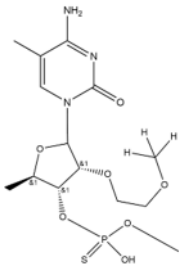
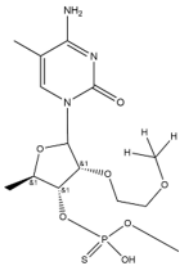
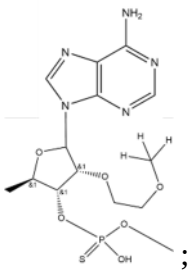
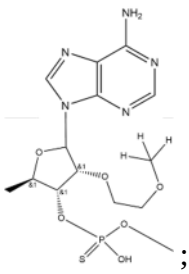
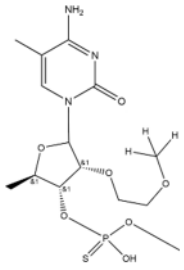
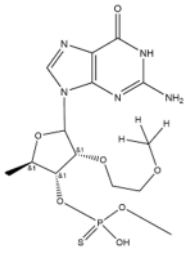
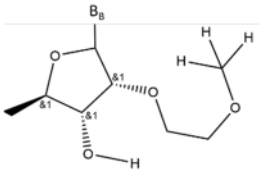
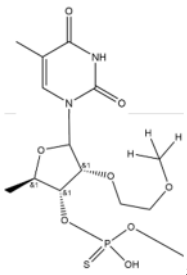
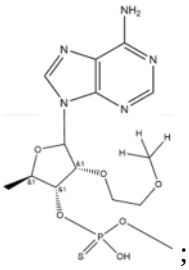
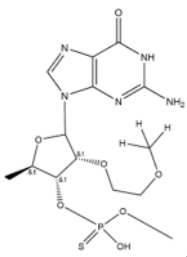
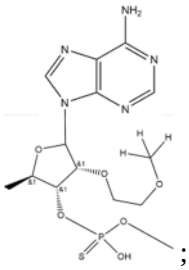
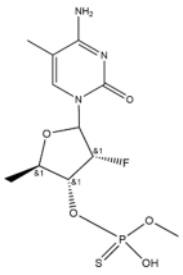
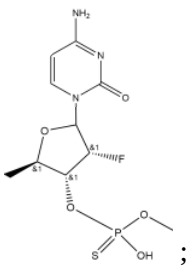
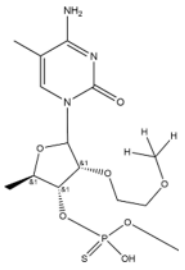
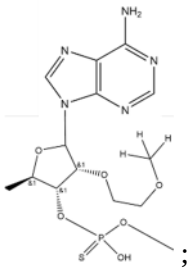
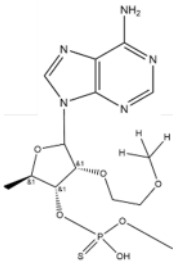
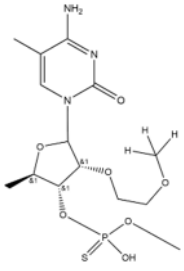
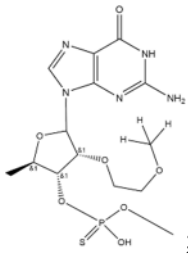
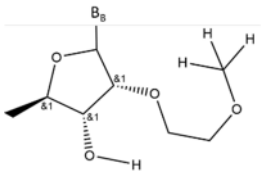
X_9 is  ; X_{10} is  ; X_{11} is  ; X_{12} is  ;

X_{14} is  ; X_{16} is  ; and X_B is  .

[0011] In some embodiments,

X_2 is  ; X_5 is  ; X_7 is  ; X_8 is  ;

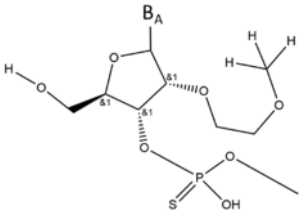
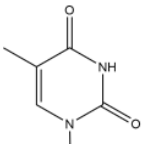
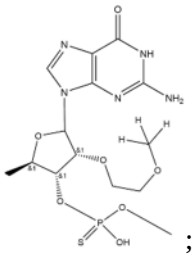
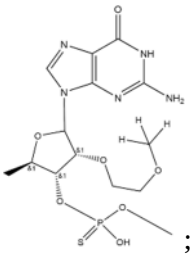
X_9 is  or  ; X_{10} is  ; X_{11} is  ;

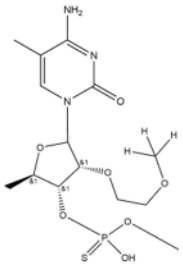
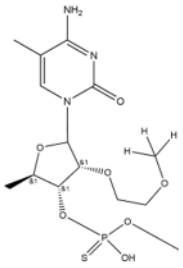
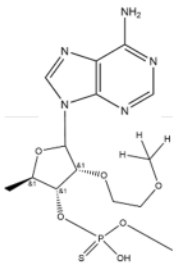
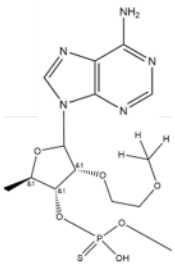
X_{12} is  ; X_{14} is  ; X_{16} is  ; and X_B is  .

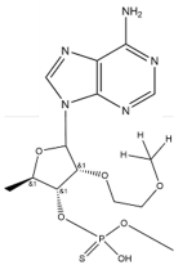
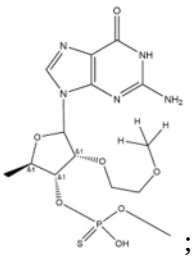
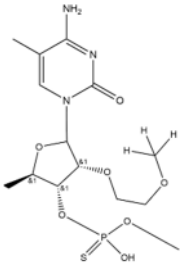
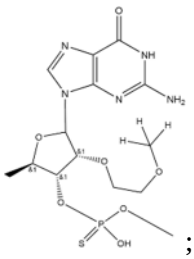
[0012] Provided herein is a compound of Formula (I):

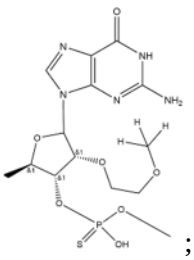
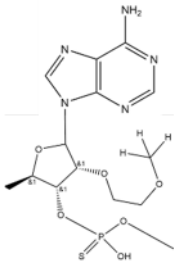
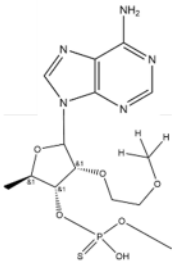
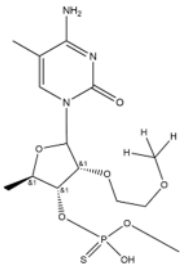
$X_AX_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}X_{17}X_B$ (SEQ ID NO: 1)

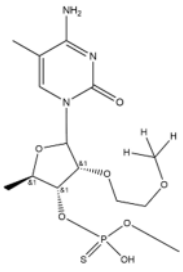
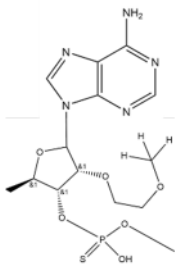
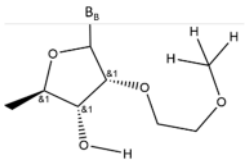
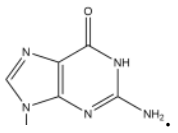
wherein

X_A is  and B_A is ; X_2 is ; X_3 is ;

X_4 is ; X_5 is ; X_6 is ; X_7 is ;

X_8 is ; X_9 is ; X_{10} is ; X_{11} is ;

X_{12} is ; X_{13} is ; X_{14} is ; X_{15} is ;

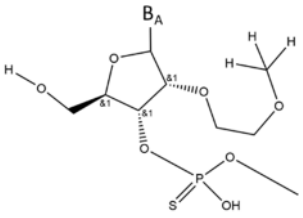
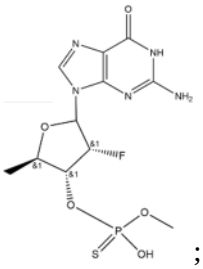
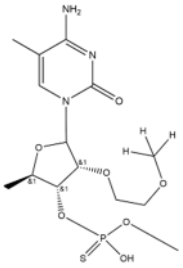
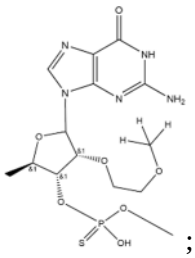
X_{16} is ; X_{17} is ; and X_B is  and B_B is .

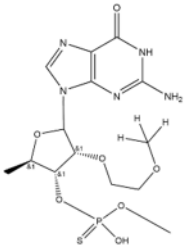
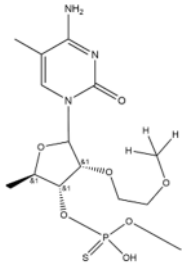
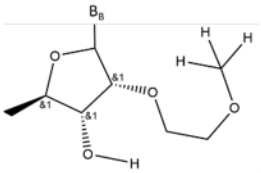
[0013] Provided herein is a compound of Formula (I):

$X_AX_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_B$ (SEQ ID NO: 2)

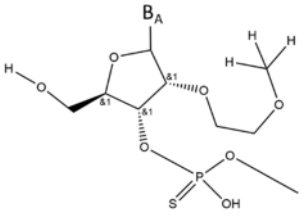
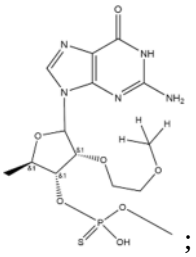
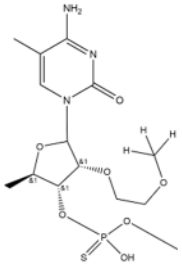
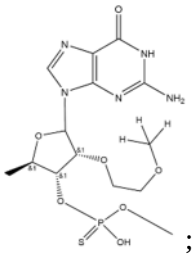
wherein

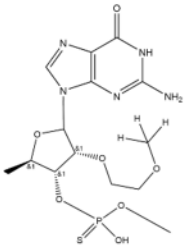
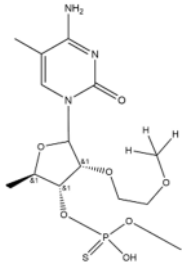
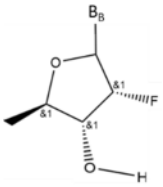
[0020] In some embodiments,

X_A is  ; X_7 is  ; X_8 is  ; X_9 is  ;

X_{10} is  ; X_{13} is  ; and X_B is  .

