The disclosure provides for an LNA antisense oligomer gapmer (which may be referred to as region A herein) comprising an LNA antisense gapmer oligomer and an asialoglycoprotein receptor targeting conjugate moiety, such as a GalNAc moiety, which may form part of a further region (referred to as region C). The LNA antisense oligomer gapmer may, for example, target a mRNA or viral RNA target.

The disclosure provides for an LNA antisense oligomer mixmer (which may be referred to as region A herein) comprising an LNA antisense mixmer oligomer and an asialoglycoprotein receptor targeting conjugate moiety, such as a GalNAc moiety, which may form part of a further region (referred to as region C). The LNA antisense oligomer mixmer may, for example target a mRNA, such as a mRNA splice site, or a microRNA target.

The disclosure provides for an LNA antisense oligomer totalmer (which may be referred to as region A herein) comprising an LNA antisense totalmer oligomer and an asialoglycoprotein receptor targeting conjugate moiety, such as a GalNAc moiety, which may form part of a further region (referred to as region C). The LNA antisense oligomer mixmer may, for example target a microRNA target.

The LNA antisense oligomer may be 7 – 30, such as 8 – 26, or in some embodiments 8 – 18, nucleosides in length and it comprises at least one LNA unit (nucleoside). The disclosure therefore provides a LNA antisense oligomer conjugate comprising an antisense oligomer and an asialoglycoprotein receptor targeting conjugate moiety, such as a GalNAc moiety, which may form part of a further region (referred to as region C).

The disclosure provides for an LNA antisense oligomer covalently joined to (e.g. linked to) a (non-nucleoside) carbohydrate moiety, such as a carbohydrate conjugate moiety. In some embodiments the carbohydrate moiety is not a linear carbohydrate polymer. The carbohydrate moiety may however be multi-valent, such as, for example 2, 3, 4 or 4 identical or non-identical carbohydrate moieties may be covalently joined to the oligomer, optionally via a linker or linkers.

The disclosure provides for an LNA antisense oligomer (conjugate) comprising an antisense oligomer and a conjugate moiety which comprises a carbohydrate, such as a carbohydrate conjugate moiety.

In one aspect, the disclosure provides for an LNA antisense oligomer conjugate, comprising a single stranded LNA antisense oligomer of 8 – 26 nucleosides in length ~~for use in modulating a nucleic acid~~ and a conjugate moiety which comprises an asialoglycoprotein receptor targeting moiety, covalently bound to the LNA antisense oligomer.

The disclosure provides for the oligomeric compound according to the disclosure for use in the inhibition of a nucleic acid target in a cell. In some embodiments the use is in vitro. In some embodiments the use is in vivo.

The disclosure provides for the oligomeric compound of the disclosure for use in medicine, such as for use as a medicament. In another aspect, the disclosure provides for the LNA antisense oligomer conjugate as defined herein, for use in medicine.

In another aspect, the disclosure provides for the LNA antisense oligomer conjugate as defined herein, for use in down-regulating a liver-expressed RNA.

The disclosure provides for the oligomeric compound of the disclosure for use in the treatment of a medical disease or disorder. In another aspect, the disclosure provides for use of the LNA antisense oligomer conjugate as defined herein in the manufacture of a medicament ~~,~~ for the ~~use in~~ treatment of a metabolic disease or disorder, such as a hepatic disease or disorder.

In another aspect, the present disclosure provides for use of the LNA antisense oligomer conjugate as defined herein in the manufacture of a medicament ~~,~~ for the ~~use in~~ treatment of hepatitis, such as hepatitis B or C.

In another aspect, the present disclosure provides for use of the LNA antisense oligomer conjugate as defined herein~~, for use~~ in the manufacture of a medicament for the treatment of a disease or disorder selected from the group consisting of Alpha-1 antitrypsin liver disease (AAT-LivD), alcohol dependence, anemia, inflammation, CKD, atherosclerosis, atherosclerosis/high Lp(a), liver cancer, cardiometabolic diseases, hemochromatosis, hemophilia A, hemophilia B, hypertriglyceridemia, hyperlipidaemia, Nonalcoholic Steatohepatitis (NASH), porphyria, rare bleeding disorders, Serum amyloid A-amyloidosis (SAA-amyloidosis), thrombosis, acromegaly, hypercholesterolemia, inflammatory disorders, obesity, transthyretin amyloidosis (TTR amyloidosis), type 2 diabetes, Cushing's Syndrome, glucose homeostasis and diabetes~~, such as those defined herein~~.

