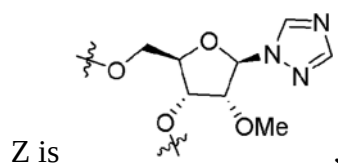


A first example of the present disclosure provides a conjugate of a double-stranded RNAi analog or a pharmaceutically acceptable salt thereof, wherein the double-stranded RNAi analog comprises a sense strand and an antisense strand capable of forming a double-stranded region,

the sense strand is 5'-as,us,Cf,Cf,a,Cf,Af,Af,u,g,a,g,a,g,u,a,c,a-3' (SEQ ID NO:1), and

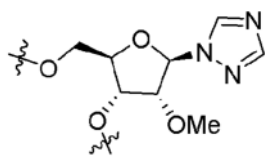
the antisense strand is 3'-a,gs,cs,a,g,u,a,Gf,g,Uf,g,u,u,a,c,u,c,Z,c,a,u,Gfs,us,A,C,A,C,U,C-5' (SEQ ID NO:2),

wherein,



the 5' end and/or 3' end of the sense strand and/or antisense strand is conjugated to a ligand, and the ligand is one or more GalNAc derivatives attached through a divalent, trivalent or tetravalent branched linker.

In one aspect, the present disclosure provides a conjugate of a double-stranded RNAi analog or a pharmaceutically acceptable salt thereof, wherein the double-stranded RNAi analog comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand is 5'-as,us,Cf,Cf,a,Cf,Af,Af,u,g,a,g,a,g,u,a,c,a-3' (SEQ ID NO:1), and the antisense strand is 3'-a,gs,cs,a,g,u,a,Gf,g,Uf,g,u,u,a,c,u,c,Z,c,a,u,Gfs,us,A,C,A,C,U,C-5' (SEQ ID NO:2), wherein, Z is



, the 5' end and/or 3' end of the sense strand and/or antisense strand is conjugated to a ligand, and the ligand is one or more GalNAc derivatives attached through a divalent, trivalent or tetravalent branched linker.

In some examples of the first aspect of the present disclosure, the ligand is one or more GalNAc derivatives attached through a divalent or trivalent branched linker.

In some examples of the first aspect of the present disclosure, the ligand is one or more GalNAc derivatives attached through a trivalent branched linker.

In some examples of the first aspect of the present disclosure, the ligand is a GalNAc derivative attached through a trivalent branched linker.

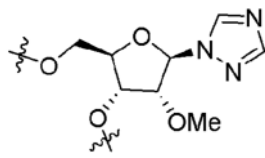
5 A second example of the present disclosure provides a conjugate of a double-stranded RNAi analog or a pharmaceutically acceptable salt thereof, wherein the double-stranded RNAi analog comprises a sense strand and an antisense strand capable of forming a double-stranded region,

the sense strand is 5'-as,us,Cf,Cf,a,Cf,Af,Af,u,g,a,g,a,Gf,u,a,c,a-3' (SEQ ID NO:3), and

the antisense strand is 3'-a,gs,cs,a,g,u,a,Gf,g,Uf,g,u,u,a,c,u,c,**Z**,c,a,u,Gfs,us,A,C,A,C,U,C-5' (SEQ

10 ID NO:2),

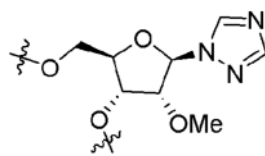
wherein,



wherein Z is

the 5' end and/or 3' end of the sense strand and/or antisense strand is conjugated to a ligand, and the ligand is one or more GalNAc derivatives attached through a divalent, trivalent or tetravalent branched linker.

5 In another aspect, the present disclosure provides a conjugate of a double-stranded RNAi analog or a pharmaceutically acceptable salt thereof, wherein the double-stranded RNAi analog comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand is 5'-as,us,Cf,Cf,a,Cf,Af,Af,u,g,a,g,a,Gf,u,a,c,a-3' (SEQ ID NO:3), and the antisense strand is 3'-a,gs,cs,a,g,u,a,Gf,g,Uf,g,u,u,a,c,u,c,Z,c,a,u,Gfs,us,A,C,A,C,U,C-5' (SEQ ID NO:2),



10 wherein, Z is ; the 5' end and/or 3' end of the sense strand and/or antisense strand is conjugated to a ligand, and the ligand is one or more GalNAc derivatives attached through a divalent, trivalent or tetravalent branched linker.

