

WHAT IS CLAIMED IS:

1. ~~1. A method for treating a neuromuscular disease or disorder comprising administering a therapeutically effective amount of a composition to a subject in need thereof wherein the composition comprises~~Use of a composition comprising

(i) an antisense oligonucleotide (ASO) complementary to a nucleotide sequence within intron 7 of human SMN2 pre-mRNA; and

(ii) a subclinical dose of a histone deacetylase inhibitor-

in the manufacture of a medicament for treating Spinal muscular Atrophy (SMA), wherein the ASO is selected from the group consisting of ATTCACCTTTCATAATGCTGG (ASO1) (SEQ ID NO:1), TGCTGGCAGACTTAC (SEQ ID NO:58), CATAATGCTGGCAGA (SEQ ID NO:59), TCATAATGCTGGCAG (SEQ ID NO:60), TTCATAATGCTGGCA (SEQ ID NO:61), TTTCATAATGCTGGC (SEQ ID NO:62), TCACTTTCATAATGCTGG (SEQ ID NO:63), AGTAAGATTCACCTT (SEQ ID NO:64), CTTTCATAATGCTGG (SEQ ID NO:65), TCATAATGCTGG (SEQ ID NO:66), ACTTTCATAATGCTG (SEQ ID NO:67), TTCATAATGCTG (SEQ ID NO:68), CACTTTCATAATGCT (SEQ ID NO:69), TTTCATAATGCT (SEQ ID NO:70), TCACTTTCATAATGC (SEQ ID NO:71), CTTTCATAATGC (SEQ ID NO:72), TTCACCTTTCATAATG (SEQ ID NO:73), ACTTTCATAATG (SEQ ID NO:74), ATTCACCTTTCATAAT (SEQ ID NO:75), CACTTTCATAAT (SEQ ID NO:76), GATTCACCTTTCATAA (SEQ ID NO:77), TCACTTTCATAA (SEQ ID NO:78), TTCACCTTTCATA (SEQ ID NO:79), ATTCACCTTTCAT (SEQ ID NO:80), or a combination thereof.

2. ~~A method for treating a neuromuscular disease or disorder comprising co-administering~~Use of a composition comprising

(i) a therapeutically effective amount of an ASO complementary to a nucleotide sequence within intron 7 of human SMN2 pre-mRNA; ~~and~~ in the manufacture of a medicament for use in combination therapy for treating SMA, wherein the ASO is to be co-administered with

(ii) a subclinical dose of a histone deacetylase inhibitor, wherein the ASO is selected from the group consisting of ATTCACCTTTCATAATGCTGG (ASO1) (SEQ ID NO:1), TGCTGGCAGACTTAC (SEQ ID NO:58), CATAATGCTGGCAGA (SEQ ID NO:59), TCATAATGCTGGCAG (SEQ ID NO:60), TTCATAATGCTGGCA (SEQ ID NO:61),

TTTCATAATGCTGGC (SEQ ID NO:62), TCACTTTCATAATGCTGG (SEQ ID NO:63),
AGTAAGATTCACTTT (SEQ ID NO:64), CTTTCATAATGCTGG (SEQ ID NO:65),
TCATAATGCTGG (SEQ ID NO:66), ACTTTCATAATGCTG (SEQ ID NO:67),
TTCATAATGCTG (SEQ ID NO:68), CACTTTCATAATGCT (SEQ ID NO:69),
TTTCATAATGCT (SEQ ID NO:70), TCACTTTCATAATGC (SEQ ID NO:71),
CTTTCATAATGC (SEQ ID NO:72), TTCACTTTCATAATG (SEQ ID NO:73),
ACTTTCATAATG (SEQ ID NO:74), ATTCACTTTCATAAT (SEQ ID NO:75),
CACTTTCATAAT (SEQ ID NO:76), GATTCACTTTCATAA (SEQ ID NO:77),
TCACTTTCATAA (SEQ ID NO:78), TTCACTTTCATA (SEQ ID NO:79), ATTCACTTTCAT
(SEQ ID NO:80), or a combination thereof.

