

ANTISENSE OLIGOMERS FOR TREATMENT OF AUTOSOMAL DOMINANT MENTAL RETARDATION-5 AND DRAVET SYNDROME

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/267,251, filed December 14, 2015, which application is incorporated herein by reference.

REFERENCE TO A SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been filed electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on December 12, 2016, is named 47991_708_601_SL.txt and is 1,460,063 bytes in size.

BACKGROUND OF THE INVENTION

[0003] Mental retardation is the most prevalent handicap of children affecting 1 to 3% of the population. Autosomal Dominant Mental Retardation-5 (MRD5) is a prevalent nonsyndromic form of the disorder characterized by the lack of associated morphologic, radiologic, and metabolic features. A case study identified de novo genetic lesions in the *SYNGAP1* gene that result in the production of truncated proteins in approximately 3% of patients with unexplained nonsyndromic mental retardation. SYNGAP1 is a GTPase-activating enzyme that is selectively expressed in the brain and required for normal development (Hamden, *et al.*, 2009, NEJM 360: 599-605).

[0004] Dravet Syndrome (DS), also known as severe myoclonic epilepsy of infancy or SMEI, was first described by Dravet in 1978. It is a childhood epilepsy characterized by an onset of seizures during the first year of life that do not remit. Mutations in the *SCN1A* gene, which is part of the *SCN1A-SCN2A-SCN3A* gene cluster that encodes alpha-pore forming subunits of the neuronal voltage gated sodium channel, are associated with development of the disease (Miller, *et al.*, 1993-2015, GeneReviews, Eds. Pagon RA, *et al.* Seattle (WA): University of Washington, Seattle, Bookshelf ID: NBK1318, and Mulley, *et al.*, 2005, Hum. Mutat. 25: 535-542).

SUMMARY

[0004a] In one aspect, provided herein is a pharmaceutical composition comprising an antisense oligomer (ASO), wherein the ASO is complementary to a targeted portion of a retained-intron-containing pre-mRNA (RIC pre-mRNA) that encodes SCN1A protein, wherein the RIC pre-mRNA comprises a retained intron, an exon flanking 5' splice site of the retained intron, and an exon flanking 3' splice site of the retained intron, and wherein binding of the ASO to the RIC pre-mRNA will cause a retained intron to be constitutively spliced from the RIC pre-mRNA in cells that express the RIC pre-mRNA, thereby increasing the level of functional RNA encoding SCN1A protein in the cells.

[0004b] In another aspect, provided herein is a pharmaceutical composition as described herein for use as a medicament.

[0004c] In another aspect, provided herein is a use of a pharmaceutical composition as described herein in the manufacture of a medicament for treating Dravet Syndrome (DS) in a subject.

[0005] Disclosed herein, in some examples, are methods of treating a Autosomal Dominant Mental Retardation 5 (MRD5) or Dravet Syndrome (DS) in a subject in need thereof, by increasing the expression of a target protein or functional RNA by cells of the subject, wherein the cells have a retained-intron-containing pre-mRNA (RIC pre-mRNA), the RIC pre-mRNA comprising a retained intron, an exon flanking the 5' splice site, an exon flanking the 3' splice site, and wherein the RIC pre-mRNA encodes the target protein or functional RNA, the method comprising contacting the cells of the subject with an antisense oligomer (ASO) complementary to a targeted portion of the RIC pre-mRNA encoding the target protein or functional RNA, whereby the retained intron is constitutively spliced from the RIC pre-mRNA encoding the target protein or functional RNA, thereby increasing the level of mRNA encoding the target

protein or functional RNA, and increasing the expression of the target protein or functional RNA in the cells of the subject.

[0006] Disclosed herein, in some examples, are methods of increasing expression of a target protein, wherein the target protein is SYNGAP1 or SCN1A, by cells having a retained-intron-containing pre-mRNA (RIC pre-mRNA), the RIC pre-mRNA comprising a retained intron, an exon flanking the 5' splice site of the retained intron, an exon flanking the 3' splice site of the retained intron, and wherein the RIC pre-mRNA encodes SYNGAP1 or SCN1A protein, the method comprising contacting the cells with an antisense oligomer (ASO) complementary to a targeted portion of the RIC pre-mRNA encoding SYNGAP1 or SCN1A protein, whereby the retained intron is constitutively spliced from the RIC pre-mRNA encoding SYNGAP1 or SCN1A protein, thereby increasing the level of mRNA encoding SYNGAP1 or SCN1A protein, and increasing the expression of SYNGAP1 or SCN1A protein in the cells.

