We claim:

1. A double-stranded ribonucleic acid (dsRNA) for inhibiting expression of ALAS1, wherein the dsRNA comprises a sense strand and an antisense strand, wherein the antisense strand comprises a region of complementarity to an ALAS1 RNA transcript , wherein the antisense strand comprises at least 15 contiguous nucleotides from the antisense sequence GAAGAUGAGACACUCUUUCUGGU (SEQ ID NO: 3579).

2. The dsRNA of claim 1, wherein said dsRNA comprises at least one modified nucleotide.

3. The dsRNA of claim 2, wherein the modified nucleotide is selected from the group consisting of: a 2'-O-methyl modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide.

4. The dsRNA of any one of the preceding claims, wherein the dsRNA has one or more of the following:

(a) comprises a duplex region of 15 to 30 base pairs in length;

(b) at least one strand comprises a 3' overhang of at least 2 nucleotides; and/or

(c) each strand is no more than 26 nucleotides in length.

5. The dsRNA of claim 4, wherein the duplex region is 21-23 nucleotide pairs or 21 nucleotide pairs in length.

6. The dsRNA of any one the preceding claims, wherein the antisense strand comprises the sequence of GAAGAUGAGACACUCUUUCUGGU (SEQ ID NO: 3579).

7. The dsRNA of any one the preceding claims, wherein the antisense strand consists of the sequence of GAAGAUGAGACACUCUUUCUGGU (SEQ ID NO: 3579).

8. The dsRNA of any one the preceding claims, wherein the sense strand comprises the sequence of CAGAAAGAGUGUCUCAUCUUC (SEQ ID NO: 3578).

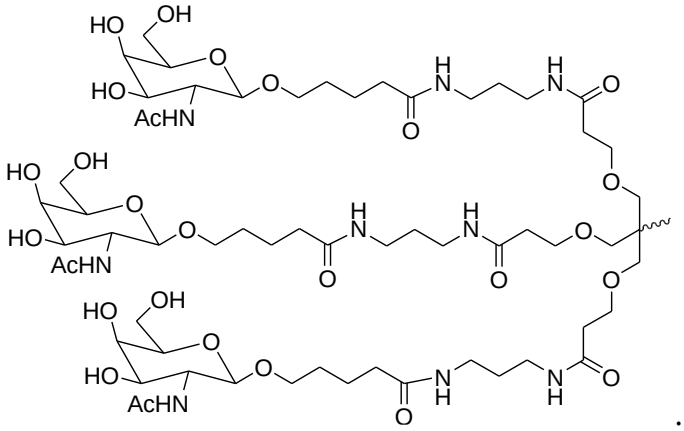
9. The dsRNA of any one the preceding claims, wherein the sense strand consists of the sequence of CAGAAAGAGUGUCUCAUCUUC (SEQ ID NO: 3578).

10. The dsRNA of any one of the preceding claims, further comprising a ligand.

11. The dsRNA of claim 10, wherein the ligand has one or more of the following:
(a) is conjugated to the 3' end of the sense strand of the dsRNA;
(b) comprises a carbohydrate; and/or
(c) targets the dsRNA to hepatocytes.

12. The dsRNA of claim 10, wherein the ligand is a GalNAc ligand.

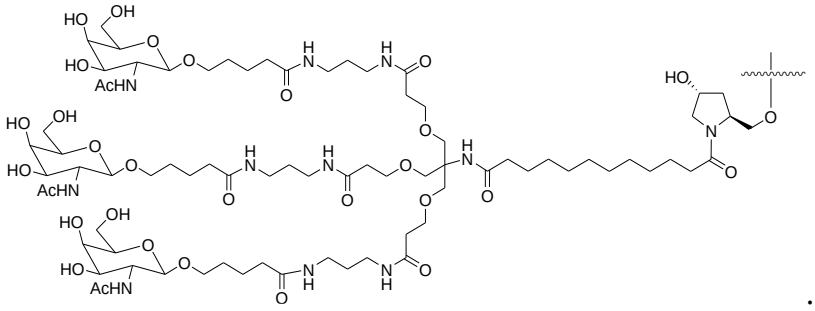
13. The dsRNA of claim 12, wherein the ligand is



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14. The dsRNA of claim 10, wherein the ligand is attached via a bivalent or trivalent branched linker.

