SUMMARY

The oligomer as described herein 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, there is provided an oligomer of between 16 - 20 nucleotides in length, which comprises a contiguous sequence of 16 nucleotides which are complementary to a corresponding length of SEQ ID NO 31.

The disclosure provides for an antisense oligonucleotide conjugate comprising the oligomer as described herein, 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) as described herein, 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 another aspect, there is provided an antisense oligonucleotide conjugate comprising (a) an antisense oligomer (A) of between 16 - 22 nucleotides in length, which comprises a contiguous sequence of 15 – 16 nucleotides which are complementary to a corresponding length of SEQ ID NO 31, and (b) at least one asialoglycoprotein receptor targeting conjugate moiety (C) covalently attached to said oligomer (A).

In some embodiments, 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.

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 as described herein, and a pharmaceutically acceptable diluent, carrier, salt or adjuvant.

In another aspect, there is provided a pharmaceutical composition comprising the oligomer or 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 as described herein, for use as a medicament, such as

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, there is provided the use of an oligomer or antisense oligonucleotide conjugate or pharmaceutical composition as described herein, for the manufacture of a medicament for the treatment of a disorder selected from the group consisting of atherosclerosis, hyperlipidemia, hypercholesterolemia, familiar hypercholesterolemia, HDL/LDL cholesterol imbalance, dyslipidemias, familial hyperlipidemia (FCHL), familial hypercholesterolemia(FHC), acquired hyperlipidemia, statin-resistant hypercholesterolemia, coronary artery disease (CAD), and coronary heart disease (CHD).

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 invention, to a patient suffering from, or likely to suffer from hypercholesterolemia or a related disorder.

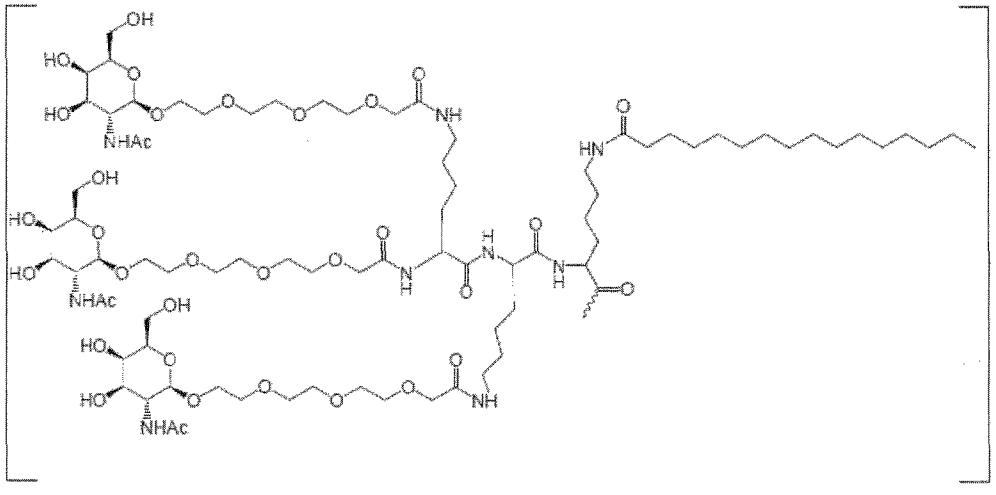
The disclosure provides for an *in vivo* or *in vitro* method for the inhibition of PCSK9 in a cell which is expressing PCSK9, said method comprising administering an oligomer or conjugate or pharmaceutical composition as described herein to said cell so as to inhibit PCSK9 in said cell.

In another aspect, there is provided an *in vitro* method for the inhibition of PCSK9 in a cell which is expressing PCSK9, said method comprising administering an oligomer or antisense oligonucleotide conjugate or pharmaceutical composition as described herein to said cell.

