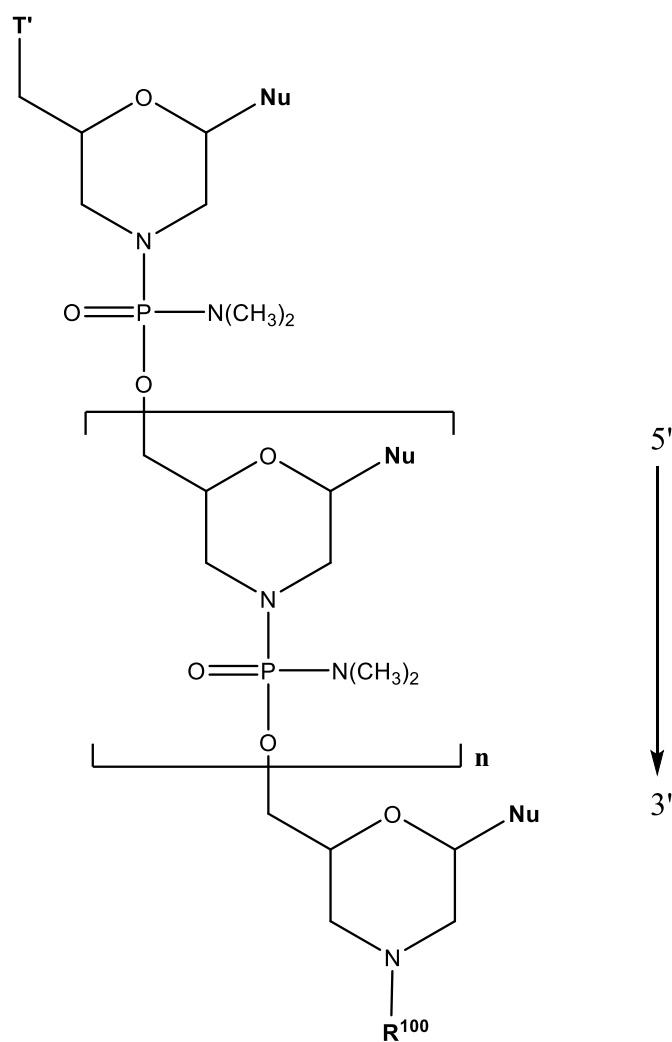


CLAIMS

1. Use of an antisense oligomer conjugate of Formula (I) in the manufacture of a medicament for the treatment of Duchenne muscular dystrophy (DMD) in a patient in need thereof who has a mutation that is amenable to exon skipping, the antisense oligomer conjugate of Formula (I):



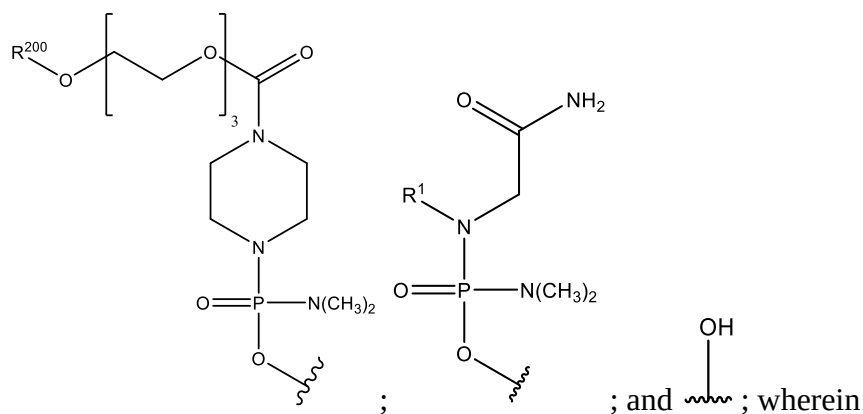
or a pharmaceutically acceptable salt thereof,

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;