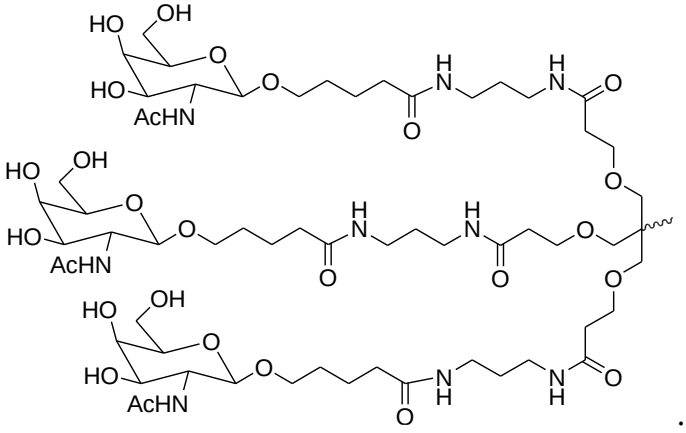
15. The dsRNA of claim 14, wherein the ligand and the linker are as shown in Formula XXIV:



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16. A double-stranded ribonucleic acid (dsRNA) for inhibiting expression of ALAS1, wherein the dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an ALAS1 RNA transcript, wherein the antisense strand comprises the nucleotide sequence of GAAGAUGAGACACUCUUUCUGGU (SEQ ID NO: 3579) and the sense strand comprises the nucleotide sequence of CAGAAAGAGUGUCUCAUCUUC (SEQ ID NO: 3578), wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucloetides selected from a 2'-O-methyl modified nucleotide and a 2'-O-fluoro modified nucleotide and wherein the 3'-end of the sense strand is conjugated to a GalNAc ligand.

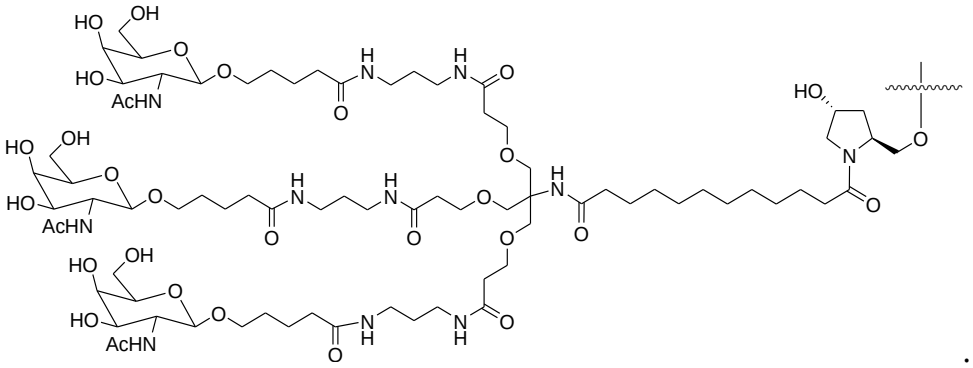
17. The dsRNA of claim 16, wherein the ligand is



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18. The dsRNA of claim 17, wherein the ligand is attached via a bivalent or trivalent branched linker.

