CLAIMS

1. A compound that is capable of allowing a target cell to produce a mutant activin receptor type-2B (ACVR2B) mRNA where a part of the sequence that encodes some or all of the intracellular region of wild-type ACVR2B is absent, or a pharmaceutically acceptable salt or hydrate thereof.

2. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 1, wherein said intracellular region of wild-type ACVR2B is encoded by exons 8, 7, 5, 6, 9, 10 or 11 ~~5 to 11~~ of wild-type ACVR2B.

3. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 1 or 2, which is capable of making the target cell produce a truncated ACVR2B protein that lacks part of the intracellular region of wild-type ACVR2B.

4. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 3, wherein the truncated ACVR2B protein lacks all or part of the intracellular region encoded by at least one exon selected from the group consisting of exons 8, 7, 5, 6, 9 and 10 ~~5, 6, 7, 8, 9 and 10~~ of ACVR2B.

5. The compound according to any one of claims 1 to 3, which is an antisense oligomer capable of inducing the skipping of an exon coding for a part of intracellular region of ACVR2B, or a pharmaceutically acceptable salt or hydrate thereof.

6. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 5, wherein said exon to be skipped is selected from the group consisting of exons 8, 7, 5, 6, 9 and 10 ~~5, 6, 7, 8, 9 and 10~~ of ACVR2B.

7. The compound according to claim 5 or 6, which comprises 10-50 nucleobases, or pharmaceutically acceptable salt or hydrate thereof.

8. The compound according to any one of claims 5 to 7, comprising a sequence complementary to 10 to 50 consecutive nucleotides of an exon selected from the group consisting of exons 8, 7, 5, 6, 9 and 10 ~~5, 6, 7, 8, 9 and 10~~ of ACVR2B, or pharmaceutically acceptable salt or hydrate thereof.

9. The compound or pharmaceutically acceptable salt or hydrate thereof according to any one of claims 5 to 8, wherein the exon comprises a sequence selected from the group consisting of SEQ ID NOs: 4, 3, 1, 2, 5 and 6~~1 to 6~~.

10. The compound according to any one of claims 5 to 9, comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 25 to 32, 46 to 70, and 90 to 98; 19 to 24, 45 and 79 to 89; 12 to 17 and 71 to 77; 18, 33 to 36, 43, 44, 78 and 99 to 111~~12 to 36 and 43 to 111~~, or pharmaceutically acceptable salt or hydrate thereof.

11. The compound according to any one of claims 5 to 10, consisting of a nucleotide sequence selected from the group consisting of SEQ ID NOs: 25 to 32, 46 to 70, and 90 to 98; 19 to 24, 45 and 79 to 89; 12 to 17 and 71 to 77; 18, 33 to 36, 43, 44, 78 and 99 to 111~~12 to 36 and 43 to 111~~, or pharmaceutically acceptable salt or hydrate thereof.

12. The compound or pharmaceutically acceptable salt or hydrate thereof according to any one of claims 5 to 11, wherein the antisense oligomer is an oligonucleotide.

13. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 12, wherein at least one sugar moiety and/or at least one phosphate bond moiety in the oligonucleotide is modified.

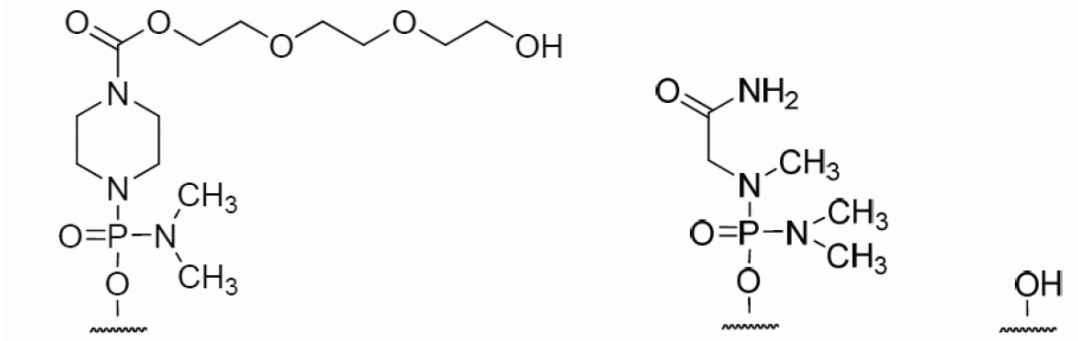
14. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 13, wherein the modified sugar moiety is a ribose in which the -OH group at the 2′-position is substituted with any group selected from the group consisting of OR, R, R′OR, SH, SR, NH_2, NHR, NR_2, N_3, CN, F, Cl, Br and I (wherein R represents alkyl or aryl, and R′ represents alkylene).

15. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 13 or 14, wherein the modified phosphate bond moiety is one selected from the group consisting of a phosphorothioate bond, a phosphorodithioate bond, an alkylphosphonate bond, a phosphoroamidate bond and a boranophosphate bond.

16. The compound or pharmaceutically acceptable salt or hydrate thereof according to any one of claims 5 to 11, wherein the antisense oligomer comprises at least one morpholino ring.

17. The compound according to claim 16, which is a morpholino oligomer or phosphorodiamidate morpholino oligomer, or pharmaceutically acceptable salt or hydrate thereof.

18. The compound according to claim 16 or 17, having any one of the groups represented by chemical formulae (1) to (3) shown below at its 5′-terminal end, or pharmaceutically acceptable salt or hydrate thereof.



（1） （2） （3）

19. A compound which is a conjugate wherein a cell penetrating peptide is bonded to the compound according to any one of claims 1 to 18, or pharmaceutically acceptable salt or hydrate thereof.

20. A pharmaceutical composition comprising the compound or pharmaceutically

acceptable salt or hydrate thereof according to any one of claims 1 to 19.

21. The pharmaceutical composition according to claim 20, which further comprises at least one pharmaceutically acceptable carrier or additive.

22. The pharmaceutical composition according to claim 20 or 21, which is lyophilized.

23. The compound or pharmaceutically acceptable salt or hydrate thereof according to any one of claims 1 to 19 or the pharmaceutical composition according to any one of claims 20 to 22 for use in therapy in a subject.

24. The compound or pharmaceutically acceptable salt or hydrate thereof for use or pharmaceutical composition for use according to claim 23, wherein the therapy is the prevention or treatment of an amyotrophic disease, a muscle wasting disease or a sarcopenic disease in a subject.

25. The compound or pharmaceutically acceptable salt or hydrate for use or pharmaceutical composition for use according to claim 24, wherein the amyotrophic disease is Duchenne muscular dystrophy.

26. The compound or pharmaceutically acceptable salt or hydrate for use or pharmaceutical composition for use according to any one of claims 23 to 25, wherein the subject is a human.

~~27. A method for treating an amyotrophic disease, a muscle wasting disease or a sarcopenic disease in a subject, which comprises administering to said subject a therapeutically effective amount of the compound or pharmaceutically acceptable salt or hydrate thereof according to any one of claims 1 to 19 or the pharmaceutical composition according to any one of claims 20 to 22.~~

~~28. The method according to claim 27, wherein the amyotrophic disease is Duchenne~~

~~muscular dystrophy.~~

~~29. The method according to claim 27 or 28, wherein the subject is a human.~~

~~30~~27. Use of the compound or pharmaceutically acceptable salt or hydrate thereof according to any one of claims 1 to 19 or the pharmaceutical composition according to any one of claims 20 to 22 in the manufacture of a medicament for preventing or treating an amyotrophic disease, a muscle wasting disease or a sarcopenic disease in a subject.

~~31~~28. The use according to claim ~~30~~27, wherein the amyotrophic disease is Duchenne muscular dystrophy.

~~32~~29. The use according to claim ~~30~~ 27 or ~~31~~28, wherein the subject is a human.

~~33~~30. A genetically manipulated animal that expresses a mutant activin receptor type-2B (ACVR2B) mRNA where a part of the sequence that encodes some or all of the intracellular region of wild-type ACVR2B is absent.