3. ~~— A method to increase the clinical efficacy of an ASO to a nucleotide sequence within intron 7 of human SMN2 pre mRNA in the treatment of a neuromuscular disease or disorder comprising co-administering (i) a therapeutically effective amount of the ASO to a subject, and (ii) subclinical dose of a histone deacetylase inhibitor.~~

4. ~~— The method of any one of claims 1 to 3, wherein the neuromuscular disease or disorder is SMA.~~

5. ~~— The method of any one of claims 1 to 4, wherein the ASO is selected from the group consisting of ATTCACTTTCATAATGCTGG (ASO1) (SEQ ID NO:1), TGCTGGCAGACTTAC (SEQ ID NO:58), CATAATGCTGGCAGA (SEQ ID NO:59), TCATAATGCTGGCAG (SEQ ID NO:60), TTCATAATGCTGGCA (SEQ ID NO:61), TTTCATAATGCTGGC (SEQ ID NO:62), TCACTTTCATAATGCTGG (nusinersen) (SEQ ID NO:63), AGTAAGATTCACTTT (SEQ ID NO:64), CTTTCATAATGCTGG (SEQ ID NO:65), TCATAATGCTGG (SEQ ID NO:66), ACTTTCATAATGCTG (SEQ ID NO:67), TTCATAATGCTG (SEQ ID NO:68), CACTTTCATAATGCT (SEQ ID NO:69), TTTCATAATGCT (SEQ ID NO:70), TCACTTTCATAATGC (SEQ ID NO:71), CTTTCATAATGC (SEQ ID NO:72), TTCACTTTCATAATG (SEQ ID NO:73), ACTTTCATAATG (SEQ ID NO:74), ATTCACTTTCATAAT (SEQ ID NO:75), CACTTTCATAAT (SEQ ID NO:76), GATTCACTTTCATAA (SEQ ID NO:77), TCACTTTCATAA (SEQ ID NO:78), TTCACTTTCATA (SEQ ID NO:79), ATTCACTTTCAT (SEQ ID NO:80), or a combination thereof.~~

6. ~~_____ The method of any one of claims 1 to 4, wherein the ASO comprises a sequence which is at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to ATTCACTTTCATAATGCTGG (ASO1) (SEQ ID NO:1), TGCTGGCAGACTTAC (SEQ ID NO:58), CATAATGCTGGCAGA (SEQ ID NO:59), TCATAATGCTGGCAG (SEQ ID NO:60), TTCATAATGCTGGCA (SEQ ID NO:61), TTTCATAATGCTGGC (SEQ ID NO:62), TCACTTTCATAATGCTGG (nusinersen) (SEQ ID NO:63), AGTAAGATTCACTTT (SEQ ID NO:64), CTTTCATAATGCTGG (SEQ ID NO:65), TCATAATGCTGG (SEQ ID NO:66), ACTTTCATAATGCTG (SEQ ID NO:67), TTCATAATGCTG (SEQ ID NO:68), CACTTTCATAATGCT (SEQ ID NO:69), TTTCATAATGCT (SEQ ID NO:70), TCACTTTCATAATGC (SEQ ID NO:71), CTTTCATAATGC (SEQ ID NO:72), TTCACTTTCATAATG (SEQ ID NO:73), ACTTTCATAATG (SEQ ID NO:74), ATTCACTTTCATAAT (SEQ ID NO:75), CACTTTCATAAT (SEQ ID NO:76), GATTCACTTTCATAA (SEQ ID NO:77), TCACTTTCATAA (SEQ ID NO:78), TTCACTTTCATA (SEQ ID NO:79), or ATTCACTTTCAT (SEQ ID NO:80)~~

7.3. ~~_____ The method of~~ according to any one of claims 1 to 4~~2~~, wherein the ASO is an ASO of SEQ ID NO: 1, nusinersen, a variant thereof, a derivative thereof, or a combination thereof

8.4. ~~_____ The method of~~ use according to any one of claims 1 to 7~~3~~, wherein the histone deacetylase inhibitor is valproic acid, trichostatin A, or a combination thereof.

