are then sequentially cleaved and activated. All pathways of complement activation lead to cleavage of the C5 molecule generating the anaphylatoxin C5a and, C5b that subsequently forms the terminal complement complex (C5b-9). C5a exerts a predominant pro-inflammatory activity through interactions with the classical G-protein coupled receptor C5aR (CD88) as well as with the non-G protein coupled receptor C5L2 (GPR77), expressed on various immune and non-immune cells. C5b-9 causes cytolysis through the formation of the membrane attack complex (MAC), and sub-lytic MAC and soluble C5b-9 also possess a multitude of non-cytolytic immune functions. These two complement effectors, C5a and C5b-9, generated from C5 cleavage, are key components of the complement system responsible for propagating and/or initiating pathology in different diseases, including paroxysmal nocturnal hemoglobinuria, rheumatoid arthritis, ischemia-reperfusion injuries and neurodegenerative diseases.

To date, only one therapeutic that targets the C5-C5a axis is available for the treatment of complement component C5-associated diseases, the anti-C5 antibody, eculizumab (Soliris®). Although eculizumab has been shown to be effective for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) and is currently being evaluated in clinical trials for additional complement component C5-associated diseases, eculizumab therapy requires weekly high dose infusions followed by biweekly maintenance infusions at a yearly cost of about $400,000. Accordingly, there is a need in the art for alternative therapies and combination therapies for subjects having a complement component C5-associated disease.

Summary ~~of the Invention~~

The present ~~invention~~ disclosure provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a C5 gene. The C5 gene may be within a cell, *e.g.,* a cell within a subject, such as a human. The present disclosure ~~invention~~ also provides methods and combination therapies for treating a subject having a disorder that would benefit from inhibiting or reducing the expression of a C5 gene, *e.g.,* a complement component C5-associated disease, such as paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) using iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a C5 gene for inhibiting the expression of a C5 gene.

Accordingly, in one aspect, the present disclosure ~~invention~~ provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein the dsRNA comprises a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15

contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5.

In another aspect, the present disclosure ~~invention~~ provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein the dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23.

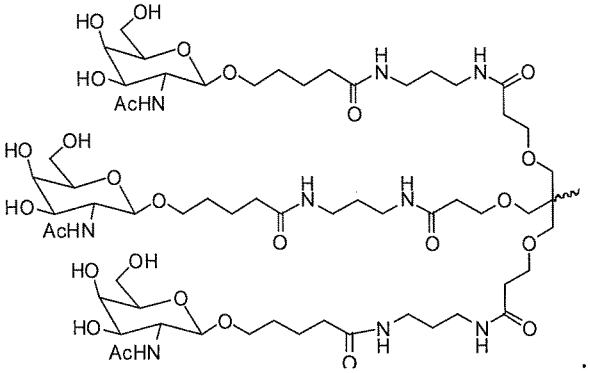
In one embodiment, the sense and antisense strands comprise sequences selected from the group consisting of A-118320, A-118321, A-118316, A-118317, A-118332, A-118333, A-118396, A-118397, A-118386, A-118387, A-118312, A-118313, A-118324, A-118325, A-119324, A-119325, A-119332, A-119333, A-119328, A-119329, A-119322, A-119323, A-119324, A-119325, A-119334, A-119335, A-119330, A-119331, A-119326, A-119327, A-125167, A-125173, A-125647, A-125157, A-125173, and A-125127. In another embodiment, the sense and antisense strands comprise sequences selected from the group consisting of any of the sequences in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23. In one embodiment, the dsRNA agent comprises at least one modified nucleotide.

~~In one aspect, t~~The present disclosure also ~~invention~~ provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises the nucleotide sequence AAGCAAGAUAUUUUUAUAAUA (SEQ ID NO:62) and wherein the antisense strand comprises the nucleotide sequence UAUUAUAAAAAUAUCUUGCUUUU (SEQ ID NO:113). In one embodiment, the dsRNA agent comprises at least one modified nucleotide, as described below.

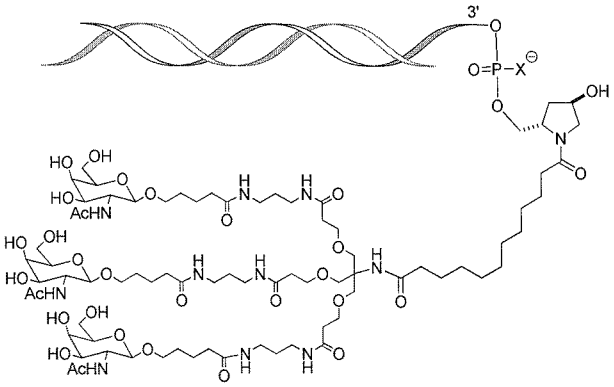
In one aspect, the present disclosure ~~invention~~ provides a double stranded RNAi agent for inhibiting expression of complement component C5 wherein the double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein the sense strand is conjugated to a ligand attached at the 3'-terminus.