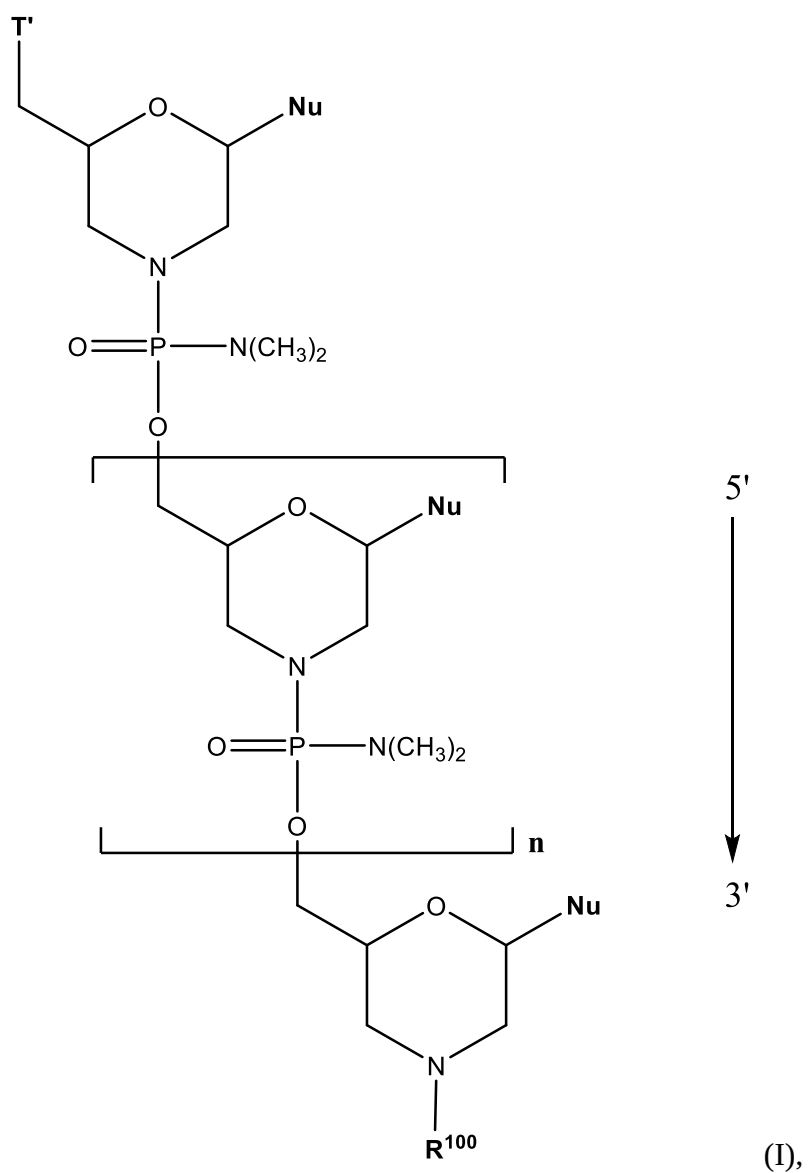
T' is a moiety selected from:



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

and wherein the conjugate is to be 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. Use of an antisense oligomer conjugate of Formula (I) in the manufacture of a medicament for the treatment of Duchenne muscular dystrophy (DMD) in a patient in need thereof who has a mutation that is amenable to exon 51 skipping, the antisense oligomer conjugate of Formula (I):



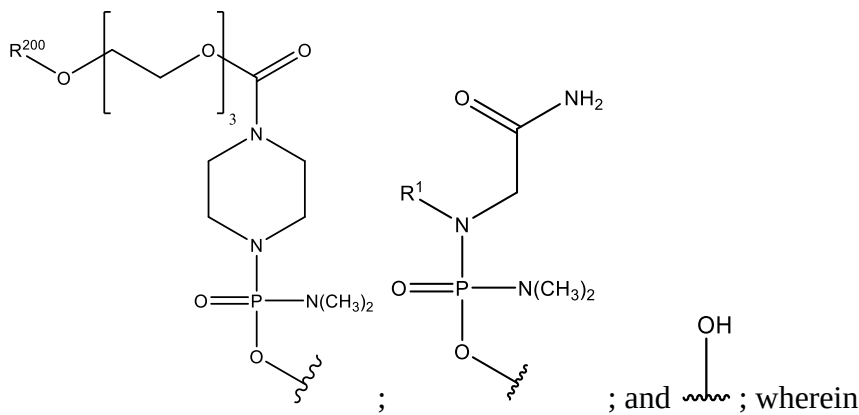
or a pharmaceutically acceptable salt thereof,

