Claims

[Claim 1]

An antisense oligomer or a pharmaceutically acceptable salt thereof, or hydrate thereof which causes simultaneous skipping of any two or more numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA,

the antisense oligomer comprising a base sequence complementary to a base sequence of region R2, wherein

the region R2 is a region that consists of a base sequence of 600 bases in the upstream direction from the 3' end of the 44th intron and a base sequence of 50 bases in the downstream direction from the 5' end of the 45th exon in the human dystrophin pre-mRNA, and

wherein the antisense oligomer consists of any one base sequence selected from the group consisting of SEQ ID NOs: 22 to 74, 76 to 111 and 231 to 232.

[Claim 2]

An antisense oligomer or the pharmaceutically acceptable salt thereof, or hydrate thereof, wherein

the antisense oligomer is a linked- type antisense oligomer consisting of

two or more unit oligomers linked to each other, wherein

any one base sequence selected from the group consisting of SEQ ID NOs: 80 to 111 and 231 to 232, or

a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 80 to 111 and 231 to 232, and has a length within ±15% of the length of the any one base sequence selected.

[Claim 3]

The antisense oligomer or the pharmaceutically acceptable salt thereof, or hydrate thereof according to any one of claims 1 to 2, wherein the antisense oligomer consists of any one base sequence selected from the group consisting of SEQ ID NOs: 26, 27, 28, 29, 35, 38, 39, 40, 41, 43, 45, 46, 47, 50, 51, 52, 53, 54, 55, 58, 59, 63, 64, 65, 66, 67, 68, 74, 76, 77, 78, 80, 82, 86, 92, 97, 98, 100, 102, 231, and 232.

[Claim 4]

The antisense oligomer or the pharmaceutically acceptable salt thereof, or hydrate thereof according to any one of claims 1 to 3, wherein the antisense oligomer consists of any one base sequence selected from the group consisting of SEQ ID NOs: 27, 28, 35, 40, 41, 43, 45, 46, 47, 50, 51, 52, 54, 55, 59, 63, 64, 65, 66, 68, 74, 76, 77, 78, and 102.

[Claim 5]

The antisense oligomer or the pharmaceutically acceptable salt thereof, or hydrate thereof according to any

one of claims 1 to 4, wherein the antisense oligomer is an oligonucleotide.

[Claim 6]

The antisense oligomer or the pharmaceutically acceptable salt thereof, or hydrate thereof according to claim 5, wherein the sugar moiety and/or the phosphate bond moiety of at least one nucleotide constituting the oligonucleotide is modified.

[Claim 7]

The antisense oligomer or the pharmaceutically acceptable salt thereof, or hydrate thereof according to claim 5 or 6, wherein the sugar moiety of at least one nucleotide constituting the oligonucleotide is a ribose in which the 2'-OH group is replaced by any one 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 is an alkyl or an aryl and R' is an alkylene).

[Claim 8]

The antisense oligomer or the pharmaceutically acceptable salt thereof, or hydrate thereof according to any one of claims 5 to 7, wherein the phosphate bond moiety of at least one nucleotide constituting the oligonucleotide is any one selected from the group consisting of a phosphorothioate bond, a phosphorodithioate bond, an alkylphosphonate bond, a

phosphoramidate bond and a boranophosphate bond.

[Claim 9]

The antisense oligomer or the pharmaceutically acceptable salt thereof, or hydrate thereof according to any one of claims 1 to 4, wherein the antisense oligomer is a morpholino oligomer.

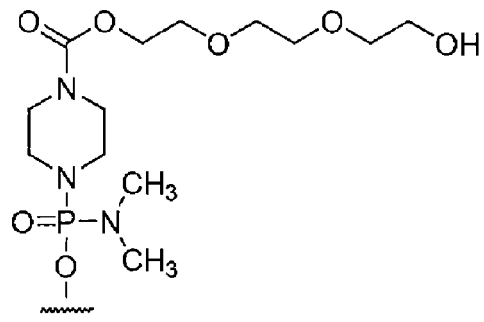
[Claim 10]

The antisense oligomer or the pharmaceutically acceptable salt thereof, or hydrate thereof according to claim 9, wherein the antisense oligomer is a phosphorodiamidate morpholino oligomer.

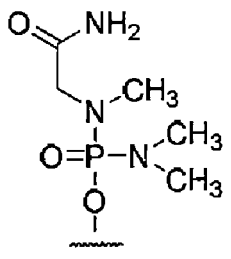
[Claim 11]

The antisense oligomer or the pharmaceutically acceptable salt thereof, or hydrate thereof according to claim 9 or 10, wherein the 5' end is any one of chemical formulae (1) to (3) below:

[Formula 15]



(1)



(2)

(3)

[Claim 12]

A pharmaceutical composition comprising the antisense oligomer or the pharmaceutically acceptable salt thereof, or hydrate thereof according to any one of claims 1 to 11, and a suppressor antisense oligomer or a pharmaceutically acceptable salt thereof, or hydrate thereof which suppresses single skipping of any one exon selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA,

the suppressor antisense oligomer comprising a base sequence complementary to

any one base sequence of a base sequence selected from the group consisting of SEQ ID NOs: 370 to 384, wherein the suppressor antisense oligomer consists of

(1) any one base sequence selected from the group consisting of SEQ ID NOs: 257 to 275, or (2) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 257 to 275, and has a length within ±15% of the length of the any one base sequence selected.

