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(54) **RNA MODULATING OLIGONUCLEOTIDES WITH IMPROVED CHARACTERISTICS FOR THE TREATMENT OF DUCHENNE AND BECKER MUSCULAR DYSTROPHY**

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(57) **ABSTRACT**

The current invention provides an improved oligonucleotide and its use for treating, ameliorating, preventing and/or delaying DMD or BMD.

Fig 1a

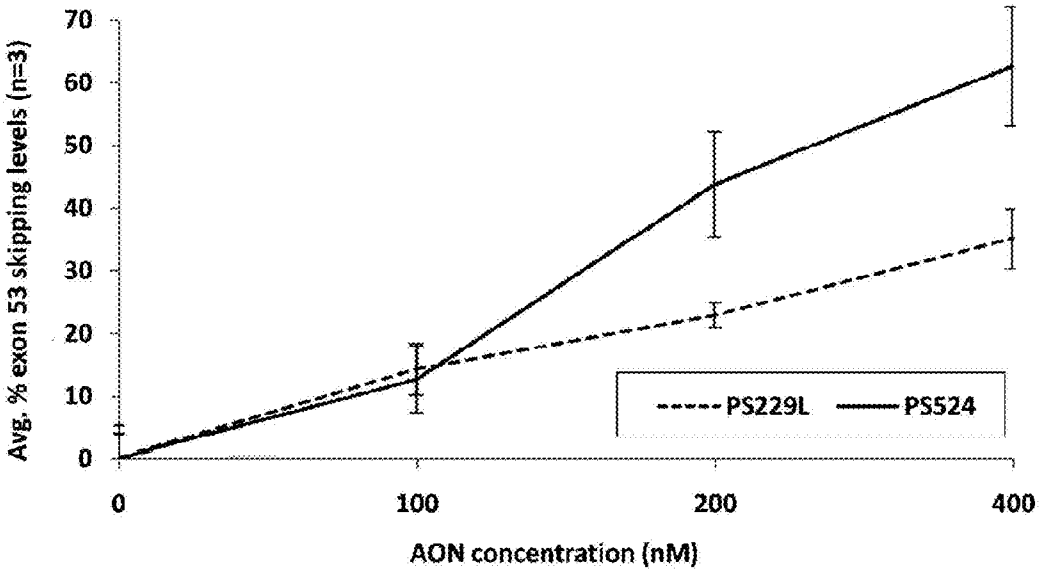

Avg. % exon 53 skipping levels (n=3)
70
60
50
40
30
20
10
0
0
100
200
400
AON concentration (nM)
PS229L
PS524

Fig 1b

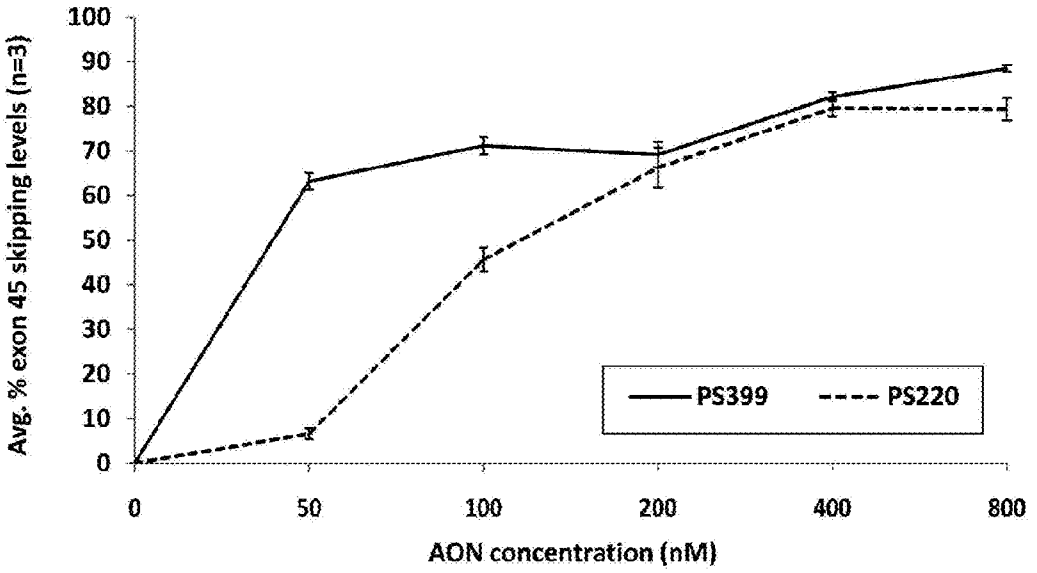
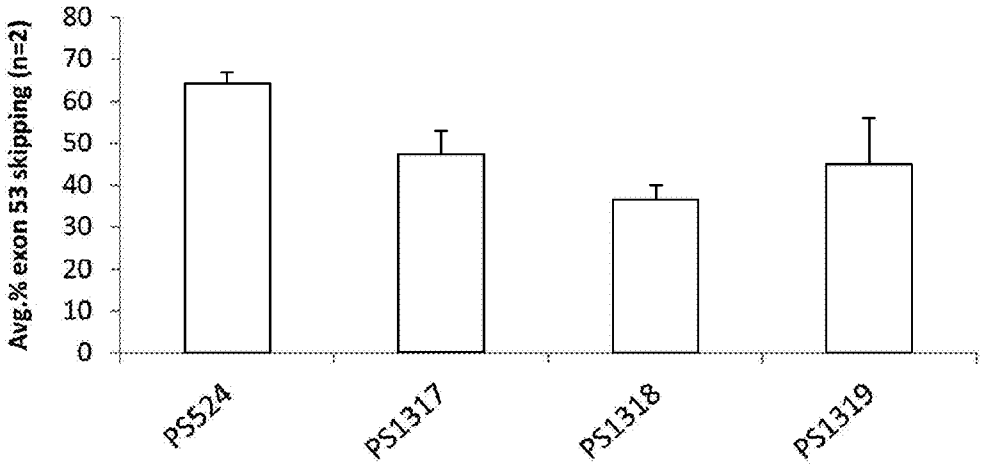

Avg. % exon 45 skipping levels (n=3)
100
90
80
70
60
50
40
30
20
10
0
0
50
100
200
400
800
AON concentration (nM)
PS399
PS220

Fig 1c



AON	Conc. (nM)	Sequence (5'-3')
PS524	400	GUUGCCUCCGGUUCUGAAGGUGUUC
PS1317	400	GUUGCCUCCGGUUCUGAAGGUGUUC
PS1318	400	GUUGCCUCCGGUUCUGAAGGUGUUC
PS1319	400	GUUGCCUCCGGUUCUGAAGGUGUUC

Fig 2a

Compound	*mdx* vs control (avg muscle)	Concentration AON (µg/g tissue) at day 14					Muscle/ liver	Muscle/ kidney	Half-life (tric)
		heart	dia	gastroc	quadr	tric			
PS229L	1.8	37.8	62.8	46.1	66.9	45.5	0.14	0.10	7
PS624	2.3	119.8	191.2	94.2	192.7	101.4	0.22	0.16	20+
PS631	1.8	52.7	85.0	64.6	76.6	56.5	0.11	0.12	10
PS652	2.0	149.5	168.7	274.7	171.3	122.8	0.10	0.10	25

Fig 2b

Compound	Dose (mg/kg)	Tmax (min)	Cmax/ dose (µg/ml)	AUC 0-24/ dose (µg.h/mL)	Cl 24h (L/kg/h)
PS229L	100	15	0.98	2.05	0.49
PS624	100	15	0.87	4.67	0.21
PS631	100	60	0.73	1.81	0.55
PS652	100	15	0.76	2.71	0.37

Fig 3a

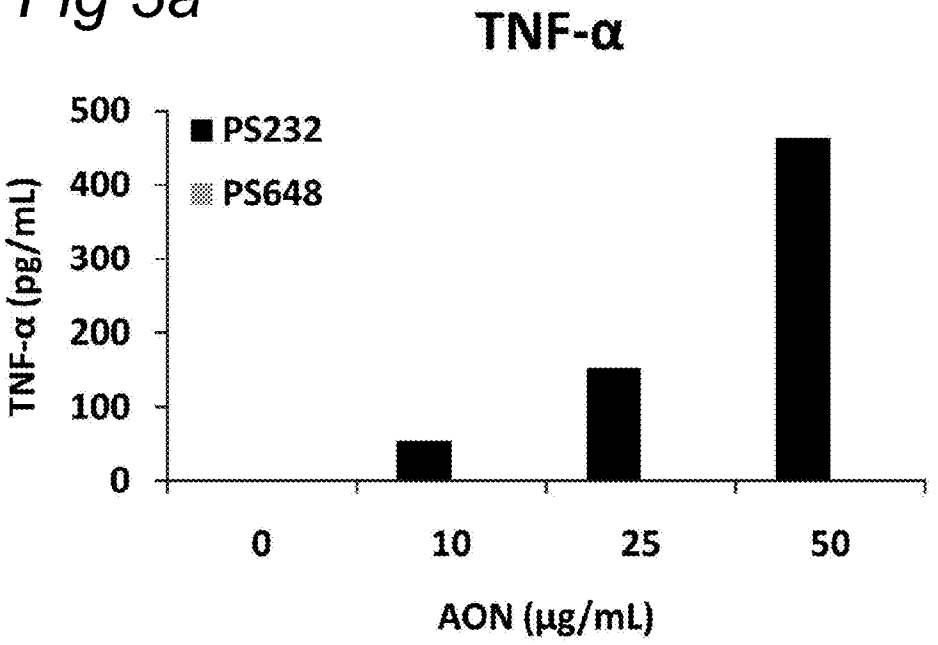

TNF-α
PS232
PS648
TNF-α (pg/mL)
500
400
300
200
100
0
0
10
25
50
AON (µg/mL)

Fig 3b

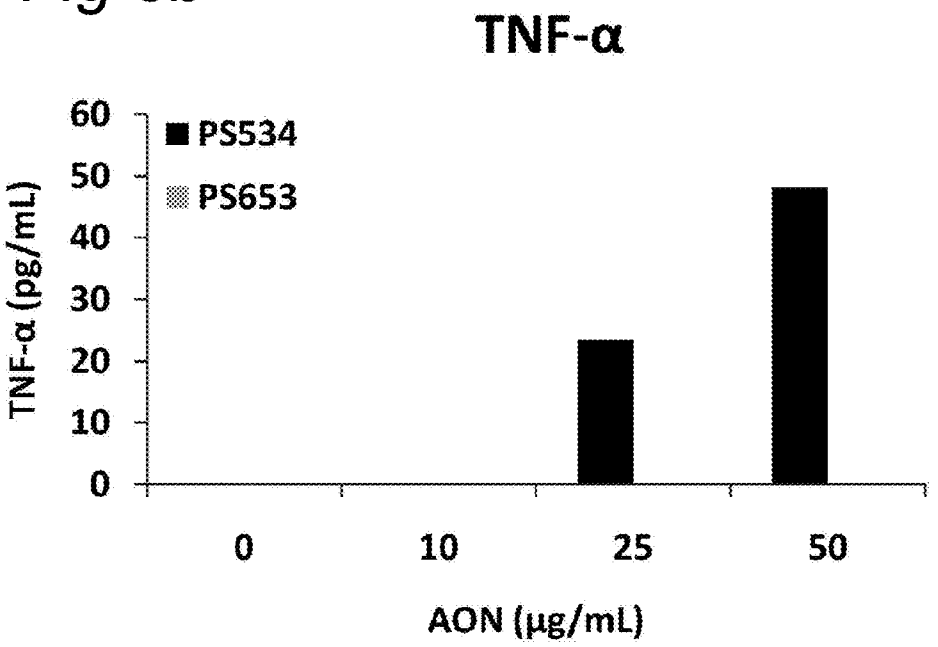

TNF-α
PS534
PS653
TNF-α (pg/mL)
60
50
40
30
20
10
0
0
10
25
50
AON (µg/mL)

Fig 3c

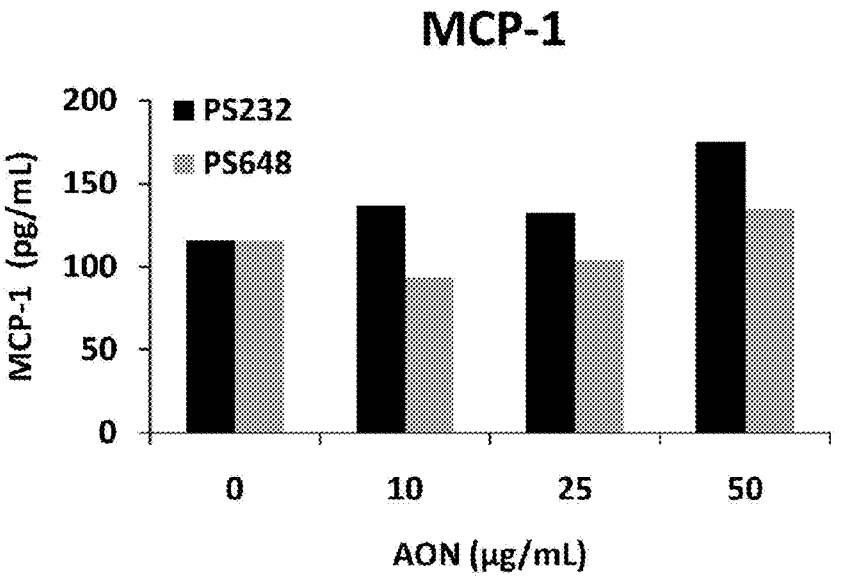

MCP-1
PS232
PS648
MCP-1 (pg/mL)
200
150
100
50
0
0
10
25
50
AON (µg/mL)

Fig 3d

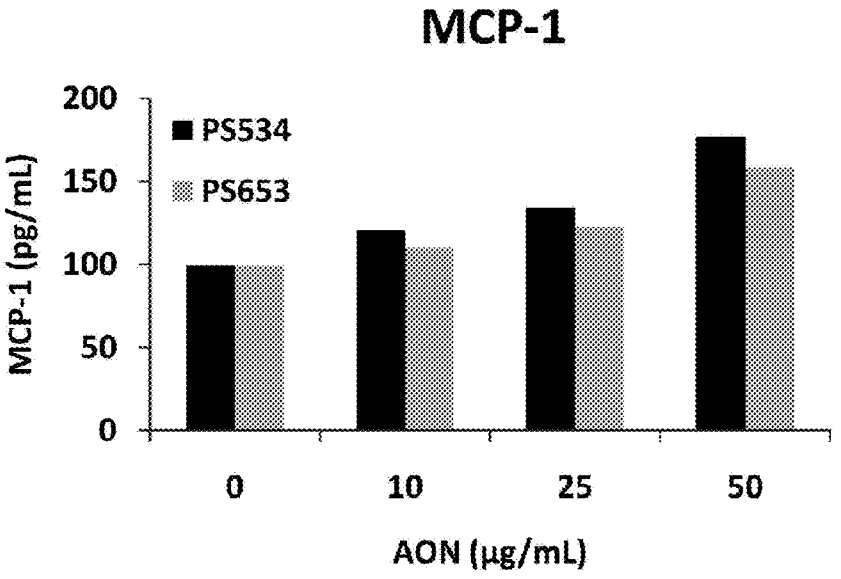

MCP-1
PS534
PS653
MCP-1 (pg/mL)
200
150
100
50
0
0
10
25
50
AON (µg/mL)

Fig 3e

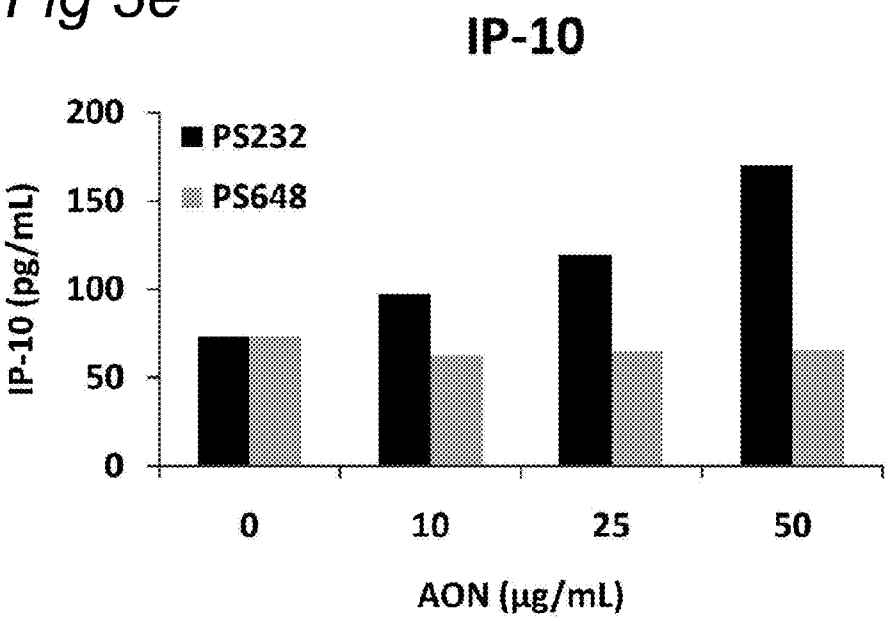

IP-10
PS232
PS648
IP-10 (pg/mL)
200
150
100
50
0
0
10
25
50
AON (µg/mL)

Fig 3f

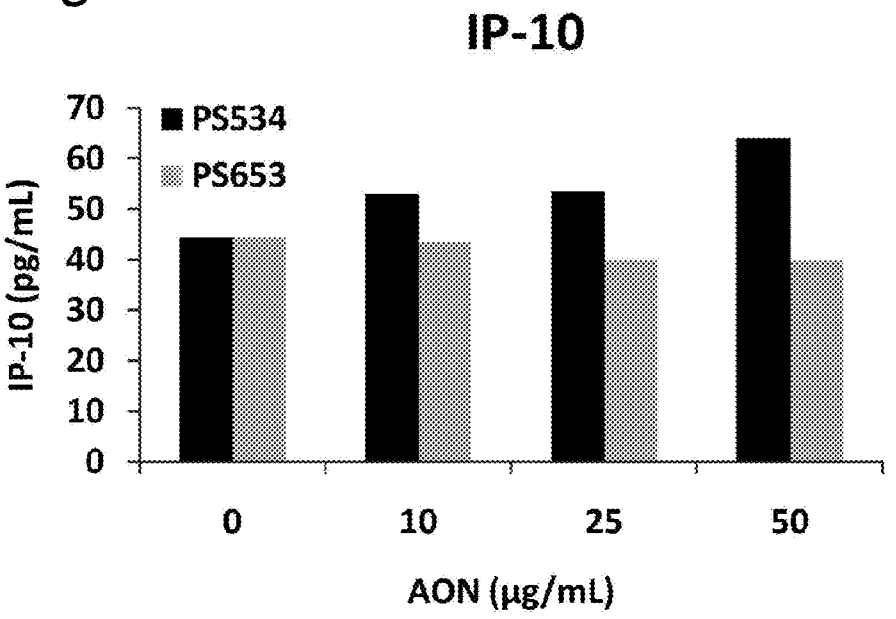

IP-10
PS534
PS653
IP-10 (pg/mL)
70
60
50
40
30
20
10
0
0
10
25
50
AON (µg/mL)

Fig 3g

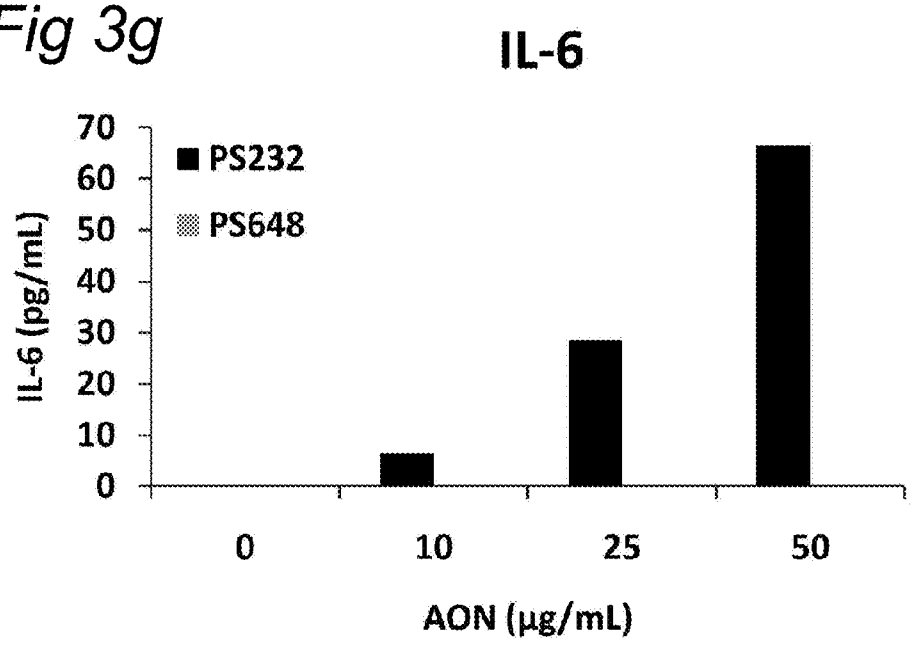

IL-6
70
60
50
40
30
20
10
0
IL-6 (pg/mL)
PS232
PS648
0
10
25
50
AON (µg/mL)

Fig 3h

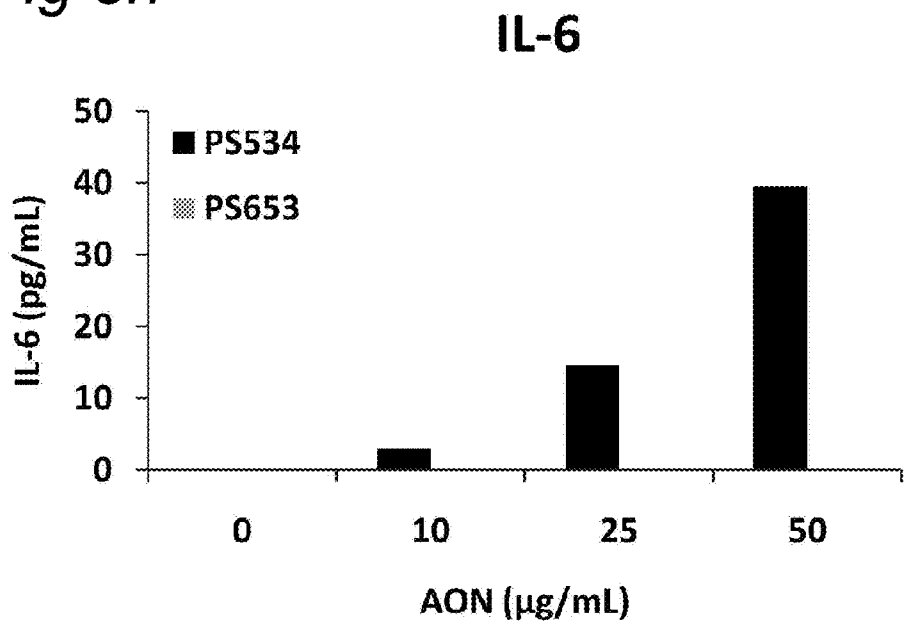
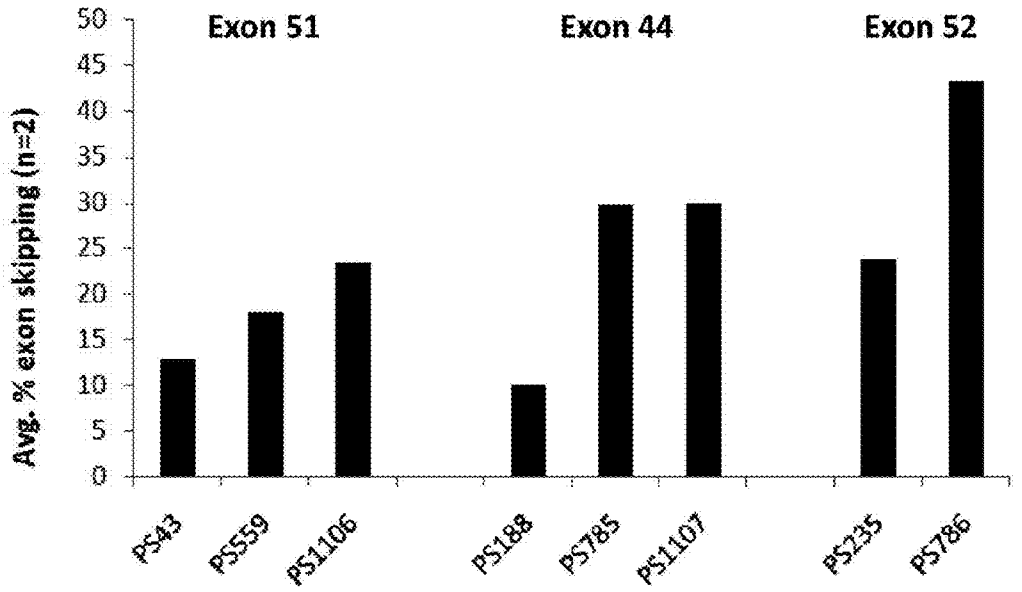
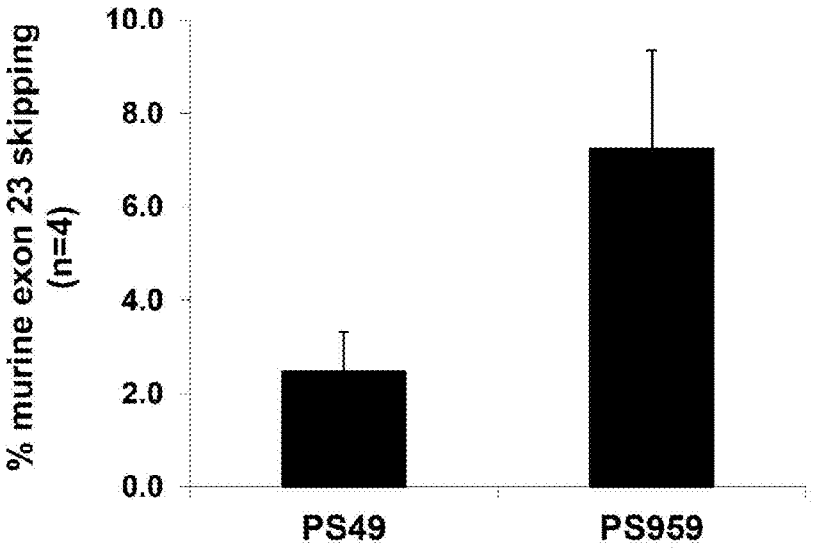

IL-6
50
40
30
20
10
0
IL-6 (pg/mL)
PS534
PS653
0
10
25
50
AON (µg/mL)

Fig 4a



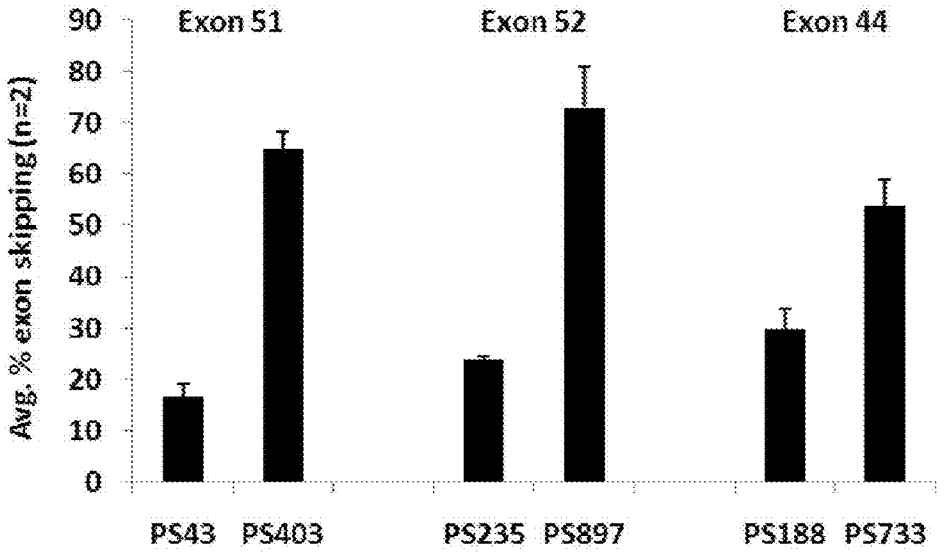
AON	Conc. (nM)	Sequence (5'-3')
PS43	200	UCAAGGAAGAUGGCAUUUCU
PS559	200	UCAAGGAAGAUGGCAUUUCU
PS1106	200	UCAAGGAAGAUGGCAUUUCU
PS188	200	UCAGCUUCUGUUAGCCACUG
PS785	200	UCAGCUUCUGUUAGCCACUG
PS1107	200	UCAGCUUCUGUUAGCCACUG
PS235	200	GGUAAUGAGUUCUUCCAACUGG
PS786	200	GGUAAUGAGUUCUUCCAACUGG

Fig 4b



AON	Sequence (5'-3')
PS49	GGCCAAACCUCGGCUUACCU
PS959	GGCCAAACCUCGGCUUACCU

Fig 5a



AON	Conc. (nM)	Sequence (5'-3')
PS43	200	UCAAGGAAGAUGGCAUUUCU
PS403	200	UCAAGGAAGAUGGCAUUUCU
PS235	200	GGUAAUGAGUUCUUCCAACUGG
PS897	200	GGUAAUGAGUUCUUCCAACUGG
PS188	200	UCAGCUUCUGUUAGCCACUG
PS733	200	UCAGCUUCUGUUAGCCACUG

Fig 5b

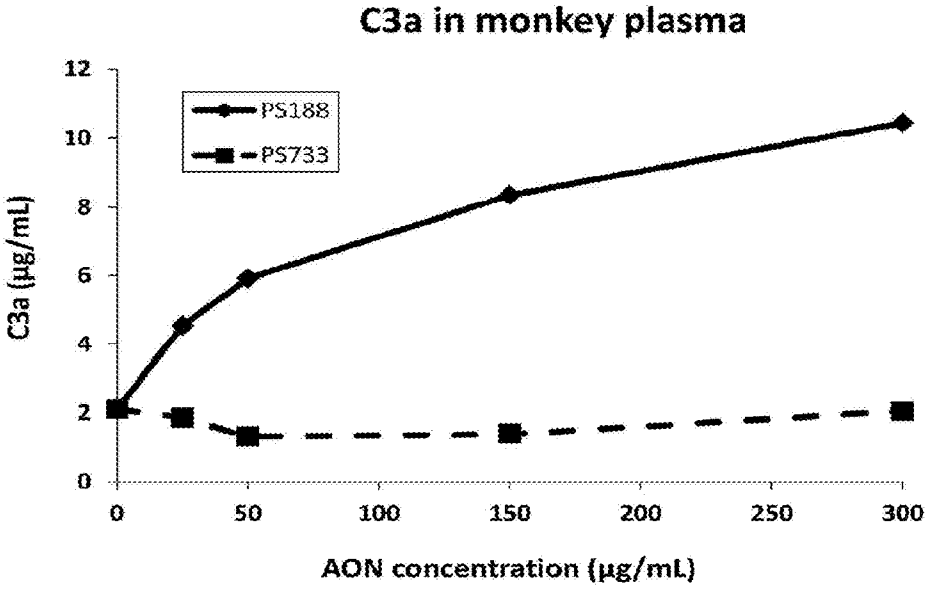
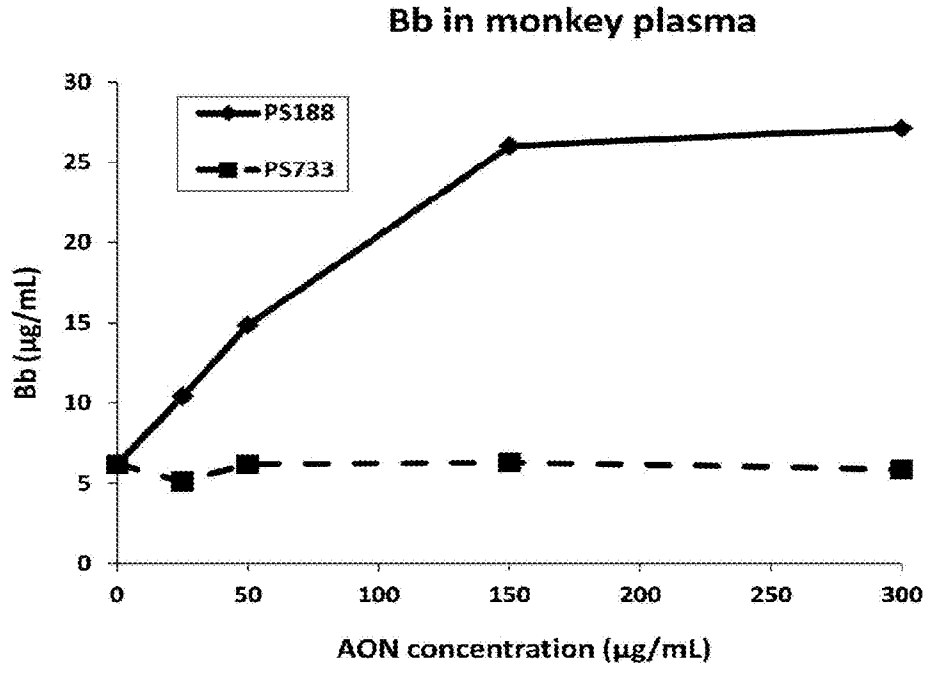

C3a in monkey plasma
PS188
PS733
C3a (µg/mL)
AON concentration (µg/mL)
0
2
4
6
8
10
12
0
50
100
150
200
250
300

Fig 5c


Bb in monkey plasma
PS188
PS733
Bb (µg/mL)
AON concentration (µg/mL)
0
5
10
15
20
25
30
0
50
100
150
200
250
300

RNA MODULATING OLIGONUCLEOTIDES WITH IMPROVED CHARACTERISTICS FOR THE TREATMENT OF DUCHENNE AND BECKER MUSCULAR DYSTROPHY

CROSS REFERENCE

[0001] This application is a continuation of international Patent Application No. PCT/NL2013/050045, filed Jan. 28, 2013, which claims the benefit of EP 12152934.1 filed Jan. 27, 2012, and U.S. Provisional Application Nos. 61/591,354 filed Jan. 27, 2012 and 61/612,467 filed Mar. 19, 2012, all of which are incorporated by reference in their entirety.

FIELD

[0002] The invention relates to the field of human genetics, more specifically neuromuscular disorders. The invention in particular relates to the use of an oligonucleotide with improved characteristics enhancing clinical applicability as further defined herein.

BACKGROUND OF THE INVENTION

[0003] Neuromuscular diseases are characterized by impaired functioning of the muscles due to either muscle or nerve pathology (myopathies and neuropathies). The myopathies include genetic muscular dystrophies that are characterized by progressive weakness and degeneration of skeletal, heart and/or smooth muscle. Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are the most common childhood forms of muscular dystrophy. DMD is a severe, lethal neuromuscular disorder resulting in a dependency on wheelchair support before the age of 12 and patients often die before the age of thirty due to respiratory- or heart failure. It is caused by reading frame-shifting deletions (~67%) or duplications (~7%) of one or more exons, or by point mutations (~25%) in the 2.24 Mb DMD gene, resulting in the absence of functional dystrophin. BMD is also caused by mutations in the DMD gene, but these maintain the open reading frame, yield semi-functional dystrophin proteins, and result in a typically much milder phenotype and longer lifespan. During the last decade, specific modification of splicing in order to restore the disrupted reading frame of the transcript has emerged as a promising therapy for DMD (van Ommen et al., 2008; Yokota et al., 2007; van Deutekom et al., 2007; Goemans et al., 2011; Cirak et al., 2011). Using highly sequence-specific antisense oligonucleotides (AONs) which bind to the exon flanking or containing the mutation and which interfere with its splicing signals, the skipping of that exon can be induced during the processing of the DMD pre-mRNA. Despite the resulting truncated transcript, the open reading frame is restored and a protein is introduced which is similar to those found in BMD patients. AON-induced exon skipping provides a mutation-specific, and thus personalized, therapeutic approach for DMD patients. Several oligonucleotides are currently being developed for skipping most relevant exons of the dystrophin pre-mRNA such as exons 2, 8, 9, 17, 29, 43, 44, 45, 46, 47, 48, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60-63, 71-78 as described in WO 02/024906, WO2004/083446, WO2006/112705, WO2007/135105, WO 2009/139630, WO 2010/050801 or WO 2010/050802.

[0004] As the majority of the mutations cluster around exons 45 to 55, the skipping of one specific exon may be therapeutic for many patients with different mutations. The skipping of exon 51 applies to the largest subset of patients (~13%), including those with deletions of exons 45 to 50, 48 to 50, 50, or 52. The AONs applied are chemically modified to resist endonucleases, exonucleases and RNaseH, and to promote RNA binding and duplex stability. Two different AON chemistries are currently being developed for exon 51 skipping in DMD: 2'-O-methyl phosphorothioate RNA AONs (2OMePS, GSK2402968/PRO051) and phosphorodiamidate morpholino oligomers (PMO, AVI-4658) (Goemans et al., 2011; Cirak et al., 2011). In two independent phase I/II studies, both were shown to specifically induce exon 51 skipping and at least partly restore dystrophin expression at the muscle fiber membranes after systemic administration. Although AONs are typically not well taken up by healthy muscle fibers, the dystrophin deficiency in DMD, resulting in damaged and thus more permeable fiber membranes, actually promotes uptake. In studies in the dystrophin-deficient mdx mouse model, 2'-O-methyl phosphorothioate RNA oligonucleotides have demonstrated an up to 10 times higher uptake in different muscle groups when compared to that in wild type mice (Heemskerk et al., 2010). Although the recent phase I/II results with both 2'-O-methyl phosphorothioate RNA and phosphorodiamidate morpholino AONs in DMD patients confirm this enhanced uptake in dystrophic muscle, the different chemical modifications seemed to result in a differential uptake by and distribution through muscle. The levels of novel dystrophin in both studies after 3 months of treatment were promising but still moderate and challenges the field to investigate next generation oligochemistry.

[0005] The particular characteristics of a chosen chemistry at least in part affects the delivery of an AON to the target transcript: administration route, biostability, biodistribution, intra-tissue distribution, and cellular uptake and trafficking. In addition, further optimization of oligonucleotide chemistry is conceived to enhance binding affinity and stability, enhance activity, improve safety, and/or to reduce cost of goods by reducing length or improving synthesis and/or purification procedures. Multiple chemical modifications have become generally and/or commercially available to the research community (such as 2'-O-methyl RNA and 5-substituted pyrimidines and 2,6-diaminopurines), whereas most others still present significant synthetic effort to obtain. Especially preliminary encouraging results have been obtained using 2'-O-methyl phosphorothioate RNA containing modifications on the pyrimidine and purine bases as identified herein.

[0006] In conclusion, to enhance the therapeutic applicability of AONs for DMD, there is a need for AONs with further improved characteristics.

DESCRIPTION OF THE INVENTION

Oligonucleotide

[0007] In a first aspect, the invention provides an oligonucleotide comprising a 2'-O-methyl RNA monomer and a phosphorothioatc backbone or consisting of 2'-O-methyl RNA monomers linked by phosphorothioate backbones, and comprising a 5-methylpyrimidine and/or a 2,6-diaminopurine base preferably for use as a medicament for treating Duchenne Muscular Dystrophy or Becker Muscular Dystrophy. Therefore, the invention provides an oligonucleotide comprising a 2'-O-methyl RNA monomer, a phosphorothioate backbone and a 5-methylpyrimidine and/or a 2,6-diami-

nopurine base preferably for use as a medicament for treating Duchenne Muscular Dystrophy or Becker Muscular Dystrophy.

[0008] Accordingly the invention also provides an oligonucleotide consisting of 2'-O-methyl RNA monomers and a phosphorothioate backbone and comprises a 5-methylpyrimidine and/or a 2,6-diaminopurine base preferably for use as a medicament for treating Duchenne Muscular Dystrophy or Becker Muscular Dystrophy.

[0009] It is clear for the skilled person that "an RNA monomer" as present in an oligonucleotide of the invention may also be identified as being "an RNA nucleotide residue". Both terms may be used interchangeably throughout the application.