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:



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

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

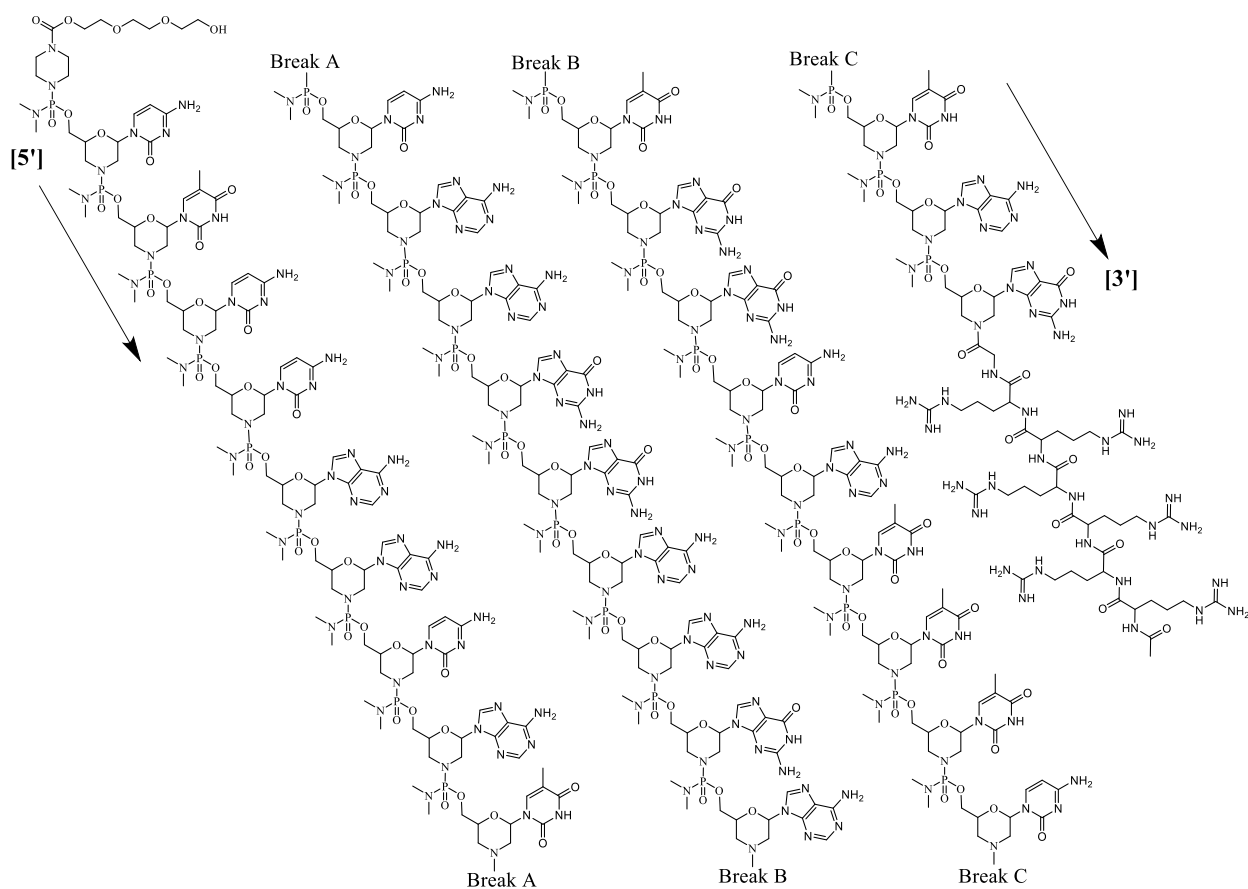
to achieve a mean AUC of between about 100 and about 200 $\mu\text{g}\cdot\text{h/mL}$, or between about 200 and about 500 $\mu\text{g}\cdot\text{h/mL}$.

3. The use of any one of claims 1-2, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use of any one of claims 1-3, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is to be administered at a dose effective to provide a mean AUC of between about 100 and about 200 ug·h/mL.
5. The use of any one of claims 1-3, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is to be administered at a dose effective to provide a mean AUC of between about 200 and about 500 ug·h/mL.
6. The use of any one of claims 1-4, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use of any one of claims 1-3 or 5, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use of any one of claims 1-7, wherein 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.
 9. The use 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 use 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 use of any one of claims 1-10, wherein the antisense oligomer conjugate causes skipping of an exon in the human dystrophin gene.
 12. The use of any one of claims 1-11, wherein the exon is chosen from exon 44, 45, 50, 51, 52, or 53.
 13. The use of any one of claims 1-12, wherein the exon is chosen from exon 45, 51, or 53.
 14. The use of any one of claims 1-13, wherein the antisense oligomer conjugate has Formula (III):

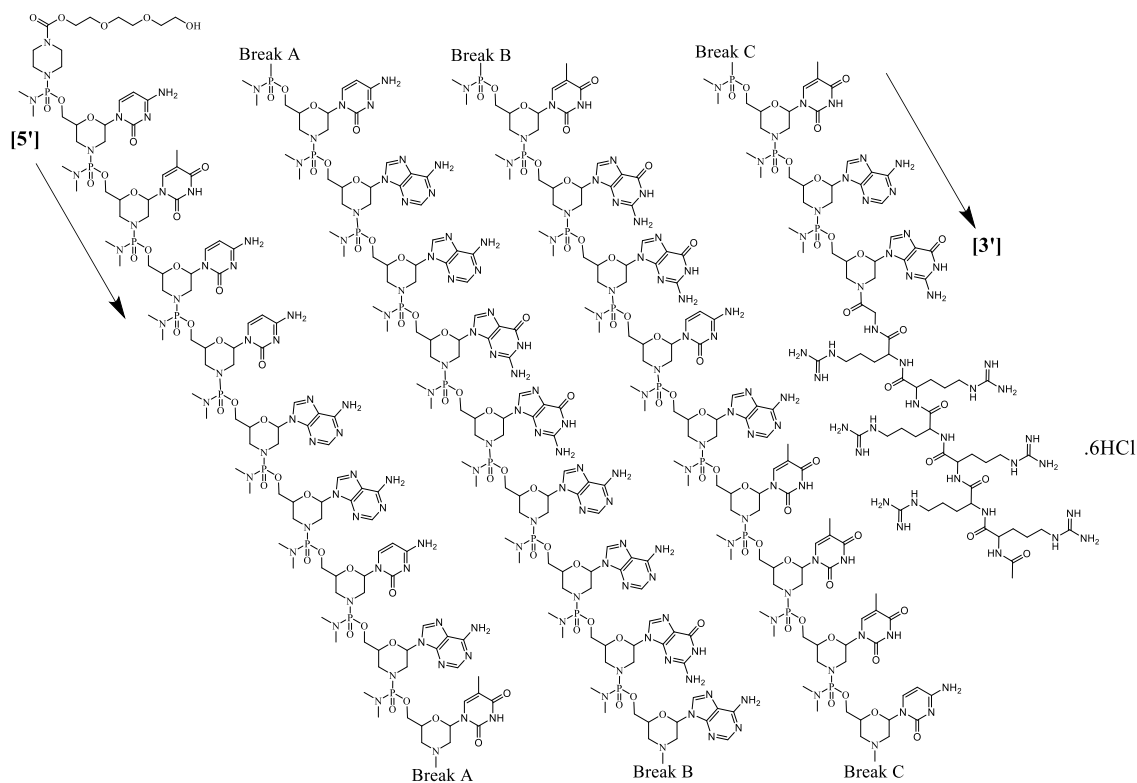
or a pharmaceutically acceptable salt thereof,

