC TGC AGG (SEQ ID NO: 711)
H44A(-08+15)	GAT CTG TCA AAT CGC CTG CAG GT (SEQ ID NO: 712)
H44A(-06+15)	GAT CTG TCA AAT CGC CTG CAG (SEQ ID NO: 713)
H44A(-08+17)	CAG ATC TGT CAA ATC GCC TGC AGG T (SEQ ID NO: 714)
H44A(-06+17)	CAG ATC TGT CAA ATC GCC TGC AG (SEQ ID NO: 715)
H50D(+04-18)	GGG ATC CAG TAT ACT TAC AGG C (SEQ ID NO: 716)
H50D(+07-18)	GGG ATC CAG TAT ACT TAC AGG CTC C (SEQ ID NO: 568)
H50D(+07-16)	GAT CCA GTA TAC TTA CAG GCT CC (SEQ ID NO: 717)
H50D(+07-17)	GGA TCC AGT ATA CTT ACA GGC TCC (SEQ ID NO: 718)
H50A(-19+07)	ACT TCC TCT TTA ACA GAA AAG CAT AC (SEQ ID NO: 719)
H50D(+07-15)	ATC CAG TAT ACT TAC AGG CTC C (SEQ ID NO: 720)
H50A(-02+23)	GAG CTC AGA TCT TCT AAC TTC CTC T (SEQ ID NO: 721)
H50D(+06-18)	GGG ATC CAG TAT ACT TAC AGG CTC (SEQ ID NO: 722)
H50D(+07-20)	ATG GGA TCC AGT ATA CTT ACA GGC TCC (SEQ ID NO: 723)
H52A(-01+24)	CTG TTC CAA ATC CTG CAT TGT TGC C (SEQ ID NO: 724)

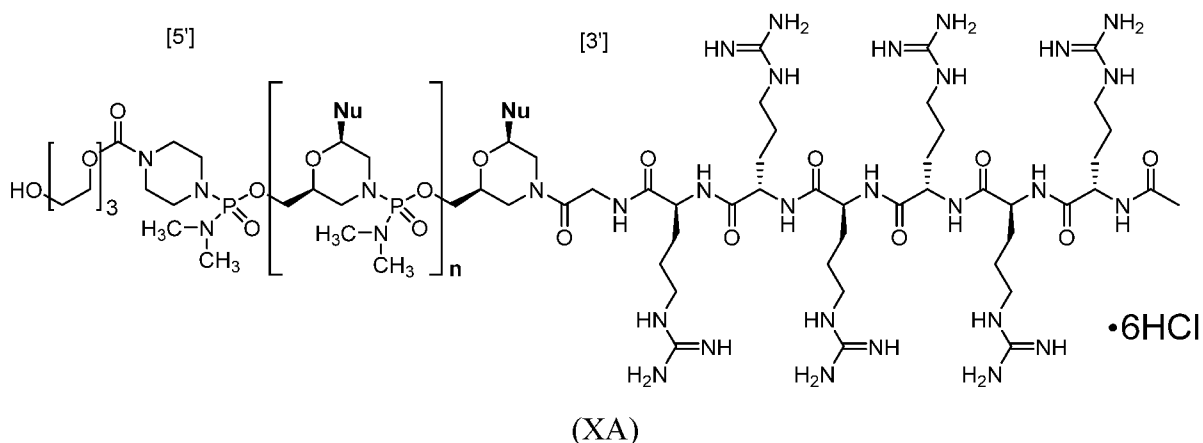
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[0330] wherein A is , C is , G is , T is , U is



, Gm is methylated guanine, Am is methylated adenine, and m5C is .

[0331] In another aspect, the disclosure provides antisense oligomers of Formula (XA):



where each **Nu** from 1 to (n+1) and 5' to 3' corresponds to the nucleobases in the following sequences:

Annealing Site	Sequence [5' to 3']
H51A(+61+90)	ACA TCA AGG AAG ATG GCA TTT CTA GTT TGG (SEQ ID NO: 725)
H51D(+16-07)	CTC ATA CCT TCT GCT TGA TGA TC (SEQ ID NO: 567)
H50D(+103+127)	GGG ATC CAG TAT ACT TAC AGG CTC C (SEQ ID NO: 568)
H51A(+81+105)	GAG CAG GTA CCT CCA ACA TCA AGG AA (SEQ ID NO: 33)
H51A(+71+100)	GGT ACC TCC AAC ATC AAG GAA GAT GGC ATT (SEQ ID NO: 726)
H51A(+48+73)	ATT TCT AGT TTG GAG ATG GCA GTT TC (SEQ ID NO: 727)
H51A(+59+84)	GGA AGA TGG CAT TTC TAG TTT GGA G (SEQ ID NO: 728)
H51A(+64+88)	CAT CAA GGA AGA TGG CAT TTC TAG TT (SEQ ID NO: 729)
H51A(+89+113)	ATC TGC CAG AGC AGG TAC CTC CAA C (SEQ ID NO: 730)
H51A(+49+68)	TAG TTT GGA GAT GGC AGT TT (SEQ ID NO: 731)
H51A(+64+83)	GGA AGA TGG CAT TTC TAG TT (SEQ ID NO: 732)
H51A(+80+98)	TAC CTC CAA CAT CAA GGA AG (SEQ ID NO: 733)
H51A(+94+113)	ATC TGC CAG AGC AGG TAC CT (SEQ ID NO: 734)
H51A(+109+128)	CCA AGC CCG GTT GAA ATC TG (SEQ ID NO: 735)

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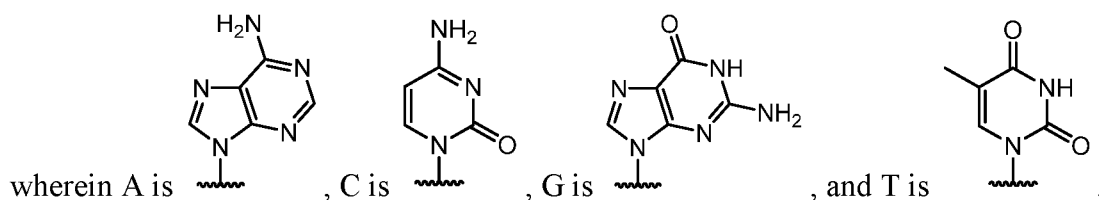
H51A(+61+82)	GAA GAT GGC ATT TCT AGT TTG G (SEQ ID NO: 569)
H51A(+61+83)	GGA AGA TGG CAT TTC TAG TTT GG (SEQ ID NO: 570)
H51A(+61+89)	CAT CAA GGA AGA TGG CAT TTC TAG TTT GG (SEQ ID NO: 571)
H51A(+66+89)	CAT CAA GGA AGA TGG CAT TTC TAG (SEQ ID NO: 572)
H51A(+66+93)	CCA ACA TCA AGG AAG ATG GCA TTT CTA G (SEQ ID NO: 573)
H51A(+69+92)	CAA CAT CAA GGA AGA TGG CAT TTC (SEQ ID NO: 574)
H51A(+69+96)	CCT CCA ACA TCA AGG AAG ATG GCA TTT C (SEQ ID NO: 575)
H51A(+74+96)	CCT CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 576)
H51A(+74+99)	GTA CCT CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 577)
H51A(+74+100)	GGT ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 578)
H51A(+74+102)	CAG GTA CCT CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 579)
H51A(+74+103)	GCA GGT ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 580)
H51A(+75+96)	CCT CCA ACA TCA AGG AAG ATG G (SEQ ID NO: 581)
H51A(+75+99)	GTA CCT CCA ACA TCA AGG AAG ATG G (SEQ ID NO: 582)
H51A(+76+99)	GTA CCT CCA ACA TCA AGG AAG ATG (SEQ ID NO: 583)
H51A(+76+105)	GAG CAG GTA CCT CCA ACA TCA AGG AAG ATG (SEQ ID NO: 584)
H51A(+80+103)	GCA GGT ACC TCC AAC ATC AAG GAA G (SEQ ID NO: 585)
H51A(+80+105)	GAG CAG GTA CCT CCA ACA TCA AGG AAG (SEQ ID NO: 586)
H51A(+80+107)	CAG AGC AGG TAC CTC CAA CAT CAA GGA AG (SEQ ID NO: 587)
H51A(+80+108)	CCA GAG CAG GTA CCT CCA ACA TCA AGG AAG (SEQ ID NO: 588)
H51A(+83+103)	GCA GGT ACC TCC AAC ATC AAG G (SEQ ID NO: 589)
H51A(+83+105)	GAG CAG GTA CCT CCA ACA TCA AGG (SEQ ID NO: 590)
H51A(+83+107)	CAG AGC AGG TAC CTC CAA CAT CAA GG (SEQ ID NO: 591)
H51A(+83+109)	GCC AGA GCA GGT ACC TCC AAC ATC AAG G (SEQ ID NO: 592)
H51A(+84+107)	CAG AGC AGG TAC CTC CAA CAT CAA G (SEQ ID NO: 593)
H51A(+84+111)	CTG CCA GAG CAG GTA CCT CCA ACA TCA AG (SEQ ID NO: 594)
H51A(+84+105)	GAG CAG GTA CCT CCA ACA TCA AG (SEQ ID NO: 595)
H51A(+87+109)	GCC AGA GCA GGT ACC TCC AAC ATC (SEQ ID NO: 596)
H51A(+93+116)	GAA ATC TGC CAG AGC AGG TAC CTC (SEQ ID NO: 597)
H51A(+75+100)	GGT ACC TCC AAC ATC AAG GAA GAT GG (SEQ ID NO: 598)
H51A(+74+101)	AGG TAC CTC CAA CAT CAA GGA AGA TGG C (SEQ ID NO: 599)
H51A(+74+98)	TAC CTC CAA CAT CAA GGA AGA TGG C (SEQ ID NO: 600)
H51A(+74+97)	ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 601)
H51A(+74+94)	TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 602)
H51A(+74+93)	CCA ACA TCA AGG AAG ATG GC (SEQ ID NO: 603)
H51A(+74+92)	CAA CAT CAA GGA AGA TGG C (SEQ ID NO: 604)
H51A(+69+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TTT C (SEQ ID NO: 605)
H51A(+70+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TTT (SEQ ID NO: 606)
H51A(+71+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TT (SEQ ID NO: 607)
H51A(+72+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA T (SEQ ID NO: 608)
H51A(+73+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA (SEQ ID NO: 609)
H51A(+77+99)	GTA CCT CCA ACA TCA AGG AAG AT (SEQ ID NO: 610)

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H51A(+78+99)	GTA CCT CCA ACA TCA AGG AAG A (SEQ ID NO: 611)
H51A(+79+99)	GTA CCT CCA ACA TCA AGG AAG
H51.SA.(-60-36)	GAA GAA AAA GAA AAA TTA GAA ACA C (SEQ ID NO: 613)
H51.SA.(-50-26)	AAG GAA AAA AGA AGA AAA AGA AAA A (SEQ ID NO: 614)
H51.SA.(-45-21)	GCA AAA AGG AAA AAA GAA GAA AAA G (SEQ ID NO: 615)
H51.SA.(-40-16)	TTT TTG CAA AAA GGA AAA AAG AAG A (SEQ ID NO: 616)
H51.SA.(-35-11)	TTG GGT TTT TGC AAA AAG GAA AAA A (SEQ ID NO: 617)
H51.SA.(-30-6)	ATA TTT TGG GTT TTT GCA AAA AGG A (SEQ ID NO: 618)
H51.SA.(-25-1)	CTA AAA TAT TTT GGG TTT TTG CAA A (SEQ ID NO: 619)
H51.SA.(-20+5)	AGG AGC TAA AAT ATT TTG GGT TTT T (SEQ ID NO: 620)
H51.SA.(-15+10)	TGA GTA GGA GCT AAA ATA TTT TGG G (SEQ ID NO: 621)
H51.SA.(-10+15)	CAG TCT GAG TAG GAG CTA AAA TAT T (SEQ ID NO: 622)
H51.SA.(-5+20)	AGT AAC AGT CTG AGT AGG AGC TAA A (SEQ ID NO: 623)
H51.SA.(-1+24)	CCA GAG TAA CAG TCT GAG TAG GAG C (SEQ ID NO: 624)
H51.SA.(-65-41)	AAA AGA AAA ATT AGA AAC ACA AGC T (SEQ ID NO: 625)
H51.SA.(-70-46)	AAA AAT TAG AAA CAC AAG CTA AAG A (SEQ ID NO: 626)
H51.SA.(-75-51)	TTA GAA ACA CAA GCT AAA GAG CCA A (SEQ ID NO: 627)
H51.SA.(-80-56)	AAC ACA AGC TAA AGA GCC AAT TTC A (SEQ ID NO: 628)
H51.SA.(-85-61)	AAG CTA AAG AGC CAA TTT CAA TAA C (SEQ ID NO: 629)
H51.SA.(-90-66)	AAA GAG CCA ATT TCA ATA ACA ATA A (SEQ ID NO: 630)
H51.SA.(-95-71)	GCC AAT TTC AAT AAC AAT AAG TCA A (SEQ ID NO: 631)
H51.SA.(-100-76)	TTT CAA TAA CAA TAA GTC AAA TTT A (SEQ ID NO: 632)
H51A(+1+30)	GTG TCA CCA GAG TAA CAG TCT GAG TAG GAG (SEQ ID NO: 633)
H51A(+10+39)	CCA CAG GTT GTG TCA CCA GAG TAA CAG TCT (SEQ ID NO: 634)
H51A(+6+35)	AGG TTG TGT CAC CAG AGT AAC AGT CTG AGT (SEQ ID NO: 736)
H51A(+49+78)	ATG GCA TTT CTA GTT TGG AGA TGG CAG TTT (SEQ ID NO: 636)
H51A(+1+25)	ACC AGA GTA ACA GTC TGA GTA GGA G (SEQ ID NO: 637)
H51A(+4+28)	GTC ACC AGA GTA ACA GTC TGA GTA G (SEQ ID NO: 638)
H51A(+16+40)	ACC ACA GGT TGT GTC ACC AGA GTA A (SEQ ID NO: 639)
H51A(+21+45)	TAG TAA CCA CAG GTT GTG TCA CCA G (SEQ ID NO: 640)
H51A(+26+50)	TTC CTT AGT AAC CAC AGG TTG TGT C (SEQ ID NO: 641)
H51A(+31+55)	GCA GTT TCC TTA GTA ACC ACA GGT T (SEQ ID NO: 642)
H51A(+36+60)	AGA TGG CAG TTT CCT TAG TAA CCA C (SEQ ID NO: 643)
H51A(+41+65)	TTT GGA GAT GGC AGT TTC CTT AGT A (SEQ ID NO: 644)
H51A(+86+110)	TGC CAG AGC AGG TAC CTC CAA CAT C (SEQ ID NO: 645)
H51A(+91+115)	AAA TCT GCC AGA GCA GGT ACC TCC A (SEQ ID NO: 646)
H51A(+96+120)	GGT TGA AAT CTG CCA GAG CAG GTA C (SEQ ID NO: 647)
H51A(+101+125)	AGC CCG GTT GAA ATC TGC CAG AGC A (SEQ ID NO: 648)
H51A(+106+130)	GTC CAA GCC CGG TTG AAA TCT GCC A (SEQ ID NO: 649)
H51A(+111+135)	GTT CTG TCC AAG CCC GGT TGA AAT C (SEQ ID NO: 650)
H51A(+116+140)	GGT AAG TTC TGT CCA AGC CCG GTT G (SEQ ID NO: 651)
H51A(+121+145)	CAG TCG GTA AGT TCT GTC CAA GCC C (SEQ ID NO: 652)

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H51A(+126+150)	AAA GCC AGT CGG TAA GTT CTG TCC A (SEQ ID NO: 653)
H51A(+131+155)	CAG AGA AAG CCA GTC GGTA AGT TCT (SEQ ID NO: 737)
H51A(+136+160)	TCA AGC AGA GAA AGC CAG TCG GTA A (SEQ ID NO: 655)
H51A(+141+165)	CTT GAT CAA GCA GAG AAA GCC AGT C (SEQ ID NO: 656)
H51A(+146+170)	TAT AAC TTGA TCA AGC AGA GAA AGC (SEQ ID NO: 738)
H51A(+151+175)	GAT TTT ATA ACT TGA TCA AGC AGA G (SEQ ID NO: 658)
H51A(+156+180)	TCT GTG ATT TTA TAA CTT GAT CAA G (SEQ ID NO: 659)
H51A(+161+185)	CAC CCT CTG TGA TTT TAT AAC TTG A (SEQ ID NO: 660)
H51A(+166+190)	ACC ATC ACC CTC TGT GAT TTT ATA A (SEQ ID NO: 661)
H51A(+171+195)	CAC CCA CCA TCA CCC TCT GTG ATT T (SEQ ID NO: 662)
H51A(+176+200)	AAG GTC ACC CAC CAT CAC CCT CTG T (SEQ ID NO: 663)
H51A(+181+205)	TCC TCA AGG TCA CCC ACC ATC ACC C (SEQ ID NO: 664)
H51A(+186+210)	TGA TAT CCT CAA GGT CAC CCA CCA T (SEQ ID NO: 665)
H51A(+191+215)	CTC GTT GAT ATC CTC AAG GTC ACC C (SEQ ID NO: 666)
H51A(+196+220)	ATC ATC TCG TTG ATA TCC TCA AGG T (SEQ ID NO: 667)
H51A(+201+225)	TGA TGA TCA TCT CGT TGA TAT CCT C (SEQ ID NO: 668)
H51A(+206+230)	CTG CTT GAT GAT CAT CTC GTT GAT A (SEQ ID NO: 669)
H51D(+211-02)	ACC TTC TGC TTG ATG ATC ATC TCG T (SEQ ID NO: 670)
H51D(+214-05)	CAT ACC TTC TGC TTG ATG ATC ATC T (SEQ ID NO: 671)
H51D(+217-08)	TCT CAT ACC TTC TGC TTG ATG ATC A (SEQ ID NO: 672)
H51D(+220-11)	TTT TCT CAT ACC TTC TGC TTG ATG A (SEQ ID NO: 673)
H51D(+223-14)	ATT TTT TCT CAT ACC TTC TGC TTG A (SEQ ID NO: 674)
H51D(+226-17)	ATC ATT TTT TCT CAT ACC TTC TGC T (SEQ ID NO: 675)
H51D(+229-20)	TTT ATC ATT TTT TCT CAT ACC TTC T (SEQ ID NO: 676)
H51D(+232-23)	ACT TTT ATC ATT TTT TCT CAT ACC T (SEQ ID NO: 677)
H51D(-02-26)	CCA ACT TTT ATC ATT TTT TCT CAT A (SEQ ID NO: 678)
H51A(+1+30)	GTG TCA CCA GAG TAA CAG TCT GAG TAG GAG (SEQ ID NO: 633)