[0010] Within the context of the invention, "a" in each of the following expressions means "at least one": a 2'-O-methyl RNA monomer, a 2'-O-methyl RNA nucleotide residue, a 2'-O-methyl phosphorothioate RNA monomer, a 5-methylpyrimidine base, a 2,6-diaminopurine base.

[0011] Within the context of the invention, it is clear for the skilled person that "an oligonucleotide comprising a 2'-O-methyl RNA monomer, a phosphorothioate backbone" could be replaced by "an oligonucleotide comprising a 2'-O-methyl RNA monomer linked by phosphorothioate backbones". The same holds for "an oligonucleotide consisting of 2'-O-methyl RNA monomers and a phosphorothioate backbone" that could be replaced by "an oligonucleotide consisting of 2'-O-methyl RNA monomer linked by phosphorothioate backbones".

[0012] In the context of the invention, the expression "for use as a medicament for treating Duchenne Muscular Dystrophy or Becker Muscular Dystrophy" could be replaced by the expression "for use in the treatment of Duchenne Muscular Dystrophy or Becker Muscular Dystrophy."

[0013] Preferably, an oligonucleotide is an oligonucleotide with less than 34 nucleotides. Said oligonucleotide may have 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides. Such oligonucleotide may also be identified as an oligonucleotide having from 10 to 33 nucleotides.

[0014] Accordingly, an oligonucleotide of the invention comprises a 2'-O-methyl RNA monomer and a phosphorothioate backbone and comprises less than 34 nucleotides (i.e. it comprises 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides).

[0015] Accordingly, an oligonucleotide of the invention consists of 2'-O-methyl RNA monomers linked by phosphorothioate backbone and comprises less than 34 nucleotides (i.e. it comprises 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides)

[0016] Accordingly, an oligonucleotide of the invention comprises a 2'-O-methyl RNA monomer, a phosphorothioate backbone, comprises less than 34 nucleotides (i.e. it comprises 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides) and a 5-methylpyrimidine and/or a 2,6-diaminopurine base.

[0017] Accordingly, an oligonucleotide of the invention consists of 2'-O-methyl RNA monomers linked by phosphorothioate backbone, and comprises less than 34 nucleotides (i.e. it comprises 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides) and a 5-methylpyrimidine and/or a 2,6-diaminopurine base.

[0018] Each of these oligonucleotides is for use or may be for use as a medicament for treating Duchenne Muscular Dystrophy or Becker Muscular Dystrophy.

[0019] An oligonucleotide of the invention comprises or consists of a 2'-O-methyl phosphorothioate RNA monomer. Such oligonucleotide comprises a 2'-O-methyl RNA monomer connected through or linked by a phosphorothioate backbone or consists of 2'-O-methyl phosphorothioate RNA. Preferably, such oligonucleotide consists of a 2'-O-methyl phosphorothioate RNA. Such chemistry is known to the skilled person. Throughout the application, an oligonucleotide comprising a 2'-O-methyl RNA monomer and a phosphorothioate backbone may be replaced by an oligonucleotide comprising a 2'-O-methyl phosphorothioate RNA. Throughout the application, an oligonucleotide consisting of 2'-O-methyl RNA monomers linked by or connected through phosphorothioate backbones may be replaced by an oligonucleotide consisting of 2'-O-methyl phosphorothioatc RNA.

[0020] In the context of the invention, "backbone" is used to identify the linkage between two sugar units or modified versions of a sugar unit or moiety as later defined herein (i.e. internucleoside linkage). Throughout the description, the words "backbone", "internucleoside linkage" and "linkage" may be used interchangeably. Thus, an oligonucleotide having 10 nucleotides contains 9 backbones, linking the 10 sugar units or modified versions of a sugar unit or moiety as later defined herein together. At least one of the backbones of the oligonucleotide according to the invention consists of a phosphorothioate moiety, linking two sugar units or modified versions of a sugar unit or moiety as later defined herein. Thus, at least one phosphodiester backbones present in RNA is replaced by phosphorothioate moiety. A naturally occurring internucleoside linkage or backbone is the 3' to 5' phosphodiester linkage.

[0021] In addition, an oligonucleotide of the invention may comprise a base modification that increases binding affinity to target strands, increases melting temperature of the resulting duplex of said oligonucleotide with its target, and/or decreases immunostimulatory effects, and/or increases biostability, and/or improves biodistribution and/or intra-tissue distribution, and/or cellular uptake and trafficking. In a more preferred embodiment, an oligonucleotide of the invention comprises a 5-methylpyrimidine and/or a 2,6-diaminopurine base. A 5-methylpyrimidine base is selected from a 5-methylcytosine and/or a 5-methyluracil and/or a thymine, in which thymine is identical to 5-methyluracil.

[0022] Accordingly, the expression "comprises a 5-methylcytosine and/or a 5-methyluracil and/or a 2,6-diaminopurine base" in the context of the modified oligonucleotide of the invention may be replaced by "comprises a base modification selected from the group consisting of: a 5-methylcytosine, a 5-methyluracil and a 2,6-diaminopurine base".

[0023] Where an oligonucleotide of the invention has two or more such base modifications, said base modifications may be identical, for example all such modified bases in the oligonucleotide are 5-methylcytosine, or said base modifications may be combinations of different base modifications, for example the oligonucleotide may have one or more 5-methylcytosines and one or more 5-methyluracils. 'Thymine' and '5-methyluracil' may be interchanged throughout the document. In analogy, 2,6-diaminopurine is identical to 2-aminoadenine and these terms may be interchanged throughout the document. The use of 2,6-diaminopurine has been disclosed in another context in U.S. Pat. No. 7,745,420.

[0024] The term "base modification" or "modified base" as identified herein refers to the modification of an existing base (i.e. pyrimidine or purine base) or to the de novo synthesis of a base. This de novo synthesized base could be qualified as "modified" by comparison to an existing base. An oligonucleotide of the invention comprising a 5-methylcytosine and/or a 5-methyluracil and/or a 2,6-diaminopurine base means that at least one of the cytosine nucleobases of said oligonucleotide has been modified by substitution of the proton at the 5-position of the pyrimidine ring with a methyl group, i.e. a 5-substituted cytosine, and/or that at least one of the uracil nucleobases of said oligonucleotide has been modified by substitution of the proton at the 5-position of the pyrimidine ring with a methyl group (i.e. a 5-methyluracil), and/or that at least one of the adenine nucleobases of said oligonucleotide has been modified by substitution of the proton at the 2-position with an amino group (i.e. a 2,6-diaminopurine), respectively. Within the context of the invention, the expression "the substitution of a proton with a methyl group in position 5 of the pyrimidine ring" may be replaced by the expression "the substitution of a pyrimidine with a 5-methylpyrimidine," with pyrimidine referring to only uracil, only cytosine or both. Likewise, within the context of the invention, the expression "the substitution of a proton with an amino group in position 2 of adenine" may be replaced by the expression "the substitution of an adenine with a 2,6-diaminopurine." If said oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or more cytosines, uracils, and/or adenines, at least one, 2, 3, 4, 5, 6, 7, 8, 9 or more cytosines, uracils and/or adenines respectively have been modified this way. Preferably all cytosines, uracils and/or adenines have been modified this way or substituted by 5-methylcytosine, 5-methyluracil and/or 2,6-diaminopurine, respectively. No need to say that this aspect of the invention could only be applied to oligonucleotides comprising at least one cytosine, uracil, or adenine, respectively, in their sequence. An oligonucleotide comprising at least one 5-methylcytosine, 5-methyluracil and/or 2,6-diaminopurine may be called a modified oligonucleotide by reference to its non-modified counterpart comprising no 5-methylcytosine, no 5-methyluracil and no 2,6-diaminopurine. A non-modified counterpart may also be identified as being an oligonucleotide comprising unmodified cytosines, unmodified uraciles and unmodified adenines. Preferred non-modified sequences are represented by one of the following base or nucleotide sequences comprising or consisting of SEQ ID NO:91, 93-170.

[0025] We discovered that the presence of a 5-methylcytosine, 5-methyluracil and/or a 2,6-diaminopurine in an oligonucleotide of the invention has a positive effect on at least one of the parameters of said oligonucleotides. In this context, parameters may include: binding affinity and/or kinetics, exon skipping activity, biostability, (intra-tissue) distribution, cellular uptake and/or trafficking, and/or immunogenicity of said oligonucleotide, as explained below. Said positive effect may be correlated with the number or percentage of base modifications incorporated. For the parameter of exon skipping activity, we found for some oligonucleotides that modification of nucleobases is not needed per se to obtain relatively high levels of exon skipping. This may be related to the specific role (and strength) of the specifically targeted sequence within the exon in its splicing process.

[0026] Binding affinity and kinetics depend on the AON's thermodynamic properties. These are at least in part determined by the melting temperature of said oligonucleotide (Tm; calculated with e.g. the oligonucleotide properties calculator (http://www.unc.edu/~cail/biotool/oligo/index.html or http://eu.idtdna.com/analyzer/Applications/OligoAnalyzer/) for single stranded RNA using the basic Tm and the nearest neighbor model), and/or the free energy of the oligonucleotide-target exon complex (using RNA structure version 4.5 or RNA mfold version 3.5). If a Tm is increased, the exon skipping activity typically increases, but when a Tm is too high, the AON is expected to become less sequence-specific. An acceptable Tm and free energy depend on the sequence of the oligonucleotide. Therefore, it is difficult to give preferred ranges for each of these parameters.

[0027] Exon skipping activity is preferably measured by analysing total RNA isolated from AON-treated muscle cell cultures or muscle tissue by reverse transcriptase polymerase chain reaction (RT-PCR) using DMD gene-specific primers flanking the targeted exon as described (Aartsma-Rus et al., 2003). RT-PCR products are analyzed on 1-2% agarose gels or with the Agilent 2100 bioanalyzer (Agilent Technologies, The Netherlands). The ratio of shorter transcript fragments, representing transcripts in which the targeted exon is skipped, to the total of transcript products is assessed (calculated as percentage of exon skipping induced by an AON). Shorter fragments may also be sequenced to determine the correctness and specificity of the targeted exon skipping. An increase in percentage of exon skipping may be detected for a modified oligonucleotide of the invention (i.e. an oligonucleotide comprising a 2'-O-methyl RNA monomer, a phosphorothioate backbone and a 5-methylpyrimidine and/or a 2,6-diaminopurine base) compared to its non-modified counterpart (i.e. an oligonucleotide comprising a 2'-O-methyl RNA monomer, a phosphorothioate backbone and not comprising any 5-methylpyrimidine and any 2,6-diaminopurine base). Said increase is preferably a detectable increase assessed as explained above using RT-PCR. Said increase is preferably an increase of at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 210%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000%, or at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 times higher, or even 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 times higher or more.

[0028] Biodistribution and biostability are preferably at least in part determined by a validated hybridization ligation assay adapted from Yu et al., 2002. In an embodiment, plasma or homogenized tissue samples are incubated with a specific capture oligonucleotide probe. After separation, a DTG-labeled oligonucleotide is ligated to the complex and detection followed using an anti-DIG antibody-linked peroxidase. Non-compartmental pharmacokinetic analysis is performed using WINNONLIN software package (model 200, version 5.2, Pharsight, Mountainview, Calif.). Levels of AON (ug) per mL plasma or mg tissue are monitored over time to assess area under the curve (AUC), peak concentration (C_{max}), time to peak concentration (T_{max}), terminal half life and absorption lag time (t_{lag}). Such a preferred assay has been disclosed in the experimental part.

[0029] AONs may stimulate an innate immune response by activating the Toll-like receptors (TLR), including TLR9 and TLR7 (Krieg et al., 1995). The activation of TLR9 typically occurs due to the presence of non-methylated CG sequences present in oligodeoxynucleotides (ODNs), by mimicking bacterial DNA which activates the innate immune system through TLR9-mediated cytokine release. The 2'-O-methyl modification is however suggested to markedly reduce such

possible effect. TLR7 has been described to recognize uracil repeats in RNA (Diebold et al., 2006).

[0030] Activation of TLR9 and TLR7 result in a set of coordinated immune responses that include innate immunity (macrophages, dendritic cells (DC), and NK cells)(Krieg et al., 1995; Krieg, 2000). Several chemo- and cytokines, such as IP-10, TNFα, IL-6, MCP-1 and IFNα (Wagner, 1999; Popovic et al., 2006) have been implicated in this process. The inflammatory cytokines attract additional defensive cells from the blood, such as T and B cells. The levels of these cytokines can be investigated by in vitro testing. In short, human whole blood is incubated with increasing concentrations of AONs after which the levels of the cytokines are determined by standard commercially available ELISA kits. Such a preferred assay has been described in the experimental part. A decrease in immunogenicity preferably corresponds to a detectable decrease of concentration of at least one of the cytokines mentioned above by comparison to the concentration of corresponding cytokine in an assay in a cell treated with an oligonucleotide comprising at least one 5-methylcytosine compared to a cell treated with a corresponding oligonucleotide having no 5-methylcytosines.

[0031] Accordingly, a preferred oligonucleotide of the invention has an improved parameter, such as an acceptable or a decreased immunogenicity and/or a better biodistribution and/or acceptable or improved RNA binding kinetics and/or thermodynamic properties by comparison to a corresponding oligonucleotide consisting of a 2'O-methyl phosphorothioate RNA without a 5-methylcytosine, a 5-methyluracil and a 2,6-diaminopurine (i.e. so called non-modified oligonucleotide). Said non-modified oligonucleotide may also be identified as being an oligonucleotide comprising unmodified cytosines, unmodified uraciles and unmodified adenines. Each of these parameters could be assessed using assays known to the skilled person or preferably as disclosed herein.

[0032] Below other chemistries and modifications of the oligonucleotide of the invention are defined. These additional chemistries and modifications may be present in combination with the chemistry already defined for said oligonucleotide, i.e. the presence of a 5-methylcytosine, a 5-methyluracil and/or a 2,6-diaminopurine, and the oligonucleotide comprising or consisting of a 2'-O-methyl phosphorothioate RNA.

[0033] A preferred oligonucleotide of the invention comprises or consists of an RNA molecule or a modified RNA molecule. In a preferred embodiment, an oligonucleotide is single stranded. The skilled person will understand that it is however possible that a single stranded oligonucleotide may form an internal double stranded structure. However, this oligonucleotide is still named a single stranded oligonucleotide in the context of this invention.

[0034] In addition to the modifications described above, the oligonucleotide of the invention may comprise further modifications such as different types of nucleic acid monomers or nucleotides as described below. Different types of nucleic acid monomers may be used to generate an oligonucleotide of the invention. Said oligonucleotide may have at least one backbone, and/or sugar modification and/or at least one base modification compared to an RNA-based oligonucleotide.

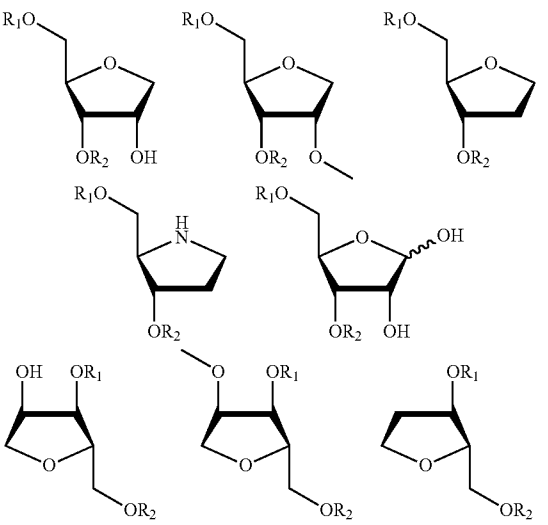
[0035] A base modification includes a modified version of the natural purine and pyrimidine bases (e.g. adenine, uracil, guanine, cytosine, and thymine), such as hypoxanthine, orotic acid, agmatidine, lysidine, 2-thiopyrimidine (e.g. 2-thiouracil, 2-thiothymine), G-clamp and its derivatives, 5-substituted pyrimidine (e.g. 5-halouracil, 5-propynyluracil, 5-propynylcytosine, 5-aminomethyluracil, 5-hydroxymethyluracil, 5-aminomethylcytosine, 5-hydroxymethylcytosine, Super T), 7-deazaguanine, 7-deazaadenine, 7-aza-2,6-diaminopurine, 8-aza-7-deazaguanine, 8-aza-7-deazaadenine, 8-aza-7-deaza-2,6-diaminopurine, Super G, Super A, and N4-ethylcytosine, or derivatives thereof; N^2-cyclopentylguanine (cPent-G), N^2-cyclopentyl-2-aminopurine (cPent-AP), and N^2-propyl-2-aminopurine (Pr-AP), pseudouracil or derivatives thereof; and degenerate or universal bases, like 2,6-difluorotoluene or absent bases like abasic sites (e.g. 1-deoxyribose, 1,2-dideoxyribose, 1-deoxy-2-O-methylribose; or pyrrolidine derivatives in which the ring oxygen has been replaced with nitrogen (azaribose)). Examples of derivatives of Super A, Super G and Super T can be found in U.S. Pat. No. 6,683,173 (Epoch Biosciences), which is incorporated here entirely by reference. cPent-G, cPent-AP and Pr-AP were shown to reduce immunostimulatory effects when incorporated in siRNA (Peacock H. et al. *J. Am. Chem. Soc.* 2011, 133, 9200).

[0036] A pseudouracil is a naturally occurring isomerized version of uracil, with a C-glycoside rather than the regular N-glycoside as in uridine. Pseudouridine-containing synthetic mRNA may have an improved safety profile compared to uridine-containing mRNA (WO 2009127230, incorporated here in its entirety by reference).

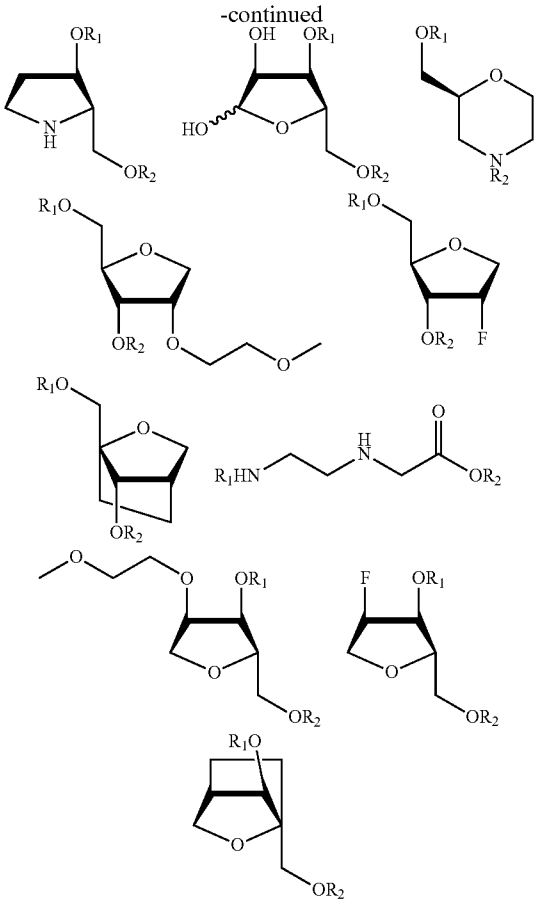
[0037] In an embodiment, an oligonucleotide of the invention comprises an abasic site or an abasic monomer. Within the context of the invention, such monomer may be called an abasic site or an abasic monomer. An abasic monomer or abasic site is a monomer or building block that lacks a nucleobase by comparison to a corresponding monomer comprising a nucleobase. Within the invention, an abasic monomer is thus a building block part of an oligonucleotide but lacking a nucleobase. Such abasic monomer may be present or linked or attached or conjugated to a free terminus of an oligonucleotide.

[0038] In a more preferred embodiment, an oligonucleotide of the invention comprises 1-20 or more abasic monomers. Therefore, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more abasic monomers may be present in an oligonucleotide of the invention.

[0039] An abasic monomer may be of any type known and conceivable by the skilled person, non-limiting examples of which are depicted below:



-continued



[0040] Herein, R_1 and R_2 are independently H, an oligonucleotide or other abasic site(s), provided that not both R_1 and R_2 are H and R_1 and R_2 are not both an oligonucleotide. An abasic monomer(s) can be attached to either or both termini of the oligonucleotide as specified before. It should be noted that an oligonucleotide attached to one or two an abasic site(s) or abasic monomer(s) may comprise less than 10 nucleotides. In this respect, the oligonucleotide according to the invention may comprise at least 10 nucleotides, optionally including one or more abasic sites or abasic monomers at one or both termini.

[0041] Depending on its length an oligonucleotide of the invention may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 base modifications. It is also encompassed by the invention to introduce more than one distinct base modification in said oligonucleotide.

[0042] A sugar modification includes a modified version of the ribosyl moiety, such as 2'-O-modified RNA such as 2'-O-alkyl or 2'-O-(substituted)alkyl e.g. 2'-O-methyl, 2'-O-(2-cyanoethyl), 2'-O-(2-methoxy)ethyl (2'-MOE), 2'-O-(2-thiomethyl)ethyl, 2'-O-butyryl, 2'-O-propargyl, 2'-O-allyl, 2'-O-(3-amino)propyl, 2'-O-(3-(dimethylamino)propyl), 2'-O-(2-amino)ethyl, 2'-O-(2-(dimethylamino)ethyl); 2'-deoxy (DNA); 2'-O-(haloalkoxy)methyl (Arai K. et al. *Bioorg. Med. Chem.* 2011, 21, 6285) e.g. 2'-O-(2-chloroethoxy)methyl (MCEM), 2'-O-(2,2-dichloroethoxy)methyl (DCEM); 2'-O-alkoxycarbonyl e.g. 2'-O-[2-(methoxycarbonyl)ethyl] (MOCE), 2'-O-[2-(N-methylcarbamoyl)ethyl] (MCE), 2'-O-[2-(N,N-dimethylcarbamoyl)ethyl] (DCME); 2'-halo e.g. 2'-F, FANA (2'-Farabinosyl nucleic acid); carbasugar, sulfa and sulfosugar and azasugar modifications; 3'-O-alkyl e.g. 3'-O-methyl, 3'-O-butyryl, 3'-O-propargyl; 4'-carboxy e.g. 4'-carboxythymidine (Hari et al.); and their derivatives.

[0043] Other sugar modification includes "bridged" or "bicylic" nucleic acid (BNA), e.g. locked nucleic acid (LNA), xylo-LNA, α-L-LNA, β-D-LNA, cEt (2'-O,4'-C constrained ethyl) LNA, cMOEt (2'-O,4'-C constrained methoxyethyl) LNA, ethylene-bridged nucleic acid (ENA), tricyclo DNA (tcDNA, tc-PS-DNA e.g. US patent application 20120149756); 3'-S-phosphorothiolate DNA (e.g. *Org. Biol. Chem.* 2013, 11, 966); doubly constrained nucleic acid (tri-NA, e.g. Hanessian et al.); unlocked nucleic acid (UNA); cyclohexenyl nucleic acid (CeNA), altriol nucleic acid (ANA), hexitol nucleic acid (HNA), fluorinated HNA (F-HNA), pyranosyl-RNA (p-RNA), 3'-deoxypyranosyl-DNA (p-DNA); molpholino (as e.g. in PMO, PPMO, PMOPlus, PMO-X); and their derivatives. Depending on its length, an oligonucleotide of the invention may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 sugar modifications. It is also encompassed by the invention to introduce more than one distinct sugar modification in said oligonucleotide. In an embodiment, an oligonucleotide as defined herein comprises or consists of an LNA or a derivative thereof. BNA derivatives are for example described in WO 2011/097641, which is incorporated in its entirety by reference. In a more preferred embodiment, an oligonucleotide of the invention is fully 2'-O-methyl modified. Examples of PMO-X are described in WO2011150408, which is incorporated here in its entirety by reference.

[0044] A backbone modification includes a modified version of the phosphodiester present in RNA, such as phosphorothioate (PS), chirally pure phosphorothioate, phosphorodithioate (PS2), phosphonoacetate (PACE), phosphonoacetamide (PACA), thiophosphonoacetate, thiophosphonoacetamide, phosphorothioate prodrug, H-phosphonate, methyl phosphonate, methyl phosphonothioate, methyl phosphate, methyl phosphorothioate, ethyl phosphate, ethyl phosphorothioate, boranophosphate, boranophosphorothioate, methyl boranophosphate, methyl boranophosphorothioate, methyl boranophosphonate, methyl boranophosphonothioate, and their derivatives. Another modification includes phosphoramidite, phosphoramidate, N3'→P5' phosphoramidate, phosphordiamidate, phosphorothiodiamidate, sulfamate, dimethylenesulfoxide, sulfonate, triazole, oxalyl, carbamate, methyleneimino (MMI), 3'-S-phosphorothiolate (*Org. Biol. Chem.* 2013, 11, 966) and thioacetamido nucleic acid (TANA); and their derivatives. Depending on its length, an oligonucleotide of the invention may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 backbone modifications. It is also encompassed by the invention to introduce more than one distinct backbone modification in said oligonucleotide.

[0045] In a preferred embodiment, an oligonucleotide of the invention comprises at least one phosphorothioate modification. In a more preferred embodiment, an oligonucleotide of the invention is fully phosphorothioate modified.

[0046] Other chemical modifications of an oligonucleotide of the invention include peptide-base nucleic acid (PNA), boron-cluster modified PNA, pyrrolidine-based oxy-peptide

nucleic acid (POPNA), glycol- or glycerol-based nucleic acid (GNA), threose-based nucleic acid (TNA), acyclic threoninol-based nucleic acid (aTNA), morpholino-based oligonucleotide (PMO, PPMO, PMO-X), cationic morpholino-based oligomers (PMOPlus), oligonucleotides with integrated bases and backbones (ONIBs), pyrrolidine-amide oligonucleotides (POMs); and their derivatives.

[0047] In another embodiment, an oligonucleotide comprises a peptide nucleic acid and/or a morpholino phosphorodiamidate or a derivative thereof.

[0048] In another embodiment, an oligonucleotide comprises a monothiophosphate moiety at the 5' position of the 5' terminal residue and/or a monothiophosphate moiety at the 3' position of the 3' terminal residue. These monothiophosphate groups have been shown to improve oligonucleotide stability (e.g. US patent application 20120148664—miRagen).

[0049] With the advent of nucleic acid mimicking technology it has become possible to generate molecules that have a similar, preferably the same hybridization characteristics in kind not necessarily in amount as nucleic acid itself. Such functional equivalents are of course also suitable for use in the invention.

[0050] The skilled person will understand that not each sugar, base, and/or backbone may be modified the same way. Several distinct modified sugars, bases and/or backbones may be combined into one single oligonucleotide of the invention.

[0051] A person skilled in the art will also recognize that there are many synthetic derivatives of oligonucleotides. A backbone modification includes a modified version of the phosphodiester present in RNA, such as phosphorothioate (PS), chirally pure phosphorothioate, phosphorodithioate (PS2), phosphonoacetate (PACE), phosphonoacetamide (PACA), thiophosphonoacetate, thiophosphonoacetamide, phosphorothioate prodrug, H-phosphonate, methyl phosphonate, methyl phosphonothioate, methyl phosphate, methyl phosphorothioate, ethyl phosphate, ethyl phosphorothioate, boranophosphate, boranophosphorothioate, methyl boranophosphate, methyl boranophosphorothioate, methyl boranophosphonate, methyl boranophosphonothioate, and their derivatives. Another modification includes phosphoramidite, phosphoramidate, N3'→P5' phosphoramidate, phosphordiamidate, phosphorothiodiamidate, sulfamate, dimethylenesulfoxide, sulfonate, and thioacetamido nucleic acid (TANA); and their derivatives.

[0052] Preferably, said oligonucleotide comprises RNA, as RNA/RNA duplexes are very stable. It is preferred that an RNA oligonucleotide comprises a modification providing the RNA with an additional property, for instance resistance to endonucleases, exonucleases, and RNaseH, additional hybridisation strength, increased stability (for instance in a bodily fluid), increased or decreased flexibility, increased activity, reduced toxicity, increased intracellular transport, tissue-specificity, etc. In addition, the mRNA complexed with the oligonucleotide of the invention is preferably not susceptible to RNaseH cleavage. Preferred modifications have been identified above.

[0053] Accordingly, the invention provides an oligonucleotide comprising a 2'-O-methyl phosphorothioate RNA monomer or consisting of 2'-O-methyl phosphorothioate RNA and comprising a 5-methylpyrimidine and/or a 2,6-diaminopurine base. Most preferably, this oligonucleotide consists of 2'-O-methyl RNA monomers connected through a phosphorothioate backbone and all of its cytosines and/or all of its uracils and/or all of its adenines, independently, have been substituted by 5-methylcytosine, 5-methyluracil and/or 2,6-diaminopurine, respectively. Preferred modified and non-modified oligonucleotides encompassed by the invention and disclosed herein comprises or consists of one of a base or nucleotide sequence selected from one of SEQ ID NO: 14-90 as identified in table 1. The expression "oligonucleotide represented by a nucleotide or base sequence selected from SEQ ID NO:14-90" could be replaced by the expression "oligonucleotide represented by a nucleotide or base sequence selected from one of SEQ ID NO:14-90" or by the expression "oligonucleotide represented by a nucleotide or base sequence selected from the list of SEQ ID NO:14-90". The same holds for other groups of SEQ ID NO referred herein.

[0054] Preferred non-modified oligonucleotides are derived from one of SEQ ID NO:14-90 and encompassed by the present invention and disclosed herein comprises or consists of one of a base or nucleotide sequences selected from SEQ ID NO: 91, 93-170.

[0055] Modified oligonucleotides are preferably derived from one of SEQ ID NO:14-90 and encompassed by the present invention and disclosed herein comprises or consists of one of a base or nucleotide sequences selected from SEQ ID NO: 92, 171-213, 215.

[0056] Please note that two SEQ ID NO present in the sequence listing are identical: SEQ ID NO:91 is identical with SEQ ID NO: 132. SEQ ID NO: 92 is identical with SEQ ID NO:199.

[0057] The sequence representing each of these oligonucleotides is disclosed in Tables 1-3 and in the sequence listing. Later on in the description, most preferred oligonucleotides are described in more detail.

[0058] Thus, an oligonucleotide of the invention may have:

[0059] At least one and preferably all cytosines substituted with 5-methylcytosines,

[0060] At least one and preferably all cytosines substituted with 5-methylcytosines and at least one and preferably all uracils substituted with 5-methyluracils,

[0061] At least one and preferably all cytosines substituted with 5-methylcytosines and at least one and preferably all adenines substituted with 2,6-diaminopurines,

[0062] At least one and preferably all cytosines substituted with 5-methylcytosines and at least one and preferably all uracils substituted with 5-methyluracils and at least one and preferably all adenines substituted with 2,6-diaminopurines,

[0063] At least one and preferably all uracils substituted with 5-methyluracils,

[0064] At least one and preferably all uracils substituted with 5-methyluracils and at least one and preferably all adenines substituted with 2,6-diaminopurines, or

[0065] At least one and preferably all adenines substituted with 2,6-diaminopurines.

[0066] However, an oligonucleotide may also have at least one or at least two or at least half or all its cytosines substituted with 5-methylcytosines. If a non-modified oligonucleotide of the invention preferably based on SEQ ID NO:14-90 has x cytosines, x being an integer ranged from 1 to 33, a corresponding modified oligonucleotide of the invention may have 1, 2, 3, . . . (x−2), (x−1), x 5-methylcytosines.

[0067] If x is 3 in such a non-modified oligonucleotide, the number of 5-methylcytosines in a corresponding modified oligonucleotide is 1, 2 or 3.

[0068] If x is 4 in such a non-modified oligonucleotide, the number of 5-methylcytosines in a corresponding modified oligonucleotide is 1, 2, 3 or 4.

[0069] If x is 5 in such a non-modified oligonucleotide, the number of 5-methylcytosines in a corresponding modified oligonucleotide is 1, 2, 3, 4 or 5.

[0070] If x is 6 in such a non-modified oligonucleotide, the number of 5-methylcytosines in a corresponding modified oligonucleotide is 1, 2, 3, 4, 5 or 6.

[0071] If x is 7 in such a non-modified oligonucleotide, the number of 5-methylcytosines in a corresponding modified oligonucleotide is 1, 2, 3, 4, 5, 6 or 7.

[0072] If x is 8 in such a non-modified oligonucleotide, the number of 5-methylcytosines in a corresponding modified oligonucleotide is 1, 2, 3, 4, 5, 6, 7, or 8.

[0073] The same holds for uracils substituted with 5-methyluracils and adenines substituted with 2,6-diaminopurines.

[0074] Preferably, an oligonucleotide of the invention is for use as a medicament for DMD, more preferably said oligonucleotide is for use in therapeutic RNA modulation. Therefore, an oligonucleotide is an antisense oligonucleotide (AON). An antisense oligonucleotide is an oligonucleotide which is reverse complementary to a specific sequence of the DMD or dystrophin pre-mRNA derived from the coding sense strand of a DNA of an individual. This oligonucleotide binds to and/or targets and/or hybridizes and/or is able to bind to and/or is able to target and/or is able to hybridize said sequence of said pre-mRNA. The objective of RNA modulation for DMD is to skip one or more specific exons in the DMD or dystrophin pre-mRNA in order to restore the open reading frame of the transcript and to induce the expression of a shorter but (more) functional dystrophin protein, with the ultimate goal to be able to interfere with the course of the disease

[0075] In a preferred embodiment, an oligonucleotide of the invention is thus used for inducing exon-skipping in the DMD or dystrophin pre-mRNA in a cell, in an organ, in a tissue and/or in an individual. Exon-skipping results in a mature DMD or dystrophin mRNA that does not contain a skipped exon and thus, when said exon codes for amino acids, can lead to the expression of a shorter protein product. The skipping of an exon is preferably induced by the binding of an AON to specific exon-internal sequences comprising splicing regulatory elements, the splice sites and/or intronic branch-point sequences.

[0076] As defined herein a DMD pre-mRNA preferably means a pre-mRNA of a DMD gene coding for a dystrophin protein. A mutated DMD pre-mRNA corresponds to a pre-mRNA of a BMD or DMD patient with a mutation when compared to a wild type DMD pre-mRNA of a non-affected person, resulting in (reduced levels of) an aberrant protein (BMD), or the absence of functional dystrophin (DMD). A DMD pre-mRNA is also named a dystrophin pre-mRNA. A DMD gene may also be named a dystrophin gene. Dystrophin and DMD may be used interchangeably throughout the application.

[0077] A patient is preferably intended to mean a patient having DMD or BMD as later defined herein or a patient susceptible to develop DMD or BMD due to his or her genetic background. In the case of a DMD patient, an oligonucleotide used will preferably correct one mutation as present in the DMD gene of said patient and create a protein that will look like a BMD protein: said protein will preferably be a functional or semi-functional dystrophin as later defined herein. In the case of a BMD patient, an oligonucleotide as used will preferably correct one mutation as present in the BMD gene of said patient and create a dystrophin which will be more functional than the dystrophin which was originally present in said BMD patient. As defined herein, a functional dystrophin is preferably a wild type dystrophin corresponding to a protein having the amino acid sequence as identified in SEQ ID NO: 1. As defined herein, a semi-functional dystrophin is preferably a BMD-like dystrophin corresponding to a protein having an acting binding domain in its N terminal part (first 240 amino acids at the N terminus), a cysteine-rich domain (amino acid 3361 till 3685) and a C terminal domain (last 325 amino acids at the C terminus) each of these domains being present in a wild type dystrophin as known to the skilled person. The amino acids indicated herein correspond to amino acids of the wild type dystrophin being represented by SEQ ID NO:1. In other words, a functional or a semi-functional dystrophin is a dystrophin which exhibits at least to some extent an activity of a wild type dystrophin. "At least to some extent" preferably means at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100% of a corresponding activity of a wild type functional dystrophin. In this context, an activity of a functional dystrophin is preferably binding to actin and to the dystrophin-associated glycoprotein complex (DGC or DAPC) (Ehmsen J et al, 2002).

[0078] Binding of dystrophin to actin and to the DGC or DAPC complex may be visualized by either co-immunoprecipitation using total protein extracts or immunofluorescence analysis of cross-sections using various antibodies reacting with the different members of the complex, from a control (non-DMD) biopsy of one from a muscle suspected to be dystrophic, pre- and/or post-treatment, as known to the skilled person.

[0079] Individuals or patients suffering from Duchenne muscular dystrophy typically have a mutation in the gene encoding dystrophin (the DMD or dystrophin gene) that prevents synthesis of the complete protein, i.e a premature stop codon prevents the synthesis of the C-terminus. In Becker muscular dystrophy the dystrophin gene also comprises a mutation compared to the wild type but the mutation does typically not result in a premature stop codon and the C-terminus is typically synthesized. As a result a functional or semi-functional dystrophin protein is synthesized that has at least the same activity in kind as the wild type protein, although not necessarily the same amount of activity. The genome of a BMD patient typically encodes a dystrophin protein comprising the N terminal part (first 240 amino acids at the N terminus), a cysteine-rich domain (amino acid 3361 till 3685) and a C-terminal domain (last 325 amino acids at the C-terminus) but in the majority of cases its central rod shaped domain is shorter than the one of a wild type dystrophin (Monaco et al., 1988). Antisense oligonucleotide-induced exon skipping for the treatment of DMD is typically directed to overcome a premature stop in the pre-mRNA by skipping an exon, preferably in the central rod-domain shaped domain, to correct the open reading frame and allow synthesis of remainder of the dystrophin protein including the C-terminus, albeit that the protein is somewhat smaller as a result of a smaller rod domain. In a preferred embodiment, an individual having DMD and being treated by an oligonucleotide as defined herein will be provided a dystrophin which exhibits at least to some extent an activity of a wild type dystrophin. More preferably, if said individual is a Duchenne patient or is suspected to be a Duchenne patient, a functional or a semi-functional dystrophin is a dystrophin of an individual having BMD: typically said dystrophin is able to inter-

act with both actin and the DGC or DAPC, but its central rod shaped domain may be shorter than the one of a wild type dystrophin (Monaco et al., 1988). The central rod domain of wild type dystrophin comprises 24 spectrin-like repeats. For example, a central rod shaped domain of a dystrophin as provided herein may comprise 5 to 23, 10 to 22 or 12 to 18 spectrin-like repeats as long as it can bind to actin and to DGC.

[0080] Alleviating one or more symptom(s) of Duchenne Muscular Dystrophy or Becker Muscular Dystrophy in an individual using an oligonucleotide of the invention may be assessed by any of the following assays: prolongation of time to loss of walking, improvement of muscle strength, improvement of the ability to lift weight, improvement of the time taken to rise from the floor, improvement in the nine-metre walking time, improvement in the time taken for four-stairs climbing, improvement of the leg function grade, improvement of the pulmonary function, improvement of cardiac function, improvement of the quality of life. Each of these assays is known to the skilled person. As an example, the publication of Manzur et al (2008) gives an extensive explanation of each of these assays. For each of these assays, as soon as a detectable improvement or prolongation of a parameter measured in an assay has been found, it will preferably mean that one or more symptoms of Duchenne Muscular Dystrophy or Becker Muscular Dystrophy has been alleviated in an individual using an oligonucleotide of the invention. Detectable improvement or prolongation is preferably a statistically significant improvement or prolongation as described in Hodgetts et al. (2006). Alternatively, the alleviation of one or more symptom(s) of Duchenne Muscular Dystrophy or Becker Muscular Dystrophy may be assessed by measuring an improvement of a muscle fiber function, integrity and/or survival. In a preferred method, one or more symptom(s) of a DMD or a BMD patient is/are alleviated and/or one or more characteristic(s) of one or more muscle cells from a DMD or a BMD patient is/are improved. Such symptoms or characteristics may be assessed at the cellular, tissue level or on the patient self.

[0081] An alleviation of one or more characteristics of a muscle cell from a patient may be assessed by any of the following assays on a myogenic cell or muscle cell from a patient: reduced calcium uptake by muscle cells, decreased collagen synthesis, altered morphology, altered lipid biosynthesis, decreased oxidative stress, and/or improved muscle fiber function, integrity, and/or survival. These parameters are usually assessed using immunofluorescence and/or histochemical analyses of cross sections of muscle biopsies.

[0082] The improvement of muscle fiber function, integrity and/or survival may be assessed using at least one of the following assays: a detectable decrease of creatine kinase in blood, a detectable decrease of necrosis of muscle fibers in a biopsy cross-section of a muscle suspected to be dystrophic, and/or a detectable increase of the homogeneity of the diameter of muscle fibers in a biopsy cross-section of a muscle suspected to be dystrophic. Each of these assays is known to the skilled person.

[0083] Creatine kinase may be detected in blood as described in Hodgetts et al. (2006). A detectable decrease in creatine kinase may mean a decrease of 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more compared to the concentration of creatine kinase in a same DMD or BMD patient before treatment.

[0084] A detectable decrease of necrosis of muscle fibers is preferably assessed in a muscle biopsy, more preferably as described in Hodgetts et al. (2006), using biopsy cross-sections. A detectable decrease of necrosis may be a decrease of 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of the area wherein necrosis has been identified using biopsy cross-sections. The decrease is measured by comparison to the necrosis as assessed in a same DMD or BMD patient before treatment.

[0085] A detectable increase of the homogeneity of the diameter of a muscle fiber is preferably assessed in a muscle biopsy cross-section, more preferably as described in Hodgetts et al. (2006). The increase is measured by comparison to the homogeneity of the diameter of a muscle fiber in a same DMD or BMD patient before treatment

[0086] Preferably, an oligonucleotide of the invention provides said individual with a functional or a semi-functional dystrophin protein (typically in the case of DMD) and is able to, for at least in part decrease the production of an aberrant dystrophin protein in said individual (typically in the case of BMD).

[0087] Decreasing the production of an aberrant dystrophin mRNA, or aberrant dystrophin protein, preferably means that 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5% or less of the initial amount of aberrant dystrophin mRNA, or aberrant dystrophin protein, is still detectable by RT PCR (mRNA) or immunofluorescence or western blot analysis (protein). An aberrant dystrophin mRNA or protein is also referred to herein as a less functional (compared to a wild type functional dystrophin protein as earlier defined herein) or a non-functional dystrophin mRNA or protein. A non functional dystrophin protein is preferably a dystrophin protein which is not able to bind actin and/or members of the DCC protein complex. A non-functional dystrophin protein or dystrophin mRNA does typically not have, or does not encode a dystrophin protein with an intact C-terminus of the protein. The detection of a functional or semi-functional dystrophin mRNA or protein may be done as for an aberrant dystrophin mRNA or protein.

[0088] Once a DMD patient is provided with a functional or a semi-functional dystrophin protein, at least part of the cause of DMD is taken away. Hence, it would then be expected that the symptoms of DMD are at least partly alleviated. The enhanced skipping frequency also increases the level of functional or a semi-functional dystrophin protein produced in a muscle cell of a DMD or BMD individual.

[0089] Exons contain one or more specific sequences comprising splicing regulatory elements which have shown to be effective targets for antisense oligonucleotides (Aartsma-Rus et al, 2010). One embodiment therefore provides an oligonucleotide for providing said individual with a functional or semi-functional dystrophin protein wherein said oligonucleotide comprises a sequence which is specifically binding, targeting and/or hybridizing with and/or blocking these splicing regulatory elements in a dystrophin pre-mRNA exon. Such oligonucleotide is also able to bind and/or target and/or hybridize with and/or block these splicing regulatory elements in a dystrophin pre-mRNA. In addition, since an exon will only be included into the resulting mRNA when both the splice sites are recognized by the spliceosome complex, splice sites are other targets for an oligonucleotide of the invention. One embodiment therefore provides an oligonucleotide for providing said individual with a functional or semi-functional dystrophin protein wherein said oligonucle-

otide comprises a sequence which is specifically binding and/or targeting and/or hybridizing with, and/or blocking one of or both the splice sites of an exon of a dystrophin pre-mRNA. Such oligonucleotide is also able to bind and/or target, hybridize with and/or block one or both of these splice sites of an exon of a dystrophin pre-mRNA. Usually a splice site of an exon comprises 1, 2, 3, or more nucleotides present in said exon and 1, 2, 3, or more nucleotides present in an adjacent or neighboring intron. In one embodiment an oligonucleotide is used which is solely binding to and/or targeting and/or hybridizing with an intron region of a dystrophin pre-mRNA. Such oligonucleotide is able to bind and/or able to target and/or able to hybridize with said intron region. This is however not necessary: it is also possible to use an oligonucleotide which targets and/or binds and/or hybridizes with and/or is able to target and/or is able to binds and/or is able to hybridizes with an intron-specific sequence as well as exon-specific sequence. Of course, an oligonucleotide is not necessarily binding to and/or targeting and/or hybridizing with the entire sequence of a dystrophin exon or intron. Such oligonucleotide is also not necessary able to bind to and/or able to target and/or able to hybridize with the entire sequence of a dystrophin exon or intron. Oligonucleotides which are specifically binding, targeting and/or hybridizing with and/or which are specifically able to bind and/or able to target and/or able to hybridize part of such exon or intron are preferred. An oligonucleotide is used, said oligonucleotide is preferably reverse complementary to, and/or binds to, and/or targets and/or hybridizes with and/or is able to bind to and/or is able to target and/or is able to hybridize with at least part of a dystrophin exon and/or intron, said part having at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides.

[0090] Splicing of a dystrophin pre-mRNA occurs via two sequential transesterification reactions involving an intronic branch point and a splice site of an adjacent intron. Hence, an oligonucleotide is used for exon skipping, wherein said oligonucleotide comprises a sequence which is binding to and/or targeting and/or hybridizing with or is able to bind to and/or is able to target and/or is able to hybridize with such branch point and/or splice site. Preferably said splice site and/or branch point is present in a dystrophin pre-mRNA.

[0091] Since splice sites contain consensus sequences, the use of an oligonucleotide part or a functional equivalent thereof comprising a sequence which is capable of binding to and/or able to bind to and/or able to target and/or able to hybridize and/or binds to and/or target and/or hybridizes with a splice site involves the risk of promiscuous hybridization. Hybridization of said oligonucleotide to other splice sites than the sites of the exon to be skipped could easily interfere with the accuracy of the splicing process. To overcome these and other potential problems related to the use of an oligonucleotide which is binding and/or hybridizing and/or targeting and/or is able to bind to and/or is able to target and/or is able to hybridize a splice site, most preferred embodiment provides an oligonucleotide for providing said individual with a functional or a semi-functional dystrophin protein, wherein said oligonucleotide or a functional equivalent thereof, binding to and/or hybridizing with and/or targeting and/or is able to bind to and/or is able to hybridize and/or is able to target a specific part of a dystrophin pre-mRNA exon. Exons contain coding sequences which are typically more specific that the non-coding intron sequences. Preferably, said oligonucleotide binding to and/or hybridizing with and/or targeting and/or able to bind to and/or able to hybridize with and/or able to target a specific part of a dystrophin pre-mRNA exon is capable of specifically blocking, interfering and/or inhibiting a splicing regulatory sequence and/or structure of the anticipated exon(s) in said dystrophin pre-mRNA. Interfering with such splicing regulatory sequence and/or structure has the advantage that such elements are located within the exon. The risk for sequence-related off-target effects is therefore limited. By providing an oligonucleotide for the interior of the exon to be skipped, it is possible to mask the exon from the splicing apparatus. The failure of the splicing apparatus to recognize the exon to be skipped thus leads to exclusion of the exon from the final mRNA. This embodiment does not interfere directly with the enzymatic process of the splicing machinery (the joining of the exons). It is thought that this allows the method to be more specific and/or reliable. It has been found that an oligonucleotide capable of binding to and/or able to bind to and/or able to target and/or able to hybridize and/or binding to and/or hybridizing with and/or targeting an exon at any point may be able to induce the skipping of said exon.

[0092] Within the context of the invention, an oligonucleotide of the invention may comprise a functional equivalent or an equivalent of an oligonucleotide. A functional equivalent or an equivalent of an oligonucleotide preferably means an oligonucleotide as defined herein wherein one or more nucleotides have been substituted and wherein an activity of said functional equivalent or equivalent is retained to at least some extent. Preferably, an activity of said oligonucleotide comprising a functional equivalent or equivalent of an oligonucleotide is providing a functional or a semi-functional dystrophin protein. Said activity of said oligonucleotide comprising a functional equivalent or an equivalent of an oligonucleotide is therefore preferably assessed by quantifying the amount of a functional or a semi-functional dystrophin protein. A functional or semi-functional dystrophin is herein preferably defined as being a dystrophin able to bind actin and members of the DCC (or DAPC) protein complex. The assessment of said activity of said functional equivalent of an oligonucleotide is preferably done by RT-PCR and sequencing (on RNA level; for detection of specific exon skipping), or by immunofluorescence and Western blot analyses (on protein level: for detection of protein restoration). Said activity is preferably retained to at least some extent when it represents at least 50%, or at least 60%, or at least 70% or at least 80% or at least 90% or at least 95% or more of corresponding activity of said oligonucleotide the functional equivalent or equivalent derives from. Throughout this application, when the word oligonucleotide is used it may be replaced by a functional equivalent thereof or an equivalent thereof as defined herein. In an embodiment, an equivalent or a functional equivalent of an oligonucleotide of the invention comprises a modification. Throughout this application, when the word oligonucleotide is used it may be replaced by an antisense oligonucleotide as defined herein unless otherwise indicated.

[0093] Hence, the use of an oligonucleotide or a functional equivalent thereof, or an equivalent thereof comprising a 2'-O-methyl phosphorothioate RNA monomer or consisting of 2'-O-methyl phosphorothioate RNA and comprising a 5-methylpyrimidine (i.e. a 5-methylcytosine and/or a 5-methyluracil) and/or a 2,6-diaminopurine base and being represented by a nucleotide sequence comprising or consisting of a sequence which is reverse complementary to, and/or binds to and/or targets and/or hybridizes and/or is able to bind to

and/or is able to target and/or is able to hybridize with a dystrophin pre-mRNA exon is assumed to have a positive effect on at least one of the parameters of said oligonucleotide, as has already been defined herein, when compared to their counterparts which do not comprise any 5-methylcytosine, 5-methyluracil and 2,6-diaminopurine (i.e. so called non-modified oligonucleotide) as indicated earlier herein, and is therefore assumed to exhibit an improved therapeutic result in a DMD or a BMD cell of a patient and/or in a DMD or a BMD patient. Such a therapeutic result may be characterized by:

[0094] alleviating one or more symptom(s) of DMD or BMD and/or

[0095] alleviating one or more characteristics of a muscle cell from a patient and/or

[0096] providing said individual with a functional or semi-functional dystrophin protein and/or

[0097] at least in part decreasing the production of an aberrant dystrophin protein in said individual.

Each of these features has already been defined herein.

[0098] Preferably, an oligonucleotide is represented by a nucleotide sequence which comprises or consists of a sequence which is binding to and/or targeting and/or being reverse complementary to and/or is hybridizing with and/or which is able to bind to and/or is able to target and/or is able to hybridize with and/or is reverse complementary to at least a part of dystrophin pre-mRNA exons 44 to 55, said oligonucleotide having a length of at least 10 nucleotides. However, the length of said oligonucleotide may be at least 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides. Throughout the invention, said sequence representing the oligonucleotide may also be called a base or a nucleotide sequence.

[0099] Preferably, an oligonucleotide of the invention is represented by a nucleotide sequence or a base sequence comprising or consisting of a sequence that is capable of binding to, and/or targeting and/or being reverse complementary to and/or hybridizing with and/or being able to bind to and/or being able to hybridize with and/or being able to target a part of an exon of dystrophin pre-mRNA. Said binding or targeted part may be at least 50% of the length of the oligonucleotide of the invention, or at least 60%, or at least 70%, or at least 80%, or at least 90% or at least 95%, or 98% and up to 100%. An oligonucleotide may be represented by a nucleotide or a base sequence, said nucleotide or base sequence comprising a sequence that binds and/or targets and/or is reverse complementary to and/or hybridizes with and/or is able to bind to and/or is able to hybridize with and/or is able to target at least a part of an exon selected from the group consisting of exons 44 to 55 of dystrophin pre-mRNA as defined herein and additional flanking sequences. In a more preferred embodiment, the length of said binding or targeted part of said oligonucleotide is of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides. Several types of flanking sequences may be used. Preferably, flanking sequences are used to modify the binding of a protein to said oligonucleotide, or to modify a thermodynamic property of said oligonucleotide, more preferably to modify target RNA binding affinity. In another preferred embodiment, additional flanking sequences are reverse complementary to sequences of the dystrophin pre-mRNA which are not present in said exon. Such flanking sequences are preferably capable of binding to and/or targeting sequences comprising or consisting of the branchpoint and/or the splice site acceptor or donor consensus sequences of said exon. In a preferred embodiment, such flanking sequences are capable of binding to and/or targeting sequences comprising or consisting of sequences of an intron of the dystrophin pre-mRNA which is adjacent to said exon.

[0100] One preferred embodiment provides an oligonucleotide for providing said individual with a functional or a semi-functional dystrophin protein, said oligonucleotide or a functional equivalent thereof or an equivalent thereof, being represented by a sequence or a base sequence which comprises:

[0101] a sequence which binds, is able to bind, targets, hybridizes or is reverse complementary to a region of a dystrophin pre-mRNA exon that is hybridized to another part of a dystrophin pre-mRNA exon (closed structure), and a sequence which binds and/or targets and/or hybridizes and/or is reverse complementary to and/or is able to bind and/or is able to target and/or is able to hybridize with a region of a dystrophin pre-mRNA exon that is not hybridized in said dystrophin pre-mRNA (open structure).

[0102] For this embodiment, reference is made to the WO 2004/083446 patent application. RNA molecules exhibit strong secondary structures, mostly due to base pairing of complementary or partly complementary stretches within the same RNA. It has long since been thought that structures in the RNA play a role in the function of the RNA. Without being bound by theory, it is believed that the secondary structure of the RNA of an exon plays a role in structuring the splicing process. Through its structure, an exon is recognized as a part that needs to be included in the mRNA. In an embodiment, an oligonucleotide is capable of interfering with the structure of the exon and therefore capable of interfering with the splicing apparatus of said exon, masking the exon from the splicing apparatus and thereby inducing the skipping of said exon. It has been found that many oligonucleotides indeed comprise this capacity, some more efficient than others. Without being bound by theory it is thought that the overlap with an open structure improves the invasion efficiency of the oligonucleotide (i.e. increases the efficiency with which the oligonucleotide can enter the structure), whereas the overlap with the closed structure subsequently increases the efficiency of interfering with the secondary structure of the RNA of the exon. It is found that the length of the partial reverse complementarity to both the closed and the open structure is not extremely restricted. We have observed high efficiencies with compounds comprising oligonucleotides with variable lengths of reverse complementarity in either structure. The term (reverse) complementarity is used herein to refer to a stretch of nucleic acids that can hybridise to another stretch of nucleic acids under physiological conditions. Hybridization conditions are later defined herein. It is thus not absolutely required that all the bases in the region of complementarity are capable of pairing with bases in the opposing strand. For instance, when designing an antisense oligonucleotide, one may want to incorporate for instance a residue that does not base pair with the base on the complementary strand. Mismatches may to some extent be allowed, if under the circumstances in the cell, the stretch of nucleotides is capable of hybridizing to the complementary part.

[0103] In a preferred embodiment a reverse complementary part of an antisense oligonucleotide (either to said open or to said closed structure) comprises at least 3, and more preferably at least 4 consecutive nucleotides. The reverse

complementary regions are preferably designed such that, when combined, they are specific for an exon in a pre-mRNA. Such specificity may be created with various lengths of reverse complementary regions as this depends on the actual sequences in other (pre-)mRNA in the system. The risk that also one or more other pre-mRNA will be able to hybridise to an oligonucleotide decreases with increasing size of said oligonucleotide. It is clear that an antisense oligonucleotide comprising mismatches in the region of reverse complementarity but that retain the capacity to hybridise to the targeted region(s) in the pre-mRNA, can be used in the present invention. However, preferably at least the reverse complementary parts do not comprise such mismatches as these typically have a higher efficiency and a higher specificity than oligonucleotide having such mismatches in one or more reverse complementary regions. It is thought that higher hybridisation strengths, (i.e. increasing number of interactions with the opposing strand) are favourable in increasing the efficiency of the process of interfering with the splicing machinery of the system. Preferably, the reverse complementarity is from 90 to 100%. In general this allows for 1 or 2 mismatch(es) in an oligonucleotide of 20 nucleotides or 1 to 4 mismatches in an oligonucleotide of 40 nucleotides. Therefore, we may have 1, 2, 3, 4, 5 mismatches in an oligonucleotide of 10 to 50 nucleotides. Preferably, 0, 1 or 2 mismatches are present in an oligonucleotide of 10 to 50 nucleotides.

[0104] The structure (i.e. open and closed structures) is best analyzed in the context of the pre-mRNA wherein the exon resides. Such structure may be analyzed in the actual RNA. However, it is currently possible to predict the secondary structure of an RNA molecule (at lowest energy costs) quite well using structure-modeling programs. Non-limiting examples of a suitable program are RNA structure version 4.5 or RNA mfold version 3.5 (Zuker et al., 2003). A person skilled in the art will be able to predict, with suitable reproducibility, a likely structure of an exon, given a nucleotide sequence. Best predictions are obtained when providing such modeling programs with both said exon and flanking intron sequences. It is typically not necessary to model the structure of the entire pre-mRNA.

[0105] The open and closed structure to which the oligonucleotide of an oligonucleotide is directed, are preferably adjacent to one another. It is thought that in this way the annealing of the oligonucleotide to the open structure induces opening of the closed structure whereupon annealing progresses into this closed structure. Through this action the previously closed structure assumes a different conformation. However, when potential (cryptic) splice acceptor and/or donor sequences are present within the targeted exon, occasionally a new exon inclusion signal or splicing regulatory sequence, element, structure, or signal is generated defining a different (neo) exon, i.e. with a different 5' end, a different 3' end, or both. This type of activity is within the scope of the present invention as the targeted exon is excluded from the mRNA. The presence of a new exon, containing part of the targeted exon, in the mRNA does not alter the fact that the targeted exon, as such, is excluded. The inclusion of a neo-exon can be seen as a side effect which occurs only occasionally. There are two possibilities when exon skipping is used to restore (part of) an open reading frame of dystrophin that is disrupted as a result of a mutation. One is that the neo-exon is functional in the restoration of the reading frame, whereas in the other case the reading frame is not restored. When selecting a compound comprising an oligonucleotide for restoring dystrophin reading frames by means of exon-skipping it is of course clear that under these conditions only those compounds comprising those oligonucleotide are selected that indeed result in exon-skipping that restores the dystrophin open reading frame, with or without a neo-exon.

[0106] Further provided is an oligonucleotide for providing said individual with a functional or a semi-functional dystrophin protein, wherein said oligonucleotide or a functional equivalent thereof or an equivalent thereof comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base and is represented by a nucleotide or a base sequence comprising a sequence that is reverse complementary to and/or binds to and/or targets and/or hybridizes with and/or is able to bind to and/or is able to target and/or is able to hybridize with a binding site for a serine-arginine (SR) protein in RNA of an exon of a dystrophin pre-mRNA. In WO 2006/112705 patent application we have disclosed the presence of a correlation between the effectivity of an exon-internal antisense oligonucleotide in inducing exon skipping and the presence of a (for example by ESEfinder) predicted SR binding site in the target pre-mRNA site of said AON. Therefore, in one embodiment an oligonucleotide is generated comprising determining a (putative) binding site for an SR (Ser-Arg) protein in RNA of a dystrophin exon and producing a corresponding compound comprising oligonucleotide that is reverse complementary to and/or binds to and/or targets and/or hybridizes with and/or is able to bind and/or is able to target and/or is able to hybridize with said RNA and that at least partly overlaps said (putative) binding site. The term "at least partly overlaps" is defined herein as to comprise an overlap of only a single nucleotide of an SR binding site as well as multiple nucleotides of said binding site as well as a complete overlap of said binding site. This embodiment preferably further comprises determining from a secondary structure of said RNA, a region that is hybridized to another part of said RNA (closed structure) and a region that is not hybridized in said structure (open structure), and subsequently generating an oligonucleotide that at least partly overlaps said (putative) binding site and that overlaps at least part of said closed structure and overlaps at least part of said open structure. In this way we increase the chance of obtaining an oligonucleotide that is capable of interfering with the exon inclusion from the pre-mRNA into mRNA. It is possible that a first selected SR-binding region does not have the requested open-closed structure in which case another (second) SR protein binding site is selected which is then subsequently tested for the presence of an open-closed structure. This process is continued until a sequence is identified which contains an SR protein binding site as well as a(n) (partly overlapping) open-closed structure. This sequence is then used to design an oligonucleotide which is reverse complementary to said sequence.

[0107] Such a method for generating an antisense oligonucleotide is also performed by reversing the described order, i.e. first generating an oligonucleotide comprising determining, from a secondary structure of RNA from a dystrophin exon, a region that assumes a structure that is hybridised to another part of said RNA (closed structure) and a region that is not hybridised in said structure (open structure), and subsequently generating an oligonucleotide, of which at least a part of said oligonucleotide is reverse complementary to said closed structure and of which at least another part of said

oligonucleotide is reverse complementary to said open structure. This is then followed by determining whether an SR protein binding site at least overlaps with said open/closed structure. In this way the method of WO 2004/083446 is improved. In yet another embodiment the selections are performed simultaneously.

[0108] Without wishing to be bound by any theory it is currently thought that use of an oligonucleotide directed to or targeting an SR protein binding site results in (at least partly) impairing the binding of an SR protein to the binding site of an SR protein which results in disrupted or impaired splicing.

[0109] Preferably, an open/closed structure and an SR protein binding site partly overlap and even more preferred an open/closed structure completely overlaps an SR protein binding site or an SR protein binding site completely overlaps an open/closed structure. This allows for an improved disruption of exon inclusion.

[0110] Besides consensus splice site and branchpoint intronic sequences, many (if not all) exons contain splicing regulatory sequences such as but not limited to exonic splicing enhancer (ESE) sequences to facilitate the recognition of genuine splice sites by the spliceosome (Cartegni et al., 2002; and Cartegni et al., 2003). A subgroup of splicing factors, called the SR proteins, can bind to these ESEs and recruit other splicing factors, such as U1 and U2AF to (weakly defined) splice sites. The binding sites of the four most abundant SR proteins (SF2/ASF, SC35, SRp40 and SRp55) have been analyzed in detail and these results are implemented in ESEfinder, a web source that predicts potential binding sites for these SR proteins (Cartegni et al., 2002; and Cartegni et al., 2003). There is a correlation between the effectiveness of an oligonucleotide and the presence/absence of an SF2/ASF, SC35 and SRp40 binding site in the site targeted by said oligonucleotide. In a preferred embodiment, the invention thus provides an oligonucleotide as described above, which is reverse complementary to and/or targets and/or binds to and/or hybridizes with and/or is able to target and/or is able to bind and/or is able to hybridize with a binding site for a SR protein. Preferably, said SR protein is SF2/ASF or SC35 or SRp40.

[0111] In one embodiment a DMD patient is provided with a functional or a semi-functional dystrophin protein by using an oligonucleotide or a functional equivalent thereof or an equivalent thereof comprising a 2'-O-methyl phosphorothioate RNA monomer or consisting of 2'-O-methyl phosphorothioate RNA and comprising a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base and being capable of specifically binding or targeting and/or being able to bind and/or being able to target and/or being able to hybridize a regulatory RNA sequence which is required for the correct splicing of a dystrophin exon in a transcript. Several cis-acting RNA sequences are required for the correct splicing of exons in a transcript. In particular, elements such as an exonic splicing enhancer (ESE), an exon recognition sequence (ERS), and/or an exonic splicing silencer (ESS) are identified to regulate specific and efficient splicing of constitutive and alternative exons. Using a sequence-specific antisense oligonucleotide or a base-specific antisense oligonucleotide (AON) that binds to and/or targets and/or is reverse complementary to and/or hybridizes with and/or is able to bind and/or is able to hybridize with and/or is able to target the elements, their regulatory function is disturbed so that the exon is skipped, as shown for DMD. Hence, in one preferred embodiment, an oligonucleotide or a functional equivalent thereof or an equivalent thereof is used which is reverse complementary to and/or binds to and/or targets and/or hybridizes with and/or is able to bind to and/or is able to target and/or is able to hybridize with an exonic splicing enhancer (ESE), an exon recognition sequence (ERS), and/or an exonic splicing silencer (ESS).

[0112] In a preferred embodiment, an oligonucleotide of the invention comprises or consists of a sequence or a base sequence that is reverse complementary to and/or binds to and/or targets and/or hybridizes with and/or is able to bind to and/or is able to target and/or is able to hybridize with at least a part of dystrophin pre-mRNA exon 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, or 55, said part having at least 10 nucleotides. However, said part may also have at least 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or, 33 nucleotides. For the dystrophin exons identified above, we provide the stretch of nucleotides (SEQ ID NO: 2 to 13 identified below) of said exon to which an oligonucleotide binds to and/or is reverse complementary to and/or targets and/or hybridizes with and/or is able to bind to and/or is able to target and/or is able to hybridize with.

(SEQ ID NO: 2)
5'-GCGAUUUGACAGAUCUGUUGAGAAAUGGCGGCGUUUUCAUUAUGAUAU

AAAGAUAUUUAAUCAGUGGCUAACAGAAGCUGAACAGUUUCUCAGAAA

GACACAAAUUCCUGAGAAUUGGGAACAUGCUAAAUACAAAUGGUAUCU

UAAG-3'
for skipping of exon 44;

(SEQ ID NO: 3)
5'-GAACUCCAGGAUGGCAUUGGGCAGCGGCAAACUGUUGUCAGAACAUUG

AAUGCAACUGGGGAAGAAAUAAUUCAGCAAUCCUCAAAAACAGAUGCC

AGUAUUCUACAGGAAAAAUUGGGAAGCCUGAAUCUGCGGUGGCAGGAG

GUCUGCAAACAGCUGUCAGACAGAAAAAAGAG-3'
for skipping of exon 45:

(SEQ ID NO: 4)
5'-GCUAGAAGAACAAAAGAAUAUCUUGUCAGAAUUUCAAAGAGAUUUAAA

UGAAUUUGUUUUAUGGUUGGAGGAAGCAGAUAACAUUGCUAGUAUCCC

ACUUGAACCUGGAAAAGAGCAGCAACUAAAAGAAAAGCUUGAGCAAGU

CAAG-3'
for skipping of exon 46;

(SEQ ID NO: 5)
5'-UUACUGGUGGAAGAGUUGCCCCUGCGCCAGGGAAUUCUCAAACAAUUA

AAUGAAACUGGAGGACCCGUGCUUGUAAGUGCUCCCAUAAGCCCAGAA

GAGCAAGAUAAACUUGAAAAUAAGCUCAAGCAGACAAAUCUCCAGUGG

AUAAAG-3'
for skipping of exon 47

(SEQ ID NO: 6)
5'-GUUUCCAGAGCUUUACCUGAGAAACAAGGAGAAAUUGAAGCUCAAAUA

AAAGACCUUGGGCAGCUUGAAAAAAAGCUUGAAGACCUUGAAGAGCAG

UUAAAUCAUCUGCUGCUGUGGUUAUCUCCUAUUAGGAAUCAGUUGGAA

AUUUAUAACCAACCAAACCAAGAAGGACCAUUUGACGUUCAG-3'
for skipping of exon 48

(SEQ ID NO: 7)
5'-GAAACUGAAAUAGCAGUUCAAGCUAAACAACCGGAUGUGGAAGAGAUU

UUGUCUAAAGGGCAGCAUUUGUACAAGGAAAAACCAGCCACUCAGCCA

-continued

GUGAAG-3'
for skipping of exon 49

(SEQ ID NO: 8)
5'-AGGAAGUUAGAAGAUCUGAGCUCUGAGUGGAAGGCGGUAAACCGUUUA

CUUCAAGAGCUGAGGGCAAAGCAGCCUGACCUAGCUCCUGGACUGACCA

CUAUUGGAGCCU-3'
for skipping of exon 50;

(SEQ ID NO: 9)
5'-CUCCUACUCAGACUGUUACUCUGGUGACACAACCUGUGGUUACUAAGG

AAACUGCCAUCUCCAAACUAGAAAUGCCAUCUUCCUUGAUGUUGGAGG

UACCUGCUCUGGCAGAUUUCAACCGGGCUUGGACAGAACUUACCGACUG

GCUUUCUCUGCUUGAUCAAGUUAUAAAAUCACAGAGGGUGAUGGUGGG

UGACCUUGAGGAUAUCAACGAGAUGAUCAUCAAGCAGAAG-3'
for skipping of exon 51;

(SEQ TD NO: 10)
5'-GCAACAAUGCAGGAUUUGGAACAGAGGCGUCCCCAGUUGGAAGAACUC

AUUACCGCUGCCCAAAAUUUGAAAAACAAGACCAGCAAUCAAGAGGCU

AGAACAAUCAUUACGGAUCGAA-3'
for skipping of exon 52;

(SEQ ID NO: 11)
5'-UUGAAAGAAUUCAGAAUCAGUGGGAUGAAGUACAAGAACACCUUCAGA

ACCGGAGGCAACAGUUGAAUGAAAUGUUAAAGGAUUCAACACAAUGGC

UGGAAGCUAAGGAAGAAGCUGAGCAGGUCUUAGGACAGGCCAGAGCCA

AGCUUGAGUCAUGGAAGGAGGGUCCCUAUACAGUAGAUGCAAUCCAAA

AGAAAAUCACAGAAACCAAG-3'
for skipping of exon 53;

(SEQ ID NO: 12)
5'-CAGUUGGCCAAAGACCUCCGCCAGUGGCAGACAAAUGUAGAUGUGGCA

AAUGACUUGGCCCUGAAACUUCUCCGGGAUUAUUCUGCAGAUGAUACC

AGAAAAGUCCACAUGAUAACAGAGAAUAUCAAUGCCUCUUGGAGAAGC

AUUCAUAAAAG-3'
for skipping of exon 54;

(SEQ ID NO: 13)
5'-GGUGAGUGAGCGAGAGGCUGCUUUGGAAGAAACUCAUAGAUUACUGCA

ACAGUUCCCCCUGGACCUGGAAAAGUUUCUUGCCUGGCUUACAGAAGCU

GAAACAACUGCCAAUGUCCUACAGGAUGCUACCCGUAAGGAAAGGCUCC

UAGAAGACUCCAAGGGAGUAAAAGAGCUGAUGAAACAAUGGCAA-3'
for skipping of exon 55.

[0113] Therefore, a preferred oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base and binds to and/or is reverse complementary to and/or targets and/or hybridizes with and/or is able to bind and/or is able to target and/or is able to hybridize with a continuous stretch of at least 10 and up to 33 nucleotides within one of the following exon nucleotide sequences selected from SEQ ID NO: 2 to 13.

[0114] Preferred oligonucleotides are also defined as follows:

[0115] comprise a 2'-O-methyl phosphorothioate RNA monomer or consist of 2'-O-methyl phosphorothioate RNA and

[0116] bind to and/or are reverse complementary to and/or target and/or hybridize with and/or is able to bind to and/or is able to target and/or is able to hybridize with a continuous stretch of at least 10 and up to 33 nucleotides within one of the following exon nucleotide sequences selected from SEQ ID NO: 2 to 13 as identified above.

[0117] More preferably, such oligonucleotides comprise a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base as earlier defined herein.

[0118] More preferred oligonucleotides comprise a 2'-O-methyl phosphorothioate RNA monomer or consist of 2'-O-methyl phosphorothioate RNA and more preferably comprise a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base and are represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 14-90 or by a nucleotide or a base sequence comprising or consisting of a fragment of SEQ ID NO: 14-90. SEQ ID NO:14-90 are identified in Table 1. In this context, "a 5-methylpyrimidine" means at least one 5-methylpyrimidine. Accordingly "at least one 5-methylpyrimindine" means at least one 5-methylcytosine and/or at least one 5-methyluracile.

[0119] Accordingly, preferred non-modified oligonucleotides are preferably derived from one of the nucleotide or base sequences SEQ ID NO:14-90 with X=C, Y=U, Z=A), and/or are represented by SEQ ID NO:91, 93, 94-170. Each of these non-modified oligonucleotides comprises no 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and no 2,6-diaminopurine. Please note that SEQ ID NO:91 is identical with SEQ ID NO: 132.

[0120] Accordingly, preferred modified oligonucleotides are derived from one of the nucleotide or base sequences SEQ ID NO:14-90 and comprise at least one 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or at least one 2,6-diaminopurine (i.e. at least one X is $m^5C{=}X_1$ and/or at least one Y is $m^5U{=}Y_1$ and/or at least one Z is $a^2A{=}Z_1$). Please note that SEQ ID NO: 92 is identical with SEQ ID NO: 199. More preferred modified oligonucleotides are represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 92, 171-213, 215, 217, 218, 219. Even more preferred modified oligonucleotides (all $X{=}m^5C{=}X_1$ and/or all $Y{=}m^5U{=}Y_1$ and/or all $Z{=}a^2A{=}Z_1$) are derived from the most preferred nucleotide or base sequences (SEQ ID NO:15, 21, 31, 40, 52, and 57) and are represented by SEQ ID NO: 92, 171-174, 185-188, 199, 200, 202-215, 217, 218, 219. The most preferred modified oligonucleotides are disclosed in Table 3.

[0121] Within the context of the invention, a fragment of SEQ ID NO:14-90, or a fragment of SEQ ID NO:91-219, preferably means a nucleotide or a base sequence comprising or consisting of at least 10 contiguous nucleotides from said SEQ ID NO:14-90 or from said SEQ ID NO:91-219.

[0122] Such more preferred oligonucleotides are also defined as follows:

[0123] comprise a 2'-O-methyl phosphorothioate RNA monomer or consist of 2'-O-methyl phosphorothioate RNA and

[0124] are represented by a nucleotide or base sequence comprising or consisting of SEQ ID NO: 14-90, 91, 93-170 or by a nucleotide or base sequence comprising or consisting of a fragment of SEQ ID NO: 14-90, 91, 93-170.

[0125] More preferably, such oligonucleotides comprise a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base as earlier defined herein.

[0126] Even more preferred oligonucleotides comprise a 2'-O-methyl phosphorothioate RNA monomer or consist of 2'-O-methyl phosphorothioate RNA and more preferably comprise a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, are represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 14-90, 92, 171-215, 217, 218, 219 or by a nucleotide or a base sequence comprising or consisting of a fragment of SEQ ID NO:14-90, 92, 171-215, 217, 218, 219 and having a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Preferred sequences (i.e. preferred nucleotide or base sequences) among SEQ ID NO:14-90, 92, and 171-215, 217, 218, 219 include SEQ ID NO: 15, 21, 31, 40, 43, 52, 57, 59, 171-174, 185-188, 199, 200, 202-213, 215, 217, 218, 219 more preferably SEQ ID NO: 40, 43, 52, 57, 59, 208, 207, 200, 210, 206, 171, 173, 199, 213, 185, 187.

[0127] Such even more preferred oligonucleotides are also defined as follows:

[0128] comprise a 2'-O-methyl phosphorothioate RNA monomer or consist of 2'-O-methyl phosphorothioate RNA and

are represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 14-90, 91, 93-170, 216 or by a nucleotide or a base sequence comprising or consisting of a fragment of SEQ ID NO: 14-90, 91, 93-170 and have a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. More preferably, such oligonucleotides comprise a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base as earlier defined herein.

[0129] Even more preferably, such modified oligonucleotides are represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 92, 171-213, 215 217, 218, 219 or by a nucleotide or a base sequence comprising or consisting of a fragment of SEQ ID NO: 92, 171-213, 215, 217, 218, 219 and have a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Even more preferred modified oligonucleotides are derived from the most preferred nucleotide or base sequences (SEQ ID NO:15, 21, 31, 40, 52, and 57) and are represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 92, 171-174, 185-188, 199, 200, 202-213, 215, 217, 218, 219 or by a nucleotide or a base sequence comprising or consisting of a fragment of. SEQ ID NO: 92, 171-174, 185-188, 199, 200, 202-213, 215, 217, 218, 219 and having a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0130] Preferred oligonucleotides for inducing the skipping of exon 44 from the dystrophin pre-mRNA are as follows below.

[0131] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 14 and has a length of 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:14 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:14.

[0132] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:14 is represented by SEQ ID NO:94 and a preferred fragment of SEQ ID NO:94 is represented by SEQ ID NO:143.

[0133] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and is represented by a nucleotide or a base sequence comprising SEQ ID NO: 94 and has a length of 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:94 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:94.

[0134] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. A preferred fragment of SEQ ID NO:14 comprises SEQ ID NO: 63 and a preferred fragment of SEQ ID NO:94 comprises SEQ ID NO: 143, and each of said preferred fragments has a length of 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0135] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0136] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 15 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:15 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:15.

[0137] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:15 is represented by SEQ ID NO:95.

[0138] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or base sequence comprising SEQ ID NO: 95 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:95 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:95.

[0139] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. A preferred fragment of SEQ ID NO:15 comprises SEQ ID NO: 64 and a preferred fragment of SEQ ID NO:95 comprises SEQ ID NO:144 and each of said fragments has a length of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0140] Such preferred oligonucleotide is also defined as follows:

[0141] comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and

[0142] is represented by a nucleotide or base sequence comprising or consisting of SEQ ID NO: 15 or 95 or 64 or 144 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a nucleotide or base sequence comprising or consisting of a fragment of SEQ ID NO: 15 or 95 or 64 or 144, said fragment comprising or consisting of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 contiguous nucleotides or bases of SEQ ID NO:15 or 95 or 64 or 144.

[0143] More preferably, such oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base as earlier defined herein

[0144] More preferably, an oligonucleotide:

[0145] consists of 2'-O-methyl phosphorothioate RNA,

[0146] all its cytosines have been replaced by 5-methylcytosines,

[0147] such oligonucleotide is represented by a nucleotide or base sequence comprising SEQ ID NO: 15 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:15 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:15. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0148] More preferably, an oligonucleotide:

[0149] consists of 2'-O-methyl phosphorothioate RNA,

[0150] all its uraciles have been replaced by 5-methyluraciles,

[0151] such oligonucleotide is represented by a nucleotide or base sequence comprising SEQ ID NO: 204 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:204 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:204. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0152] More preferably, an oligonucleotide:

[0153] consists of 2'-O-methyl phosphorothioate RNA,

[0154] all its cytosines have been replaced by 5-methylcytosines,

[0155] such oligonucleotide is represented by a nucleotide or base sequence comprising SEQ ID NO: 208 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:208 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:208. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0156] More preferably, an oligonucleotide:

[0157] consists of 2'-O-methyl phosphorothioate RNA,

[0158] all its uraciles have been replaced by 5-methyluraciles and all its cytosines have been replaced by 5-methylcytosines,

[0159] such oligonucleotide is represented by a nucleotide or base sequence comprising SEQ ID NO: 205 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:205 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:205. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0160] More preferably, an oligonucleotide:

[0161] consists of 2'-O-methyl phosphorothioate RNA,

[0162] all its adenines have been replaced by 2,6-diaminopurines,

[0163] such oligonucleotide is represented by a nucleotide or base sequence comprising SEQ ID NO: 207 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:207 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:207. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0164] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or base sequence comprising SEQ ID NO: 16 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:16 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:16.

[0165] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:16 is represented by SEQ ID NO:96.

[0166] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 96 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:96 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:96.

[0167] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0168] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0169] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 17 and has a length of 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:17 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:17.

[0170] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:17 is represented by SEQ ID NO:97 and a preferred fragment of SEQ ID NO:97 is represented by SEQ ID NO:145.

[0171] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 97 and has a length of 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:97 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:97.

[0172] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. A preferred fragment of SEQ ID NO:17 comprises SEQ ID NO: 65 and a preferred fragment of SEQ ID NO: 97 comprises SEQ ID NO: 145, each of said fragments has a length of 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0173] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base.

[0174] Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0175] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 18 and has a length of 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:18 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:18.

[0176] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:18 is represented by SEQ ID NO:98 and a preferred fragment of SEQ ID NO:98 is represented by SEQ ID NO:146.

[0177] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. A preferred fragment of SEQ ID NO:18 comprises SEQ ID NO: 66 and a preferred fragment of SEQ ID NO: 98 comprises SEQ ID NO: 146, each of said fragments has a length of 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0178] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 98 and has a length of 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:98 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:98.