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

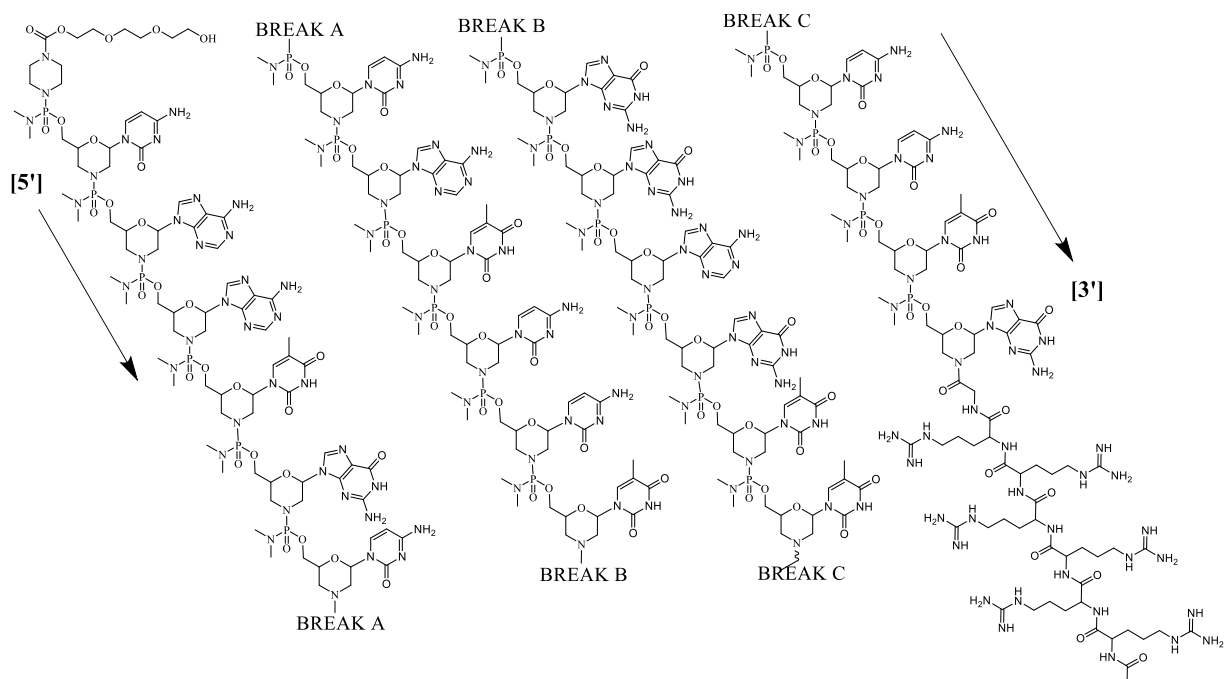


or a pharmaceutically acceptable salt thereof.