In one embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

In one embodiment, substantially all of the nucleotides of the sense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-



In one embodiment, the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

In one embodiment, the X is O.

In one embodiment, the region of complementarity consists of one of the antisense sequences of any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23.

In one embodiment, the dsRNA agent is selected from the group consisting of AD-58123, AD-58111, AD-58121, AD-58116, AD-58133, AD-58099, AD-58088, AD-58642, AD-58644, AD-58641, AD-58647, AD-58645, AD-58643, AD-58646, AD-62510, AD-62643, AD-62645, AD-62646, AD-62650, and AD-62651.

~~In another aspect, t~~The present ~~invention~~ disclosure also provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises the nucleotide sequence AAGCAAGAUAUUUUUAUAAUA (SEQ ID NO:62) and wherein the antisense strand comprises the nucleotide sequence UAUUAUAAAAAUAUCUUGCUUUUdTdT (SEQ ID NO:2899).

~~In another aspect, t~~The present disclosure also ~~invention~~ provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises the nucleotide sequence asasGfcAfaGfaUfAfUfuUfuuAfuAfauaL96 (SEQ ID NO:2876) and

wherein the antisense strand comprises the nucleotide sequence usAfsUfuAfuaAfaAfauaUfcUfuGfcuususudTdT (SEQ ID NO:2889).

In one aspect, the present ~~invention~~ disclosure provides a double stranded RNAi agent capable of inhibiting the expression of complement component C5 in a cell, wherein the double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C5, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q' are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each n_p, n_p', n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and

wherein the sense strand is conjugated to at least one ligand.

In one embodiment, i is 0; j is 0; i is 1; j is 1; both i and j are 0; or both i and j are 1.

In one embodiment, k is 0; l is 0; k is 1; l is 1; both k and l are 0; or both k and l are 1.

In one embodiment, XXX is complementary to X'X'X', YYY is complementary to Y'Y'Y', and ZZZ is complementary to Z'Z'Z'.

In one embodiment, the YYY motif occurs at or near the cleavage site of the sense strand.

In one embodiment, the Y'Y'Y' motif occurs at the 11, 12 and 13 positions of the antisense strand from the 5'-end.

In one embodiment, the Y' is 2'-O-methyl.

In one embodiment, formula (III) is represented by formula (IIIa):

sense: $5'\ n_p\text{-}N_a\text{-}Y\ Y\ Y\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_{p'}\text{-}N_{a'}\text{-}Y'Y'Y'\text{-}N_{a'}\text{-}n_{q'}\ 5'$ (IIIa).

In another embodiment, formula (III) is represented by formula (IIIb):

In one embodiment, the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

In one embodiment, the Y nucleotides contain a 2′-fluoro modification.

In one embodiment, the Y′ nucleotides contain a 2′-O-methyl modification.

In one embodiment, p′>0.

In one embodiment, p′=2.

In one embodiment, q'=0, p=0, q=0, and p' overhang nucleotides are complementary to the target mRNA.

In one embodiment, q'=0, p=0, q=0, and p' overhang nucleotides are non-complementary to the target mRNA.

In one embodiment, the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

In one embodiment, at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage.

In one embodiment, all n_p' are linked to neighboring nucleotides via phosphorothioate linkages.

In one embodiment, the RNAi agent is selected from the group of RNAi agents listed in Table 4, Table 18, Table 19, or Table 23. In another embodiment, the RNAi agent is selected from the group consisting of AD-58123, AD-58111, AD-58121, AD-58116, AD-58133, AD-58099, AD-58088, AD-58642, AD-58644, AD-58641, AD-58647, AD-58645, AD-58643, AD-58646, AD-62510, AD-62643, AD-62645, AD-62646, AD-62650, and AD-62651.

In one aspect, the present ~~invention~~ disclosure provides a double stranded RNAi agent capable of inhibiting the expression of complement component C5 in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said antisense strand comprises a region complementary to part of an mRNA encoding complement component C5, wherein each strand is about 14 to about 30 nucleotides in length, wherein said double stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q′ are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each n_p, n_p', n_q, and n_q', each of which may or may not be present independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2'-O-methyl or 2'-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and

wherein the sense strand is conjugated to at least one ligand.