[0007] In some examples of any of the aforementioned methods, the method is a method of treating MRD5 and the target protein is SYNGAP1, or the method is a method of treating DS and the target protein is SCN1A. In some examples, the target protein or the functional RNA is a compensating protein or a compensating functional RNA that functionally augments or replaces a target protein or functional RNA that is deficient in amount or activity in the subject. In some examples, the cells are in or from a subject having a condition caused by a deficient amount or activity of SYNGAP1 or SCN1A protein. In some examples, the deficient amount of the target protein is caused by haploinsufficiency of the target protein, wherein the subject has a first allele encoding a functional target protein, and a second allele from which the target protein is not produced, or a second allele encoding a nonfunctional target protein, and wherein the antisense oligomer binds to a targeted portion of a RIC pre-mRNA transcribed from the first allele. In some examples, the subject has a condition caused by a disorder resulting from a deficiency in the amount or function of the target protein, wherein the subject has (a) a first mutant allele from which (i) the target protein is produced at a reduced level compared to production from a wild-type allele, (ii) the target protein is produced in a form having reduced function compared to an equivalent wild-type protein, or (iii) the target protein is not produced, and (b) a second mutant allele from which (i) the target protein is produced at a reduced level compared to production from a wild-type allele, (ii) the target protein is produced in a form having reduced function compared to an equivalent wild-type protein, or (iii) the target protein is not produced, and wherein when the subject has a first mutant allele (a)(iii), the second mutant allele is (b)(i) or (b)(ii), and wherein when the subject has a second mutant allele (b)(iii), the first mutant allele is (a)(i) or (a)(ii), and wherein the RIC pre-mRNA is transcribed from either the first mutant allele that is (a)(i) or (a)(ii), and/or the second allele that is (b)(i) or (b)(ii). In some examples, the target protein is produced in a form having reduced function compared to the equivalent wild-type protein. In some examples, the target protein is produced in a form that is fully-functional compared to the equivalent wild-type protein.

[0008] In some examples of any of the aforementioned methods, the targeted portion of the RIC pre-mRNA is in the retained intron within the region +6 relative to the 5' splice site of the retained intron to -16 relative to the 3' splice site of the retained intron. In some examples, the targeted portion of the

RIC pre-mRNA is in the retained intron within: (a) the region +6 to +499 relative to the 5' splice site of the retained intron; or (b) the region -16 to -496 relative to the 3' splice site of the retained intron. In some examples, the targeted portion of the RIC pre-mRNA is within: (a) the region +2e to -4e in the exon flanking the 5' splice site of the retained intron; or (b) the region +2e to -4e in the exon flanking the 3' splice site of the retained intron. In some examples, the targeted portion of the RIC pre-mRNA is within: (a) the region -4e to -1,054e relative to the 5' splice site of the retained intron; (b) the region +6 to +499 relative to the 5' splice site of the retained intron; (c) the region -16 to -496 relative to the 3' splice site of the retained intron; or (d) the region +2e to +1,912e relative to the 3' splice site of the retained intron.

[0009] In some examples of any of the aforementioned methods, the target protein is SCN1A. In some examples, the RIC pre-mRNA comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 4-7. In some examples, the RIC pre-mRNA is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to SEQ ID NO: 1. In some examples, the targeted portion of the RIC pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleic acids of SEQ ID NO: 2593. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 10-1037. In some examples, the targeted portion of the RIC pre-mRNA is within the region -264e to +496 relative to the 5' splice site of the retained intron 21 or within the region -496 to +37e relative to the 3' splice site of the retained intron 21. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 10-266 or 524-1037. In some examples, the targeted portion of the RIC pre-mRNA is within the region -264e to -4e relative to the 5' splice site of the retained intron 21. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 10-62, 524-576, or 781-833. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 21 within the region +6 to +496 relative to the 5' splice site of the retained intron 21. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 63-162, 577-675, or 834-932. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 21 within the region -16 to -496 relative to the 3' splice site of the retained intron 21. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 163-258, 676-772, or 933-1029. In some examples, the targeted portion of the RIC pre-mRNA is within the region +2e to +37e relative to the 3' splice site of the retained intron 21. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 259-266, 773-780, or 1030-1037.