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



17. The use of any one of claims 1-14, wherein the antisense oligomer conjugate has Formula (VI):

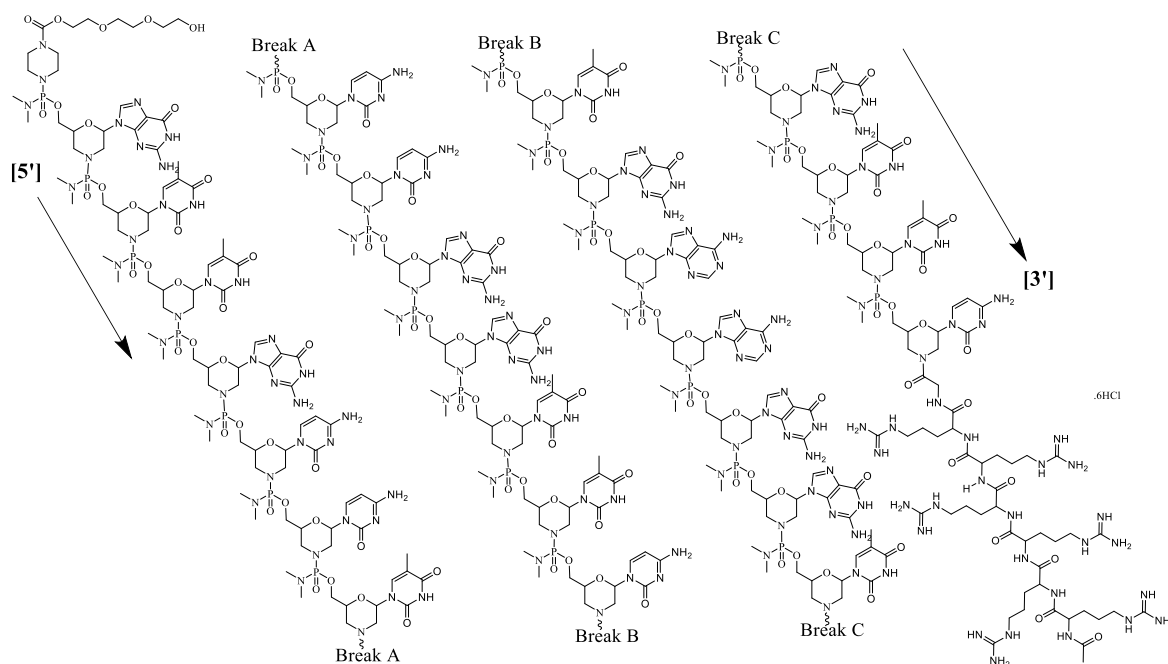


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or a pharmaceutically acceptable salt thereof.

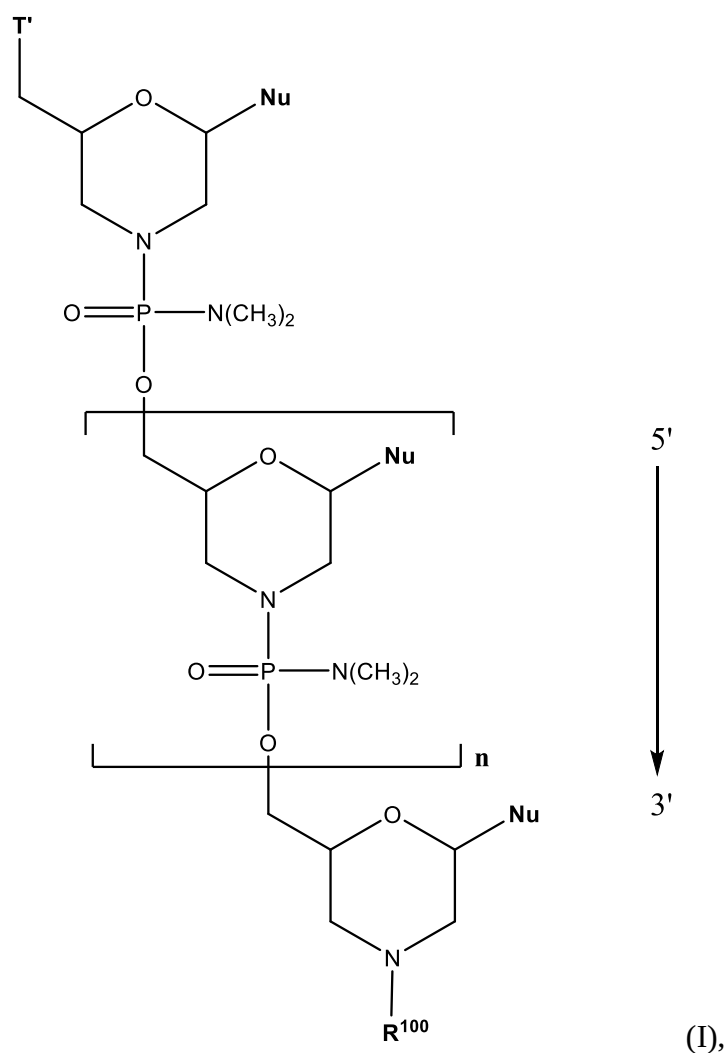
20. The use of any one of claims 1-14 or 19, wherein the antisense oligomer conjugate has Formula (VIII A):



