

CLAIMS

1. A single-stranded oligonucleotide that is 10-80 nucleosides in length and having a nucleobase sequence comprising a portion of 10 contiguous nucleobases having at least 80% complementary to an equal length portion of a target region of a human PCDH19 gene, a pre-mRNA transcript thereof and/or an mRNA transcript thereof.
2. The oligonucleotide of claim 1, wherein the target region is within the nucleotide sequence set forth in SEQ ID NO:1 or a variant thereof having at least or about 80% sequence identity thereto.
3. The oligonucleotide of claim 1 or 2, wherein the mRNA transcript or pre-mRNA transcript includes at least one PCDH19 mutation.
4. The oligonucleotide of claim 3, wherein the at least one PCDH19 mutation is selected from mutations that encode N340S, E307K, V441E, Q85X, N557K, D594H, S671X, L677fsx717, I119fsX122, and P364fsX375 or is a mutation selected from Table 1.
5. The oligonucleotide of claim 3 or 4, wherein the oligonucleotide selectively hybridizes to the mRNA transcript or pre-mRNA transcript that includes the at least one PCDH19 mutation over a wild-type mRNA transcript or pre-mRNA transcript.
6. The oligonucleotide of any one of claims 1 to 5, wherein the oligonucleotide consists of 12 to 40 nucleobases, 16 to 30 nucleobases, or 18 to 22 nucleobases.
7. The oligonucleotide of any one of claims 1 to 6, wherein the oligonucleotide comprises:
 - (a) a gap segment comprising linked deoxyribonucleosides;
 - (b) a 5' wing segment comprising linked nucleosides; and
 - (c) a 3' wing segment comprising linked nucleosides;wherein the gap segment comprises a region of at least 10 contiguous nucleobases having at least 80% complementarity to an equal length portion of the target region of the pre-mRNA transcript or the mRNA transcript of the human PCDH19 gene positioned between the 5' wing segment and the 3' wing segment; wherein the 5' wing segment and the 3' wing segment

each comprises at least two linked nucleosides; and wherein at least one nucleoside of each wing segment comprises an alternative nucleoside.

8. The oligonucleotide of any one of claims 1 to 7, wherein the oligonucleotide comprises at least one alternative internucleoside linkage, at least one alternative nucleobase and/or at least one alternative sugar moiety.

9. The oligonucleotide of claim 8, wherein the at least one alternative internucleoside linkage selected from a phosphorothioate internucleoside linkage, a 2'-alkoxy internucleoside linkage or an alkyl phosphate internucleoside linkage.

10. The oligonucleotide of claim 8, wherein the alternative nucleobase is 5'-methylcytosine, pseudouridine, or 5-methoxyuridine.

11. The oligonucleotide of claim 8, wherein the alternative sugar moiety is 2'-OMe modified sugar moiety or a bicyclic sugar moiety.

12. The oligonucleotide of any one of claims 1 to 11, wherein the oligonucleotide further comprises a ligand conjugated to the 5' end or the 3' end of the oligonucleotide through a monovalent or branched bivalent or trivalent linker.

13. The oligonucleotide of any one of claims 1 to 12, wherein the oligonucleotide comprises a region complementary to at least 17 or at least 19 contiguous nucleotides of a PCDH19 gene.

14. The oligonucleotide of any one of claims 1 to 13, wherein the oligonucleotide comprises a sequence set forth in any one of SEQ ID NOs: 2 to 385.

15. A pharmaceutical composition comprising an oligonucleotide of any one of claims 1 to 14 and a pharmaceutically acceptable carrier or excipient.

16. The composition of claim 15, comprising a lipid nanoparticle, a polyplex nanoparticle, a lipoplex nanoparticle, or a liposome.

17. Use of an oligonucleotide of any one of claims 1 to 14 or a pharmaceutical composition of claim 15 or 16 in the manufacture of a medicament for treating, preventing, or delaying the progression of a PCDH19 related disorder in a subject in need thereof, or of inhibiting transcription or reducing a level and/or activity of PCDH19 in a cell of a subject having a PCDH19 related disorder, wherein the oligonucleotide or pharmaceutical composition is to be administered to the subject in an amount and for a duration sufficient to treat, prevent, or delay the progression of the PCDH19 related disorder, obtain degradation of an mRNA transcript of the PCDH19 gene, or reduce the level and/or activity of PCDH19 in the cell.
18. The use of claim 17, wherein the cell is a cell of the central nervous system.
19. The use of claim 17 or 18, wherein the PCDH19 related disorder is selected from the group consisting of epilepsy, schizophrenia, and autism.
20. The use of any one of claims 17 to 19, wherein the subject has a mutation in at least one allele of the PCDH19 gene.
21. The use of claim 20, wherein the oligonucleotide selectively reduces expression of the allele comprising the mutation relative to an allele not comprising the mutation, or wherein the oligonucleotide reduces expression of the allele comprising the mutation and an allele comprising a wild-type sequence.
22. The use of claim 20, wherein the mutation is a missense mutation, a nonsense mutation or a frameshift mutation.
23. The use of any one of claims 17 to 22, wherein administration of the oligonucleotide or pharmaceutical composition reduces one or more symptoms of the PCDH19 related disorder.
24. The use of claim 23, wherein the one or more symptoms of the PCDH19 related disorder is selected from the group consisting of prolonged seizures, frequent seizures, behavioral and developmental delays, movement and balance issues, orthopedic conditions, delayed language and speech issues, growth and nutrition issues, sleeping difficulties, chronic infection, sensory integration disorder, disruption of the autonomic nervous system, and sweating.