[0021] In some embodiments,

X_A is  ; X_7 is  ; X_8 is  ; X_9 is  ;

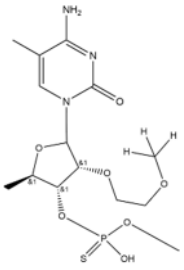
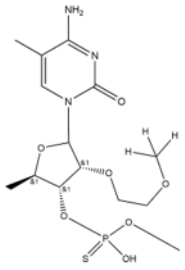
X_{10} is  ; X_{13} is  ; and X_B is  .

[0022] Provided herein is a compound of Formula (I):

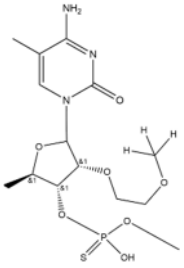
$X_AX_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_B$ (SEQ ID NO: 3)

wherein

[0024] In some embodiments,

X_{13} is , X_{14} is , and X_{15} is absent.

[0025] In some embodiments,

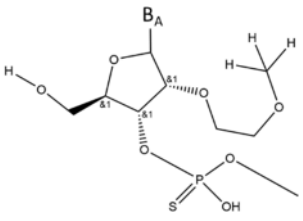
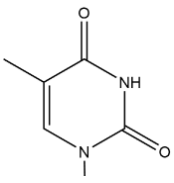
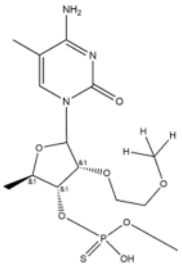
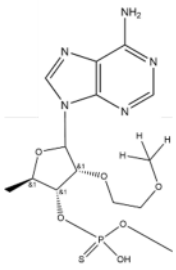
X_{13} is  and each of X_{14} and X_{15} is absent.

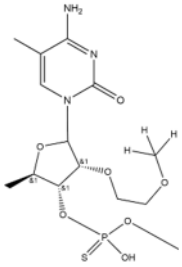
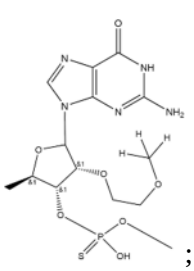
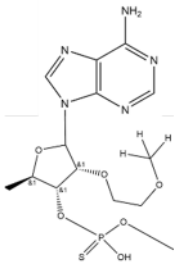
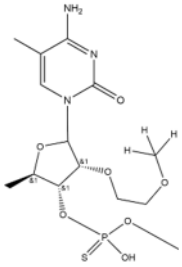
[0026] In some embodiments, each of X_{13}, X_{14}, and X_{15} is absent.

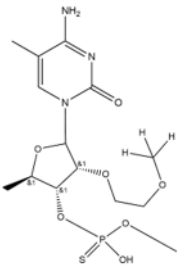
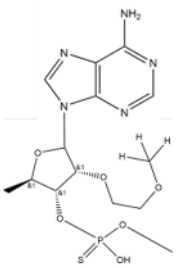
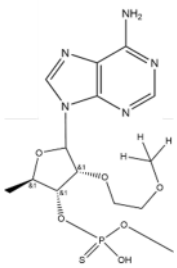
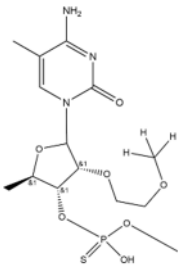
[0027] Provided herein is a compound of Formula (I):

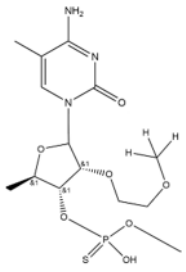
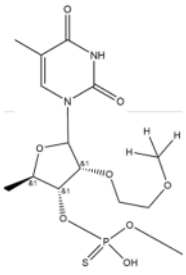
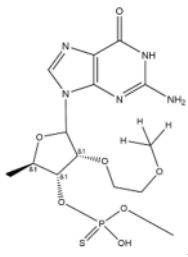
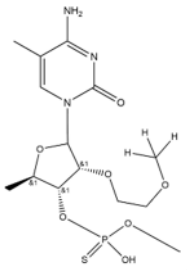
$X_AX_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_B$ (SEQ ID NO: 4)

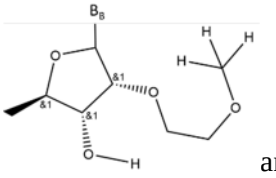
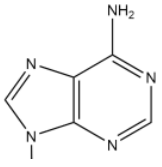
wherein

X_A is  and B_A is ; X_2 is ; X_3 is ;

X_4 is ; X_5 is ; X_6 is ; X_7 is ;

X_8 is ; X_9 is ; X_{10} is ; X_{11} is ;

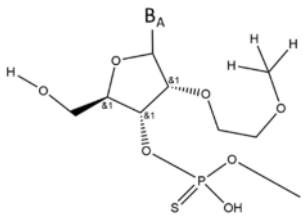
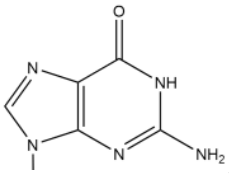
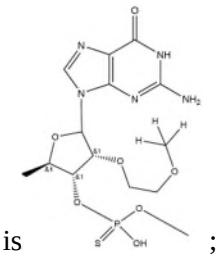
X_{12} is  ; X_{13} is  ; and X_{14} is  ; X_{15} is  ;

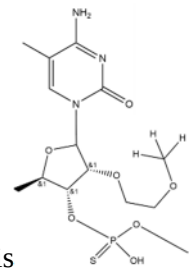
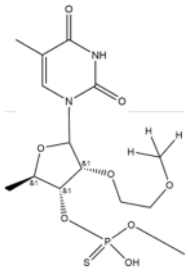
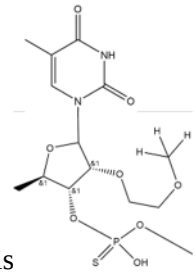
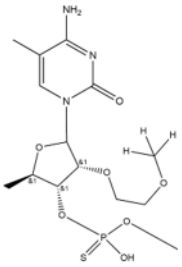
X_B is  and B_B is  .

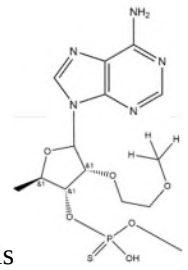
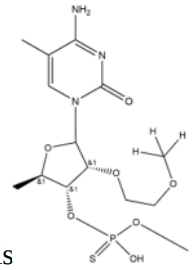
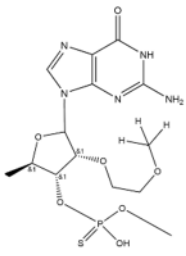
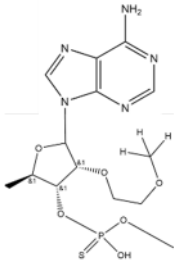
[0028] Provided herein is a compound of Formula (I):

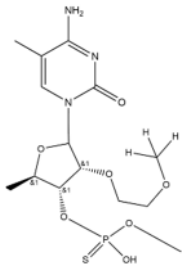
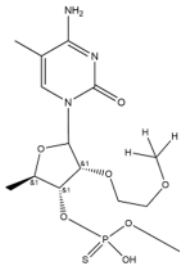
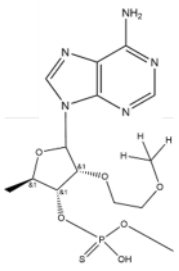
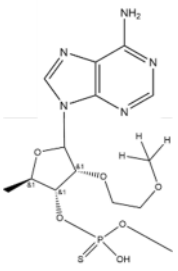
$X_AX_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_B$ (SEQ ID NO: 5)

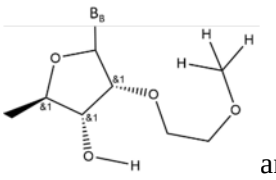
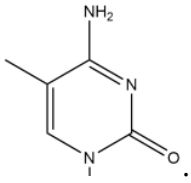
wherein:

X_A is  and B_A is  ; X_2 is  ;

X_3 is  ; X_4 is  ; X_5 is  ; X_6 is  ;

X_7 is  ; X_8 is  ; X_9 is  ; X_{10} is  ;

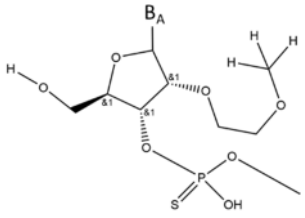
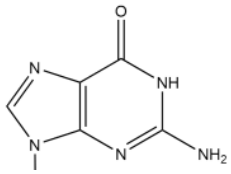
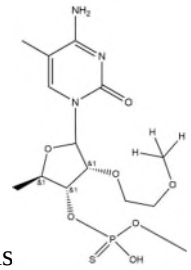
X_{11} is  ; X_{12} is  ; X_{13} is  ; X_{14} is  ; and

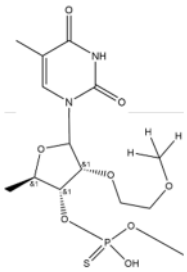
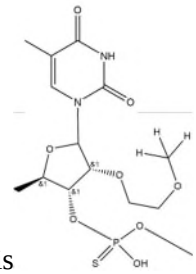
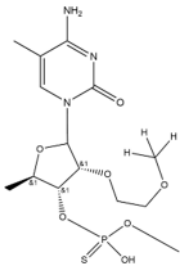
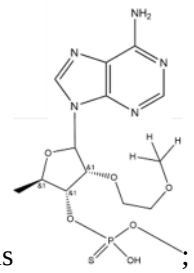
X_B is  and B_B is  .

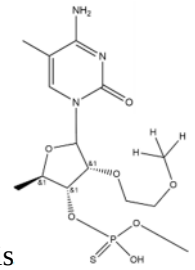
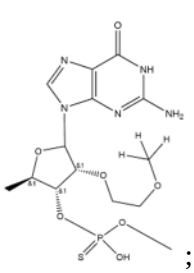
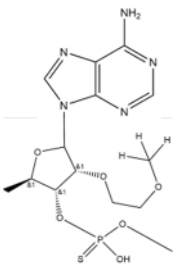
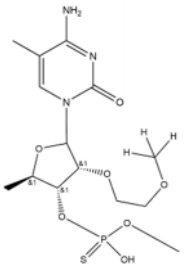
[0029] Provided herein is a compound of Formula (I):

$X_AX_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_B$ (SEQ ID NO: 6)

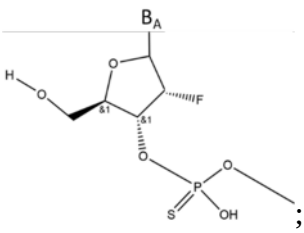
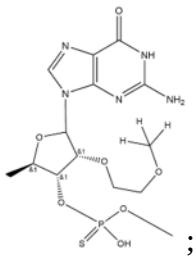
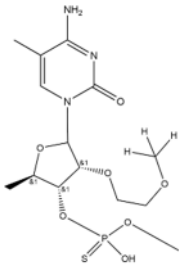
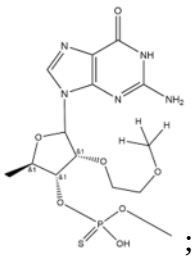
wherein

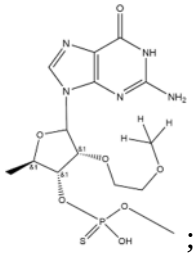
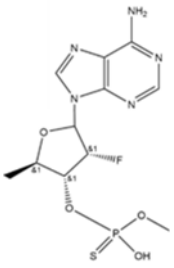
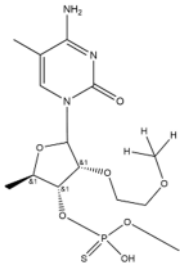
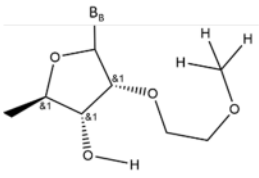
X_A is  and B_A is  ; X_2 is  ;

X_3 is  ; X_4 is  ; X_5 is  ; X_6 is  ;

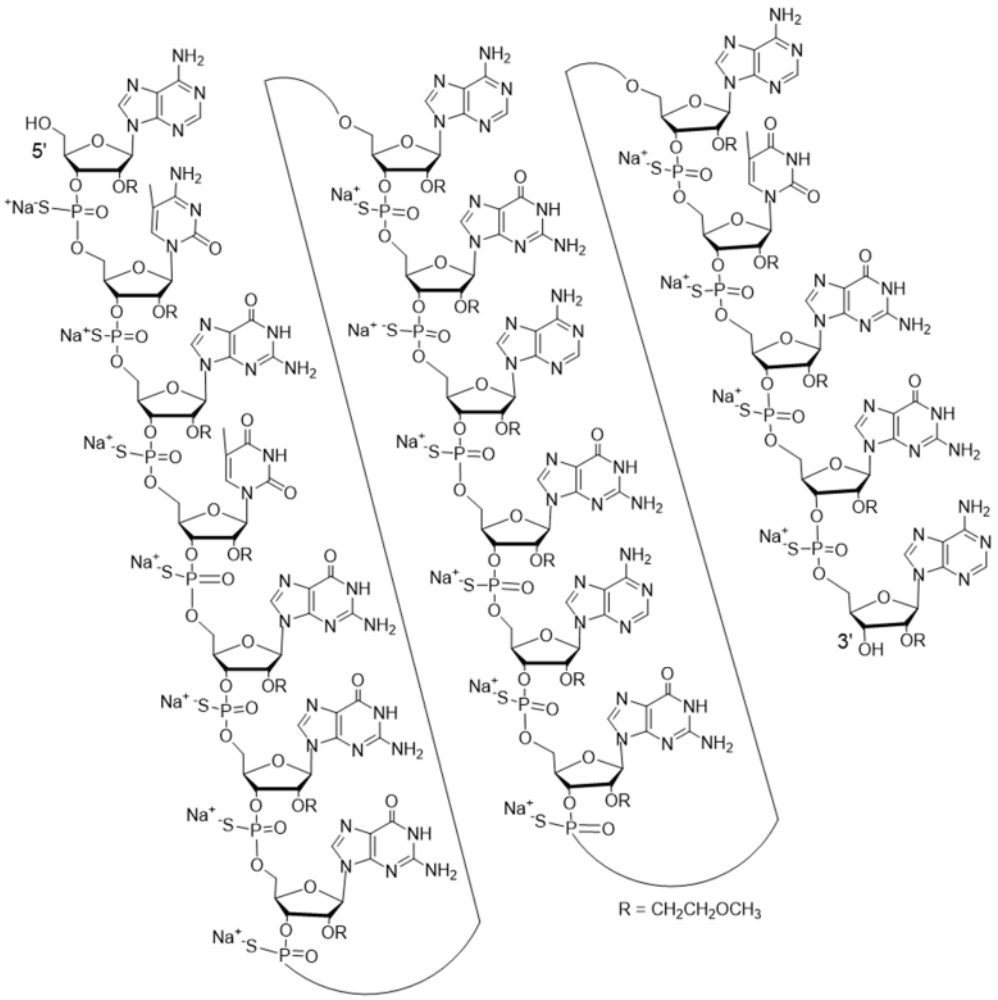
X_7 is  ; X_8 is  ; X_9 is  ; X_{10} is  ;

[0032] In some embodiments,

X_A is  ; X_7 is  ; X_8 is  ; X_9 is  ;

X_{10} is  ; X_{12} is  ; X_{13} is  ; and X_B is  .

[0033] Also provided herein is a compound selected from the group consisting of (SEQ ID NOS 7-16, 1, 18-25, and 25-29 disclosed below, respectively, in order of appearance):



,

mismatches to a target sequence of the pre-mRNA transcript. The sequence of the polynucleic acid polymer may have no mismatches to a target sequence of the pre-mRNA transcript.

[0314] In some embodiments, the polynucleic acid polymer may specifically hybridize to a target sequence of the pre-mRNA transcript. For example, the polynucleic acid polymer may have 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 100% sequence complementarity to a target sequence of the pre-mRNA transcript. The hybridization may be under high stringent hybridization conditions.

[0315] The polynucleic acid polymer may have a sequence with at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5% sequence identity to a sequence of **Table 1** or **Table 2**. The polynucleic acid polymer may have a sequence with 100% sequence identity to a sequence selected from the group consisting of the sequences of **Table 1** and **Table 2**. In some embodiments, the polynucleic acid polymer comprises a sequence with at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5% sequence identity to any one selected from the group consisting of the sequences of **Table 1** and **Table 2**. In some embodiments, the polynucleic acid polymer comprises a sequence with 100% sequence identity to any one selected from the group consisting of the sequences of **Table 1** and **Table 2**. In some embodiments the polynucleic acid polymer is a polynucleic acid polymer of at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5% sequence identity to any one selected from the group consisting of the sequences of **Table 1** and **Table 2**. In some embodiments, the polynucleic acid polymer is a polynucleic acid polymer of any one selected from the group consisting of the sequences of **Table 1** and **Table 2**.

Table 1. Exemplary ASOs targeting NSAE event

ASO (Bold= 2'MOE, Italicized= LNA, underlined C= 5methylC)		**ASO sequence with no mismatches**		**Coordinate**			**Name**
Sequence 5'-3'	**SEQ ID NO:**	**Sequence 5'-3'**	**SEQ ID NO:**	**Chr**	**Start**	**End**	**Position ID**
ATGGGAGAGAGATGGAGG	30			chr6	33440369	33440387	SYNGAP1-IVS10-166
CAGAGATGGGAGAGAGAT	31			chr6	33440374	33440392	SYNGAP1-IVS10-161
AGAGACAGAGATGGGAGA	32			chr6	33440379	33440397	SYNGAP1-IVS10-156
CAGGGAGAGACAGAGATG	33			chr6	33440384	33440402	SYNGAP1-IVS10-151
GACACCAGGGAGAGACAG	34			chr6	33440389	33440407	SYNGAP1-IVS10-146
AAACAGACACCAGGGAGA	35			chr6	33440394	33440412	SYNGAP1-IVS10-141
AAGAAAAACAGACACCAG	36			chr6	33440399	33440417	SYNGAP1-IVS10-136
AGGAGAAGAAAAACAGAC	37			chr6	33440404	33440422	SYNGAP1-IVS10-131
AGAGGAGGAGAAGAAAAA	38			chr6	33440409	33440427	SYNGAP1-IVS10-126
CAAGGAGAGGAGGAGAAG	39			chr6	33440414	33440432	SYNGAP1-IVS10-121