[0010] In some examples of any of the aforementioned methods, the target protein is SCN1A. In some examples, the targeted portion of the RIC pre-mRNA is within the region -264e to +496 relative to the 5' splice site of the retained intron 23 or within the region -496 to +37e relative to the 3' splice site

of the retained intron 23. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 267-523. In some examples, the targeted portion of the RIC pre-mRNA is within the region -264e to -4e relative to the 5' splice site of the retained intron 23. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 267-319. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 23 within the region +6 to +496 relative to the 5' splice site of the retained intron 23. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 320-418. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 23 within the region -16 to -496 relative to the 3' splice site of the retained intron 23. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 419-515. In some examples, the targeted portion of the RIC pre-mRNA is within the region +2e to +37e relative to the 3' splice site of the retained intron 23. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 516-523.

[0011] In some examples of any of the aforementioned methods, the target protein is SYNGAP1. In some examples, the RIC pre-mRNA comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 8 or 9. In some examples, the RIC pre-mRNA is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to SEQ ID NO: 2 or 3. In some examples, the targeted portion of the RIC pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleic acids of SEQ ID NO: 2592, 2594, or 2595. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1038-2591. In some examples, the targeted portion of the RIC pre-mRNA is within the region -73e to +499 relative to the 5' splice site of the retained intron 18 or within the region -496 to +1,912e relative to the 3' splice site of the retained intron 19. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1038-1509 or 1815- 2286. In some examples, the targeted portion of the RIC pre-mRNA is within the region -73e to -4e relative to the 5' splice site of the retained intron 18. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1038-1050 or 1815-1827. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 18 within the region +6 to +499 relative to the 5' splice site of the retained intron 18. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1051-1136 or 1828-1913. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 19 within the region -16 to -496 relative to the 3' splice site of the retained intron 19. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1137-1228 or 1914-2005. In some examples, the

targeted portion of the RIC pre-mRNA is within the region +17e to +1,912e relative to the 3' splice site of the retained intron 19. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1229-1509 or 2006-2286.

[0012] In some examples of any of the aforementioned methods, the target protein is SYNGAP1. In some examples, the targeted portion of the RIC pre-mRNA is within the region -1,054e to +251 relative to the 5' splice site of the retained intron 15 or within the region -256 to +157e relative to the 3' splice site of the retained intron 15. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1510-1814 or 2287-2591. In some examples, the targeted portion of the RIC pre-mRNA is within the region -4e to -1,054e relative to the 5' splice site of the retained intron 15. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1510-1686 or 2287-2463. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 15 within the region +6 to +251 relative to the 5' splice site of the retained intron 15. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1687-1736 or 2464-2513. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 15 within the region -16 to -256 relative to the 3' splice site of the retained intron 15. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1737-1785 or 2514-2562. In some examples, the targeted portion of the RIC pre-mRNA is within the region +2e to +157e relative to the 3' splice site of the retained intron 15. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1786-1814 or 2563-2591.

[0013] In some examples of any of the aforementioned methods, the antisense oligomer does not increase the amount of the target protein or the functional RNA by modulating alternative splicing of pre-mRNA transcribed from a gene encoding the functional RNA or target protein. In some examples, the antisense oligomer does not increase the amount of the target protein or the functional RNA by modulating aberrant splicing resulting from mutation of the gene encoding the target protein or the functional RNA. In some examples, the RIC pre-mRNA was produced by partial splicing of a full-length pre-mRNA or partial splicing of a wild-type pre-mRNA. In some examples, the mRNA encoding the target protein or functional RNA is a full-length mature mRNA, or a wild-type mature mRNA. In some examples, the target protein produced is full-length protein, or wild-type protein. In some examples, the total amount of the mRNA encoding the target protein or functional RNA produced in the cell contacted with the antisense oligomer is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least

about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the total amount of the mRNA encoding the target protein or functional RNA produced in a control cell. In some examples, the total amount of target protein produced by the cell contacted with the antisense oligomer is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the total amount of target protein produced by a control cell.

[0014] In some examples of any of the aforementioned methods, the antisense oligomer comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage. In some examples, the antisense oligomer comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl, a 2'-Fluoro, or a 2'-O-methoxyethyl moiety. In some examples, the antisense oligomer comprises at least one modified sugar moiety. In some examples, each sugar moiety is a modified sugar moiety. In some examples, the antisense oligomer consists of from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases. In some examples, the antisense oligomer is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, complementary to the targeted portion of the RIC pre-mRNA encoding the protein.