[0179] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0180] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 19 and has a length of 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:19 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:19.

[0181] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:19 is represented by SEQ ID NO:99.

[0182] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 99 and has a length of 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:99 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:99.

[0183] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0184] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0185] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 20 and has a length of 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:20 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:20.

[0186] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:20 is represented by SEQ ID NO:100 and a preferred fragment of SEQ ID NO:100 is represented by SEQ ID NO:147, 148 or 149.

[0187] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 100 and has a length of 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:100 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:100.

[0188] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. A preferred fragment of SEQ ID NO:20 comprises SEQ ID NO: 67 and a preferred fragment of SEQ ID NO:100 comprises SEQ ID NO:147, each of said fragments has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Another preferred fragment of SEQ ID NO:20 comprises SEQ ID NO: 68 and another preferred fragment of SEQ ID NO:100 comprises SEQ ID NO: 148, each of said fragments has a length of 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Another preferred fragment of SEQ ID NO:20 comprises SEQ ID NO: 69 and another preferred fragment of SEQ ID NO:100 comprises SEQ ID NO: 149, each of said

fragments has a length of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0189] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0190] Preferred oligonucleotides for inducing the skipping of exon 45 from the dystrophin pre-mRNA are as follows below.

[0191] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 21 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:21 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:21.

[0192] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:21 is represented by SEQ ID NO:101 and a preferred fragment of SEQ ID NO:101 is represented by SEQ ID NO:150, 151 or 152.

[0193] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 101 and has a length 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:101 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:101.

[0194] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. A preferred fragment of SEQ ID NO:21 comprises SEQ ID NO: 70 and a preferred fragment of SEQ ID NO:101 comprises SEQ ID NO:150, each of said fragments has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Another preferred fragment of SEQ ID NO:21 comprises SEQ ID NO: 71 and another preferred fragment of SEQ ID NO:101 comprises SEQ ID NO:151, each of said fragments has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Another preferred fragment of SEQ ID NO:21 comprises SEQ ID NO: 72 and a preferred fragment of SEQ ID NO:101 comprises SEQ ID NO:152, each of said fragments has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0195] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0196] Such preferred oligonucleotide is also defined as follows:

- **[0197]** comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and
- **[0198]** is represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 21 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a nucleotide or a base sequence comprising or consisting of a fragment of SEQ ID NO: 21, said fragment comprising or consisting of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 contiguous nucleotides or bases of SEQ ID NO:21.

[0199] More preferably, such oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base as earlier defined herein.

[0200] More preferably, an oligonucleotide:

- **[0201]** consists of 2'-O-methyl phosphorothioate RNA,
- **[0202]** all its cytosines have been replaced by 5-methylcytosines,
- **[0203]** such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 21 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:21 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:21.

[0204] Accordingly, said oligonucleotide is particularly represented by a nucleotide or a base sequence comprising SEQ ID NO: 200 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:200 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:200.

[0205] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0206] More preferably, an oligonucleotide:

- **[0207]** consists of 2'-O-methyl phosphorothioate RNA,
- **[0208]** all its uraciles have been replaced by 5-methyluraciles and all its cytosines have been replaced by 5-methylcytosines,
- **[0209]** such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 21 or SEQ ID NO:209 in particular, and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:21 or 209 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO: 21 or 209. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0210] More preferably, an oligonucleotide:

- **[0211]** consists of 2'-O-methyl phosphorothioate RNA,
- **[0212]** all its adenines have been replaced by 2,6-diaminopurines,
- **[0213]** such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 21 or SEQ ID NO: 210 in particular, and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:21 or 210 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:21 or 210. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0214] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 22 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ

ID NO:22 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:22.

[0215] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:22 is represented by SEQ ID NO:102.

[0216] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 102 and has a length 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:102 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:102.

[0217] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0218] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified.

[0219] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 23 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:23 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:23.

[0220] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:23 is represented by SEQ ID NO:103.

[0221] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or base sequence comprising SEQ ID NO: 103 and has a length 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:103 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:103.

[0222] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0223] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0224] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 24 and has a length of 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:24 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:24.

[0225] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:24 is represented by SEQ ID NO:104.

[0226] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or base sequence comprising SEQ ID NO: 104 and has a length 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:104 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:104.

[0227] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0228] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0229] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 25 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:25 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:25.

[0230] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:25 is represented by SEQ ID NO:105.

[0231] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 105 and has a length 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:105 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:105.

[0232] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0233] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0234] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioatc RNA monomer or consists of 2'-O-methyl phosphorothioatc RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 26 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:26 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:26.

[0235] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:26 is represented by SEQ ID NO:106.

[0236] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 106 and has a length 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:106 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:106.

[0237] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0238] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0239] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 27 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:27 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:27.

[0240] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:27 is represented by SEQ ID NO:107.

[0241] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioatc RNA monomer or consists of 2'-O-methyl phosphorothioatc RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 107 and has a length 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:107 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:107.

[0242] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0243] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base.

[0244] Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0245] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 28 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:28 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:28.

[0246] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:28 is represented by SEQ ID NO:108. Each of SEQ ID NO:28 and SEQ ID NO:108 identified in table 1 comprises an hypoxanthine base at position 7.

[0247] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 108 and has a length 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:108 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:108.

[0248] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0249] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0250] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 29 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:29 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:29.

[0251] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:29 is represented by SEQ ID NO:109.

[0252] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 109 and has a length 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:109 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ NO:109.

[0253] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0254] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0255] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 30 and has a length of 30, 31, 32 or 33 nucleotides or by a fragment of SEQ ID NO:30 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:30.

[0256] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:30 is represented by SEQ ID NO:110.

[0257] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 110 and has a length 30, 31, 32, or 33 nucleotides

or by a fragment of SEQ ID NO:110 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:110.

[0258] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0259] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0260] Preferred oligonucleotides for inducing the skipping of exon 51 from the dystrophin pre-mRNA are as follows below.

[0261] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 31 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:31 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:31.

[0262] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:31 is represented by SEQ ID NO:111 and a preferred fragment of SEQ ID NO:111 is represented by SEQ ID NO:153 or 154.

[0263] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 111 and has a length 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:111 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:111.

[0264] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. A preferred fragment of SEQ ID NO:31 comprises SEQ ID NO: 73 and a preferred fragment of SEQ ID NO: 111 comprises SEQ ID NO: 153, and each of said fragments has a length of 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Another preferred fragment of SEQ ID NO:31 comprises SEQ ID NO: 74 and another preferred fragment of SEQ ID NO: 111 comprises SEQ ID NO: 154, and each of said fragments has a length of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0265] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0266] Such preferred oligonucleotide is also defined as follows:

[0267] comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and

[0268] is represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 31 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a nucleotide or a base sequence comprising or consisting of a fragment of SEQ ID NO: 31, said fragment comprising or consisting of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 contiguous nucleotides or bases of SEQ ID NO:31.

[0269] More preferably, such oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base as earlier defined herein.

[0270] More preferably, an oligonucleotide:

[0271] consists of 2'-O-methyl phosphorothioate RNA,

[0272] all its cytosines have been replaced by 5-methylcytosines,

[0273] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 31 or SEQ ID NO: 215 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:31 or SEQ ID NO:215 comprising or consisting of at least 10 contiguous nucleotides of SEQ ID NO:31 or of SEQ ID NO: 215. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0274] More preferably, an oligonucleotide:

[0275] consists of 2'-O-methyl phosphorothioate RNA,

[0276] all its uraciles have been replaced by 5-methyluraciles,

[0277] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 202 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:202 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:202. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0278] More preferably, an oligonucleotide:

[0279] consists of 2'-O-methyl phosphorothioate RNA,

[0280] all its cytosines have been replaced by 5-methylcytosines and all its uraciles have been replaced by 5-methyluraciles,

[0281] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 203 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:203 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:203. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0282] More preferably, an oligonucleotide:

[0283] consists of 2'-O-methyl phosphorothioate RNA,

[0284] all its adenines have been replaced by 2,6-diaminopurines,

[0285] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 206 and has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:206 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:206. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0286] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 32 and has a length of 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:32 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:32.

[0287] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:32 is represented by SEQ ID NO:112.

[0288] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 112 and has a length 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:112 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:112.

[0289] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0290] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0291] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 33 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:33 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:33.

[0292] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:33 is represented by SEQ ID NO:113.

[0293] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 113 and has a length 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:113 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:113.

[0294] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0295] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0296] In another embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and is represented by a nucleotide or a base sequence comprising SEQ ID NO: 34 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:34 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:34.

[0297] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:34 is represented by SEQ ID NO:114.

[0298] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consist of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide sequence comprising SEQ ID NO: 114 and has a length 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:114 comprising or consisting of at least 10 contiguous nucleotides of SEQ ID NO:114.

[0299] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0300] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. A preferred fragment of SEQ ID NO: 34 comprises or consists of SEQ ID NO: 93 (PS1116: 5'-CAACAUCAAGGAAGAUGGCAUUUCU-3').

[0301] Such preferred oligonucleotide is also defined as follows:

[0302] comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and

[0303] is represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 34 or 93 or 114 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a nucleotide sequence comprising or consisting of a fragment of SEQ ID NO: 34 or 93 or 114, said fragment comprising or consisting of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 contiguous nucleotides or bases of SEQ ID NO:34 or 93 or 114.

[0304] More preferably, such oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base as earlier defined herein

[0305] More preferably, an oligonucleotide:

[0306] consists of 2'-O-methyl phosphorothioatc RNA,

[0307] all its cytosines have been replaced by 5-methylcytosines,

[0308] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 34 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:34 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:34. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0309] More preferably, an oligonucleotide:

[0310] consists of 2'-O-methyl phosphorothioate RNA,

[0311] all its adenines have been replaced by 2,6-diaminopurines

[0312] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 34 and

has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:34 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:34. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0313] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 35 and has a length of 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:35 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:35.

[0314] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:35 is represented by SEQ ID NO:115.

[0315] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 115 and has a length 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:115 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:115.

[0316] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0317] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0318] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 36 and has a length of 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:36 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:36.

[0319] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:36 is represented by SEQ ID NO:116 and a preferred fragment of SEQ ID NO:116 is represented by SEQ ID NO:155 or 156 or 157.

[0320] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 116 and has a length 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:116 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:116.

[0321] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. A preferred fragment of SEQ ID NO:36 comprises SEQ ID NO: 75 or a preferred fragment of SEQ ID NO: 116 comprises SEQ ID NO: 155, and each of said fragments has a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Another preferred fragment of SEQ ID NO:36 comprises SEQ ID NO: 76 or another preferred fragment of SEQ ID NO: 116 comprises SEQ ID NO: 156, and each of said fragments has a length of 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Another preferred fragment of SEQ ID NO:36 comprises SEQ ID NO: 77 or another preferred fragment of SEQ ID NO: 116 comprises SEQ ID NO: 157, and each of said fragments has a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0322] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0323] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 37 and has a length of 30, 31, 32 or 33 nucleotides or by a fragment of SEQ ID NO:37 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:37.

[0324] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:37 is represented by SEQ ID NO:117.

[0325] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 117 and has a length 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:117 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:117.

[0326] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0327] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0328] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 38 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:38 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:38.

[0329] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:38 is represented by SEQ ID NO:118.

[0330] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA

is represented by a nucleotide or a base sequence comprising SEQ ID NO: 118 and has a length 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:118 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:118.

[0331] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0332] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0333] Preferred oligonucleotides for inducing the skipping of exon 52 from the dystrophin pre-mRNA are as follows below.

[0334] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 39 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:39 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:39.

[0335] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:39 is represented by SEQ ID NO:119.

[0336] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 119 and has a length 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:119 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:119.

[0337] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0338] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0339] More preferably, an oligonucleotide:

[0340] consists of 2'-O-methyl phosphorothioate RNA,

[0341] all its cytosines have been replaced by 5-methylcytosines,

[0342] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 201 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:201 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:201. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0343] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 40 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:40 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:40. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0344] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:40 is represented by SEQ ID NO:120 and a preferred fragment of SEQ ID NO:120 is represented by SEQ ID NO:158 or 159 or 160.

[0345] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 120 and has a length 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:120 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:120.

[0346] A preferred fragment of SEQ ID NO:40 comprises SEQ ID NO: 78 and a preferred fragment of SEQ ID NO:120 comprises SEQ ID NO:158, and each fragment has a length of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Another preferred fragment of SEQ ID NO:40 comprises SEQ ID NO: 79 and another preferred fragment of SEQ ID NO:120 comprises SEQ ID NO:159, and each fragment has a length of 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Another preferred fragment of SEQ ID NO:40 comprises SEQ ID NO: 80 and another preferred fragment of SEQ ID NO:120 comprises SEQ ID NO:160, and each fragment has a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0347] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

Such preferred oligonucleotide is also defined as follows:

[0348] comprises a 2'-O-methyl phosphorothioatc RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and

[0349] is represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 40 or 120 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a nucleotide sequence comprising or consisting of a fragment of SEQ ID NO: 40 or 120, said fragment comprising or consisting of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 contiguous nucleotides or bases of SEQ ID NO:40 or 120.

[0350] More preferably, such oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base as earlier defined herein

[0351] More preferably, an oligonucleotide:

[0352] consists of 2'-O-methyl phosphorothioate RNA,

[0353] all its cytosines have been replaced by 5-methylcytosines,

[0354] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 40 and

has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:40 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:40. Accordingly, said oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 171 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:171 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:171. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 4 cytosines of SEQ ID NO:40 are modified as represented in SEQ ID NO:171. It is encompassed that 1, 2 or 3 of these cytosines are modified.

[0355] More preferably, an oligonucleotide:

[0356] consists of 2'-O-methyl phosphorothioate RNA,

[0357] all its uraciles have been replaced by 5-methyluraciles,

[0358] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO:172 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:172 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:172. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 7 uraciles of SEQ ID NO:40 are modified as represented in SEQ ID NO:172. It is encompassed that 1, 2, 3, 4, 5 or 6 of these uraciles are modified.

[0359] More preferably, an oligonucleotide:

[0360] consists of 2'-O-methyl phosphorothioate RNA,

[0361] all its adenines have been replaced by 2,6-diaminopurines,

[0362] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 173 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:173 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:173. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 5 adenines of SEQ ID NO:40 are modified as represented in SEQ ID NO:173. It is encompassed that 1, 2, 3 or 4 of these adenines are modified.

[0363] More preferably, an oligonucleotide:

[0364] consists of 2'-O-methyl phosphorothioate RNA,

[0365] all its cytosines have been replaced by 5-methylcytosines and all its uraciles have been replaced by 5-methyluraciles,

[0366] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 174 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:174 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:174. Accordingly, said oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 174 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:174 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:174. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 4 cytosines and not all the 7 uraciles of SEQ ID NO:40 are modified as represented in SEQ ID NO:174. It is encompassed that 1, 2 or 3 of these cytosines and-or 1, 2, 3, 4, 5 or 6 of these uraciles are modified.

[0367] More preferably, an oligonucleotide:

[0368] consists of 2'-O-methyl phosphorothioate RNA,

[0369] all its cytosines have been replaced by 5-methylcytosines and all its adenines have been replaced by 2,6-diaminopurines,

[0370] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 175 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:175 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:175. Accordingly, said oligonucleotide is represented by a nucleotide sequence comprising SEQ ID NO: 175 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:175 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:175. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides It is also encompassed that not all the 4 cytosines and not all the 5 adenines of SEQ ID NO:40 are modified as represented in SEQ ID NO:175. It is encompassed that 1, 2 or 3 of these cytosines and-or 1, 2, 3 or 4 of these adenines are modified.

[0371] More preferably, an oligonucleotide:

[0372] consists of 2'-O-methyl phosphorothioate RNA,

[0373] all its adenines have been replaced by 2,6-diaminopurines and all its uraciles have been replaced by 5-methyluraciles,

[0374] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 176 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:176 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:176. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 5 adenines and not all the 7 uraciles of SEQ ID NO: 40 are modified as represented in SEQ ID NO:176. It is encompassed that 1, 2, 3 or 4 of these adenines and-or 1, 2, 3, 4, 5 or 6 of these uraciles are modified.

[0375] More preferably, an oligonucleotide:

[0376] consists of 2'-O-methyl phosphorothioate RNA,

[0377] all its adenines have been replaced by 2,6-diaminopurines, all its cytosines have been replaced by 5-methylcytosines and all its uraciles have been replaced by 5-methyluraciles,

[0378] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 177 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:177 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:177. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31,

32 or 33 nucleotides. It is also encompassed that not all the 4 cytosines and not all the 7 uraciles and not all the 5 adenines of SEQ ID NO:40 are modified as represented in SEQ ID NO:177. It is encompassed that 1, 2 or 3 of these cytosines and-or 1, 2, 3, 4, 5 or 6 of these uraciles and-or 1, 2, 3 or 4 of these adenines are modified.

[0379] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide sequence or a base comprising SEQ ID NO: 41 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:41 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:41.

[0380] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:41 is represented by SEQ ID NO:121.

[0381] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 121 and has a length 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:121 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:121.

[0382] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0383] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0384] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 42 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:42 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:42.

[0385] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:42 is represented by SEQ ID NO:122.

[0386] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 122 and has a length 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:122 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:122.

[0387] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0388] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0389] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 43 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:43 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:43.

[0390] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0391] Such preferred oligonucleotide is also defined as follows:

[0392] comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and

[0393] is represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 43 or 123 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a nucleotide sequence comprising or consisting of a fragment of SEQ ID NO: 43 or 123, said fragment comprising or consisting of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 contiguous nucleotides or bases of SEQ ID NO:43 or 123. Accordingly a non-modified oligonucleotide derived from SEQ ID NO:43 is represented by SEQ ID NO:123 and a preferred fragment of SEQ ID NO:123 is represented by SEQ ID NO: 161.

[0394] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 123 and has a length 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:123 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:123.

[0395] More preferably, such oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base as earlier defined herein. Even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0396] More preferably, an oligonucleotide:

[0397] consists of 2'-O-methyl phosphorothioate RNA,

[0398] all its cytosines have been replaced by 5-methylcytosines,

[0399] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 43 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:43 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:43. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Accordingly, said oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 178 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:178 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:178. It is also

encompassed that not all the 6 cytosines of SEQ ID NO:43 are modified as represented in SEQ ID NO:178. It is encompassed that 1, 2, 3, 4 or 5 of these cytosines are modified.

[0400] A preferred fragment of SEQ ID NO:43 comprises SEQ ID NO: 81 and a preferred fragment of SEQ ID NO:123 comprises SEQ ID NO:161, each of said fragments has a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0401] More preferably, an oligonucleotide:

[0402] consists of 2'-O-methyl phosphorothioate RNA,

[0403] all its uraciles have been replaced by 5-methyluraciles,

[0404] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO:179 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:179 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:179. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 11 uraciles of SEQ ID NO:43 are modified as represented in SEQ ID NO:179. It is encompassed that 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 of these uraciles are modified.

[0405] More preferably, an oligonucleotide:

[0406] consists of 2'-O-methyl phosphorothioate RNA,

[0407] all its adenines have been replaced by 2,6-diaminopurines,

[0408] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 180 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:180 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:180. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 2 adenines of SEQ ID NO:43 are modified as represented in SEQ ID NO:180. It is encompassed that 1 of these adenines are modified.

[0409] More preferably, an oligonucleotide:

[0410] consists of 2'-O-methyl phosphorothioate RNA,

[0411] all its cytosines have been replaced by 5-methylcytosines and all its uraciles have been replaced by 5-methyluraciles,

[0412] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 181 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:181 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:181. Accordingly, said oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 181 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:181 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:181. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 6 cytosines and not all the 11 uraciles of SEQ ID NO: 43 are modified as represented in SEQ ID NO:181. It is encompassed that 1, 2, 3, 4 or 5 of these cytosines and-or 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 of these uraciles are modified.

[0413] More preferably, an oligonucleotide:

[0414] consists of 2'-O-methyl phosphorothioate RNA,

[0415] all its cytosines have been replaced by 5-methylcytosines and all its adenines have been replaced by 2,6-diaminopurines,

[0416] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 182 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:182 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:182. Accordingly, said oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 182 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:182 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:182. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 6 cytosines and not all the 2 adenines of SEQ ID NO:43 are modified as represented in SEQ ID NO:182. It is encompassed that 1, 2, 3, 4 or 5 of these cytosines and-or 1 of these adenines are modified.

[0417] More preferably, an oligonucleotide:

[0418] consists of 2'-O-methyl phosphorothioate RNA,

[0419] all its adenines have been replaced by 2,6-diaminopurines and all its uraciles have been replaced by 5-methyluraciles,

[0420] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 183 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:183 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:183. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 2 adenines and not all the 11 uraciles of SEQ ID NO:43 are modified as represented in SEQ ID NO:183. It is encompassed that 1 of these adenines and/or 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 of these uraciles are modified.

[0421] More preferably, an oligonucleotide:

[0422] consists of 2'-O-methyl phosphorothioate RNA,

[0423] all its adenines have been replaced by 2,6-diaminopurines, all its cytosines have been replaced by 5-methylcytosines and all its uraciles have been replaced by 5-methyluraciles,

[0424] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 184 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:184 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:184. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 6 cytosines and not all the 11 uraciles and not all the 2 adenines of SEQ ID NO:43 are modified as represented in SEQ ID NO:184. It is encompassed that 1, 2, 3, 4 or 5 of these cytosines and-or 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 of these uraciles and-or 1 of these adenines are modified.

[0425] Preferred oligonucleotides for inducing the skipping of exon 53 from the dystrophin pre-mRNA are as follows below.

[0426] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 44 and has a length of 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:44 comprising or consisting of at least 10 contiguous or bases nucleotides of SEQ ID NO:44.

[0427] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:44 is represented by SEQ ID NO:124.

[0428] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 124 and has a length 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:124 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:124.

[0429] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0430] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0431] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 45 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:45 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:45.

[0432] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:45 is represented by SEQ ID NO:125.

[0433] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 125 and has a length 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:125 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:125.

[0434] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0435] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0436] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 46 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:46 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:46.

[0437] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:46 is represented by SEQ ID NO:126.

[0438] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 126 and has a length 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:126 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:126.

[0439] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0440] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0441] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 47 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:47 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:47.

[0442] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:47 is represented by SEQ ID NO:127.

[0443] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 127 and has a length 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:127 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:127.

[0444] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0445] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0446] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methyl-

cytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 48 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:48 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:48.

[0447] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:48 is represented by SEQ ID NO:128.

[0448] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 128 and has a length 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:128 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:128.

[0449] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0450] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0451] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 49 and has a length of 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:49 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:49.

[0452] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:49 is represented by SEQ ID NO:129.

[0453] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 129 and has a length 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:129 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:129.

[0454] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0455] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0456] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 50 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:50 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:50.

[0457] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:50 is represented by SEQ ID NO:130.

[0458] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 130 and has a length 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:130 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:130.

[0459] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0460] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0461] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 51 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:51 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:51.

[0462] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:51 is represented by SEQ ID NO:131.

[0463] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 131 and has a length 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:131 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:131.

[0464] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0465] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0466] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 52 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:52 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:52.

[0467] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:52 is represented by SEQ ID NO:

91 and a preferred fragment of SEQ ID NO:91 is represented by SEQ ID NO:162, 163 or 164. SEQ ID NO: 91 is identical with SEQ ID NO: 132.

[0468] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 91 and has a length 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:191 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:91.

[0469] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0470] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0471] Such preferred oligonucleotide is also defined as follows:

[0472] comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and

[0473] is represented by a nucleotide or base sequence comprising or consisting of SEQ ID NO: 52 or 91 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a nucleotide sequence comprising or consisting of a fragment of SEQ ID NO: 52 or 91, said fragment comprising or consisting of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 contiguous nucleotides or bases of SEQ ID NO:52 or 91.

[0474] More preferably, such oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base as earlier defined herein.

[0475] More preferably, an oligonucleotide:

[0476] consists of 2'-O-methyl phosphorothioate RNA,

[0477] all its cytosines have been replaced by 5-methylcytosines,

[0478] such oligonucleotide is represented by a nucleotide or base sequence comprising SEQ ID NO: 52 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:52 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:52. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0479] A preferred fragment of SEQ ID NO:52 comprises SEQ ID NO: 82 and a preferred fragment of SEQ ID NO:91 comprises SEQ ID NO:162, each of said fragments has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Another preferred fragment of SEQ ID NO:52 comprises SEQ ID NO: 83 and another preferred fragment of SEQ ID NO:91 comprises SEQ ID NO:163, each of said fragments has a length of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Another preferred fragment of SEQ ID NO:52 comprises SEQ ID NO: 84 and another preferred fragment of SEQ ID NO:91 comprises SEQ ID NO:164, each of said fragments has a length of 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. A most preferred fragment of SEQ ID NO: 52 comprises or consists of SEQ ID NO: 91 (PS229L: 5'-GUUGCCUCCGGUUCUGAAGGUGUUC-3'). Another most preferred fragment of SEQ ID NO: 52 comprises or consists of SEQ ID NO: 92 (PS524: 5'-GUUGXXUXXGGUUXUGAAGGUGUUX-3'; wherein X is 5-methylcytosine).

[0480] Such preferred oligonucleotide is also defined as follows:

[0481] comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and

[0482] is represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 82, 83, 84, 91 or 92 or 162 or 163 or 164 and has a length of 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a nucleotide or a base sequence comprising or consisting of a fragment of SEQ ID NO: 82, 83, 84, 91 or 92, or 162 or 163 or 164, said fragment comprising or consisting of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 contiguous nucleotides or bases of SEQ ID NO:82, 83, 84, 91, or 92 or 162, 163 or 164.

[0483] More preferably, such oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base as earlier defined herein

[0484] More preferably, an oligonucleotide:

[0485] consists of 2'-O-methyl phosphorothioate RNA,

[0486] all its cytosines have been replaced by 5-methylcytosines,

[0487] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 82, 83, 84 or 92 and has a length of 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:82, 83, 84, or 92 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:82, 83, 84, or 92. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. SEQ ID NO: 92 is identical with SEQ ID NO: 199. It is also encompassed that not all the 6 cytosines of SEQ ID NO:52 are modified as represented in SEQ ID NO:92. It is encompassed that 1, 2, 3, 4 or 5 of these cytosines are modified.

[0488] More preferably, an oligonucleotide:

[0489] consists of 2'-O-methyl phosphorothioate RNA,

[0490] two of its cytosines have been replaced by 5-methylcytosines,

[0491] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 218 and has a length of 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:218 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:218. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0492] More preferably, an oligonucleotide:

[0493] consists of 2'-O-methyl phosphorothioate RNA,

[0494] three of its cytosines have been replaced by 5-methylcytosines,

[0495] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 219 and has a length of 17, 18, 19, 20, 21, 22, 23, 24, 25, 26,

27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:219 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:219. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0496] More preferably, an oligonucleotide:

[0497] consists of 2'-O-methyl phosphorothioate RNA,

[0498] four of its cytosines have been replaced by 5-methylcytosines,

[0499] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 217 and has a length of 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:217 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:217. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0500] More preferably, an oligonucleotide:

[0501] consists of 2'-O-methyl phosphorothioate RNA,

[0502] all its uraciles have been replaced by 5-methyluraciles,

[0503] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 211 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:211 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:211. Accordingly, said oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 211 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:211 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:211. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 9 uraciles of SEQ ID NO:52 are modified as represented in SEQ ID NO:211. It is encompassed that 1, 2, 3, 4, 5, 6, 7, or 8 of these uraciles are modified.

[0504] More preferably, an oligonucleotide:

[0505] consists of 2'-O-methyl phosphorothioate RNA,

[0506] all its cytosines have been replaced by 5-methylcytosines and all its uraciles have been replaced by 5-methyluraciles,

[0507] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 212 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:212 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:212. Accordingly, said oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 212 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:212 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:212. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 6 cytosines and not all the 9 uraciles of SEQ ID NO:52 are modified as represented in SEQ ID NO:212. It is encompassed that 1, 2, 3, 4, or 5 of these cytosines and/or 1, 2, 3, 4, 5, 6, 7, or 8 of these uraciles are modified.

[0508] More preferably, an oligonucleotide:

[0509] consists of 2'-O-methyl phosphorothioate RNA,

[0510] all its adenines have been replaced by 2,6-diaminopurines,

[0511] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 213 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:213 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:213. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 2 adenines of SEQ ID NO:52 are modified as represented in SEQ ID NO:213. It is encompassed that 1 of these adenines are modified.

[0512] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 53 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:53 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:53.

[0513] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:53 is represented by SEQ ID NO:133.

[0514] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 133 and has a length 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:133 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:133.

[0515] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0516] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0517] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 54 and has a length of 30, 31, 32 or 33 nucleotides, or by a fragment of SEQ ID NO:54 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:54.

[0518] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:54 is represented by SEQ ID NO:134.

[0519] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA

monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 134 and has a length 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:134 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:134.

[0520] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0521] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0522] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioatc RNA monomer or consists of 2'-O-methyl phosphorothioatc RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 55 and has a length of 30, 31, 32 or 33 nucleotides, or by a fragment of SEQ ID NO:55 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:55.

[0523] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:55 is represented by SEQ ID NO:135.

[0524] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 135 and has a length 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:135 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:135.

[0525] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0526] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0527] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 56 and has a length of 33, 34 or 35 nucleotides or by a fragment of SEQ ID NO:56 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:56.

[0528] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:56 is represented by SEQ ID NO:136.

[0529] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioatc RNA monomer or consists of 2'-O-methyl phosphorothioatc RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 136 and has a length 33, 34 or 35 nucleotides, or by a fragment of SEQ ID NO:136 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:136.

[0530] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0531] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0532] Preferred oligonucleotides for inducing the skipping of exon 55 from the dystrophin pre-mRNA are as follows below.

[0533] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 57 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:57 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:57. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Such preferred oligonucleotide is also defined as follows:

[0534] comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and

[0535] is represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 57 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a nucleotide sequence comprising or consisting of a fragment of SEQ ID NO: 57, said fragment comprising or consisting of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 contiguous nucleotides or bases of SEQ ID NO:57.

[0536] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:57 is represented by SEQ ID NO:137 and a preferred fragment of SEQ ID NO:137 is represented by SEQ ID NO:165 or 166.

[0537] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and is represented by a nucleotide or a base sequence comprising SEQ ID NO: 137 and has a length 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:137 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:137.

[0538] More preferably, such oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base as earlier defined herein. Even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0539] More preferably, an oligonucleotide:

[0540] consists of 2'-O-methyl phosphorothioate RNA,

[0541] all its cytosines have been replaced by 5-methylcytosines,

[0542] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 57 and

has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:57 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:57.

[0543] Accordingly, said oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 185 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:185 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:185. It is also encompassed that not all the 8 cytosines of SEQ ID NO:57 are modified as represented in SEQ ID NO:185. It is encompassed that 1, 2, 3, 4, 5, 6, or 7 of these cytosines are modified.

[0544] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0545] A preferred fragment of SEQ ID NO:57 comprises SEQ ID NO: 85 and a preferred fragment of SEQ ID NO:137 comprises SEQ ID NO: 165, each of said fragments has a length of 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Another preferred fragment of SEQ ID NO:57 comprises SEQ ID NO: 86 and another preferred fragment of SEQ ID NO:137 comprises SEQ ID NO: 166, each of said fragments has a length of 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0546] More preferably, an oligonucleotide:

[0547] consists of 2'-O-methyl phosphorothioate RNA,

[0548] all its uraciles have been replaced by 5-methyluraciles,

[0549] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO:186 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:186 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:186. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 7 uraciles of SEQ ID NO:57 are modified as represented in SEQ ID NO:186. It is encompassed that 1, 2, 3, 4, 5 or 6 of these uraciles are modified.

[0550] More preferably, an oligonucleotide:

[0551] consists of 2'-O-methyl phosphorothioate RNA,

[0552] all its adenines have been replaced by 2,6-diaminopurines,

[0553] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 187 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:187 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:187. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 5 adenines of SEQ ID NO:57 are modified as represented in SEQ ID NO:187. It is encompassed that 1, 2, 3 or 4 of these adenines are modified.

[0554] More preferably, an oligonucleotide:

[0555] consists of 2'-O-methyl phosphorothioate RNA,

[0556] all its cytosines have been replaced by 5-methylcytosines and all its uraciles have been replaced by 5-methyluraciles,

[0557] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 188 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:188 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:188. Accordingly, said oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 188 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:188 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:188. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 8 cytosines and not all the 7 uraciles of SEQ ID NO:57 are modified as represented in SEQ ID NO:188. It is encompassed that 1, 2, 3, 4, 5, 6 or 7 of these cytosines and-or 1, 2, 3, 4, 5 or 6 of these uraciles are modified.

[0558] More preferably, an oligonucleotide:

[0559] consists of 2'-O-methyl phosphorothioate RNA,

[0560] all its cytosines have been replaced by 5-methylcytosines and all its adenines have been replaced by 2,6-diaminopurines,

[0561] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 189 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:189 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:189. Accordingly, said oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 189 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:189 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:189. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides It is also encompassed that not all the 8 cytosines and not all the 5 adenines of SEQ ID NO:57 are modified as represented in SEQ ID NO:189. It is encompassed that 1, 2, 3, 4, 5, 6 or 7 of these cytosines and-or 1, 2, 3 or 4 of these adenines are modified.

[0562] More preferably, an oligonucleotide:

[0563] consists of 2'-O-methyl phosphorothioate RNA,

[0564] all its adenines have been replaced by 2,6-diaminopurines and all its uraciles have been replaced by 5-methyluraciles,

[0565] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 190 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:190 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:190. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 5 adenines and not all the 7 uraciles of SEQ ID NO:57 are modified as represented in SEQ ID NO:190. It is encompassed that 1, 2, 3 or 4 of these adenines and-or 1, 2, 3, 4, 5 or 6 of these uraciles are modified.

[0566] More preferably, an oligonucleotide:

[0567] consists of 2'-O-methyl phosphorothioate RNA,

[0568] all its adenines have been replaced by 2,6-diaminopurines, all its cytosines have been replaced by 5-methylcytosines and all its uraciles have been replaced by 5-methyluraciles,

[0569] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 191 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:191

comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:191. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 8 cytosines and not all the 7 uraciles and not all the 5 adenines of SEQ ID NO:57 are modified as represented in SEQ ID NO:191. It is encompassed that 1, 2, 3, 4, 5, 6 or 7 of these cytosines and-or 1, 2, 3, 4, 5 or 6 of these uraciles and-or 1, 2, 3 or 4 of these adenines are modified.

[0570] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 58 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:58 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:58.

[0571] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:58 is represented by SEQ ID NO:138.

[0572] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 138 and has a length 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides, or by a fragment of SEQ ID NO:138 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:138.

[0573] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0574] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0575] Such preferred oligonucleotide is also defined as follows:

[0576] comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and

[0577] is represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 58 or 138 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a nucleotide or a base sequence comprising or consisting of a fragment of SEQ ID NO: 58 or 138, said fragment comprising or consisting of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 contiguous nucleotides or bases of SEQ ID NO:58 or 138.

[0578] More preferably, such oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base as earlier defined herein

[0579] More preferably, an oligonucleotide:

[0580] consists of 2'-O-methyl phosphorothioate RNA,

[0581] all its cytosines have been replaced by 5-methylcytosines,

[0582] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 58 and has a length of 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:58 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:58. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0583] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 59 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:59 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:59. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0584] Such preferred oligonucleotide is also defined as follows:

[0585] comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and

[0586] is represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 59 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a nucleotide sequence comprising or consisting of a fragment of SEQ ID NO: 59, said fragment comprising or consisting of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 contiguous nucleotides or bases of SEQ ID NO:59.

[0587] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:59 is represented by SEQ ID NO:139 and a preferred fragment of SEQ ID NO:139 is represented by SEQ ID NO: 167 or 168 or 169 or 170.

[0588] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and is represented by a nucleotide or a base sequence comprising SEQ ID NO: 139 and has a length 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:139 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:139.

[0589] More preferably, such oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base as earlier defined herein. Even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0590] More preferably, an oligonucleotide:

[0591] consists of 2'-O-methyl phosphorothioate RNA,

[0592] all its cytosines have been replaced by 5-methylcytosines,

[0593] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 59 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:59 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:59.

[0594] Accordingly, said oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 192 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:192 comprising

or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:192. It is also encompassed that not all the 5 cytosines of SEQ ID NO:59 are modified as represented in SEQ ID NO:192. It is encompassed that 1, 2, 3 or 4 of these cytosines are modified.

[0595] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0596] A preferred fragment of SEQ ID NO:59 comprises SEQ ID NO: 87 and a preferred fragment of SEQ ID NO:139 comprises SEQ ID NO:167, each of said fragments has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Another preferred fragment of SEQ ID NO:59 comprises SEQ ID NO: 88 and another preferred fragment of SEQ ID NO:139 comprises SEQ ID NO:168, each of said fragments has a length of 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Another preferred fragment of SEQ ID NO:59 comprises SEQ ID NO: 89 and another preferred fragment of SEQ ID NO:139 comprises SEQ ID NO:169, each of said fragments has a length of 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. Another preferred fragment of SEQ ID NO:59 comprises SEQ ID NO: 90 and another preferred fragment of SEQ ID NO:139 comprises SEQ ID NO:170, each of said fragments has a length of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0597] More preferably, an oligonucleotide:

[0598] consists of 2'-O-methyl phosphorothioate RNA,

[0599] all its uraciles have been replaced by 5-methyluraciles,

[0600] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO:193 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:193 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:193. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 6 uraciles of SEQ ID NO:59 are modified as represented in SEQ ID NO:193. It is encompassed that 1, 2, 3, 4 or 5 of these uraciles are modified.

[0601] More preferably, an oligonucleotide:

[0602] consists of 2'-O-methyl phosphorothioate RNA,

[0603] all its adenines have been replaced by 2,6-diaminopurines,

[0604] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 194 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:194 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:194. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 6 adenines of SEQ ID NO:59 are modified as represented in SEQ ID NO:194. It is encompassed that 1, 2, 3, 4 or 5 of these adenines are modified.

[0605] More preferably, an oligonucleotide:

[0606] consists of 2'-O-methyl phosphorothioate RNA,

[0607] all its cytosines have been replaced by 5-methylcytosines and all its uraciles have been replaced by 5-methyluraciles,

[0608] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 195 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:195 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:195. Accordingly, said oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 195 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:195 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:195. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 5 cytosines and not all the 6 uraciles of SEQ ID NO:59 are modified as represented in SEQ ID NO:195. It is encompassed that 1, 2, 3 or 4 of these cytosines and-or 1, 2, 3, 4 or 5 of these uraciles are modified.

[0609] More preferably, an oligonucleotide:

[0610] consists of 2'-O-methyl phosphorothioate RNA,

[0611] all its cytosines have been replaced by 5-methylcytosines and all its adenines have been replaced by 2,6-diaminopurines,

[0612] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 196 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:196 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:196. Accordingly, said oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 196 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:196 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:196. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides It is also encompassed that not all the 5 cytosines and not all the 6 adenines of SEQ ID NO:59 are modified as represented in SEQ ID NO:196. It is encompassed that 1, 2, 3 or 4 of these cytosines and/or 1, 2, 3, 4 or 5 of these adenines are modified.

[0613] More preferably, an oligonucleotide:

[0614] consists of 2'-O-methyl phosphorothioate RNA,

[0615] all its adenines have been replaced by 2,6-diaminopurines and all its uraciles have been replaced by 5-methyluraciles,

[0616] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 197 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:197 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:197. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 6 adenines and not all the 6 uraciles of SEQ ID NO:59 are modified as represented in SEQ ID NO:197. It is encompassed that 1, 2, 3, 4 or 5 of these adenines and/or 1, 2, 3, 4 or 5 of these uraciles are modified.

[0617] More preferably, an oligonucleotide:

[0618] consists of 2'-O-methyl phosphorothioate RNA,

[0619] all its adenines have been replaced by 2,6-diaminopurines, all its cytosines have been replaced by 5-methylcytosines and all its uraciles have been replaced by 5-methyluraciles,

[0620] such oligonucleotide is represented by a nucleotide or a base sequence comprising SEQ ID NO: 198 and has a length of 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:198 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:198. Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides. It is also encompassed that not all the 5 cytosines and not all the 6 uraciles and not all the 6 adenines of SEQ ID NO:59 are modified as represented in SEQ ID NO:198. It is encompassed that 1, 2, 3 or 4 of these cytosines and/or 1, 2, 3, 4 or 5 of these uraciles and/or 1, 2, 3, 4 or 5 of these adenines are modified.