ASO (Bold= 2'MOE, Italicized= LNA, underlined C= 5methylC)		ASO sequence with no mismatches		Coordinate			Name
AGAGACAAGGAGAGGAGG	40			chr6	33440419	33440437	SYNGAP1-IVS10-116
GGGAGAGAGACAAGGAGA	41			chr6	33440424	33440442	SYNGAP1-IVS10-111
GGTGTGGGAGAGAGACAA	42			chr6	33440429	33440447	SYNGAP1-IVS10-106
GGAGGGTTGTGGGAGAGA	43	**GGAGGGGTGTGGGAGAGA**	173	chr6	33440434	33440452	SYNGAP1-IVS10-101
GAGATGGATGGGTGTGGG	44	**GAGATGGAGGGGTGTGGG**	174	chr6	33440439	33440457	SYNGAP1-IVS10-96
GGAGAGAGATGGATGGGT	45	**GGAGAGAGATGGAGGGGT**	175	chr6	33440444	33440462	SYNGAP1-IVS10-91
ACGTGGGAGAGAGATGGA	46			chr6	33440449	33440467	SYNGAP1-IVS10-86
GAGACACGTGGGAGAGAG	47			chr6	33440454	33440472	SYNGAP1-IVS10-81
AGGGAGAGACACGTGGGA	48	**GGGGAGAGACACGTGGGA**	176	chr6	33440459	33440477	SYNGAP1-IVS10-76
GGTGAGGGAAGAGACACG	49	**GGTGAGGGGAGAGACACG**	177	chr6	33440464	33440482	SYNGAP1-IVS10-71
GAGAAGGTGAAGGGAGAG	50	**GAGAAGGTGAGGGGAGAG**	178	chr6	33440469	33440487	SYNGAP1-IVS10-66
AGGGAGAGAAGGTGAGGG	51	**GGGGAGAGAAGGTGAGGG**	179	chr6	33440474	33440492	SYNGAP1-IVS10-61
TGGAGGGAGAGAGAAGGT	52	**TGGAGGGGGAGAGAAGGT**	180	chr6	33440479	33440497	SYNGAP1-IVS10-56
AGAAATGGAGAGGGAGAG	53	**AGAAATGGAGGGGGAGAG**	181	chr6	33440484	33440502	SYNGAP1-IVS10-51
GAGAGAGAAATGGAGGGA	54	**GAGAGAGAAATGGAGGGG**	182	chr6	33440489	33440507	SYNGAP1-IVS10-46
TTAGGGAGAGAGAAATGG	55			chr6	33440494	33440512	SYNGAP1-IVS10-41
ACAGATTAGGGAGAGAGA	56			chr6	33440499	33440517	SYNGAP1-IVS10-36
AACAGACAGATTAGGGAG	57			chr6	33440504	33440522	SYNGAP1-IVS10-31
GAGGGAACAGACAGATTA	58			chr6	33440509	33440527	SYNGAP1-IVS10-26
TGGCAGAGGGAACAGACA	59			chr6	33440514	33440532	SYNGAP1-IVS10-21
GGCCATGGCAGAGGGAAC	60			chr6	33440519	33440537	SYNGAP1-IVS10-16
AAGGGAGCCATGGCAGAG	61	**AAGGGGGCCATGGCAGAG**	183	chr6	33440524	33440542	SYNGAP1-IVS10-11
TGAAGAAGGAGGCCATGG	62	**TGAAGAAGGGGGCCATGG**	184	chr6	33440529	33440547	SYNGAP1-IVS10-6
CTGCTTGAAGAAGAGGGC	63	**CTGCTTGAAGAAGGGGGC**	185	chr6	33440534	33440552	SYNGAP1-IVS10-1
GGAGGCTGCTTGAAGAAG	64			chr6	33440539	33440557	SYNGAP1-I10AltE11+5
AGATGGGAGGCTGCTTGA	65			chr6	33440544	33440562	SYNGAP1-I10AltE11+10
GAGCAAGATGGGAGGCTG	66			chr6	33440549	33440567	SYNGAP1-I10AltE11+15
CAGGAGCAAGATGGGAGG	67			chr6	33440552	33440570	SYNGAP1-AltEx11+1
GACCGCAGGAGCAAGATG	68			chr6	33440557	33440575	SYNGAP1-AltEx11+6
GGAGGGACCGCAGGAGCA	69			chr6	33440562	33440580	SYNGAP1-AltEx11+11
GGGAAGGAGGGACCGCAG	70			chr6	33440567	33440585	SYNGAP1-AltEx11+16
AGACAGGGAAGGAGGGAC	71			chr6	33440572	33440590	SYNGAP1-AltEx11+21
GAGAGAGACAGGGAAGGA	72			chr6	33440577	33440595	SYNGAP1-AltEx11+26
AGGGTGAGAGAGACAGGG	73	**GGGGTGAGAGAGACAGGG**	186	chr6	33440582	33440600	SYNGAP1-AltEx11+31
AAACAGGGATGAGAGAGA	74	**AAACAGGGGTGAGAGAGA**	187	chr6	33440587	33440605	SYNGAP1-AltEx11+36
TGTGGAAACAAGGGTGAG	75	**TGTGGAAACAGGGGTGAG**	188	chr6	33440592	33440610	SYNGAP1-AltEx11+41
GAGGGTGTGGAAACAGGG	76			chr6	33440597	33440615	SYNGAP1-AltEx11+46
GAGGTGAGGGTGTGGAAA	77			chr6	33440602	33440620	SYNGAP1-AltEx11+51
GGTAGGAGGTGAGGGTGT	78			chr6	33440607	33440625	SYNGAP1-AltEx11+56
AGGGTGGTAGGAGGTGAG	79	**GGGGTGGTAGGAGGTGAG**	189	chr6	33440612	33440630	SYNGAP1-AltEx11+61
TGAGGGAGGTGGTAGGAG	80	**TGAGGGGGGTGGTAGGAG**	190	chr6	33440617	33440635	SYNGAP1-AltEx11+66
CATGCTGAGGAGGGTGGT	81	**CATGCTGAGGGGGGTGGT**	191	chr6	33440622	33440640	SYNGAP1-AltEx11+71

ASO (Bold= 2'MOE, Italicized= LNA, underlined C= 5methylC)		ASO sequence with no mismatches		Coordinate			Name
GGGAACATGCTGAGAGGG	82	**GGGAACATGCTGAGGGGG**	192	chr6	33440627	33440645	SYNGAP1-AltEx11+76
TTCCAGGGAACATGCTGA	83			chr6	33440632	33440650	SYNGAP1-AltEx11+81
TCAGCTTCCAGGGAACAT	84			chr6	33440637	33440655	SYNGAP1-AltEx11+86
GGGAGAGAGATGGATGGG	85	**GGGAGAGAGATGGAGGGG**	193	chr6	33440445	33440463	SYNGAP1-IVS10-90
TGGGAGAGAGATGGAGGG	86			chr6	33440446	33440464	SYNGAP1-IVS10-89
GTGGGAGAGAGATGGAGG	87			chr6	33440447	33440465	SYNGAP1-IVS10-88
CGTGGGAGAGAGATGGAG	88			chr6	33440448	33440466	SYNGAP1-IVS10-87
CACGTGGGAGAGAGATGG	89			chr6	33440450	33440468	SYNGAP1-IVS10-85
ACACGTGGGAGAGAGATG	90			chr6	33440451	33440469	SYNGAP1-IVS10-84
GACACGTGGGAGAGAGAT	91			chr6	33440452	33440470	SYNGAP1-IVS10-83
AGACACGTGGGAGAGAGA	92			chr6	33440453	33440471	SYNGAP1-IVS10-82
AGAGACACGTGGGAGAGA	93			chr6	33440455	33440473	SYNGAP1-IVS10-80
GAGAGACACGTGGGAGAG	94			chr6	33440456	33440474	SYNGAP1-IVS10-79
GGAGAGACACGTGGGAGA	95			chr6	33440457	33440475	SYNGAP1-IVS10-78
GGGAGAGACACGTGGGAG	96			chr6	33440458	33440476	SYNGAP1-IVS10-77
AGGGAACATGCTGATGGG	97	**AGGGAACATGCTGAGGGG**	194	chr6	33440628	33440646	SYNGAP1-AltEX11+77
CAGGGAACATGCTGAGGG	98			chr6	33440629	33440647	SYNGAP1-AltEX11+78
CCAGGGAACATGCTGAGG	99			chr6	33440630	33440648	SYNGAP1-AltEX11+79
TCCAGGGAACATGCTGAG	100			chr6	33440631	33440649	SYNGAP1-AltEX11+80
CTTCCAGGGAACATGCTG	101			chr6	33440633	33440651	SYNGAP1-AltEX11+82
GCTTCCAGGGAACATGCT	102			chr6	33440634	33440652	SYNGAP1-AltEX11+83
AGCTTCCAGGGAACATGC	103			chr6	33440635	33440653	SYNGAP1-AltEX11+84
CAGCTTCCAGGGAACATG	104			chr6	33440636	33440654	SYNGAP1-AltEX11+85
GAGACACGTGGGAGAG	105			chr6	33440456	33440472	SYNGAP1-IVS10-81(16)
GACACGTGGGAGAGAG	106			chr6	33440454	33440470	SYNGAP1-IVS10-83(16)
CACGTGGGAGAGAGAT	107			chr6	33440452	33440468	SYNGAP1-IVS10-85(16)
CGTGGGAGAGAGATGG	108			chr6	33440450	33440466	SYNGAP1-IVS10-87(16)
GTGGGAGAGAGATGGA	109			chr6	33440449	33440465	SYNGAP1-IVS10-88(16)
GAGACACGTGGGAG	110			chr6	33440458	33440472	SYNGAP1-IVS10-81(14)
GACACGTGGGAGAG	111			chr6	33440456	33440470	SYNGAP1-IVS10-83(14)
CACGTGGGAGAGAG	112			chr6	33440454	33440468	SYNGAP1-IVS10-85(14)
CGTGGGAGAGAGAT	113			chr6	33440452	33440466	SYNGAP1-IVS10-87(14)
TGGGAGAGAGATGG	114			chr6	33440450	33440464	SYNGAP1-IVS10-89(14)
GGGAGAGAGATGGA	115			chr6	33440449	33440463	SYNGAP1-IVS10-90(14)
GAGACACGTGGG	116			chr6	33440460	33440472	SYNGAP1-IVS10-81(12)
GACACGTGGGAG	117			chr6	33440458	33440470	SYNGAP1-IVS10-83(12)
CACGTGGGAGAG	118			chr6	33440456	33440468	SYNGAP1-IVS10-85(12)
CGTGGGAGAGAG	119			chr6	33440454	33440466	SYNGAP1-IVS10-87(12)
TGGGAGAGAGAT	120			chr6	33440452	33440464	SYNGAP1-IVS10-89(12)
GGAGAGAGATGG	121			chr6	33440450	33440462	SYNGAP1-IVS10-91(12)
GAGAGAGATGGA	122			chr6	33440449	33440461	SYNGAP1-IVS10-92(12)
CCAGGGAGAGACAGAGAT	123			chr6	33440385	33440403	SYNGAP1-IVS10-150