In some examples of the second aspect of the present disclosure, the ligand is one or more GalNAc derivatives attached through a divalent or trivalent branched linker.

15 In some examples of the second aspect of the present disclosure, the ligand is one or more GalNAc derivatives attached through a trivalent branched linker.

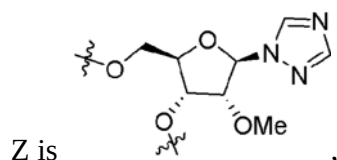
In some examples of the second aspect of the present disclosure, the ligand is a GalNAc derivative attached through a trivalent branched linker.

20 A third example of the present disclosure provides a conjugate of a double-stranded RNAi analog or a pharmaceutically acceptable salt thereof, wherein the double-stranded RNAi analog comprises a sense strand and an antisense strand capable of forming a double-stranded region,

the sense strand is 5'-as,us,Cf,Cf,a,Cf,Af,Af,u,g,a,Gf,a,g,u,a,c,a-3' (SEQ ID NO:4), and

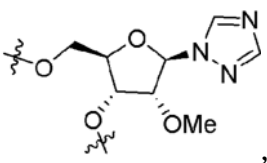
the antisense strand is 3'-a,gs,cs,a,g,u,a,Gf,g,Uf,g,u,u,a,c,u,c,Z,c,a,u,Gfs,us,A,C,A,C,U,C-5' (SEQ ID NO: 2),

wherein,



the 5' end and/or 3' end of the sense strand and/or antisense strand is conjugated to a ligand, and the ligand is one or more GalNAc derivatives attached through a divalent, trivalent or tetravalent branched linker.

In yet another example, the present disclosure provides a conjugate of a double-stranded RNAi analog or a pharmaceutically acceptable salt thereof, wherein the double-stranded RNAi analog comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand is 5'-as,us,Cf,Cf,a,Cf,Af,Af,u,g,a,Gf,a,g,u,a,c,a-3' (SEQ ID NO:4), and the antisense strand is 3'-a,gs,cs,a,g,u,a,Gf,g,Uf,g,u,u,a,c,u,c,Z,c,a,u,Gfs,us,A,C,A,C,U,C-5' (SEQ ID NO: 2),

wherein, Z is , the 5' end and/or 3' end of the sense strand and/or antisense strand is conjugated to a ligand, and the ligand is one or more GalNAc derivatives attached through a divalent, trivalent or tetravalent branched linker.

In some examples of the third aspect of the present disclosure, the ligand is one or more GalNAc derivatives attached through a divalent or trivalent branched linker.

In some examples of the third aspect of the present disclosure, the ligand is one or more GalNAc derivatives attached through a trivalent branched linker.

In some examples of the third aspect of the present disclosure, the ligand is a GalNAc derivative attached through a trivalent branched linker.

5 In some technical examples of the present disclosure, the ligand is conjugated to the 3' end of the sense strand, and other variables are as defined in the present disclosure.

In some technical examples of the present disclosure, the ligand is conjugated to the 5' end of the sense strand, and other variables are as defined in the present disclosure.

10 In some technical examples of the present disclosure, the ligand is conjugated to the 3' end of the antisense strand, and other variables are as defined in the present disclosure.

In some technical examples of the present disclosure, the ligand is conjugated to the 5' end of the antisense strand, and other variables are as defined in the present disclosure.

In some technical examples of the first, second and/or third aspect of the present disclosure, the ligand is conjugated to the 3' end of the sense strand, and other variables are as defined in the present disclosure.

15 In some technical examples of the first, second and/or third aspect of the present disclosure, the ligand is conjugated to the 5' end of the sense strand, and other variables are as defined in the present disclosure.

In some technical examples of the first, second and/or third aspect of the present disclosure, the ligand is conjugated to the 3' end of the antisense strand, and other variables are as defined in the present disclosure.

20 In some technical examples of the first, second and/or third aspect of the present disclosure, the ligand is conjugated to the 5' end of the antisense strand, and other variables are as defined in the present disclosure.