[0621] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 60 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides, or by a fragment of SEQ ID NO:60 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:60.

[0622] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:60 is represented by SEQ ID NO:140.

[0623] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 140 and has a length 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides, or by a fragment of SEQ ID NO:140 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:140.

[0624] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0625] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0626] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 61 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:61 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:61.

[0627] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:61 is represented by SEQ ID NO:141.

[0628] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 141 and has a length 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides or by a fragment of SEQ ID NO:141 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:141.

[0629] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0630] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

[0631] In a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA and more preferably comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base, is represented by a nucleotide or a base sequence comprising SEQ ID NO: 62 and has a length of 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 nucleotides or by a fragment of SEQ ID NO:62 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:62.

[0632] Accordingly a non-modified oligonucleotide derived from SEQ ID NO:62 is represented by SEQ ID NO:142.

[0633] Accordingly, in a preferred embodiment, an oligonucleotide comprises a 2'-O-methyl phosphorothioate RNA monomer or consists of 2'-O-methyl phosphorothioate RNA is represented by a nucleotide or a base sequence comprising SEQ ID NO: 142 and has a length 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides or by a fragment of SEQ ID NO:142 comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO:142.

[0634] Such fragment has preferably a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

[0635] Accordingly, more preferably, said oligonucleotide comprises a 5-methylpyrimidine (i.e. a 5-methylcytosine, and/or a 5-methyluracil) and/or a 2,6-diaminopurine base. Accordingly, even more preferably, said oligonucleotide has all its cytosines and/or all its uracil and/or all its adenines that have been substituted or modified as defined herein.

Composition

[0636] In a second aspect, there is provided a composition comprising an oligonucleotide as described in the previous section entitled "Oligonucleotide". This composition preferably comprises or consists of an oligonucleotide as described above.

[0637] In a preferred embodiment, said composition is for use as a medicament. Said composition is therefore a pharmaceutical composition. A pharmaceutical composition usually comprises a pharmaceutically accepted carrier, diluent and/or excipient. In a preferred embodiment, a composition of the current invention comprises a compound as defined herein and optionally further comprises a pharmaceutically acceptable formulation, filler, preservative, solubilizer, carrier, diluent, excipient, salt, adjuvant and/or solvent. Such pharmaceutically acceptable carrier, filler, preservative, solu-

bilizer, diluent, salt, adjuvant, solvent and/or excipient may for instance be found in Remington: The Science and Practice of Pharmacy, 20th Edition. Baltimore, Md.: Lippincott Williams & Wilkins, 2000. The compound as described in the invention may possess at least one ionizable group. An ionizable group may be a base or acid, and may be charged or neutral. An ionizable group may be present as ion pair with an appropriate counterion that carries opposite charge(s). Examples of cationic counterions are sodium, potassium, cesium, Tris, lithium, calcium, magnesium, trialkylammonium, triethylammonium, and tetraalkylammonium. Examples of anionic counterions are chloride, bromide, iodide, lactate, mesylate, acetate, trifluoroacetate, dichloroacetate, and citrate. Examples of counterions have been described [e.g. Kumar, 2008, which is incorporated here in its entirety by reference].

[0638] In a preferred embodiment, a composition comprises the oligonucleotide of the invention and sodium as counterion. Said oligonucleotide present in said composition may also be named as an oligonucleotide in its sodium form.

[0639] In another preferred embodiment, a composition comprises the oligonucleotide of the invention and calcium and/or magnesium as counterion. Said oligonucleotide present in said composition may also be named as an oligonucleotide in its calcium or magnesium or mixed calcium/magnesium form.

[0640] Such type of composition comprising an oligonucleotide of the invention and a counterion may be obtained through either formulating the counterion salt of the oligonucleotide or by adding appropriate amounts of said salt to an oligonucleotide. A positive effect of calcium salts present in composition comprising an oligonucleotide with respect to immunostimulatory effects of said oligonucleotides has been described (e.g. patent application WO 2012021985 (Replicor), incorporated here in its entirety by reference).

[0641] A pharmaceutical composition may comprise an aid in enhancing the stability, solubility, absorption, bioavailability, activity, pharmacokinetics, pharmacodynamics and cellular uptake of said compound, in particular an excipient capable of forming complexes, nanoparticles, microparticles, nanotubes, nanogels, hydrogels, poloxamers or pluronics, polymersomes, colloids, microbubbles, vesicles, micelles, lipoplexes, and/or liposomes. Examples of nanoparticles include polymeric nanoparticles, gold nanoparticles, magnetic nanoparticles, silica nanoparticles, lipid nanoparticles, sugar particles, protein nanoparticles and peptide nanoparticles.

[0642] A preferred composition comprises at least one excipient that may further aid in enhancing the targeting and/or delivery of said composition and/or said oligonucleotide to a tissue and/or a cell and/or into a tissue and/or a cell. A preferred tissue or cell is a muscle tissue or cell.

[0643] Many of these excipients are known in the art (e.g. see Bruno, 2011) and may be categorized as a first type of excipient. Examples of first type of excipients include polymers (e.g. polyethyleneimine (PEI), poly-2-hydroxypropylcneimine (pHP), polypropyleneimine (PPI), dextran derivatives, butylcyanoacrylate (PBCA), hexylcyanoacrylate (PHCA), poly(lactic-co-glycolic acid) (PLGA), polyamines (e.g. spermine, spermidine, putrescine, cadaverine), chitosan, poly(amido amines) (PAMAM), poly(ester amine), polyvinyl ether, polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG) cyclodextrins, hyaluronic acid, colominic acid, and derivatives thereof), dendrimers (e.g. poly(amidoamine)), lipids {e.g. 1,2-dioleoyl-3-dimethylammonium propane (DODAP), dioleoyldimethylammonium chloride (DODAC), phosphatidylcholine derivatives [e.g 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)], lyso-phosphatidylcholine derivaties [e.g. 1-stearoyl-2-lyso-sn-glycero-3-phosphocholine (S-LysoPC)], sphingomyeline, 2-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-N-ditetracedyl carbamoyl methylacetamide (RPR209120), phosphoglycerol derivatives [e.g. 1,2-dipalmitoyl-sn-glycero-3-phosphoglycerol, sodium salt (DPPG-Na), phosphaticid acid derivatives [1,2-distearoyl-sn-glycero-3-phosphaticid acid, sodium salt (DSPA), phosphatidylethanolamine derivatives [e.g. dioleoyl-L-R-phosphatidylethanolamine (DOPE), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE), 2-diphytanoyl-sn-glycero-3-phosphoethanolamine (DPhyPE),], N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium (DOTAP), N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium (DOTMA), 1,3-di-oleoyloxy-2-(6-carboxy-spermyl)-propylamid (DOSPER), (1,2-dimyristyolxypropyl-3-dimethylhydroxy ethyl ammonium (DMRIE), (N1-cholesteryloxycarbonyl-3,7-diazanonane-1,9-diamine (CDAN), dimethyldioctadecylammonium bromide (DDAB), 1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine (POPC), (b-L-Arginyl-2,3-L-diaminopropionic acid-N-palmityl-N-olelyl-amide trihydrochloride (AtuFECT01), 1,N,N-dimethyl-3-aminopropane derivatives [e.g. 1,2-distearoyloxy-N,N-dimethyl-3-aminopropane (DSDMA), 1,2-dioleyloxy-N,N-dimethyl-3-aminopropane (DoDMA), 1,2-Dilinoleyloxy-N,N-3-dimethylaminopropane (DLinDMA), 2,2-dilinoleyl-4-dimethylaminomethyl[1,3]-dioxolane (DLin-K-DMA), phosphatidylserine derivatives [1,2-dioleyl-sn-glycero-3-phospho-L-serine, sodium salt (DOPS)], cholesterol}proteins (e.g. albumin, gelatins, atellocollagen), and peptides (e.g. protamine, PepFects, NickFects, polyarginine, polylysine, CADY, MPG).

[0644] Another preferred composition may comprise at least one excipient categorized as a second type of excipient. A second type of excipient may comprise or contain a conjugate group as described herein to enhance targeting and/or delivery of the composition and/or of the oligonucleotide of the invention to a tissue and/or cell and/or into a tissue and/or cell, as for example muscle tissue or cell. Both types of excipients may be combined together into one single composition as identified herein.

[0645] The skilled person may select, combine and/or adapt one or more of the above or other alternative excipients and delivery systems to formulate and deliver a compound for use in the present invention.

[0646] Such a pharmaceutical composition of the invention may be administered in an effective concentration at set times to an animal, preferably a mammal. More preferred mammal is a human being. An oligonucleotide or a composition as defined herein for use according to the invention may be suitable for direct administration to a cell, tissue and/or an organ in vivo of individuals affected by or at risk of developing a disease or condition as identified herein, and may be administered directly in vivo, ex vivo or in vitro. Administration may be via topical, systemic and/or parenteral routes, for example intravenous, subcutaneous, intraperitoneal, intrathecal, intramuscular, ocular, nasal, urogenital, intradermal, dermal, enteral, intravitreal, intracavernous, intracerebral, intrathecal, epidural or oral route.

[0647] Preferably, such a pharmaceutical composition of the invention may be encapsulated in the form of an emulsion,

suspension, pill, tablet, capsule or soft-gel for oral delivery, or in the form of aerosol or dry powder for delivery to the respiratory tract and lungs.

[0648] In an embodiment an oligonucleotide of the invention may be used together with another compound already known to be used for the treatment of said disease. Such other compounds may be used for reducing inflammation, preferably for reducing muscle tissue inflammation, and/or an adjunct compound for improving muscle fiber function, integrity and/or survival and/or improve, increase or restore cardiac function. Examples are, but not limited to, a steroid, preferably a (gluco)corticosteroid, an ACE inhibitor (preferably perindopril), an angiotensin II type 1 receptor blocker (preferably losartan), a tumor necrosis factor-alpha (TNFα) inhibitor, a TGFβ inhibitor (preferably decorin), human recombinant biglycan, a source of mIGF-1, a myostatin inhibitor, mannose-6-phosphate, an antioxidant, an ion channel inhibitor, a protease inhibitor, a phosphodiesterase inhibitor (preferably a PDE5 inhibitor, such as sildenafil or tadalafil), a histone deacetylase inhibitor (HDAC inhibitor, androgen receptor modulator, creatine, creatine phosphate, and/or L-arginine. Such combined use may be a sequential use: each component is administered in a distinct composition. Alternatively each compound may be used together in a single composition.

Use

[0649] In a further aspect, there is provided the use of a composition or an oligonucleotide as described in the previous sections for use as a medicament or part of therapy, or applications in which said oligonucleotide exerts its activity intracellularly.

[0650] Preferably, an oligonucleotide or composition of the invention is for use as a medicament or part of a therapy for preventing, delaying, curing, ameliorating and/or treating DMD or BMD.

Method

[0651] In a further aspect, there is provided a method for preventing, treating, curing, ameliorating and/or delaying a condition or disease as defined in the previous section in an individual, in a cell, tissue or organ of said individual. The method comprising administering an oligonucleotide or a composition of the invention to said individual or a subject in the need thereof.

[0652] The method according to the invention wherein an oligonucleotide or a composition as defined herein may be suitable for administration to a cell, tissue and/or an organ in vivo of individuals affected by any of the herein defined diseases, and may be administered in vivo, ex vivo or in vitro. An individual or a subject in need is preferably a mammal, more preferably a human being.

[0653] In a further aspect, there is provided a method for diagnosis wherein the oligonucleotide of the invention is provided with a radioactive label or fluorescent label.

[0654] In an embodiment, in a method of the invention, a concentration of an oligonucleotide or composition is ranged from 0.01 nM to 1 μM. More preferably, the concentration used is from 0.05 to 500 nM, or from 0.1 to 500 nM, or from 0.02 to 500 nM, or from 0.05 to 500 nM, even more preferably from 1 to 200 nM.

[0655] Dose ranges of an oligonucleotide or composition according to the invention are preferably designed on the basis of rising dose studies in clinical trials (in vivo use) for which rigorous protocol requirements exist. An oligonucleotide as defined herein may be used at a dose which is ranged from 0.01 to 200 mg/kg or 0.05 to 100 mg/kg or 0.1 to 50 mg/kg or 0.1 to 20 mg/kg, preferably from 0.5 to 10 mg/kg.

[0656] The ranges of concentration or dose of oligonucleotide or composition as given above are preferred concentrations or doses for in vitro or ex vivo uses. The skilled person will understand that depending on the identity of the oligonucleotide used, the target cell to be treated, the gene target and its expression levels, the medium used and the transfection and incubation conditions, the concentration or dose of oligonucleotide used may further vary and may need to be optimised any further.

[0657] In this document and in its claims, the verb "to comprise" and its conjugations is used in its non-limiting sense to mean that items following the word are included, but items not specifically mentioned are not excluded. In addition the verb "to consist" may be replaced by "to consist essentially of" meaning that an oligonucleotide or a composition as defined herein may comprise additional component(s) than the ones specifically identified, said additional component(s) not altering the unique characteristic of the invention. In addition, reference to an element by the indefinite article "a" or "an" does not exclude the possibility that more than one of the element is present, unless the context clearly requires that there be one and only one of the elements. The indefinite article "a" or "an" thus usually means "at least one".

[0658] Each embodiment as identified herein may be combined together unless otherwise indicated. All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

DEFINITIONS

[0659] Throughout the application, the word "binds", "targets", "hybridizes" could be used interchangeably when used in the context of an antisense oligonucleotide which is reverse complementary to a part of a pre-mRNA as identified herein.

[0660] In addition, throughout the application, the expression "able to bind", "able to target", "able to hybridize" could be used interchangeably when used in the context of an antisense oligonucleotide which is reverse complementary to a part of a pre-mRNA as identified herein and for which conditions could be found wherein said oligonucleotide could bind, target or hybridize with said part of said pre-mRNA.

[0661] As used herein, "hybridization" refers to the pairing of complementary oligomeric compounds (e.g., an antisense compound and its target nucleic acid). While not limited to a particular mechanism, the most common mechanism of pairing involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleoside or nucleotide bases (nucleobases). For example, the natural base adenine is nucleobase complementary to the natural nucleobases thymine and uracil which pair through the formation of hydrogen bonds. The natural base guanine is nucleobase complementary to the natural bases cytosine and 5-methylcytosine. Hybridization can occur under varying circumstances.

[0662] As used herein, "specifically hybridizes" refers to the ability of an oligomeric compound to hybridize to one nucleic acid site with greater affinity than it hybridizes to another nucleic acid site. In certain embodiments, an anti sense oligonucleotide specifically hybridizes to more than one target site.

[0663] In the context of the invention, "hybridizes" is used under physiological conditions in a cell, preferably a muscular cell unless otherwise indicated.

[0664] As used herein, "nucleoside" refers to a compound comprising a heterocyclic base moiety and a sugar moiety. Nucleosides include, but are not limited to, naturally occurring nucleosides (as found in DNA and RNA), abasic nucleosides, modified nucleosides, and sugar-modified nucleosides. Nucleosides may be modified with any of a variety of substituents.

[0665] As used herein, "sugar moiety" means a natural (furanosyl), a modified sugar moiety or a sugar surrogate.

[0666] As used herein, "modified sugar moiety" means a chemically-modified furanosyl sugar or a non-furanosyl sugar moiety. Also, embraced by this term are furanosyl sugar analogs and derivatives including tricyclic sugars, bicyclic sugars, tetrahydropyrans, morpholinos, 2'-modified sugars, 4'-modified sugars, 5'-modified sugars, and 4'-substituted sugars.

[0667] As used herein, "sugar-modified nucleoside" means a nucleoside comprising a modified sugar moiety.

[0668] As used herein the term "sugar surrogate" refers to a structure that is capable of replacing the furanose ring of a naturally occurring nucleoside. In certain embodiments, sugar surrogates are non-furanose (or 4'-substituted furanose) rings or ring systems or open systems. Such structures include simple changes relative to the natural furanose ring, such as a six membered ring or may be more complicated as is the case with the non-ring system used in peptide nucleic acid. Sugar surrogates includes without limitation morpholinos and cyclohexenyls and cyclohexitols. In most nucleosides having a sugar surrogate group the heterocyclic base moiety is generally maintained to permit hybridization.

[0669] As used herein, "nucleotide" refers to a nucleoside further comprising a modified or unmodified phosphate linking group or a non-phosphate internucleoside linkage.

[0670] As used herein, "linked nucleosides" may or may not be linked by phosphate linkages and thus includes "linked nucleotides".

[0671] As used herein, "nucleobase" refers to the heterocyclic base portion of a nucleoside. Nucleobases may be naturally occurring or may be modified and therefore include, but are not limited to adenine, cytosine, guanine, uracil, thymine and analogues thereof such as 5-methylcytosine. In certain embodiments, a nucleobase may comprise any atom or group of atoms capable of hydrogen bonding to a base of another nucleic acid.

[0672] As used herein, "modified nucleoside" refers to a nucleoside comprising at least one modification compared to naturally occurring RNA or DNA nucleosides. Such modification may be at the sugar moiety and/or at the nucleobases.

[0673] As used herein, "T_m" means melting temperature which is the temperature at which the two strands of a duplex nucleic acid separate. T_m is often used as a measure of duplex stability or the binding affinity of an antisense compound toward a complementary RNA molecule.

[0674] As used herein, "2'-modified" or "2'-substituted" refers to a nucleoside comprising a sugar comprising a substituent at the 2' position other than H or OH. 2'-modified nucleosides include, but are not limited to, bicyclic nucleosides wherein the bridge connecting two carbon atoms of the sugar ring connects the 2' carbon and another carbon of the sugar ring; and nucleosides with non-bridging 2'-substituents, such as allyl, amino, azido, thio, O-allyl, O—C_1-C_{10} alkyl, —OCF_3, O—$(CH_2)_2$—O—CH_3, 2'-O$(CH_2)_2SCH_3$, O—$(CH_2)_2$—O—N$(R_m)(R_n)$, or O—CH_2—C(=O)—N$(R_m)(R_n)$, wherein each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl. 2'-modified nucleosides may further comprise other modifications, for example at other positions of the sugar and/or at the nucleobase.

[0675] As used herein, "2'-OMe" or "2'-OCH_3" or "2'-O-methyl" each refers to a nucleoside comprising a sugar comprising an —OCH_3 group at the 2' position of the sugar ring.

[0676] As used herein, "MOE" or "2'-MOE" or "2'-$OCH_2CH_2OCH_3$" or "2'-O-methoxyethyl" each refers to a nucleoside comprising a sugar comprising a —$OCH_2CH_2OCH_3$ group at the 2' position of the sugar ring.

[0677] As used herein, the term "adenine analogue" means a chemically-modified purine nucleobase that, when incorporated into an oligomer, is capable with forming a Watson-Crick base pair with either a thymine or uracil of a complementary strand of RNA or DNA.

[0678] As used herein, the term "uracil analogue" means a chemically-modified pyrimidine nucleobase that, when incorporated into an oligomer, is capable with forming a Watson-Crick base pair with either a adenine of a complementary strand of RNA or DNA.

[0679] As used herein, the term "thymine analogue" means a chemically-modified pyrimidine nucleobase that, when incorporated into an oligomer, is capable with forming a Watson-Crick base pair with an adenine of a complementary strand of RNA or DNA.

[0680] As used herein, the term "cytosine analogue" means a chemically-modified pyrimidine nucleobase that, when incorporated into an oligomer, is capable with forming a Watson-Crick base pair with a guanine of a complementary strand of RNA or DNA. For example, cytosine analogue can be a 5-methylcytosine.

[0681] As used herein, the term "guanine analogue" means a chemically-modified purine nucleobase that, when incorporated into an oligomer, is capable with forming a Watson-Crick base pair with a cytosine of a complementary strand of RNA or DNA.

[0682] As used herein, the term "guanosine" refers to a nucleoside or sugar-modified nucleoside comprising a guanine or guanine analog nucleobase.

[0683] As used herein, the term "uridine" refers to a nucleoside or sugar-modified nucleoside comprising a uracil or uracil analog nucleobase.

[0684] As used herein, the term "thymidine" refers to a nucleoside or sugar-modified nucleoside comprising a thymine or thymine analog nucleobase.

[0685] As used herein, the term "cytidine" refers to a nucleoside or sugar-modified nucleoside comprising a cytosine or cytosine analog nucleobase.

[0686] As used herein, the term "adenosine" refers to a nucleoside or sugar-modified nucleoside comprising an adenine or adenine analog nucleobase.

[0687] As used herein, "oligonucleotide" refers to a compound comprising a plurality of linked nucleosides. In certain embodiments, one or more of the plurality of nucleosides is modified. In certain embodiments, an oligonucleotide comprises one or more ribonucleosides (RNA) and/or deoxyribonucleosides (DNA).

[0688] As used herein "oligonucleoside" refers to an oligonucleotide in which none of the internucleoside linkages contains a phosphorus atom. As used herein, oligonucleotides include oligonucleosides.

[0689] As used herein, "modified oligonucleotide" or "chemically-modified oligonucleotide" refers to an oligonucleotide comprising at least one modified sugar, a modified nucleobase and/or a modified internucleoside linkage or backbone.

[0690] As used herein, "internucleoside linkage" or "backbone" refers to a covalent linkage between adjacent nucleosides.

[0691] As used herein "naturally occurring internucleoside linkage" refers to a 3' to 5' phosphodiester linkage.

[0692] As used herein, "modified internucleoside linkage" refers to any internucleoside linkage other than a naturally occurring internucleoside linkage.

[0693] As used herein, "oligomeric compound" refers to a polymeric structure comprising two or more sub-structures. In certain embodiments, an oligomeric compound is an oligonucleotide. In certain embodiments, an oligomeric compound is a single-stranded oligonucleotide. In certain embodiments, an oligomeric compound is a double-stranded duplex comprising two oligonucleotides. In certain embodiments, an oligomeric compound is a single-stranded or double-stranded oligonucleotide comprising one or more conjugate groups and/or terminal groups.

[0694] As used herein, "conjugate" refers to an atom or group of atoms bound to an oligonucleotide or oligomeric compound. In general, conjugate groups modify one or more properties of the compound to which they are attached, including, but not limited to pharmacodynamic, pharmacokinetic, binding, absorption, cellular distribution, cellular uptake, charge and clearance. Conjugate groups are routinely used in the chemical arts and are linked directly or via an optional linking moiety or linking group to the parent compound such as an oligomeric compound. In certain embodiments, conjugate groups includes without limitation, intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, thioethers, polyethers, cholesterols, thiocholesterols, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins and dyes. In certain embodiments, conjugates are terminal groups. In certain embodiments, conjugates are attached to a 3' or 5' terminal nucleoside or to an internal nucleosides of an oligonucleotide.

[0695] As used herein, "conjugate linking group" refers to any atom or group of atoms used to attach a conjugate to an oligonucleotide or oligomeric compound. Linking groups or bifunctional linking moieties such as those known in the art are amenable to the present invention.

[0696] As used herein, "antisense compound" refers to an oligomeric compound, at least a portion of which is at least partially complementary to a target nucleic acid to which it hybridizes and modulates the activity, processing or expression of said target nucleic acid.

[0697] As used herein, "expression" refers to the process by which a gene ultimately results in a protein. Expression includes, but is not limited to, transcription, splicing, post-transcriptional modification, and translation.

[0698] As used herein, "antisense oligonucleotide" refers to an antisense compound that is an oligonucleotide.

[0699] As used herein, "antisense activity" refers to any detectable and/or measurable activity attributable to the hybridization of an anti sense compound to its target nucleic acid. In certain embodiments, such activity may be an increase or decrease in an amount of a nucleic acid or protein. In certain embodiments, such activity may be a change in the ratio of splice variants of a nucleic acid or protein. Detection and/or measuring of antisense activity may be direct or indirect. In certain embodiments, antisense activity is assessed by observing a phenotypic change in a cell or animal.

[0700] As used herein, "target nucleic acid" refers to any nucleic acid molecule the expression, amount, or activity of which is capable of being modulated by an antisense compound. In certain embodiments, the target nucleic acid is DNA or RNA. In certain embodiments, the target RNA is mRNA, pre-mRNA, non-coding RNA, pri-microRNA, pre-microRNA, mature microRNA, promoter-directed RNA, or natural antisense transcripts. For example, the target nucleic acid can be a cellular gene (or mRNA transcribed from the gene) whose expression is associated with a particular disorder or disease state, or a nucleic acid molecule from an infectious agent. In certain embodiments, target nucleic acid is a viral or bacterial nucleic acid.

[0701] As used herein, "target mRNA" refers to a preselected RNA molecule that encodes a protein.

[0702] As used herein, "targeting" or "targeted to" refers to the association of an antisense compound to a particular target nucleic acid molecule or a particular region of nucleotides within a target nucleic acid molecule. An anti sense compound targets a target nucleic acid if it is sufficiently complementary to the target nucleic acid to allow hybridization under physiological conditions.

[0703] As used herein, "target site" refers to a region of a target nucleic acid that is bound by an antisense compound. In certain embodiments, a target site is at least partially within the 3' untranslated region of an RNA molecule. In certain embodiments, a target site is at least partially within the 5' untranslated region of an RNA molecule. In certain embodiments, a target site is at least partially within the coding region of an RNA molecule. In certain embodiments, a target site is at least partially within an exon of an RNA molecule. In certain embodiments, a target site is at least partially within an intron of an RNA molecule. In certain embodiments, a target site is at least partially within a microRNA target site of an RNA molecule. In certain embodiments, a target site is at least partially within a repeat region of an RNA molecule.

[0704] As used herein, "target protein" refers to a protein, the expression of which is modulated by an antisense compound. In certain embodiments, a target protein is encoded by a target nucleic acid. In certain embodiments, expression of a target protein is otherwise influenced by a target nucleic acid.

[0705] As used herein, "complementarily" in reference to nucleobases refers to a nucleobase that is capable of base pairing with another nucleobase. For example, in DNA, adenine (A) is complementary to thymine (T). For example, in RNA, adenine (A) is complementary to uracil (U). In certain embodiments, complementary nucleobase refers to a nucleobase of an antisense compound that is capable of base pairing with a nucleobase of its target nucleic acid. For example, if a nucleobase at a certain position of an antisense compound is capable of hydrogen bonding with a nucleobase at a certain position of a target nucleic acid, then the position of hydrogen bonding between the oligonucleotide and the target nucleic acid is considered to be complementary at that nucleobase pair. Nucleobases comprising certain modifications may maintain the ability to pair with a counterpart nucleobase and thus, are still capable of nucleobase complementarity.

[0706] As used herein, "non-complementary" in reference to nucleobases refers to a pair of nucleobases that do not form hydrogen bonds with one another or otherwise support hybridization.

[0707] As used herein, "complementary" in reference to linked nucleosides, oligonucleotides, or nucleic acids, refers to the capacity of an oligomeric compound to hybridize to another oligomeric compound or nucleic acid through nucleobase complementarity. In certain embodiments, an antisense compound and its target are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleobases that can bond with each other to allow stable association between the anti sense compound and the target. One skilled in the art recognizes that the inclusion of mismatches is possible without eliminating the ability of the oligomeric compounds to remain in association. Therefore, described herein are antisense compounds that may comprise up to about 20% nucleotides that are mismatched (i.e., are not nucleobase complementary to the corresponding nucleotides of the target). Preferably the antisense compounds contain no more than about 15%, more preferably not more than about 10%, most preferably not more than 5% or no mismatches. The remaining nucleotides are nucleobase complementary or otherwise do not disrupt hybridization (e.g., universal bases). One of ordinary skill in the art would recognize the compounds provided herein are at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% complementary to a target nucleic acid.

[0708] As used herein, "modulation" refers to a perturbation of amount or quality of a function or activity when compared to the function or activity prior to modulation. For example, modulation includes the change, either an increase (stimulation or induction) or a decrease (inhibition or reduction) in gene expression. As a further example, modulation of expression can include perturbing splice site selection of pre-mRNA processing, resulting in a change in the amount of a particular splice-variant present compared to conditions that were not perturbed. As a further example, modulation includes perturbing translation of a protein.

[0709] As used herein, "motif" refers to a pattern of modifications in an oligomeric compound or a region thereof. Motifs may be defined by modifications at certain nucleosides and/or at certain linking groups of an oligomeric compound.

[0710] As used herein, "nucleoside motif" refers to a pattern of nucleoside modifications in an oligomeric compound or a region thereof. The linkages of such an oligomeric compound may be modified or unmodified. Unless otherwise indicated, motifs herein describing only nucleosides are intended to be nucleoside motifs. Thus, in such instances, the linkages are not limited.

[0711] As used herein, "linkage motif" refers to a pattern of linkage modifications in an oligomeric compound or region thereof. The nucleosides of such an oligomeric compound may be modified or unmodified. Unless otherwise indicated, motifs herein describing only linkages are intended to be linkage motifs. Thus, in such instances, the nucleosides are not limited.

[0712] As used herein, "the same modifications" refer to modifications relative to naturally occurring molecules that are the same as one another, including absence of modifications. Thus, for example, two unmodified DNA nucleoside have "the same modification," even though the DNA nucleoside is unmodified.

[0713] As used herein, "type of modification" in reference to a nucleoside or a nucleoside of a "type" refers to the modification of a nucleoside and includes modified and unmodified nucleosides. Accordingly, unless otherwise indicated, a "nucleoside having a modification of a first type" may be an unmodified nucleoside.

[0714] As used herein, "separate regions" refers to a portion of an oligomeric compound wherein the nucleosides and internucleoside linkages within the region all comprise the same modifications; and the nucleosides and/or the internucleoside linkages of any neighboring portions include at least one different modification.

[0715] As used herein, "pharmaceutically acceptable salts" refers to salts of active compounds that retain the desired biological activity of the active compound and do not impart undesired toxicological effects thereto.

[0716] As used herein, "cap structure" or "terminal cap moiety" refers to chemical modifications incorporated at either terminus of an anti sense compound.

[0717] As used herein, the term "independently" means that each occurrence of a repetitive variable within a claimed oligonucleotide is selected independent of one another. For example, each repetitive variable can be selected so that (i) each of the repetitive variables are the same, (ii) two or more are the same, or (iii) each of the repetitive variables can be different.

General Chemistry Definitions

[0718] As used herein, "alkyl" refers to a saturated straight or branched hydrocarbon substituent or radical, typically containing up to twenty four carbon atoms. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, butyl, isopropyl, n-hexyl, octyl, decyl, dodecyl and the like. Alkyl groups typically include from 1 to 24 carbon atoms, more typically from 1 to 12 carbon atoms (C_1-C_{12} alkyl) with from 1 to 6 carbon atoms (C_1-C_6 alkyl) being more preferred. The term "lower alkyl" as used herein includes from 1 to 6 carbon atoms (C_1-C_6 alkyl). Alkyl groups as used herein may optionally include one or more further substituent groups.

[0719] As used herein, "alkenyl" refers to a straight or branched hydrocarbon chain radical or substituent, typically containing up to twenty four carbon atoms, and having at least one carbon-carbon double bond. Examples of alkenyl groups include, but are not limited to, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, dienes such as 1,3-butadienyl and the like. Alkenyl groups typically include from 2 to 24 carbon atoms, more typically from 2 to 12 carbon atoms with from 2 to 6 carbon atoms being more preferred. Alkenyl groups as used herein may optionally include one or more further substituent groups.

[0720] As used herein, "alkynyl" refers to a straight or branched hydrocarbon radical or substituent, typically containing up to twenty four carbon atoms, and having at least one carbon-carbon triple bond. Examples of alkynyl groups include, but are not limited to, ethynyl, 1-propynyl, 1-butynyl, and the like. Alkynyl groups typically include from 2 to 24 carbon atoms, more typically from 2 to 12 carbon atoms with from 2 to 6 carbon atoms being more preferred. Alkynyl groups as used herein may optionally include one or more further substituent groups.

[0721] As used herein, "aminoalkyl" refers to an amino substituted alkyl radical or substituent. This term is meant to include C_1-C_{12} alkyl groups having an amino substituent at any position and wherein the aminoalkyl group is attached to the parent molecule via its alkyl moiety. The alkyl and/or amino portions of the aminoalkyl group can be further substituted with substituent groups.

[0722] As used herein, "aliphatic" refers to a straight or branched hydrocarbon radical or substituent, typically containing up to twenty four carbon atoms, wherein the saturation between any two carbon atoms is a single, double or triple bond. An aliphatic group preferably contains from 1 to 24 carbon atoms, more typically from 1 to 12 carbon atoms with from 1 to 6 carbon atoms being more preferred. The straight or branched chain of an aliphatic group may be interrupted with one or more heteroatoms that include nitrogen, oxygen, sulfur and phosphorus. Such aliphatic groups interrupted by heteroatoms include without limitation polyalkoxys, such as polyalkylene glycols, polyamines, and polyimines. Aliphatic groups as used herein may optionally include further substituent groups.

[0723] As used herein, "alicyclic" or "alicyclyl" refers to a cyclic radical or substituent, wherein the ring system is aliphatic. The ring system can comprise one or more rings wherein at least one ring is aliphatic. Preferred alicyclic moieties include rings having from 5 to 9 carbon atoms in the ring. Alicyclic groups as used herein may optionally include further substituent groups.

[0724] As used herein, "alkoxy" refers to a radical or substituent comprising an alkyl group and an oxygen atom, wherein the alkoxy group is attached to a parent molecule via its oxygen atom. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, n-pentoxy, neopentoxy, n-hexoxy and the like. Alkoxy groups as used herein may optionally include further substituent groups.

[0725] As used herein, "halo", "halide" and "halogen" refer to an atom, radical or substituent selected from fluorine, chlorine, bromine and iodine.

[0726] As used herein, "aryl" and "aromatic" refer to a radical or substituent comprising a mono- or polycyclic carbocyclic ring system having one or more aromatic rings. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, idenyl and the like. Preferred aryl ring systems have from 5 to 20 carbon atoms in one or more rings. Aryl groups as used herein may optionally include further substituent groups.

[0727] As used herein, "aralkyl" and "arylalkyl" refer to a radical or substituent comprising an alkyl group and an aryl group, wherein the aralkyl or arylalkyl group is attached to a parent molecule via its alkyl moiety. Examples include, but are not limited to, benzyl, phenethyl and the like. Aralkyl groups as used herein may optionally include further substituent groups attached to the alkyl, the aryl or both groups that form the radical or substituent.

[0728] As used herein, "heterocyclyl" refers to a radical or substituent comprising a mono- or polycyclic ring system that includes at least one heteroatom and is unsaturated, partially saturated or fully saturated, thereby including heteroaryl groups. Heterocyclyl is also meant to include fused ring system moieties wherein one or more of the fused rings contain at least one heteroatom and the other rings can contain one or more heteroatoms or optionally contain no heteroatoms. A heterocyclic group typically includes at least one atom selected from sulfur, nitrogen or oxygen. Examples of heterocyclic groups include [1,3]dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl and the like. Heterocyclic groups as used herein may optionally include further substituent groups.

[0729] As used herein, "heteroaryl" and "heteroaromatic" refer to a radical or substituent comprising a mono- or polycyclic aromatic ring, ring system or fused ring system wherein at least one of the rings is aromatic and includes one or more heteroatom. Heteroaryl is also meant to include fused ring systems including systems where one or more of the fused rings contain no heteroatoms. Heteroaryl groups typically include one ring atom selected from sulfur, nitrogen or oxygen. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxalinyl, and the like. Heteroaryl radicals or substituents can be attached to a parent molecule directly or through a linking moiety such as an aliphatic group or a heteroatom. Heteroaryl groups as used herein may optionally include further substituent groups.

[0730] As used herein, "heteroarylalkyl" refers to a radical or substituent comprising a heteroaryl group as previously defined and an alkyl moiety, wherein the heteroarylalkyl group is attached to a parent molecule via its alkyl moiety. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl, napthyridinylpropyl and the like. Heteroarylalkyl groups as used herein may optionally include further substituent groups on one or both of the heteroaryl or alkyl portions.

[0731] As used herein, "mono or polycyclic" refers to any ring systems, such as a single ring or a polycyclic system having rings that are fused or linked, and is meant to be inclusive of single and mixed ring systems individually selected from aliphatic, alicyclic, aryl, heteroaryl, aralkyl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic and heteroarylalkyl. Such mono and polycyclic structures can contain rings that have a uniform or varying degree of saturation, including fully saturated, partially saturated or fully unsaturated rings. Each ring can comprise ring atoms selected from C, N, O and S to give rise to heterocyclic rings as well as rings comprising only C ring atoms. Heterocyclic and all-carbon rings can be present in a mixed motif, such as for example benzimidazole wherein one ring of the fused ring system has only carbon ring atoms and the other ring has two nitrogen atoms. The mono or polycyclic structures can be further substituted with substituent groups such as for example phthalimide which has two oxo groups (═O) attached to one of the rings. In another aspect, mono or polycyclic structures can be attached to a parent molecule directly through a ring atom, through a substituent group or a bifunctional linking moiety. As used herein, "acyl" refers to a radical or substituent comprising a carbonyl moiety (C═O or —C(O)—) and a further substituent X, wherein the acyl group is attached to a parent molecule via its carbonyl moiety. As such, an acyl group is formally obtained by removal of a hydroxyl group from an organic acid and has the general formula —C(O)—X, wherein X is typically aliphatic, alicyclic or aromatic. The term "acyl" is also meant to include heteroacyl radicals or substituents with general formula —$Y(O)_n$—X, wherein X is as defined above and $Y(O)_n$ is typically sulfonyl, sulfinyl or

phosphate. Examples of acyl groups include aliphatic carbonyls, aromatic carbonyls, aliphatic sulfonyls, aromatic sulfinyls, aliphatic sulfinyls, aromatic phosphates, aliphatic phosphates and the like. Acyl groups as used herein may optionally include further substituent groups.

[0732] As used herein, "substituent" and "substituent group" include groups that are typically added to other substituents or parent compounds to enhance desired properties or give desired effects. Substituent groups can be protected or unprotected and can be attached to one available site or to many available sites in a parent compound. Substituent groups may also be further substituted with other substituent groups and may be attached directly or via a linking group such as an alkyl or hydrocarbyl group to a parent compound. Herein, "hydrocarbyl" refers to any group comprising C, O and H. Included are straight, branched and cyclic groups having any degree of saturation.

[0733] Such hydrocarbyl groups can include one or more heteroatoms selected from N, O and S and can be further substituted with one or more substituent groups.

[0734] Unless otherwise indicated, the term substituted or "optionally substituted" refers to the optional presence of any of the following substituents: halogen, hydroxyl, alkyl, alkenyl, alkynyl, acyl (—$C(O)R_{aa}$), carboxyl (—$C(O)O—R_{aa}$), aliphatic groups, alicyclic groups, alkoxy, substituted oxo (—$O—R_{aa}$), aryl, aralkyl, heterocyclic, heteroaryl, heteroarylalkyl, amino (—$NR_{bb}R_{cc}$), imino (=NR_{bb}), amido (—$C(O)NR_{bb}R_{cc}$ or —$N(R_{bb})C(O)R_{aa}$), azido (—N_3), nitro (—NO_2), cyano (—CN), carbamido (—$OC(O)NR_{bb}R_{cc}$ or —$N(R_{bb})C(O)OR_{aa}$), ureido (—$N(R_{bb})C(O)NR_{bb}R_{cc}$), thioureido (—$N(R_{bb})C(S)NR_{bb}R_{cc}$), guanidinyl (—$N(R_{bb})C(=NR_{bb})NR_{bb}R_{cc}$), amidinyl (—$C(=NR_{bb})NR_{bb}R_{cc}$ or —$N(R_{bb})C(NR_{bb})R_{aa}$), thiol (—$SR_{bb}$), sulfinyl (—$S(O)R_{bb}$), sulfonyl (—$S(O)_2R_{bb}$), sulfonamidyl (—$S(O)_2NR_{bb}R_{cc}$ or —$N(R_{bb})S(O)_2R_{bb}$) and conjugate groups. Herein, each R_{aa}, R_{bb} and R_{cc} is, independently, H, an optionally linked chemical functional group or a further substituent group, preferably but without limitation chosen from the group consisting of H, alkyl, alkenyl, alkynyl, aliphatic, alkoxy, acyl, aryl, aralkyl, heteroaryl, alicyclic, heterocyclic and heteroarylalkyl. Selected substituents within the compounds described herein are present to a recursive degree.