9.5. ~~_____ The method of~~ according to any one of claims 1 to 8~~4~~, wherein (i) the ASO is ~~administered~~ at a dose lower than about 0.20 mg/kg, lower than about 0.19 mg/kg, lower than about 0.18 mg/kg, lower than about 0.17 mg/kg, lower than about 0.16 mg/kg, lower than about 0.15 mg/kg, lower than about 0.14 mg/kg, lower than about 0.13 mg/kg, lower than about 0.12 mg/kg, lower than about 0.11 mg/kg, lower than about 0.1 mg/kg, lower than about 0.09 mg/kg, lower than about 0.08 mg/kg, lower than about 0.07 mg/kg, lower than about 0.06 mg/kg, lower than about 0.05 mg/kg, lower than about 0.04 mg/kg, lower than about 0.03 mg/kg, lower than about 0.02 mg/kg, or lower than about 0.01 mg/kg per dose; and (ii) the histone deacetylase inhibitor is ~~administered~~ at a dose lower than about 15 mg/kg, lower than about 15 mg/kg, lower than about 13 mg/kg, lower than

about 12 mg/kg, lower than about 11 mg/kg, lower than about 10 mg/kg, lower than about 9 mg/kg, lower than about 8 mg/kg, lower than about 7 mg/kg, lower than about 6 mg/kg, lower than about 5 mg/kg, lower than about 4 mg/kg, lower than about 3 mg/kg, lower than about 2 mg/kg, lower than about 1 mg/kg per dose.

~~10.6.~~ The method of use according to any one of claims 1 to ~~94~~, wherein (i) the ASO is ~~administered~~ at a dose lower than about 12 mg/dose, lower than about 11 mg/dose, lower than about 10 mg/dose, lower than about 9 mg/dose, lower than about 8 mg/dose, lower than about 7 mg/dose, lower than about 6 mg/dose, lower than about 5 mg/dose, lower than about 4 mg/dose, lower than about 3 mg/dose, lower than about 2 mg/dose, or lower than about 1 mg/dose; and (ii) the histone deacetylase inhibitor is ~~administered~~ at a dose lower than about 600 mg/dose, lower than about 550 mg/dose, lower than about 500 mg/dose, lower than about 450 mg/dose, lower than about 400 mg/dose, lower than about 350 mg/dose, lower than about 300 mg/dose, lower than about 250 mg/dose, lower than about 200 mg/dose, lower than about 175 mg/dose, lower than about 150 mg/dose, lower than about 125 mg/dose, lower than about 100 mg/dose, lower than about 90 mg/dose, lower than about 80 mg/dose, lower than about 70 mg/dose, lower than about 60 mg/dose, lower than about 50 mg/dose, lower than about 40 mg/dose, lower than about 30 mg/dose, lower than about 20 mg/dose, or lower than about 10 mg/dose.

~~11.7.~~ The method of use according to any one of claims 1 to ~~104~~, wherein (i) the ASO is ~~administered~~ at a dose lower than about 12 mg/dose/day, lower than about 11 mg/dose/day, lower than about 10 mg/dose/day, lower than about 9 mg/dose/day, lower than about 8 mg/dose/day, lower than about 7 mg/dose/day, lower than about 6 mg/dose/day, lower than about 5 mg/dose/day, lower than about 4 mg/dose/day, lower than about 3 mg/dose/day, lower than about 2 mg/dose/day, or lower than about 1 mg/dose/day; and (ii) the histone deacetylase inhibitor is ~~administered~~ at a dose lower than about 600 mg/dose/day, lower than about 550 mg/dose/day, lower than about 500 mg/dose/day, lower than about 450 mg/dose/day, lower than about 400 mg/dose/day, lower than about 350 mg/dose/day, lower than about 300 mg/dose/day, lower than about 250 mg/dose/day, lower than about 200 mg/dose/day, lower than about 175 mg/dose/day, lower than about 150 mg/dose/day, lower than about 125 mg/dose/day, lower than about 100 mg/dose/day, lower than about 90 mg/dose/day, lower than about 80 mg/dose/day, lower than about 70 mg/dose/day, lower than about 60

mg/dose/day, lower than about 50 mg/dose/day, lower than about 40 mg/dose/day, lower than about 30 mg/dose/day, lower than about 20 mg/dose/day, or lower than about 10 mg/dose/day.

~~12.8.~~ The method of use according to any one of claims 1 to ~~114~~, wherein (i) the ASO is ~~administered~~ at a dose of about 0.20 mg/kg, about 0.19 mg/kg, about 0.18 mg/kg, about 0.17 mg/kg, about 0.16 mg/kg, about 0.15 mg/kg, about 0.14 mg/kg, about 0.13 mg/kg, about 0.12 mg/kg, about 0.11 mg/kg, about 0.1 mg/kg, about 0.09 mg/kg, about 0.08 mg/kg, about 0.07 mg/kg, about 0.06 mg/kg, about 0.05 mg/kg, about 0.04 mg/kg, about 0.03 mg/kg, about 0.02 mg/kg, or about 0.01 mg/kg per dose; and (ii) the histone deacetylase inhibitor is ~~administered~~ at a dose about 15 mg/kg, about 15 mg/kg, about 13 mg/kg, about 12 mg/kg, about 11 mg/kg, about 10 mg/kg, about 9 mg/kg, about 8 mg/kg, about 7 mg/kg, about 6 mg/kg, about 5 mg/kg, about 4 mg/kg, about 3 mg/kg, about 2 mg/kg, about 1 mg/kg per dose.

~~13.9.~~ The method of use according to any one of claims 1 to 12, wherein (i) the ASO is ~~administered~~ at a dose of about 12 mg/dose, about 11 mg/dose, about 10 mg/dose, about 9 mg/dose, about 8 mg/dose, about 7 mg/dose, about 6 mg/dose, about 5 mg/dose, about 4 mg/dose, about 3 mg/dose, about 2 mg/dose, or about 1 mg/dose; and (ii) the histone deacetylase inhibitor is ~~administered~~ at a dose about 600 mg/dose, about 550 mg/dose, about 500 mg/dose, about 550 mg/dose, about 500 mg/dose, about 450 mg/dose, about 400 mg/dose, about 350 mg/dose, about 300 mg/dose, about 250 mg/dose, about 200 mg/dose, about 175 mg/dose, about 150 mg/dose, about 125 mg/dose, about 100 mg/dose, about 90 mg/dose, about 80 mg/dose, about 70 mg/dose, about 60 mg/dose, about 50 mg/dose, about 40 mg/dose, about 30 mg/dose, about 20 mg/dose, or about 10 mg/dose.

~~14.10.~~ The method of use according to any one of claims 1 to ~~134~~, wherein (i) the ASO is ~~administered~~ at a dose of about 12 mg/dose/day, about 11 mg/dose/day, about 10 mg/dose/day, about 9 mg/dose/day, about 8 mg/dose/day, about 7 mg/dose/day, about 6 mg/dose/day, about 5 mg/dose/day, about 4 mg/dose/day, about 3 mg/dose/day, about 2 mg/dose/day, or about 1 mg/dose/day; and (ii) the histone deacetylase inhibitor is ~~administered~~ at a dose about 600 mg/dose/day, about 550 mg/dose/day, about 500 mg/dose/day, about 550 mg/dose/day, about 500 mg/dose/day, about 450 mg/dose/day, about 400 mg/dose/day, about 350 mg/dose/day, about 300 mg/dose/day, about 250 mg/dose/day, about 200 mg/dose/day, about 175 mg/dose/day, about 150 mg/dose/day, about 125 mg/dose/day, about 100 mg/dose/day, about 90 mg/dose/day, about 80

mg/dose/day, about 70 mg/dose/day, about 60 mg/dose/day, about 50 mg/dose/day, about 40 mg/dose/day, about 30 mg/dose/day, about 20 mg/dose/day, or about 10 mg/dose/day.

~~15.11.~~ The method of use according to any one of claims 1 to 14~~10~~, wherein the administration of the ASO complementary to a nucleotide sequence within intron 7 of human SMN2 pre-mRNA; and the subclinical dose of a histone deacetylase inhibitor results in (i) an increase in inclusion of exon 7 of SMN2, (ii) an increase in the expression of SMN2 protein with exon 7, (iii) a decrease in the expression of SMN2 protein without exon 7, (iv) an increase in time of survival, (v) increase in body mass, (vi) increase in muscle coordination, (vii) improvement in neuromuscular function or (viii) any combination thereof.