Another example of the present disclosure provides the following conjugates or pharmaceutically acceptable salts thereof,

Conjugate 1:

25

sense strand: 5'-as,us,Cf, Cf,a,Cf, Af,Af,u,g,a,g,a,g,u,a,c,a,D01 (SEQ ID NO:5)

antisense strand: 3'-a,gs,cs,a,g,u,a,Gf,g,Uf,g,u,u,a,c,u,c,Z,c,a,u,Gfs,us,A,C,A,C,U,C-5' (SEQ ID NO:2);

Conjugate 2:

5 sense strand: 5'-as,us,Cf,Cf,a,Cf,Af,Af,u,g,a,g,a,Gf,u,a,c,a,D01 (SEQ ID NO:6)

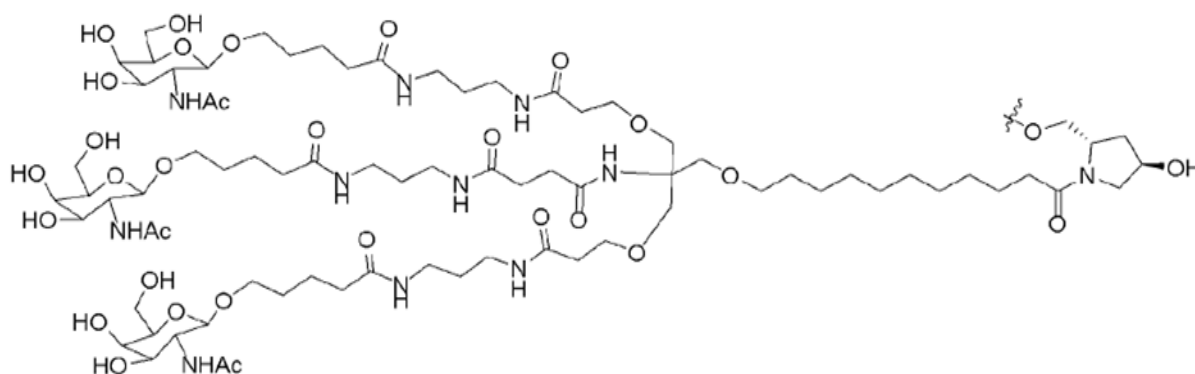
antisense strand: 3'-a,gs,cs,a,g,u,a,Gf,g,Uf,g,u,u,a,c,u,c,Z,c,a,u,Gfs,us,A,C,A,C,U,C-5' (SEQ ID NO:2);

Conjugate 3:

sense strand: 5'-as,us,Cf,Cf,a,Cf,Af,Af,u,g,a,Gf,a,g,u,a,c,a,D01 (SEQ ID NO:7)

10 antisense strand: 3'-a,gs,cs,a,g,u,a,Gf,g,Uf,g,u,u,a,c,u,c,Z,c,a,u,Gfs,us,A,C,A,C,U,C-5' (SEQ ID NO:2);

wherein the structure of the D01 is as follows:



the D01 is linked to a via a phosphodiester bond.

15 Another example of the present disclosure provides a pharmaceutical composition, which comprises an effective dose of a conjugate defined in any technical example mentioned above, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In yet another aspect, the present disclosure provides a pharmaceutical composition comprising an effective dose of the conjugate or pharmaceutically acceptable salt and a pharmaceutically acceptable carrier thereof as disclosed herein.

20 In some examples of the present disclosure, the pharmaceutical composition comprises an effective dose of any one, two, three, four or five conjugates of double-stranded RNAi analogs mentioned above, or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier.

In some examples of the present disclosure, the pharmaceutical composition comprises an effective dose of any one conjugate of double-stranded RNAi analog mentioned above, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

5 Another example of the present disclosure provides use of any conjugate of double-stranded RNAi analog mentioned above, or the pharmaceutically acceptable salt thereof in preparing a drug for treatment of an AGT-related disease.

In yet another aspect, the present disclosure provides a use of the conjugate or pharmaceutically acceptable salt thereof as disclosed herein or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating an AGT-related disease.