ASO (Bold= 2'MOE, Italicized= LNA, underlined C= 5methylC)		ASO sequence with no mismatches		Coordinate			Name
A<u>C</u><u>C</u>AGGGAGAGA<u>C</u>AGAGA	124			chr6	33440386	33440404	SYNGAP1-IVS10-149
<u>C</u>A<u>C</u><u>C</u>AGGGAGAGA<u>C</u>AGAG	125			chr6	33440387	33440405	SYNGAP1-IVS10-148
A<u>C</u>A<u>C</u><u>C</u>AGGGAGAGA<u>C</u>AGA	126			chr6	33440388	33440406	SYNGAP1-IVS10-147
AGA<u>C</u>A<u>C</u><u>C</u>AGGGAGAGA<u>C</u>A	127			chr6	33440390	33440408	SYNGAP1-IVS10-145
<u>C</u>AGA<u>C</u>A<u>C</u><u>C</u>AGGGAGAGA<u>C</u>	128			chr6	33440391	33440409	SYNGAP1-IVS10-144
A<u>C</u>AGA<u>C</u>A<u>C</u><u>C</u>AGGGAGAGA	129			chr6	33440392	33440410	SYNGAP1-IVS10-143
AA<u>C</u>AGA<u>C</u>A<u>C</u><u>C</u>AGGGAGAG	130			chr6	33440393	33440411	SYNGAP1-IVS10-142
AAAA<u>C</u>AGA<u>C</u>A<u>C</u><u>C</u>AGGGAG	131			chr6	33440395	33440413	SYNGAP1-IVS10-140
AAAAA<u>C</u>AGA<u>C</u>A<u>C</u><u>C</u>AGGGA	132			chr6	33440396	33440414	SYNGAP1-IVS10-139
GAAAAA<u>C</u>AGA<u>C</u>A<u>C</u><u>C</u>AGGG	133			chr6	33440397	33440415	SYNGAP1-IVS10-138
AGAAAAA<u>C</u>AGA<u>C</u>A<u>C</u><u>C</u>AGG	134			chr6	33440398	33440416	SYNGAP1-IVS10-137
GAGA<u>C</u>AGGGAAGGAGGGA	135			chr6	33440573	33440591	SYNGAP1-AltEx11+22
AGAGA<u>C</u>AGGGAAGGAGGG	136			chr6	33440574	33440592	SYNGAP1-AltEx11+23
GAGAGA<u>C</u>AGGGAAGGAGG	137			chr6	33440575	33440593	SYNGAP1-AltEx11+24
AGAGAGA<u>C</u>AGGGAAGGAG	138			chr6	33440576	33440594	SYNGAP1-AltEx11+25
TGAGAGAGA<u>C</u>AGGGAAGG	139			chr6	33440578	33440596	SYNGAP1-AltEx11+27
GTGAGAGAGA<u>C</u>AGGGAAG	140			chr6	33440579	33440597	SYNGAP1-AltEx11+28
GGTGAGAGAGA<u>C</u>AGGGAA	141			chr6	33440580	33440598	SYNGAP1-AltEx11+29
GGGTGAGAGAGA<u>C</u>AGGGA	142			chr6	33440581	33440599	SYNGAP1-AltEx11+30
TT<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TGA GG	143			chr6	33440630	33440650	SYNGAP1-AltEX11+79
AGGGAA<u>C</u>ATG<u>C</u>TGAGG	144			chr6	33440630	33440646	SYNGAP1-AltEX11+79
<u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TGAG	145			chr6	33440631	33440647	SYNGAP1-AltEX11+80
<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TGA	146			chr6	33440632	33440648	SYNGAP1-AltEX11+81
T<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TG	147			chr6	33440633	33440649	SYNGAP1-AltEX11+82
TT<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>T	148			chr6	33440634	33440650	SYNGAP1-AltEx11+83
<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TGAGG	149			chr6	33440630	33440648	SYNGAP1-AltEX11+79
T<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TGAG	150			chr6	33440631	33440649	SYNGAP1-AltEX11+80
TT<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TGA	151			chr6	33440632	33440650	SYNGAP1-AltEx11+81
AGGGAA<u>C</u>ATG<u>C</u>TGAGG	152			chr6	33440630	33440646	SYNGAP1-AltEX11+79
<u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TGAG	153			chr6	33440631	33440647	SYNGAP1-AltEX11+80
<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TGA	154			chr6	33440632	33440648	SYNGAP1-AltEX11+81
T<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TG	155			chr6	33440633	33440649	SYNGAP1-AltEX11+82
TT<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>T	156			chr6	33440634	33440650	SYNGAP1-AltEx11+83
<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TGAGG	157			chr6	33440630	33440648	SYNGAP1-AltEX11+79a
T<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TGAG	158			chr6	33440631	33440649	SYNGAP1-AltEX11+80a
TT<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TGA	159			chr6	33440632	33440650	SYNGAP1-AltEx11+81a
AGGGAA<u>C</u>ATG<u>C</u>TGAGG	160			chr6	33440630	33440646	SYNGAP1-AltEX11+79a
<u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TGAG	161			chr6	33440631	33440647	SYNGAP1-AltEX11+80a
<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TGA	162			chr6	33440632	33440648	SYNGAP1-AltEX11+81a
T<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>TG	163			chr6	33440633	33440649	SYNGAP1-AltEX11+82a
TT<u>C</u><u>C</u>AGGGAA<u>C</u>ATG<u>C</u>T	164			chr6	33440634	33440650	SYNGAP1-AltEx11+83a
<u>C</u>AGA<u>C</u>A<u>C</u><u>C</u>AGGGAGAGA<u>C</u> AG	165			chr6	33440389	33440409	SYNGAP1-IVS10-146(20)

ASO (Bold= 2'MOE, Italicized= LNA, underlined C= 5methylC)		ASO sequence with no mismatches		Coordinate			Name
A<u>C</u>AGA<u>C</u>A<u>CC</u>AGGGAGAGA C<u>A</u>G	166			chr6	33440389	33440410	SYNGAP1-IVS10-146(21)
AA<u>C</u>AGA<u>C</u>A<u>CC</u>AGGGAGAG A<u>C</u>AG	167			chr6	33440389	33440411	SYNGAP1-IVS10-146(22)
AAA<u>C</u>AGA<u>C</u>A<u>CC</u>AGGGAGA GA<u>C</u>AG	168			chr6	33440389	33440412	SYNGAP1-IVS10-146(23)
CAGACACCAGGGAGAGAC AG	169			chr6	33440389	33440409	SYNGAP1-IVS10-146(20)-P
ACAGACACCAGGGAGAGA CAG	170			chr6	33440389	33440410	SYNGAP1-IVS10-146(21)-P
AACAGACACCAGGGAGAG ACAG	171			chr6	33440389	33440411	SYNGAP1-IVS10-146(22)-P
AAACAGACACCAGGGAGA GACAG	172			chr6	33440389	33440412	SYNGAP1-IVS10-146(23)-P
ATGGGAGAGAGATGGAGG	30			chr6	33440369	33440387	SYNGAP1-IVS10-166
<u>C</u>AGAGATGGGAGAGAGAT	31			chr6	33440374	33440392	SYNGAP1-IVS10-161
AGAGA<u>C</u>AGAGATGGGAGA	32			chr6	33440379	33440397	SYNGAP1-IVS10-156
<u>C</u>AGGGAGAGA<u>C</u>AGAGATG	33			chr6	33440384	33440402	SYNGAP1-IVS10-151
GA<u>C</u>A<u>CC</u>AGGGAGAGA<u>C</u>AG	34			chr6	33440389	33440407	SYNGAP1-IVS10-146
AAA<u>C</u>AGA<u>C</u>A<u>CC</u>AGGGAGA	35			chr6	33440394	33440412	SYNGAP1-IVS10-141
AAGAAAAA<u>C</u>AGA<u>C</u>A<u>CC</u>AG	36			chr6	33440399	33440417	SYNGAP1-IVS10-136
AGGAGAAGAAAAA<u>C</u>AGA<u>C</u>	37			chr6	33440404	33440422	SYNGAP1-IVS10-131
AGAGGAGGAGAAGAAAAA	38			chr6	33440409	33440427	SYNGAP1-IVS10-126
<u>C</u>AAGGAGAGGAGGAGAAG	39			chr6	33440414	33440432	SYNGAP1-IVS10-121
AGAGA<u>C</u>AAGGAGAGGAGG	40			chr6	33440419	33440437	SYNGAP1-IVS10-116
GGGAGAGAGA<u>C</u>AAGGAGA	41			chr6	33440424	33440442	SYNGAP1-IVS10-111
GGTGTGGGAGAGAGA<u>C</u>AA	42			chr6	33440429	33440447	SYNGAP1-IVS10-106
GGAGGGTTGTGGGAGAGA	43			chr6	33440434	33440452	SYNGAP1-IVS10-101
GAGATGGATGGGTGTGGG	44			chr6	33440439	33440457	SYNGAP1-IVS10-96
GGAGAGAGATGGATGGGT	45			chr6	33440444	33440462	SYNGAP1-IVS10-91
A<u>C</u>GTGGGAGAGAGATGGA	46			chr6	33440449	33440467	SYNGAP1-IVS10-86
GAGA<u>C</u>A<u>C</u>GTGGGAGAGAG	47			chr6	33440454	33440472	SYNGAP1-IVS10-81
AGGGAGAGA<u>C</u>A<u>C</u>GTGGGA	48			chr6	33440459	33440477	SYNGAP1-IVS10-76
GGTGAGGGAAGAGA<u>C</u>A<u>C</u>G	49			chr6	33440464	33440482	SYNGAP1-IVS10-71
GAGAAGGTGAAGGGAGAG	50			chr6	33440469	33440487	SYNGAP1-IVS10-66
AGGGAGAGAAGGTGAGGG	51			chr6	33440474	33440492	SYNGAP1-IVS10-61
TGGAGGGAGAGAGAAGGT	52			chr6	33440479	33440497	SYNGAP1-IVS10-56
AGAAATGGAGAGGGAGAG	53			chr6	33440484	33440502	SYNGAP1-IVS10-51
GAGAGAGAAATGGAGGGA	54			chr6	33440489	33440507	SYNGAP1-IVS10-46
TTAGGGAGAGAGAAATGG	55			chr6	33440494	33440512	SYNGAP1-IVS10-41
A<u>C</u>AGATTAGGGAGAGAGA	56			chr6	33440499	33440517	SYNGAP1-IVS10-36
AA<u>C</u>AGA<u>C</u>AGATTAGGGAG	57			chr6	33440504	33440522	SYNGAP1-IVS10-31
GAGGGAA<u>C</u>AGA<u>C</u>AGATTA	58			chr6	33440509	33440527	SYNGAP1-IVS10-26
TGG<u>C</u>AGAGGGAA<u>C</u>AGA<u>C</u>A	59			chr6	33440514	33440532	SYNGAP1-IVS10-21
GG<u>CC</u>ATGG<u>C</u>AGAGGGAA<u>C</u>	60			chr6	33440519	33440537	SYNGAP1-IVS10-16
AAGGGAG<u>CC</u>ATGG<u>C</u>AGAG	61			chr6	33440524	33440542	SYNGAP1-IVS10-11