[0015] In some examples of any of the aforementioned methods, the cell comprises a population of RIC pre-mRNAs transcribed from the gene encoding the target protein or functional RNA, wherein the population of RIC pre-mRNAs comprises two or more retained introns, and wherein the antisense oligomer binds to the most abundant retained intron in the population of RIC pre-mRNAs. In some examples, the binding of the antisense oligomer to the most abundant retained intron induces splicing out of the two or more retained introns from the population of RIC pre-mRNAs to produce mRNA encoding the target protein or functional RNA. In some examples, the cell comprises a population of RIC pre-mRNAs transcribed from the gene encoding the target protein or functional RNA, wherein the population of RIC pre-mRNAs comprises two or more retained introns, and wherein the antisense

oligomer binds to the second most abundant retained intron in the population of RIC pre-mRNAs. In some examples, the binding of the antisense oligomer to the second most abundant retained intron induces splicing out of the two or more retained introns from the population of RIC pre-mRNAs to produce mRNA encoding the target protein or functional RNA. In some examples, the method further comprises assessing SYNGAP1 or SCN1A protein expression.

[0016] In some examples of any of the aforementioned methods, the MRD5 is treated and wherein the antisense oligomer binds to a targeted portion of a *SYNGAP1* RIC pre-mRNA, wherein the targeted portion is within a sequence selected from SEQ ID NOs: 1038-2591, or wherein DS is treated and wherein the antisense oligomer binds to a targeted portion of a *SCN1A* RIC pre-mRNA, wherein the targeted portion is within a sequence selected from SEQ ID NOs: 10-1037. In some examples, the subject is a human. In some examples, the subject is a non-human animal. In some examples, the subject is a fetus, an embryo, or a child. In some examples, the cells are *ex vivo*. In some examples, the antisense oligomer is administered by intrathecal injection, intracerebroventricular injection, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection of the subject. In some examples, the 9 nucleotides at -3e to -1e of the exon flanking the 5' splice site and +1 to +6 of the retained intron, are identical to the corresponding wild-type sequence. In some examples, the 16 nucleotides at -15 to -1 of the retained intron and +1e of the exon flanking the 3' splice site are identical to the corresponding wild-type sequence. Disclosed herein, in some examples, are antisense oligomers as described in any of the aforementioned methods.

[0017] Disclosed herein, in some examples, are antisense oligomers comprising a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 10-2591.

[0018] Also disclosed herein, in some examples, are pharmaceutical compositions comprising the antisense oligomer of claim 90 or 91 and a pharmaceutically acceptable excipient, diluent, or carrier.

[0019] Disclosed herein, in some examples, are methods of treating a subject in need thereof, by administering the pharmaceutical composition of claim 92 by intrathecal injection, intracerebroventricular injection, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection.

[0020] Disclosed herein, in some examples, are compositions comprising an antisense oligomer for use in a method of increasing expression of a target protein or a functional RNA by cells to treat MRD5 or DS in a subject in need thereof, associated with a deficient protein or deficient functional RNA, wherein the deficient protein or deficient functional RNA is deficient in amount or activity in the subject, wherein the antisense oligomer enhances constitutive splicing of a retained intron-containing pre-mRNA (RIC pre-mRNA) encoding the target protein or the functional RNA, wherein the target protein is: (a) the deficient protein; or (b) a compensating protein which functionally augments or replaces the deficient protein or in the subject; and wherein the functional RNA is: (c) the deficient RNA; or (d) a compensating functional RNA which functionally augments or replaces the deficient functional RNA in the subject; wherein the RIC pre-mRNA comprises a retained intron, an exon flanking the 5' splice site and an exon flanking the 3' splice site, and wherein the retained intron is spliced from the RIC pre-mRNA encoding the

target protein or the functional RNA, thereby increasing production or activity of the target protein or the functional RNA in the subject.