~~16. The method of any one of claims 1 to 15, wherein the administration of the ASO complementary to a nucleotide sequence within intron 7 of human SMN2 pre mRNA; and the subclinical dose of a histone deacetylase inhibitor results in an increase in time of survival, increase in body mass, increase in muscle coordination, improvement in neuromuscular function, or any combination thereof.~~

~~17.12.~~ The method of use according to any one of claims 1 to 15~~11~~, wherein (i) the ASO and the subclinical dose of a histone deacetylase inhibitor are administered together; (ii) the ASO and the subclinical dose of a histone deacetylase inhibitor are to be administered separately; (iii) the ASO and the subclinical dose of a histone deacetylase inhibitor are to be administered at the same time; (iv) the ASO is to be administered prior to the administration of the subclinical dose of histone deacetylase inhibitor; or (v) wherein the subclinical dose of histone deacetylase inhibitor is to be administered prior to the administration of the ASO.

~~18. The method of any one of claims 1 to 15, wherein the ASO and the subclinical dose of a histone deacetylase inhibitor are administered separately.~~

~~19. The method of any one of claims 1 to 18, wherein the ASO and the subclinical dose of a histone deacetylase inhibitor are administered at the same time.~~

~~20. The method of any one of claims 1 to 18, wherein the ASO is administered prior to the administration of the subclinical dose of histone deacetylase inhibitor.~~

~~21. The method of any one of claims 1 to 18, wherein the subclinical dose of histone deacetylase inhibitor is administered prior to the administration of the ASO.~~

~~22.13. The method of use according to any one of claim 1 to 20, wherein the ASO is to be administered intrathecally or intravenously, and the histone deacetylase inhibitor is to be administered orally or intravenously.~~

~~23. The method of any one of claims 1 to 22, wherein the histone deacetylase inhibitor administered orally or intravenously~~

~~24.14. The method of use according to any one of claims 1 to 2313, wherein the ASO is a gapmer, a mixmer, or a totalmer.~~

~~25.15. The method of use according to any one of claims 1 to 2414 wherein the ASO comprises one or more nucleoside analogs.~~

~~26. The method of claim 26, wherein one or more of the nucleoside analogs comprises a 2' O-alkyl RNA; 2' O-methyl RNA (2' OMe); 2' alkoxy RNA; 2' O-methoxyethyl RNA (2' MOE); 2'-amino DNA; 2' fluoro RNA; 2' fluoro DNA; arabino nucleic acid (ANA); 2' fluoro ANA; or bicyclic nucleoside analog.~~

~~27.16. The method of use according to claim 25 or 2615, wherein one or more of the nucleoside analogs is a sugar modified nucleoside.~~

~~28. The method of claim 27, wherein the sugar modified nucleoside is an affinity enhancing 2' sugar modified nucleoside.~~

~~29.17. The method of any one of claims 25 to 28, use according to claim 15 or claim 16, wherein (i) one or more of the nucleoside analogs comprises a nucleoside comprising a bicyclic sugar; (ii) one or more of the nucleoside analogs comprises an LNA; (iii) one or more of the nucleotide analogs is selected from the group consisting of constrained ethyl nucleoside (cEt), 2',4'-constrained 2'-O-methoxyethyl (cMOE), α -L-LNA, β -D-LNA, 2'-O,4'-C-ethylene-bridged nucleic acids (ENA), amino-LNA, oxy-LNA, thio-LNA, and any combination thereof.~~

30. — ~~The method of any one of claims 25 to 29, wherein one or more of the nucleoside analogs comprises an LNA.~~

31. — ~~The method of any one of claim 25 to 30, wherein one or more of the nucleotide analogs is selected from the group consisting of constrained ethyl nucleoside (cEt), 2',4' constrained 2' O-methoxyethyl (cMOE), α L LNA, β D LNA, 2' O,4' C ethylene bridged nucleic acids (ENA), amino LNA, oxy LNA, thio LNA, and any combination thereof.~~

~~32.18. The method of~~ use according to any one of claims 1 to ~~34~~17, wherein the ASO comprises one or more 5'-methyl-cytosine nucleobases.

33. — ~~The method of any one of claims 1 to 32, wherein the ASO is from 15 to 25 nucleotides in length.~~

~~34.19. The method of~~ use according to any one of claims 1 to ~~33~~18, wherein the ASO comprises one or more modified internucleoside linkages.

~~35.20. The method of claim 34~~ use according to claim 19, wherein the one or more modified internucleoside linkages is a phosphorothioate linkage.

36. — ~~The method of claims 34 or 35, wherein at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% of internucleoside linkages are modified.~~

37. — ~~The method of claim 36, wherein each of the internucleoside linkages in the ASO is a phosphorothioate linkage.~~