[0332] In one aspect, the base sequence and annealing site are selected from one of the following:

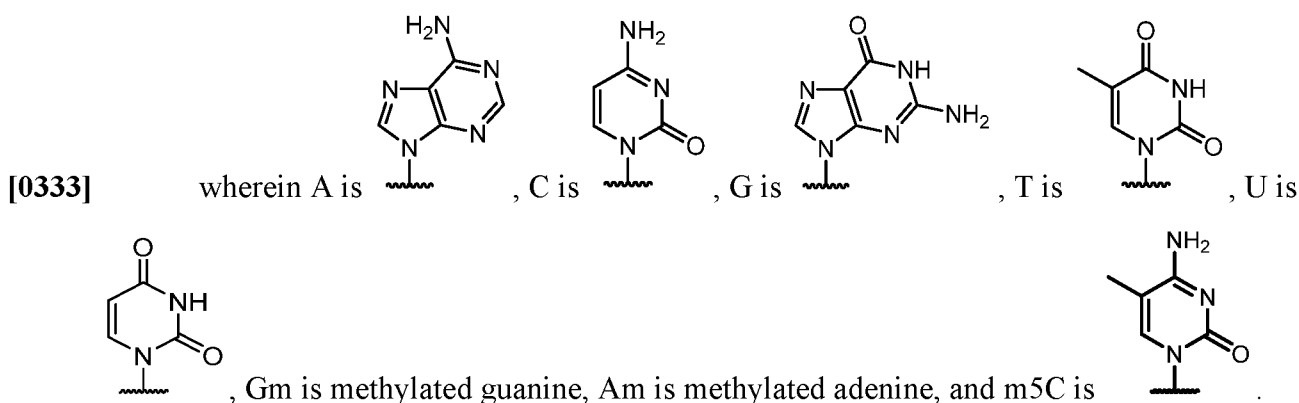
Annealing Site	Base Sequence [5' to 3']
H51A(+66+95)	CTC CAA CAT CAA GGA AGA TGG CAT TTC TAG (SEQ ID NO: 679)
H51A(+74+97)	ACC TCC AAC ATC AAG GAA GAT GGC (SEQ ID NO: 601)
H51A(+70+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA TTT (SEQ ID NO: 606)
H51A(+72+99)	GTA CCT CCA ACA TCA AGG AAG ATG GCA T (SEQ ID NO: 608)

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H51A(+68+87)	TCA AGG AAG ATG GCA TTT CT (SEQ ID NO: 680)
H51A(+68+87)	UCA AGG AmAGm AmUGm GmCA UUU CU (SEQ ID NO: 681)
H53A(+36+60)	GTT GCC TCC GGT TCT GAA GGT GTT C (SEQ ID NO: 682)
H53A(+36+60)	GTT G5mC5mC T5mC5mC GGT T5mC T GAA GGT GTT 5mC (SEQ ID NO: 683)
H53A(+36+56)	CCT CCG GTT CTG AAG GTG TTC (SEQ ID NO: 684)
H53A(+23+47)	CTG AAG GTG TTC TTG TAC TTC ATC C (SEQ ID NO: 34)
H53A(+32+56)	CCT CCG GTT CTG AAG GTG TTC TTG T (SEQ ID NO: 685)
H53A(+33+60)	GTT GCC TCC GGT TCT GAA GGT GTT CTT G (SEQ ID NO: 686)
H53A(+30+59)	TTG CCT CCG GTT CTG AAG GTG TTC TTG TAC (SEQ ID NO: 687)
H53A(+39+62)	CTG TTG CCT CCG GTT CTG AAG GTG (SEQ ID NO: 688)
H53A(+36+69)	CAT TCA ACT GTT GCC TCC GGT TCT GAA GGT G (SEQ ID NO: 689)
H53A(+45+62)	CTG TTG CCT CCG GTT CTG (SEQ ID NO: 690)
H45A(-03+19)	CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 691)
H45A(-09+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA T (SEQ ID NO: 692)
H45A(-03+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 693)
H45A(-06+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA A (SEQ ID NO: 694)
H45A(-12+19)	CAA TGC CAT CCT GGA GTT CCT GTA AGA TAC C (SEQ ID NO: 695)
H45A(-09+19)	CAA TGC CAT CCT GGA GTT CCT GTA AGA T (SEQ ID NO: 696)
H45A(-12+16)	TGC CAT CCT GGA GTT CCT GTA AGA TAC C (SEQ ID NO: 697)
H45A(-14+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA TAC CAA (SEQ ID NO: 698)
H45A(-08+19)	CAA TGC CAT CCT GGA GTT CCT GTA AGA (SEQ ID NO: 699)
HM45A(-07+25)	GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA AG (SEQ ID NO: 700)
H45A(-12+22)	GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA TAC C (SEQ ID NO: 701)
H45A(-09+22)	GCC CAA TGC CAT CCT GGA GTT CCT GTA AGA T (SEQ ID NO: 702)
H45A(-09+30)	TTG CCG CTG CCC AAT GCC ATC CTG GAG TTC CTG TAA GAT (SEQ ID NO: 703)
H45A(-06+22)	GCC CAA TGC CAT CCT GGA GTT CCT GTA A (SEQ ID NO: 704)
H45A(-06+28)	GCC GCT GCC CAA TGC CAT CCT GGA GTT CCT GTA A (SEQ ID NO: 705)
H45A(-03+22)	GCC CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 706)
H45A(-03+28)	GCC GCT GCC CAA TGC CAT CCT GGA GTT CCT G (SEQ ID NO: 707)
H45A(+9+26)	m5C-G-m5C-T-G-C-m5C-m5C-A-A-T-G-m5C-m5C-A-U-m5C-m5C (SEQ ID NO: 708)
H44A(-10+15)	GAT CTG TCA AAT CGC CTG CAG GTA A (SEQ ID NO: 709)
H44A(-07+15)	GAT CTG TCA AAT CGC CTG CAG G (SEQ ID NO: 710)
H44M(-07+17)	CAG ATC TGT CAA ATC GCC TGC AGG (SEQ ID NO: 711)
H44A(-08+15)	GAT CTG TCA AAT CGC CTG CAG GT (SEQ ID NO: 712)
H44A(-06+15)	GAT CTG TCA AAT CGC CTG CAG (SEQ ID NO: 713)
H44A(-08+17)	CAG ATC TGT CAA ATC GCC TGC AGG T (SEQ ID NO: 714)
H44A(-06+17)	CAG ATC TGT CAA ATC GCC TGC AG (SEQ ID NO: 715)

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H50D(+04-18)	GGG ATC CAG TAT ACT TAC AGG C (SEQ ID NO: 716)
H50D(+07-18)	GGG ATC CAG TAT ACT TAC AGG CTC C (SEQ ID NO: 568)
H50D(+07-16)	GAT CCA GTA TAC TTA CAG GCT CC (SEQ ID NO: 717)
H50D(+07-17)	GGA TCC AGT ATA CTT ACA GGC TCC (SEQ ID NO: 718)
H50A(-19+07)	ACT TCC TCT TTA ACA GAA AAG CAT AC (SEQ ID NO: 719)
H50D(+07-15)	ATC CAG TAT ACT TAC AGG CTC C (SEQ ID NO: 720)
H50A(-02+23)	GAG CTC AGA TCT TCT AAC TTC CTC T (SEQ ID NO: 721)
H50D(+06-18)	GGG ATC CAG TAT ACT TAC AGG CTC (SEQ ID NO: 722)
H50D(+07-20)	ATG GGA TCC AGT ATA CTT ACA GGC TCC (SEQ ID NO: 723)
H52A(-01+24)	CTG TTC CAA ATC CTG CAT TGT TGC C (SEQ ID NO: 724)



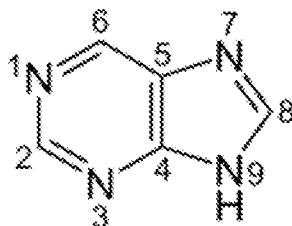
Nucleobase Modifications and Substitutions

[0334] In certain embodiments, antisense oligomer conjugates of the disclosure are composed of RNA nucleobases and DNA nucleobases (often referred to in the art simply as "base"). RNA bases are commonly known as adenine (A), uracil (U), cytosine (C) and guanine (G). DNA bases are commonly known as adenine (A), thymine (T), cytosine (C) and guanine (G). In various embodiments, antisense oligomer conjugates of the disclosure are composed of cytosine (C), guanine (G), thymine (T), adenine (A), 5-methylcytosine (5mC), uracil (U), and hypoxanthine (I).

[0335] In certain embodiments, one or more RNA bases or DNA bases in an oligomer may be modified or substituted with a base other than a RNA base or DNA base. Oligomers containing a modified or substituted base include oligomers in which one or more purine or pyrimidine bases most commonly found in nucleic acids are replaced with less common or non-natural bases.

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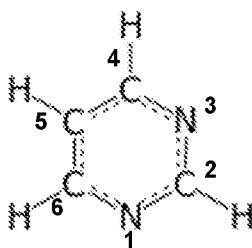
[0336] Purine bases comprise a pyrimidine ring fused to an imidazole ring, as described by the following general formula.



Purine

[0337] Adenine and guanine are the two purine nucleobases most commonly found in nucleic acids. Other naturally-occurring purines include, but not limited to, N⁶-methyladenine, N²-methylguanine, hypoxanthine, and 7-methylguanine.

[0338] Pyrimidine bases comprise a six-membered pyrimidine ring as described by the following general formula.



Pyrimidine

[0339] Cytosine, uracil, and thymine are the pyrimidine bases most commonly found in nucleic acids. Other naturally-occurring pyrimidines include, but not limited to, 5-methylcytosine, 5-hydroxymethylcytosine, pseudouracil, and 4-thiouracil. In one embodiment, the oligomers described herein contain thymine bases in place of uracil.

[0340] Other suitable bases include, but are not limited to: 2,6-diaminopurine, orotic acid, agmatidine, lysidine, 2-thiopyrimidines (e.g. 2-thiouracil, 2-thiothymine), G-clamp and its derivatives, 5-substituted pyrimidines (e.g. 5-halouracil, 5-propynyluracil, 5-propynylcytosine, 5-aminomethyluracil, 5-hydroxymethyluracil, 5-aminomethylcytosine, 5-hydroxymethylcytosine, Super T), 7-deazaguanine, 7-deazaadenine, 7-aza-2,6-diaminopurine, 8-aza-7-deazaguanine, 8-aza-7-deazaadenine, 8-aza-7-deaza-2,6-diaminopurine, Super G, Super A, and N⁴-ethylcytosine, or derivatives thereof; N²-

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cyclopentylguanine (cPent-G), N²-cyclopentyl-2-aminopurine (cPent-AP), and N²-propyl-2-aminopurine (Pr-AP), pseudouracil, or derivatives thereof; and degenerate or universal bases, like 2,6-difluorotoluene or absent bases like a basic sites (e.g. 1-deoxyribose, 1,2-dideoxyribose, 1-deoxy-2-O-methylribose; or pyrrolidine derivatives in which the ring oxygen has been replaced with nitrogen (azaribose)). Examples of derivatives of Super A, Super G, and Super T can be found in U.S. Patent 6,683,173 (Epoch Biosciences), which is incorporated here entirely by reference. cPent-G, cPent-AP, and Pr-AP were shown to reduce immunostimulatory effects when incorporated in siRNA (Peacock H. et al. J. Am. Chem. Soc. 2011, 133, 9200). Pseudouracil is a naturally occurring isomerized version of uracil, with a C-glycoside rather than the regular N-glycoside as in uridine. Pseudouridine-containing synthetic mRNA may have an improved safety profile compared to uridine-containing mPvNA (WO 2009127230, incorporated here in its entirety by reference).

[0341] Certain nucleobases are particularly useful for increasing the binding affinity of the antisense oligomer conjugates of the disclosure. These include 5-substituted pyrimidines, 6-azapyrimidines, and N-2, N-6, and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil, and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2 °C and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications. Additional exemplary modified nucleobases include those wherein at least one hydrogen atom of the nucleobase is replaced with fluorine.

Pharmaceutically Acceptable Salts of Antisense Oligomer Conjugates

[0342] Certain embodiments of antisense oligomer conjugates described herein may contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable acids. The term "pharmaceutically-acceptable salts" in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of antisense oligomer conjugates of the present disclosure. These salts can be prepared in situ in the administration vehicle or the dosage form manufacturing process, or by separately reacting a purified antisense oligomer conjugate of the disclosure in its free base form with a suitable organic or inorganic acid, and

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isolating the salt thus formed during subsequent purification. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, e.g., Berge et al. (1977) "Pharmaceutical Salts", J. Pharm. Sci. 66:1-19).

[0343] The pharmaceutically acceptable salts of the subject antisense oligomer conjugates include the conventional nontoxic salts or quaternary ammonium salts of the antisense oligomer conjugates, e.g., from non-toxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

[0344] In certain embodiments, the antisense oligomer conjugates of the present disclosure may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable bases. The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of antisense oligomer conjugates of the present disclosure. These salts can likewise be prepared in situ in the administration vehicle or the dosage form manufacturing process, or by separately reacting the purified antisense oligomer conjugate in its free acid form with a suitable base, such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically-acceptable metal cation, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary, or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, e.g., Berge et al., *supra*).

Formulations and Modes of Administration

[0345] In certain embodiments, the present disclosure provides formulations or pharmaceutical compositions suitable for the therapeutic delivery of antisense oligomer conjugates, as described herein. Pharmaceutical formulations comprising antisense oligomers conjugated to cell-penetrating peptides (e.g., PPMOs) for DMD has been described in, e.g., U.S. Patent No. 10,888,578, the disclosure of which is incorporated by reference herein. In certain embodiments, the present disclosure provides pharmaceutically acceptable compositions that comprise a therapeutically-effective amount of one or more of the antisense oligomer conjugates described herein, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. While it is possible for an antisense oligomer conjugate of the present disclosure to be administered alone, it is preferable to administer the antisense oligomer conjugate as a pharmaceutical formulation (composition). In an embodiment, the antisense oligomer conjugate of the formulation is according to Formula (I).

[0346] In another aspect, the disclosure provides pharmaceutical compositions that include the antisense oligomers, or a pharmaceutically acceptable salt thereof, of the disclosure, and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutically acceptable carrier is a saline solution that includes a phosphate buffer.

[0347] The phrase "pharmaceutically acceptable" means the substance or composition must be compatible, chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the subject being treated therewith.

[0348] The phrase "pharmaceutically-acceptable carrier" as used herein means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material, or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are: sugars such as lactose, glucose, and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; glycols such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and

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aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate; coloring agents; releasing agents; coating agents; sweetening agents; flavoring agents; perfuming agents; preservatives; and antioxidants; according to the judgment of the formulator.

[0349] Methods for the delivery of nucleic acid molecules, which can be applicable to the antisense oligomer conjugates of the present disclosure, are described, for example, in: Akhtar et al., 1992, Trends Cell Bio., 2:139; Delivery Strategies for Antisense Oligonucleotide Therapeutics, ed. Akhtar, 1995, CRC Press; and Sullivan et al., PCT WO 94/02595. These and other protocols can be utilized for the delivery of virtually any nucleic acid molecule, including the antisense oligomer conjugates of the present disclosure.

[0350] The pharmaceutical compositions of the present disclosure may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets (targeted for buccal, sublingual, or systemic absorption), boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous, or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream, or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally.

[0351] Some examples of materials that can serve as pharmaceutically-acceptable carriers include, without limitation: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid;

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(16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates, and/or polyanhydrides; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

[0352] Additional non-limiting examples of agents suitable for formulation with the antisense oligomer conjugates of the instant disclosure include: PEG conjugated nucleic acids; phospholipid conjugated nucleic acids; nucleic acids containing lipophilic moieties; phosphorothioates; P-glycoprotein inhibitors (such as Pluronic P85) which can enhance entry of drugs into various tissues; biodegradable polymers, such as poly (D,L-lactide-coglycolide) microspheres for sustained release delivery after implantation (Emerich, D F et al., 1999, *Cell Transplant*, 8, 47-58) Alkermes, Inc. Cambridge, Mass.; and loaded nanoparticles, such as those made of polybutylcyanoacrylate, which can deliver drugs across the blood brain barrier and can alter neuronal uptake mechanisms (Prog Neuropsychopharmacol Biol Psychiatry, 23, 941-949, 1999).

