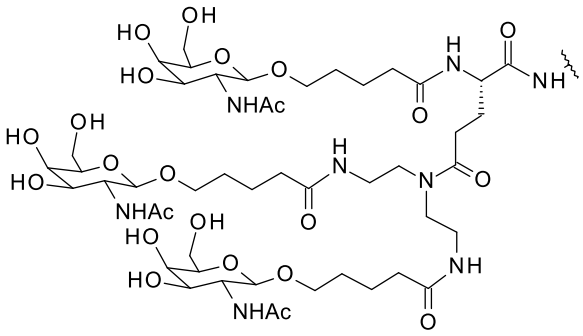
targeting ANGPTL8 have been described, e.g., WO2020104649. However, only four siRNA molecules are approved for use in humans, and no therapeutic siRNAs targeting ANGPTL8 are yet approved. Moreover, limited information is available preclinically and clinically about the ideal attributes for a therapeutic siRNA in vivo, especially for diseases of the liver or involving the liver such as cardiovascular disease, dyslipidemia, e.g. high triglycerides, and inflammatory liver diseases.

There remains a need to provide alternative RNAi agents comprising a delivery moiety comprising GalNAc and one or more oligonucleotides to decrease ANGPTL8 expression. More particularly, there is a need to provide RNAi agents comprising a novel GalNAc delivery moiety and a sense strand and an antisense strand, wherein the antisense strand is complementary to ANGPTL8 mRNA, wherein such an RNAi agent exhibits one or more of: improved tissue exposure, suitably improved exposure in the liver; improved liver to kidney exposure ratios; improved knockdown; an improved durable response; an improved pharmacokinetic profile; fewer off target effects; an improved toxicity profile; an improved safety profile, fewer side effects, improved tolerability, improved control of cholesterol and/or triglyceride levels in a patient, improved cardiovascular risk profile in a patient, improved and/or simplified synthesis, synthetic processes with fewer degradation products, or any combination thereof.

Summary

In a first aspect of the present disclosure, there is provided an RNA interference (RNAi) agent comprising a delivery moiety of Formula I conjugated to R:



Formula I,

wherein R comprises a sense strand and an antisense strand,

wherein the antisense strand comprises at least 15 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs: 405-525, and wherein the sense strand and the antisense strand form a region of complementarity of at least 15 nucleotides, and wherein the sense strand and antisense strand are each independently 18 to 23 nucleotides in length, and optionally wherein the sense strand and antisense strand each independently comprise one or more modified nucleotides, and optionally wherein the sense strand and the antisense strand each independently comprise one or more modified internucleotide linkages, and wherein R is optionally conjugated to Formula I via a linker.

In another aspect of the present disclosure, there is provided the RNAi agent as disclosed herein, for use in therapy.

In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the RNAi agent as disclosed herein, and one or more pharmaceutically acceptable excipients.

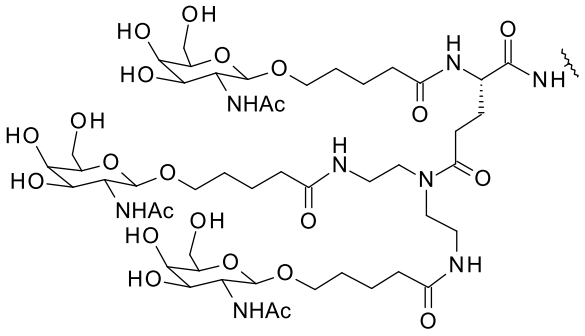
In a further aspect of the present disclosure, there is provided a use of the RNAi agent as disclosed herein in the manufacture of a medicament for the treatment of dyslipidemia.

Description

In one embodiment of the present disclosure is an RNA interference (RNAi) agent comprising a delivery moiety of Formula I:

What is Claimed is

1. An RNA interference (RNAi) agent comprising a delivery moiety of Formula I conjugated to R:



Formula I,

wherein R comprises a sense strand and an antisense strand,
wherein the antisense strand comprises at least 15 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs: 405-525, and wherein the sense strand and the antisense strand form a region of complementarity of at least 15 nucleotides, and wherein the sense strand and antisense strand are each independently 18 to 23 nucleotides in length, and optionally wherein the sense strand and antisense strand each independently comprise one or more modified nucleotides, and optionally wherein the sense strand and the antisense strand each independently comprise one or more modified internucleotide linkages, and wherein R is optionally conjugated to Formula I via a linker.

