In one embodiment, the methods further include plasma infusion in the subject. In one embodiment, eculizumab is administered to the subject at a dose less than about 300 mg.

In one embodiment, eculizumab is administered to the subject at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 15 mg/kg. In another embodiment, eculizumab is administered to the subject at a dose of about 5 mg/kg to about 15 mg/kg.

In another embodiment, eculizumab is administered to the subject at a dose selected from the group consisting of 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 3 mg/kg, 5 mg/kg, 7 mg/kg, 10 mg/kg, and 30 mg/kg.

In one embodiment, eculizumab is administered to the subject via an intravenous infusion. In another embodiment, eculizumab is administered to the subject subcutaneously.

In one embodiment, the dsRNA agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 15 mg/kg.

In one embodiment, the dsRNA agent is administered at a dose of about 10 mg/kg to about 30 mg/kg. In another embodiment,the dsRNA agent is administered at a dose selected from the group consisting of 0.5 mg/kg 1 mg/kg, 1.5 mg/kg, 3 mg/kg, 5 mg/kg, 10 mg/kg, and 30 mg/kg.

In one embodiment, the dsRNA agent is administered to the subject once a week. In another embodiment, the dsRNA agent is administered to the subject twice a week. In another embodiment, the dsRNA agent is administered to the subject twice a month.

In one embodiment, the dsRNA agent is administered to the subject subcutaneously.

In one embodiment, the dsRNA agent and the eculizumab are administered to the subject subcutaneously. In another embodiment, the dsRNA agent and the eculizumab are administered to the subject simultaneously.

In one embodiment, the dsRNA agent is administered to the subject first for a period of time sufficient to reduce the levels of complement component C5 in the subject, and eculizumab is administered subsequently at a dose less than about 600 mg.

In one embodiment, the levels of complement component C5 in the subject are reduced by at least about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90%.

In one embodiment, eculizumab is administered at a dose of about 100-500 mg.

In one embodiment, the dsRNA agent is conjugated to a ligand.

In one embodiment, the ligand is conjugated to the 3'- end of the sense strand of the dsRNA agent.

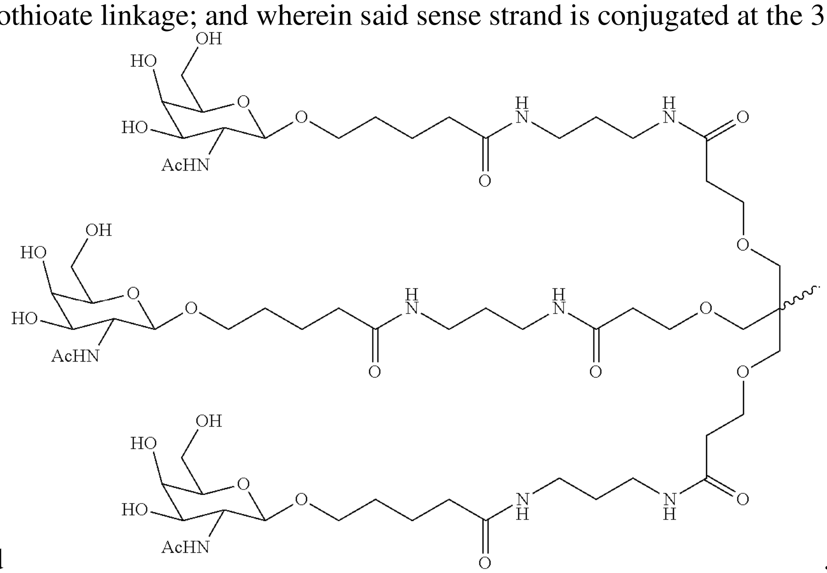
In one embodiment, the ligand is an N-acetylgalactosamine (GalNAc) derivative.

In one aspect, the present invention provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein said dsRNA agent comprises a sense strand and an antisense strand, the antisense strand comprising a

region of complementarity which comprises at least 17 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5'-UAUUAUAAAAAUAUCUUGCUUUU-3' (SEQ ID NO:113), and wherein said dsRNA agent comprises at least one modified nucleotide.