[0353] The disclosure also features the use of the composition comprising surface-modified liposomes containing poly(ethylene glycol) ("PEG") lipids (PEG-modified, branched and unbranched or combinations thereof, or long-circulating liposomes or stealth liposomes). Oligomer conjugates of the disclosure can also comprise covalently attached PEG molecules of various molecular weights. These formulations offer a method for increasing the accumulation of drugs in target tissues. This class of drug carriers resists opsonization and elimination by the mononuclear phagocytic system (MPS or RES), thereby enabling longer blood circulation times and enhanced tissue exposure for the encapsulated drug (Lasic et al. *Chem. Rev.* 1995, 95, 2601-2627; Ishiwata et al., *Chem. Pharm. Bull.* 1995, 43, 1005-1011). Such liposomes have been shown to accumulate selectively in tumors, presumably by extravasation and capture in the neovascularized target tissues (Lasic et al., *Science* 1995, 267, 1275-1276; Oku et al., 1995, *Biochim. Biophys. Acta*, 1238, 86-90). The long-circulating liposomes enhance the pharmacokinetics and pharmacodynamics of DNA and RNA, particularly compared to conventional cationic liposomes which are known to accumulate in tissues of the MPS (Liu et al., *J. Biol. Chem.* 1995, 270, 24864-24870; Choi et al., International PCT Publication No. WO 96/10391; Ansell et al., International PCT Publication No. WO 96/10390; Holland et al., International PCT Publication No. WO

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96/10392). Long-circulating liposomes are also likely to protect drugs from nuclease degradation to a greater extent compared to cationic liposomes, based on their ability to avoid accumulation in metabolically aggressive MPS tissues such as the liver and spleen.

[0354] In a further embodiment, the present disclosure includes antisense oligomer conjugate pharmaceutical compositions prepared for delivery as described in U.S. Pat. Nos.: 6,692,911; 7,163,695; and 7,070,807. In this regard, in one embodiment, the present disclosure provides an antisense oligomer conjugate of the present disclosure in a composition comprising copolymers of lysine and histidine (HK) (as described in U.S. Pat. Nos.: 7,163,695; 7,070,807; and 6,692,911) either alone or in combination with PEG (e.g., branched or unbranched PEG or a mixture of both), in combination with PEG and a targeting moiety, or any of the foregoing in combination with a crosslinking agent. In certain embodiments, the present disclosure provides antisense oligomer conjugates in pharmaceutical compositions comprising gluconic-acid-modified polyhistidine or gluconylated-polyhistidine/transferrin-polylysine. One skilled in the art will also recognize that amino acids with properties similar to His and Lys may be substituted within the composition.

[0355] Wetting agents, emulsifiers and lubricants (such as sodium lauryl sulfate and magnesium stearate), coloring agents, release agents, coating agents, sweetening agents, flavoring agents, perfuming agents, preservatives, and antioxidants can also be present in the compositions.

[0356] Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0357] Methods of preparing these formulations or pharmaceutical compositions include the step of bringing into association an antisense oligomer conjugate of the present disclosure with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association an antisense

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oligomer conjugate of the present disclosure with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0358] Formulations of the disclosure suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of an antisense oligomer conjugate of the present disclosure as an active ingredient. An antisense oligomer conjugate of the present disclosure may also be administered as a bolus, electuary, or paste.

[0359] Pharmaceutical compositions suitable for parenteral administration may comprise one or more oligomer conjugates of the disclosure in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents. Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the disclosure include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. In an embodiment, the antisense oligomer conjugate of the pharmaceutical composition is according to Formula (I).

[0360] These pharmaceutical compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms upon the subject oligomer conjugates may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars,

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sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0361] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility, among other methods known in the art. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0362] Injectable depot forms may be made by forming microencapsule matrices of the subject oligomer conjugates in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of oligomer to polymer, and the nature of the particular polymer employed, the rate of oligomer release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations may also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissues.

[0363] When the antisense oligomer conjugates of the present disclosure are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99% (more preferably, 10 to 30%) of the antisense oligomer conjugate in combination with a pharmaceutically acceptable carrier.

[0364] In certain aspects, an antisense oligomer conjugate is administered in a liquid pharmaceutical formulation, wherein the concentration of the conjugate is about 50 mg/ml.

[0365] Regardless of the route of administration selected, the antisense oligomer conjugates of the present disclosure, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present disclosure, may be formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art. Actual dosage levels of the active ingredients in the pharmaceutical compositions of this disclosure may be varied so as to obtain an amount of the active ingredient which is

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effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being unacceptably toxic to the patient.

Methods of Use

- [0366] Dosage regimens described in the present disclosure can be used to treat a patient with an antisense oligomer CPP conjugate in need of such treatment.
- [0367] In one aspect, the disclosure provides a method for treating DMD in a subject in need thereof wherein the subject has a mutation of the dystrophin gene that is amenable to exon skipping, the method comprising administering to the subject an antisense oligomer CPP conjugate according to the dosing regimens described herein. In some aspects, the exon is exon 44, exon 45, exon 50, exon 51, exon 52, or exon 53 of the human dystrophin gene.
- [0368] In another aspect, the disclosure provides a method of restoring an mRNA reading frame to induce dystrophin production in a subject having a mutation of the dystrophin gene that is amenable to exon skipping (for example, exon 44, exon 45, exon 50, exon 51, exon 52, exon 53 skipping), the method comprising administering to the subject an antisense oligomer CPP conjugate according to the dosing regimens described herein.
- [0369] In another aspect, the disclosure provides a method of excluding an exon (for example, exon 44, exon 45, exon 50, exon 51, exon 52, exon 53) from dystrophin pre-mRNA during mRNA processing in a subject having a mutation of the dystrophin gene that is amenable to exon skipping, the method comprising administering to the subject an antisense oligomer CPP conjugate according to the dosing regimens described herein. In another aspect, the disclosure provides a method of binding exon (for example, exon 44, exon 45, exon 50, exon 51, exon 52, exon 53) of dystrophin pre-mRNA in a subject having a mutation of the dystrophin gene that is amenable to exon skipping (for example, exon 44, exon 45, exon 50, exon 51, exon 52, exon 53 skipping), the method comprising administering to the subject an antisense oligomer CPP conjugate according to the dosing regimens described herein.
- [0370] In another aspect, the disclosure provides a method of targeting an exposure level of an antisense oligomer CPP conjugate in a patient with DMD who has a mutation that is amenable to exon skipping (for example, exon 44, exon 45, exon 50, exon 51, exon 52, exon

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53 skipping), the method comprising administering to the subject an antisense oligomer CPP conjugate according to the dosing regimens described herein.

[0371] In another aspect, the disclosure provides a method of reducing the severity and/or frequency of hypomagnesemia in a patient who is being treated with an antisense oligomer CPP conjugate, the method comprising administering to the subject an antisense oligomer CPP conjugate according to the dosing regimens described herein and a magnesium supplement.

[0372] In another aspect, the disclosure provides a method for alleviating one or more symptoms of DMD in a human patient, comprising administering to the patient an antisense oligomer CPP conjugate according to the dosing regimens described herein, wherein the patient is receiving a steroid treatment. In some aspects, the conjugate is administered to induce exon (for example, exon 44, exon 45, exon 50, exon 51, exon 52, exon 53 of the human dystrophin gene) skipping. In some aspects, the administration of the conjugate according to the dosing regimens described herein and the steroid treatments are started at the same time. In other aspects, the patient was receiving the steroid treatment prior to the administration of the antisense oligomer CPP conjugate according to the dosing regimens described herein. In this aspect, it is preferred that said steroid is administered at least one day, more preferred at least one week, more preferred at least two weeks, more preferred at least three weeks prior to administering the antisense oligomer CPP conjugate according to the dosing regimens described herein. In one particular embodiment, the prior steroid treatment is for a period of at least three weeks prior to the administration of the antisense oligomer CPP conjugate according to the dosing regimens described herein.

[0373] In some aspects, the steroid is a glucocorticosteroid. The glucocorticosteroid can be chosen from, for example, prednisone, dexamethasone, prednisolone, or deflazacort. Dose ranges of a steroid (e.g., a glucocorticosteroid) to be used in the therapeutic applications as described herein are designed on the basis of rising dose studies in clinical trials for which rigorous protocol requirements exist. The usual doses are about 0.5-1.0 mg/kg/day, preferably about 0.75 mg/kg/day for prednisone and prednisolone, and about 0.4-1.4 mg/kg/day, preferably about 0.9 mg/kg/day for deflazacort.

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[0374] The term “restoration” with respect to dystrophin synthesis or production refers generally to the production of a dystrophin protein including truncated forms of dystrophin in a patient with muscular dystrophy following treatment with an antisense oligomer conjugate described herein. In some embodiments, treatment results in an increase in novel dystrophin production in a patient by 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% (including all integers in between). In some embodiments, treatment increases the number of dystrophin-positive fibers to at least about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or about 95% to 100% of normal in the subject. In other embodiments, treatment increases the number of dystrophin-positive fibers to about 20% to about 60%, or about 30% to about 50%, of normal in the subject. The percent of dystrophin-positive fibers in a patient following treatment can be determined by a muscle biopsy using known techniques. For example, a muscle biopsy may be taken from a suitable muscle, such as the biceps brachii muscle in a patient.

[0375] Analysis of the percentage of positive dystrophin fibers may be performed pre-treatment and/or post-treatment or at time points throughout the course of treatment. In some embodiments, a post-treatment biopsy is taken from the contralateral muscle from the pre-treatment biopsy. Pre- and post-treatment dystrophin expression analysis may be performed using any suitable assay for dystrophin. In some embodiments, immunohistochemical detection is performed on tissue sections from the muscle biopsy using an antibody that is a marker for dystrophin, such as a monoclonal or a polyclonal antibody. For example, the MANDYS106 antibody can be used which is a highly sensitive marker for dystrophin. Any suitable secondary antibody may be used.

[0376] In some embodiments, the percent dystrophin-positive fibers are calculated by dividing the number of positive fibers by the total fibers counted. Normal muscle samples have 100% dystrophin-positive fibers. Therefore, the percent dystrophin-positive fibers can be expressed as a percentage of normal. To control for the presence of trace levels of dystrophin in the pretreatment muscle, as well as revertant fibers, a baseline can be set using sections of pre-treatment muscles from a patient when counting dystrophin-positive fibers in post-treatment muscles. This may be used as a threshold for counting dystrophin-positive fibers in sections of post-treatment muscle in that patient. In other embodiments, antibody-

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stained tissue sections can also be used for dystrophin quantification using Bioquant image analysis software (Bioquant Image Analysis Corporation, Nashville, TN). The total dystrophin fluorescence signal intensity can be reported as a percentage of normal. In addition, Western blot analysis with monoclonal or polyclonal anti-dystrophin antibodies can be used to determine the percentage of dystrophin positive fibers. For example, the anti-dystrophin antibody NCL-Dys1 from Leica Biosystems may be used. The percentage of dystrophin-positive fibers can also be analyzed by determining the expression of the components of the sarcoglycan complex (β,γ) and/or neuronal NOS.

[0377] In some embodiments, treatment with an antisense oligomer conjugate of the disclosure slows or reduces the progressive respiratory muscle dysfunction and/or failure in patients with DMD that would be expected without treatment. In some embodiments, treatment with an antisense oligomer conjugate of the disclosure may reduce or eliminate the need for ventilation assistance that would be expected without treatment. In some embodiments, measurements of respiratory function for tracking the course of the disease, as well as the evaluation of potential therapeutic interventions include maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), and forced vital capacity (FVC). MIP and MEP measure the level of pressure a person can generate during inhalation and exhalation, respectively, and are sensitive measures of respiratory muscle strength. MIP is a measure of diaphragm muscle weakness.

[0378] In some embodiments, MEP may decline before changes in other pulmonary function tests, including MIP and FVC. In certain embodiments, MEP may be an early indicator of respiratory dysfunction. In certain embodiments, FVC may be used to measure the total volume of air expelled during forced exhalation after maximum inspiration. In patients with DMD, FVC increases concomitantly with physical growth until the early teens. However, as growth slows or is stunted by disease progression, and muscle weakness progresses, the vital capacity enters a descending phase and declines at an average rate of about 8 to 8.5 percent per year after 10 to 12 years of age. In certain embodiments, MIP percent predicted (MIP adjusted for weight), MEP percent predicted (MEP adjusted for age), and FVC percent predicted (FVC adjusted for age and height) are supportive analyses.

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- [0379]** The terms "subject" and "patient" as used herein include any animal that exhibits a symptom, or is at risk for exhibiting a symptom, which can be treated with an antisense oligomer conjugate of the disclosure, such as a subject (or patient) that has or is at risk for having DMD or BMD, or any of the symptoms associated with these conditions (e.g., muscle fiber loss). Suitable subjects (or patients) include laboratory animals (such as mouse, rat, rabbit, or guinea pig), farm animals, and domestic animals or pets (such as a cat or dog). Non-human primates and, preferably, human patients (or subjects), are included. Also included are methods of producing dystrophin in a subject (or patient) having a mutation of the dystrophin gene that is amenable to exon skipping (for example, exon 44, exon 45, exon 50, exon 51, exon 52, exon 53 skipping).
- [0380]** The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.
- [0381]** The phrase "targeting sequence" refers to a sequence of nucleobases of an oligomer that is complementary to a sequence of nucleotides in a target pre-mRNA. In some aspects of the disclosure, the sequence of nucleotides in the target pre-mRNA is an exon 51 annealing site in the dystrophin pre-mRNA designated as H51A(+66+95). In some aspect of the disclosure, the sequence of nucleotides in the target pre-mRNA is an exon 45 annealing site in the dystrophin pre-mRNA designated as H45A(-03+19). In some aspect, the sequence of nucleotides in the target pre-mRNA is an exon 53 annealing site in the dystrophin pre-mRNA designated as H53A(+36+60).
- [0382]** "Treatment" of a subject (e.g. a mammal, such as a human) is any type of intervention used in an attempt to alter the natural course of the subject. Treatment includes, but is not limited to, administration of an antisense oligomer conjugate or a pharmaceutical composition thereof, and may be performed either prophylactically or subsequent to the initiation of a pathologic event or contact with an etiologic agent. Treatment includes any desirable effect on the symptoms or pathology of a disease or condition associated with the dystrophin protein, as in certain forms of muscular dystrophy, and may include, for example,

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minimal changes or improvements in one or more measurable markers of the disease or condition being treated. Also included are "prophylactic" treatments, which can be directed to reducing the rate of progression of the disease or condition being treated, delaying the onset of that disease or condition, or reducing the severity of its onset. "Treatment" or "prophylaxis" does not necessarily indicate complete eradication, cure, or prevention of the disease or condition, or associated symptoms thereof.

[0383] In some embodiments, treatment with an antisense oligomer CPP conjugate of the disclosure increases novel dystrophin production, delays disease progression, slows or reduces the loss of ambulation, reduces muscle inflammation, reduces muscle damage, improves muscle function, reduces loss of pulmonary function, and/or enhances muscle regeneration that would be expected without treatment. In some embodiments, treatment maintains, delays, or slows disease progression. In some embodiments, treatment maintains ambulation or reduces the loss of ambulation. In some embodiments, treatment maintains pulmonary function or reduces loss of pulmonary function. In some embodiments, treatment maintains or increases a stable walking distance in a patient, as measured by, for example, the 6 Minute Walk Test (6MWT). In some embodiments, treatment maintains or reduces the time to walk/run 10 meters (i.e., the 10 meter walk/run test). In some embodiments, treatment maintains or reduces the time to stand from supine (*i.e.*, time to stand test). In some embodiments, treatment maintains or reduces the time to climb four standard stairs (*i.e.*, the four-stair climb test). In some embodiments, treatment maintains or reduces muscle inflammation in the patient, as measured by, for example, MRI (e.g., MRI of the leg muscles). In some embodiments, MRI measures T2 and/or fat fraction to identify muscle degeneration. MRI can identify changes in muscle structure and composition caused by inflammation, edema, muscle damage, and fat infiltration.

[0384] In some embodiments, treatment with an antisense oligomer conjugate of the disclosure increases novel dystrophin production and slows or reduces the loss of ambulation that would be expected without treatment. For example, treatment may stabilize, maintain, improve or increase walking ability (e.g., stabilization of ambulation) in the subject. In some embodiments, treatment maintains or increases a stable walking distance in a patient, as measured by, for example, the 6 Minute Walk Test (6MWT), described by McDonald, et al.

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(Muscle Nerve, 2010; 42:966-74, herein incorporated by reference). A change in the 6 Minute Walk Distance (6MWD) may be expressed as an absolute value, a percentage change or a change in the %-predicted value. In some embodiments, treatment maintains or improves a stable walking distance in a 6MWT from a 20% deficit in the subject relative to a healthy peer. The performance of a DMD patient in the 6MWT relative to the typical performance of a healthy peer can be determined by calculating a %-predicted value. For example, the %-predicted 6MWD may be calculated using the following equation for males: $196.72 + (39.81 \times \text{age}) - (1.36 \times \text{age}^2) + (132.28 \times \text{height in meters})$. For females, the %-predicted 6MWD may be calculated using the following equation: $188.61 + (51.50 \times \text{age}) - (1.86 \times \text{age}^2) + (86.10 \times \text{height in meters})$ (Henricson et al. PLoS Curr., 2012, version 2, herein incorporated by reference). In some embodiments, treatment with an antisense oligomer increases the stable walking distance in the patient from baseline to greater than 3, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, or 50 meters (including all integers in between).

[0385] Loss of muscle function in patients with DMD may occur against the background of normal childhood growth and development. Indeed, younger children with DMD may show an increase in distance walked during 6MWT over the course of about 1 year despite progressive muscular impairment. In some embodiments, the 6MWD from patients with DMD is compared to typically developing control subjects and to existing normative data from age and sex matched subjects. In some embodiments, normal growth and development can be accounted for using an age and height based equation fitted to normative data. Such an equation can be used to convert 6MWD to a percent-predicted (%-predicted) value in subjects with DMD. In certain embodiments, analysis of %-predicted 6MWD data represents a method to account for normal growth and development, and may show that gains in function at early ages (e.g., less than or equal to age 7) represent stable rather than improving abilities in patients with DMD (Henricson et al. PLoS Curr., 2012, version 2, herein incorporated by reference).

[0386] An antisense molecule nomenclature system was proposed and published to distinguish between the different antisense molecules (see Mann et al., (2002) J Gen Med 4, 644-654). This nomenclature became especially relevant when testing several slightly different antisense molecules, all directed at the same target region, as shown below:

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H#A/D(x:y).