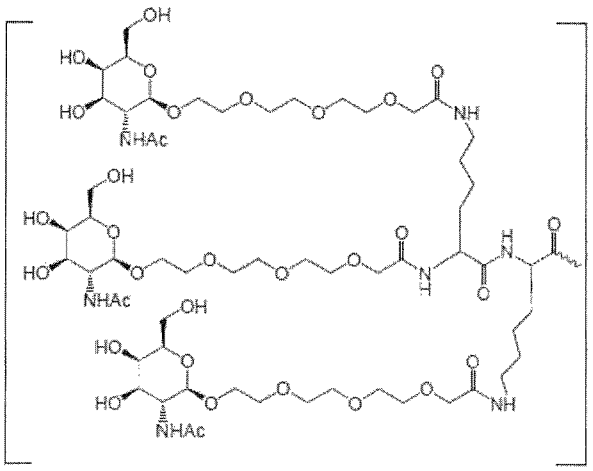
The disclosure also provides for an oligomer as described herein, such as an LNA oligomer, comprising a contiguous region of 10 – 22, such as 12 – 18, such as 13, 14, 15, 16 or 17 phosphorothioate linked nucleosides, (i.e. region A, which typically is complementary to a corresponding region of the target 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

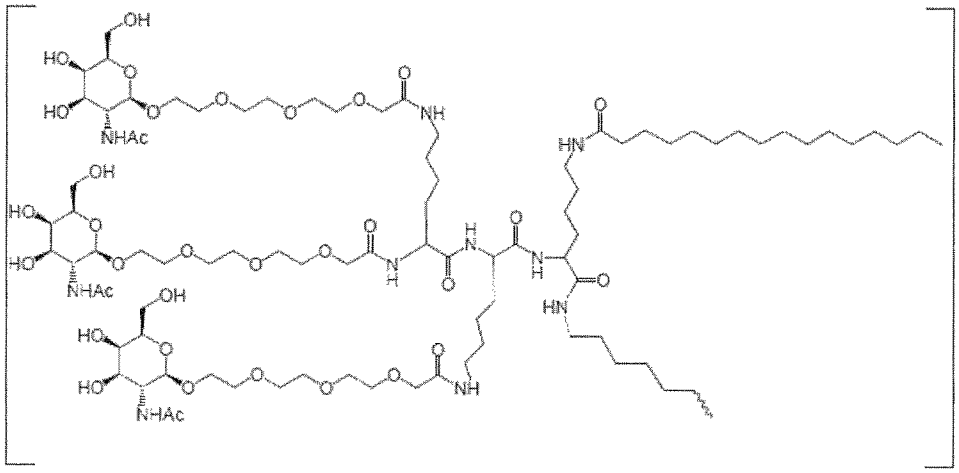
CLAIMS

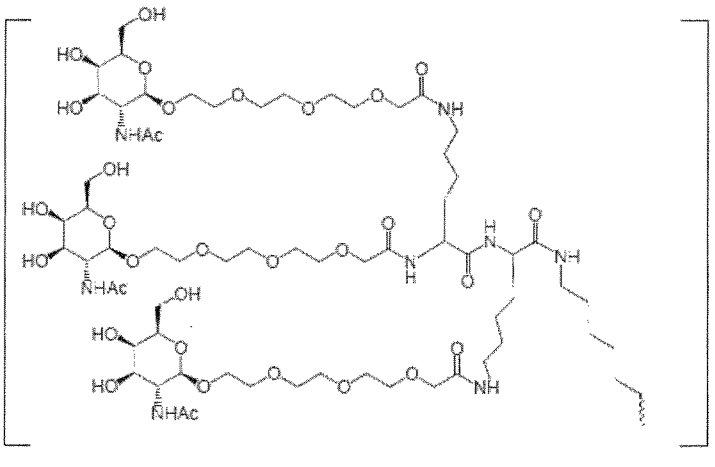
1. An antisense oligonucleotide conjugate comprising
   a. an antisense oligomer (A) of between 16 - 22 nucleotides in length, which comprises a contiguous sequence of 15 – 16 nucleotides which are complementary to a corresponding length of SEQ ID NO 31, and
   b. at least one asialoglycoprotein receptor targeting conjugate moiety (C) covalently attached to said oligomer (A).
2. The oligonucleotide conjugate according to claim 1, wherein the antisense oligomer comprises the contiguous sequence SEQ ID NO 26.
3. The oligonucleotide conjugate according to any one of claims 1 or 2, wherein the antisense oligomer targets PCSK9.
4. The oligonucleotide conjugate according to any one of the claims 1 to 3, wherein the antisense oligomer comprises a contiguous sequence selected from the group consisting of SEQ ID NO 2 and 3.
5. The oligonucleotide conjugate according to any one of the claims 1 to 4, wherein the conjugate moiety (C) comprises an N-acetylgalactosamine (GalNAc), such as a mono-valent, di-valent , tri-valent of tetra-valent GalNAc.
6. The antisense oligonucleotide conjugate according to any one of claims 1 to 5, wherein the conjugate moiety (C) enhances delivery and/or uptake to liver cells.