[0735] In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given claim. One of ordinary skill in the art of medicinal chemistry and organic chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by way of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target and practical properties such as ease of synthesis. Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal and organic chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in a claim of the invention, the total number will be determined as set forth above.

[0736] The terms "stable compound" and "stable structure" as used herein are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. Only stable compounds are contemplated herein.

[0737] As used herein, a zero (0) in a range indicating number of a particular unit means that the unit may be absent. For example, an oligomeric compound comprising 0-2 regions of a particular motif means that the oligomeric compound may comprise one or two such regions having the particular motif, or the oligomeric compound may not have any regions having the particular motif. In instances where an internal portion of a molecule is absent, the portions flanking the absent portion are bound directly to one another. Likewise, the term "none" as used herein, indicates that a certain feature is not present.

[0738] As used herein, "analogue" or "derivative" means either a compound or moiety similar in structure but different in respect to elemental composition from the parent compound regardless of how the compound is made. For example, an analogue or derivative compound does not need to be made from the parent compound as a chemical starting material.

[0739] The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

LEGENDS TO THE FIGURES

[0740] FIGS. **1A-1C**

[0741] Comparison of AONs with or without cytosine to 5-methylcytosine substitution in differentiated healthy muscle cells in vitro after transfection with (A) PS229L/PS524, SEQ ID NO:52 (corresponding to SEQ ID NO: 91 for the non-modified sequence, corresponding to SEQ ID NO: 92 wherein all cytosines are modified) or (B) PS220/PS339 (SEQ ID NO:21, corresponding to SEQ ID NO:101 for the non-modified sequence, corresponding to SEQ ID NO:200 wherein all cytosines are modified) or (C)PS524/PS1317/PS1318/PS1319, SEQ ID NO:52 (corresponding to SEQ ID NO: 92 (PS524) wherein all 6 cytosines are modified, to SEQ ID NO: 217 (PS1317) wherein 4 of the 6 cytosines are modified, to SEQ ID NO: 218 (PS1318) wherein 2 of the 6 cytosines are modified and to SEQ ID NO:219 (PS1319) wherein 3 of the 6 cytosines are modified SEQ ID NO:217). Average skipping percentages were calculated from triplo (n=3) (A,B) or duplo (n=2) (C) transfections per concentration. Solid lines refer to AONs with 5-methylcytosines, dotted lines to AONs with non-substituted cytosines (A,B).

[0742] FIGS. **2A-2B**

[0743] Summary of the pharmacokinetic study in wild type (control) and mdx mice, comparing plasma and muscle tissue profiles of AONs with 5-methylcytosines (PS524, SEQ ID NO:52 (i.e. corresponding to SEQ ID NO: 92 wherein all cytosines are modified) and PS652, SEQ ID NO:57 (i.e. corresponding to SEQ ID NO: 185 wherein all cytosines are modified) and AONs with unmodified (non-methylated) cytosines (PS229L, SEQ ID NO:52 corresponding to SEQ ID NO: 91 for the non-modified sequence, and PS531, SEQ ID NO:57 corresponding to SEQ ID NO: 137 for the non-modified sequence). (A) Pharmacokinetic tissue analysis of: 1) the ratio between the average levels of AON in muscle in mdx mice versus control mice after one single sc injection; 2) the levels of the AONs (μg/g) in several mdx muscles (dia=diaphragm, gastroc=gastrocnemius, quadr=quadriceps, tric=triceps) at 14 days; 3) the relative muscle/kidney and muscle/liver levels at day 14, and 4) the estimated half-life of the different AONs in triceps. B) Pharmacokinetic plasma

analysis of 1) Tmax (time at which Cmaxwas reached, only two time points of analysis included (15 or 60 min), 2) Cmax (highest plasma concentration reached), 3) AUC (area under curve; indicative for bioavailability) an 4) Cl (plasma clearance at 24 h.

[0744] FIGS. **3**A-**3**H

[0745] Analysis of cytokine levels in human whole blood upon incubation with 0, 10, 25, or 50 μg/ml of AONs with unmodified cytosines PS232 (SEQ ID NO: 39, corresponding to SEQ ID NO: 119 for the non-modified sequence) and PS534 (SEQ ID NO:59, corresponding to SEQ ID NO: 139 for the non-modified sequence) (black bars) or AONs with 5-methylcytosines PS648 (SEQ ID NO: 39, corresponding to SEQ ID NO: 201 wherein all cytosines are modified) and PS653 (SEQ ID NO:59, to SEQ ID NO: 192 wherein all cytosines are modified) (grey bars). The levels of TNFα (A, B), MCP-1 (D, E), IP-10 (E, F), and IL6 (G, H) were determined using commercially available ELISA kits. Each experiment was repeated four times (n=4). Data is shown for the most pronounced response of each cytokine.

[0746] FIGS. **4**A-**4**B

[0747] Activity comparisons of AONs with 5-methylcytosines and/or 5-methyluracils with corresponding AONs without these base modifications, (A) Transfection of 200 nM, in duplo, into differentiated healthy muscle cells in vitro. Activity was expressed as average percentage exon 51 (PS43, non-modified sequence represented by SEQ ID NO: 111, PS559 corresponding to SEQ ID NO: 202, wherein all uraciles are modified, PS1106 corresponding to SEQ ID NO:203, wherein all cytosines and all uraciles are modified. All sequences are derived from SEQ ID NO: 31), exon 44 (PS188, non-modified sequence represented by SEQ ID NO: 95, PS785, corresponding to SEQ ID NO: 204, wherein all uraciles are modified, PS1107: corresponding to SEQ ID NO:205, wherein all cytosines and all uraciles are modified. All sequences are derived from SEQ ID NO 15); or exon 52 (PS235, non-modified sequence represented by SEQ ID NO: 120, PS786: corresponding to SEQ ID NO: 172, wherein all uraciles are modified. All sequences are derived from SEQ ID NO 40) skipping (n=2). AON sequences (5' to 3') and base modifications (bold, underlined nucleotides) are shown in the table underneath. (B) Intramuscular injection of 20 μg of PS49 (non-modified sequence, SEQ ID NO: 216) or PS959 (modified sequence wherein all uracils are modified, SEQ ID NO:214) in the gastrocnemius muscles of mdx mice. Activity was expressed as average percentage murine exon 23 skipping (n=4). AON sequences (5' to 3') and base modifications (bold, underlined nucleotides) are shown in the table underneath.

[0748] FIGS. **5**A-**5**C

[0749] Activity comparisons of AONs with 2,6-diaminopurines with corresponding AONs without this base modification. (A), Transfection of 200 nM, in duplo, into differentiated healthy muscle cells in vitro. Activity was expressed as average percentage exon 51 (PS43, non-modified sequence represented by SEQ ID NO: 111, PS403, corresponding to SEQ ID NO: 206, wherein all adenines have been modified. All sequences are derived from SEQ ID NO: 31), exon 52 (PS235, non-modified sequence represented by SEQ ID NO: 120, PS897: corresponding to SEQ ID NO: 173, wherein all adenines have been modified. All sequences are derived from SEQ ID NO: 40), or exon 44 (PS188, non-modified sequence represented by SEQ ID NO: 95, PS733: corresponding to SEQ ID NO: 207, wherein all adenines have been modified. All sequences are derived from SEQ ID NO: 15) skipping (n=2). AON sequences (5' to 3') and base modifications (bold, underlined nucleotides) are shown in the table underneath. (B) and (C) The effect of substituting all unmodified adenines (PS188; SEQ ID NO: 95) with 2,6-diaminopurines (PS733; SEQ ID NO:207) on in vitro safety. As markers for activation of the alternative complement pathway, split factors C3a (B) and Bb (C) were measured in monkey plasma.

EXAMPLES

[0750]

TABLE 1

General structures of AONs. X = C or m^5C, Y = U or m^5U, Z = A or a^2A; 1 = inosine (hypoxanthine base), X_1 = m^5C, Y_1 = m^5U, Z_1 = a^2A

DMD Exon	AON Sequence (5'→3')	SEQ ID NO
44	GXXZYYYXYXZZXZGZYXY	14
	GCCAUUUCUCAACAGAUCU	94
44	YXZGXYYXYGYYZGXXZXYG	15
	UCAGCUUCUGUUAGCCACUG	95
	Y_1CAGCY_1Y_1CY_1GY_1Y_1AGCCACY_1G	204
	UX_1AGX$_1$UUX$_1$UGUUAGX$_1X_1$AX$_1$UG	208
	Y_1X_1AGX$_1Y_1Y_1X_1Y_1$GY$_1Y_1$AGX$_1X_1$AX$_1Y_1$G	205
	UCZ$_1$GCUUCUGUUZ$_1$GCCZ$_1$CUG	207
44	YYYGYZYYYZGXZYGYYXXX	16
	UUUGUAUUUAGCAUGUUCCC	96
44	ZYYXYXZGGZZYYYGYGYXYYYX	17
	AUUCUCAGGAAUUUGUGUCUUUC	97
44	XXZYYYGYZYYYZGXZYGYYXXX	18
	CCAUUUGUAUUUAGCAUGUUCCC	98
44	YXYXZGGZZYYYGYGYXYYYX	19
	UCUCAGGAAUUUGUGUCUUUC	99
44	GXXZYYYXYXZZXZGZYXYGYXZ	20
	GCCAUUUCUCAACAGAUCUGUCA	100
45	YYYGXXGXYGXXXZZYGXXZYXXYG	21
	UUUGCCGCUGCCCAAUGCCAUCCUG	101
	UUUGX$_1$X$_1$GX$_1$UGX$_1$X$_1$X$_1$AAUGX$_1$X$_1$AUX$_1$X$_1$UG	200
	$Y_1Y_1Y_1$GX$_1$X$_1$GX$_1Y_1$GX$_1$X$_1$X$_1$AAY$_1$GX$_1$X$_1$AY$_1$X$_1$X$_1Y_1$G	209
	UUUGCCGCUGCCCZ$_1$Z$_1$UGCCZ$_1$UCCUG	210
45	YYGXXGXYGXXXZZYGXXZYXXYG	22
	UUGCCGCUGCCCAAUGCCAUCCUG	102
45	YYGXXGXYGXXXZZYGXXZYXXYGG	23
	UUGCCGCUGCCCAAUGCCAUCCUGG	103
45	YGXXGXYGXXXZZYGXXZYXXYG	24
	UGCCGCUGCCCAAUGCCAUCCUG	104
45	YGXXGXYGXXXZZYGXXZYXXYGG	25
	UGCCGCUGCCCAAUGCCAUCCUGG	105
45	GXXGXYGXXXZZYGXXZYXXYG	26
	GCCGCUGCCCAAUGCCAUCCUG	106
45	XXGXYGXXXZZYGXXZYXXYGG	27
	CCGCUGCCCAAUGCCAUCCUGG	107
45	YYYGXXIXYGXXXZZYGXXZYXXYG	28
	UUUGCCICUGCCCAAUGCCAUCCUG	108
45	XZGYYYGXXGXYGXXXZZYGXXZYX	29
	CAGUUUGCCGCUGCCCAAUGCCAUC	109

TABLE 1 -continued

General structures of AONs. X = C or m^5C, Y = U or m^5U, Z = A or a^2A; 1 = inosine (hypoxanthine base), X_1 = m^5C, Y_1 = m^5U, Z_1 = a^2A

DMD Exon	AON Sequence (5'→3')	SEQ ID NO
45	XZGYYYGXXGXYGXXXZZYGXXZYXXYGGZ	30
	CAGUUUGCCGCUGCCCAAUGCCAUCCUGGA	110
51	YXZZGGZZGZYGGXZYYYXY	31
	UCAAGGAAGAUGGCAUUUCU	111
	Y_1CAAGGAAGAY$_1$GGCAY$_1$Y$_1$Y$_1$CY$_1$	202
	Y$_1$X$_1$AAGGAAGAY$_1$GGX$_1$AY$_1$Y$_1$Y$_1$X$_1$Y$_1$	203
	UCZ$_1$Z$_1$GGZ$_1$Z$_1$GZ$_1$UGGCZ$_1$UUUCU	206
	UX$_1$AAGGAAGAUGGX$_1$AUUUX$_1$U	215
51	YGGXZYYYXYZGYYYGG	32
	UGGCAUUUCUAGUUUGG	112
51	XZYXZZGGZZGZYGGXZYYYXY	33
	CAUCAAGGAAGAUGGCAUUUCU	113
51	XZZXZYXZZGGZZGZYGGXZYYYXY	34
	CAACAUCAAGGAAGAUGGCAUUUCU	114
51	XXYXYGYGZYYYYZYZZXYYGZY	35
	CCUCUGUGAUUUUAUAACUUGAU	115
51	XXZGZGXZGGYZXXYXXZZXZYX	36
	CCAGAGCAGGUACCUCCAACAUC	116
51	ZXZYXZZGGZZGZYGGXZYYYXYZGYYYGG	37
	ACAUCAAGGAAGAUGGCAUUUCUAGUUUGG	117
51	ZXZYXZZGGZZGZYGGXZYYYXYZG	38
	ACAUCAAGGAAGAUGGCAUUUCUAG	118
52	XYXYYGZYYGXYGGYXYYGYYYYYX	39
	CUCUUGAUUGCUGGUCUUGUUUUUC	119
	X$_1$UX$_1$UUGAUUGX$_1$UGGUX$_1$UUGUUUUUX$_1$	201
52	GGYZZYGZGYYXYYXXZZXYGG	40
	GGUAAUGAGUUCUUCCAACUGG	120
	GGUAAUGAGUUX$_1$UUX$_1$X$_1$AAX$_1$UGG	171
	GGY$_1$AAY$_1$GAGY$_1$Y$_1$CY$_1$Y$_1$CCAACY$_1$GG	172
	GGUZ$_1$Z$_1$UGZ$_1$GUUCUUCCZ$_1$Z$_1$CUGG	173
	GGY$_1$AAY$_1$GAGY$_1$Y$_1$X$_1$Y$_1$Y$_1$X$_1$X$_1$AAX$_1$Y$_1$GG	174
	GGUZ$_1$Z$_1$UGZ$_1$GUUX$_1$UUX$_1$X$_1$Z$_1$Z$_1$X$_1$UGG	175
	GGY$_1$Z$_1$Z$_1$Y$_1$GZ$_1$GY$_1$Y$_1$CY$_1$Y$_1$CCZ$_1$Z$_1$CY$_1$GG	176
	GGY$_1$Z$_1$Z$_1$Y$_1$GZ$_1$GY$_1$Y$_1$X$_1$Y$_1$Y$_1$X$_1$X$_1$Z$_1$Z$_1$X$_1$Y$_1$GG	177
52	YXYYGZYYGXYGGYXYYGYYYYYXZ	41
	UCUUGAUUGCUGGUCUUGUUUUUCA	121
52	YYXXZZXYGGGGZXGXXYXYGYYXX	42
	UUCCAACUGGGGACGCCUCUGUUCC	122
52	YGYYXYZGXXYXYYGZYYGXYGGYX	43
	UGUUCUAGCCUCUUGAUUGCUGGUC	123
	UGUUX$_1$UAGX$_1$UX$_1$UUGAUUGX$_1$UGGUX$_1$	178
	Y$_1$GY$_1$Y$_1$CY$_1$AGCCY$_1$CY$_1$Y$_1$GAY$_1$Y$_1$GCY$_1$GGY$_1$C	179
	UGUUCUZ$_1$GCCUCUUGZ$_1$UUGCUGGUC	180
	Y$_1$GY$_1$Y$_1$X$_1$Y$_1$AGX$_1$X$_1$Y$_1$X$_1$Y$_1$Y$_1$GAY$_1$Y$_1$GX$_1$Y$_1$GGY$_1$X$_1$	181
	UGUUX$_1$UZ$_1$GX$_1$X$_1$UX$_1$UUGZ$_1$UUGX$_1$UGGUX$_1$	182
	Y$_1$GY$_1$Y$_1$CY$_1$Z$_1$GCCY$_1$CY$_1$Y$_1$GZ$_1$Y$_1$Y$_1$GCY$_1$GGY$_1$C	183
	Y$_1$GY$_1$Y$_1$X$_1$Y$_1$Z$_1$GX$_1$X$_1$Y$_1$X$_1$Y$_1$Y$_1$GZ$_1$Y$_1$Y$_1$GX$_1$Y$_1$GGY$_1$X$_1$	184
53	XYGYYGXXYXXGGYYXYG	44
	CUGUUGCCUCCGGUUCUG	124
53	XZZXYGYYGXXYXXGGYYXYGZ	45
	CAACUGUUGCCUCCGGUUCUGA	125
53	XZZXYGYYGXXYXXGGYYXYGZZ	46
	CAACUGUUGCCUCCGGUUCUGAA	126

TABLE 1 -continued

General structures of AONs. X = C or m^5C, Y = U or m^5U, Z = A or a^2A; 1 = inosine (hypoxanthine base), X_1 = m^5C, Y_1 = m^5U, Z_1 = a^2A

DMD Exon	AON Sequence (5'→3')	SEQ ID NO
53	XZZXYGYYGXXYXXGGYYXYGZZG	47
	CAACUGUUGCCUCCGGUUCUGAAG	127
53	XYGYYGXXYXXGGYYXYGZZGG	48
	CUGUUGCCUCCGGUUCUGAAGG	128
53	XYGYYGXXYXXGGYYXYGZZGGY	49
	CUGUUGCCUCCGGUUCUGAAGGU	129
53	XYGYYGXXYXXGGYYXYGZZGGYG	50
	CUGUUGCCUCCGGUUCUGAAGGUG	130
53	XYGYYGXXYXXGGYYXYGZZGGYGY	51
	CUGUUGCCUCCGGUUCUGAAGGUGU	131
53	GYYGXXYXXGGYYXYGZZGGYGYYX	52
	GUUGCCUCCGGUUCUGAAGGUGUUC	91
	GUUGX$_1$X$_1$UX$_1$X$_1$GGUUX$_1$UGAAGGUGUUX$_1$	92
	GUUGX$_1$X$_1$UCCGGUUX$_1$UGAAGGUGUUX$_1$	217
	GUUGX$_1$X$_1$UCCGGUUCUGAAGGUGUUC	218
	GUUGCX$_1$UCCGGUUX$_1$UGAAGGUGUUX$_1$	219
	G Y$_1$ Y$_1$GCC Y$_1$CCGG Y$_1$ Y$_1$C Y$_1$GAAGG Y$_1$GY$_1$ Y$_1$C	211
	G Y$_1$ Y$_1$GX$_1$X$_1$ Y$_1$X$_1$X$_1$GG Y$_1$ Y$_1$X$_1$ Y$_1$GAAGG Y$_1$GY$_1$ Y$_1$X$_1$	212
	GUUGCCUCCGGUUCUGZ$_1$Z$_1$GGUGUUC	213
53	GXXYXXGGYYXYGZZGGYGYYXYYG	53
	GCCUCCGGUUCUGAAGGUGUUCUUG	133
53	YYGXXYXXGGYYXYGZZGGYGYYXYYGYZX	54
	UUGCCUCCGGUUCUGAAGGUGUUCUUGUAC	134
53	XYGYYGXXYXXGGYYXYGZZGGYGYYXYYG	55
	CUGUUGCCUCCGGUUCUGAAGGUGUUCUUG	135
53	XZZXYGYYGXXYXXGGYYXYGZZGGYGYYXYYG	56
	CAACUGUUGCCUCCGGUUCUGAAGGUGUUCUUG	136
55	GZGYYYXYYXXZZZGXZGXXYXYX	57
	GAGUUUCUUCCAAAGCAGCCUCUC	137
	GAGUUUX$_1$UUX$_1$X$_1$AAAGX$_1$AGX$_1$X$_1$UX$_1$UX$_1$	185
	GAGY$_1$Y$_1$Y$_1$CY$_1$Y$_1$CCAAAGCAGCCY$_1$CY$_1$C	186
	GZ$_1$GUUUCUUCCZ$_1$Z$_1$Z$_1$GCZ$_1$GCCUCUC	187
	GAGY$_1$Y$_1$Y$_1$X$_1$Y$_1$Y$_1$X$_1$X$_1$AAAGX$_1$AGX$_1$X$_1$Y$_1$X$_1$Y$_1$X$_1$	188
	GZ$_1$GUUUX$_1$UUX$_1$X$_1$Z$_1$Z$_1$Z$_1$GX$_1$Z$_1$GX$_1$X$_1$UX$_1$UX$_1$	189
	GZ$_1$GY$_1$Y$_1$Y$_1$CY$_1$Y$_1$CCZ$_1$Z$_1$Z$_1$GCZ$_1$GCCY$_1$CY$_1$C	190
	GZ$_1$GY$_1$Y$_1$Y$_1$X$_1$Y$_1$Y$_1$X$_1$X$_1$Z$_1$Z$_1$Z$_1$GX$_1$Z$_1$GX$_1$X$_1$Y$_1$X$_1$Y$_1$X$_1$	191
55	YZYGZGYYYXYYXXZZZGXZGXXYX	58
	UAUGAGUUUCUUCCAAAGCAGCCUC	138
55	ZGXZYXXYGYZGGZXZYYGGXZGY	59
	AGCAUCCUGUAGGACAUUGGCAGU	139
	AGX$_1$AUX$_1$X$_1$UGUAGGAX$_1$AUUGGX$_1$AGU	192
	AGCAY$_1$CCY$_1$GY$_1$AGGACAY$_1$Y$_1$GGCAGY$_1$	193
	Z$_1$GCZ$_1$UCCUGUZ$_1$GGZ$_1$CZ$_1$UUGGCZ$_1$GU	194
	AGX$_1$AY$_1$X$_1$X$_1$Y$_1$GY$_1$AGGAX$_1$AY$_1$Y$_1$GGX$_1$AGY$_1$	195
	Z$_1$GX$_1$Z$_1$UX$_1$X$_1$UGUZ$_1$GGZ$_1$X$_1$Z$_1$UUGGX$_1$Z$_1$GU	196
	Z$_1$GCZ$_1$Y$_1$CCY$_1$GY$_1$Z$_1$GGZ$_1$CZ$_1$Y$_1$Y$_1$GGCZ$_1$GY$_1$	197
	Z$_1$GX$_1$Z$_1$Y$_1$X$_1$X$_1$Y$_1$GY$_1$Z$_1$GGZ$_1$X$_1$Z$_1$Y$_1$Y$_1$GGX$_1$Z$_1$GY$_1$	198
55	XZYXXYGYZGGZXZYYGGXZGYYG	60
	CAUCCUGUAGGACAUUGGCAGUUG	140
55	YXXYGYZGGZXZYYGGXZGYYGYY	61
	UCCUGUAGGACAUUGGCAGUUGUU	141
55	XYGYZGGZXZYYGGXZGYYGYYYX	62
	CUGUAGGACAUUGGCAGUUGUUUC	142

TABLE 2

General structures of AONs. X = C or m^5C, Y = U or m^5U, Z = A or a^2A; I = inosine (hypoxanthine base), X_I = m^5C, Y_I = m^5U, Z_I = a^2A

DMD Exon	AON Sequence (5'→3')	SEQ ID NO
44	ZYYYXYXZZXZGZ	63
	AUUUCUCAACAGA	143
44	ZGXYYXYGYYZGXXZ	64
	AGCUUCUGUUAGCCA	144
44	ZYYXYXZGGZZ	65
	AUUCUCAGGAA	145
44	ZYYYGYZYYYZGXZ	66
	AUUUGUAUUUAGCA	146
44	ZYYYXYXZZXZGZYXYGYXZ	67
	AUUUCUCAACAGAUCUGUCA	147
44	ZYYYXYXZZXZGZ	68
	AUUUCUCAACAGA	148
44	ZXZGZYXYGYXZ	69
	ACAGAUCUGUCA	149
45	YYYGXXGXYGXXXZZYGXXZ	70
	UUUGCCGCUGCCCAAUGCCA	150
45	XGXYGXXXZZYGXXZYXXYG	71
	CGCUGCCCAAUGCCAUCCUG	151
45	GXXGXYGXXXZZYGXXZYXX	72
	GCCGCUGCCCAAUGCCAUCC	152
51	ZZGGZZGZYGGXZ	73
	AAGGAAGAUGGCA	153
51	ZGGZZGZYGGXZ	74
	AGGAAGAUGGCA	154
51	ZGZGXZGGYZ	75
	AGAGCAGGUA	155
51	ZGXZGGYZXXYXXZ	76
	AGCAGGUACCUCCA	156

TABLE 2 -continued

General structures of AONs. X = C or m^5C, Y = U or m^5U, Z = A or a^2A; I = inosine (hypoxanthine base), X_I = m^5C, Y_I = m^5U, Z_I = a^2A

DMD Exon	AON Sequence (5'→3')	SEQ ID NO
51	ZXXYXXZZXZ	77
	ACCUCCAACA	157
52	ZZYGZGYYXYYXXZZ	78
	AAUGAGUUCUUCCAA	158
52	ZYGZGYYXYYXXZ	79
	AUGAGUUCUUCCA	159
52	ZGYYXYYXXZ	80
	AGUUCUUCCA	160
52	ZGXXYXYYGZ	81
	AGCCUCUUGA	161
53	GYYGXXYXXGGYYXYGZZGG	82
	GUUGCCUCCGGUUCUGAAGG	162
53	XYXXGGYYXYGZZGGYGYYX	83
	CUCCGGUUCUGAAGGUGUUC	163
53	XXYXXGGYYXYGZZGGY	84
	CCUCCGGUUCUGAAGGU	164
55	ZGYYYXYYXXZZZGXZ	85
	AGUUUCUUCCAAAGCA	165
55	ZGYYYXYYXXZ	86
	AGUUUCUUCCA	166
55	ZGXZYXXYGYZGGZXZYYGGXZ	87
	AGCAUCCUGUAGGACAUUGGCA	167
55	ZGXZYXXYGYZ	88
	AGCAUCCUGUA	168
55	ZYXXYGYZGGZ	89
	AUCCUGUAGGA	169
55	ZGGZXZYYGGXZ	90
	AGGACAUUGGCA	170

TABLE 3

Most preferred AONs
General structures of AONs. X = C or m^5C, Y = U or m^5U, Z = A or a^2A; I = inosine (hypoxanthine base), X_I = m^5C, Y_I = m^5U, Z_I = a^2A

DMD Exon	AON Sequence (5'→3')	SEQ ID NO		
44	YXZGXYYXYGYYZGXXZXYG	15		
	UCAGCUUCUGUUAGCCACUG	95	PS188	FIG. 4, 5
	$Y_ICAGCY_IY_ICY_IGY_IY_IAGCCACY_IG$	204	PS785	FIG. 4
	$UX_IAGX_IUUX_IUGUUAGX_IX_IAX_IUG$	208	PS658	
	$Y_IX_IAGX_IY_IY_IX_IY_IGY_IY_IAGX_IX_IAX_IY_IG$	205	PS1107	FIG. 4
	$UCZ_IGCUUCUGUUZ_IGCCZ_ICUG$	207	PS733	FIG. 5
45	YYYGXXGXYGXXXZZYGXXZYXXYG	21		
	UUUGCCGCUGCCCAAUGCCAUCCUG	101	PS220	FIG. 1b
	$UUUGX_IX_IGX_IUGX_IX_IX_IAAUGX_IX_IAUX_IX_IUG$	200	PS399	FIG. 1b
	$Y_IY_IY_IGX_IX_IGX_IY_IGX_IX_IX_IAAY_IGX_IX_IAY_IX_IX_IY_IG$	209	PS1108	
	$UUUGCCGCUGCCCZ_IZ_IUGCCZ_IUCCUG$	210	PS1229	
	YYYGXXIXYGXXXZZYGXXZYXXYG	28		
	UUUGCCICUGCCCAAUGCCAUCCUG	108	PS305	

TABLE 3 -continued

Most preferred AONs
General structures of AONs. X = C or m^5C, Y = U or m^5U, Z = A or a^2A;
I = inosine (hypoxanthine base), X_1 = m^5C, Y_1 = m^5U, Z_1 = a^2A

DMD Exon	AON Sequence (5'→3')	SEQ ID NO		
51	YXZZGGZZGZYGGXZYYYXY	31		
	UCAAGGAAGAUGGCAUUUCU	111	PS43	FIG. 4, 5
	Y_1CAAGGAAGAY$_1$GGCAY$_1$Y$_1$Y$_1$CY$_1$	202	PS559	FIG. 4
	Y_1X_1AAGGAAGAY$_1$GGX$_1$AY$_1$Y$_1$Y$_1$X$_1$Y$_1$	203	PS1106	FIG. 4
	UCZ$_1$Z$_1$GGZ$_1$Z$_1$GZ$_1$UGGCZ$_1$UUUCU	206	PS403	FIG. 5
	UX$_1$AAGGAAGAUGGX$_1$AUUUX$_1$U	215	PS401	
52	GGYZZYGZGYYXYYXXZZXYGG	40		
	GGUAAUGAGUUCUUCCAACUGG	120	PS235	FIG. 4, 5
	GGUAAUGAGUUX$_1$UUX$_1$X$_1$AAX$_1$UGG	171	PS650	
	GGY$_1$AAY$_1$GAGY$_1$Y$_1$CY$_1$Y$_1$CCAACY$_1$GG	172	PS786	FIG. 4
	GGUZ$_1$Z$_1$UGZ$_1$GUUCUUCCZ$_1$Z$_1$CUGG	173	PS897	FIG. 5
	GGY$_1$AAY$_1$GAGY$_1$Y$_1$X$_1$Y$_1$Y$_1$X$_1$X$_1$AAX$_1$Y$_1$GG	174	PS1110	
53	GYYGXXYXXGGYYXYGZZGGYGYYX	52		
	GUUGCCUCCGGUUCUGAAGGUGUUC	91	PS229L	FIG. 1a, 2
	GUUGX$_1$X$_1$UX$_1$X$_1$GGUUX$_1$UGAAGGUGUUX$_1$	92	PS524	FIG. 1a, c, 2
	GUUGX$_1$X$_1$UCCGGUUX$_1$UGAAGGUGUUX$_1$	217	PS1317	FIG. 1c
	GUUGX$_1$X$_1$UCCGGUUCUGAAGGUGUUC	218	PS1318	FIG. 1c
	GUUGCX$_1$UCCGGUUX$_1$UGAAGGUGUUX$_1$	219	PS1319	FIG. 1c
	G Y_1 Y_1GCC Y_1CCGG Y_1 Y_1C Y_1GAAGG Y_1G Y_1 Y_1C	211		
	G Y_1 Y_1GX$_1$X$_1$ $Y_1X_1X_1$GG Y_1 Y_1X_1 Y_1GAAGG Y_1G Y_1 Y_1X_1	212	PS1109	
	GUUGCCUCCGGUUCUG Z_1 Z_1GGUGUUC	213		
55	GZGYYYXYYXXZZZGXZGXXYXYX	57		
	GAGUUUCUUCCAAAGCAGCCUCUC	137	PS531	FIG. 2
	GAGUUUX$_1$UUX$_1$X$_1$AAAGX$_1$AGX$_1$X$_1$UX$_1$UX$_1$	185	PS652	FIG. 2
	GAGY$_1$Y$_1$Y$_1$CY$_1$Y$_1$CCAAAGCAGCCY$_1$CY$_1$C	186		
	GZ$_1$GUUUCUUCCZ$_1$Z$_1$Z$_1$GCZ$_1$GCCUCUC	187		
	GAGY$_1$Y$_1$Y$_1$X$_1$Y$_1$Y$_1$X$_1$X$_1$AAAGX$_1$AGX$_1$X$_1$Y$_1$X$_1$Y$_1$X$_1$	188	PS1112	

[0751] Preferred non modified oligonucleotides (X═C, Y═U, Z═A) are more preferably derived from each of the oligonucleotide basis sequence (SEQ ID NO:14-90) and are represented by a nucleotide or base sequence SEQ ID NO:91, 93-170

[0752] Preferred modified oligonucleotides derived from one of the nucleotide or base sequences SEQ ID NO:14-90 and comprising at least one X is m^5C and/or at least one Y is m^5U and/or at least one Z is a^2A are represented by a nucleotide or a base sequence comprising or consisting of SEQ ID NO: 92, 171-213, 215, 217, 218, 219. Even more preferred modified oligonucleotides (all X=m^5C═X_1 and/or all Y=m^5U Y_1 and/or all Z=a^2A=Z_1) are derived from the most preferred nucleotide or base sequences (SEQ ID NO:15, 21, 31, 40, 52, and 57) and are represented by SEQ ID NO: 92, 171-174, 185-188, 199, 200, 202-213, 215, 217, 218, 219. The most preferred modified oligonucleotides are disclosed in Table 3.

Example 1

Material and Methods

AONs

[0753] All oligonucleotides (PS220/PS399, based on SEQ ID NO:21 corresponding to SEQ ID NO:101 for the non-modified sequence (PS220) and to SEQ ID NO:200 wherein all cytosines are modified (PS399); PS229L/PS524/PS1317/PS1318/PS1319, based on SEQ ID NO:52 corresponding to SEQ ID NO:91 for the non-modified sequence (PS229L), to SEQ ID NO:92 (PS524) wherein all 6 cytosines are modified, to SEQ ID NO: 217 (PS1317) wherein 4 of the 6 cytosines are modified, to SEQ ID NO: 218 (PS1318) wherein 2 of the 6 cytosines are modified and to SEQ ID NO:219 (PS1319) wherein 3 of the 6 cytosines are modified; PS232/PS648, based on SEQ ID NO: 39 corresponding to SEQ ID NO:119 for the non-modified sequence (PS232) and to SEQ ID NO:201 wherein all cytosines are modified (PS648); PS531/PS652, based on SEQ ID NO:57 corresponding to SEQ ID NO:137 for the non-modified sequence (PS531) and to SEQ ID NO:185 wherein all cytosines are modified (PS652); PS534/PS653, based on SEQ ID NO:59 corresponding to SEQ ID NO:139 for the non-modified sequence (PS534) and to SEQ ID NO:192 wherein all cytosines are modified (PS653)) were 2'-O-methyl phosphorothioate RNA, and synthesized using an OP-10 synthesizer (GE/ÄKTA Oligopilot), through standard phosphoramidite protocols, or obtained from commercial suppliers, in 40 nmol-4.5 mmol synthesis scale. Prosensa-synthesized oligonucleotides were cleaved and deprotected in a two step sequence (DIEA followed by conc. NH_4OH treatment), purified by HPLC and dissolved in water and an excess of NaCl was added to exchange ions. After evaporation, compounds were redissolved in water, desalted by FPLC or ultrafiltration and lyophilized. Mass spectrometry confirmed the identity of all compounds, and purity (determined by UPLC) was found acceptable for all compounds (>75-80%); compounds obtained from commercial sources were used as received: PS399 (ChemGenes, 1 μmol synthesis scale, used as received), PS1317, PS1318, and

PS1319 (ChemGenes, 200 nmol synthesis scale, used as received), PS229L, PS232, PS524, and PS648 (EuroGentec, 40=01 synthesis scale, used as received), PS229L (Prosensa, 5.9 g obtained material, purity 81%), PS524 (Avecia, 4.5 mmol synthesis scale, purity 93%), PS534 (Prosensa, 2 μmol synthesis scale, purity 86%), PS653 (Prosensa, 40 nmol synthesis scale, purity 77%), PS531 (Avecia, 4.6 g obtained material, purity 85%), PS652 (Avecia, 2.4 g obtained material, purity 84% and 3.8 g obtained material, purity 82%). For the in vitro transfection experiments described herein, 50 μM working solutions of the AONs were prepared in 20 mM phosphate buffer (pH 7.0). For the whole blood cytokine release assays in this example, the concentrations of the stock solutions (prepared in DNase/RNase-free distilled water (Invitrogen)) varied: PS232 (8.75 mg/mL), PS534 (7.02 mg/mL), PS648 (8.55 mg/mL), PS653 (8.12 mg/mL).

Transfection and RT-PCR Analysis

[0754] Differentiated human healthy control muscle cells (myotubes) were transfected in 6-wells plates with a triplo AON concentration series of 0-100-200-400 nM (FIG. **1***a*, PS229L/PS524, SEQ ID NO:91/92) or 0-50-100-200-400-800 nM (FIG. **1***b*, PS220/PS399, SEQ ID NO: 101/200) or with an in duplo concentration of 400 nM (FIG. **1***c*, PS524/PS1317/PS1318/PS1319, SEQ ID NO:92/217/218/219), according to non-GLP standard operating procedures. For transfection polyethylenimine (ExGen500, Fermentas) was used (2 μl per μg AON, in 0.15M NaCl). Aforementioned transfection procedures were adapted from previously reported material and methods (Aartsma-Rus et al., 2003). At 24 hrs after transfection, RNA was isolated and analyzed by RT-PCR. Briefly, to generate dystrophin-specific cDNA, a DMD gene specific reverse primer in exon 47 (PS220/PS399) or exon 55 (PS229L/PS524/PS1317/PS1318/PS1319) was used in the reverse transcriptase (RT) reaction on 1000 ng input RNA. The PCR analysis was subsequently done on 3 μl of dystrophin cDNA for each sample, and included a first and nested PCR using DMD gene specific primers in exons flanking exon 45 (PS220/PS399) or 53 (PS229L/PS524/PS1317/PS1318/PS1319). The RNA isolation and RT-PCR analysis were performed according to non-GLP standard operating procedures as described (Aartsma-Rus et al., 2003). RT-PCR products were analyzed by gel electrophoresis (2% agarose gels). The resulting RT-PCR fragments were quantified through DNA Lab-on-a-Chip analysis (Agilent). The data was processed by "Agilent 2100 Bioanalyzer" software and Excel 2007. The ratio of the smaller transcript product (containing the exon 45(PS220/PS399) or 53 skip (PS229L/PS524/PS1317/PS1318/PS1319)) to the total amount of transcript products was assessed (representing the exon 45 or 53 skipping efficiencies in percentages) and directly compared to that in non-transfected cells.

Pharmacokinetic Study in Wild Type and Mdx Mice

[0755] Mdx (C57Bl/10ScSn-Dmd$_{mdx}$/J) and wild-type (C57Bl/10ScSnJ) mice at 5 weeks of age were obtained from Jackson Laboratory (Maine USA). The AONs (PS229L/PS524 corresponding to SEQ ID NO: 91/92, PS531/PS652 corresponding to SEQ ID NO: 137/185) were administered in physiological saline at a dose of 100 mg/kg by subcutaneous injections three times per week for two weeks. To determine the plasma profile of the AONs, plasma samples were taken from 2 animals per time-point (per AON group) at the following times for the animals: 15 min, 1 h, 2 h, 6 h and 24 hours after dosing. To obtain plasma, venous whole blood was collected into Li-Heparin tubes, centrifuged and kept at −80° C. until analysis. For distribution analysis 7 organs (heart, kidney cortex, liver, diaphragm, gastrocnemius, quadriceps & triceps) were harvested upon sacrifice of the animals. The tissues were snap frozen and stored at −80° C. until analysis.

AON Hybridisation Assay

[0756] To determine the concentration of the AONs (PS229L/PS524 corresponding to SEQ ID NO: 91/92, PS531/PS652 corresponding to SEQ ID NO: 137/185) in plasma and tissue an AON hybridization assay was used, which is based on the assay described by Yu et al., 2002. For the tissue distribution analysis, tissues were homogenized, using a MagNaLyzer (Roche) to a concentration of 60 mg/ml in protK buffer (100 mmol/l Tris-HCl pH8.5, 200 mmol/l NaCl, 5 mmol/l EDTA, 0.2% SDS) containing 2 mg/ml proteinase K, followed by a 2 hours incubation (liver) or 4 hours incubation (all other organs) in a rotating hybridization oven at 55° C. and then stored −20° C. until use. All tissue homogenates and calibration curves were diluted (fit to criteria of the assay) in 60 times diluted pooled mdx control tissue homogenate (kidney, liver, several muscle groups). A template probe specific for each AON (5' gaatagacg-anti-AON-biotin 3', DNA phosphate oligonucleotide) and a ligation probe (p-cgtctattc-DIG DNA phosphate oligonucleotide) were used in the hybridization assay. The homogenates were incubated for 1 h at 37° C. with template probe (50 nmol/l) and the hybridized samples were transferred to streptavidin coated 96-well plates and incubated for 30 min at 37° C. Subsequently, the plate was washed 4 times and the digoxigenin-labeled ligation (2 nmol/l) was added and incubated for 30 min at ambient temperature. The DIG-label was detected using an anti-DIG-POD (1:7,500-1:30,000; Roche Diagnostics), which was visualized with a 3,3',5,5'-tetramethylbenzidine substrate (Sigma Aldrich, the Netherlands), and the reaction was stopped using an acidic solution (Sigma Aldrich). The absorption was measured at 450 nm using a BioTek Synergy HT plate reader (Beun de Ronde, Abcoude, The Netherlands). Plasma samples were analyzed according to the same protocol, using 100 times diluted pooled mdx plasma.