- [0387] The first letter designates the species (e.g. H: human, M: murine, C: canine). "#" designates target dystrophin exon number. "A/D" indicates acceptor or donor splice site at the beginning and end of the exon, respectively. (x y) represents the annealing coordinates where "-" or "+" indicate intronic or exonic sequences respectively. For example, A(-6+18) would indicate the last 6 bases of the intron preceding the target exon and the first 18 bases of the target exon. The closest splice site would be the acceptor so these coordinates would be preceded with an "A". Describing annealing coordinates at the donor splice site could be D(+2-18) where the last 2 exonic bases and the first 18 intronic bases correspond to the annealing site of the antisense molecule. Entirely exonic annealing coordinates that would be represented by A(+65+85), that is the site between the 65th and 85th nucleotide from the start of that exon.

Restoration of the Dystrophin Reading Frame using Exon Skipping

- [0388] A potential therapeutic approach to the treatment of DMD caused by out-of-frame mutations in the dystrophin gene is suggested by the milder form of dystrophinopathy known as BMD, which is caused by in-frame mutations. The ability to convert an out-of-frame mutation to an in-frame mutation would hypothetically preserve the mRNA reading frame and produce an internally shortened yet functional dystrophin protein. Antisense oligomer conjugates of the disclosure were designed to accomplish this.
- [0389] Clinical outcomes for analyzing the effect of an antisense oligomer conjugate that is complementary to a target region of the human dystrophin pre-mRNA and induces exon skipping include percent dystrophin positive fibers (PDPF), six-minute walk test (6MWT), loss of ambulation (LOA), North Star Ambulatory Assessment (NSAA), pulmonary function tests (PFT), ability to rise (from a supine position) without external support, *de novo* dystrophin production, and other functional measures.
- [0390] In some embodiments, the present disclosure provides methods for producing dystrophin in a subject having a mutation of the dystrophin gene that is amenable to exon skipping (e.g., exon 44, 45, 50, 51, 52, 53), the method comprising administering to the subject an antisense oligomer conjugate, or pharmaceutically acceptable salt thereof, as

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described herein. In certain embodiments, the present disclosure provides methods for restoring an mRNA reading frame to induce dystrophin protein production in a subject with Duchenne muscular dystrophy (DMD) who has a mutation of the dystrophin gene that is amenable to exon skipping (*e.g.*, exon 44, 45, 50, 51, 52, 53). Protein production can be measured by reverse-transcription polymerase chain reaction (RT-PCR), western blot analysis, or immunohistochemistry (IHC).

[0391] In some embodiments, the present disclosure provides methods for treating DMD in a subject in need thereof, wherein the subject has a mutation of the dystrophin gene that is amenable to exon skipping (*e.g.*, exon 44, 45, 50, 51, 52, 53), the method comprising administering to the subject an antisense oligomer conjugate, or pharmaceutically acceptable salt thereof, as described herein. In various embodiments, treatment of the subject is measured by delay of disease progression. In some embodiments, treatment of the subject is measured by maintenance of ambulation in the subject or reduction of loss of ambulation in the subject. In some embodiments, ambulation is measured using the 6 Minute Walk Test (6MWT). In certain embodiments, ambulation is measured using the North Start Ambulatory Assessment (NSAA).

[0392] In various embodiments, the present disclosure provides methods for maintaining pulmonary function or reducing loss of pulmonary function in a subject with DMD, wherein the subject has a mutation of the DMD gene that is amenable to exon skipping (*e.g.*, exon 44, 45, 50, 51, 52, 53), the method comprising administering to the subject an antisense oligomer conjugate, or pharmaceutically acceptable salt thereof, as described herein. In some embodiments, pulmonary function is measured as Maximum Expiratory Pressure (MEP). In certain embodiments, pulmonary function is measured as Maximum Inspiratory Pressure (MIP). In some embodiments, pulmonary function is measured as Forced Vital Capacity (FVC).

[0393] In certain aspects, the methods of the present disclosure include administering to a subject with DMD a pharmaceutical formulation comprising an antisense oligomer conjugate, or pharmaceutically acceptable salt thereof, as described herein, wherein the concentration of the conjugate in the formulation is about 50 mg/ml.

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[0394] In certain embodiments, there is described an antisense oligomer conjugate as described herein for use in therapy. In certain embodiments, there is described an antisense oligomer conjugate as described herein for use in the treatment of Duchenne muscular dystrophy. In certain embodiments, there is described an antisense oligomer conjugate as described herein for use in the manufacture of a medicament for use in therapy. In certain embodiments, there is described an antisense oligomer conjugate as described herein for use in the manufacture of a medicament for the treatment of Duchenne muscular dystrophy.

EXAMPLES

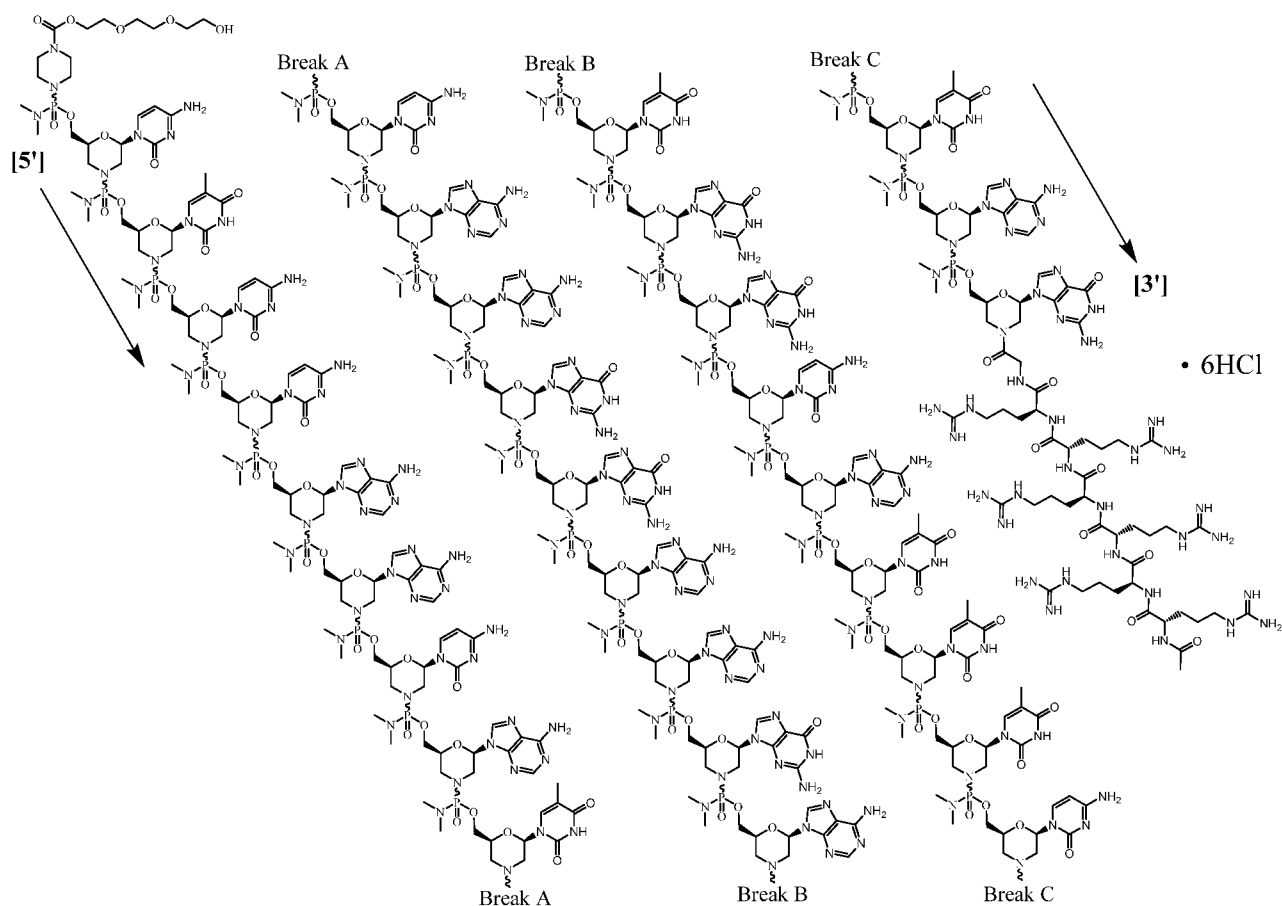
[0395] Although the foregoing disclosure has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to one of ordinary skill in the art in light of the teachings of this disclosure that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims. The following examples are provided by way of illustration only and not by way of limitation. Those of skill in the art will readily recognize a variety of noncritical parameters that could be changed or modified to yield essentially similar results.

Example 1. Toxicity and Toxikinetik Study of PPMO-1in Non-Human Primates

[0396] Study 1. A 12-Week Intravenous Infusion (Once Every 4 Weeks) Toxicity and Toxicokinetic Study in Cynomolgus Monkeys with a 4 Week Recovery.

[0397] Non-human primates (NHPs) received three 1-hour IV infusions of vehicle control or PPMO-1 at dose levels of 30 or 60 mg/kg on Days 1, 29, and 57. PPMO-1 is an antisense oligo CPP conjugate with the following structure:

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[0398] Blood samples were collected predose and at 1, 2, 4, 8, 12, 16, and 24 hours post-infusion for plasma PK analysis after the first and third doses. The mean body weights were 5.99 ± 0.84 Kg (n = 7), range 5.1-7.5 Kg on Day 1.

[0399] Study 2. Non-GLP (good laboratory practices) Pharmacokinetic (PK), Pharmacodynamic and Renal Safety Assessment of PPMO-1 After Four Once Every 4 Week (Q4W) Repeated Intravenous Dosing in Cynomolgus Monkeys.

[0400] NHPs received four 1-hour IV infusions of vehicle control or PPMO-1 at dose levels of 30 or 60 mg/kg on Days 1, 29, 57, and 85. Blood samples were collected predose and at 1, 2, 4, 8, 12, 16, and 24 hours post- infusion for plasma PK analysis after the first and fourth doses. the mean body weights were 2.25 ± 0.1 Kg (n = 8), range 2.1-2.4 Kg on Day 1.

[0401] As shown in Figure 1, animals in Study 1 had higher initial body weight than animals in Study 2.

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- [0402] As shown in Figure 2 animals in Study 1 had higher plasma AUC (AUC_{last} ($h \cdot \mu g/mL$) and C_{max} ($\mu g/kg$) exposures at the same 60 mg/kg dose than animals in Study 1. First and last dose PK were used in the analysis.
- [0403] As shown in Figure 3, there is an association of dose normalized PK to body weight. Higher body weight is associated with higher PK, both AUC and C_{max} .

Example 2. Developing a new dose paradigm to achieve target drug exposure in DMD patients

- [0404] Correlation between body weight and plasma exposure of PPMO-1 was observed in the current ongoing clinical trial. As shown in Figure 4, C_{max} of PPMO-1 at 20 mg/kg in Study 5051-102 was 2.6x higher than that at 20 mg/kg in Study 5051-201. Notably, the observed C_{max} difference was associated with pronounced body weight difference, 55.9 ± 17.1 kg in 5051-102 vs. 33.0 ± 16.5 kg (Mean $\pm$ SD). Indeed, a good correlation was observed between C_{max} and body weight at 20 and 30 mg/kg (Figure 5). This suggests that a body-weight based, fixed mg/kg approach for a broad DMD patient population with body-weight range of about 10 to about 100 kg may cause evidently variable drug exposure and lead to heterogeneous outcome of treatment effect on efficacy and safety. For example, for patients with lighter body weight, the drug exposure may fall below optimal target exposure range, leading to suboptimal efficacy or even no efficacy, whereas for patients with heavier body weight, the drug exposure may exceed optimal target exposure range, leading to potential safety issue.
- [0405] Thus, a body-weight-band approach has been developed to bin the DMD patients into certain body weight band and different dose is chosen within each body weight band to achieve targeted drug exposure. Target exposure was defined based on clinical data on exposure vs. response relationship on efficacy and safety. A population pharmacokinetic model was developed based on the existing clinical data of SRP-5051, and the simulation was conducted to inform the body weight band and dose selection to achieve the target exposure across the DMD population. A similar methodology was described in Model-Based Approach for Optimization of Atazanir Dose Recommendations for HIV-Infected Pediatric Patients (Hong, Y. et al, *Antimicrobial Agents and Chemotherapy*, Dec. 2011, p. 5746-5752).

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[0406] Two target exposure of area under the plasma concentration vs. time curve (AUC) was selected: a lower one with median value of 150 $\mu\text{g/mL}\cdot\text{h}$ and range of 100-200 $\mu\text{g/mL}\cdot\text{h}$ and a higher one with median value of 300 $\mu\text{g/mL}\cdot\text{h}$ and range of 200-500 $\mu\text{g/mL}\cdot\text{h}$. The body weight across the DMD population may be divided into different bands (1, 2, 3, or more) and a flat fixed mg dose may be selected within each body weight band. As demonstrated in Table 1B, for the higher target exposure:

- If the number of body weight band = 1, a flat dose of 1200 mg is anticipated to achieve target exposure across the body weight from 15 to 100 kg.
- If the number of body weight band = 2, 15-40 kg is selected as the first band with flat dose of 1100 mg and 40-100 kg is selected as the second band with flat dose of 1300 mg.
- If the number of body weight band = 3, 15-25 kg is selected as the first band with flat dose of 1100 mg, 25-50 kg as the second band with flat dose of 1200 mg and 50-100 kg as the third band with flat dose of 1400 mg.
- The more body weight bands are chosen, the less variability of drug exposure is anticipated.
- For those patients with the body weight less than 15 kg, a different dose may be selected based on their pharmacokinetic characteristics.
- Overall, this demonstrates that the body weight band approach (with the band number ≥ 1 and flat dose within each band, e.g. 900-1800 mg) can adequately achieve the target higher exposure.

[0407] Similarly, Table 2A demonstrates the body weight band approach for lower target exposure.

[0408] In summary, this demonstrates that the body-weight-band approach (with the band number ≥ 1 and flat dose within each band) can adequately achieve the target lower and higher exposure.

Table 2. Body weight band dosing for PPMO-1 to achieve a lower (A) and higher (B) target exposure.

(A)

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Body weight range	# of BW Band	Proposed dose	Simulated AUC		Simulated C _{max}	
			Median	95% CI	Median	95% CI
15≤x≤25 kg	3	600	152	[104,222]	95	[69,128]
25<x≤50 kg		650	150	[102,219]	95	[69,128]
50<x≤100 kg		750	157	[107,228]	98	[72,132]
15≤x≤40 kg	2	600	145	[98,212]	91	[66,124]
40<x≤100 kg		700	147	[100,216]	93	[68,125]
15≤x≤25 kg	1	700	180	[119,264]	110	[79,151]
25<x≤50 kg			163	[112,234]	102	[75,138]
50<x≤100 kg			145	[99,212]	92	[68,124]

(B)

Body weight range	# of BW Band	Proposed dose	Simulated AUC		Simulated C _{max}	
			Median	95% CI	Median	95% CI
15≤x≤25 kg	3	1100	293	[199,433]	174	[127,236]
25<x≤50 kg		1200	292	[197,429]	176	[128,237]
50<x≤100 kg		1400	308	[208,451]	184	[136,247]
15≤x≤40 kg	2	1100	280	[188,412]	168	[121,228]
40<x≤100 kg		1300	288	[195,426]	173	[127,234]
15≤x≤25 kg	1	1200	321	[213,476]	190	[136,260]
25<x≤50 kg			292	[200,425]	175	[129,238]

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50<x≤100 kg			260	[177,383]	158	[117,213]
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Example 3. Clinical Dosing Rationale

[0409] Clinical and nonclinical findings suggest that higher drug exposure is associated with higher body weight. This was consistently observed among boys with DMD, between heavier adult healthy volunteers and DMD boys, and in nonclinical studies, and raised a challenge in achieving consistent and less variable drug exposure in a diverse and broad DMD pediatric population.

[0410] To avoid the possible overdose for heavier body weight patients and underdose for lighter body weight patients, a population PK model informed, body-weight-tiered, dose regimen is being implemented: the targeted DMD population in the study is binned into two body-weight tiers (18 to 50 kg, and >50 kg) and a flat dose is used within each tier to achieve target exposure.

[0411] Two target exposures for the study are selected by anchoring drug plasma exposure of those patients who previously underwent muscle biopsy at 20 and 30 mg/kg, respectively, as follows:

[0412] 1. Lower target exposure with AUC of 180 $\mu\text{g}\cdot\text{h/mL}$ (range: 120 to 240 $\mu\text{g}\cdot\text{h/mL}$). This is to bracket the exposure for the biopsied patients at 20 mg/kg (AUC geometric mean 128 $\mu\text{g}\cdot\text{h/mL}$, N = 2) and the lower part of the exposure for the biopsied patients at 30 mg/kg. Based on the relationship between dystrophin expression and AUC, an AUC of 180 $\mu\text{g}\cdot\text{h/mL}$ appears to be associated with about a 5% increase in dystrophin protein level from baseline.

[0413] 2. Higher target exposure with AUC of 300 $\mu\text{g}\cdot\text{h/mL}$ (range: 200 to 500 $\mu\text{g}\cdot\text{h/mL}$). This is to mimic the exposure for the biopsied patients at 30 mg/kg (AUC geometric mean 310 $\mu\text{g}\cdot\text{h/mL}$, range 184 to 504 $\mu\text{g}\cdot\text{h/mL}$, N = 4). Based on the relationship between dystrophin expression and AUC, an AUC of 300 $\mu\text{g}\cdot\text{h/mL}$ appears to be associated with a $\geq 5\%$ increase in dystrophin protein levels from baseline.

[0414] Thus, these two target exposures differ by $\sim 1.7\text{x}$ with slightly overlapping AUCs (overlapped AUC from 200 to 240 $\mu\text{g}\cdot\text{h/mL}$), which is a reasonable difference for exposure separation for assessing the optimal balance between benefit and risk. The proposed target exposure is supported by existing nonclinical safety data. The higher target AUC (300 $\mu\text{g}\cdot\text{h/mL}$) is about 1.6x, 2.7x, and 1.3x lower than that at the NOAEL of 60 mg/kg in the SR-19-051 (NHP

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non-GLP), SR-20-027 (NHP GLP), and SR-20-028 (juvenile rat GLP) studies, respectively. Higher safety margins exist for the lower target AUC with about 2.7x, 4.6x, and 2.2x lower, respectively.