ASO (Bold= 2'MOE, Italicized= LNA, underlined C= 5methylC)		ASO sequence with no mismatches		Coordinate			Name
TGAAGAAGGAGGCCATGG	62			chr6	33440529	33440547	SYNGAP1-IVS10-6
CTGCTTGAAGAAGAGGGC	63			chr6	33440534	33440552	SYNGAP1-IVS10-1
GGAGGCTGCTTGAAGAAG	64			chr6	33440539	33440557	SYNGAP1-I10AltE11+5
AGATGGGAGGCTGCTTGA	65			chr6	33440544	33440562	SYNGAP1-I10AltE11+10
GAGCAAGATGGGAGGCTG	66			chr6	33440549	33440567	SYNGAP1-I10AltE11+15
CAGGAGCAAGATGGGAGG	67			chr6	33440554	33440572	SYNGAP1-AltEx11+1
GACCGCAGGAGCAAGATG	68			chr6	33440559	33440577	SYNGAP1-AltEx11+6
GGAGGGACCGCAGGAGCA	69			chr6	33440564	33440582	SYNGAP1-AltEx11+11
GGGAAGGAGGGACCGCAG	70			chr6	33440569	33440587	SYNGAP1-AltEx11+16
AGACAGGGAAGGAGGGAC	71			chr6	33440574	33440592	SYNGAP1-AltEx11+21
GAGAGAGACAGGGAAGGA	72			chr6	33440579	33440597	SYNGAP1-AltEx11+26
AGGGTGAGAGAGACAGGG	73			chr6	33440584	33440602	SYNGAP1-AltEx11+31
AAACAGGGATGAGAGAGA	74			chr6	33440589	33440607	SYNGAP1-AltEx11+36
TGTGGAAACAAGGGTGAG	75			chr6	33440594	33440612	SYNGAP1-AltEx11+41
GAGGGTGTGGAAACAGGG	76			chr6	33440599	33440617	SYNGAP1-AltEx11+46
GAGGTGAGGGTGTGGAAA	77			chr6	33440604	33440622	SYNGAP1-AltEx11+51
GGTAGGAGGTGAGGGTGT	78			chr6	33440609	33440627	SYNGAP1-AltEx11+56
AGGGTGGTAGGAGGTGAG	79			chr6	33440614	33440632	SYNGAP1-AltEx11+61
TGAGGGAGGTGGTAGGAG	80			chr6	33440619	33440637	SYNGAP1-AltEx11+66
CATGCTGAGGAGGGTGGT	81			chr6	33440624	33440642	SYNGAP1-AltEx11+71
GGGAACATGCTGAGAGGG	82			chr6	33440629	33440647	SYNGAP1-AltEx11+76
TTCCAGGGAACATGCTGA	83			chr6	33440634	33440652	SYNGAP1-AltEx11+81
TCAGCTTCCAGGGAACAT	84			chr6	33440639	33440657	SYNGAP1-AltEx11+86
GGGAGAGAGATGGATGGG	85			chr6	33408222	33408239	SYNGAP1-IVS10-90
TGGGAGAGAGATGGAGGG	86			chr6	33408223	33408240	SYNGAP1-IVS10-89
GTGGGAGAGAGATGGAGG	87			chr6	33408224	33408241	SYNGAP1-IVS10-88
CGTGGGAGAGAGATGGAG	88			chr6	33408225	33408242	SYNGAP1-IVS10-87
CACGTGGGAGAGAGATGG	89			chr6	33408227	33408244	SYNGAP1-IVS10-85
ACACGTGGGAGAGAGATG	90			chr6	33408228	33408245	SYNGAP1-IVS10-84
GACACGTGGGAGAGAGAT	91			chr6	33408229	33408246	SYNGAP1-IVS10-83
AGACACGTGGGAGAGAGA	92			chr6	33408230	33408247	SYNGAP1-IVS10-82
AGAGACACGTGGGAGAGA	93			chr6	33408232	33408249	SYNGAP1-IVS10-80
GAGAGACACGTGGGAGAG	94			chr6	33408233	33408250	SYNGAP1-IVS10-79
GGAGAGACACGTGGGAGA	95			chr6	33408234	33408251	SYNGAP1-IVS10-78
GGGAGAGACACGTGGGAG	96			chr6	33408235	33408252	SYNGAP1-IVS10-77
AGGGAACATGCTGATGGG	97			chr6	33408405	33408422	SYNGAP1-AltEX11+77
CAGGGAACATGCTGAGGG	98			chr6	33408406	33408423	SYNGAP1-AltEX11+78
CCAGGGAACATGCTGAGG	99			chr6	33408407	33408424	SYNGAP1-AltEX11+79
TCCAGGGAACATGCTGAG	100			chr6	33408408	33408425	SYNGAP1-AltEX11+80

ASO (Bold= 2'MOE, Italicized= LNA, underlined C= 5methylC)		ASO sequence with no mismatches		Coordinate			Name
CTTCCAGGGAACATGCTG	101			chr6	33408410	33408427	SYNGAP1-AltEX11+82
GCTTCCAGGGAACATGCT	102			chr6	33408411	33408428	SYNGAP1-AltEX11+83
AGCTTCCAGGGAACATGC	103			chr6	33408412	33408429	SYNGAP1-AltEX11+84
CAGCTTCCAGGGAACATG	104			chr6	33408413	33408430	SYNGAP1-AltEX11+85
GAGACACGTGGGAGAG	105			chr6	33408233	33408248	SYNGAP1-IVS10-81(16)
GACACGTGGGAGAGAG	106			chr6	33408231	33408246	SYNGAP1-IVS10-83(16)
CACGTGGGAGAGAGAT	107			chr6	33408229	33408244	SYNGAP1-IVS10-85(16)
CGTGGGAGAGAGATGG	108			chr6	33408227	33408242	SYNGAP1-IVS10-87(16)
GTGGGAGAGAGATGGA	109			chr6	33408226	33408241	SYNGAP1-IVS10-88(16)
GAGACACGTGGGAG	110			chr6	33408235	33408248	SYNGAP1-IVS10-81(14)
GACACGTGGGAGAG	111			chr6	33408233	33408246	SYNGAP1-IVS10-83(14)
CACGTGGGAGAGAG	112			chr6	33408231	33408244	SYNGAP1-IVS10-85(14)
CGTGGGAGAGAGAT	113			chr6	33408229	33408242	SYNGAP1-IVS10-87(14)
TGGGAGAGAGATGG	114			chr6	33408227	33408240	SYNGAP1-IVS10-89(14)
GGGAGAGAGATGGA	115			chr6	33408226	33408239	SYNGAP1-IVS10-90(14)
GAGACACGTGGG	116			chr6	33408237	33408248	SYNGAP1-IVS10-81(12)
GACACGTGGGAG	117			chr6	33408235	33408246	SYNGAP1-IVS10-83(12)
CACGTGGGAGAG	118			chr6	33408233	33408244	SYNGAP1-IVS10-85(12)
CGTGGGAGAGAG	119			chr6	33408231	33408242	SYNGAP1-IVS10-87(12)
TGGGAGAGAGAT	120			chr6	33408229	33408240	SYNGAP1-IVS10-89(12)
GGAGAGAGATGG	121			chr6	33408227	33408238	SYNGAP1-IVS10-91(12)
GAGAGAGATGGA	122			chr6	33408226	33408237	SYNGAP1-IVS10-92(12)

Table 2. Exemplary ASOs targeting NMD Exon 18x event

ASO (Bold = 2' MOE, Italicized = 2' O-Me, Underlined C = 5methylC Bold and italicized = 2'-Fluoro)		Genomic Coordinates (GRCh38/ hg38)			Name
Sequence 5'-3'	**SEQ ID NO:**	**Chr**	**Start**	**End**	**Position ID**
AGGAGTATGGGTAGGAAA	195	chr6	33448685	33448703	SYNGAP1:NM_006772:IVS17:-86
CAAAGAGGAGTATGGGTA	196	chr6	33448690	33448708	SYNGAP1:NM_006772:IVS17:-81
CAGAGCAAAGAGGAGTAT	197	chr6	33448695	33448713	SYNGAP1:NM_006772:IVS17:-76
GCAGTCAGAGCAAAGAGG	198	chr6	33448700	33448718	SYNGAP1:NM_006772:IVS17:-71
GCCTAGCAGTCAGAGCAA	199	chr6	33448705	33448723	SYNGAP1:NM_006772:IVS17:-66
GGGGAGCCTAGCAGTCAG	200	chr6	33448710	33448728	SYNGAP1:NM_006772:IVS17:-61
GGCGGGGGGAGCCTAGCA	201	chr6	33448715	33448733	SYNGAP1:NM_006772:IVS17:-56
TGGCAGGCGGGGGGAGCC	202	chr6	33448720	33448738	SYNGAP1:NM_006772:IVS17:-51
GGGGATGGCAGGCGGGGG	203	chr6	33448725	33448743	SYNGAP1:NM_006772:IVS17:-46

