SUMMARY

The oligomer of the disclosure may comprise between 10 – 22, such as 12 - 18 nucleotides in length, which either comprises a) contiguous sequence of 10 – 16 nucleotides which are complementary to a corresponding length of SEQ ID NO 33 or 34 or 45, or b) a contiguous sequence of 16 nucleotides which are complementary to a corresponding length of SEQ ID NO 31.

In one aspect, the present disclosure provides a compound consisting of an antisense oligomer that is 16 to 22 contiguous nucleotides in length, wherein the sequence of the antisense oligomer comprises a contiguous sequence 16 nucleotides in length which is 100% complementary to the sequence of SEQ ID NO: 31, wherein the antisense oligomer is a gapmer comprising at least one LNA unit, and wherein the antisense oligomer targets mRNA encoding PCSK9.

The disclosure provides for an antisense oligonucleotide conjugate comprising the oligomer according to the disclosure, and at least one non-nucleotide or non-polynucleotide moiety covalently attached to said oligomer.

The disclosure also provides for an antisense oligonucleotide conjugate comprising the oligomer (A) according to the disclosure, and at least one non-nucleotide or non-polynucleotide moiety covalently attached to said oligomer (C), optionally via a linker region (B and/or Y) positioned between the contiguous sequence of the oligomer and the conjugate moiety.

In some examples, the disclosure also provides for an antisense oligonucleotide conjugate comprising an oligomer of 10 – 22, such as 12 - 18 nucleotides in length, wherein said oligomer comprises a) a contiguous sequence of 10 – 16 nucleotides which are complementary to a corresponding length of SEQ ID NO 33 or 34, or 45 or b) a contiguous sequence of 16 nucleotides which are complementary to a corresponding length of SEQ ID NO 31.

In another aspect, the present disclosure provides an antisense oligonucleotide conjugate comprising:

(i) an antisense oligomer that is 16 to 22 contiguous nucleotides, wherein the sequence of the antisense oligomer comprises a contiguous sequence 16 nucleotides in length which is 100% complementary to the sequence of SEQ ID NO: 31, and wherein the antisense oligomer is a gapmer comprising at least one LNA unit, and

(ii) at least one non-nucleotide or non-polynucleotide moiety covalently attached to said antisense oligomer directly or via a linker positioned between the contiguous oligomer sequence and the non-nucleotide or non-polynucleotide moiety,

wherein the antisense oligonucleotide conjugate targets mRNA encoding PCSK9.

In another aspect, the present disclosure provides an antisense oligonucleotide conjugate of SEQ ID NO: 18 or SEQ ID NO:19





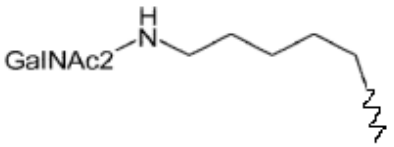
wherein

a superscript ^{L} identifies a beta-D-oxy LNA unit,

a ^{Me}C identifies a 5-methylcytosine unit,

a subscript $_s$ identifies a phosphorothioate internucleoside linkage,

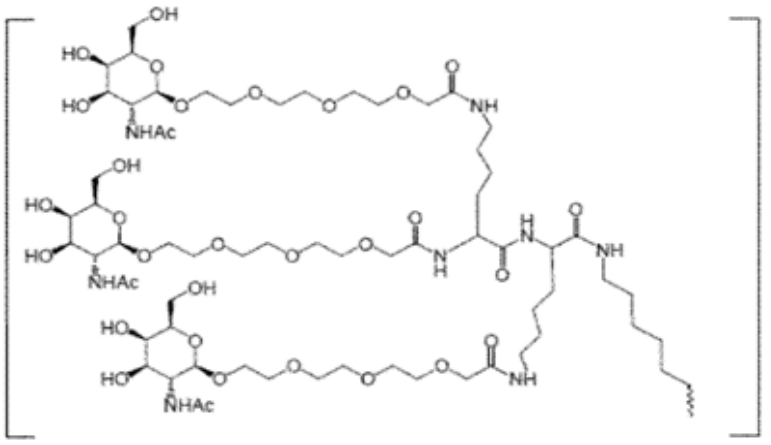
and wherein



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is a Conj 2a asialoglycoprotein receptor targeting conjugate moiety

Conj 2a=



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and wherein the antisense oligonucleotide conjugate targets mRNA encoding PCSK9.