2. The RNAi agent of claim 1, wherein the antisense strand comprises at least 18 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs: 405-525.

3. The RNAi agent of claim 1 or 2, wherein the antisense strand comprises at least 18 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs: 405, 408, 412, 413, 414, 415, 418, 420, 425, 426, 428, 429, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 448, 449, 451, 452, 454, 457, 458, 459, 463, 464, 465, 466, 467, 468, 469, 471, 472, 473, 474, 475, 476, 479, 490, 491, 492, 493, 495, 499, 500, 501,502, 503, 504, 505, 506, 507, 508, and 509.

4. The RNAi agent of any one of claims 1 to 3, wherein the antisense strand is 23 nucleotides in length.

5. The RNAi agent of any one of claims 1 to 4, wherein the sense strand is 21 nucleotides in length.

6. The RNAi agent of any one of claims 1 to 5, wherein the antisense strand is selected from the group consisting of SEQ ID NOs: 231-361, or a sequence having at least 90% sequence identity thereto.

7. The RNAi agent of any one of claims 1 to 6, wherein the sense strand is selected from the group consisting of SEQ ID NOs: 124-230, or a sequence having at least 90% sequence identity thereto.

8. The RNAi agent of any one of claims 1 to 7, wherein, in the region of complementarity comprises 0, 1, 2, or 3 mismatches between the sense strand and the antisense strand.

9. The RNAi agent of any one of claims 1 to 8, wherein the sense strand and the antisense strand each independently comprise one or more modified nucleotides and the one or more modified nucleotides are independently 2’ fluoro modified nucleotides or 2’-O-methyl modified nucleotides.

10. The RNAi agent of any one of claims 1 to 9, wherein each nucleotide of the sense strand and each nucleotide of the antisense strand is a modified nucleotide.

11. The RNAi agent of any one of claims 1 to 10, wherein the sense strand and antisense strand each independently comprise one or more modified internucleotide linkages, and wherein each modified internucleotide linkage is a phosphorothioate linkage.

12. The RNAi agent of claim 11, wherein the sense strand and antisense strand each independently comprise four phosphorothioate linkages.

13. The RNAi agent of any one of claims 1 to 12, wherein the 5' nucleotide of the antisense strand comprises a phosphate group or a phosphate analog.

14. The RNAi agent of any one of claims 1 to 13, wherein the antisense strand comprises a sequence selected from the group consisting of SEQ ID NOs: 367-372 and 389-404, or a sequence having at least 90% sequence identity thereto.

15. The RNAi agent of any one of claims 1 to 13, wherein the sense strand comprises a sequence selected from the group consisting of SEQ ID NOs: 361-366 and 373-388, or a sequence having at least 90% sequence identity thereto.

16. The RNAi agent of any one of claims 1 to 15, wherein the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:

a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 90% sequence identity thereto;

b. a sense strand having the sequence set forth in SEQ ID NO:362, or a sequence having at least 90% sequence identity thereto, and the antisense

strand having the sequence set forth in SEQ ID NO:368, or a sequence having at least 90% sequence identity thereto;

c. a sense strand having the sequence set forth in SEQ ID NO:363, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:369, or a sequence having at least 90% sequence identity thereto;

d. a sense strand having the sequence set forth in SEQ ID NO:364, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:370, or a sequence having at least 90% sequence identity thereto;

e. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 90% sequence identity thereto;

f. a sense strand having the sequence set forth in SEQ ID NO:366, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:372, or a sequence having at least 90% sequence identity thereto;

g. a sense strand having the sequence set forth in SEQ ID NO:373, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:389, or a sequence having at least 90% sequence identity thereto;

h. a sense strand having the sequence set forth in SEQ ID NO:374, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO: 390 or a sequence having at least 90% sequence identity thereto;

i. a sense strand having the sequence set forth in SEQ ID NO:375, or a sequence having at least 90% sequence identity thereto, and an antisense

strand having the sequence set forth in SEQ ID NO:391, or a sequence having at least 90% sequence identity thereto;

j. a sense strand having the sequence set forth in SEQ ID NO:376, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:392, or a sequence having at least 90% sequence identity thereto;

k. a sense strand having the sequence set forth in SEQ ID NO:377, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:393, or a sequence having at least 90% sequence identity thereto;

l. a sense strand having the sequence set forth in SEQ ID NO:378, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:394, or a sequence having at least 90% sequence identity thereto;

