

WHAT IS CLAIMED IS:

1. 1. 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 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), TTTTCATAATGCTGGC (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), TTTTCATAATGCT (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.

2. Use of a composition comprising a therapeutically effective amount of an ASO complementary to a nucleotide sequence within intron 7 of human SMN2 pre-mRNA in the manufacture of a medicament for use in combination therapy for treating SMA, wherein the ASO is to be co-administered with a subclinical dose of a histone deacetylase inhibitor, 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), TTTTCATAATGCTGGC (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), TCACTTTCATAATG (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), TCACTTTCATA (SEQ ID NO:79), ATTCACTTTCAT (SEQ ID NO:80), or a combination thereof.

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

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

5. The according to any one of claims 1 to 4, wherein (i) the ASO is 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 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.

6. The use according to any one of claims 1 to 4, wherein (i) the ASO is 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 at a dose lower than about 600 mg/dose, lower than about 550 mg/dose, lower than about 500 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.

7. The use according to any one of claims 1 to 4, wherein (i) the ASO is 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 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.

8. The use according to any one of claims 1 to 4, wherein (i) the ASO is 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 at a dose about 15 mg/kg, about 14 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.

9. The use according to any one of claims 1 to 12, wherein (i) the ASO is 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 at a dose about 600 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.

10. The use according to any one of claims 1 to 4, wherein (i) the ASO is 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 at a dose about 600 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.

11. The use according to any one of claims 1 to 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.

12. The use according to any one of claims 1 to 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.

13. The 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.

14. The use according to any one of claims 1 to 13, wherein the ASO is a gapmer, a mixmer, or a totalmer.

15. The use according to any one of claims 1 to 14 wherein the ASO comprises one or more nucleoside analogs.

16. The use according to claim 15, wherein one or more of the nucleoside analogs is a sugar modified nucleoside.

17. The 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.

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

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

20. The use according to claim 19, wherein the one or more modified internucleoside linkages is a phosphorothioate linkage.