The disclosure also provides for a compound selected from the group consisting of SEQ ID NO 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 17, 16, 18, 19, 20, 21, 22, 23, and 24.

The disclosure provides for a pharmaceutical composition comprising the oligomer or the conjugate according to the disclosure, and a pharmaceutically acceptable diluent, carrier, salt or adjuvant.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as described herein or an antisense oligonucleotide conjugate as described herein and a pharmaceutically acceptable diluent, carrier, salt, or adjuvant.

The disclosure provides for an oligomer or conjugate or pharmaceutical composition according to the disclosure, for use as a medicament, such as for the treatment of hypercholesterolemia or related disorder, such as a disorder selected from the group consisting of atherosclerosis, hyperlipidemia, hypercholesterolemia, familiar hypercholesterolemia *e.g.* gain of function mutations in PCSK9, HDL/LDL cholesterol imbalance, dyslipidemias, *e.g.,* familial hyperlipidemia (FCHL) orfamilial hypercholesterolemia (FHC), acquired hyperlipidemia, statin-resistant hypercholesterolemia, coronary artery disease (CAD), and coronary heart disease (CHD).

The disclosure provides for the use of an oligomer or conjugate or pharmaceutical composition of the disclosure, for the manufacture of a medicament for the treatment of hypercholesterolemia or a related disorder, such as a disorder selected from the group consisting of atherosclerosis, hyperlipidemia, hypercholesterolemia, familiar hypercholesterolemia *e.g.* gain of function mutations in PCSK9, HDL/LDL cholesterol

imbalance, dyslipidemias, *e.g.,* familial hyperlipidemia (FCHL) or familial hypercholesterolemia (FHC), acquired hyperlipidemia, statin-resistant hypercholesterolemia, coronary artery disease (CAD), and coronary heart disease (CHD).

In another aspect, the present disclosure provides use of a compound as described herein, an antisense oligonucleotide conjugate as described herein, or a pharmaceutical composition as described herein in the manufacture of a medicament for treating a disease or condition caused by abnormal expression levels and/or activity of PCSK9 in a subject in need thereof, wherein the abnormal levels and/or activity of PCSK9 are caused by a gene whose protein product is associated with or interacts with PCSK9, and wherein administration of the compound, antisense oligonucleotide conjugate, or pharmaceutical composition reduces the level of serum PCSK9 and/or reduces the level of serum LDL cholesterol.

In another aspect, the present disclosure provides use of a compound as described herein, an antisense oligonucleotide conjugate as described herein, or a pharmaceutical composition as described herein in the manufacture of a medicament for treating a disorder selected from the group consisting of atherosclerosis, hyperlipidemia, hypercholesterolemia, HDL/LDL cholesterol imbalance, coronary artery disease (CAD), or coronary heart disease (CHD) in a subject in need thereof.

In another aspect, the present disclosure provides use of a compound as described herein, an antisense oligonucleotide conjugate as described herein, or a pharmaceutical composition as described herein in the manufacture of a medicament for reducing expression levels and/or activity of PCSK9 in a subject in need thereof.

In another aspect, the present disclosure provides use of a compound as described herein, an antisense oligonucleotide conjugate as described herein, or a pharmaceutical composition as described herein in the manufacture of a medicament for reducing cholesterol levels in a subject in need thereof.