[0021] Disclosed herein, in some examples, are compositions comprising an antisense oligomer for use in a method of treating a condition associated with SYNGAP1 or SCN1A protein in a subject in need thereof, the method comprising the step of increasing expression of SYNGAP1 or SCN1A protein by cells of the subject, wherein the cells have a retained-intron-containing pre-mRNA (RIC pre-mRNA) comprising a retained intron, an exon flanking the 5' splice site of the retained intron, an exon flanking the 3' splice site of the retained intron, and wherein the RIC pre-mRNA encodes the SYNGAP1 or SCN1A protein, the method comprising contacting the cells with the antisense oligomer, whereby the retained intron is constitutively spliced from the RIC pre-mRNA transcripts encoding SYNGAP1 or SCN1A protein, thereby increasing the level of mRNA encoding SYNGAP1 or SCN1A protein, and increasing the expression of SYNGAP1 or SCN1A protein, in the cells of the subject. In some examples, the condition is a disease or disorder. In some examples, the disease or disorder is AD mental retardation 5 or Dravet syndrome. In some examples, the target protein and RIC pre-mRNA are encoded by the *SYNGAP1* or *SCN1A* gene. In some examples, the antisense oligomer targets a portion of the RIC pre-mRNA that is in the retained intron within the region +6 relative to the 5' splice site of the retained intron to -16 relative to the 3' splice site of the retained intron. In some examples, the antisense oligomer targets a portion of the RIC pre-mRNA that is in the retained intron within: (a) the region +6 to +499 relative to the 5' splice site of the retained intron; or (b) the region -16 to -496 relative to the 3' splice site of the retained intron. In some examples, the antisense oligomer targets a portion of the RIC pre-mRNA that is within the region about 100 nucleotides downstream of the 5' splice site of the at least one retained intron, to about 100 nucleotides upstream of the 3' splice site of the at least one retained intron. In some examples, the targeted portion of the RIC pre-mRNA is within: (a) the region +2e to -4e in the exon flanking the 5' splice site of the retained intron; or (b) the region +2e to -4e in the exon flanking the 3' splice site of the retained intron. In some examples, the targeted portion of the RIC pre-mRNA is within: (a) the region -4e to -1,054e relative to the 5' splice site of the retained intron; (b) the region +6 to +499 relative to the 5' splice site of the retained intron; (c) the region -16 to -496 relative to the 3' splice site of the retained intron; or (d) the region +2e to +1,912e relative to the 3' splice site of the retained intron.

[0022] In some examples of any of the aforementioned compositions, the target protein is SCN1A. In some examples, the RIC pre-mRNA comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 4-7. In some examples, the RIC pre-mRNA is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to SEQ ID NO: 1. In some examples, the targeted portion of the RIC pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleic acids of SEQ ID NO: 2593. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 10-1037. In some examples, the targeted portion of the RIC pre-mRNA is

within the region -264e to +496 relative to the 5' splice site of the retained intron 21 or within the region -496 to +37e relative to the 3' splice site of the retained intron 21. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 10-266 or 524-1037. In some examples, the targeted portion of the RIC pre-mRNA is within the region -264e to -4e relative to the 5' splice site of the retained intron 21. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 10-62, 524-576, or 781-833. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 21 within the region +6 to +496 relative to the 5' splice site of the retained intron 21. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 63-162, 577-675, or 834-932. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 21 within the region -16 to -496 relative to the 3' splice site of the retained intron 21. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 163-258, 676-772, or 933-1029. In some examples, the targeted portion of the RIC pre-mRNA is within the region +2e to +37e relative to the 3' splice site of the retained intron 21. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 259-266, 773-780, or 1030-1037.

[0023] In some examples of any of the aforementioned compositions, the target protein is SCN1A. In some examples, the targeted portion of the RIC pre-mRNA is within the region -264e to +496 relative to the 5' splice site of the retained intron 23 or within the region -496 to +37e relative to the 3' splice site of the retained intron 23. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 267-523. In some examples, the targeted portion of the RIC pre-mRNA is within the region -264e to -4e relative to the 5' splice site of the retained intron 23. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 267-319. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 23 within the region +6 to +496 relative to the 5' splice site of the retained intron 23. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 320-418. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 23 within the region -16 to -496 relative to the 3' splice site of the retained intron 23. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 419-515. In some examples, the targeted portion of the RIC pre-mRNA is within the region +2e to +37e relative to the 3' splice site of the retained intron 23. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 516-523.

[0024] In some examples of any of the aforementioned compositions, the target protein is SYNGAP1. In some examples, the RIC pre-mRNA comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 8 or 9. In some

examples, the RIC pre-mRNA is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to SEQ ID NO: 2 or 3. In some examples, the targeted portion of the RIC pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleic acids of SEQ ID NO: 2592, 2594, or 2595. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1038-2591. In some examples, the targeted portion of the RIC pre-mRNA is within the region -73e to +499 relative to the 5' splice site of the retained intron 18 or within the region -496 to +1,912e relative to the 3' splice site of the retained intron 19. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1038-1509 or 1815-2286. In some examples, the targeted portion of the RIC pre-mRNA is within the region -73e to -4e relative to the 5' splice site of the retained intron 18. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1038-1050 or 1815-1827. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 18 within the region +6 to +499 relative to the 5' splice site of the retained intron 18. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1051-1136 or 1828-1913. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 19 within the region -16 to -496 relative to the 3' splice site of the retained intron 19. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1137-1228 or 1914-2005. In some examples, the targeted portion of the RIC pre-mRNA is within the region +17e to +1,912e relative to the 3' splice site of the retained intron 19. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1229-1509 or 2006-2286.