Whole Blood Cytokine Release Assay

[0757] For the detection of possible cytokine stimulation induced by selected AONs (PS232/PS648 corresponding to SEQ ID NO: 119/201 and PS534/PS653 corresponding to SEQ ID NO: 139/192) whole blood (anticoagulant CPD) from healthy human volunteers was used. Varying AON concentrations (ranging from 0 to 50 μg/ml, in a dilution of approximately 1:0.01 (v/v)) were added to the blood and the samples were incubated for 4 hours at 37° C. under 5% CO_2 atmosphere. After incubation, the samples were centrifuged at 3200×g for 15 minutes at 4° C. and plasma supernatants were collected and stored at −20° C. until cytokine quantification. MCP-1, IL-6, TNF-α, and IP-10 concentrations were determined by sandwich ELISA (human MCP-1, IL-6, TNF-α, IP-10 ELISA kits (R&D Systems). The experiments with human whole blood were repeated three to four times. FIG. **3** is based on one experiment only, but considered representative.

Results

[0758] The effect on AON activity (i.e. inducing exon skipping efficiency) of substituting all cytosines with 5-methylcytosines (m5C) was tested in cultured, differentiated, healthy muscle cells in vitro. In FIGS. **1***a* and **1***b* two examples are shown. When comparing PS229L and PS524 (=PS229L-m5C) (i.e. non-modified sequence SEQ ID NO: 91 compared with the modified sequence SEQ ID NO: 92 wherein all cytosines have been modified) in a dose-response transfection experiment using 0-100-200-400 nM, PS524 was clearly more efficient than PS229L at 200 and 400 nM (1.9-fold higher exon 53 skipping levels) (FIG. **1***a*). Similarly, when comparing PS220 and PS399 (=PS220-m5C) (i.e. non-modified sequence SEQ ID NO: 101 compared with the modified sequence SEQ ID NO: 200 wherein all cytosines have been modified) in a dose-response transfection experiment using 0-50-100-200-400-800 nM, PS399 was clearly more efficient than PS220, especially at lower concentrations (up to 10-fold higher exon 45 skipping levels at 50 nM) (FIG. **1***b*). These results demonstrate that the presence of 5-methylcytosines has a positive effect on the activity of the AONs. In PS524 (SEQ ID NO:92) all 6 cytosines are substituted with 5-methylcytosines (m5C) which had a positive effect on the exon skipping activity when compared to the non-modified counterpart oligonucleotide PS229L (SEQ ID NO:91) (FIG. **1***a*). To test whether such positive effect may be correlated with the number or percentage of base modifications incorporated, PS1317, PS1318, and PS1319, with respectively 4, 2, and 3 of the 6 cytosines substituted with 5-methylcytosines (m5C), were tested and directly compared to PS524 in cultured, differentiated, healthy muscle cells in vitro. PS1317, PS1318, and PS1319 were all effective in inducing exon 53 skipping (47%, 37%, and 45% respectively) (FIG. **1***c*). When compared to the levels obtained with PS524 however (64%), these results indeed suggest that reducing the number of 5-methylcytosines (m5C), from 6 to 4, 3, or 2 5-methylcytosines, leads to a reduced positive effect on exon skipping activity of the AON.

[0759] To investigate whether 5-methylcytosines affect bio-stability, -distribution, and/or -availability, a pharamacokinetic study was performed both in wild type (control) and mdx mice. The mdx mouse model for DMD has a natural nonsense mutation in exon 23 and is therefore dystrophin-deficient. The lack of dystrophin at the membranes increases the permeability of the muscle fibers for relatively small molecules as AONs, and has indeed been demonstrated to enhance 2'-O-methyl phosphorothioate RNA AON uptake by muscle up to 10-fold (Heemskerk et al., 2010). The mice were injected subcutaneously with 100 mg/kg of either 5-methylcytosine-containing AONs (PS524, PS652 corresponding to SEQ ID NO: 92, 185) or their counterparts with unmodified cytosines (PS229L, PS531 corresponding to SEQ ID NO: 91, 137), three times per week for two weeks. At different time-points (day 1, 7, 14) after the last injection, the mice were sacrificed and different muscle groups (heart, diaphragm, gastrocnemius, quadriceps, and triceps) and liver and kidney were isolated to determine AON concentrations therein (FIG. **2**A). As anticipated, for all compounds the concentrations in mdx muscles (average of all samples) was higher than those in control mice. The ratio mdx to control AON levels appeared relatively higher for the AONs with 5-methylcytosines. More specifically, in the mdx mice, the levels of PS524 and PS652 were 2- to 3-fold higher than that of PS229L and PS531. (FIG. **2**A). When monitoring the levels of AON in kidney and liver (known toxicity organs), the ratios between muscle tissue and toxicity tissues remained similar, or were even favorable for PS524. These results suggest that AONs with 5-methylcytosine are taken up better by or more stable in muscle than AONs with unmodified cytosines. Indeed the half life in muscle was longer for PS524 (>20 days) and PS652 (25 days) when compared to PS229L (7 days) and PS531 (10 days). In plasma, the Cmaxvalues of the AONs injected were similar, which confirms that the mice received equal doses (FIG. **2**B). Remarkably, the AUC values (as indicator for bioavailability) were 1.5 to 2.3-fold higher for the 5-methylcytosine containing AONs. This was associated with a lower clearance which supports their higher muscle tissue levels. The results from this pharmacokinetic study thus demonstrate that the presence of 5-methylcytosines has a positive effect on the bio-stability, -distribution, and/or -availability of the AONs, while the muscle/toxicity organ ratios were similar to those with the AONs with unmodified cytosines.

[0760] The in vitro safety profile of AONs with 5-methylcytosines (PS648, PS653 corresponding to SEQ ID NO: 201, 192) was compared to that of AONs with unmodified cytosines (PS232, PS534, corresponding to SEQ ID NO: 119, 139). AONs may stimulate an innate immune response by activating the Toll-like receptors (including TLR7, TLR8, TLR9), which results in set of coordinated immune responses that include innate immunity. Several chemo- and cytokines, such as IP-10, TNFα, TL-6 and MCP-1 play a role in this process, and were therefore monitored in human whole blood incubated with 0 to 50 μg/ml of each AON (using commercially available ELISA kits). PS232 and PS534 both have unmodified cytosines and induced the release of TNF-α (FIG. **3**A, B), MCP-1 (FIG. **3**C, D), IP-10 (FIG. **3**E, F), and IL-6 (FIG. **3**G, H) at increasing doses. In contrast, both PS648 and PS653 (with 5-methylcytosines) did not have any effect on TNF-α, IP-10 and IL-6. PS653, not PS648, seemed to induce a minor release of MCP-1 only. In conclusion, the presence of 5-methylcytosines improved the safety profile of these AONs in vitro.

Example 2

Material and Methods

AONs

[0761] All oligonucleotides (PS43/PS559/PS1106, all based on SEQ ID NO:31, and corresponding to SEQ ID NO: 111 (PS43) non modified sequence, SEQ ID NO: 202 (PS559) wherein all uraciles have been modified, and SEQ ID NO: 203 (PS1106) wherein all uraciles and all cytosines have been modified; PS188/PS785/PS1107, all based on SEQ ID NO:15, and corresponding to SEQ ID NO: 95 (PS188) non-modified sequence, SEQ ID NO: 204 (PS785) wherein all uraciles have been modified, and SEQ ID NO: 205 (PS1107) wherein all uraciles and all cytosines have been modified; PS235/PS786, both based on SEQ ID NO:40, and corresponding to SEQ ID NO: 120 (PS235) non-modified sequence and SEQ ID NO: 172 (PS786) wherein all uraciles have been modified), and PS49 (SEQ ID NO:216) non-modified sequence and PS959 (SEQ ID NO:214) wherein all cytosines have been modified, were 2'-O-methyl phosphorothioate RNA, and synthesized using an OP-10 synthesizer (GE/ÄKTA Oligopilot) through standard phosphoramidite protocols, or obtained from commercial suppliers, in 200 nmol-286.1 g scale. Prosensa-synthesized oligonucleotides

were cleaved and deprotected in a two step sequence (DIEA followed by conc. NH_4OH treatment), purified by HPLC and dissolved in water and an excess of NaCl was added to exchange ions. After evaporation, compounds were redissolved in water, desalted by FPLC or ultrafiltration and lyophilized. Mass spectrometry confirmed the identity of all compounds, and purity (determined by UPLC) was found acceptable for all compounds (>75-80%); compounds obtained from commercial sources were used as received: PS188 (Girindus, 286.1 g obtained product, purity 93%), PS785, PS786, PS1106, and PS1107 (ChemGenes, 200 nmol synthesis scale, used as received), PS43 (Prosensa, 1 μmol synthesis scale, purity 90%), PS559 (ChemGenes, 1 μmol synthesis scale, used as received), PS235 (Prosensa, 1.92 mmol synthesis scale, purity 91%). For the in vitro transfection experiments described herein, 50 μM working solutions of the AONs were prepared in 20 mM phosphate buffer (pH 7.0).

Transfection and RT-PCR Analysis

[0762] Differentiated human healthy control muscle cells (myotubes) were transfected in 6-wells plates with a fixed AON concentration of 200 nM, according to non-GLP standard operating procedures. For transfection polyethylenimine (ExGen500, Fermentas) was used (2 μl per μg AON, in 0.15M NaCl). Aforementioned transfection procedures were adapted from previously reported material and methods (Aartsma-Rus et al., 2003). At 24 hrs after transfection, RNA was isolated and analyzed by RT-PCR. Briefly, to generate dystrophin-specific cDNA, a DMD gene specific reverse primer in exon 53 (PS43/PS559/PS1106, SEQ ID NO: 111, 202, 203), exon 46 (PS188/PS785/PS1107 SEQ ID NO: 95, 204, 205) or exon 54 (PS235/PS786, SEQ ID NO: 120, 172) was used in the reverse transcriptase (RT) reaction on 1000 ng input RNA. The PCR analysis was subsequently done on 3 μl of dystrophin cDNA for each sample, and included a first and nested PCR using DMD gene specific primers in exons flanking exon 51 (PS43/PS559/PS1106), exon 44 (PS188/PS785/PS1107) or exon 52 (PS235/PS786). The RNA isolation and RT-PCR analysis were performed according to non-GLP standard operating procedures as described [Aartsma-Rus et al., Hum Mol Genet 2003; 12(8):907-14]. RT-PCR products were analyzed by gel electrophoresis (2% agarose gels). The resulting RT-PCR fragments were quantified through DNA Lab-on-a-Chip analysis (Agilent). The data was processed by "Agilent 2100 Bioanalyzer" software and Excel 2007. The ratio of the smaller transcript product (containing the exon 51 (PS43/PS559/PS1106), exon 44 (PS188/PS785/PS1107), or exon 52 skip (PS235/PS786) to the total amount of transcript products was assessed (representing the exon 51, 44, or 52 skipping efficiencies in percentages) and directly compared to that in non-transfected cells.

In Vivo Administration and RT-PCR

[0763] The experiments with the mdx mouse model (C57Bl/10ScSn-mdx/J; Charles River Laboratories) were approved by the local LUMC Animal Ethics Committee (DEC number 11145). Two mdx mice per group were anaesthetized using isoflurane and then injected intramuscularly in both gastrocnemius muscles, with 20 ug PS49 (SEQ ID NO: 216) or PS959 (SEQ ID NO:214), diluted in sterile saline to a total volume of 50 μl per injection, on two consecutive days. Animals were sacrificed 1 week after the last injection by cervical dislocation and muscles were isolated and snap frozen in magnalyzer greenbead tubes (Roche). Six-hundred μl Tripure (Roche) was added to the tubes and muscles were homogenized using the bulletblender machine, 3×1 min speed 10. The lysate was transferred to a clean tube to which 120 μl of chloroform was added. Samples were vigorously shaken en incubated on ice for 5 minutes, then centrifuged for 15 minutes at maximum speed at 4° C. The supernatant was transferred to another tube and 1 volume of isopropanol was added. Samples were mixed and incubated at 4 degrees for at least 30 minutes. Then samples were centrifuged for 15 minutes at maximum speed at 4° C., washed with 70% ethanol followed by a second centrifugation step of 10 minutes at maximum speed at 4° C. RNA pellets were airdried and solved in DEPC treated water. cDNA was generated using 400 ng total RNA with random hexamer primers using Transcriptor reverse transcriptase (RT) (Roche Diagnostics) according to the manufacturer's instructions. PCRs were performed by 30 cycles of 94 degrees for 30 s, 60 degrees for 30 s and 72 degrees for 30 s in a 50 μl reaction using 1.5 μl cDNA as template using primers specific for mouse exon 22 and exon 24. PCR products were visualized on 2% agarose gels quantified the Agilent 2100 Bioanalyzer (Agilent, Santa Clara, Calif., USA).

Results

[0764] The effect on AON activity (i.e. inducing exon skipping efficiency) of substituting all unmodified cytosines with 5-methylcytosines and substituting all unmodified uracils with 5-methyluracils (as in PS1106, PS1107, SEQ ID NO: 203, 205), and of only substituting all unmodified uracils with 5-methyluracils (as in PS559, PS785, PS786, SEQ ID NO: 202, 204, 172), was first tested at a fixed 200 nM AON concentration in cultured, differentiated, healthy muscle cells in vitro (FIG. **4**A). The AONs with 5-methyluracils (PS559, PS785, and PS786) increased the exon skipping efficiencies 1.3- to 3-fold when compared to their counterparts with unmodified uracils. When also replacing the unmodified cytosines by 5-methylcytosines, the skipping levels were further increased (PS1106 versus PS559, SEQ ID NO: 203 versus 202) or similar (PS1107 versus PS785, SEQ ID NO: 205 versus 204). The effect on AON activity (i.e. inducing exon skipping efficiency) of substituting all unmodified uracils (as in PS49; SEQ ID NO:216) with 5-methyluracils (as in PS959; SEQ ID NO:214) was then also tested in muscle of the mdx mouse model. PS959 with all 5-methyluracils increased the exon 23 skipping efficiencies approximately 3-fold when compared to PS49 with unmodified uracils (n=4 per AON) (FIG. **4**B). These results demonstrate that not only 5-methylcytosines may have a positive effect on exon skipping activity (as also shown in FIG. **1**) but also, 5-methyluracils, both in vitro and in vivo. In addition the combined use of these 5-methylpyrimidines may even further increase activity.

Example 3

Material and Methods

AONs

[0765] All oligonucleotides (PS43/PS403, based on SEQ ID NO:31, and corresponding to SEQ ID NO: 111 (PS43) for the non-modified and SEQ ID NO: 206 (PS403) for the sequence wherein all adenines have been modified; PS188/PS733, based on SEQ ID NO:15, and corresponding to SEQ

ID NO: 95 (PS188) for the non-modified and SEQ ID NO: 207 (PS733) for the sequence wherein all adenines have been modified; PS235/PS897, based on SEQ ID NO:40, and corresponding to SEQ ID NO: 120 (PS235) for the non-modified and SEQ ID NO: 173 (PS897) for the sequence wherein all adenines have been modified) were 2'-O-methyl phosphorothioate RNA, and synthesized using an OP-10 synthesizer (GE/ÄKTA Oligopilot) through standard phosphoramidite protocols, or obtained from commercial suppliers, in 200 nmol-151 g scale. Prosensa-synthesized oligonucleotides were cleaved and deprotected in a two step sequence (DIEA followed by cone. NH_4OH treatment), purified by HPLC and dissolved in water and an excess of NaCl was added to exchange ions. After evaporation, compounds were redissolved in water, desalted by FPLC or ultrafiltration and lyophilized. Mass spectrometry confirmed the identity of all compounds, and purity (determined by UPLC) was found acceptable for all compounds (>75-80%); compounds obtained from commercial sources were used as received: PS188 (Girindus, 151 g obtained, purity 92%), PS733 (TriLink or ChemGenes, 200 nmol/1 mg synthesis scale, used as received, PS43 (Prosensa, 10 μmol synthesis scale, purity 86%), PS403 (ChemGenes, 1 μmol synthesis scale, used as received), PS235 (Prosensa, 1.92 mmol synthesis scale, purity 91%), PS897 (ChemGenes, 200 nmol synthesis scale, used as received). For the in vitro transfection experiments described herein, 50 μM working solutions of the AONs were prepared in 20 mM phosphate buffer (pH 7.0). For the in vitro complement activation assays described herein, 3 mg/mL stock solutions of PS188 and PS733 were prepared in 20 mM phosphate buffer (pH 7.0).

Transfection and RT-PCR Analysis

[0766] Differentiated human healthy control muscle cells (myotubes) were transfected in 6-wells plates with a fixed AON concentration of 200 nM, according to non-GLP standard operating procedures. For transfection polyethylenimine (ExGen500, Fermentas) was used (2 μl per μg AON, in 0.15M NaCl). Aforementioned transfection procedures were adapted from previously reported material and methods (Aartsma-Rus et al., 2003). At 24 hrs after transfection, RNA was isolated and analyzed by RT-PCR. Briefly, to generate dystrophin-specific cDNA, a DMD gene specific reverse primer in exon 53 (PS43/PS403, SEQ ID NO: 111/206), exon 46 (PS188/PS733, SEQ ID NO: 95/207) or exon 54 (PS235/PS897, SEQ ID NO: 120/173) was used in the reverse transcriptase (RT) reaction on 1000 ng input RNA. The PCR analysis was subsequently done on 3 μl of dystrophin cDNA for each sample, and included a first and nested PCR using DMD gene specific primers in exons flanking exon 51 (PS43/PS403), exon 44 (PS188/PS733) or exon 52 (PS235/PS897). The RNA isolation and RT-PCR analysis were performed according to non-GLP standard operating procedures as described [Aartsma-Rus et al., Hum Mol Genet 2003; 12(8): 907-14]. RT-PCR products were analyzed by gel electrophoresis (2% agarose gels). The resulting RT-PCR fragments were quantified through DNA Lab-on-a-Chip analysis (Agilent). The data was processed by "Agilent 2100 Bioanalyzer" software and Excel 2007. The ratio of the smaller transcript product (containing the exon 51 (PS43/PS403), exon 44 (PS188/PS733), or exon 52 skip (PS235/PS897) to the total amount of transcript products was assessed (representing the exon 51, 44, or 52 skipping efficiencies in percentages) and directly compared to that in non-transfected cells.

Complement Activation Assay

[0767] Antisense oligonucleotides may activate the alternative complement pathway, which contains several split factors, such as C3a and factor Bb (the latter is unique to the alternative pathway). The ability of AONs to possibly activate the complement pathway was assessed in plasma from Cynomolgus monkeys (LiHe plasma, CIT, France). Increasing concentrations (from 0 to 300 μg/mL) of PS188 (SEQ ID NO: 95) and PS733 (PS207), in a dilution of 1:10 (v/v)), were added to the plasma and incubated at 37° C. for 30 min. The reaction was terminated by transferring the samples to ice and making dilutions in ice-cold diluent. Bb and C3a concentrations were determined by ELISA (Quidel, San Diego, Calif.).

Results

[0768] The effect on AON activity (i.e. inducing exon skipping efficiency) of substituting all unmodified adenines with 2,6-diaminopurines was tested at a fixed AON concentration (200 nM) in cultured, differentiated, healthy muscle cells in vitro. In FIG. **5**A examples for three different AON sequences are shown. The AONs with 2,6-diaminopurines (PS403, PS897, and PS733, SEQ ID NO: 206, 207, 173) increased the exon skipping efficiencies 2- to 4-fold when compared to their counterparts with unmodified adenines (compared to SEQ ID NO: 111, 95, 120). There seemed to be a correlation with the number of 2,6-diaminopurines in each AON.

[0769] The effect of substituting all unmodified adenines (as in PS188; SEQ ID NO: 95) with 2,6-diaminopurines (as in PS733; SEQ ID NO:207) on in vitro safety, i.e. possible activation of the alternative complement pathway, was tested in monkey plasma. Whereas PS188 induced relatively high levels of both split factors Bb and C3 a, the 2,6-diaminopurines in PS733 completely abolished the effect on the alternative pathway, showing no increase in either Bb or C3a levels (FIG. **5**B). Thus the presence of 2,6-diaminopurines seemed to improve the safety profile of PS188 in vitro.

[0770] These results demonstrate the positive effect of 2,6-diaminopurines on the exon skipping activity and safety of AONs.

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SEQUENCE LISTING

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<210> SEQ ID NO 1
<211> LENGTH: 3685
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

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            20                  25                  30

Gly Lys Gln His Ile Glu Asn Leu Phe Ser Asp Leu Gln Asp Gly Arg
        35                  40                  45

Arg Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Gln Lys Leu Pro Lys
    50                  55                  60

Glu Lys Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Lys Ala
65                  70                  75                  80

Leu Arg Val Leu Gln Asn Asn Asn Val Asp Leu Val Asn Ile Gly Ser
                85                  90                  95

Thr Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Ile Trp
            100                 105                 110

Asn Ile Ile Leu His Trp Gln Val Lys Asn Val Met Lys Asn Ile Met
        115                 120                 125

Ala Gly Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
    130                 135                 140

Arg Gln Ser Thr Arg Asn Tyr Pro Gln Val Asn Val Ile Asn Phe Thr
145                 150                 155                 160

Thr Ser Trp Ser Asp Gly Leu Ala Leu Asn Ala Leu Ile His Ser His
                165                 170                 175

Arg Pro Asp Leu Phe Asp Trp Asn Ser Val Val Cys Gln Gln Ser Ala
            180                 185                 190

Thr Gln Arg Leu Glu His Ala Phe Asn Ile Ala Arg Tyr Gln Leu Gly
        195                 200                 205

Ile Glu Lys Leu Leu Asp Pro Glu Asp Val Asp Thr Thr Tyr Pro Asp
    210                 215                 220

Lys Lys Ser Ile Leu Met Tyr Ile Thr Ser Leu Phe Gln Val Leu Pro
225                 230                 235                 240

Gln Gln Val Ser Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg
                245                 250                 255

Pro Pro Lys Val Thr Lys Glu Glu His Phe Gln Leu His His Gln Met
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           260                 265                 270

His Tyr Ser Gln Gln Ile Thr Val Ser Leu Ala Gln Gly Tyr Glu Arg
        275                 280                 285

Thr Ser Ser Pro Lys Pro Arg Phe Lys Ser Tyr Ala Tyr Thr Gln Ala
    290                 295                 300

Ala Tyr Val Thr Thr Ser Asp Pro Thr Arg Ser Pro Phe Pro Ser Gln
305                 310                 315                 320

His Leu Glu Ala Pro Glu Asp Lys Ser Phe Gly Ser Ser Leu Met Glu
                325                 330                 335

Ser Glu Val Asn Leu Asp Arg Tyr Gln Thr Ala Leu Glu Glu Val Leu
            340                 345                 350

Ser Trp Leu Leu Ser Ala Glu Asp Thr Leu Gln Ala Gln Gly Glu Ile
        355                 360                 365

Ser Asn Asp Val Glu Val Val Lys Asp Gln Phe His Thr His Glu Gly
    370                 375                 380

Tyr Met Met Asp Leu Thr Ala His Gln Gly Arg Val Gly Asn Ile Leu
385                 390                 395                 400

Gln Leu Gly Ser Lys Leu Ile Gly Thr Gly Lys Leu Ser Glu Asp Glu
                405                 410                 415

Glu Thr Glu Val Gln Glu Gln Met Asn Leu Leu Asn Ser Arg Trp Glu
            420                 425                 430

Cys Leu Arg Val Ala Ser Met Glu Lys Gln Ser Asn Leu His Arg Val
        435                 440                 445

Leu Met Asp Leu Gln Asn Gln Lys Leu Lys Glu Leu Asn Asp Trp Leu
    450                 455                 460

Thr Lys Thr Glu Glu Arg Thr Arg Lys Met Glu Glu Glu Pro Leu Gly
465                 470                 475                 480

Pro Asp Leu Glu Asp Leu Lys Arg Gln Val Gln Gln His Lys Val Leu
                485                 490                 495

Gln Glu Asp Leu Glu Gln Glu Gln Val Arg Val Asn Ser Leu Thr His
            500                 505                 510

Met Val Val Val Val Asp Glu Ser Ser Gly Asp His Ala Thr Ala Ala
        515                 520                 525

Leu Glu Glu Gln Leu Lys Val Leu Gly Asp Arg Trp Ala Asn Ile Cys
    530                 535                 540

Arg Trp Thr Glu Asp Arg Trp Val Leu Leu Gln Asp Ile Leu Leu Lys
545                 550                 555                 560

Trp Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ala Trp Leu Ser
                565                 570                 575

Glu Lys Glu Asp Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp
            580                 585                 590

Gln Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala
        595                 600                 605

Asp Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys
    610                 615                 620

Gln Asp Leu Leu Ser Thr Leu Lys Asn Lys Ser Val Thr Gln Lys Thr
625                 630                 635                 640

Glu Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln
                645                 650                 655

Lys Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr
            660                 665                 670
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Gln Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val
        675                 680                 685

Thr Thr Arg Glu Gln Ile Leu Val Lys His Ala Gln Glu Glu Leu Pro
    690                 695                 700

Pro Pro Pro Pro Gln Lys Lys Arg Gln Ile Thr Val Asp Ser Glu Ile
705                 710                 715                 720

Arg Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr
                725                 730                 735

Arg Ser Glu Ala Val Leu Gln Ser Pro Glu Phe Ala Ile Phe Arg Lys
            740                 745                 750

Glu Gly Asn Phe Ser Asp Leu Lys Glu Lys Val Asn Ala Ile Glu Arg
        755                 760                 765

Glu Lys Ala Glu Lys Phe Arg Lys Leu Gln Asp Ala Ser Arg Ser Ala
    770                 775                 780

Gln Ala Leu Val Glu Gln Met Val Asn Glu Gly Val Asn Ala Asp Ser
785                 790                 795                 800

Ile Lys Gln Ala Ser Glu Gln Leu Asn Ser Arg Trp Ile Glu Phe Cys
                805                 810                 815

Gln Leu Leu Ser Glu Arg Leu Asn Trp Leu Glu Tyr Gln Asn Asn Ile
            820                 825                 830

Ile Ala Phe Tyr Asn Gln Leu Gln Gln Leu Glu Gln Met Thr Thr Thr
        835                 840                 845

Ala Glu Asn Trp Leu Lys Ile Gln Pro Thr Thr Pro Ser Glu Pro Thr
    850                 855                 860

Ala Ile Lys Ser Gln Leu Lys Ile Cys Lys Asp Glu Val Asn Arg Leu
865                 870                 875                 880

Ser Gly Leu Gln Pro Gln Ile Glu Arg Leu Lys Ile Gln Ser Ile Ala
                885                 890                 895

Leu Lys Glu Lys Gly Gln Gly Pro Met Phe Leu Asp Ala Asp Phe Val
            900                 905                 910

Ala Phe Thr Asn His Phe Lys Gln Val Phe Ser Asp Val Gln Ala Arg
        915                 920                 925

Glu Lys Glu Leu Gln Thr Ile Phe Asp Thr Leu Pro Pro Met Arg Tyr
    930                 935                 940

Gln Glu Thr Met Ser Ala Ile Arg Thr Trp Val Gln Gln Ser Glu Thr
945                 950                 955                 960

Lys Leu Ser Ile Pro Gln Leu Ser Val Thr Asp Tyr Glu Ile Met Glu
                965                 970                 975

Gln Arg Leu Gly Glu Leu Gln Ala Leu Gln Ser Ser Leu Gln Glu Gln
            980                 985                 990

Gln Ser Gly Leu Tyr Tyr Leu Ser  Thr Thr Val Lys Glu  Met Ser Lys
        995                 1000                1005

Lys Ala  Pro Ser Glu Ile Ser  Arg Lys Tyr Gln Ser  Glu Phe Glu
    1010                1015                1020

Glu Ile  Glu Gly Arg Trp Lys  Lys Leu Ser Ser Gln  Leu Val Glu
    1025                1030                1035

His Cys  Gln Lys Leu Glu Glu  Gln Met Asn Lys Leu  Arg Lys Ile
    1040                1045                1050

Gln Asn  His Ile Gln Thr Leu  Lys Lys Trp Met Ala  Glu Val Asp
    1055                1060                1065
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Val Phe  Leu Lys Glu Glu Trp  Pro Ala Leu Gly Asp  Ser Glu Ile
    1070                1075                1080

Leu Lys  Lys Gln Leu Lys Gln  Cys Arg Leu Leu Val  Ser Asp Ile
    1085                1090                1095

Gln Thr  Ile Gln Pro Ser Leu  Asn Ser Val Asn Glu  Gly Gly Gln
    1100                1105                1110

Lys Ile  Lys Asn Glu Ala Glu  Pro Glu Phe Ala Ser  Arg Leu Glu
    1115                1120                1125

Thr Glu  Leu Lys Glu Leu Asn  Thr Gln Trp Asp His  Met Cys Gln
    1130                1135                1140

Gln Val  Tyr Ala Arg Lys Glu  Ala Leu Lys Gly Gly  Leu Glu Lys
    1145                1150                1155

Thr Val  Ser Leu Gln Lys Asp  Leu Ser Glu Met His  Glu Trp Met
    1160                1165                1170

Thr Gln  Ala Glu Glu Glu Tyr  Leu Glu Arg Asp Phe  Glu Tyr Lys
    1175                1180                1185

Thr Pro  Asp Glu Leu Gln Lys  Ala Val Glu Glu Met  Lys Arg Ala
    1190                1195                1200

Lys Glu  Glu Ala Gln Gln Lys  Glu Ala Lys Val Lys  Leu Leu Thr
    1205                1210                1215

Glu Ser  Val Asn Ser Val Ile  Ala Gln Ala Pro Pro  Val Ala Gln
    1220                1225                1230

Glu Ala  Leu Lys Lys Glu Leu  Glu Thr Leu Thr Thr  Asn Tyr Gln
    1235                1240                1245

Trp Leu  Cys Thr Arg Leu Asn  Gly Lys Cys Lys Thr  Leu Glu Glu
    1250                1255                1260

Val Trp  Ala Cys Trp His Glu  Leu Leu Ser Tyr Leu  Glu Lys Ala
    1265                1270                1275

Asn Lys  Trp Leu Asn Glu Val  Glu Phe Lys Leu Lys  Thr Thr Glu
    1280                1285                1290

Asn Ile  Pro Gly Gly Ala Glu  Glu Ile Ser Glu Val  Leu Asp Ser
    1295                1300                1305

Leu Glu  Asn Leu Met Arg His  Ser Glu Asp Asn Pro  Asn Gln Ile
    1310                1315                1320

Arg Ile  Leu Ala Gln Thr Leu  Thr Asp Gly Gly Val  Met Asp Glu
    1325                1330                1335

Leu Ile  Asn Glu Glu Leu Glu  Thr Phe Asn Ser Arg  Trp Arg Glu
    1340                1345                1350

Leu His  Glu Glu Ala Val Arg  Arg Gln Lys Leu Leu  Glu Gln Ser
    1355                1360                1365

Ile Gln  Ser Ala Gln Glu Thr  Glu Lys Ser Leu His  Leu Ile Gln
    1370                1375                1380

Glu Ser  Leu Thr Phe Ile Asp  Lys Gln Leu Ala Ala  Tyr Ile Ala
    1385                1390                1395

Asp Lys  Val Asp Ala Ala Gln  Met Pro Gln Glu Ala  Gln Lys Ile
    1400                1405                1410

Gln Ser  Asp Leu Thr Ser His  Glu Ile Ser Leu Glu  Glu Met Lys
    1415                1420                1425

Lys His  Asn Gln Gly Lys Glu  Ala Ala Gln Arg Val  Leu Ser Gln
    1430                1435                1440

Ile Asp  Val Ala Gln Lys Lys  Leu Gln Asp Val Ser  Met Lys Phe
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    1445                1450                1455

Arg Leu  Phe Gln Lys Pro Ala  Asn Phe Glu Gln Arg  Leu Gln Glu
    1460                1465                1470

Ser Lys  Met Ile Leu Asp Glu  Val Lys Met His Leu  Pro Ala Leu
    1475                1480                1485

Glu Thr  Lys Ser Val Glu Gln  Glu Val Val Gln Ser  Gln Leu Asn
    1490                1495                1500

His Cys  Val Asn Leu Tyr Lys  Ser Leu Ser Glu Val  Lys Ser Glu
    1505                1510                1515

Val Glu  Met Val Ile Lys Thr  Gly Arg Gln Ile Val  Gln Lys Lys
    1520                1525                1530

Gln Thr  Glu Asn Pro Lys Glu  Leu Asp Glu Arg Val  Thr Ala Leu
    1535                1540                1545

Lys Leu  His Tyr Asn Glu Leu  Gly Ala Lys Val Thr  Glu Arg Lys
    1550                1555                1560

Gln Gln  Leu Glu Lys Cys Leu  Lys Leu Ser Arg Lys  Met Arg Lys
    1565                1570                1575

Glu Met  Asn Val Leu Thr Glu  Trp Leu Ala Ala Thr  Asp Met Glu
    1580                1585                1590

Leu Thr  Lys Arg Ser Ala Val  Glu Gly Met Pro Ser  Asn Leu Asp
    1595                1600                1605

Ser Glu  Val Ala Trp Gly Lys  Ala Thr Gln Lys Glu  Ile Glu Lys
    1610                1615                1620

Gln Lys  Val His Leu Lys Ser  Ile Thr Glu Val Gly  Glu Ala Leu
    1625                1630                1635

Lys Thr  Val Leu Gly Lys Lys  Glu Thr Leu Val Glu  Asp Lys Leu
    1640                1645                1650

Ser Leu  Leu Asn Ser Asn Trp  Ile Ala Val Thr Ser  Arg Ala Glu
    1655                1660                1665

Glu Trp  Leu Asn Leu Leu Leu  Glu Tyr Gln Lys His  Met Glu Thr
    1670                1675                1680

Phe Asp  Gln Asn Val Asp His  Ile Thr Lys Trp Ile  Ile Gln Ala
    1685                1690                1695

Asp Thr  Leu Leu Asp Glu Ser  Glu Lys Lys Lys Pro  Gln Gln Lys
    1700                1705                1710

Glu Asp  Val Leu Lys Arg Leu  Lys Ala Glu Leu Asn  Asp Ile Arg
    1715                1720                1725

Pro Lys  Val Asp Ser Thr Arg  Asp Gln Ala Ala Asn  Leu Met Ala
    1730                1735                1740

Asn Arg  Gly Asp His Cys Arg  Lys Leu Val Glu Pro  Gln Ile Ser
    1745                1750                1755

Glu Leu  Asn His Arg Phe Ala  Ala Ile Ser His Arg  Ile Lys Thr
    1760                1765                1770

Gly Lys  Ala Ser Ile Pro Leu  Lys Glu Leu Glu Gln  Phe Asn Ser
    1775                1780                1785

Asp Ile  Gln Lys Leu Leu Glu  Pro Leu Glu Ala Glu  Ile Gln Gln
    1790                1795                1800

Gly Val  Asn Leu Lys Glu Glu  Asp Phe Asn Lys Asp  Met Asn Glu
    1805                1810                1815

Asp Asn  Glu Gly Thr Val Lys  Glu Leu Leu Gln Arg  Gly Asp Asn
    1820                1825                1830
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Leu Gln  Gln Arg Ile Thr Asp  Glu Arg Lys Arg Glu  Glu Ile Lys
    1835                1840                1845

Ile Lys  Gln Gln Leu Leu Gln  Thr Lys His Asn Ala  Leu Lys Asp
    1850                1855                1860

Leu Arg  Ser Gln Arg Arg Lys  Lys Ala Leu Glu Ile  Ser His Gln
    1865                1870                1875

Trp Tyr  Gln Tyr Lys Arg Gln  Ala Asp Asp Leu Leu  Lys Cys Leu
    1880                1885                1890

Asp Asp  Ile Glu Lys Lys Leu  Ala Ser Leu Pro Glu  Pro Arg Asp
    1895                1900                1905

Glu Arg  Lys Ile Lys Glu Ile  Asp Arg Glu Leu Gln  Lys Lys Lys
    1910                1915                1920

Glu Glu  Leu Asn Ala Val Arg  Arg Gln Ala Glu Gly  Leu Ser Glu
    1925                1930                1935

Asp Gly  Ala Ala Met Ala Val  Glu Pro Thr Gln Ile  Gln Leu Ser
    1940                1945                1950

Lys Arg  Trp Arg Glu Ile Glu  Ser Lys Phe Ala Gln  Phe Arg Arg
    1955                1960                1965

Leu Asn  Phe Ala Gln Ile His  Thr Val Arg Glu Glu  Thr Met Met
    1970                1975                1980

Val Met  Thr Glu Asp Met Pro  Leu Glu Ile Ser Tyr  Val Pro Ser
    1985                1990                1995

Thr Tyr  Leu Thr Glu Ile Thr  His Val Ser Gln Ala  Leu Leu Glu
    2000                2005                2010

Val Glu  Gln Leu Leu Asn Ala  Pro Asp Leu Cys Ala  Lys Asp Phe
    2015                2020                2025

Glu Asp  Leu Phe Lys Gln Glu  Glu Ser Leu Lys Asn  Ile Lys Asp
    2030                2035                2040

Ser Leu  Gln Gln Ser Ser Gly  Arg Ile Asp Ile Ile  His Ser Lys
    2045                2050                2055

Lys Thr  Ala Ala Leu Gln Ser  Ala Thr Pro Val Glu  Arg Val Lys
    2060                2065                2070

Leu Gln  Glu Ala Leu Ser Gln  Leu Asp Phe Gln Trp  Glu Lys Val
    2075                2080                2085

Asn Lys  Met Tyr Lys Asp Arg  Gln Gly Arg Phe Asp  Arg Ser Val
    2090                2095                2100

Glu Lys  Trp Arg Arg Phe His  Tyr Asp Ile Lys Ile  Phe Asn Gln
    2105                2110                2115

Trp Leu  Thr Glu Ala Glu Gln  Phe Leu Arg Lys Thr  Gln Ile Pro
    2120                2125                2130

Glu Asn  Trp Glu His Ala Lys  Tyr Lys Trp Tyr Leu  Lys Glu Leu
    2135                2140                2145

Gln Asp  Gly Ile Gly Gln Arg  Gln Thr Val Val Arg  Thr Leu Asn
    2150                2155                2160

Ala Thr  Gly Glu Glu Ile Ile  Gln Gln Ser Ser Lys  Thr Asp Ala
    2165                2170                2175

Ser Ile  Leu Gln Glu Lys Leu  Gly Ser Leu Asn Leu  Arg Trp Gln
    2180                2185                2190

Glu Val  Cys Lys Gln Leu Ser  Asp Arg Lys Lys Arg  Leu Glu Glu
    2195                2200                2205
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Gln Lys  Asn Ile Leu Ser Glu  Phe Gln Arg Asp Leu  Asn Glu Phe
    2210                2215                2220

Val Leu  Trp Leu Glu Glu Ala  Asp Asn Ile Ala Ser  Ile Pro Leu
    2225                2230                2235

Glu Pro  Gly Lys Glu Gln Gln  Leu Lys Glu Lys Leu  Glu Gln Val
    2240                2245                2250

Lys Leu  Leu Val Glu Glu Leu  Pro Leu Arg Gln Gly  Ile Leu Lys
    2255                2260                2265