In another aspect, the present ~~invention~~ disclosure provides a double stranded RNAi agent capable of inhibiting the expression of complement component C5 in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said antisense strand comprises a region complementary to part of an mRNA encoding complement component C5, wherein each strand is about 14 to about 30 nucleotides in length, wherein said double stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q' are each independently 0-6;

$n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2'-O-methyl or 2'-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and

wherein the sense strand is conjugated to at least one ligand.

In another aspect, the present disclosure ~~invention~~ provides a double stranded RNAi agent capable of inhibiting the expression of complement component C5 in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said antisense strand comprises a region complementary to part of an mRNA encoding complement component C5, wherein each strand is about 14 to about 30 nucleotides in length, wherein said double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X'X'X')$_k$-N_b'-Y'Y'Y'-N_b'-(Z'Z'Z')$_l$-N_a'- n_q' 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q' are each independently 0-6;

n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2'-O-methyl or 2'-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In yet another aspect, the present disclosure ~~invention~~ provides a double stranded RNAi agent capable of inhibiting the expression of complement component C5 in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said antisense strand comprises a region complementary to part of an mRNA encoding complement component C5, wherein each strand is about 14 to about 30 nucleotides in length, wherein said double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X'X'X')$_k$-N_b'-Y'Y'Y'-N_b'-(Z'Z'Z')$_l$-N_a'- n_q' 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

$n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′;

wherein the sense strand comprises at least one phosphorothioate linkage; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another aspect, the present disclosure ~~invention~~ provides a double stranded RNAi agent capable of inhibiting the expression of complement component C5 in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said antisense strand comprises a region complementary to part of an mRNA encoding complement component C5, wherein each strand is about 14 to about 30 nucleotides in length, wherein said double stranded RNAi agent is represented by formula (III):

sense: 5′ n_p -N_a -Y Y Y - N_a - n_q 3′

antisense: 3′ n_p'-N_a'- Y′Y′Y′- N_a'- n_q' 5′ (IIIa)

wherein:

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

$n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

YYY and Y'Y'Y' each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2'-O-methyl or 2'-fluoro modifications;

wherein the sense strand comprises at least one phosphorothioate linkage; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one aspect, the present disclosure ~~invention~~ provides a double stranded RNAi agent for inhibiting expression of complement component C5, wherein the double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, wherein substantially all of the nucleotides of the sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus, wherein substantially all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and wherein the sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus.

In one embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides. In another embodiment, each strand has 19-30 nucleotides.

In one aspect, the present disclosure ~~invention~~ provides a cell containing a dsRNA agent of the disclosure~~invention~~.

In one aspect, the present disclosure ~~invention~~ provides a vector encoding at least one strand of a dsRNA agent, wherein the dsRNA agent comprises a region of complementarity to at least a part of an mRNA encoding complement component C5, wherein the dsRNA is 30 base pairs or less in length, and wherein the dsRNA agent targets the mRNA for cleavage.

In one embodiment, the region of complementarity is at least 15 nucleotides in length. In another embodiment, the region of complementarity is 19 to 21 nucleotides in length. In another embodiment, each strand has 19-30 nucleotides.

In one aspect, the present disclosure ~~invention~~ provides a cell comprising a vector of the disclosure~~invention~~.

In one aspect, the present disclosure ~~invention~~ provides a pharmaceutical composition for inhibiting expression of a complement component C5 gene comprising a dsRNA agent of the disclosure or the vector of the disclosure~~invention~~.

In one embodiment, the RNAi agent is administered in an unbuffered solution.

In one embodiment, the unbuffered solution is saline or water.

In one embodiment, the RNAi agent is administered with a buffer solution.

In one embodiment, the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

In another embodiment, the buffer solution is phosphate buffered saline (PBS).

In another aspect, the present disclosure ~~invention~~ provides a pharmaceutical composition comprising a double stranded RNAi agent of the disclosure ~~invention~~ and a lipid formulation.

In one embodiment, the lipid formulation comprises a LNP. In another embodiment,the lipid formulation comprises a MC3.

~~In one aspect, t~~The present disclosure also~~invention~~ provides a composition comprising an antisense polynucleotide agent selected from the group consisting of the sequences listed in any one of Tables 3, 4, 5, 6, 19, 18, 20, 21, and 23.