[0415] As shown in Table 3, to achieve a high target exposure of 300 $\mu\text{g}\cdot\text{h/mL}$, less dose (total mg) is proposed for the lower body weight tier, with 1250 mg for ≥ 18 to < 50 kg and 1350 mg for ≥ 50 kg. The anticipated 95% prediction interval of AUC falls well within the target range (200 to 500 $\mu\text{g}\cdot\text{h/mL}$); the upper boundary, in particular, is up to 420 $\mu\text{g}\cdot\text{h/mL}$ (well below 500 $\mu\text{g}\cdot\text{h/mL}$) and may offer additional cushion for safety while rendering adequate dystrophin expression. A similar scenario is proposed to target low target exposure.

[0416] In summary, the body-weight-tiered dose regimen targeting two exposures maximizes the opportunity of achieving an optimal benefit and risk ratio.

Table 3. Weight-tiered Dosing Regimen to Achieve Target Exposure Range Across 18 to 100 kg

Target Exposure (AUC _{0-24hr}) median and range	Body Weight Tier*	SRP-5051 Dose	Simulated Exposure (AUC _{0-24hr}) median and 95% Prediction Interval
180 $\mu\text{g}\cdot\text{h/mL}$ (120-240 $\mu\text{g}\cdot\text{h/mL}$)	≥ 18 but < 50 kg	750 mg	171 $\mu\text{g}\cdot\text{h/mL}$ (126, 234)
	≥ 50 kg	850 mg	178 $\mu\text{g}\cdot\text{h/mL}$ (130, 243)
300 $\mu\text{g}\cdot\text{h/mL}$ (200-500 $\mu\text{g}\cdot\text{h/mL}$)	≥ 18 but < 50 kg	1250 mg	296 $\mu\text{g}\cdot\text{h/mL}$ (218, 420)
	≥ 50 kg	1350 mg	298 $\mu\text{g}\cdot\text{h/mL}$ (217, 406)

AUC = area under the concentration-time curve

*For simulation purposes, the upper boundary of body weight is set as 100 kg.

[0417] In addition to the embodiments described above, the following embodiments are also contemplated by the present disclosure:

[0418] In one embodiment, the disclosure relates to a method of treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation that is amenable to exon skipping, comprising administering to the patient an antisense oligomer conjugate of Formula (IV), as described above, wherein the conjugate is administered in a dose effective to provide a mean area under the curve (AUC) of the conjugate, or the pharmaceutically acceptable

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salt thereof between about 100 and about 200 ug·h/mL, between about 120 and about 240 ug·h/mL, or is between about 200 and about 500 ug·h/mL.

[0419] In one embodiment, the disclosure relates to a method of treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation that is amenable to exon skipping, comprising administering to the patient an antisense oligomer conjugate of Formula (IV), as described above, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 1500 mg of the 6HCl salt of the conjugate once every four weeks, to achieve a mean AUC of between about between about 100 and about 200 ug·h/mL, between about 120 and about 240 ug·h/mL, or between about 200 and about 500 ug·h/mL.

[0420] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a mean AUC of between about 100 and about 200 ug·h/mL. In another embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a mean AUC of between about 120 and about 240 ug·h/mL. In another embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a mean AUC of between about 200 and about 500 ug·h/mL.

[0421] In certain embodiments, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, or about 900 mg of the 6HCl salt of the conjugate. In certain other embodiments, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, or about 1500 mg of the 6HCl salt of the conjugate.

[0422] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 700 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.

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- [0423] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 600 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.
- [0424] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 900 mg to about 1200 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.
- [0425] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1100 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.
- [0426] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof is administered at a dose equivalent to about 750 mg to about 1250 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 18 kg to about 50 kg.
- [0427] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof is administered at a dose equivalent to about 600 mg to about 800 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
- [0428] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 650 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
- [0429] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1000 mg of the 6HCl salt of the conjugate to about 1300 mg once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
- [0430] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1200 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.

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[0431] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 750 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 18 kg to about 50 kg.

[0432] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1250 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 18 kg to about 50 kg.

[0433] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 700 mg to about 900 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.

[0434] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 750 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.

[0435] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1200 mg to about 1500 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.

[0436] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1400 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.

[0437] In one embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 850 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs greater than or equal to about 50 kg.

[0438] In another embodiment, the conjugate of formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1350 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs greater than or equal to about 50 kg.

[0439] In one embodiment, the disclosure relates to a method of treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation that is amenable to exon skipping, comprising administering to the patient an antisense oligomer conjugate of Formula (VI), as described above, wherein the conjugate is administered in a dose effective to

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provide a mean area under the curve (AUC) of the conjugate, or the pharmaceutically acceptable salt thereof between about 100 and about 200 ug·h/mL, 120 and about 240 ug·h/mL, or is between about 200 and about 500 ug·h/mL.

[0440] In one embodiment, the disclosure relates to a method of treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation that is amenable to exon skipping, comprising administering to the patient an antisense oligomer conjugate of Formula (VI), as described above, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 1500 mg of the 6HCl salt of the conjugate once every four weeks, to achieve a mean AUC of between about 100 and about 200 ug·h/mL, between about 120 and about 240 ug·h/mL, or between about 200 and about 500 ug·h/mL.

[0441] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a mean AUC of between about 100 and about 200 ug·h/mL. In another embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a mean AUC of between about 120 and about 240 ug·h/mL. In another embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a mean AUC of between about 200 and about 500 ug·h/mL.

[0442] In certain embodiments, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, or about 900 mg of the 6HCl salt of the conjugate. In certain other embodiments, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, or about 1500 mg of the 6HCl salt of the conjugate.

[0443] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 700 mg of the 6HCl

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salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.

[0444] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 600 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.

[0445] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 900 mg to about 1200 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.

[0446] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1100 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.

[0447] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 750 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 18 kg to about 50 kg.

[0448] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1250 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 18 kg to about 50 kg.

[0449] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof is administered at a dose equivalent to about 600 mg to about 800 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.

[0450] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 650 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.

[0451] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1000 mg of the 6HCl salt of the conjugate to about 1300 mg once every four weeks to a patient that weighs from about 25 kg to about 50 kg.

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- [0452] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1200 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
- [0453] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 700 mg to about 900 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
- [0454] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 750 mg to about 950 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs greater than or equal to about 50 kg.
- [0455] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1250 mg to about 1500 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
- [0456] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 750 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
- [0457] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1200 mg to about 1500 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
- [0458] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1400 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
- [0459] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 850 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs greater than or equal to about 50 kg.

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[0460] In one embodiment, the conjugate of formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1350 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs greater than or equal to about 50 kg.

[0461] In one embodiment, the disclosure relates to a method of treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation that is amenable to exon skipping, comprising administering to the patient an antisense oligomer conjugate of Formula (VIII), as described above, wherein the conjugate is administered in a dose effective to provide a mean area under the curve (AUC) of the conjugate, or the pharmaceutically acceptable salt thereof between about 100 and about 200 ug·h/mL, between about 120 and about 240 ug·h/mL, or is between about 200 and about 500 ug·h/mL.

[0462] In one embodiment, the disclosure relates to a method of treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation that is amenable to exon skipping, comprising administering to the patient an antisense oligomer conjugate of Formula (VIII), as described above, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 1500 mg of the 6HCl salt of the conjugate once every four weeks, to achieve a mean AUC of between about 100 and about 200 ug·h/mL, between about 120 and about 240 ug·h/mL, or between about 200 and about 500 ug·h/mL.

[0463] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a mean AUC of between about 100 and about 200 ug·h/mL. In another embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a mean AUC of between about 120 and about 240 ug·h/mL. In another embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a mean AUC of between about 200 and about 500 ug·h/mL.

[0464] In certain embodiments, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, or about 900 mg of the 6HCl salt of the conjugate. In certain other embodiments, the conjugate of formula (VIII), or a pharmaceutically

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acceptable salt thereof, is administered at a dose equivalent to about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, or about 1500 mg of the 6HCl salt of the conjugate.

[0465] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 700 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.

[0466] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 600 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.

[0467] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 900 mg to about 1200 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.

[0468] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1100 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.

[0469] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 750 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 18 kg to about 50 kg.

[0470] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1250 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 18 kg to about 50 kg.

[0471] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof is administered at a dose equivalent to about 600 mg to about 800 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.

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- [0472] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 650 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
- [0473] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1000 mg of the 6HCl salt of the conjugate to about 1300 mg once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
- [0474] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1200 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
- [0475] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 700 mg to about 900 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
- [0476] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 750 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
- [0477] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1200 mg to about 1500 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
- [0478] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1400 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
- [0479] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 850 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs greater than about 50 kg.
- [0480] In one embodiment, the conjugate of formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1350 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs greater than about 50 kg.

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- [0481]** One embodiment of the present disclosure relates to a method of targeting an exposure level of an antisense oligomer conjugate of Formula (IV), as described above, or a pharmaceutically acceptable salt thereof, in a patient with Duchenne muscular dystrophy (DMD) who has a mutation that is amenable to exon 51 skipping, comprising administering to the patient the conjugate, or a pharmaceutically acceptable salt thereof, at a dose equivalent to about 300 mg to about 900 mg of the .6HCl salt of the conjugate once every four weeks to achieve the exposure level corresponding to an AUC of between about 100 and about 200 ug·h/mL.
- [0482]** One embodiment of the present disclosure relates to a method of targeting an exposure level of an antisense oligomer conjugate of Formula (IV), as described above, or a pharmaceutically acceptable salt thereof, in a patient with Duchenne muscular dystrophy (DMD) who has a mutation that is amenable to exon 51 skipping, comprising administering to the patient the conjugate, or a pharmaceutically acceptable salt thereof, at a dose equivalent to about 700 mg to about 900 mg of the .6HCl salt of the conjugate once every four weeks to achieve the exposure level corresponding to an AUC of between about 120 and about 240 ug·h/mL.
- [0483]** One embodiment of the present disclosure relates to a method of targeting an exposure level of an antisense oligomer conjugate of Formula (IV), as described above, or a pharmaceutically acceptable salt thereof, in a patient with Duchenne muscular dystrophy (DMD) who has a mutation that is amenable to exon 51 skipping, comprising administering to the patient the conjugate, or a pharmaceutically acceptable salt thereof, at a dose equivalent to about 800 mg to about 1400 mg of the .6HCl salt of the conjugate once every four weeks to achieve the exposure level corresponding to an AUC of between about 200 and about 500 ug·h/mL.
- [0484]** One embodiment of the present disclosure relates to a method of targeting an exposure level of an antisense oligomer conjugate of Formula (IV), as described above, or a pharmaceutically acceptable salt thereof, in a patient with Duchenne muscular dystrophy (DMD) who has a mutation that is amenable to exon 51 skipping, comprising administering to the patient the conjugate, or a pharmaceutically acceptable salt thereof, at a dose equivalent to about 950 mg to about 1500 mg of the .6HCl salt of the conjugate once every four weeks to achieve the exposure level corresponding to an AUC of between about 200 and about 500 ug·h/mL.
- [0485]** One embodiment of the present disclosure relates to a method of targeting an exposure level of an antisense oligomer conjugate of Formula (IV), as described above, or a

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pharmaceutically acceptable salt thereof, in a patient with Duchenne muscular dystrophy (DMD) who has a mutation that is amenable to exon 51 skipping, comprising administering to the patient the conjugate, or a pharmaceutically acceptable salt thereof, at a dose equivalent to the dose of the .6HCl salt of the conjugate according to the following schedule:

- i) about 300 mg to about 700 mg, or about 900 mg to about 1200 mg, once every four weeks for a patient that weighs from about 10 kg to about 25 kg;
- ii) about 600 mg to about 800 mg, or about 1000 mg to about 1300 mg, once every four weeks for a patient that weighs from about 25 kg to about 50 kg; or
- iii) about 700 mg to about 900 mg, or about 1200 mg to about 1500 mg, once every four weeks for a patient that weighs from about 50 kg to about 100 kg;

to achieve the exposure level corresponding to an AUC of between about 100 and about 200 ug·h/mL, or is between about 200 and about 500 ug·h/mL.

[0486] One embodiment of the present disclosure relates to a method of treating DMD in a patient comprising administering to the patient an antisense oligomer conjugate of Formula (IV), as described above, or a pharmaceutically acceptable salt thereof, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the .6HCl salt of the conjugate according to the following schedule:

- i) about 500 mg to about 700 mg, or about 1000 mg to about 1200 mg, once every four weeks for a patient that weighs from about 15 kg to about 40 kg; or
- ii) about 600 mg to about 800 mg, or about 1100 mg to about 1400 mg, once every four weeks for a patient that weighs from about 40 kg to about 100 kg;

to achieve a mean AUC between about 100 and about 200 ug·h/mL, or is between about 200 and about 500 ug·h/mL.

[0487] One embodiment of the present disclosure relates to a method of treating DMD in a patient comprising administering to the patient an antisense oligomer conjugate of Formula (VI), as described above, or a pharmaceutically acceptable salt thereof, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the .6HCl salt of the conjugate according to the following schedule:

- i) about 500 mg to about 700 mg, or about 1000 mg to about 1200 mg, once every four weeks for a patient that weighs from about 15 kg to about 40 kg; or

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ii) about 600 mg to about 800 mg, or about 1100 mg to about 1400 mg, once every four weeks for a patient that weighs from about 40 kg to about 100 kg; to achieve a mean AUC between about 100 and about 200 ug·h/mL, or is between about 200 and about 500 ug·h/mL.

[0488] One embodiment of the present disclosure relates to a method of treating DMD in a patient comprising administering to the patient an antisense oligomer conjugate of Formula (VIII), as described above, or a pharmaceutically acceptable salt thereof, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the .6HCl salt of the conjugate according to the following schedule:

- i) about 500 mg to about 700 mg, or about 1000 mg to about 1200 mg, once every four weeks for a patient that weighs from about 15 kg to about 40 kg; or
- ii) about 600 mg to about 800 mg, or about 1100 mg to about 1400 mg, once every four weeks for a patient that weighs from about 40 kg to about 100 kg; to achieve a mean AUC between about 100 and about 200 ug·h/mL, or is between about 200 and about 500 ug·h/mL.

[0489] One embodiment of the present disclosure relates to a method of treating DMD in a patient comprising administering to the patient an antisense oligomer conjugate of Formula (VIII), as described above, or a pharmaceutically acceptable salt thereof, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to the dose of the .6HCl salt of the conjugate according to the following schedule:

- iii) about 700 mg to about 800 mg, or about 1200 mg to about 1250 mg, once every four weeks for a patient that weighs from about 18 kg to about 50 kg; or
- iv) about 800 mg to about 900 mg, or about 1300 mg to about 1400 mg, once every four weeks for a patient that weighs from about 40 kg to about 100 kg; to achieve a mean AUC between about 120 and about 240 ug·h/mL, or is between about 200 and about 500 ug·h/mL.

[0490] One embodiment of the present disclosure relates to a method of treating a patient with Duchenne muscular dystrophy (DMD) with an antisense oligomer conjugate, comprising administering to the patient:

- i) an antisense oligomer conjugate of Formula (IV); and

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ii) a magnesium supplement,

wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 20 mg/kg, about 30 mg/kg, or about 40 mg/kg of the 6HCl salt of the conjugate once every 4 weeks, and wherein the magnesium supplement is administered at a dose sufficient to normalize patient's serum magnesium level

[0491] One embodiment of the present disclosure relates to a method of treating a patient with Duchenne muscular dystrophy (DMD) with an antisense oligomer conjugate, comprising administering to the patient:

iii) an antisense oligomer conjugate of Formula (IV); and

iv) a magnesium supplement.

[0492] In some embodiment, the conjugate of Formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 1200 mg, about 300 mg to about 1000 mg, about 300 mg to about 750 mg, about 300 mg to about 500 mg, about 400 mg to about 1400 mg, about 400 mg to about 1100 mg, about 400 mg to about 900 mg, about 400 mg to about 600 mg, about 500 mg to about 1500 mg, about 500 mg to about 1300 mg, about 500 mg to about 1000 mg, about 500 mg to about 950 mg, about 500 mg to about 850 mg, about 500 mg to about 750 mg, about 500 mg to about 650 mg, about 600 mg to about 1400 mg, about 600 mg to about 1200 mg, about 600 mg to about 1200 mg, about 600 mg to about 1000, or about 600 mg to about 900 mg of the 6HCl salt of the conjugate; and the magnesium supplement is administered at a dose sufficient to normalize patient's serum magnesium level. In one embodiment, the conjugate is administered once every four weeks. In one embodiments, the magnesium supplement is administered at a dose equivalent to about 400 to about 2400 mg magnesium oxide per day.

[0493] In some embodiment, the conjugate of Formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, or about 900 mg of the 6HCl salt of the conjugate, and the magnesium supplement is administered at a dose sufficient to normalize patient's serum magnesium level. In one embodiment, the conjugate is

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administered once every four weeks. In one embodiment, the magnesium supplement is administered at a dose equivalent to about 400 to about 2400 mg magnesium oxide per day.

[0494] In some embodiment, the conjugate of Formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, or about 1500 mg of the 6HCl salt of the conjugate, and the magnesium supplement is administered at a dose sufficient to normalize patient's serum magnesium level. In one embodiment, the conjugate is administered once every four weeks. In one embodiment, the magnesium supplement is administered at a dose equivalent to about 400 to about 2400 mg magnesium oxide per day.

[0495] In some embodiment, the conjugate of Formula (IV), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 20 mg/kg, about 30 mg/kg, or about 40 mg/kg of the 6HCl salt of the conjugate once every 4 weeks, and the magnesium supplement is administered at a dose sufficient to normalize patient's serum magnesium level. In one embodiment, the conjugate is administered once every four weeks. In one embodiment, the magnesium supplement is administered at a dose equivalent to about 400 to about 2400 mg magnesium oxide per day.