[0025] In some examples of any of the aforementioned compositions, the target protein is SYNGAP1. In some examples, the targeted portion of the RIC pre-mRNA is within the region -1,054e to +251 relative to the 5' splice site of the retained intron 15 or within the region -256 to +157e relative to the 3' splice site of the retained intron 15. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1510-1814 or 2287-2591. In some examples, the targeted portion of the RIC pre-mRNA is within the region -4e to -1,054e relative to the 5' splice site of the retained intron 15. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1510-1686 or 2287-2463. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 15 within the region +6 to +251 relative to the 5' splice site of the retained intron 15. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1687-1736 or 2464-2513. In some examples, the targeted portion of the RIC pre-mRNA is in retained intron 15 within the region -16 to -256 relative to the 3' splice site of the retained intron 15. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to

any one of SEQ ID NOs: 1737-1785 or 2514-2562. In some examples, the targeted portion of the RIC pre-mRNA is within the region +2e to +157e relative to the 3' splice site of the retained intron 15. In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1786-1814 or 2563-2591.

[0026] In some examples of any of the aforementioned compositions, the antisense oligomer does not increase the amount of target protein or functional RNA by modulating alternative splicing of the pre-mRNA transcribed from a gene encoding the target protein or functional RNA. In some examples, the antisense oligomer does not increase the amount of the functional RNA or functional protein by modulating aberrant splicing resulting from mutation of the gene encoding the target protein or functional RNA. In some examples, the RIC pre-mRNA was produced by partial splicing from a full-length pre-mRNA or a wild-type pre-mRNA. In some examples, the mRNA encoding the target protein or functional RNA is a full-length mature mRNA, or a wild-type mature mRNA. In some examples, the target protein produced is full-length protein, or wild-type protein. In some examples, the retained intron is a rate-limiting intron. In some examples, the retained intron is the most abundant retained intron in said RIC pre-mRNA. In some examples, the retained intron is the second most abundant retained intron in said RIC pre-mRNA.

[0027] In some examples of any of the aforementioned compositions, the antisense oligomer comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage. In some examples, the antisense oligomer is an antisense oligonucleotide. In some examples, the antisense oligomer comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl, a 2'-Fluoro, or a 2'-O-methoxyethyl moiety. In some examples, the antisense oligomer comprises at least one modified sugar moiety. In some examples, each sugar moiety is a modified sugar moiety. In some examples, the antisense oligomer consists of from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases.

[0028] Disclosed herein, in some examples, are pharmaceutical compositions comprising the antisense oligomer of any of the compositions of claims 94 to 167, and a pharmaceutically acceptable excipient, diluent, or carrier. Also disclosed herein, in some examples, are methods of treating a subject in need thereof, by administering the pharmaceutical composition of claim 168 by intrathecal injection, intracerebroventricular injection, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection.

[0029] Disclosed herein, in some examples, are pharmaceutical compositions comprising: an antisense oligomer that hybridizes to a target sequence of a *SCN1A* or *SYNGAPI* mRNA transcript, wherein the *SCN1A* or *SYNGAPI* mRNA transcript comprises a retained intron, wherein the antisense oligomer induces splicing out of the retained intron from the *SCN1A* or *SYNGAPI* mRNA transcript; and a pharmaceutically acceptable excipient, diluent, or carrier. In some examples, the *SCN1A* or *SYNGAPI* mRNA transcript is a *SCN1A* or *SYNGAPI* RIC pre-mRNA transcript. In some examples, the targeted portion of the *SCN1A* or *SYNGAPI* RIC pre-mRNA transcript is in the retained intron within the region +500 relative to the 5' splice site of the retained intron to -500 relative to the 3' spliced site of the retained intron. In some examples, the *SCN1A* or *SYNGAPI* RIC pre-mRNA transcript is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to any one of SEQ ID NOs: 1-3. In some examples, the *SCN1A* or *SYNGAPI* RIC pre-mRNA transcript comprises a sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to any one of SEQ ID NOs: 4-9. In some examples, the antisense oligomer comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage. In some examples, the antisense oligomer is an antisense oligonucleotide. In some examples, the antisense oligomer comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl, a 2'-Fluoro, or a 2'-O-methoxyethyl moiety. In some examples, the antisense oligomer comprises at least one modified sugar moiety. In some examples, the antisense oligomer comprises from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases. In some examples, the antisense oligomer is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or is 100% complementary to a targeted portion of the *SCN1A* or *SYNGAPI* RIC pre-mRNA transcript. In some examples, the targeted portion of the *SCN1A* or *SYNGAPI* RIC pre-mRNA transcript is within a sequence selected from SEQ ID NOs: 2592-2595. In some examples, the antisense oligomer comprises a nucleotide sequence that is at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 10-2591. In some examples, the antisense oligomer comprises a nucleotide sequence selected from SEQ ID NOs: 10-2591. In some examples, the pharmaceutical composition is formulated for intrathecal injection, intracerebroventricular injection, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection.

[0030] Disclosed herein, in some examples, are methods of inducing processing of a deficient *SCN1A* or *SYNGAPI* mRNA transcript to facilitate removal of a retained intron to produce a fully

processed *SCN1A* or *SYNGAP1* mRNA transcript that encodes a functional form of a SCN1A or SYNGAP1 protein, the method comprising: (a) contacting an antisense oligomer to a target cell of a subject; (b) hybridizing the antisense oligomer to the deficient *SCN1A* or *SYNGAP1* mRNA transcript, wherein the deficient *SCN1A* or *SYNGAP1* mRNA transcript is capable of encoding the functional form of a SCN1A or SYNGAP1 protein and comprises at least one retained intron; (c) removing the at least one retained intron from the deficient *SCN1A* or *SYNGAP1* mRNA transcript to produce the fully processed *SCN1A* or *SYNGAP1* mRNA transcript that encodes the functional form of SCN1A or SYNGAP1 protein; and (d) translating the functional form of SCN1A or SYNGAP1 protein from the fully processed *SCN1A* or *SYNGAP1* mRNA transcript. In some examples, the retained intron is an entire retained intron. In some examples, the deficient *SCN1A* or *SYNGAP1* mRNA transcript is a *SCN1A* or *SYNGAP1* pre-mRNA transcript.

[0031] Disclosed herein, in some examples, are methods of treating a subject having a condition caused by a deficient amount or activity of SCN1A or SYNGAP1 protein comprising administering to the subject an antisense oligomer comprising a nucleotide sequence with at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 10-2591.

INCORPORATION BY REFERENCE

[0032] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings.

[0034] FIG. 1 depicts a schematic representation of an exemplary retained-intron-containing (RIC) pre-mRNA transcript. In FIG. 1, the 5' splice site consensus sequence is indicated with underlined letters (letters are nucleotides; upper case: exonic portion; and lower case: intronic portion) from -3e to -1e and +1 to +6 (numbers labeled "e" are exonic and unlabeled numbers are intronic). The 3' splice site consensus sequence is indicated with underlined letters (letters are nucleotides; upper case: exonic portion and lower case: intronic portion) from -15 to -1 and +1e (numbers labeled "e" are exonic and unlabeled numbers are intronic). Intronic target regions for ASO screening comprise nucleotides +6 relative to the 5' splice site of the retained intron (arrow at left) to -16 relative to the 3' splice site of the retained intron (arrow at right). In embodiments, intronic target regions for ASO screening comprise nucleotides +6 to +496 relative to the 5' splice site of the retained intron and -16 to -499 relative to the 3' splice site of the retained intron. Exonic target regions comprise nucleotides +2e to -4e in the exon flanking the 5' splice site of the retained intron and +2e to -4e in the exon flanking the 3' splice site of the retained intron. "n"

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising an antisense oligomer (ASO), wherein the ASO is complementary to a targeted portion of a retained-intron-containing pre-mRNA (RIC pre-mRNA) that encodes SCN1A protein, wherein the RIC pre-mRNA comprises a retained intron, an exon flanking 5' splice site of the retained intron, and an exon flanking 3' splice site of the retained intron, and wherein binding of the ASO to the RIC pre-mRNA will cause a retained intron to be constitutively spliced from the RIC pre-mRNA in cells that express the RIC pre-mRNA, thereby increasing the level of functional RNA encoding SCN1A protein in the cells.
2. A pharmaceutical composition according to claim 1 for use as a medicament.
3. Use of a pharmaceutical composition according to claim 1 in the manufacture of a medicament for treating Dravet Syndrome (DS) in a subject.
4. A pharmaceutical composition according to claim 1 or 2, or a use according to claim 3, wherein the retained intron is intron 21 and the targeted portion of the RIC pre-mRNA is within the region +6 relative to the 5' splice site of the retained intron 21 to -16 relative to the 3' splice site of the retained intron 21.
5. A pharmaceutical composition according to claim 1, claim 2 or claim 4 or a use according to claims 3 or 4, wherein the RIC pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 4-7.
6. A pharmaceutical composition according to claim 1, claim 2, claim 4 or claim 5, or a use according to any of claims 3 to 5, wherein the targeted portion of the RIC pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleic acids of SEQ ID NO: 2593.
7. A pharmaceutical composition according to claim 1, claim 2, or any of claims 4 to 6, or a use according to any of claims 3 to 6, wherein the ASO comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% identity to a sequence selected from SEQ ID NOs: 246, 255, 10-245, 247-254, 256-266 or 524-1037, preferably SEQ ID NOs: 246 or 255.
8. A pharmaceutical composition according to claim 1, claim 2 or any of claims 4 to 7, or a use according to any of claims 3 to 7, wherein either:

i) the SCN1A protein is produced in a form having reduced function compared to an equivalent wild-type protein; or

ii) the SCN1A protein is produced in a form that is fully-functional compared to an equivalent wild-type protein.

9. A pharmaceutical composition according to claim 1, claim 2 or any of claims 4 to 8, or a use according to any of claims 3 to 8, wherein the ASO comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage; or a modified sugar moiety or a sugar analog, optionally comprising a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl moiety, a 2'-Fluoro moiety, or a 2'-O-methoxyethyl moiety.

10. A pharmaceutical composition according to claim 1, claim 2 or any of claims 4 to 9, or a use according to any of claims 3 to 9, wherein the ASO consists of from 8 to 50 nucleobases.

11. A pharmaceutical composition according claim 2, or a use according to any of claims 3 to 10, wherein the SCN1A protein is deficient in amount or activity in the subject to be treated.

12. A pharmaceutical composition according to claim 2, or a use according to any of claims 3 to 11, wherein the SCN1A protein is deficient in amount or activity in the subject to be treated, and the deficient amount of the SCN1A protein is caused by haploinsufficiency of the SCN1A protein, wherein the subject has a first allele encoding a functional SCN1A protein, and a second allele from which the SCN1A protein is not produced, or a second allele encoding a nonfunctional SCN1A protein, and wherein the ASO binds to a targeted portion of a RIC pre-mRNA transcribed from the first allele.

13. A pharmaceutical composition according to claim 2, or a use according to any of claims 3 to 11, wherein the SCN1A protein is deficient in amount or activity in the subject to be treated, and the subject has

a. a first mutant allele from which

- i. the SCN1A protein is produced at a reduced level compared to production from a wild-type allele,
- ii. the SCN1A protein is produced in a form having reduced function compared to an equivalent wild-type SCN1A protein, or
- iii. the SCN1A protein is not produced, and

b. a second mutant allele from which

- i. the SCN1A protein is produced at a reduced level compared to production from a wild-type allele,

- ii. the SCN1A protein is produced in a form having reduced function compared to an equivalent wild-type SCN1A protein, or
- iii. the SCN1A protein is not produced, and

wherein when the subject has first mutant allele a.iii., the second mutant allele is b.i. or b.ii., wherein when the subject has a second mutant allele b.iii., the first mutant allele is a.i. or a.ii., and wherein the RIC pre-mRNA is transcribed from the first mutant allele that is a.i. or a.ii. or the second allele that is b.i. or b.ii.

14. A pharmaceutical composition according to claim 2, or a use according to any of claims 3 to 13, wherein the ASO is to be administered by intrathecal injection, intracerebroventricular injection, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection of the subject.

15. A pharmaceutical composition according to claim 1, claim 2 or any of claims 4 to 8, or a use according to any of claims 3 to 14, wherein the ASO does not increase the amount of SCN1A protein or functional RNA encoding SCN1A protein in the cells by modulating alternative splicing of pre-mRNA transcribed from a gene encoding the functional RNA or SCN1A protein.