m. a sense strand having the sequence set forth in SEQ ID NO:379, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:395, or a sequence having at least 90% sequence identity thereto;

n. a sense strand having the sequence set forth in SEQ ID NO:380 or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:396, or a sequence having at least 90% sequence identity thereto;

o. a sense strand having the sequence set forth in SEQ ID NO: 381, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:396, or a sequence having at least 90% sequence identity thereto;

p. a sense strand having the sequence set forth in SEQ ID NO:382, or a sequence having at least 90% sequence identity thereto, and an antisense

strand having the sequence set forth in SEQ ID NO:397, or a sequence having at least 90% sequence identity thereto;

q. a sense strand having the sequence set forth in SEQ ID NO:383, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:398, or a sequence having at least 90% sequence identity thereto;

r. a sense strand having the sequence set forth in SEQ ID NO:384, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:399, or a sequence having at least 90% sequence identity thereto;

s. a sense strand having the sequence set forth in SEQ ID NO:385, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:400, or a sequence having at least 90% sequence identity thereto;

t. a sense strand having the sequence set forth in SEQ ID NO:386, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:401, or a sequence having at least 90% sequence identity thereto;

u. a sense strand having the sequence set forth in SEQ ID NO:387, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:402, or a sequence having at least 90% sequence identity thereto;

v. a sense strand having the sequence set forth in SEQ ID NO:388, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:403, or a sequence having at least 90% sequence identity thereto; and

w. a sense strand having the sequence set forth in SEQ ID NO:389, or a sequence having at least 90% sequence identity thereto, and an antisense

strand having the sequence set forth in SEQ ID NO:404, or a sequence having at least 90% sequence identity thereto.

17. The RNAi agent of any one of claims 1 to 16, wherein the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:

a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 95% sequence identity thereto;

b. a sense strand having the sequence set forth in SEQ ID NO:362, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:368, or a sequence having at least 95% sequence identity thereto;

c. a sense strand having the sequence set forth in SEQ ID NO:363, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:369, or a sequence having at least 95% sequence identity thereto;

d. a sense strand having the sequence set forth in SEQ ID NO:364, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:370, or a sequence having at least 95% sequence identity thereto;

e. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 95% sequence identity thereto;

f. a sense strand having the sequence set forth in SEQ ID NO:366, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:372, or a sequence having at least 95% sequence identity thereto;

g. a sense strand having the sequence set forth in SEQ ID NO:373, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:389, or a sequence having at least 95% sequence identity thereto;

h. a sense strand having the sequence set forth in SEQ ID NO:374, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO: 390 or a sequence having at least 95% sequence identity thereto;

i. a sense strand having the sequence set forth in SEQ ID NO:375, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:391, or a sequence having at least 95% sequence identity thereto;

j. a sense strand having the sequence set forth in SEQ ID NO:376, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:392, or a sequence having at least 95% sequence identity thereto;

k. a sense strand having the sequence set forth in SEQ ID NO:377, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:393, or a sequence having at least 95% sequence identity thereto;

l. a sense strand having the sequence set forth in SEQ ID NO:378, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:394, or a sequence having at least 95% sequence identity thereto;

m. a sense strand having the sequence set forth in SEQ ID NO:379, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:395, or a sequence having at least 95% sequence identity thereto;

n. a sense strand having the sequence set forth in SEQ ID NO:380 or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:396, or a sequence having at least 95% sequence identity thereto;

o. a sense strand having the sequence set forth in SEQ ID NO: 381, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:396, or a sequence having at least 95% sequence identity thereto;

p. a sense strand having the sequence set forth in SEQ ID NO:382, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:397, or a sequence having at least 95% sequence identity thereto;

q. a sense strand having the sequence set forth in SEQ ID NO:383, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:398, or a sequence having at least 95% sequence identity thereto;

r. a sense strand having the sequence set forth in SEQ ID NO:384, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:399, or a sequence having at least 95% sequence identity thereto;

s. a sense strand having the sequence set forth in SEQ ID NO:385, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:400, or a sequence having at least 95% sequence identity thereto;

t. a sense strand having the sequence set forth in SEQ ID NO:386, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:401, or a sequence having at least 95% sequence identity thereto;

u. a sense strand having the sequence set forth in SEQ ID NO:387, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:402, or a sequence having at least 95% sequence identity thereto;

v. a sense strand having the sequence set forth in SEQ ID NO:388, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:403, or a sequence having at least 95% sequence identity thereto; and

w. a sense strand having the sequence set forth in SEQ ID NO:389, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:404, or a sequence having at least 95% sequence identity thereto.