[0496] One embodiment of the present disclosure relates to a method of treating a patient with Duchenne muscular dystrophy (DMD) with an antisense oligomer conjugate, comprising administering to the patient:

- v) an antisense oligomer conjugate of Formula (VI); and
- vi) a magnesium supplement.

[0497] In some embodiment, the conjugate of Formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 1200 mg, about 300 mg to about 1000 mg, about 300 mg to about 750 mg, about 300 mg to about 500 mg, about 400 mg to about 1400 mg, about 400 mg to about 1100 mg, about 400 mg to about 900 mg, about 400 mg to about 600 mg, about 500 mg to about 1500 mg, about 500 mg to about 1300 mg, about 500 mg to about 1000 mg, about 500 mg to about 950 mg, about 500 mg to about 850 mg, about 500 mg to about 750 mg, about 500 mg to about 650 mg, about 600 mg to

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about 1400 mg, about 600 mg to about 1200 mg, about 600 mg to about 1200 mg, about 600 mg to about 1000, or about 600 mg to about 900 mg of the 6HCl salt of the conjugate; and the magnesium supplement is administered at a dose sufficient to normalize patient's serum magnesium level. In one embodiment, the conjugate is administered once every four weeks. In one embodiment, the magnesium supplement is administered at a dose equivalent to about 400 to about 2400 mg magnesium oxide per day.

[0498] In some embodiment, the conjugate of Formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, or about 900 mg of the 6HCl salt of the conjugate, and the magnesium supplement is administered at a dose sufficient to normalize patient's serum magnesium level. In one embodiment, the conjugate is administered once every four weeks. In one embodiment, the magnesium supplement is administered at a dose equivalent to about 400 to about 2400 mg magnesium oxide per day.

[0499] In some embodiment, the conjugate of Formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, or about 1500 mg of the 6HCl salt of the conjugate, and the magnesium supplement is administered at a dose sufficient to normalize patient's serum magnesium level. In one embodiment, the conjugate is administered once every four weeks. In one embodiment, the magnesium supplement is administered at a dose equivalent to about 400 to about 2400 mg magnesium oxide per day.

[0500] In some embodiment, the conjugate of Formula (VI), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 20 mg/kg, about 30 mg/kg, or about 40 mg/kg of the 6HCl salt of the conjugate once every 4 weeks, and the magnesium supplement is administered at a dose sufficient to normalize patient's serum magnesium level. In one embodiment, the conjugate is administered once every four weeks. In one embodiment, the magnesium supplement is administered at a dose equivalent to about 400 to about 2400 mg magnesium oxide per day.

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[0501] One embodiment of the present disclosure relates to a method of treating a patient with Duchenne muscular dystrophy (DMD) with an antisense oligomer conjugate, comprising administering to the patient:

- vii) an antisense oligomer conjugate of Formula (VIII); and
- viii) a magnesium supplement.

[0502] In some embodiment, the conjugate of Formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 1200 mg, about 300 mg to about 1000 mg, about 300 mg to about 750 mg, about 300 mg to about 500 mg, about 400 mg to about 1400 mg, about 400 mg to about 1100 mg, about 400 mg to about 900 mg, about 400 mg to about 600 mg, about 500 mg to about 1500 mg, about 500 mg to about 1300 mg, about 500 mg to about 1000 mg, about 500 mg to about 950 mg, about 500 mg to about 850 mg, about 500 mg to about 750 mg, about 500 mg to about 650 mg, about 600 mg to about 1400 mg, about 600 mg to about 1200 mg, about 600 mg to about 1200 mg, about 600 mg to about 1000, or about 600 mg to about 900 mg of the 6HCl salt of the conjugate; and the magnesium supplement is administered at a dose sufficient to normalize patient's serum magnesium level. In one embodiment, the conjugate is administered once every four weeks. In one embodiment, the magnesium supplement is administered at a dose equivalent to about 400 to about 2400 mg magnesium oxide per day.

[0503] In some embodiment, the conjugate of Formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, or about 900 mg of the 6HCl salt of the conjugate, and the magnesium supplement is administered at a dose sufficient to normalize patient's serum magnesium level. In one embodiment, the conjugate is administered once every four weeks. In one embodiment, the magnesium supplement is administered at a dose equivalent to about 400 to about 2400 mg magnesium oxide per day.

[0504] In some embodiment, the conjugate of Formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, or about 1500 mg of the 6HCl salt of the

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conjugate, and the magnesium supplement is administered at a dose sufficient to normalize patient's serum magnesium level. In one embodiment, the conjugate is administered once every four weeks. In one embodiment, the magnesium supplement is administered at a dose equivalent to about 400 to about 2400 mg magnesium oxide per day.

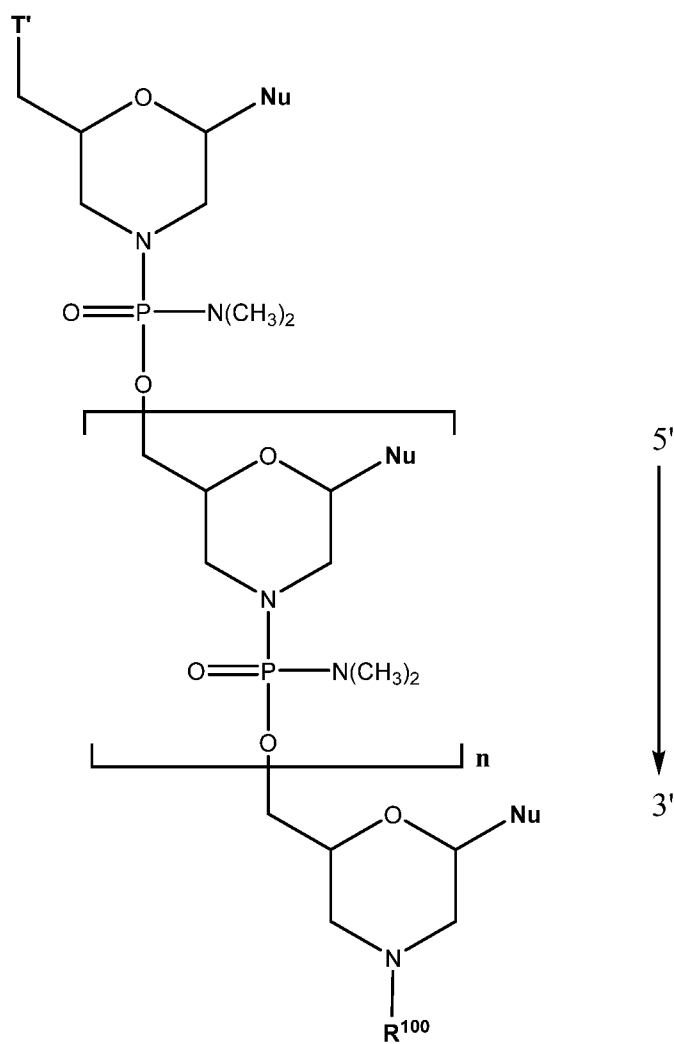
[0505] In some embodiment, the conjugate of Formula (VIII), or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 20 mg/kg, about 30 mg/kg, or about 40 mg/kg of the 6HCl salt of the conjugate once every 4 weeks, and the magnesium supplement is administered at a dose sufficient to normalize patient's serum magnesium level. In one embodiment, the magnesium supplement is administered at a dose equivalent to about 400 to about 2400 mg magnesium oxide per day.

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CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation that is amenable to exon skipping, comprising administering to the patient an antisense oligomer conjugate of Formula (I):



or a pharmaceutically acceptable salt thereof,

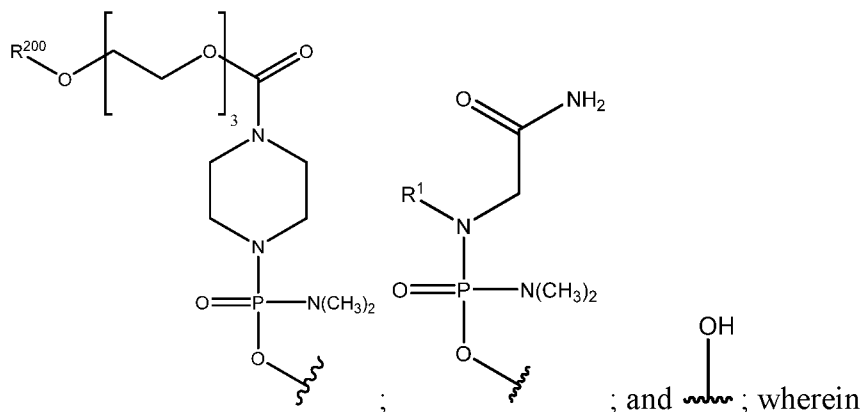
wherein:

n is 1-40;

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each **Nu** is a nucleobase, which, taken together, form a targeting sequence complementary to an exon annealing site in the dystrophin pre-mRNA;

T' is a moiety selected from:

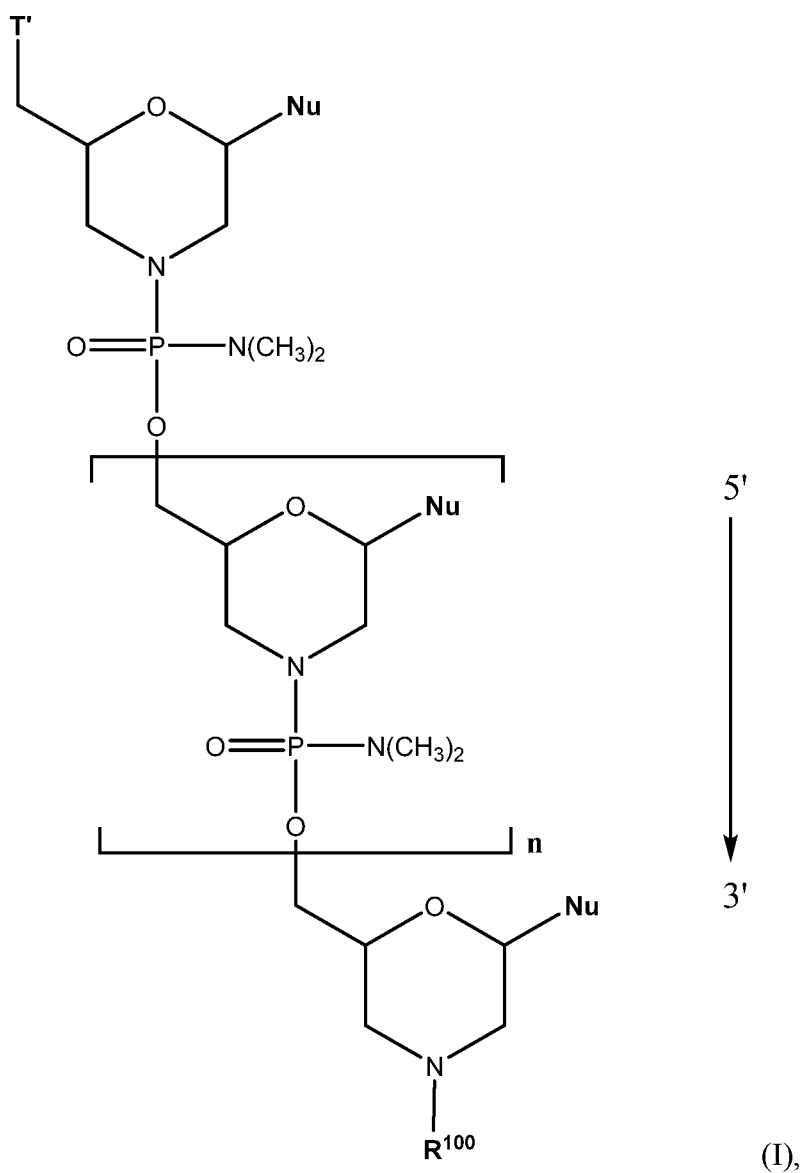


R¹⁰⁰ a cell-penetrating peptide, **R**²⁰⁰ is hydrogen, and **R**¹ is C₁-C₆ alkyl,

and wherein the conjugate is administered in a dose effective to provide a mean AUC of the conjugate, or the pharmaceutically acceptable salt thereof, is between about 100 and about 200 ug·h/mL, or is between about 200 and about 500 ug·h/mL.

2. A method of treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation that is amenable to exon 51 skipping, comprising administering to the patient an antisense oligomer conjugate of Formula (I):

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or a pharmaceutically acceptable salt thereof,

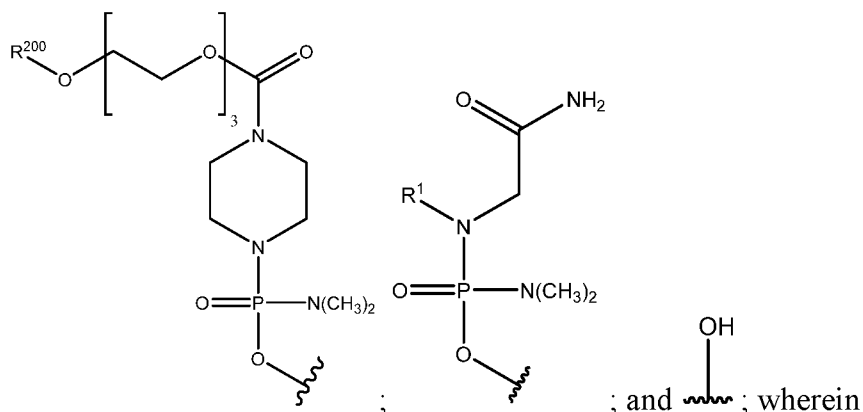
wherein:

n is 1-40;

each **Nu** is a nucleobase, which, taken together, form a targeting sequence complementary to an exon annealing site in the dystrophin pre-mRNA;

T' is a moiety selected from:

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R^{100} a cell-penetrating peptide, R^{200} is hydrogen, and R^1 is C_1 - C_6 alkyl,

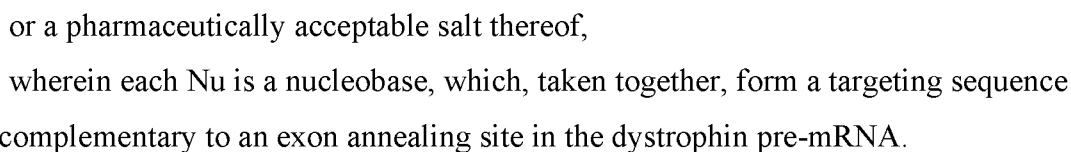
wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 1500 mg of the 6HCl salt of the conjugate once every four weeks,

to achieve a mean AUC of between about between about 100 and about 200 $\mu\text{g}\cdot\text{h/mL}$, or between about 200 and about 500 $\mu\text{g}\cdot\text{h/mL}$.

3. The method of any one of claims 1-2, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 1200 mg, about 300 mg to about 1000 mg, about 300 mg to about 750 mg, about 300 mg to about 500 mg, about 400 mg to about 1400 mg, about 400 mg to about 1100 mg, about 400 mg to about 900 mg, about 400 mg to about 600 mg, about 500 mg to about 1500 mg, about 500 mg to about 1300 mg, about 500 mg to about 1000 mg, about 500 mg to about 950 mg, about 500 mg to about 850 mg, about 500 mg to about 750 mg, about 500 mg to about 650 mg, about 600 mg to about 1400 mg, about 600 mg to about 1200 mg, about 600 mg to about 1200 mg, about 600 mg to about 1000, or about 600 mg to about 900 mg of the 6HCl salt of the conjugate.
4. The method of any one of claims 1-3, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a mean AUC of between about 100 and about 200 $\mu\text{g}\cdot\text{h/mL}$.