ASO (Bold = 2' MOE, Italicized = 2' O-Me, Underlined C = 5methylC Bold and italicized = 2'-Fluoro)		Genomic Coordinates (GRCh38/ hg38)			Name
GGTGGGGGGATGGCAGGC	204	chr6	33448730	33448748	SYNGAP1:NM_006772:IVS17:-41
GCCTTGGTGGGGGGATGG	205	chr6	33448735	33448753	SYNGAP1:NM_006772:IVS17:-36
CAGGAGCCTTGGTGGGGG	206	chr6	33448740	33448758	SYNGAP1:NM_006772:IVS17:-31
GGGGTCAGGAGCCTTGGT	207	chr6	33448745	33448763	SYNGAP1:NM_006772:IVS17:-26
GTCATGGGGTCAGGAGCC	208	chr6	33448750	33448768	SYNGAP1:NM_006772:IVS17:-21
GTGGGGTCATGGGGTCAG	209	chr6	33448755	33448773	SYNGAP1:NM_006772:IVS17:-16
AGAGAGTGGGGTCATGGG	210	chr6	33448760	33448778	SYNGAP1:NM_006772:IVS17:-11
GTGGGAGAGAGTGGGGTC	211	chr6	33448765	33448783	SYNGAP1:NM_006772:IVS17:-6
CTGCAGTGGGAGAGAGTG	212	chr6	33448770	33448788	SYNGAP1:NM_006772:IVS17:-1
AGGAGCTGCAGTGGGAGA	213	chr6	33448775	33448793	SYNGAP1:NM_006772:IVS17-EX18x:+5
TGATGAGGAGCTGCAGTG	214	chr6	33448780	33448798	SYNGAP1:NM_006772:IVS17-EX18x:+10
TTACCTGATGAGGAGCTG	215	chr6	33448785	33448803	SYNGAP1:NM_006772:IVS17-EX18x:+15
GAATTACCTGATGAGGAG	216	chr6	33448788	33448806	SYNGAP1:NM_006772:EX18x:+1
CAGGAGAATTACCTGATG	217	chr6	33448793	33448811	SYNGAP1:NM_006772:EX18x:+6
GGAACCAGGAGAATTACC	218	chr6	33448798	33448816	SYNGAP1:NM_006772:EX18x:+11
AAAGCGGAACCAGGAGAA	219	chr6	33448803	33448821	SYNGAP1:NM_006772:EX18x:+16
TGGCCAAAGCGGAACCAG	220	chr6	33448808	33448826	SYNGAP1:NM_006772:EX18x:+21
GCCCGTGGCCAAAGCGGA	221	chr6	33448813	33448831	SYNGAP1:NM_006772:EX18x:+26
CCTCCGCCCGTGGCCAAA	222	chr6	33448818	33448836	SYNGAP1:NM_006772:EX18x:+31
CCTGTGTCCTCCGCCCGT	223	chr6	33448825	33448843	SYNGAP1:NM_006772:EX18x:-26
CTCCCCCTGTGTCCTCCG	224	chr6	33448830	33448848	SYNGAP1:NM_006772:EX18x:-21
GTCACCTCCCCCTGTGTC	225	chr6	33448835	33448853	SYNGAP1:NM_006772:EX18x:-16
CCGGAGTCACCTCCCCCT	226	chr6	33448840	33448858	SYNGAP1:NM_006772:EX18x:-11
GTGGTCCGGAGTCACCTC	227	chr6	33448845	33448863	SYNGAP1:NM_006772:EX18x:-6
CTGCAGTGGTCCGGAGTC	228	chr6	33448850	33448868	SYNGAP1:NM_006772:EX18x:-1
AACCTGCAGTGGTCCGGA	229	chr6	33448853	33448871	SYNGAP1:NM_006772:EX18x-IVS18:-15
CGACCAACCTGCAGTGGT	230	chr6	33448858	33448876	SYNGAP1:NM_006772:EX18x-IVS18:-10
CTTCACGACCAACCTGCA	231	chr6	33448863	33448881	SYNGAP1:NM_006772:EX18x-IVS18:-5
GTGGGCTTCACGACCAAC	232	chr6	33448868	33448886	SYNGAP1:NM_006772:IVS18:+1
AGGGAGTGGGCTTCACGA	233	chr6	33448873	33448891	SYNGAP1:NM_006772:IVS18:+6
GTTGGAGGGAGTGGGCTT	234	chr6	33448878	33448896	SYNGAP1:NM_006772:IVS18:+11
GAGGTGTTGGAGGGAGTG	235	chr6	33448883	33448901	SYNGAP1:NM_006772:IVS18:+16
CTCCGGAGGTGTTGGAGG	236	chr6	33448888	33448906	SYNGAP1:NM_006772:IVS18:+21
AGAGGCTCCGGAGGTGTT	237	chr6	33448893	33448911	SYNGAP1:NM_006772:IVS18:+26
AGGGGAGAGGCTCCGGAG	238	chr6	33448898	33448916	SYNGAP1:NM_006772:IVS18:+31
GTGAGAGGGGAGAGGCTC	239	chr6	33448903	33448921	SYNGAP1:NM_006772:IVS18:+36
CAGCAGTGAGAGGGGAGA	240	chr6	33448908	33448926	SYNGAP1:NM_006772:IVS18:+41
GAGGGCAGCAGTGAGAGG	241	chr6	33448913	33448931	SYNGAP1:NM_006772:IVS18:+46
GTGTGGAGGGCAGCAGTG	242	chr6	33448918	33448936	SYNGAP1:NM_006772:IVS18:+51

ASO (Bold = 2' MOE, Italicized = 2' O-Me, Underlined C = 5methylC Bold and italicized = 2'-Fluoro)		Genomic Coordinates (GRCh38/ hg38)			Name
TCTGGGTGTGGAGGGCAG	243	chr6	33448923	33448941	SYNGAP1:NM_006772:IVS18:+56
GGTTCTCTGGGTGTGGAG	244	chr6	33448928	33448946	SYNGAP1:NM_006772:IVS18:+61
GTGGAGGTTCTCTGGGTG	245	chr6	33448933	33448951	SYNGAP1:NM_006772:IVS18:+66
AGTCTGTGGAGGTTCTCT	246	chr6	33448938	33448956	SYNGAP1:NM_006772:IVS18:+71
GCTGGAGTCTGTGGAGGT	247	chr6	33448943	33448961	SYNGAP1:NM_006772:IVS18:+76
GGAGGGCTGGAGTCTGTG	248	chr6	33448948	33448966	SYNGAP1:NM_006772:IVS18:+81
GTGTCGGAGGGCTGGAGT	249	chr6	33448953	33448971	SYNGAP1:NM_006772:IVS18:+86
AAAGCGGAACCAG	250	chr6	33448808	33448821	
CAAAGCGGAACCAG	251	chr6	33448808	33448822	
CCAAAGCGGAACCAG	252	chr6	33448808	33448823	
GCCAAAGCGGAACCAG	253	chr6	33448808	33448824	
GCCAAAGCG*7dG*AACCAG	254	chr6	33448808	33448824	
GCCAAAGCGGAAC*C*AG	255	chr6	33448808	33448824	
***G*CCAAAGCGGAACCAG**	256	chr6	33448808	33448824	
GCCAAAG*C*GGAACCAG	257	chr6	33448808	33448824	
GCCAAAGC*G*GAACCAG	258	chr6	33448808	33448824	
GCCAAAG*C*GGAACCAG	259	chr6	33448808	33448824	
GCCAAAGCGGAACCA*G*	260	chr6	33448808	33448824	
CTTCACGACCAACCTG	261	chr6	33448865	33448881	
CTTCACGACCAACCT	262	chr6	33448866	33448881	
CTTCACGACCAACC	263	chr6	33448867	33448881	
CTTCACGACCAAC	264	chr6	33448868	33448881	
TCACGACCAACCTGCA	265	chr6	33448863	33448879	
GGCTTCACGACCAAC	266	chr6	33448868	33448883	
GCTTCACGACCAAC	267	chr6	33448868	33448882	
CTTC*A*C*GA*CC*AA*CCT*G*C*A*	268	chr6	33448863	33448881	SYNGAP1:NM_006772:EX18x-IVS18:-5
CTTCACGAC*C*AACCTGCA	269	chr6	33448863	33448881	SYNGAP1:NM_006772:EX18x-IVS18:-5
CTTCACGACCAACCT*7dG*CA	270	chr6	33448863	33448881	SYNGAP1:NM_006772:EX18x-IVS18:-5
CTTCACGACCAAC*C*TGCA	271	chr6	33448863	33448881	SYNGAP1:NM_006772:EX18x-IVS18:-5
C*U*TCACGACCAACCTGCA	272	chr6	33448863	33448881	SYNGAP1:NM_006772:EX18x-IVS18:-5
CTTCACGAC*C*AACCTGCA	273	chr6	33448863	33448881	SYNGAP1:NM_006772:EX18x-IVS18:-5
CTTCACCACCAACCTGCA	274	chr17	26967755	26967773	
GTCAAAGCGGAACCAG	275	chr17	26967700	26967716	

Table 3. SYNGAP1 sequences related to NSAE event

SYNGAP1	
Canonical intron chr6:33438919-33440728	gtgagactgggaacgctgggctgggggccagggtcgggggaattatgtgttcatctgttcatcta tctgtccatcctcaaagaggactgagcaccatttatgggcaaagcattgttctaggcgctatagagc aaacaggtgaaagaggcctggtccctgccctcagagggcctccaccagaatggggacaaattag aagaaaaaaaaaaaaagccacagagccataatggtgtgtaagtgctgagtaagggtccccccaa cctctgtgtgacataaggtcagagagaaggcagagctttgagataagtggggaagaggtgcccc cttgggtaggctttgaagactggtttaggttctgatatatggacatagttggcaagaaagacatttca gaagaaggctgtgagaaaggcacatgtgtgatggtgaaaaggcccaggagttttcaggggacatt aaagtaggttagtagcaattacatcaggtttagtggagcatgtgcctcataatggggagtggcggg agagatgtctgggcaggaagattagctttagaaactggaaggcctcaaggagtctgaggtcattg gtaggccttgggatgccattaaaggtgtcagaaatattgtgatttagaagattaatccataggctggg cacggtggctcacacctgtaataccagcactttgggaggctgaggcgggcagaccacctgaggt caggagtttgagaccaggctgaccaacatggagaaaccctgtctctactaaaaatacaaaattagc cagatgtggtggcacatgcctgtaatcccagctattcgggaggctaaggcaggagaatcacttga atctgggaggtggaggttgtagtgagccgagatcacacgattgcactctagcctgggcaacaaga gtgaaactccatctcaaaaaaaaaaaattaatccataagtagagtgtatgtagtagagtagagggat gtatgttgggggatgactggaatagagccagctgggggctcggaggcatgaaagtcagatcctg aatcagaacagtgacagaagttaggaaggagctactggaaggaccctctcgggaaaggatcagt aggaattgtcagcttattggaaaggagggagcatgtctgtggggagtcacggatgactcaagagg ccatgaggctggtggttgggagaccggtggcctcattgacaaccaggaaagtcaggaggagga gccagttggaggtgtgggggcgatggtgagctctgctttacaccagccgagtttaaggtgtcagtg ggacattgaagtggaactgggaggtgcggggagtgagctctgagccattccagggactggggat catgcctggggcacctccatccccatttccctggaatccagaagagttggggggtccgagctccct gtacctcaagtgaccctccatctctctcccatctctgtctctccctggtgtctgttttttcttctcctctc cttgtctctctcccacacccctccatctctctcccacgtgtctctcccctcaccttctctcccccctccatt tctctctccctaatctgtctgttccctctgccatggcccccttcttcaagcagcctcccatcttgctcctg cggtccctccttccctgtctctctcaccccctgtttccacaccctcacctcctaccacccccctcagcat gttccctggaagctgagggtctctggggctcagtcccggtctctctctttctctctctctctctgtct ccccgacccttcccccccag (SEQ ID NO: 276)
Alternative intron chr6:33438919-33440552	gtgagactgggaacgctgggctgggggccagggtcgggggaattatgtgttcatctgttcatcta tctgtccatcctcaaagaggactgagcaccatttatgggcaaagcattgttctaggcgctatagagc aaacaggtgaaagaggcctggtccctgccctcagagggcctccaccagaatggggacaaattag aagaaaaaaaaaaaaagccacagagccataatggtgtgtaagtgctgagtaagggtccccccaa cctctgtgtgacataaggtcagagagaaggcagagctttgagataagtggggaagaggtgcccc cttgggtaggctttgaagactggtttaggttctgatatatggacatagttggcaagaaagacatttca gaagaaggctgtgagaaaggcacatgtgtgatggtgaaaaggcccaggagttttcaggggacatt aaagtaggttagtagcaattacatcaggtttagtggagcatgtgcctcataatggggagtggcggg