18. The RNAi agent of any one of claims 1-16, wherein the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:

a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 90% sequence identity thereto;

b. a sense strand having the sequence set forth in SEQ ID NO:362, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:368, or a sequence having at least 90% sequence identity thereto;

c. a sense strand having the sequence set forth in SEQ ID NO:363, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:369, or a sequence having at least 90% sequence identity thereto;

d. a sense strand having the sequence set forth in SEQ ID NO:364, or a sequence having at least 90% sequence identity thereto, and the antisense

strand having the sequence set forth in SEQ ID NO:370, or a sequence having at least 90% sequence identity thereto; and

e. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 90% sequence identity thereto.

19. The RNAi agent of any one claims 1 to 16 or claim 18, wherein the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:

a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 95% sequence identity thereto;

b. a sense strand having the sequence set forth in SEQ ID NO:362, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:368, or a sequence having at least 95% sequence identity thereto;

c. a sense strand having the sequence set forth in SEQ ID NO:363, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:369, or a sequence having at least 95% sequence identity thereto;

d. a sense strand having the sequence set forth in SEQ ID NO:364, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:370, or a sequence having at least 95% sequence identity thereto; and

e. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 95% sequence identity thereto, and the antisense

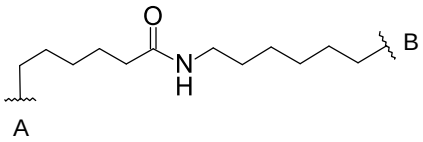
strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 95% sequence identity thereto.

20. The RNAi agent of any one of claims 1 to 18, wherein the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:
    a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 90% sequence identity thereto; and
    b. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 90% sequence identity thereto.

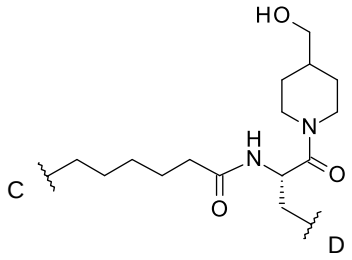
21. The RNAi agent of any one of claims 1 to 20, wherein the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:
    a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 95% sequence identity thereto; and
    b. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 95% sequence identity thereto.

22. The RNAi agent of any one of the claims 1 to 21, wherein R is conjugated to Formula I via a linker.

23. The RNAi agent of claim 22, wherein R is conjugated to Formula I via a linker, and wherein linker comprises a linker of Formula II having connection points A and B or the linker comprises Formula III having connection points C and D, and wherein connection point A or connection point C is conjugated to Formula I and connection point B or connection point D is conjugated to a phosphate group which is conjugated to R;

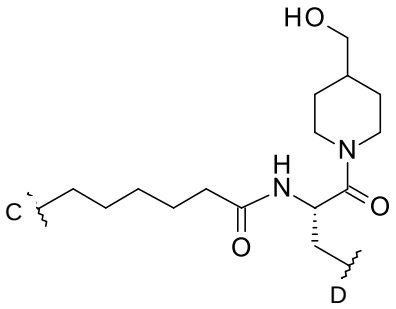


Formula II;



Formula III.

24. The RNAi agent of any one of claims 1 to 23, wherein R is conjugated to Formula I via a linker, and wherein the linker is a linker comprising Formula III having connection points C and D, and wherein connection point C is conjugated to Formula I and connection point D is conjugated to a phosphate group which is conjugated to R;



Formula III.

25. The RNAi agent of any one of claims 1 to 24, wherein the sense strand and the antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:
    a. a sense strand consisting of the sequence set forth in SEQ ID NO:361 and an antisense strand consisting of the sequence set forth in SEQ ID NO:367; and
    b. a sense strand consisting of the sequence set forth in SEQ ID NO:365 and an antisense strand consisting of the sequence set forth in SEQ ID NO:371,

26. The RNAi agent of any one of claims 1 to 25, wherein the RNAi agent is capable of decreasing expression of the ANGPTL8 gene in a liver cell.

27. The RNAi agent of any one of claims 1 to 26, for use in therapy.

28. A pharmaceutical composition comprising the RNAi agent of any one of claims 1-26, and one or more pharmaceutically acceptable excipients.

29. Use of the RNAi agent of any one of claims 1-26 in the manufacture of a medicament for the treatment of dyslipidemia.