The disclosure provides for a method of treating hypercholesterolemia or a related disorder, such as a disorder selected from the group consisting atherosclerosis, hyperlipidemia, hypercholesterolemia, familiar hypercholesterolemia *e.g.* gain of function mutations in PCSK9, HDL/LDL cholesterol imbalance, dyslipidemias, *e.g.,* familial hyperlipidemia (FCHL) or familial hypercholesterolemia (FHC), acquired hyperlipidemia, statin-resistant hypercholesterolemia, coronary artery disease (CAD), and coronary heart disease (CHD), said method comprising administering an effective amount of an oligomer or conjugate or pharmaceutical composition according to the disclosure, to a patient suffering from, or likely to suffer from hypercholesterolemia or a related disorder.

The disclosure provides for an *in vivo* or *in vitro* method for the inhibition of PCSK9 in a cell which is expressing PCSK9, said method comprising administering an oligomer or conjugate or pharmaceutical composition according to the disclosure to said cell so as to inhibit PCSK9 in said cell.

In another aspect, the present disclosure provides an *in vitro* method of reducing expression levels and/or activity of PCSK9 in a cell comprising administering an effective amount of a compound as described herein, an antisense oligonucleotide conjugate as described herein, or a pharmaceutical composition as described herein to the cell.

The disclosure also provides for an oligomer according to the disclosure, such as an LNA oligomer, comprising a contiguous region of 10 – 22, such as 12 – 18, such as 13, 14, 15, 16 or 17 phosphorothioate linked nucleosides, (i.e. region A, which typically is complementary to a corresponding region of the target sequence, such as SEQ ID NO 46) and further comprising between 1 and 6 DNA nucleosides which are contiguous with the LNA oligomer, wherein the inter-nucleoside linkages between the DNA, and/or adjacent to the DNA nucleoside(s), is physiologically labile, such as is / are phosphodiester linkages. Such an LNA oligomer may be in the form of a conjugate, as described herein, or may, for example be an intermediate to be used in a subsequent conjugation step. When conjugated, the conjugate may, for example be or comprise a sterol, such as cholesterol or tocopherol, or may be or comprise a (non-nucleotide) carbohydrate, such as a GalNAc conjugate, or another conjugate as described herein.

In another aspect, the present disclosure provides a method of manufacturing a compound consisting of an antisense oligomer that is 16 to 26 contiguous nucleotides in length, the method comprising chemically synthesizing the compound using sequential solid phase oligonucleotide synthesis, wherein the sequence of the antisense oligomer comprises a contiguous sequence 16 nucleotides in length which is 100% complementary to the sequence of SEQ ID NO: 31, wherein the antisense oligomer is a gapmer comprising at least one LNA unit, and wherein the antisense oligomer targets mRNA encoding PCSK9.

In another aspect, the present disclosure provides a method of manufacturing an antisense oligonucleotide conjugate comprising covalently attaching at least one non-nucleotide or non-polynucleotide moiety covalently to an antisense oligomer that is 16 to 26 contiguous nucleotides in length directly or via a linker positioned between the antisense oligomer sequence and the non-nucleotide or non-polynucleotide moiety, wherein the sequence of the antisense oligomer comprises a contiguous sequence 16 nucleotides in length which is 100%

complementary to the sequence of SEQ ID NO: 31, wherein the antisense oligomer is a gapmer comprising at least one LNA unit, and wherein the antisense oligonucleotide conjugate targets mRNA encoding PCSK9.

The disclosure also provides a gapmer oligomer which comprises at least one cET, such as (S)-cET nucleotides, of between 10 – 22, such as 12 – 18, such as 13, 14, 15, 16 or 17 nucleotides in length, which targets (*i.e.* has a sequence which is complementary to a corresponding part of) human PCSK9.

BRIEF DESCRIPTION OF FIGURES

Figure 1: Examples of tri-GalNAc conjugates which may be used. Conjugates 1 – 4 illustrate 4 suitable GalNAc conjugate moieties, and conjugates 1a – 4a refer to the same conjugates with an additional linker moiety (Y) which is used to link the conjugate to the oligomer (region A or to