10 In some examples of the present disclosure, the AGT-related disease mentioned above is hypertension.

In some examples of the present disclosure, the AGT-related disease mentioned above is a cardiovascular disease.

15 Another example of the present disclosure provides a method for treating an AGT-related disease in a subject in need thereof, comprising administering to the subject an effective dose of conjugate as defined in any technical examples mentioned above, or a pharmaceutically acceptable salt thereof or a pharmaceutical composition.

When the information in the sequence listing of the present disclosure is inconsistent with the specification, the specification shall control.

20 The present disclosure also provides test methods below:

Test method 1: Free uptake experiment of primary human hepatocyte (PHH)

1. Experimental principle:

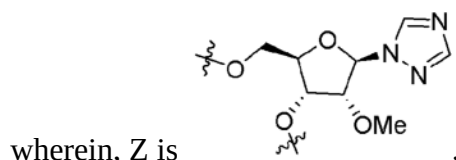
A sample to be tested is incubated with primary human hepatocytes. The downregulation degree of AGT mRNA by the sample to be tested is evaluated.

5 2. Experimental materials:

Primary human hepatocytes (PHH), RNeasy® 96 Kit (12) (QIAGEN-74182), FastKing RT Kit (With gDNase) (Tiangen- KR116-02), TaqMan Gene Expression Assay (GAPDH, Thermo, Assay ID-Hs02786624_g1), TaqMan Gene Expression Assay (AGT, Thermo, Assay ID-Hs01586213_m1).

CLAIMS

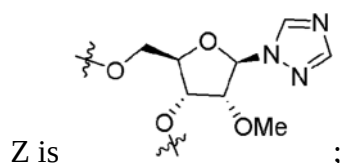
1. A conjugate of a double-stranded RNAi analog or a pharmaceutically acceptable salt thereof, wherein the double-stranded RNAi analog comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand is 5'-as,us,Cf,Cf,a,Cf,Af,Af,u,g,a,g,a,g,u,a,c,a-3' (SEQ ID NO:1), and the antisense strand is 3'-a,gs,cs,a,g,u,a,Gf,g,Uf,g,u,u,a,c,u,c,**Z**,c,a,u,Gfs,us,A,C,A,C,U,C-5' (SEQ ID NO:2),



the 5' end and/or 3' end of the sense strand and/or antisense strand is conjugated to a ligand, and the ligand is one or more GalNAc derivatives attached through a divalent, trivalent or tetravalent branched linker.

2. A conjugate of a double-stranded RNAi analog or a pharmaceutically acceptable salt thereof, wherein the double-stranded RNAi analog comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand is 5'-as,us,Cf,Cf,a,Cf,Af,Af,u,g,a,g,a,Gf,u,a,c,a-3' (SEQ ID NO:3), and the antisense strand is 3'-a,gs,cs,a,g,u,a,Gf,g,Uf,g,u,u,a,c,u,c,**Z**,c,a,u,Gfs,us,A,C,A,C,U,C-5' (SEQ ID NO:2),

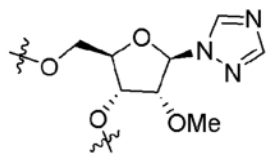
wherein,



the 5' end and/or 3' end of the sense strand and/or antisense strand is conjugated to a ligand, and the ligand is one or more GalNAc derivatives attached through a divalent, trivalent or tetravalent branched linker.

3. A conjugate of a double-stranded RNAi analog or a pharmaceutically acceptable salt thereof, wherein the double-stranded RNAi analog comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand is 5'-

as,us,Cf,Cf,a,Cf,Af,Af,u,g,a,Gf,a,g,u,a,c,a-3' (SEQ ID NO:4), and the antisense strand is 3'-a,gs,cs,a,g,u,a,Gf,g,Uf,g,u,u,a,c,u,c,**Z**,c,a,u,Gfs,us,A,C,A,C,U,C-5' (SEQ ID NO: 2),



wherein, Z is

the 5' end and/or 3' end of the sense strand and/or antisense strand is conjugated to a ligand, and the ligand is one or more GalNAc derivatives attached through a divalent, trivalent or tetravalent branched linker.