[Claim 13]

The pharmaceutical composition according to claim 12, wherein the suppressor antisense oligomer consists of any one base sequence selected from the group consisting of SEQ ID NOs: 260, 261, and 263.

[Claim 14]

The pharmaceutical composition according to claim 12 or

13, wherein

(1) the antisense oligomer is an oligomer consisting of SEQ ID NO: 75, and the suppressor antisense oligomer is an oligomer consisting of SEQ ID NO: 260,

(2) the antisense oligomer is an oligomer consisting of SEQ ID NO: 75, and the suppressor antisense oligomer is an oligomer consisting of SEQ ID NO: 261, or

(3) the antisense oligomer is an oligomer consisting of SEQ ID NO: 75, and the suppressor antisense oligomer is an oligomer consisting of SEQ ID NO: 263.

[Claim 15]

A pharmaceutical composition comprising (i) an antisense oligomer or a pharmaceutically acceptable salt thereof, or hydrate thereof which causes simultaneous skipping of any two or more numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA, and (ii) a suppressor antisense oligomer or a pharmaceutically acceptable salt thereof, or hydrate thereof which suppresses single skipping of any one exon selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA, wherein

(1) the antisense oligomer is an oligomer consisting of SEQ ID NO: 75, and the suppressor antisense oligomer is an oligomer consisting of SEQ ID NO: 262, or

(2) the antisense oligomer is an oligomer consisting of SEQ ID NO: 73, and the suppressor antisense oligomer is an oligomer consisting of SEQ ID NO: 260.

[Claim 16]

The pharmaceutical composition according to any one of claims 12 to 15, wherein the suppressor antisense oligomer is an oligonucleotide.

[Claim 17]

The pharmaceutical composition according to claim 16, wherein the sugar moiety and/or the phosphate bond moiety of at least one nucleotide constituting the oligonucleotide is modified.

[Claim 18]

The pharmaceutical composition according to claim 16 or 17, wherein the sugar moiety of at least one nucleotide constituting the oligonucleotide is a ribose in which the 2'-OH group is replaced by any one 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 is an alkyl or an aryl and R' is an alkylene).

[Claim 19]

The pharmaceutical composition according to any one of claims 16 to 18, wherein the phosphate bond moiety of at least one nucleotide constituting the oligonucleotide is any one

selected from the group consisting of a phosphorothioate bond, a phosphorodithioate bond, an alkylphosphonate bond, a phosphoramidate bond and a boranophosphate bond.

[Claim 20]

The pharmaceutical composition according to any one of claims 12 to 13, wherein the suppressor antisense oligomer is a morpholino oligomer.

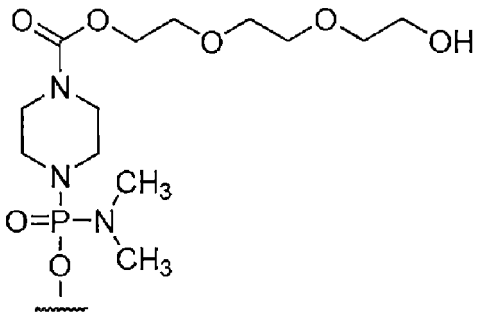
[Claim 21]

The pharmaceutical composition according to claim 20, wherein the suppressor antisense oligomer is a phosphorodiamidate morpholino oligomer.

[Claim 22]

The pharmaceutical composition according to claim 20 or 21, wherein the 5' end is any one of chemical formulae (1) to (3) below:

[Formula 16]



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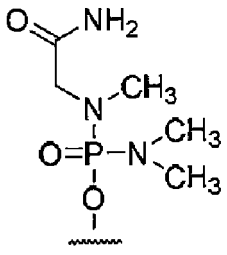

(2)

(3)

[Claim 23]

A pharmaceutical composition comprising the antisense

oligomer or the pharmaceutically acceptable salt thereof, or hydrate thereof according to any one of claims 1 to 11.

[Claim 24]

The pharmaceutical composition according to any one of claims 12 to 23, further comprising a pharmaceutically acceptable carrier.

[Claim 25]

The pharmaceutical composition according to any one of claims 12 to 23 for use as a medicament.

[Claim 26]

Use of the antisense oligomer or the pharmaceutically acceptable salt thereof, or hydrate thereof according to any one of claims 1 to 11, or the pharmaceutical composition according to any one of claims 23 to 24 in manufacturing of a medicament in the treatment of muscular dystrophy.

[Claim 27]

The use according to claim 26, wherein the medicament is to be administered to a human patient.

[Claim 28]

The use according to claim 26 or 27, wherein the medicament causes skipping of any two or more numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA.