

nucleobases in length and located in SCN1A intron 20, causes degradation of the SCN1A transcript (Carvill et al., 2018).

Currently there remains a need for therapies to treat Dravet Syndrome, GEFS+, and other DEEs. It is therefore an object herein to provide oligomeric compounds, methods, and pharmaceutical compositions for the treatment of such diseases.

Summary

Provided herein are compounds, methods, and pharmaceutical compositions for modulating expression of SCN1A RNA and/or protein in a cell or a subject. In certain examples, the amount of SCN1A RNA and/or SCN1A protein is increased. In certain examples, the compounds, methods, or pharmaceutical compositions modulate splicing of SCN1A RNA. In certain examples, the amount of full-length SCN1A RNA and/or full-length SCN1A protein is increased. In certain examples, the amount of SCN1A RNA including an NIE is reduced. In certain examples, the amount of SCN1A RNA excluding an NIE is increased. In certain examples, the NIE is NIE-1. In certain examples, the compounds, methods, and pharmaceutical compositions are useful for treating a disease or disorder associated with SCN1A. In certain examples, the disease or disorder associated with SCN1A is an SCN1A haploinsufficiency. In certain examples, the disease or disorder associated with SCN1A is a developmental or epileptic encephalopathic disease (DEE). In certain examples, the developmental or epileptic encephalopathic disease is any of Genetic Epilepsy with Febrile Seizures Plus (GEFS+), febrile seizures, Idiopathic/Generic Generalized Epilepsies (IGE/GGE), Temporal Lobe Epilepsy, Myoclonic Astatic Epilepsy (MAE), Lennox-Gastaut Syndrome, or Migrating Partial Epilepsy of Infancy (MMPSE). In certain examples, the developmental or epileptic encephalopathic disease is Dravet Syndrome. In certain examples, the DEE is treated by increasing the amount of full-length SCN1A RNA and/or full-length SCN1A protein in a subject, or cell thereof, with compounds capable of excluding an NIE from an SCN1A RNA. In certain examples, exclusion of an NIE from an SCN1A RNA reduces or prevents degradation of the SCN1A transcript via the NMD pathway. In certain examples, exclusion of an NIE from an SCN1A RNA increases full-length SCN1A RNA and/or full-length SCN1A protein wherein removal of the NIE prevents degradation of the SCN1A transcript via the NMD pathway. In certain examples, compounds useful for modulating splicing of SCN1A RNA are oligomeric compounds. In certain examples, the oligomeric compound comprises or consists of a modified oligonucleotide.

Also provided are methods useful for ameliorating at least one symptom or hallmark of a disease or disorder associated with SCN1A. In some examples, the disease or disorder associated with SCN1A is a DEE. In certain examples, the DEE is Dravet Syndrome. In certain examples, symptoms or hallmarks of the DEE include seizures that are prolonged in duration (often lasting longer than 10 minutes), frequent seizures (for example, convulsive, myoclonic, absence, focal, obtundation status, and tonic seizures), sudden unexpected death in epilepsy, status epilepticus, behavioral dysfunctions (for example, aggressiveness, agitation, obsessiveness, preservation, hoarding behavior, or sleep disorders), movement and balance dysfunctions, orthopedic conditions, motor system dysfunctions (for example, ataxia, tremors, dysarthria, pyramidal, and extrapyramidal signs), cognitive impairment, delayed language and speech, visual motor integration dysfunctions, visual perception dysfunctions, executive dysfunctions, and dysautonomia.

In one aspect, the present disclosure provides an oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

$A_{ns}G_{no}T_{ns}T_{no}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 24);
 $A_{ns}G_{no}T_{ns}T_{ns}G_{no}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 25);
 $A_{ns}G_{no}T_{no}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 23);
 $A_{ns}G_{no}T_{ns}T_{ns}G_{ns}G_{no}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 26);
 $A_{ns}G_{no}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{no}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 27);
 $A_{ns}G_{ns}T_{ns}T_{no}G_{no}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 28);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{no}^mC_{no}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 29);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{no}A_{no}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 30);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{no}A_{no}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 31);
 $A_{ns}G_{no}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{no}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 32);
 $A_{ns}G_{no}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{no}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 33);
 $A_{ns}G_{no}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{no}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 34);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{no}A_{no}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 35);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{no}T_{no}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 36);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{no}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{no}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 37);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{no}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{no}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 38);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{no}G_{ns}A_{ns}T_{ns}T_{no}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 39);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{no}T_{ns}T_{no}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 40);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{no}A_{ns}A_{ns}G_{ns}A_{ns}T_{no}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 41);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{no}A_{ns}T_{no}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 42);
 $A_{no}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 43); or
 $A_{no}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_{no}^mC_n$ (SEQ ID NO: 44);

wherein:

A = an adenine nucleobase,

^mC = a 5-methylcytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

n = a 2'-NMA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

In another aspect, the present disclosure provides an oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

$A_{ns}T_{ns}^mC_{no}^mC_{no}A_{ns}A_{no}G_{no}T_{ns}T_{no}G_{no}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_{ns}^mC_{ns}T_n$ (SEQ ID NO: 47);
 $T_{ns}^mC_{ns}^mC_{no}A_{no}A_{ns}G_{no}T_{no}T_{ns}G_{no}G_{no}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_{ns}^mC_{ns}T_{ns}A_n$ (SEQ ID NO: 48);
 $^mC_{ns}^mC_{ns}A_{no}A_{no}G_{ns}T_{no}T_{no}G_{ns}G_{no}A_{no}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_{ns}^mC_{ns}T_{ns}A_{ns}T_n$ (SEQ ID NO: 49);
 $^mC_{ns}A_{ns}A_{no}G_{no}T_{ns}T_{no}G_{no}G_{ns}A_{no}G_{no}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_{ns}^mC_{ns}T_{ns}A_{ns}T_{ns}A_n$ (SEQ ID NO: 50);

$A_{ns}T_{ns}{}^mC_{no}{}^mC_{no}A_{ns}A_{no}G_{no}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_n$ (SEQ ID NO: 51);
 $T_{ns}{}^mC_{ns}{}^mC_{no}A_{no}A_{ns}G_{no}T_{no}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_{ns}A_n$ (SEQ ID NO: 52);
 ${}^mC_{ns}{}^mC_{ns}A_{no}A_{no}G_{ns}T_{no}T_{no}G_{ns}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_{ns}A_{ns}T_n$ (SEQ ID NO: 53);
 ${}^mC_{ns}A_{ns}A_{no}G_{no}T_{ns}T_{no}G_{no}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_{ns}A_{ns}T_{ns}A_n$ (SEQ ID NO: 54);
 $A_{ns}T_{ns}{}^mC_{no}{}^mC_{no}A_{ns}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_n$ (SEQ ID NO: 55);
 $T_{ns}{}^mC_{ns}{}^mC_{no}A_{no}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_{ns}A_n$ (SEQ ID NO: 56);
 ${}^mC_{ns}{}^mC_{ns}A_{no}A_{no}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_{ns}A_{ns}T_n$ (SEQ ID NO: 57); or
 ${}^mC_{ns}A_{ns}A_{no}G_{no}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_{ns}A_{ns}T_{ns}A_n$ (SEQ ID NO: 58),

wherein:

A = an adenine nucleobase,

${}^mC$ = a 5-methylcytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

n = a 2'-NMA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

In yet another aspect, the present disclosure provides an oligomeric compound comprising a modified oligonucleotide consisting of 17 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 consecutive nucleobases of any of the nucleobase sequences of SEQ ID NOs:19-22, wherein each nucleoside of the modified oligonucleotide comprises a modified sugar moiety and each modified sugar moiety is a 2'-NMA sugar moiety, and wherein the modified oligonucleotide comprises at least one phosphorothioate internucleoside linkage and at least one phosphodiester internucleoside linkage.

In yet another aspect, the present disclosure provides a population of oligomeric compounds of the present disclosure in which all of the modified oligonucleotides of the population have the same molecular formula, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

In yet another aspect, the present disclosure provides a pharmaceutical composition comprising an oligomeric compound of the present disclosure or a population of oligomeric compounds of the present disclosure, and a pharmaceutically acceptable diluent.

In yet another aspect, the present disclosure provides an oligomeric compound of the present disclosure, a population of oligomeric compounds of the present disclosure, or a pharmaceutical composition of the present disclosure, for use in therapy.

In yet another aspect, the present disclosure provides an oligomeric compound of the present disclosure, a population of oligomeric compounds of the present disclosure, or pharmaceutical composition of the present disclosure, for use in treating a developmental or epileptic encephalopathic disease.

In yet another aspect, the present disclosure provides use of an oligomeric compound of the present disclosure, a population of oligomeric compounds of the present disclosure, or a pharmaceutical composition of the present disclosure in the manufacture of a medicament for treating a developmental or epileptic encephalopathic disease.

CLAIMS:

1. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

$A_{ns}G_{no}T_{ns}T_{no}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 24);
 $A_{ns}G_{no}T_{ns}T_{ns}G_{no}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 25);
 $A_{ns}G_{no}T_{no}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 23);
 $A_{ns}G_{no}T_{ns}T_{ns}G_{ns}G_{no}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 26);
 $A_{ns}G_{no}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{no}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 27);
 $A_{ns}G_{ns}T_{ns}T_{no}G_{no}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 28);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{no}^mC_{no}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 29);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{no}A_{no}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 30);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{no}A_{no}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 31);
 $A_{ns}G_{no}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{no}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 32);
 $A_{ns}G_{no}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{no}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 33);
 $A_{ns}G_{no}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{no}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 34);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{no}A_{no}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 35);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{no}T_{no}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 36);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{no}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{no}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 37);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{no}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{no}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 38);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{no}G_{ns}A_{ns}T_{ns}T_{no}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 39);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{no}T_{ns}T_{no}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 40);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{no}A_{ns}A_{ns}G_{ns}A_{ns}T_{no}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 41);
 $A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{no}A_{ns}T_{no}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 42);
 $A_{no}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_n$ (SEQ ID NO: 43); or
 $A_{no}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_{no}^mC_n$ (SEQ ID NO: 44);

wherein:

A = an adenine nucleobase,

^mC = a 5-methylcytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

n = a 2'-NMA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

2. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

$A_{ns}T_{ns}^mC_{no}^mC_{no}A_{ns}A_{no}G_{no}T_{ns}T_{no}G_{no}G_{ns}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_{ns}^mC_{ns}T_n$ (SEQ ID NO: 47);
 $T_{ns}^mC_{ns}^mC_{no}A_{no}A_{ns}G_{no}T_{no}T_{ns}G_{no}G_{no}A_{ns}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_{ns}^mC_{ns}T_{ns}A_n$ (SEQ ID NO: 48);
 $^mC_{ns}^mC_{ns}A_{no}A_{no}G_{ns}T_{no}T_{no}G_{ns}G_{no}A_{no}G_{ns}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_{ns}^mC_{ns}T_{ns}A_{ns}T_n$ (SEQ ID NO: 49);
 $^mC_{ns}A_{ns}A_{no}G_{no}T_{ns}T_{no}G_{no}G_{ns}A_{no}G_{no}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}^mC_{ns}^mC_{ns}T_{ns}A_{ns}T_{ns}A_n$ (SEQ ID NO: 50);

$A_{ns}T_{ns}{}^mC_{no}{}^mC_{no}A_{ns}A_{no}G_{no}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_n$ (SEQ ID NO: 51);
 $T_{ns}{}^mC_{ns}{}^mC_{no}A_{no}A_{ns}G_{no}T_{no}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_{ns}A_n$ (SEQ ID NO: 52);
 ${}^mC_{ns}{}^mC_{ns}A_{no}A_{no}G_{ns}T_{no}T_{no}G_{ns}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_{ns}A_{ns}T_n$ (SEQ ID NO: 53);
 ${}^mC_{ns}A_{ns}A_{no}G_{no}T_{ns}T_{no}G_{no}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_{ns}A_{ns}T_{ns}A_n$ (SEQ ID NO: 54);
 $A_{ns}T_{ns}{}^mC_{no}{}^mC_{no}A_{ns}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_n$ (SEQ ID NO: 55);
 $T_{ns}{}^mC_{ns}{}^mC_{no}A_{no}A_{ns}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_{ns}A_n$ (SEQ ID NO: 56);
 ${}^mC_{ns}{}^mC_{ns}A_{no}A_{no}G_{ns}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_{ns}A_{ns}T_n$ (SEQ ID NO: 57); or
 ${}^mC_{ns}A_{ns}A_{no}G_{no}T_{ns}T_{ns}G_{ns}G_{ns}A_{ns}G_{ns}{}^mC_{ns}A_{ns}A_{ns}G_{ns}A_{ns}T_{ns}T_{ns}A_{ns}T_{ns}{}^mC_{ns}{}^mC_{ns}T_{ns}A_{ns}T_{ns}A_n$ (SEQ ID NO: 58),

wherein:

A = an adenine nucleobase,

${}^mC$ = a 5-methylcytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

n = a 2'-NMA sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

3. The oligomeric compound of claim 1 or claim 2, consisting of the modified oligonucleotide.
4. The oligomeric compound of any of claims 1-3, wherein:
 - a. the modified oligonucleotide is a free acid; or
 - b. the modified oligonucleotide is a salt, optionally wherein the modified oligonucleotide is a sodium salt or a potassium salt.
5. An oligomeric compound comprising a modified oligonucleotide consisting of 17 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 consecutive nucleobases of any of the nucleobase sequences of SEQ ID NOs: 19-22, wherein each nucleoside of the modified oligonucleotide comprises a modified sugar moiety and each modified sugar moiety is a 2'-NMA sugar moiety, and wherein the modified oligonucleotide comprises at least one phosphorothioate internucleoside linkage and at least one phosphodiester internucleoside linkage.
6. The oligomeric compound of claim 5, wherein the modified oligonucleotide consists of 18-25 linked nucleosides.
7. The oligomeric compound of claim 5, wherein the modified oligonucleotide consists of 18, 23 or 25 linked nucleosides.
8. The oligomeric compound of any of claims 5-7, wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs: 19-22.
9. The oligomeric compound of any of claims 5-7, wherein the nucleobase sequence of the modified oligonucleotide consists of the nucleobase sequence of any of SEQ ID Nos: 19-22.
10. The oligomeric compound of any of claims 5-9, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage and a phosphorothioate internucleoside linkage.

11. The oligomeric compound of any of claims 5-10, wherein the modified oligonucleotide comprises at least one modified nucleobase, optionally wherein the modified nucleobase is a 5-methylcytosine.
12. A population of oligomeric compounds of any of claims 1-11 in which all of the modified oligonucleotides of the population have the same molecular formula, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.
13. A pharmaceutical composition comprising an oligomeric compound of any of claims 1-11 or a population of oligomeric compounds of claim 12, and a pharmaceutically acceptable diluent.
14. The pharmaceutical composition of claim 13, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or PBS.
15. The pharmaceutical composition of claim 13 or claim 14, wherein the pharmaceutical composition consists essentially of the oligomeric compound or population of oligomeric compounds and aCSF or PBS.
16. An oligomeric compound of any of claims 1-11, a population of oligomeric compounds of claim 12, or a pharmaceutical composition of any of claims 13-15, for use in therapy.
17. An oligomeric compound of any of claims 1-11, a population of oligomeric compounds of claim 12, or pharmaceutical composition of any of claims 13-15, for use in treating a developmental or epileptic encephalopathic disease, optionally wherein:
 - a. the developmental or epileptic encephalopathic disease is:
 - i. Dravet Syndrome; and/or
 - ii. any of Genetic Epilepsy with Febrile Seizures Plus (GEFS+), febrile seizures, Idiopathic/Generic Generalized Epilepsies (IGE/GGE), Temporal Lobe Epilepsy, Myoclonic Astatic Epilepsy (MAE), Lennox-Gastaut Syndrome, or Migrating Partial Epilepsy of Infancy (MMPSI); and/or
 - b. treatment with the oligomeric compound, the population of oligomeric compounds, or the pharmaceutical composition reduces the frequency of seizures, reduces the duration of seizures, reduces status epilepticus, improves behavioral functions, improves movement and balance, improves orthopedic conditions, improves motor functions, reduces cognitive impairment, improves language and speech, improves visual motor integration functions, improves visual perception functions, improves executive functions, or reduces dysautonomia, optionally wherein:
 - i. the seizures are frequent or prolonged in duration; and/or
 - ii. the seizure is any of convulsive, myoclonic, absence, focal, obtundation status, or tonic; and/or
 - c. the subject is human.
18. Use of an oligomeric compound of any of claims 1-11, a population of oligomeric compounds of claim 12, or a pharmaceutical composition of any of claims 13-15 in the manufacture of a medicament for treating a developmental or epileptic encephalopathic disease.
19. The use of claim 18, wherein:
 - a. the developmental or epileptic encephalopathic disease is:
 - i. Dravet Syndrome; and/or

ii. any of Genetic Epilepsy with Febrile Seizures Plus (GEFS+), febrile seizures, Idiopathic/Generic Generalized Epilepsies (IGE/GGE), Temporal Lobe Epilepsy, Myoclonic Astatic Epilepsy (MAE), Lennox-Gastaut Syndrome, or Migrating Partial Epilepsy of Infancy (MMPSI); and/or

- b. treatment with the oligomeric compound, the population of oligomeric compounds, or the pharmaceutical composition reduces the frequency of seizures, reduces the duration of seizures, reduces status epilepticus, improves behavioral functions, improves movement and balance, improves orthopedic conditions, improves motor functions, reduces cognitive impairment, improves language and speech, improves visual motor integration functions, improves visual perception functions, improves executive functions, or reduces dysautonomia, optionally wherein:
 - i. the seizures are frequent or prolonged in duration; and/or
 - ii. the seizure is any of convulsive, myoclonic, absence, focal, obtundation status, or tonic; and/or
- c. the subject is human.