	agagatgtctgggcaggaagattagctttagaaactggaaggcctcaaggagtctgaggtcattg gtaggccttgggatgccattaaaggtgtcagaaatattgtgatttagaagattaatccataggctggg cacggtggctcacacctgtaataccagcactttgggaggctgaggcgggcagaccacctgaggt caggagtttgagaccaggctgaccaacatggagaaaccctgtctctactaaaaatacaaaattagc cagatgtggtggcacatgcctgtaatcccagctattcgggaggctaaggcaggagaatcacttga atctgggaggtggaggttgtagtgagccgagatcacacgattgcactctagcctgggcaacaaga gtgaaactccatctcaaaaaaaaaaaattaatccataagtagagtgtatgtagtagagtagagggat gtatgttgggggatgactggaatagagccagctgggggctcggaggcatgaaagtcagatcctg aatcagaacagtgacagaagttaggaaggagctactggaaggaccctctcgggaaaggatcagt aggaattgtcagcttattggaaaggagggagcatgtctgtggggagtcacggatgactcaagagg ccatgaggctggtggttgggagaccggtggcctcattgacaaccaggaaagtcaggaggagga gccagttggaggtgtgggggcgatggtgagctctgctttacaccagccgagtttaaggtgtcagtg ggacattgaagtggaactgggaggtgcggggagtgagctctgagccattccagggactggggat catgcctggggcacctccatccccatttccctggaatccagaagagttgggggtccgagctccct gtacctcaagtgaccctccatctctctcccatctctgtctctccctggtgtctgtttttcttctcctcctc cttgtctctctcccacacccctccatctctctcccacgtgtctctcccctcaccttctctcccccctccatt tctctctccctaatctgtctgttccctctgccatggccccccttcttcaagcag (SEQ ID NO: 277)
Canonical exon chr6:33440729-33440965	CGTGTTCCCGAGGGAGCTGAAGGAGGTGTTTGCTTCGTGGC GGCTGCGCTGCGCAGAGCGAGGCCGGGAGGACATCGCAGA CAGGCTTATCAGCGCCTCACTCTTCCTGCGCTTCCTCTGCCC AGCGATTATGTCGCCCAGTCTCTTTGGGCTTATGCAGGAGT ACCCAGATGAGCAGACCTCACGAACCCTCACCCTCATTGCC AAGGTCATCCAGAACCTGGCCAACTTTTCCAA (SEQ ID NO: 278)
Alternative exon chr6:33440553-33440965	CCTCCCATCTTGCTCCTGCGGTCCCTCCTTCCCTGTCTC TCTCACCCCTGTTTCCACACCCTCACCTCCTACCACCC CCCTCAGCATGTTCCCTGGAAGCTGAGGGTCTCTGGG GCTCAGTCCCGGTCTCTCTCTTTCTCTCTCTCTCTCTCT GTCTCCCCGACCCTTCCCCCCAGCGTGTTCCCGAGGGA GCTGAAGGAGGTGTTTGCTTCGTGGCGGCTGCGCTGC GCAGAGCGAGGCCGGGAGGACATCGCAGACAGGCTT ATCAGCGCCTCACTCTTCCTGCGCTTCCTCTGCCCAGC GATTATGTCGCCCAGTCTCTTTGGGCTTATGCAGGAGT ACCCAGATGAGCAGACCTCACGAACCCTCACCCTCAT TGCCAAGGTCATCCAGAACCTGGCCAACTTTTCCAA (SEQ ID NO: 279)

gactgaaaagaagatgggagtggaaaagaataaagccagtttctgcttcccagggatgcagagattggggcatgctgtgtctgcagaa
gctcctagtcatttccgccataattgtgagagagaggggcagccctcccacaagatttttcccttcccatatcacttccctgaatccccttcct
ttcccccccagtacagttaaacctctctctaatttggaatgttatatttgagaagatggccactgtgaataagtgacaaacggaatgacagtgt
ctatttaatgaaatgcatgtcttcaaaatatatacagaactcgatgaacaaggctttttccactcctcagggagcatgcattaatgaatagata
ggattcaaaagtctgttttctggtatgggttaaatatcccctcctacagacatatttccaccactaatttgcttagtacacctttttcttcacagata
aaggaaaatgcaagctcagtttttcttcagattatgaagaaattccaaatccacaggggtttggattaatgaggttttgctgtactgcctcccc
ttattcctcaacatgaagttcccacctcggattggggatgggtgggaggggggtttcaagaggaggagggtgggatgggcaaggaatata
cacaggtgaagccagagaagggttaggttgggggtgcggtgggaacttgctgttttgatctggtttcctggtgtgacactctgggttaaag
gcttgaaggcccctgttaggagtctaggggtgagattctcttctctctgatcccagaggacgttaacttctactgcaggtgagaaacaaaat
aggaggatggtggggactgtcctgggaggaggggggtggtccatggcttgtggtgtgggctggctataggggaggccactgctagggg
actggcatccaggccccctgaagcgtctcaataagtccgcgctctccttttggtgtcttgcag (SEQ ID NO: 280)

Gene: SYNGAP1

SYNGAP1 exon 18x: GRCh38/hg38: chr6 33448789 33448868

SYNGAP1 exon 18x sequence:

Ctcctcatcaggtaattctcctggttccgctttggccacgggcggaggacacagggggaggtgactccggaccactgcag (SEQ ID NO: 281)

[0316] For example, in some embodiments, SYNGAP1 (Gene ID: 8831) is an exemplary target of the NMD-inducing Alternative 5' splice site event or the NMD-inducing Alternative 3' splice site event. In some embodiments, the compositions or the methods as described herein may be used to treat AD mental retardation 5 (OMIM: 612621) related to the haploinsufficiency of SYNGAP1 in the CNS.

[0317] In some embodiments, the compositions or the methods as described herein are used to treat a condition or disease selected from the group consisting autosomal dominant mental retardation-5 (MRD5; AD Mental Retardation 5). In some embodiments, the compositions or the methods as described herein are used to treat a condition or disease of **Table 5B**. In some embodiments, the compositions or the methods as described herein are used to prevent, delay the progression and/or development of a sign or a symptom, or alleviate a sign or a symptom associated with a condition or disease of **Table 5B**.

Table 5A

Gene	Region coordinates			Event coordinates	Event type*
	chr	start	end	exon	
SYNGAP1	chr6	33438920	33440552	chr6 33440553 33440728 +	alt_3ss

*alt_3ss refers to an alternative 3’ splice site of an intron, which is equivalent to the alternative 5’ splice site of the exon immediately downstream of the intron. coordinate of alternative intron. Region coordinates: coordinates of alternative intron. Event coordinates: coordinates of intronic

ASO was intracerebroventricularly injected (ICV) into P2 *Syngap1* heterozygous (*Syngap1*$^{+/-}$) mice. Four weeks later, brains were dissected, and their hippocampi were assayed for Exon 18X inclusion by RT-PCR. The levels of the a1-isoform of SYNGAP1 protein were normalized to total protein via a ProteinSimple JESS assay.

Example 7: Evaluation of *in vivo* ASO target engagement and corresponding changes in SYNGAP1 protein expression levels in various brain regions of a *Syngap1*$^{+/-}$ mouse model

[0373] Male and female *Syngap1* heterozygous (*Syngap1*$^{+/-}$) mouse pups received intracerebroventricular injections of various amounts (3 µg, 10 µg, 20 µg, and 30 µg) of four different ASO compounds (compounds mm59, mm60, mm61, and mm62) (**Table 8**) on postnatal day 2 (PND2). Mouse brains were collected four weeks after ASO treatment and dissected such that ASO target engagement was analyzed in regions from the brain's left hemisphere and SYNGAP1 protein expression levels were analyzed in regions from the brain's right hemisphere.

[0374] After treatment with various ASO compounds, Exon 18X levels were measured by quantitative RT-PCR of exons 18-19. ASO target engagement was evaluated as the fold change in nonproductive mRNA normalized to mitochondrial ribosomal protein L16 (MRPL16) RNA. Protein levels were measured by capillary immuno-electrophoresis via ProteinSimple JESS assays. Effective ASO-mediated target engagement was measured as a decrease in Exon 18X inclusion and increase in protein levels of the alpha 1 (a1) isoform of SYNGAP1. The levels of the a1-isoform of SYNGAP1 protein were normalized to Actin. PBS was used as a negative control.

Table 8. Exemplary ASOs targeting the NMD Exon 18x event in mice and humans

Mouse ASO ID	Mouse Sequence (Bold = 2' MOE, Underlined C = 5methylC *Bold and italicized* = 2'-Fluoro) (Sequence 5'->3')	Human ASO ID	Human Sequence (Bold = 2' MOE, Underlined C = 5methylC *Bold and italicized* = 2'-Fluoro) (Sequence 5'->3')
mm59	**GTCAAAGCGGAACCAG (SEQ ID NO: 275)**	59	**GCCAAAGCGGAACCAG (SEQ ID NO: 253)**
mm60	***G*TCAAAGCGGAACCAG (SEQ ID NO: 282)**	59-3	***G*CCAAAGCGGAACCAG (SEQ ID NO: 256)**
mm61	**GTCAAAGCGGAA*A*CCAG (SEQ ID NO: 283)**	59-8	**GCCAAAGCGGAA*A*CCAG (SEQ ID NO: 285)**
mm62	***G*TCAAAGCGGAA*A*CCAG (SEQ ID NO: 284)**	59-9	***G*CCAAAGCGGAA*A*CCAG (SEQ ID NO: 17)**

[0375] Cerebral cortex

[0376] All four tested compounds resulted in an observable, dose-responsive decrease in nonproductive mRNA levels such that higher doses of each ASO resulted in greater decreases in nonproductive mRNA (**FIG. 10A**) in the cerebral cortex. ASO compound mm59 delivered intracerebroventricularly at 30 µg resulted in a decrease of nonproductive mRNA to about 0.3-fold of PBS-treated *Syngap1*$^{+/-}$ mice. ASO compound mm60 delivered intracerebroventricularly