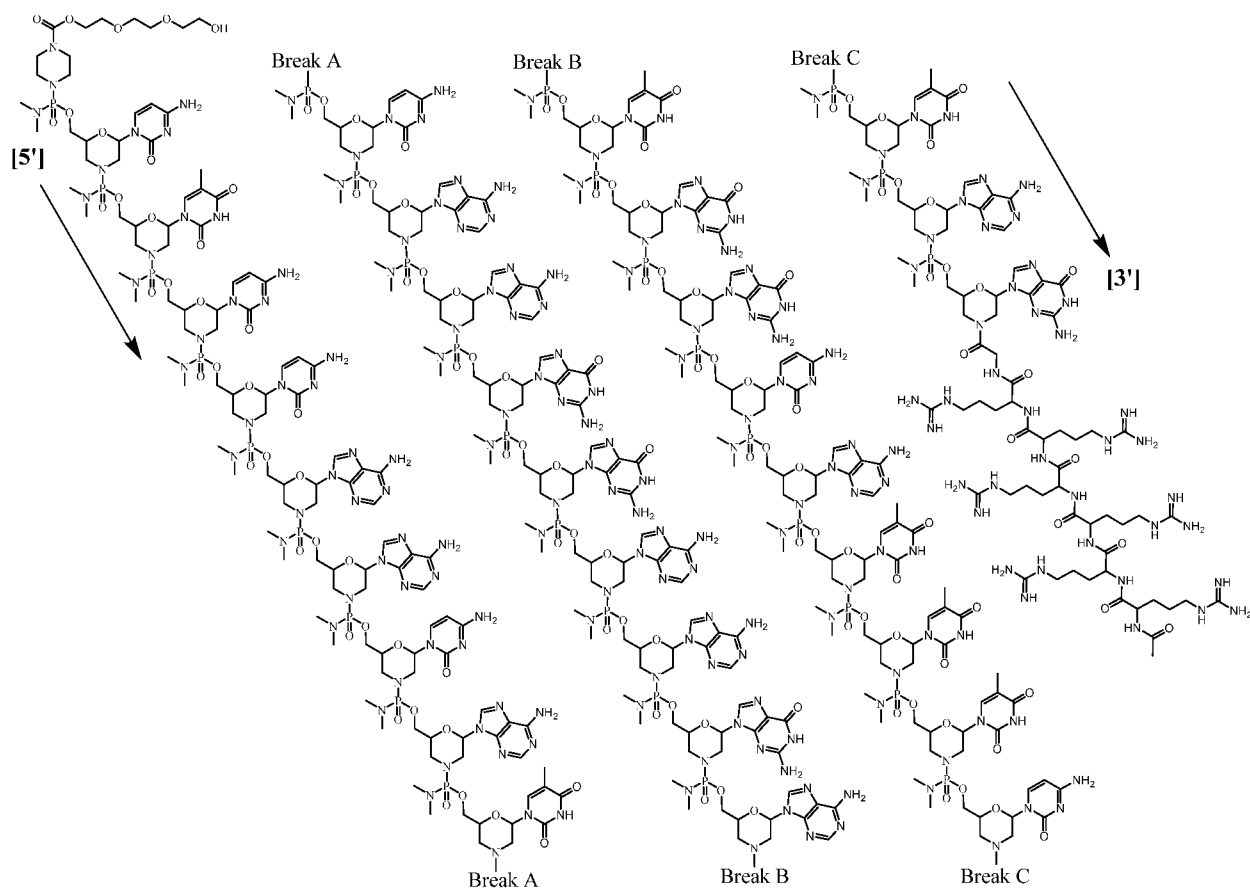
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5. The method of any one of claims 1-3, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose effective to provide a mean AUC of between about 200 and about 500 ug·h/mL.
6. The method of any one of claims 1-4, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, or about 900 mg of the 6HCl salt of the conjugate.
7. The method of any one of claims 1-3 or 5, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, or about 1500 mg of the 6HCl salt of the conjugate.
8. The method of any one of claims 1-7, wherein the cell-penetrating peptide is chosen from RRRRXXRRXXR (SEQ ID NO: 18), RFFRFFRFFR (SEQ ID NO: 19), RRRRXXRRXXRXB (SEQ ID NO: 20), RFFRFFRFFRG (SEQ ID NO: 21), RRRRRRG (SEQ ID NO: 22), RRRRRR (SEQ ID NO: 23), RRRRRG (SEQ ID NO: 24), or RRRRR (SEQ ID NO: 25), wherein R is arginine, X is 6-aminohexanoic acid, B is β -alanine, F is phenylalanine, and G is glycine.
9. The method of any one of claims 1-8, wherein the cell-penetrating peptide is chosen from RRRRRRG (SEQ ID NO: 22), RRRRRR (SEQ ID NO: 23), RRRRRG (SEQ ID NO: 24), or RRRRR (SEQ ID NO: 25), wherein R is arginine and G is glycine.
10. The method of any one of claims 1-9, wherein the cell-penetrating peptide is RRRRRRG (SEQ ID NO: 22), wherein R is arginine and G is glycine.
11. The method of any one of claims 1-10, wherein the antisense oligomer conjugate causes skipping of an exon in the human dystrophin gene.



15. The method of any one of claims 1-14, wherein the antisense oligomer conjugate has Formula (IV):

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or a pharmaceutically acceptable salt thereof.

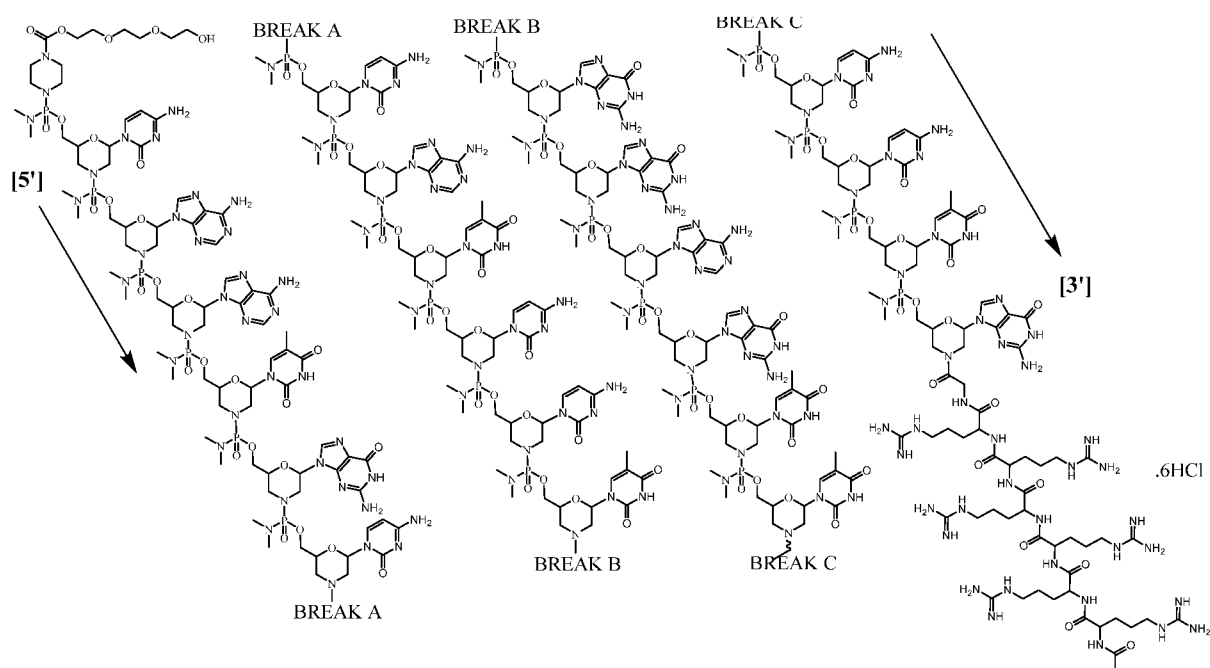
16. The method of any one of claims 1-15, wherein the antisense oligomer conjugate has Formula (IVA):

-
- The reaction scheme illustrates the synthesis of poly(amide-imine)s **3'** and **5'** from monomers **1** and **2**. Monomer **1** is a bis-amine with two 2-amino-6-methylpyrimidin-4-yl groups. Monomer **2** is a bis-amine with two 2-amino-6-methylpyrimidin-4-yl groups. The reaction conditions are $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{NH}_2$, $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{NH}_2$, and $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{NH}_2$. The resulting polymers **3'** and **5'** are shown with labels for Break A, Break B, and Break C, indicating the cleavage sites in the polymer backbone.

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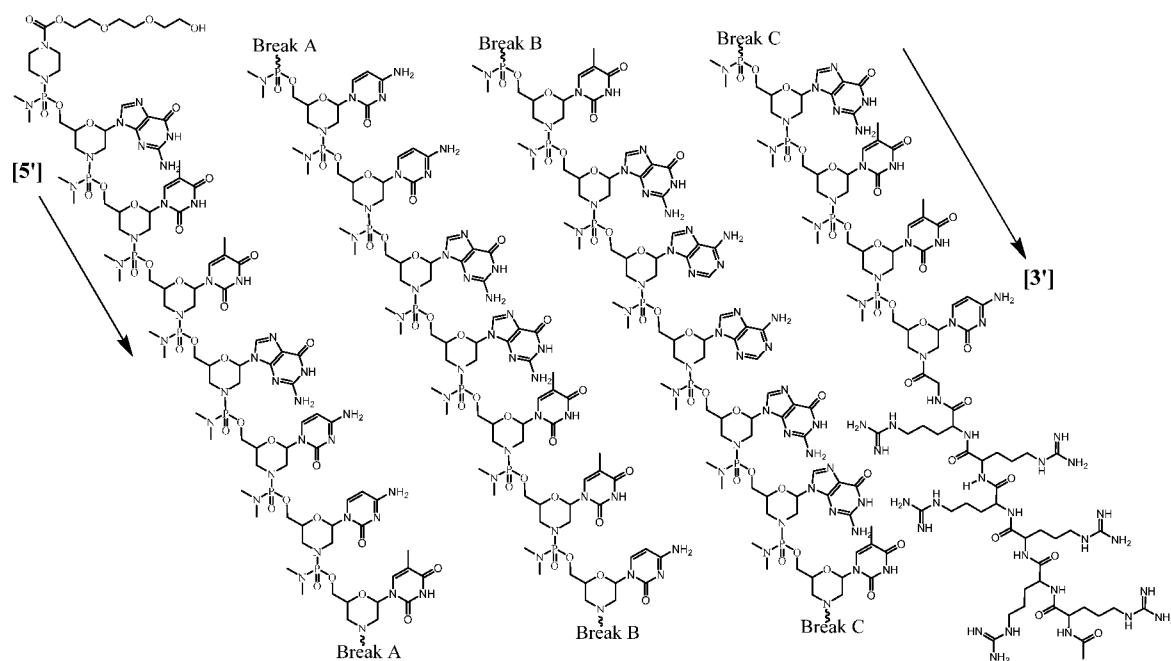
or a pharmaceutically acceptable salt thereof.

18. The method of any one of claims 1-11 or 17, wherein the antisense oligomer conjugate has Formula (VIA):



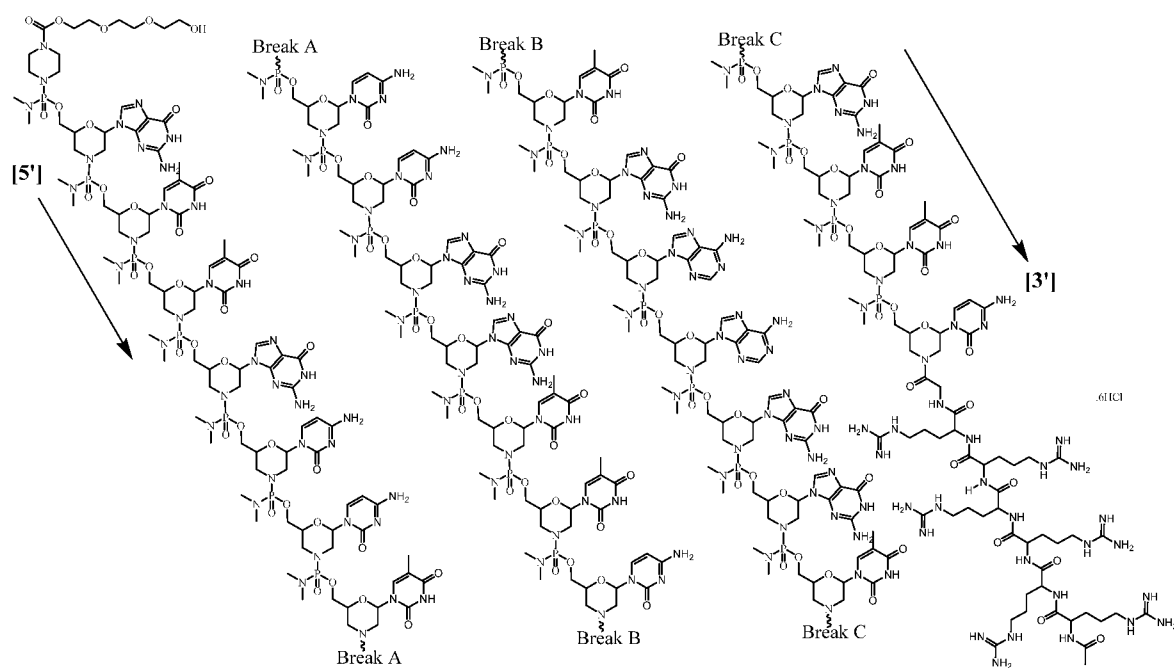
19. The method of any one of claims 1-14, wherein the antisense oligomer conjugate has Formula (VIII):

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or a pharmaceutically acceptable salt thereof.

20. The method of any one of claims 1-14 or 19, wherein the antisense oligomer conjugate has Formula (VIII A):



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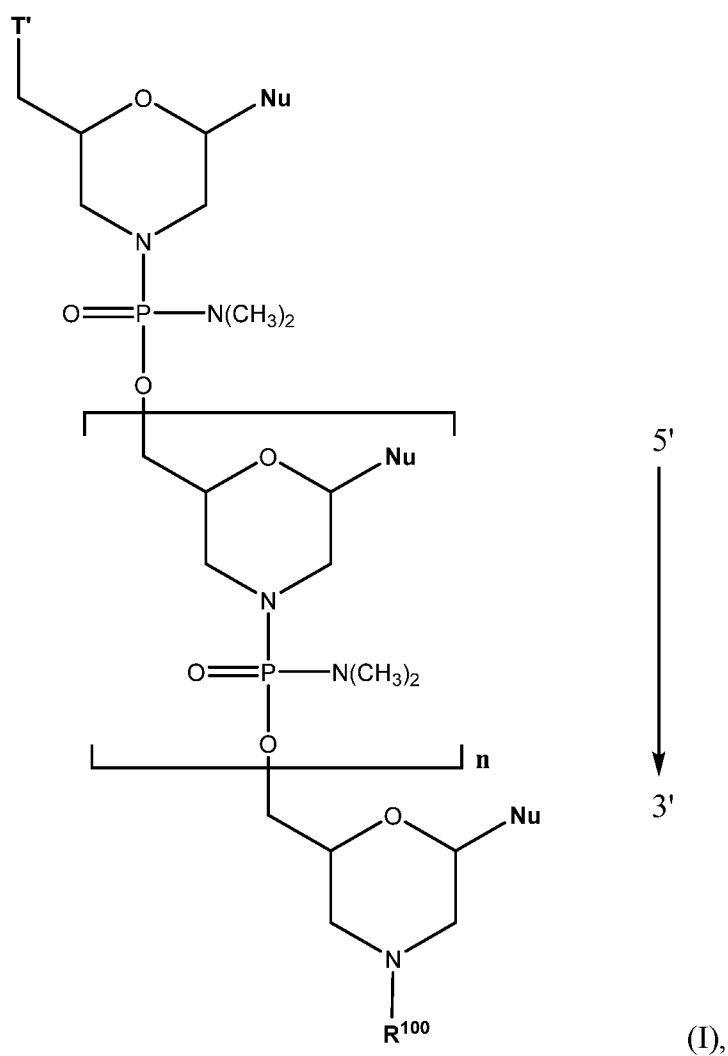
21. The method of any one of claims 1-20, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 700 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.
22. The method of any one of claims 1-21, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 600 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.
23. The method of any one of claims 1-20, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 900 mg to about 1200 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.
24. The method of any one of claims 1-20 or 23 wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1100 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.
25. The method of any one of claims 1-20, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof is administered at a dose equivalent to about 600 mg to about 800 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
26. The method of any one of claims 1-20 or 25, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 650 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
27. The method of any one of claims 1-20, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1000

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mg of the 6HCl salt of the conjugate to about 1300 mg once every four weeks to a patient that weighs from about 25 kg to about 50 kg.

28. The method of any one of claims 1-20 or 27, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1200 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
29. The method of any one of claims 1-20, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 700 mg to about 900 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
30. The method of any one of claims 1-20 or 29, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 750 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
31. The method of any one of claims 1-20, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1200 mg to about 1500 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
32. The method of any one of claims 1-20 or 31, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 1400 mg of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.
33. A method of treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation that is amenable to exon 51 skipping, comprising administering to the patient an antisense oligomer conjugate of Formula (I):

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or a pharmaceutically acceptable salt thereof,

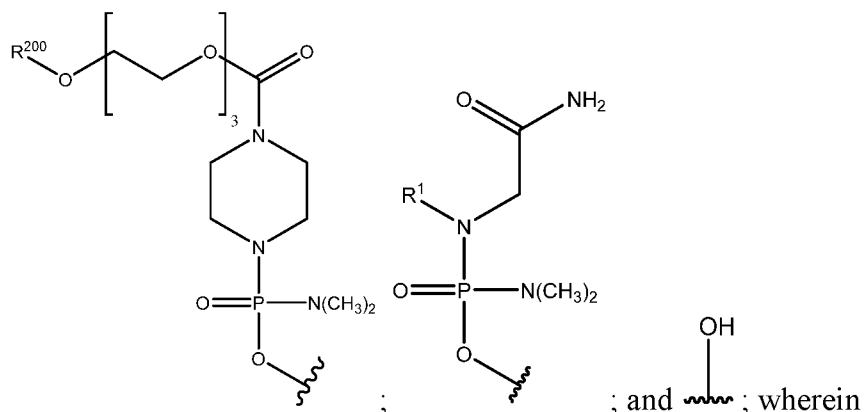
wherein:

n is 1-40;

each **Nu** is a nucleobase, which, taken together, form a targeting sequence complementary to an exon annealing site in the dystrophin pre-mRNA;

T' is a moiety selected from:

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R¹⁰⁰ a cell-penetrating peptide, **R²⁰⁰** is hydrogen, and **R¹** is C₁-C₆ alkyl,

at a dose equivalent to the dose of the 6HCl salt of the conjugate according to the following schedule:

- i) about 300 mg to about 700 mg, or about 900 mg to about 1200 mg, once every four weeks for a patient that weighs from about 10 kg to about 25 kg;
- ii) about 600 mg to about 800 mg, or about 1000 mg to about 1300 mg, once every four weeks for a patient that weighs from about 25 kg to about 50 kg; or
- iii) about 700 mg to about 900 mg, or about 1200 mg to about 1500 mg, once every four weeks for a patient that weighs from about 50 kg to about 100 kg;

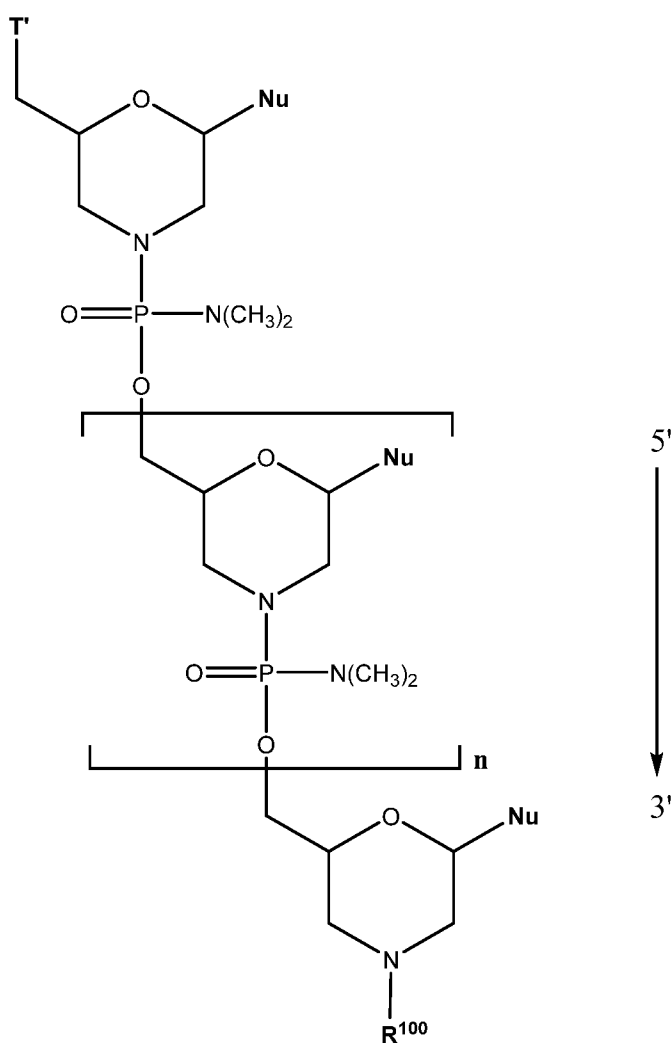
to achieve a mean AUC between about 100 and about 200 ug·h/mL, or is between about 200 and about 500 ug·h/mL.