19. The dsRNA of claim 18, wherein the ligand and the linker are as shown in Formula XXIV:



20. The dsRNA of claim 1, wherein:

(i) the antisense strand comprises the sequence of usAfsaGfaUfgAfgAfcacUfcUfuUfcUfgsgsu (SEQ ID NO: 4157), and/or the sense strand comprises the sequence of CfsasGfaAfaGfaGfUfGfuCfuCfaUfcUfuAf (SEQ ID NO: 4156);

(ii) the antisense strand consists of the sequence of usAfsaGfaUfgAfgAfcacUfcUfuUfcUfgsgsu (SEQ ID NO: 4157), and/or the sense strand consists of the sequence of CfsasGfaAfaGfaGfUfGfuCfuCfaUfcUfuAf (SEQ ID NO: 4156);

(iii) the antisense strand comprises the sequence of usAfsaGfaUfgAfgAfcacUfcdTuUfcUfgsgsu (SEQ ID NO: 4165), and/or the sense strand comprises the sequence of csasgaaaGfaGfuGfuCfuCfaucuua (SEQ ID NO: 4164); or

(ii) the antisense strand consists of the sequence of usAfsaGfaUfgAfgAfcacUfcdTuUfcUfgsgsu (SEQ ID NO: 4165), and/or the sense strand consists of the sequence of csasgaaaGfaGfuGfuCfuCfaucuua (SEQ ID NO: 4164).

21. A cell comprising the dsRNA of any one of claims 1 to 20.

22. A pharmaceutical composition comprising the dsRNA of any one of claims 1 to 20.

23. The pharmaceutical composition of claim 22, wherein the composition comprises water for injection.

24. The pharmaceutical composition of claim 22 or 23, wherein the composition is suitable for subcutaneous administration.

25. Use of the dsRNA of any one of claims 1 to 20, or the composition of any one of claims 22 to 24, in the manufacture of a medicament treating a porphyria in a subject.

26. The use of claim 25, wherein the porphyria is hepatic porphyria or an acute intermittent porphyria (AIP).

27. The use of claim 26, wherein the porphyria is acute hepatic porphyria.

28. The use of any one of claims 25 to 27, wherein the use has one or more of the following:
(a) the subject is at risk for developing, or is diagnosed with, a porphyria;
(b) the porphyria is acute intermittent porphyria or ALA-dehydratase deficiency porphyria;
(c) (i) the dsRNA or composition comprising dsRNA is to be administered after an acute attack of porphyria; (ii) the dsRNA or composition is to be administered during an acute attack of porphyria, or (iii) the dsRNA or composition is to be administered prophylactically to prevent an acute attack of porphyria;
(d) the dsRNA is to be administered at a dose of 0.05 to 50 mg/kg bodyweight of the subject, or at a dose of 0.01 mg/kg to 5 mg/kg bodyweight of the subject;
(e) the use (i) decreases a level of a porphyrin or a porphyrin precursor in the subject, or wherein the level is decreased by at least 30%; or wherein the level is decreased by at least 40%, and/or (ii) inhibits ALAS1 expression in the subject;
(I) said use (i) ameliorates a symptom associated with an ALAS1 related disorder,

(ii) decreases frequency of acute attacks of symptoms associated with a porphyria in the subject, and/or (v) decreases incidence of acute attacks of symptoms associated with a porphyria in the subject when the subject is exposed to a precipitating factor;

(g) the dsRNA or composition comprising the dsRNA is to be administered according to a dosing regimen; or wherein the dsRNA is to be administered monthly at a dose of 2.5 mg/kg bodyweight of the subject;

(h) the dsRNA is to be administered before an acute attack of porphyria;

(i) the subject has an elevated level of ALA and/or PBG or wherein the subject suffers from chronic pain;

(j) the use decreases the elevated level of ALA and/or PBG;

(k) the use decreases or prevents pain, neuropathy, and/or nerve damage;

(l) the method prevents acute attacks of porphyria; or

(m) the dsRNA or composition comprising the dsRNA is to be administered repeatedly.

29. A dsRNA of any one of claims 1 to 20, or a pharmaceutical composition of any one of claims 22 to 24 for use in treating a disease or disorder.