7. The antisense oligonucleotide conjugate according to any one of claims 1 to 6, wherein the conjugate moiety (C) comprises a trivalent GalNAc.
8. The antisense oligonucleotide conjugate according to claim 7, wherein the three GalNAc moieties are attached to a di-lysine branch point group via PEG spacers, such as those shown

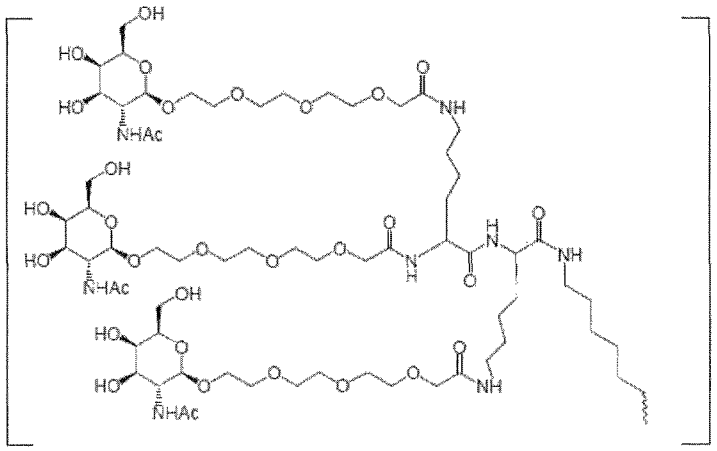
as Conj 1 

,

Conj 2, ,

Conj 1a  or

Conj 2a .

9. The antisense oligonucleotide conjugate according to claim 7 or 8, wherein the conjugate moiety (C) comprises Conj 2a .

10. The antisense oligonucleotide conjugate according to any one of claims 1 to 9, which is selected from the group consisting of SEQ ID NO 18 and 19.

11. The antisense oligonucleotide conjugate according to any one of claims 1 to 10, wherein the antisense oligomer (A) is conjugated to the conjugate moiety (C) via a linker region positioned between the contiguous sequence of the oligomer and the conjugate moiety (B and/or Y).

12. The antisense oligonucleotide conjugate according to claim 0, wherein the linker is selected from a C6 to C12 amino alkyl groups or a biocleavable phosphate nucleotide linker comprising between 1 to 6 nucleotides.

13. The antisense oligonucleotide according to any one of claims 1 to 12 wherein the contiguous sequence comprises affinity enhancing nucleotide analogues.

14. The antisense oligonucleotide according to 13 wherein said nucleotide analogues are sugar modified nucleotides independently or dependently selected from the group consisting of Locked Nucleic Acid (LNA) units, 2'-O-alkyl-RNA units, 2'-OMe-RNA units, 2'-amino-DNA units, and 2'-fluoro-DNA units.

15. An oligomer of between 16 - 20 nucleotides in length, which comprises
    a contiguous sequence of 16 nucleotides which are complementary to a corresponding length of SEQ ID NO 31.