In one aspect, the present invention provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein said dsRNA agent comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 17 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5'-UAUUAUAAAAAUAUCUUGCUUUU-3' (SEQ ID NO:113), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, and wherein said sense strand is conjugated to a ligand attached at the 3'-terminus.

In one aspect, the present invention provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein said dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises 5'-asasGfcAfaGfaUfAfUfuUfuuAfuAfaua-3' (SEQ ID NO:2876) and the antisense strand comprises 5'-usAfsUfuAfuaAfaAfauaUfcUfuGfcuususudTdT-3' (SEQ ID NO:2889), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2'-fluoro A, G, C and U, respectively; dT is a deoxy-thymine nucleotide; and s is a phosphorothioate linkage; and wherein said sense strand is conjugated at the 3'-terminus to the ligand



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In one aspect, the present invention provides a pharmaceutical composition for inhibiting expression of a complement component C5 gene comprising the dsRNA agent as described herein.

In one aspect, the present invention provides an *in vitro* method of inhibiting complement component C5 expression in a cell, the method comprising: (a) contacting the

cell with the dsRNA agent as described herein; and (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a complement component C5 gene, thereby inhibiting expression of the complement component C5 gene in the cell.

In one aspect, the present invention provides a use of a therapeutically effective amount of the dsRNA agent as described herein in the manufacture of a medicament for treating a subject having a disease or disorder that would benefit from a reduction in complement component C5 expression, wherein the medicament is to be administered to the subject.

In one aspect, the present invention provides a use of a prophylactically effective amount of the dsRNA agent as described herein in the manufacture of a medicament for preventing at least one symptom in a subject having or prone to having a disease or disorder that would benefit from a reduction in complement component C5 expression, wherein the medicament is to be administered to the subject.

In one aspect, there present invention provides a dsRNA agent as described herein for use in therapy.

We claim:

1. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein said dsRNA agent comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 17 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5'-UAUUAUAAAAAUAUCUUGCUUUU-3' (SEQ ID NO:113), and wherein said dsRNA agent comprises at least one modified nucleotide.

2. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein said dsRNA agent comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 17 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5'-UAUUAUAAAAAUAUCUUGCUUUU-3' (SEQ ID NO:113),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, and

wherein said sense strand is conjugated to a ligand attached at the 3'-terminus.

3. The dsRNA agent of claim 2, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand are modified nucleotides.

4. The dsRNA agent of claim 2, wherein the modified nucleotide is selected from the group consisting of a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 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, a non-natural base comprising nucleotide, a nucleotide comprising a 5'-phosphorothioate group, and a terminal nucleotide linked to a cholesteryl derivative or a dodecanoic acid bisdecylamide group.

5. The dsRNA agent of claim 4, wherein the modified nucleotide is a 2'-O-methyl nucleotide or a 2'-fluoro nucleotide.

6. The dsRNA agent of claim 1, wherein the region of complementarity is between 19 and 23 nucleotides in length.

7. The dsRNA agent of claim 1, wherein each strand is no more than 30 nucleotides in length.

8. The dsRNA agent of claim 1, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

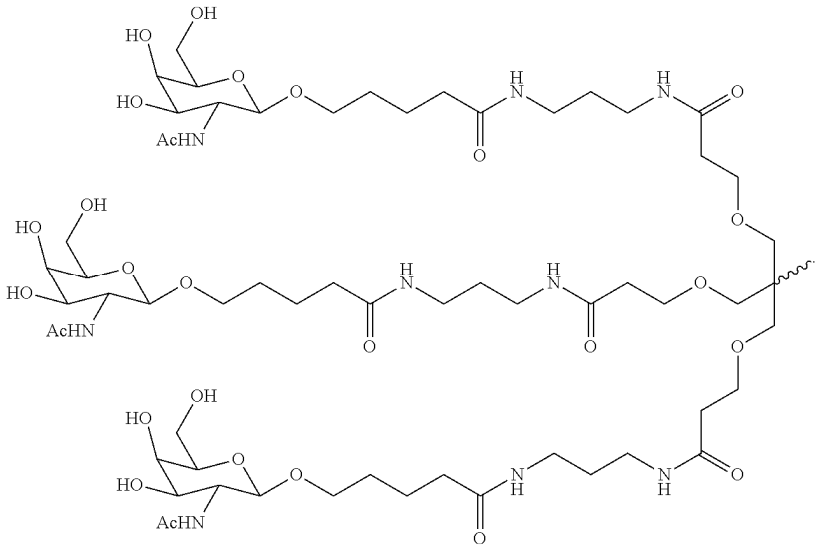
9. The dsRNA agent of claim 1, wherein said agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