Gln Leu  Asn Glu Thr Gly Gly  Pro Val Leu Val Ser  Ala Pro Ile
    2270                2275                2280

Ser Pro  Glu Glu Gln Asp Lys  Leu Glu Asn Lys Leu  Lys Gln Thr
    2285                2290                2295

Asn Leu  Gln Trp Ile Lys Val  Ser Arg Ala Leu Pro  Glu Lys Gln
    2300                2305                2310

Gly Glu  Ile Glu Ala Gln Ile  Lys Asp Leu Gly Gln  Leu Glu Lys
    2315                2320                2325

Lys Leu  Glu Asp Leu Glu Glu  Gln Leu Asn His Leu  Leu Leu Trp
    2330                2335                2340

Leu Ser  Pro Ile Arg Asn Gln  Leu Glu Ile Tyr Asn  Gln Pro Asn
    2345                2350                2355

Gln Glu  Gly Pro Phe Asp Val  Gln Glu Thr Glu Ile  Ala Val Gln
    2360                2365                2370

Ala Lys  Gln Pro Asp Val Glu  Glu Ile Leu Ser Lys  Gly Gln His
    2375                2380                2385

Leu Tyr  Lys Glu Lys Pro Ala  Thr Gln Pro Val Lys  Arg Lys Leu
    2390                2395                2400

Glu Asp  Leu Ser Ser Glu Trp  Lys Ala Val Asn Arg  Leu Leu Gln
    2405                2410                2415

Glu Leu  Arg Ala Lys Gln Pro  Asp Leu Ala Pro Gly  Leu Thr Thr
    2420                2425                2430

Ile Gly  Ala Ser Pro Thr Gln  Thr Val Thr Leu Val  Thr Gln Pro
    2435                2440                2445

Val Val  Thr Lys Glu Thr Ala  Ile Ser Lys Leu Glu  Met Pro Ser
    2450                2455                2460

Ser Leu  Met Leu Glu Val Pro  Ala Leu Ala Asp Phe  Asn Arg Ala
    2465                2470                2475

Trp Thr  Glu Leu Thr Asp Trp  Leu Ser Leu Leu Asp  Gln Val Ile
    2480                2485                2490

Lys Ser  Gln Arg Val Met Val  Gly Asp Leu Glu Asp  Ile Asn Glu
    2495                2500                2505

Met Ile  Ile Lys Gln Lys Ala  Thr Met Gln Asp Leu  Glu Gln Arg
    2510                2515                2520

Arg Pro  Gln Leu Glu Glu Leu  Ile Thr Ala Ala Gln  Asn Leu Lys
    2525                2530                2535

Asn Lys  Thr Ser Asn Gln Glu  Ala Arg Thr Ile Ile  Thr Asp Arg
    2540                2545                2550

Ile Glu  Arg Ile Gln Asn Gln  Trp Asp Glu Val Gln  Glu His Leu
    2555                2560                2565

Gln Asn  Arg Arg Gln Gln Leu  Asn Glu Met Leu Lys  Asp Ser Thr
    2570                2575                2580

Gln Trp  Leu Glu Ala Lys Glu  Glu Ala Glu Gln Val  Leu Gly Gln
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    2585                2590                2595

Ala Arg  Ala Lys Leu Glu Ser  Trp Lys Glu Gly Pro  Tyr Thr Val
    2600                2605                2610

Asp Ala  Ile Gln Lys Lys Ile  Thr Glu Thr Lys Gln  Leu Ala Lys
    2615                2620                2625

Asp Leu  Arg Gln Trp Gln Thr  Asn Val Asp Val Ala  Asn Asp Leu
    2630                2635                2640

Ala Leu  Lys Leu Leu Arg Asp  Tyr Ser Ala Asp Asp  Thr Arg Lys
    2645                2650                2655

Val His  Met Ile Thr Glu Asn  Ile Asn Ala Ser Trp  Arg Ser Ile
    2660                2665                2670

His Lys  Arg Val Ser Glu Arg  Glu Ala Ala Leu Glu  Glu Thr His
    2675                2680                2685

Arg Leu  Leu Gln Gln Phe Pro  Leu Asp Leu Glu Lys  Phe Leu Ala
    2690                2695                2700

Trp Leu  Thr Glu Ala Glu Thr  Thr Ala Asn Val Leu  Gln Asp Ala
    2705                2710                2715

Thr Arg  Lys Glu Arg Leu Leu  Glu Asp Ser Lys Gly  Val Lys Glu
    2720                2725                2730

Leu Met  Lys Gln Trp Gln Asp  Leu Gln Gly Glu Ile  Glu Ala His
    2735                2740                2745

Thr Asp  Val Tyr His Asn Leu  Asp Glu Asn Ser Gln  Lys Ile Leu
    2750                2755                2760

Arg Ser  Leu Glu Gly Ser Asp  Asp Ala Val Leu Leu  Gln Arg Arg
    2765                2770                2775

Leu Asp  Asn Met Asn Phe Lys  Trp Ser Glu Leu Arg  Lys Lys Ser
    2780                2785                2790

Leu Asn  Ile Arg Ser His Leu  Glu Ala Ser Ser Asp  Gln Trp Lys
    2795                2800                2805

Arg Leu  His Leu Ser Leu Gln  Glu Leu Leu Val Trp  Leu Gln Leu
    2810                2815                2820

Lys Asp  Asp Glu Leu Ser Arg  Gln Ala Pro Ile Gly  Gly Asp Phe
    2825                2830                2835

Pro Ala  Val Gln Lys Gln Asn  Asp Val His Arg Ala  Phe Lys Arg
    2840                2845                2850

Glu Leu  Lys Thr Lys Glu Pro  Val Ile Met Ser Thr  Leu Glu Thr
    2855                2860                2865

Val Arg  Ile Phe Leu Thr Glu  Gln Pro Leu Glu Gly  Leu Glu Lys
    2870                2875                2880

Leu Tyr  Gln Glu Pro Arg Glu  Leu Pro Pro Glu Glu  Arg Ala Gln
    2885                2890                2895

Asn Val  Thr Arg Leu Leu Arg  Lys Gln Ala Glu Glu  Val Asn Thr
    2900                2905                2910

Glu Trp  Glu Lys Leu Asn Leu  His Ser Ala Asp Trp  Gln Arg Lys
    2915                2920                2925

Ile Asp  Glu Thr Leu Glu Arg  Leu Gln Glu Leu Gln  Glu Ala Thr
    2930                2935                2940

Asp Glu  Leu Asp Leu Lys Leu  Arg Gln Ala Glu Val  Ile Lys Gly
    2945                2950                2955

Ser Trp  Gln Pro Val Gly Asp  Leu Leu Ile Asp Ser  Leu Gln Asp
    2960                2965                2970
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His Leu  Glu Lys Val Lys Ala  Leu Arg Gly Glu Ile  Ala Pro Leu
    2975                2980                2985

Lys Glu  Asn Val Ser His Val  Asn Asp Leu Ala Arg  Gln Leu Thr
    2990                2995                3000

Thr Leu  Gly Ile Gln Leu Ser  Pro Tyr Asn Leu Ser  Thr Leu Glu
    3005                3010                3015

Asp Leu  Asn Thr Arg Trp Lys  Leu Leu Gln Val Ala  Val Glu Asp
    3020                3025                3030

Arg Val  Arg Gln Leu His Glu  Ala His Arg Asp Phe  Gly Pro Ala
    3035                3040                3045

Ser Gln  His Phe Leu Ser Thr  Ser Val Gln Gly Pro  Trp Glu Arg
    3050                3055                3060

Ala Ile  Ser Pro Asn Lys Val  Pro Tyr Tyr Ile Asn  His Glu Thr
    3065                3070                3075

Gln Thr  Thr Cys Trp Asp His  Pro Lys Met Thr Glu  Leu Tyr Gln
    3080                3085                3090

Ser Leu  Ala Asp Leu Asn Asn  Val Arg Phe Ser Ala  Tyr Arg Thr
    3095                3100                3105

Ala Met  Lys Leu Arg Arg Leu  Gln Lys Ala Leu Cys  Leu Asp Leu
    3110                3115                3120

Leu Ser  Leu Ser Ala Ala Cys  Asp Ala Leu Asp Gln  His Asn Leu
    3125                3130                3135

Lys Gln  Asn Asp Gln Pro Met  Asp Ile Leu Gln Ile  Ile Asn Cys
    3140                3145                3150

Leu Thr  Thr Ile Tyr Asp Arg  Leu Glu Gln Glu His  Asn Asn Leu
    3155                3160                3165

Val Asn  Val Pro Leu Cys Val  Asp Met Cys Leu Asn  Trp Leu Leu
    3170                3175                3180

Asn Val  Tyr Asp Thr Gly Arg  Thr Gly Arg Ile Arg  Val Leu Ser
    3185                3190                3195

Phe Lys  Thr Gly Ile Ile Ser  Leu Cys Lys Ala His  Leu Glu Asp
    3200                3205                3210

Lys Tyr  Arg Tyr Leu Phe Lys  Gln Val Ala Ser Ser  Thr Gly Phe
    3215                3220                3225

Cys Asp  Gln Arg Arg Leu Gly  Leu Leu Leu His Asp  Ser Ile Gln
    3230                3235                3240

Ile Pro  Arg Gln Leu Gly Glu  Val Ala Ser Phe Gly  Gly Ser Asn
    3245                3250                3255

Ile Glu  Pro Ser Val Arg Ser  Cys Phe Gln Phe Ala  Asn Asn Lys
    3260                3265                3270

Pro Glu  Ile Glu Ala Ala Leu  Phe Leu Asp Trp Met  Arg Leu Glu
    3275                3280                3285

Pro Gln  Ser Met Val Trp Leu  Pro Val Leu His Arg  Val Ala Ala
    3290                3295                3300

Ala Glu  Thr Ala Lys His Gln  Ala Lys Cys Asn Ile  Cys Lys Glu
    3305                3310                3315

Cys Pro  Ile Ile Gly Phe Arg  Tyr Arg Ser Leu Lys  His Phe Asn
    3320                3325                3330

Tyr Asp  Ile Cys Gln Ser Cys  Phe Phe Ser Gly Arg  Val Ala Lys
    3335                3340                3345
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Gly His  Lys Met His Tyr Pro  Met Val Glu Tyr Cys  Thr Pro Thr
    3350                3355                3360

Thr Ser  Gly Glu Asp Val Arg  Asp Phe Ala Lys Val  Leu Lys Asn
    3365                3370                3375

Lys Phe  Arg Thr Lys Arg Tyr  Phe Ala Lys His Pro  Arg Met Gly
    3380                3385                3390

Tyr Leu  Pro Val Gln Thr Val  Leu Glu Gly Asp Asn  Met Glu Thr
    3395                3400                3405

Pro Val  Thr Leu Ile Asn Phe  Trp Pro Val Asp Ser  Ala Pro Ala
    3410                3415                3420

Ser Ser  Pro Gln Leu Ser His  Asp Asp Thr His Ser  Arg Ile Glu
    3425                3430                3435

His Tyr  Ala Ser Arg Leu Ala  Glu Met Glu Asn Ser  Asn Gly Ser
    3440                3445                3450

Tyr Leu  Asn Asp Ser Ile Ser  Pro Asn Glu Ser Ile  Asp Asp Glu
    3455                3460                3465

His Leu  Leu Ile Gln His Tyr  Cys Gln Ser Leu Asn  Gln Asp Ser
    3470                3475                3480

Pro Leu  Ser Gln Pro Arg Ser  Pro Ala Gln Ile Leu  Ile Ser Leu
    3485                3490                3495

Glu Ser  Glu Glu Arg Gly Glu  Leu Glu Arg Ile Leu  Ala Asp Leu
    3500                3505                3510

Glu Glu  Glu Asn Arg Asn Leu  Gln Ala Glu Tyr Asp  Arg Leu Lys
    3515                3520                3525

Gln Gln  His Glu His Lys Gly  Leu Ser Pro Leu Pro  Ser Pro Pro
    3530                3535                3540

Glu Met  Met Pro Thr Ser Pro  Gln Ser Pro Arg Asp  Ala Glu Leu
    3545                3550                3555

Ile Ala  Glu Ala Lys Leu Leu  Arg Gln His Lys Gly  Arg Leu Glu
    3560                3565                3570

Ala Arg  Met Gln Ile Leu Glu  Asp His Asn Lys Gln  Leu Glu Ser
    3575                3580                3585

Gln Leu  His Arg Leu Arg Gln  Leu Leu Glu Gln Pro  Gln Ala Glu
    3590                3595                3600

Ala Lys  Val Asn Gly Thr Thr  Val Ser Ser Pro Ser  Thr Ser Leu
    3605                3610                3615

Gln Arg  Ser Asp Ser Ser Gln  Pro Met Leu Leu Arg  Val Val Gly
    3620                3625                3630

Ser Gln  Thr Ser Asp Ser Met  Gly Glu Glu Asp Leu  Leu Ser Pro
    3635                3640                3645

Pro Gln  Asp Thr Ser Thr Gly  Leu Glu Glu Val Met  Glu Gln Leu
    3650                3655                3660

Asn Asn  Ser Phe Pro Ser Ser  Arg Gly Arg Asn Thr  Pro Gly Lys
    3665                3670                3675

Pro Met  Arg Glu Asp Thr Met
    3680                3685


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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

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gcgauuugac agaucuguug agaaauggcg gcguuuucau uaugauauaa agauauuuaa 60

ucaguggcua acagaagcug aacaguuucu cagaaagaca caaauuccug agaauuggga 120

acaugcuaaa uacaaauggu aucuuaag 148

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gaagaaauaa uucagcaauc cucaaaaaca gaugccagua uucuacagga aaaauuggga 120

agccugaauc ugcgguggca ggaggucugc aaacagcugu cagacagaaa aaagag 176

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augguuggag gaagcagaua acauugcuag uaucccacuu gaaccuggaa aagagcagca 120

acuaaaagaa aagcuugagc aagucaag 148

<210> SEQ ID NO 5
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

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ggacccgugc uuguaagugc ucccauaagc ccagaagagc aagauaaacu ugaaaauaag 120

cucaagcaga caaaucucca guggauaaag 150

<210> SEQ ID NO 6
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

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cagcuugaaa aaaagcuuga agaccuugaa gagcaguuaa aucaucugcu gcugugguua 120

ucuccuauua ggaaucaguu ggaaauuuau aaccaaccaa accaagaagg accauuugac 180

guucag 186

<210> SEQ ID NO 7
<211> LENGTH: 102
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

gaaacugaaa uagcaguuca agcuaaacaa ccggaugugg aagagauuuu gucuaaaggg 60

cagcauuugu acaaggaaaa accagccacu cagccaguga ag 102

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<210> SEQ ID NO 8
<211> LENGTH: 109
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

aggaaguuag aagaucugag cucugagugg aaggcgguaa accguuuacu ucaagagcug 60

agggcaaagc agccugaccu agcuccugga cugaccacua uuggagccu 109

<210> SEQ ID NO 9
<211> LENGTH: 233
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

cuccuacuca gacuguuacu cuggugacac aaccuguggu uacuaaggaa acugccaucu 60

ccaaacuaga aaugccaucu uccuugaugu uggagguacc ugcucuggca gauuucaacc 120

gggcuuggac agaacuuacc gacuggcuuu cucugcuuga ucaaguuaua aaaucacaga 180

gggugauggu gggugaccuu gaggauauca acgagaugau caucaagcag aag 233

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<212> TYPE: RNA
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caaaauuuga aaaacaagac cagcaaucaa gaggcuagaa caaucauuac ggaucgaa 118

<210> SEQ ID NO 11
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

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aggucuuagg acaggccaga gccaagcuug agucauggaa ggaggguccc uauacaguag 180

augcaaucca aaagaaaauc acagaaacca ag 212

<210> SEQ ID NO 12
<211> LENGTH: 155
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

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cugaaacuuc uccgggauua uucugcagau gauaccagaa aaguccacau gauaacagag 120

aauaucaaug ccucuuggag aagcauucau aaaag 155

<210> SEQ ID NO 13
<211> LENGTH: 190
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 13

ggugagugag cgagaggcug cuuuggaaga aacucauaga uuacugcaac aguuccccu 60

ggaccuggaa aaguuucuug ccuggcuuac agaagcugaa acaacugcca auguccuaca 120

ggaugcuacc cguaaggaaa ggcuccuaga agacuccaag ggaguaaaag agcugaugaa 180

acaauggcaa 190

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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
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<222> LOCATION: (17)..(17)
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
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<400> SEQUENCE: 14

gnnnnnnnnn nnnngnnnn 19

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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<400> SEQUENCE: 25

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<220> FEATURE:
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<400> SEQUENCE: 26

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<400> SEQUENCE: 29

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<400> SEQUENCE: 39

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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
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<222> LOCATION: (24)..(24)
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine

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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine

<400> SEQUENCE: 45

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<210> SEQ ID NO 46
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<222> LOCATION: (22)..(22)
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<400> SEQUENCE: 46

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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
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<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
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<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<220> FEATURE:
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<220> FEATURE:
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
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<221> NAME/KEY: misc_feature
<222> LOCATION: (23)..(23)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine

<400> SEQUENCE: 47

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<210> SEQ ID NO 48
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<220> FEATURE:
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
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<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine

<400> SEQUENCE: 48

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<210> SEQ ID NO 49
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: Oligonucleotide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<220> FEATURE:
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<222> LOCATION: (23)..(23)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil

<400> SEQUENCE: 49

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<210> SEQ ID NO 50
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (23)..(23)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil

<400> SEQUENCE: 50

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<210> SEQ ID NO 51
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<213> ORGANISM: Artificial
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<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<222> LOCATION: (9)..(8)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: n is a, c, g, or u
<220> FEATURE:
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature

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<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
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<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
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<222> LOCATION: (23)..(23)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (25)..(25)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil

<400> SEQUENCE: 51

nngnngnnnn nggnnnngnn ggngn 25

<210> SEQ ID NO 52
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature

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<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
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<222> LOCATION: (21)..(21)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (23)..(23)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (24)..(24)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (25)..(25)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine

<400> SEQUENCE: 52

gnngnnnnng gnnnngnngg ngnnn 25

<210> SEQ ID NO 53
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<400> SEQUENCE: 55

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<400> SEQUENCE: 56

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<400> SEQUENCE: 58

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<210> SEQ ID NO 59
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<220> FEATURE:
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
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<400> SEQUENCE: 59

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<210> SEQ ID NO 60
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial

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<400> SEQUENCE: 61

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<222> LOCATION: (24)..(24)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine

<400> SEQUENCE: 62

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<210> SEQ ID NO 63
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<220> FEATURE:
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<220> FEATURE:
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<400> SEQUENCE: 63

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<210> SEQ ID NO 64
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<220> FEATURE:
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<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<400> SEQUENCE: 64

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<210> SEQ ID NO 65
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<400> SEQUENCE: 65

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<210> SEQ ID NO 66
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<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
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<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine

<400> SEQUENCE: 66

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<210> SEQ ID NO 67
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<220> FEATURE:
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<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<220> FEATURE:
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<222> LOCATION: (8)..(8)
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
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<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
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<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine

<400> SEQUENCE: 67

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<210> SEQ ID NO 68
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<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine

<400> SEQUENCE: 68

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<210> SEQ ID NO 69
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<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
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<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: n is uracil or 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<400> SEQUENCE: 69

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<400> SEQUENCE: 70

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<220> FEATURE:
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<400> SEQUENCE: 71

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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine

<400> SEQUENCE: 72

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<210> SEQ ID NO 73
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
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<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
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<400> SEQUENCE: 73

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<210> SEQ ID NO 74
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
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<220> FEATURE:
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<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine

<400> SEQUENCE: 74

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<210> SEQ ID NO 75
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<212> TYPE: RNA
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<220> FEATURE:
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<222> LOCATION: (5)..(5)
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<400> SEQUENCE: 75

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<210> SEQ ID NO 76
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<400> SEQUENCE: 76

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<210> SEQ ID NO 77
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
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<400> SEQUENCE: 77

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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
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<400> SEQUENCE: 79

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<210> SEQ ID NO 80
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<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
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<400> SEQUENCE: 80

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<210> SEQ ID NO 81
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<400> SEQUENCE: 82

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<400> SEQUENCE: 83

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<400> SEQUENCE: 84

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<400> SEQUENCE: 85

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<400> SEQUENCE: 86

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<400> SEQUENCE: 88

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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<400> SEQUENCE: 89

nnnnngnngg n 11

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<220> FEATURE:
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<223> OTHER INFORMATION: n is adenine or 2,6-diaminopurine
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<223> OTHER INFORMATION: n is uracil or 5-methyluracil
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<223> OTHER INFORMATION: n is cytosine or 5-methylcytosine
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<400> SEQUENCE: 90

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<210> SEQ ID NO 91
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<212> TYPE: RNA
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<400> SEQUENCE: 91

guugccuccg guucugaagg uguuc 25

<210> SEQ ID NO 92
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<212> TYPE: RNA
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<223> OTHER INFORMATION: 5-methylcytosine
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<400> SEQUENCE: 92

guugnnunng guunugaagg uguun 25

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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 93

caacaucaag gaagauggca uuucu 25

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<212> TYPE: RNA
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<400> SEQUENCE: 94

gccauuucuc aacagaucu 19

<210> SEQ ID NO 95
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 95

ucagcuucug uuagccacug 20

<210> SEQ ID NO 96
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 96

uuuguauuua gcauguuccc 20

<210> SEQ ID NO 97
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 97

auucucagga auuugugucu uuc 23

<210> SEQ ID NO 98
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 98

ccauuuguau uuagcauguu ccc 23

<210> SEQ ID NO 99
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial

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<220> FEATURE:
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<400> SEQUENCE: 99

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<400> SEQUENCE: 100

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<400> SEQUENCE: 101

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<210> SEQ ID NO 102
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<212> TYPE: RNA
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<400> SEQUENCE: 102

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<210> SEQ ID NO 103
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<400> SEQUENCE: 103

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<210> SEQ ID NO 104
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<212> TYPE: RNA
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<400> SEQUENCE: 104

ugccgcugcc caaugccauc cug 23

<210> SEQ ID NO 105
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 105

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ugccgcugcc caaugccauc cugg 24

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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 106

gccgcugccc aaugccaucc ug 22

<210> SEQ ID NO 107
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 107

ccgcugccca augccauccu gg 22

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<220> FEATURE:
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<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: n is inosine

<400> SEQUENCE: 108

uuugccncug cccaaugcca uccug 25

<210> SEQ ID NO 109
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 109

caguuugccg cugcccaaug ccauc 25

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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 110

caguuugccg cugcccaaug ccauccugga 30

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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 111

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ucaaggaaga uggcauuucu 20

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<212> TYPE: RNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 112

uggcauuucu aguuugg 17

<210> SEQ ID NO 113
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 113

caucaaggaa gauggcauuu cu 22

<210> SEQ ID NO 114
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 114

caacaucaag gaagauggca uuucu 25

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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 115

ccucugugau uuuauaacuu gau 23

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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 116

ccagagcagg uaccuccaac auc 23

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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 117

acaucaagga agauggcauu ucuaguuugg 30

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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 118

acaucaagga agauggcauu ucuag 25

<210> SEQ ID NO 119
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<212> TYPE: RNA
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<400> SEQUENCE: 119

cucuugauug cuggucuugu uuuuc 25

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<400> SEQUENCE: 120

gguaaugagu ucuuccaacu gg 22

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<400> SEQUENCE: 121

ucuugauugc uggucuuguu uuuca 25

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<400> SEQUENCE: 122

uuccaacugg ggacgccucu guucc 25

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<400> SEQUENCE: 123

uguucuagcc ucuugauugc ugguc 25

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<213> ORGANISM: Artificial

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<220> FEATURE:
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<400> SEQUENCE: 124

cuguugccuc cgguucug 18

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<212> TYPE: RNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 125

caacuguugc cuccgguucu ga 22

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<212> TYPE: RNA
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<400> SEQUENCE: 126

caacuguugc cuccgguucu gaa 23

<210> SEQ ID NO 127
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 127

caacuguugc cuccgguucu gaag 24

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<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 128

cuguugccuc cgguucugaa gg 22

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<400> SEQUENCE: 129

cuguugccuc cgguucugaa ggu 23

<210> SEQ ID NO 130
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 130

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cuguugccuc cgguucugaa ggug 24

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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 131

cuguugccuc cgguucugaa ggugu 25

<210> SEQ ID NO 132
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 132

guugccuccg guucugaagg uguuc 25

<210> SEQ ID NO 133
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 133

gccuccgguu cugaaggugu ucuug 25

<210> SEQ ID NO 134
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 134

uugccuccgg uucugaaggu guucuuguac 30

<210> SEQ ID NO 135
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 135

cuguugccuc cgguucugaa gguguucuug 30

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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 136

caacuguugc cuccgguucu gaagguguuc uug 33

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<210> SEQ ID NO 137
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 137

gaguuucuuc caaagcagcc ucuc 24

<210> SEQ ID NO 138
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 138

uaugaguuuc uuccaaagca gccuc 25

<210> SEQ ID NO 139
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 139

agcauccugu aggacauugg cagu 24

<210> SEQ ID NO 140
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 140

cauccuguag gacauuggca guug 24

<210> SEQ ID NO 141
<211> LENGTH: 24
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 141

uccuguagga cauuggcagu uguu 24

<210> SEQ ID NO 142
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 142

cuguaggaca uuggcaguug uuuc 24

<210> SEQ ID NO 143
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 143

auuucucaac aga 13

<210> SEQ ID NO 144
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 144

agcuucuguu agcca 15

<210> SEQ ID NO 145
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 145

auucucagga a 11

<210> SEQ ID NO 146
<211> LENGTH: 14
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 146

auuuguauuu agca 14

<210> SEQ ID NO 147
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 147

auuucucaac agaucuguca 20

<210> SEQ ID NO 148
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 148

auuucucaac aga 13

<210> SEQ ID NO 149
<211> LENGTH: 12
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 149

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acagaucugu ca 12

<210> SEQ ID NO 150
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 150

uuugccgcug cccaaugcca 20

<210> SEQ ID NO 151
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 151

cgcugcccaa ugccauccug 20

<210> SEQ ID NO 152
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 152

gccgcugccc aaugccaucc 20

<210> SEQ ID NO 153
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 153

aaggaagaug gca 13

<210> SEQ ID NO 154
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 154

aggaagaugg ca 12

<210> SEQ ID NO 155
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 155

agagcaggua 10

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<210> SEQ ID NO 156
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 156

agcagguacc ucca 14

<210> SEQ ID NO 157
<211> LENGTH: 10
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 157

accuccaaca 10

<210> SEQ ID NO 158
<211> LENGTH: 15
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 158

aaugaguucu uccaa 15

<210> SEQ ID NO 159
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 159

augaguucuu cca 13

<210> SEQ ID NO 160
<211> LENGTH: 10
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 160

aguucuucca 10

<210> SEQ ID NO 161
<211> LENGTH: 10
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 161

agccucuuga 10

<210> SEQ ID NO 162
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial

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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 162

guugccuccg guucugaagg 20

<210> SEQ ID NO 163
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 163

cuccgguucu gaagguguuc 20

<210> SEQ ID NO 164
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 164

ccuccgguuc ugaaggu 17

<210> SEQ ID NO 165
<211> LENGTH: 16
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 165

aguuucuucc aaagca 16

<210> SEQ ID NO 166
<211> LENGTH: 11
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 166

aguuucuucc a 11

<210> SEQ ID NO 167
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 167

agcauccugu aggacauugg ca 22

<210> SEQ ID NO 168
<211> LENGTH: 11
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 168

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agcauccugu a 11

<210> SEQ ID NO 169
<211> LENGTH: 11
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 169

auccuguagg a 11

<210> SEQ ID NO 170
<211> LENGTH: 12
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 170

aggacauugg ca 12

<210> SEQ ID NO 171
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide
<220> FEATURE:
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<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: n is 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: n is 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: n is 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: n is 5-methylcytosine

<400> SEQUENCE: 171

gguaaugagu unuunnaanu gg 22

<210> SEQ ID NO 172
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature

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<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: n is 5-methyluracil

<400> SEQUENCE: 172

ggnaangagn ncnnccaacn gg 22

<210> SEQ ID NO 173
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide
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<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: n is 2,6-diaminopurine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is 2,6-diaminopurine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: n is 2,6-diaminopurine
<220> FEATURE:
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<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: n is 2,6-diaminopurine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: n is 2,6-diaminopurine

<400> SEQUENCE: 173

ggunnugngu ucuuccnncu gg 22

<210> SEQ ID NO 174
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methyluracil
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<223> OTHER INFORMATION: n is 5-methylcytosine
<220> FEATURE:
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<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: n is 5-methyluracil

<400> SEQUENCE: 174

ggnaangagn nnnnnnaann gg 22

<210> SEQ ID NO 175
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide
<220> FEATURE:
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<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: n is 2,6-diaminopurine
<220> FEATURE:
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<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is 2,6-diaminopurine
<220> FEATURE:
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<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: n is 2,6-diaminopurine
<220> FEATURE:
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<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: n is 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 2,6-diaminopurine
<220> FEATURE:
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<223> OTHER INFORMATION: n is 2,6-diaminopurine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: n is 5-methylcytosine

<400> SEQUENCE: 175

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ggunnugngu unuunnnnnu gg 22

<210> SEQ ID NO 176
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<220> FEATURE:
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<220> FEATURE:
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<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
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<223> OTHER INFORMATION: n is 2,6-diaminopurine
<220> FEATURE:
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<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is 2,6-diaminopurine
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<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
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<223> OTHER INFORMATION: n is 2,6-diaminopurine
<220> FEATURE:
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<223> OTHER INFORMATION: n is 5-methyluracil

<400> SEQUENCE: 176

ggnnnngngn ncnnccnncn gg 22

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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<220> FEATURE:
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<222> LOCATION: (3)..(3)
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<223> OTHER INFORMATION: n is 5-methyluracil

<400> SEQUENCE: 177

ggnnnngngn nnnnnnnnnn gg 22

<210> SEQ ID NO 178
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<220> FEATURE:
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine

<400> SEQUENCE: 178

uguunuagnn unuugauugn uggun 25

<210> SEQ ID NO 179
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<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (24)..(24)
<223> OTHER INFORMATION: n is 5-methyluracil

<400> SEQUENCE: 179

ngnncnagcc ncnnganngc nggnc 25

<210> SEQ ID NO 180
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<220> FEATURE:
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<400> SEQUENCE: 180

uguucungcc ucuugnuugc ugguc 25

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<223> OTHER INFORMATION: n is 5-methyluracil
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<223> OTHER INFORMATION: n is 5-methylcytosine

<400> SEQUENCE: 181

ngnnnnagnn nnnnganngn nggnn 25

<210> SEQ ID NO 182
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<223> OTHER INFORMATION: n is 5-methylcytosine

<400> SEQUENCE: 182

uguunungnn unuugnuugn uggun 25

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<223> OTHER INFORMATION: n is 5-methyluracil

<400> SEQUENCE: 183

ngnncnngcc ncnngnnngc nggnc 25

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<222> LOCATION: (3)..(3)
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
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<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (25)..(25)
<223> OTHER INFORMATION: n is 5-methylcytosine

<400> SEQUENCE: 184

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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<220> FEATURE:
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<222> LOCATION: (24)..(24)
<223> OTHER INFORMATION: n is 5-methylcytosine

<400> SEQUENCE: 185

gaguuunuun naaagnagnn unun 24

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<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
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<223> OTHER INFORMATION: n is 5-methyluracil
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<223> OTHER INFORMATION: n is 5-methyluracil
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<223> OTHER INFORMATION: n is 5-methyluracil
<220> FEATURE:
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<222> LOCATION: (23)..(23)
<223> OTHER INFORMATION: n is 5-methyluracil

<400> SEQUENCE: 186

gagnnncnnc caaagcagcc ncnc 24

<210> SEQ ID NO 187
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<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: n is 2,6-diaminopurine
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<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: n is 2,6-diaminopurine

<400> SEQUENCE: 187

gnguuucuuc cnnngcngcc ucuc 24

<210> SEQ ID NO 188
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<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methyluracil
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<223> OTHER INFORMATION: n is 5-methylcytosine

<400> SEQUENCE: 188

gagnnnnnnn naaagnagnn nnnn 24

<210> SEQ ID NO 189
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<223> OTHER INFORMATION: n is 5-methylcytosine

<400> SEQUENCE: 189

gnguuunuun nnnngnngnn unun 24

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<223> OTHER INFORMATION: n is 5-methyluracil
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<400> SEQUENCE: 190

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<210> SEQ ID NO 191
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methyluracil
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<223> OTHER INFORMATION: n is 5-methylcytosine

<400> SEQUENCE: 191

gngnnnnnnn nnnngnngnn nnnn 24

<210> SEQ ID NO 192
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: n is 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine

<400> SEQUENCE: 192

agnaunnugu agganauugg nagu 24

<210> SEQ ID NO 193
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<212> TYPE: RNA
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<223> OTHER INFORMATION: n is 5-methyluracil
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<223> OTHER INFORMATION: n is 5-methyluracil

<400> SEQUENCE: 193

agcanccngn aggacanngg cagn 24

<210> SEQ ID NO 194
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<212> TYPE: RNA
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<223> OTHER INFORMATION: n is 2,6-diaminopurine
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<223> OTHER INFORMATION: n is 2,6-diaminopurine
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<223> OTHER INFORMATION: n is 2,6-diaminopurine
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<400> SEQUENCE: 194

ngcnuccugu nggncnuugg cngu 24

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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methyluracil
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methyluracil

<400> SEQUENCE: 195

agnannnngn agganannggg nagn 24

<210> SEQ ID NO 196
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<212> TYPE: RNA
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<220> FEATURE:
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<222> LOCATION: (21)..(21)
<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 2,6-diaminopurine

<400> SEQUENCE: 196

ngnnunnugu nggnnnuugg nngu 24

<210> SEQ ID NO 197
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: n is 5-methyluracil
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<223> OTHER INFORMATION: n is 5-methyluracil
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<223> OTHER INFORMATION: n is 2,6-diaminopurine
<220> FEATURE:
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<222> LOCATION: (24)..(24)
<223> OTHER INFORMATION: n is 5-methyluracil

<400> SEQUENCE: 197

ngcnnccngn nggncnnngg cngn 24

<210> SEQ ID NO 198
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial

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<223> OTHER INFORMATION: n is 2,6-diaminopurine
<220> FEATURE:
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<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: n is 5-methylcytosine
<220> FEATURE:
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<222> LOCATION: (4)..(4)
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<223> OTHER INFORMATION: n is 5-methyluracil
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methyluracil
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 2,6-diaminopurine
<220> FEATURE:
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<223> OTHER INFORMATION: n is 5-methyluracil

<400> SEQUENCE: 198

ngnnnnnngn nggnnnnngg nngn 24

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<210> SEQ ID NO 199
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
<220> FEATURE:
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<222> LOCATION: (25)..(25)
<223> OTHER INFORMATION: n is 5-methylcytosine

<400> SEQUENCE: 199

guugnnunng guunugaagg uguun 25

<210> SEQ ID NO 200
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
<220> FEATURE:
<221> NAME/KEY: misc_feature

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<222> LOCATION: (22)..(22)
<223> OTHER INFORMATION: n is 5-methylcytosine
<220> FEATURE:
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<223> OTHER INFORMATION: n is 5-methylcytosine

<400> SEQUENCE: 200

uuugnngnug nnnaaugnna unnug 25

<210> SEQ ID NO 201
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<223> OTHER INFORMATION: n is 5-methylcytosine
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<222> LOCATION: (25)..(25)
<223> OTHER INFORMATION: n is 5-methylcytosine

<400> SEQUENCE: 201

nunuugauug nuggunuugu uuuun 25

<210> SEQ ID NO 202
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: n is 5-methyluracil
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<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: n is 5-methyluracil
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<223> OTHER INFORMATION: n is 5-methyluracil
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<223> OTHER INFORMATION: n is 5-methyluracil
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uuugccgcug cccnnugccn uccug 25

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<400> SEQUENCE: 219

guugcnuccg guunugaagg uguun 25

1. An oligonucleotide comprising a 2'-O-methyl RNA monomer and a phosphorothioate backbone and comprising a 5-methyluracil and/or a 5-methylcytosine and/or a 2,6-diaminopurine base, said oligonucleotide being able to induce skipping of an exon of the dystrophin pre-mRNA.

2. An oligonucleotide according to claim **1**, wherein said oligonucleotide comprises a 5-methylcytosine and/or a 5-methyluracil base.

3. An oligonucleotide according to claim **1**, wherein said oligonucleotide comprises a 2,6-diaminopurine base.

4. An oligonucleotide according to claim **1**, wherein said oligonucleotide has an improved parameter by comparison to a corresponding oligonucleotide comprising a 2'-O-methyl RNA monomer and a phosphorothioate backbone without a 5-methylcytosine, and a 5-methyluracil and a 2,6-diaminopurine wherein said improved parameter is selected from the group consisting of: increased binding affinity, longer half-life, increased exon skipping activity, increased biostability, wider (intratissue) distribution, increased cellular uptake, increased trafficking, and/or lower immunogenicity.

5. An oligonucleotide according to claim **1**, wherein the length of said oligonucleotide is less than 34 nucleotides.

6. An oligonucleotide according to claim **1**, wherein said oligonucleotide is reverse complementary to and/or binds to and/or targets and/or hybridizes with at least a part of a dystrophin exon and/or non-exon region.

7. An oligonucleotide according to claim **1**, wherein said oligonucleotide comprises or consists of a sequence which is reverse complementary to and/or binds to and/or targets and/or hybridizes at least a part of dystrophin pre-mRNA exons 44 to 55, said oligonucleotide part having from 10 to 33 nucleotides.

8. An oligonucleotide according to claim **7**, wherein said oligonucleotide comprises a 2'-O-methyl RNA monomer and a phosphorothioate backbone, said oligonucleotide is represented by a nucleotide or a base sequence comprising or consisting of one of SEQ ID NO: 52, 14-51, 53-90 or by a nucleotide sequence comprising or consisting of a fragment of one of SEQ ID NO: 52, 14-51, 53-90 and said oligonucleotide comprises a 5-methyluracil and/or a 5-methylcytosine and/or a 2,6-diaminopurine base.

9. An oligonucleotide according to claim **8**, wherein said oligonucleotide is represented by a nucleotide or a base sequence comprising or consisting of one of SEQ ID NO: 52, 15, 21, 31, 40, 57, or by a nucleotide or a base sequence comprising or consisting of a fragment of one of SEQ ID NO: 52, 15, 21, 31, 40, 57.

10. An oligonucleotide according to claim **8**, wherein said oligonucleotide is represented by a nucleotide or a base sequence comprising or consisting of one of SEQ ID NO:92, 171-215, 217, 218, 219 or by a nucleotide or a base sequence comprising or consisting of a fragment of one of SEQ ID NO: 92, 171-215, 217, 218, 219.

11. An oligonucleotide according to claim **10**, wherein said oligonucleotide is represented by a nucleotide or a base sequence comprising or consisting of one of SEQ ID NO:92, 171, 173, 185, 187, 200, 206, 207, 208, 210, 213, 217, 218 or 219 or by a nucleotide or a base sequence comprising or consisting of a fragment of one of SEQ ID NO: 92, 171, 173, 185, 187, 200, 206, 207, 208, 210, 213, 217, 218 or 219 said fragment comprising or consisting of at least 10 contiguous nucleotides or bases of SEQ ID NO: 92, 171, 173, 185, 187, 200, 206, 207, 208, 210, 213, 217, 218 or 219 and such fragment having a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or 33 nucleotides.

12. A composition comprising an oligonucleotide as defined in claim **1**.

13. A composition according to claim **12**, comprising at least one excipient that may enhance the targeting and/or delivery of said composition and/or said oligonucleotide to a tissue and/or cell and/or into a tissue and/or cell.

14. A method for preventing, treating, and/or delaying Duchenne Muscular Dystrophy or Becker Muscular Dystrophy by administering an oligonucleotide as defined in claim **1** to a subject in the need thereof.

15. A method for preventing, treating, and/or delaying Duchenne Muscular Dystrophy or Becker Muscular Dystrophy by administering a composition as defined in claim **12** to a subject in the need thereof.

* * * * *