16. The oligomer according to claim 15, which comprises a sequence of 16 nucleotides corresponding to SEQ ID NO 26.

17. The oligomer according any one of claims 15 or 16, wherein the oligomer targets PCSK9.

18. The oligomer according to any one of claims 15 to 17 wherein the contiguous sequence comprises affinity enhancing nucleotide analogues.

19. The oligomer according to 18 wherein said nucleotide analogues are sugar modified nucleotides independently or dependently selected from the group consisting of Locked Nucleic Acid (LNA) units, 2'-O-alkyl-RNA units, 2'-OMe-RNA units, 2'-amino-DNA units, and 2'-fluoro-DNA units.

20. The oligomer according to any one of claims 15 to 18, which is a gapmer.

21. The oligomer according to any one of claims 15 to 20, wherein the oligomer comprises one or more nucleoside linkages selected from the group consisting of phosphorothioate, phosphorodithioate and boranophosphate.

22. The oligomer according to any one of claims 15 to 21, which comprises a contiguous sequence of SEQ ID NO 2 or 3.

23. A pharmaceutical composition comprising the oligomer or antisense oligonucleotide conjugate according to any one of claims 1 to 22 and a pharmaceutically acceptable diluent, carrier, salt or adjuvant.

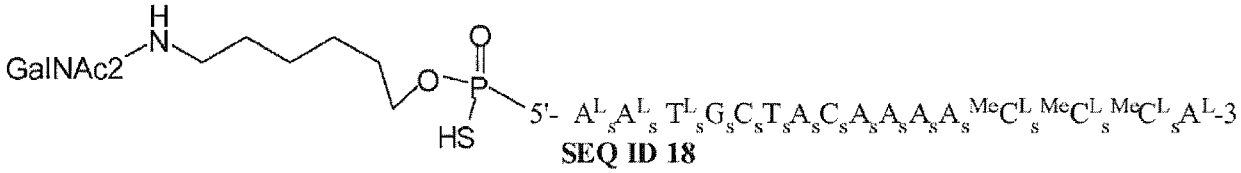
24. The oligomer or antisense oligonucleotide conjugate or pharmaceutical composition according to any one of claims 1 to 23, for use as a medicament, such as for the treatment of hypercholesterolemia or related disorder, such as a disorder selected from the group

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) or familial hypercholesterolemia (FHC), acquired hyperlipidemia, statin-resistant hypercholesterolemia, coronary artery disease (CAD), and coronary heart disease (CHD).

25. The use of an oligomer or antisense oligonucleotide conjugate or pharmaceutical composition according to any one of the claims 1 to 23, for the manufacture of a medicament for the treatment of a disorder selected from the group consisting of atherosclerosis, hyperlipidemia, hypercholesterolemia, familiar hypercholesterolemia, HDL/LDL cholesterol imbalance, dyslipidemias, familial hyperlipidemia (FCHL), familial hypercholesterolemia(FHC), acquired hyperlipidemia, statin-resistant hypercholesterolemia, coronary artery disease (CAD), and coronary heart disease (CHD).

26. An in vitro method for the inhibition of PCSK9 in a cell which is expressing PCSK9, said method comprising administering an oligomer or antisense oligonucleotide conjugate or pharmaceutical composition according to any one of the claims 1 to 23 to said cell.

27. The antisense oligonucleotide conjugate of claim 1, wherein the oligonucleotide conjugate consist of SEQ ID NO:18 or SEQ ID NO:19



SEQ ID 18



SEQ ID 19

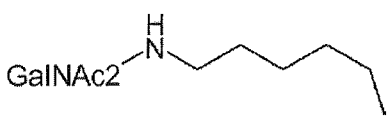
wherein

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

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

a subscript ^{s} identifies a phosphorothioate internucleoside linkage,

and wherein



is a Conj(2a) asialoglycoprotein receptor targeting conjugate moiety

Conj 2a=