21. The use of any one of claims 1-20, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use of any one of claims 1-21, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use of any one of claims 1-20, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use of any one of claims 1-20 or 23 wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use of any one of claims 1-20, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof is to be 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 use of any one of claims 1-20 or 25, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use of any one of claims 1-20, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is to be 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.
28. The use of any one of claims 1-20 or 27, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use of any one of claims 1-20, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use of any one of claims 1-20 or 29, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use of any one of claims 1-20, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use of any one of claims 1-20 or 31, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is to be 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. Use of an antisense oligomer conjugate of Formula (I) in the manufacture of a medicament for the treatment of Duchenne muscular dystrophy (DMD) in a patient in need thereof who has a mutation that is amenable to exon 51 skipping, the antisense oligomer conjugate of Formula (I):

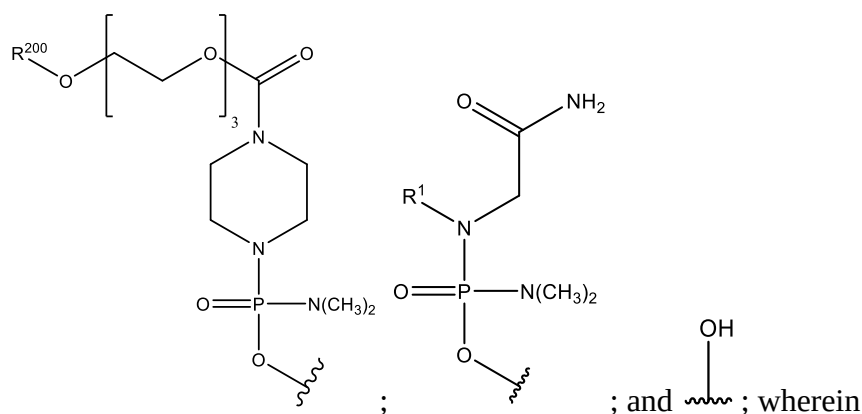


or a pharmaceutically acceptable salt thereof,
wherein:

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:

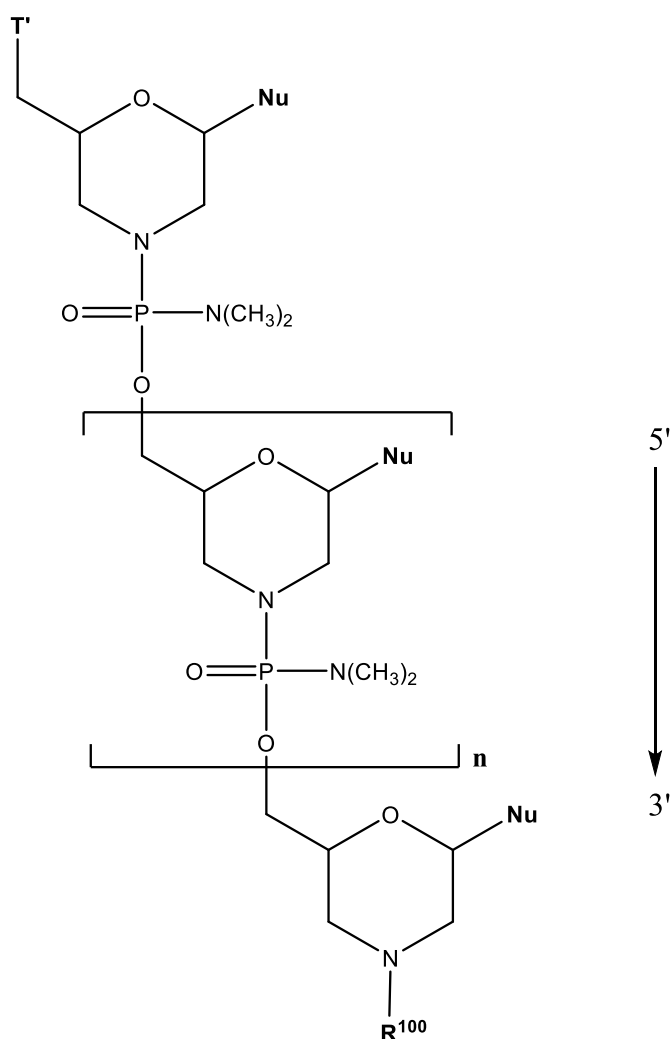


R¹⁰⁰ a cell-penetrating peptide, **R**²⁰⁰ is hydrogen, and **R**¹ is C₁-C₆ alkyl, is to be administered at a dose equivalent to the dose of the 6HCl salt of the conjugate according to the following schedule:

- 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 use of claim 33, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use of claim 33, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use of claim 33, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is to be 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.

37. The use of any one of claims 1-36, further comprises a magnesium supplement to be administered to the patient.
38. Use of an antisense oligomer conjugate in the manufacture of a medicament for the treatment of Duchenne muscular dystrophy (DMD) in a patient, wherein
 - i) an antisense oligomer conjugate of Formula (I):



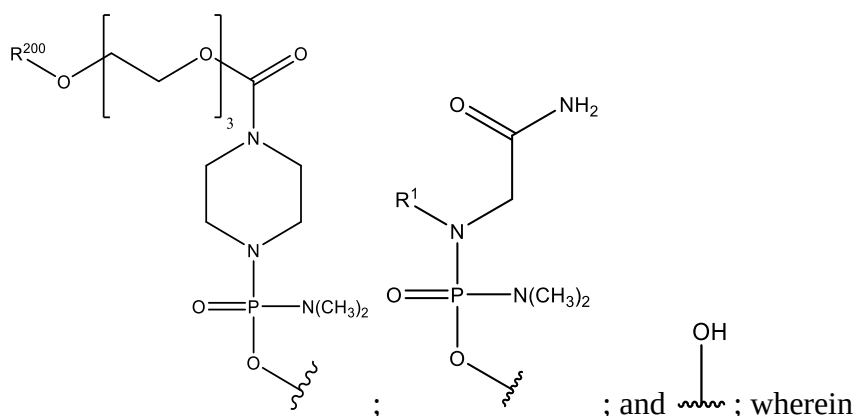
or a pharmaceutically acceptable salt thereof,

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:



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

ii) a magnesium supplement, are to be administered to the patient.

39. The use of claim 38, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use of any one of claims 38-39, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is to be 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.
41. The use of any one of claims 38-40, wherein the conjugate, or a pharmaceutically acceptable salt thereof, is to be 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 use 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), 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.
43. The use 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 use 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 use 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 use of any one of claims 38-45, wherein the exon is chosen from exon 44, 45, 50, 51, 52, or 53.
47. The use 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 to be administered in an amount effective to provide a normal serum magnesium level.
49. The use of any one of claims 38-48, wherein the magnesium supplement is to be administered at a dose equivalent to about 100 to about 2400 mg magnesium oxide per day.
50. The use of any one of claims 38-49, wherein the magnesium supplement is to be administered at a dose equivalent to about 400 to about 2400 mg magnesium oxide per day.
51. The use 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 use of any one of claims 38-51, further comprising a second dose of magnesium supplement be administered, at a dose based upon the measured serum magnesium level.
53. The use 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 use of any one of claims 38-53, wherein the magnesium supplement is from magnesium oxide.
55. The use of any one of claims 38-54, wherein the antisense oligomer conjugate, or a pharmaceutically acceptable salt thereof, is to be administered in a pharmaceutical formulation, wherein the concentration of the conjugate in the formulation is about 50 mg/ml.