In another aspect, the present disclosure provides for an *in vitro* method of inhibiting the expression of a target gene in a cell, the method comprising administering the LNA antisense oligomer conjugate as defined herein to a cell which is expressing said target gene, suitably in an amount effective to reduce the expression of the target gene in said cell.

In another aspect, the present disclosure provides for the LNA antisense oligomer conjugate as defined herein for use in inhibiting the expression of a RNA in a liver.

The disclosure provides for the use of the oligomeric compound of the disclosure for the preparation of a medicament for the treatment of a disease or disorder, such as a metabolic disease or disorder. In another aspect, the present disclosure provides for use of

the LNA antisense oligomer conjugate as defined herein in the manufacture of a medicament for the treatment of a liver disease.

The disclosure also provides for an LNA oligomer, comprising a contiguous region of 8 – 24 phosphorothioate linked nucleosides, and further comprising between 1 and 6 DNA nucleosides which are contiguous with the LNA oligomer, wherein the internucleoside 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. When conjugated, the conjugate may, for example a carbohydrate, such as a GalNac conjugate, such as a GalNac cluster, e.g. triGalNac, or another conjugate as described herein.

BRIEF DESCRIPTION OF FIGURES

Figure 1: LNA Oligonucleotide GalNAc conjugation Step

Figure 2: FVII protein levels

Figure 3: FVII mRNA levels

Figure 4a - d: Example 3 - FVII levels in serum

Figure 5a -d: Example 3 - FVII mRNA levels in liver

Figure 6: Example 3 - Oligonucleotide content in liver and kidney

Figure 7a &b: *In vivo* silencing of ApoB mRNA with different monoGalNAc conjugates. Mice were treated with with different ApoB monoGalNAc conjugates either without biocleavable linker, with Dithio-linker (SS) or with DNA/PO-linker (PO) (A) and MonoGalNAc with DNA/PO-linker was compared to GalNAc cluster (B). RNA was isolated from liver (A)and kidney samples (B) and analysed for ApoB mRNA knock down. Data is shown compared to Saline (=1).

Figure 8: Example 5 - ApoB mRNA expression

Figure 9: Example 5 - Total cholesterol in serum

CLAIMS

1. An LNA antisense oligomer conjugate, comprising a single stranded LNA antisense oligomer of 8 – 26 nucleosides in lengthfor use in modulating a nucleic acid and a conjugate moiety which comprises an asialoglycoprotein receptor targeting moiety, covalently bound to the LNA antisense oligomer.
2. The LNA antisense oligomer conjugate according to claim 1, wherein the asialoglycoprotein receptor targeting moiety is selected from the group consisting of galactose, galactosamine, N-formyl-galactosamine, N-acetylgalactosamine, N-propionyl-galactosamine, N-n-butanoyl-galactosamine, and N-isobutanoylgalactose-amine.
3. The LNA antisense conjugate according to claim 1 or 2, wherein the asialoglycoprotein receptor targeting moiety is not Tyr-Glu-Glu-(aminohexyl GalNAc)3 or L3G4 or cholane-based galactose clusters.
4. The LNA antisense conjugate according to any one of claims 1 to 3or 2, wherein the conjugate moiety further comprises a pharmacokinetic modulator selected from the group consisting of C8 – C36 saturated or un-saturated fatty acid, sterol, cholesterol, palmitoyl, hexadec-8-enoyl, oleyl, (9E, 12E)-octadeca-9,12-dienoyl, dioctanoyl, and C16-C20 acyl.
5. The LNA antisense oligomer conjugate according to any one of claims 1 – 43, wherein the conjugate moiety comprises a galactose cluster.
6. The LNA antisense oligomer conjugate according to claim 54, wherein the galactose cluster consists of an N-acetylgalactosamine trimer.
7. The LNA antisense oligomer conjugate according to any one of claims 1 – 65, wherein the conjugate moiety is covalently linked to the oligomer via a physiologically cleavable linker.
8. The LNA antisense oligomer conjugate according to claim 76, wherein the physiologically cleavable linker is selected from the group consisting of, an acid labile linker, a disulphide linker, and a region of phosphodiester linker linked nucleosides (region B).
9. The LNA antisense oligomer conjugate according to any one of claims 4 3 – 87, wherein the pharmacokinetic modulator is attached to the conjugate moiety via a linker, such as a physiologically cleavable linker.
10. The LNA antisense oligomer conjugate of any one of claim 1 - 98, wherein the oligonucleotide has 7 8 – 26 such as 7 8 – 18, 7 8 – 10, 10 – 16, 12 – 14 contiguous nucleosides.
11. The LNA antisense oligomer conjugate of any one of claims 1 – 109, wherein the LNA antisense oligomer is an LNA gapmer, an LNA mixmer, an LNA totalmer, or an LNA tiny oligomer.