10. The dsRNA agent of claim 1, further comprising a ligand.

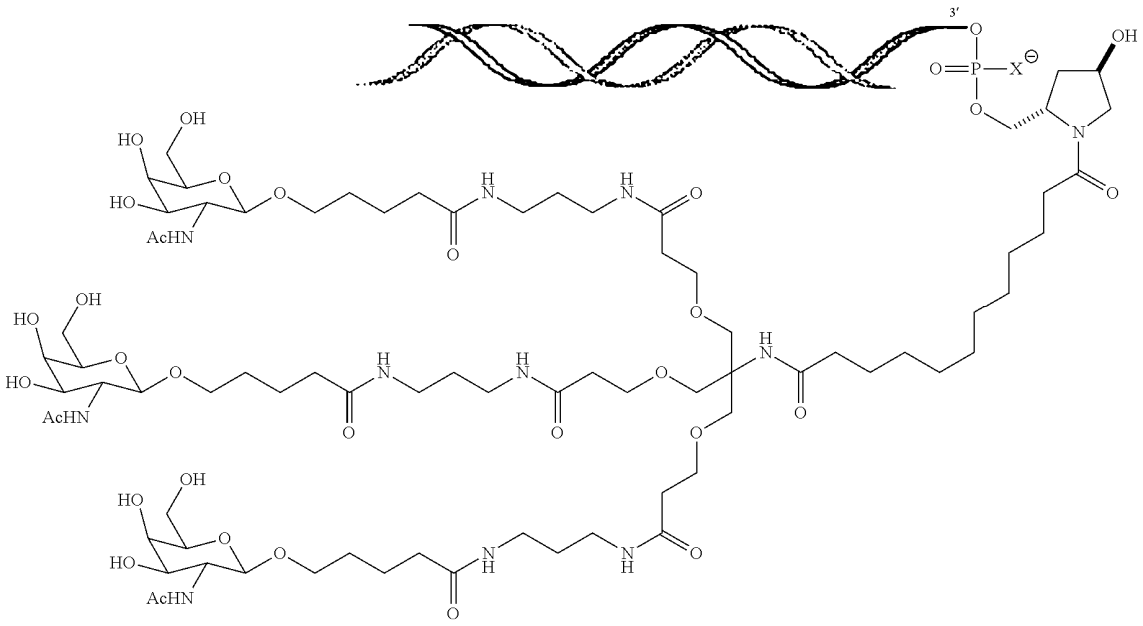
11. The dsRNA agent of claim 10, wherein the ligand is conjugated to the 3' end of the sense strand of the agent.

12. The dsRNA agent of claim 11, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

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



14. The dsRNA agent of claim 13, wherein the agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

15. The dsRNA agent of claim 14, wherein the X is O.

16. The dsRNA agent of claim 1, wherein the region of complementarity consists of the nucleotide sequence of 5'-UAUUAUAAAAAUAUCUUGCUUUU-3' (SEQ ID NO:113).

17. The dsRNA agent of claim 1, wherein the agent comprises a sense strand comprising the nucleotide sequence of 5'-AAGCAAGAUAUUUUUAUAAUA-3' (SEQ ID NO:62), and an antisense strand comprising the nucleotide sequence of 5'-UAUUAUAAAAAUAUCUUGCUUUU-3' (SEQ ID NO:113).