34. The method of claim 33, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 600 mg, or about 1100 mg, of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 10 kg to about 25 kg.
35. The method of claim 33, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 650 mg, or about 1200 mg, of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 25 kg to about 50 kg.
36. The method of claim 33, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 750 mg, or about 1400

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mg, of the 6HCl salt of the conjugate once every four weeks to a patient that weighs from about 50 kg to about 100 kg.

37. The method of any one of claims 1-36, wherein the method further comprises administering a magnesium supplement to the patient.
38. A method of treating a patient with Duchenne muscular dystrophy (DMD) with an antisense oligomer conjugate, comprising administering to the patient:
 - iii) an antisense oligomer conjugate of Formula (I):



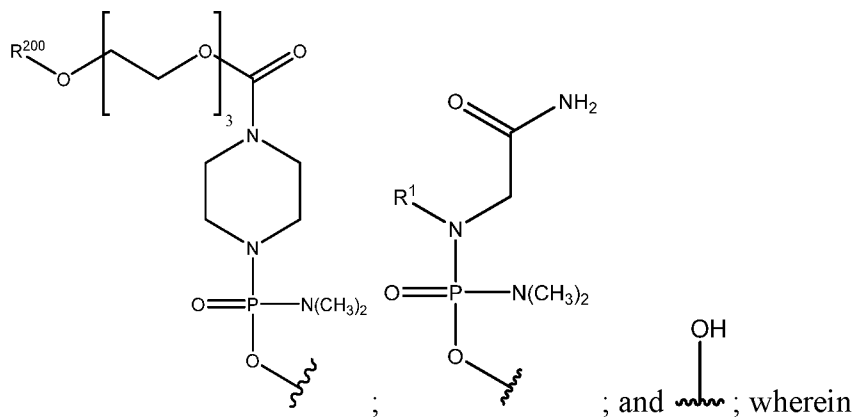
or a pharmaceutically acceptable salt thereof,
wherein:

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n is 1-40;

each **Nu** is a nucleobase, which, taken together, form a targeting sequence complementary to an exon annealing site in the dystrophin pre-mRNA;

T' is a moiety selected from:



R¹⁰⁰ a cell-penetrating peptide, **R**²⁰⁰ is hydrogen, and **R**¹ is C₁-C₆ alkyl; and

iv) a magnesium supplement.

39. The method of claim 38, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg to about 1200 mg, about 300 mg to about 1000 mg, about 300 mg to about 750 mg, about 300 mg to about 500 mg, about 400 mg to about 1400 mg, about 400 mg to about 1100 mg, about 400 mg to about 900 mg, about 400 mg to about 600 mg, about 500 mg to about 1500 mg, about 500 mg to about 1300 mg, about 500 mg to about 1000 mg, about 500 mg to about 950 mg, about 500 mg to about 850 mg, about 500 mg to about 750 mg, about 500 mg to about 650 mg, about 600 mg to about 1400 mg, about 600 mg to about 1200 mg, about 600 mg to about 1200 mg, about 600 mg to about 1000, or about 600 mg to about 900 mg of the 6HCl salt of the conjugate.
40. The method of any one of claims 38-39, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, or about 900 mg of the 6HCl salt of the conjugate.

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41. The method of any one of claims 38-40, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is administered at a dose equivalent to about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, or about 1500 mg of the 6HCl salt of the conjugate.
42. The method of any one of claims 38-41, wherein the cell-penetrating peptide is chosen from RXRRXRRXRRXR (SEQ ID NO: 18), RFFRFFRFFR (SEQ ID NO: 19), RXRRXRRXRRXRXB (SEQ ID NO: 20), RFFRFFRFFRGG (SEQ ID NO: 21), RRRRRRG (SEQ ID NO: 22), RRRRRR (SEQ ID NO: 23), RRRRRG (SEQ ID NO: 24), or RRRRR (SEQ ID NO: 25), wherein R is arginine, X is 6-aminohexanoic acid, B is β -alanine, F is phenylalanine, and G is glycine.
43. The method of any one of claims 38-42, wherein the cell-penetrating peptide is chosen from RRRRRRG (SEQ ID NO: 22), RRRRRR (SEQ ID NO: 23), RRRRRG (SEQ ID NO: 24), or RRRRR (SEQ ID NO: 25), wherein R is arginine and G is glycine.
44. The method of any one of claims 38-43, wherein the cell-penetrating peptide is RRRRRRG (SEQ ID NO: 22), wherein R is arginine and G is glycine.
45. The method of any one of claims 38-44, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, causes skipping of an exon in the human dystrophin gene.
46. The method of any one of claims 38-45, wherein the exon is chosen from exon 44, 45, 50, 51, 52, or 53.
47. The method of any one of claims 38-46, wherein the exon is chosen from exon 45, 51, or 53.
48. The method of any one of claims 38-47, wherein the magnesium supplement is administered in an amount effective to provide a normal serum magnesium level.

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49. The method of any one of claims 38-48, wherein the magnesium supplement is administered at a dose equivalent to about 100 to about 2400 mg magnesium oxide per day.
50. The method of any one of claims 38-49, wherein the magnesium supplement is administered at a dose equivalent to about 400 to about 2400 mg magnesium oxide per day.
51. The method of any one of claims 38-50, further comprising measuring serum magnesium level of said patient at two or more weeks from said administration.
52. The method of any one of claims 38-51, further comprising administering a second dose of magnesium supplement, at a dose based upon the measured serum magnesium level.
53. The method of any one of claims 38-52, wherein the magnesium supplement is chosen from magnesium oxide, magnesium citrate, magnesium carbonate, magnesium hydrogen phosphate, magnesium glycerophosphate, magnesium trisilicate, magnesium hydroxide, magnesium hydroxide carbonate, magnesium acetate, magnesium citrate, magnesium lactate, magnesium gluconate, magnesium chloride, magnesium aspartate, magnesium caprilate, magnesium ascorbate; magnesium taurate, magnesium malate, and magnesium diglycinate, magnesium pidulate, or magnesium sulfate.
54. The method of any one of claims 38-53, wherein the magnesium supplement is from magnesium oxide.
55. A method of treating a patient with an antisense oligomer conjugate, comprising administering to a patient in need of said treatment an antisense oligomer conjugate and a magnesium supplement.
56. The method of any one of claims 38-55, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is administered in a pharmaceutical formulation, wherein the concentration of the conjugate in the formulation is about 50 mg/ml.

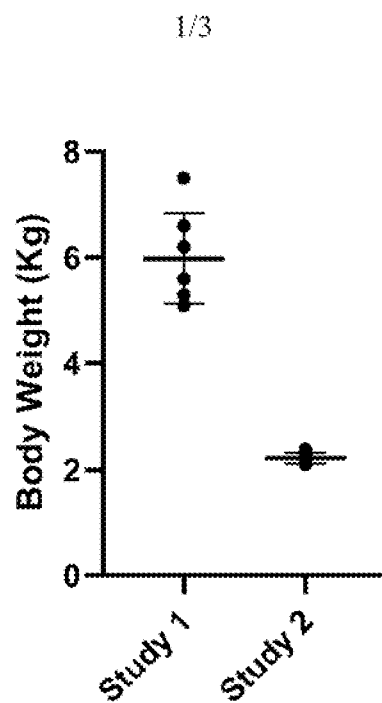
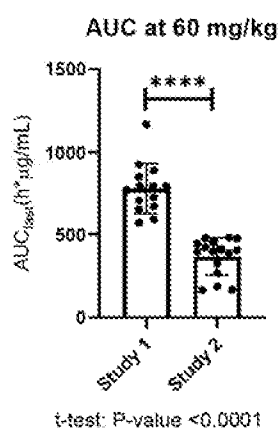
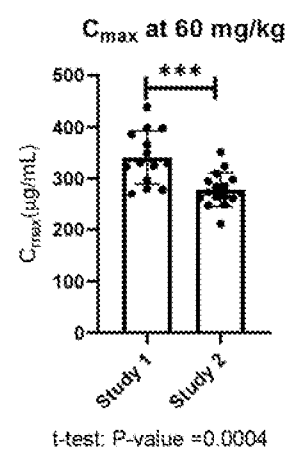


Figure 1



	Study 1	Study 2
Number of values	14	16
Minimum	571.0	167.4
Maximum	1170	481.2
Range	599.0	313.8
Mean	778.7	368.1
Std. Deviation	154.2	110.5
Std. Error of Mean	41.26	27.61



	Study 1	Study 2
Number of values	14	16
Minimum	270.0	211.0
Maximum	409.0	382.0
Range	139.0	171.0
Mean	341.1	278.1
Std. Deviation	51.48	33.45
Std. Error of Mean	13.76	8.361

Figure 2

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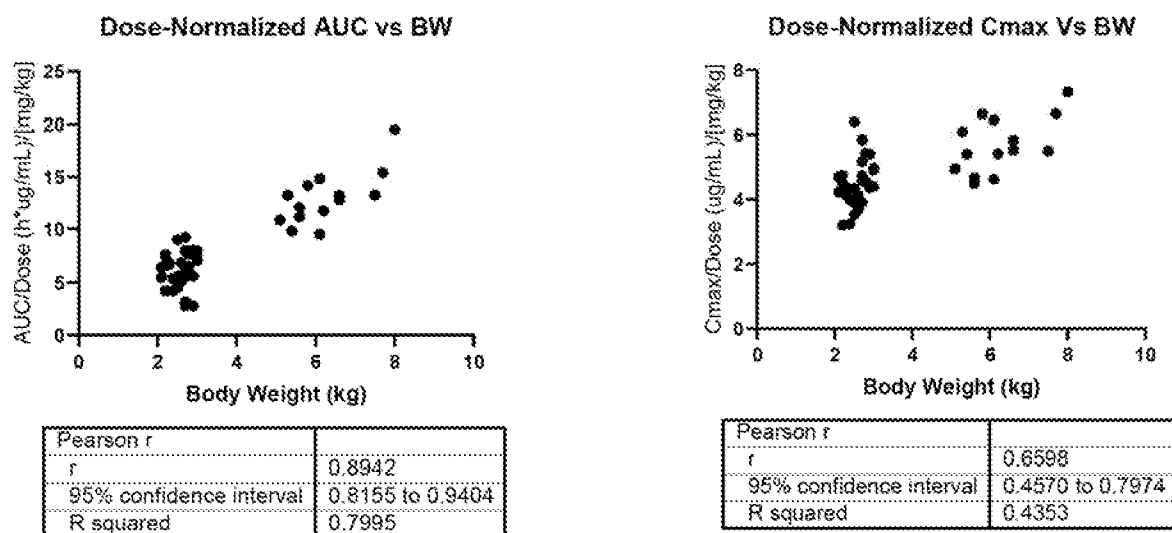


Figure 3

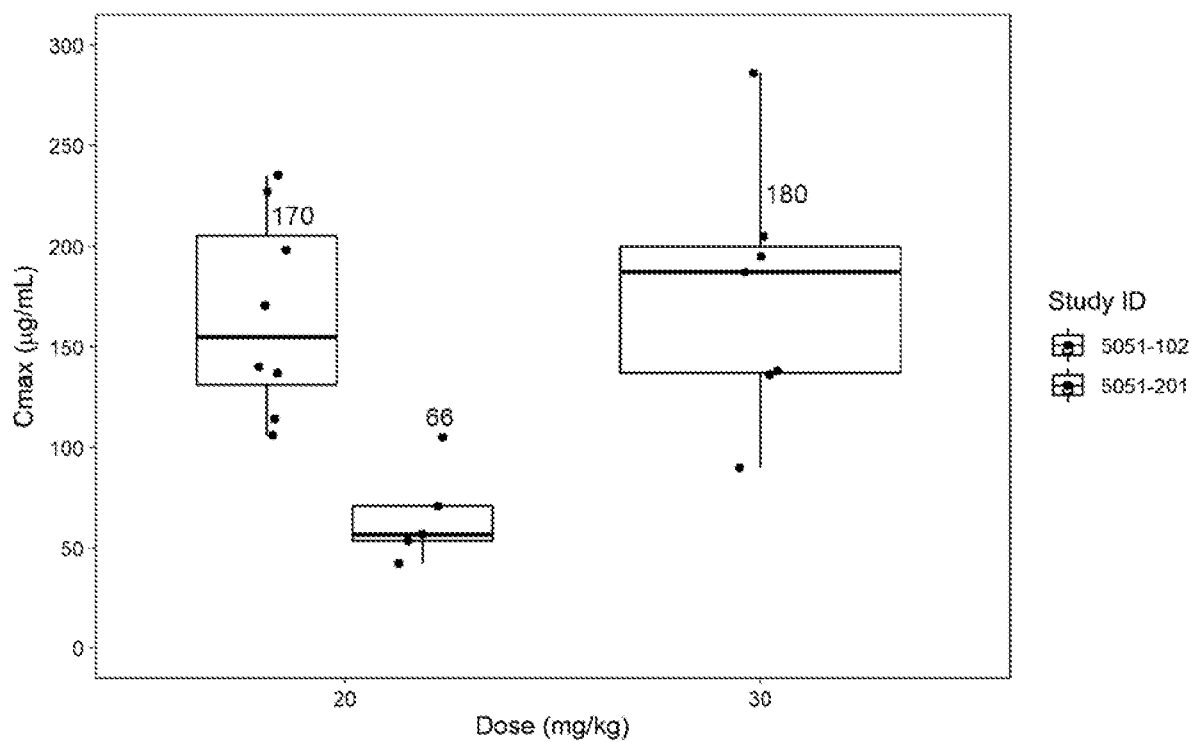
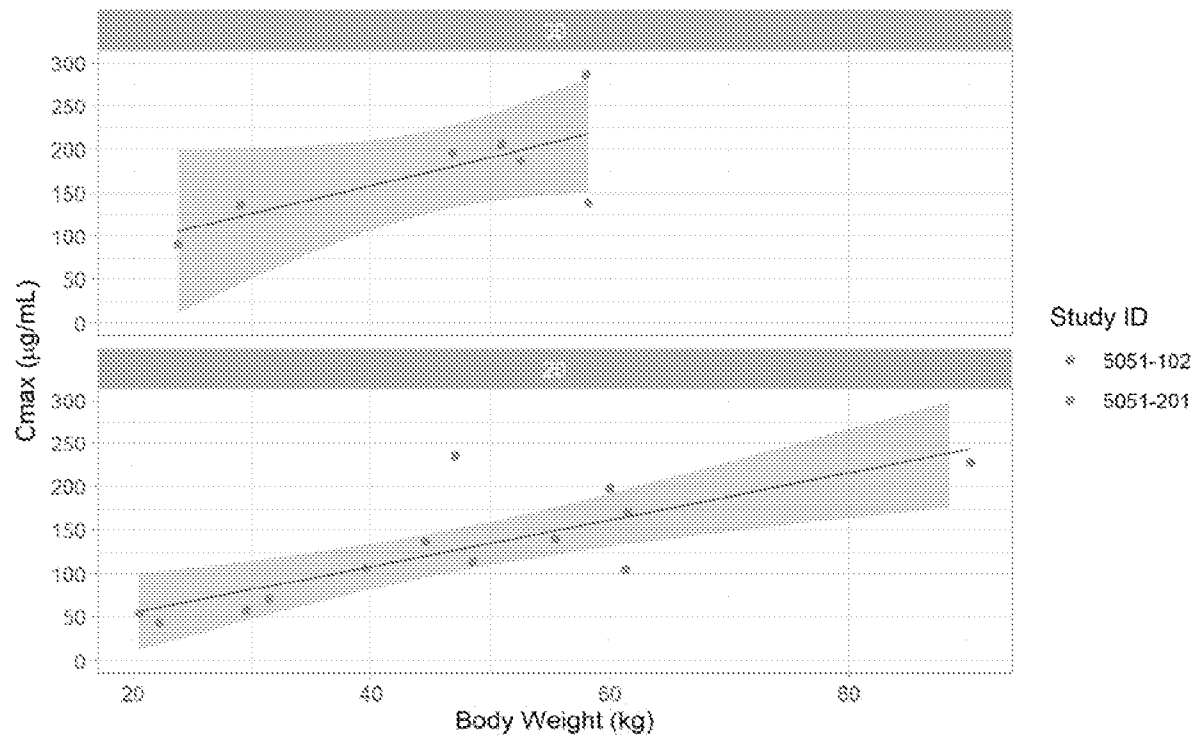


Figure 4

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**Figure 5**