~~12.~~11. The LNA antisense oligomer conjugate of any one of claims 1 – ~~10~~9, wherein the LNA antisense has at least 90% phosphorothioate internucleoside linkages.

~~13.~~12. The LNA antisense oligomer conjugate according to any one of claims 1 – ~~12~~11, wherein the oligomer targets a liver-expressed nucleic acid, such as a RNA, such as a liver-expressed mRNA or microRNA or a viral nucleic acid.

~~14.~~13. The LNA antisense oligomer conjugate according to claim ~~13~~12, wherein the liver-expressed RNA is a mRNA, selected from the group consisting of: (complement) FactorVII, complement Factor C6, Bcl2, TTR, PCSK9, ApoB, GCGR, CRP, DGAT2, GCCR, PTEN, PTP1B, SGLT2 and SOD1, or a viral RNA such as hepatitis C or hepatitis B.

~~15.~~14. The LNA antisense oligomer conjugate according to claim ~~13~~ 12 or ~~14~~13, wherein the oligomer is a gapmer or a shortmer oligomer.

~~16.~~15. The LNA antisense oligomer conjugate according to claim ~~13~~12, wherein the oligomer targets a liver-expressed microRNA, such as miR-122.

~~17.~~16. The LNA antisense oligomer conjugate according to claim ~~13~~ 12 or ~~16~~15, wherein the oligomer is between 8 – 18 nucleotides in length.

~~18.~~17. The LNA oligomer conjugate according to any one of the preceeding claims which targets a hepatitis B nucleic acid, such as a HBV DNA and/or RNA sequence.

~~19.~~18. The LNA antisense oligomer conjugate according to any one of the preceeding claims, for use in medicine.

~~20.~~19. The LNA antisense oligomer conjugate according to any one of claims 1 – ~~18~~17, for use in down-regulating a liver-expressed RNA.

~~21.~~20. Use of the ~~The~~ LNA antisense oligomer conjugate according to any one of claims 1 – ~~18~~17 in the manufacture of a medicament ~~,~~ for the ~~use in~~ treatment of a metabolic disease or disorder, such as a hepatic disease or disorder.

~~22.~~21. Use of the ~~The~~ LNA antisense oligomer conjugate according to any one of claims ~~16~~ 15 ~~–~~ ~~18~~17 in the manufacture of a medicament ~~,~~ for the ~~use in~~ treatment of hepatitis, such as hepatitis B or C.

~~23.~~22. Use of the ~~The~~ LNA antisense oligomer conjugate according to any one of claims 1 – ~~18~~17 ~~, for use~~ in the manufacture of a medicament for the treatment of a disease or disorder selected from the group consisting of Alpha-1 antitrypsin liver disease (AAT-LivD), alcohol dependence, anemia, inflammation, CKD, atherosclerosis, atherosclerosis/high Lp(a), liver cancer, cardiometabolic diseases, hemochromatosis, hemophilia A, hemophilia B, hypertriglyceridemia, hyperlipidaemia, Nonalcoholic Steatohepatitis (NASH), porphyria, rare bleeding disorders, Serum amyloid A-amyloidosis (SAA-amyloidosis), thrombosis, acromegaly, hypercholesterolemia, inflammatory disorders, obesity, transthyretin amyloidosis (TTR amyloidosis), type 2 diabetes, Cushing's Syndrome, glucose homeostasis and diabetes~~, such as those defined in any of the claims~~.

~~24.~~23. A pharmaceutical composition comprising the LNA antisense oligomer conjugate according to any one of the proceeding claims, and a pharmaceutically acceptable diluent, carrier, salt or adjuvant.

~~25.~~24. The pharmaceutical composition according to claim ~~24~~23 wherein the composition comprises a buffered saline solution and the LNA antisense oligomer conjugate.

~~26.~~25. An *in vitro* method of inhibiting the expression of a target gene in a cell, said method comprising administering the LNA antisense oligomer conjugate according to any one of the proceeding claims to a cell which is expressing said target gene, suitably in an amount effective to reduce the expression of the target gene in said cell.

~~27.~~26. The LNA antisense oligomer conjugate according to any one of claims 1 - ~~18~~ 17 for use in inhibiting the expression of a RNA in a liver.

~~28.~~27. Use of the LNA antisense oligomer conjugate according to any one of claims 1 - ~~18~~17 in the manufacture of a medicament for the treatment of a liver disease or disorder.