18. The dsRNA agent of claim 17, wherein the sense strand comprises 5'-asasGfcAfaGfaUfAfUfuUfuuAfuAfaua-3' (SEQ ID NO:2876) and the antisense strand comprises 5'-usAfsUfuAfuaAfaAfauaUfcUfuGfcuususudTdT-3' (SEQ ID NO:2889),

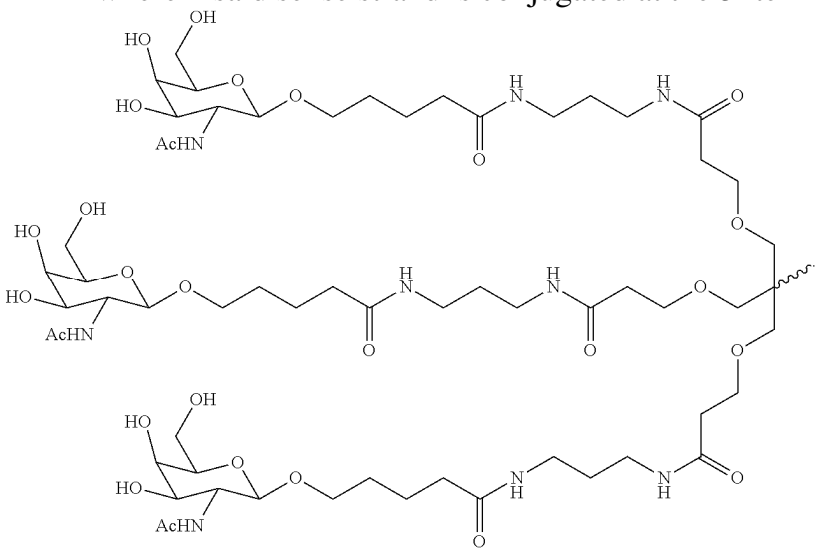
wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2'-fluoro A, G, C and U, respectively; dT is a deoxy-thymine nucleotide; and s is a phosphorothioate linkage.

19. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein said dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises 5'-asasGfcAfaGfaUfAfUfuUfuuAfuAfaua-3' (SEQ ID NO:2876) and the antisense

strand comprises 5'-usAfsUfuAfuaAfaAfauaUfcUfuGfcuusudTdT-3' (SEQ ID NO:2889),

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2'-fluoro A, G, C and U, respectively; dT is a deoxy-thymine nucleotide; and s is a phosphorothioate linkage; and

wherein said sense strand is conjugated at the 3'-terminus to the ligand



20. A cell comprising the dsRNA agent of claim 19.

21. A pharmaceutical composition for inhibiting expression of a complement component C5 gene comprising the dsRNA agent of claim 19.

22. An *in vitro* method of inhibiting complement component C5 expression in a cell, the method comprising: (a) contacting the cell with the dsRNA agent of claim 19; and (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a complement component C5 gene, thereby inhibiting expression of the complement component C5 gene in the cell.

23. Use of a therapeutically effective amount of the dsRNA agent of claim 19 in the manufacture of a medicament for treating a subject having a disease or disorder that would benefit from a reduction in complement component C5 expression, wherein the medicament is to be administered to the subject.

24. The use of claim 23, wherein the disorder is a complement component C5-associated disease.

25. Use of a prophylactically effective amount of the dsRNA agent of claim 19 in

the manufacture of a medicament for preventing at least one symptom in a subject having or prone to having a disease or disorder that would benefit from a reduction in complement component C5 expression, wherein the medicament is to be administered to the subject.

26. The method of claim 22, further comprising contacting the cell with an anti-complement component C5 antibody, or antigen-binding fragment thereof.

27. The use of claim 23, wherein an anti-complement component C5 antibody, or antigen-binding fragment thereof is to be further administered to the subject.

28. The use of claim 25, wherein an anti-complement component C5 antibody, or antigen-binding fragment thereof is to be further administered to the subject.

29. The dsRNA agent of claim 19 for use in therapy.