4. The conjugate or pharmaceutically acceptable salt thereof according to any one of claims 1-3, wherein the ligand is conjugated at the 3' end of the sense strand.

5. The conjugate or pharmaceutically acceptable salt thereof according to any one of claims 1-3, wherein the ligand is conjugated at the 5' end of the sense strand.

6. The conjugate or pharmaceutically acceptable salt thereof according to any one of claims 1-3, wherein the ligand is conjugated at the 3' end of the antisense strand.

7. The conjugate or pharmaceutically acceptable salt thereof according to any one of claims 1-3, wherein the ligand is conjugated at the 5' end of the antisense strand.

8. The conjugate or pharmaceutically acceptable salt thereof according to any one of claims 1-3, wherein the conjugate is selected from:

Conjugate 1:

sense strand: 5'-as,us,Cf, Cf,a,Cf, Af,Af,u,g,a,g,a,g,u,a,c,a,D01 (SEQ ID NO:5)

antisense strand: 3'-a,gs,cs,a,g,u,a,Gf,g,Uf,g,u,u,a,c,u,c,**Z**,c,a,u,Gfs,us,A,C,A,C,U,C-5' (SEQ ID NO:2);

Conjugate 2:

sense strand: 5'-as,us,Cf,Cf,a,Cf,Af,Af,u,g,a,g,a,Gf,u,a,c,a,D01 (SEQ ID NO:6)

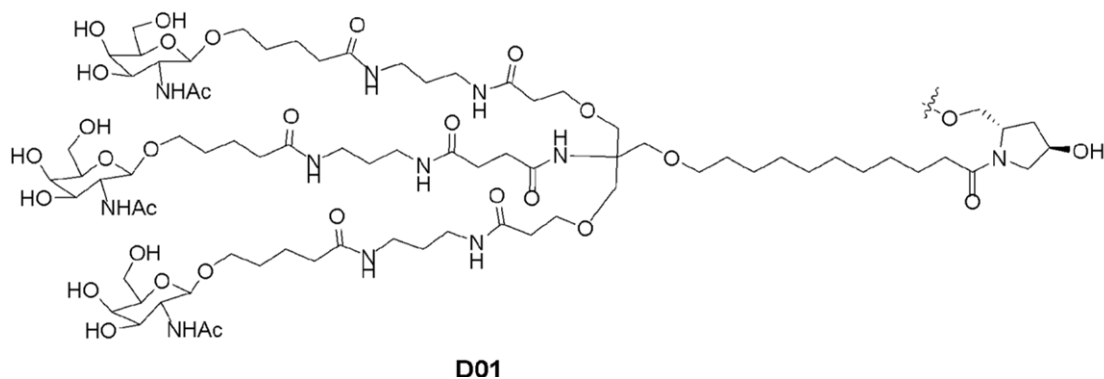
antisense strand: 3'-a,gs,cs,a,g,u,a,Gf,g,Uf,u,u,a,c,u,c,**Z**,c,a,u,Gfs,us,A,C,A,C,U,C-5' (SEQ ID NO:2);

Conjugate 3:

sense strand: 5'-as,us,Cf,Cf,a,Cf,Af,Af,u,g,a,Gf,a,g,u,a,c,a,D01 (SEQ ID NO:7)

antisense strand: 3'-a,gs,cs,a,g,u,a,Gf,g,Uf,g,u,u,a,c,u,c,Z,c,a,u,Gfs,us,A,C,A,C,U,C-5' (SEQ ID NO:2);

wherein, the structure of the D01 is as follows:



the D01 is linked to a via a phosphodiester bond.

9. A pharmaceutical composition comprising an effective dose of the conjugate or pharmaceutically acceptable salt and a pharmaceutically acceptable carrier thereof of any one of claims 1-8.

10. The pharmaceutical composition of claim 9, further comprising a pharmaceutically acceptable carrier.

11. Use of the conjugate or pharmaceutically acceptable salt thereof of any one of claims 1-8 or the pharmaceutical composition of any one of claims 9-10, in the manufacture of a medicament for treating an AGT-related disease.

12. The use of claim 11, wherein the AGT-related disease is hypertension.

13. The use of claim 11, wherein the AGT-related disease is a cardiovascular disease.