~~In another aspect, t~~The present disclosure also~~invention~~ provides a composition comprising a sense polynucleotide agent selected from the group consisting of the sequences listed in any one of Tables 3, 4, 5, 6, 19, 18, 20, 21, and 23.

~~In yet another aspect, t~~The present disclosure also~~invention~~ provides a modified antisense polynucleotide agent selected from the group consisting of the antisense sequences listed in any one of Tables 4, 6, 18, 19, 21, and 23.

~~In a further aspect, t~~The present disclosure also~~invention~~ provides a modified sense polynucleotide agent selected from the group consisting of the sense sequences listed in any one of Tables 4, 6, 18, 19, 21, and 23.

~~In one aspect t~~The present disclosure also~~invention~~ provides methods of treating a subject having a disease or disorder that would benefit from reduction in complement component C5 expression. The methods include administering to the subject a therapeutically effective amount of a dsRNA agent comprising a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, thereby treating the subject.

In another aspect, the present disclosure provides the dsRNA agent of the disclosure or a pharmaceutical composition of the disclosure, for use in treating a having a disease or disorder that would benefit from reduction in complement component C5 expression.

~~In another aspect, t~~The present disclosure also~~invention~~ provides methods of preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement component C5 expression. The methods include administering to the subject a therapeutically effective amount of a dsRNA agent comprising a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand

comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in C5 expression.

In another aspect, the present disclosure provides the dsRNA agent of the disclosure or a pharmaceutical composition of the disclosure for use in preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement component C5 expression.

~~In another aspect, t~~The present disclosure also~~invention~~ provides methods of treating a subject having a disease or disorder that would benefit from reduction in complement component C5 expression. The methods include administering to the subject a therapeutically effective amount of a dsRNA agent comprising a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, 23, thereby treating the subject.

~~In yet another aspect, t~~The present disclosure also~~invention~~ provides methods of preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement component C5 expression. The methods include administering to the subject a prophylactically effective amount of a dsRNA agent comprising a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in C5 expression.

~~In one aspect, T~~the present disclosure also~~invention~~ provides methods of treating a subject having a disease or disorder that would benefit from reduction in complement component C5 expression which include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, wherein the double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, wherein substantially all of the nucleotides of the antisense strand and substantially all of the nucleotides of the sense strand are modified nucleotides and, wherein the sense strand is conjugated to one or more ligands at the 3'-terminus.

In one embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In one embodiment, the administration is subcutaneous administration.

In one embodiment, substantially all of the nucleotides of the sense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, substantially all of the

nucleotides of the antisense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, the modified nucleotides are a short sequence of deoxy-thymine (dT) nucleotides. In another embodiment, the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus. In one embodiment, the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus. In yet another embodiment, the sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus.

~~In another aspect, t~~The present disclosure also~~invention~~ provides methods of preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement component C5 expression which include administering to the subject a prophylactically effective amount of a double stranded RNAi agent, wherein the double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, wherein substantially all of the nucleotides of the antisense strand and substantially all of the nucleotides of the sense strand are modified nucleotides and, wherein the sense strand is conjugated to a ligand at the 3'-terminus.

In one embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In one embodiment, the administration is subcutaneous administration.

In one embodiment, substantially all of the nucleotides of the sense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, substantially all of the nucleotides of the antisense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, the modified nucleotides are a short sequence of deoxy-thymine (dT) nucleotides. In another embodiment, the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus. In one embodiment, the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus. In yet another embodiment, the sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus.

~~In one aspect, t~~The present disclosure also~~invention~~ provides methods of treating a subject having a disease or disorder that would benefit from reduction in complement component C5 expression. The methods include administering to the subject a therapeutically effective amount of a dsRNA agent comprising a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C5, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q' are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each n_p, n_p', n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and

wherein the sense strand is conjugated to at least one ligand, thereby treating the subject, thereby treating a subject having a disease or disorder that would benefit from reduction in complement component C5 expression.

~~In another aspect, t~~The present disclosure also~~invention~~ provides methods of preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement component C5 expression. The methods include administering to the subject a prophylactically effective amount of a dsRNA agent comprising a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C5, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (III)

wherein:

autoimmune hemolytic anemia (AIHA), ITP, Goodpasture syndrome, Degos disease, antiphospholipid syndrome (APS), catastrophic APS (CAPS), a cardiovascular disorder, myocarditis, a cerebrovascular disorder, a peripheral vascular disorder, a renovascular disorder, a mesenteric/enteric vascular disorder, vasculitis, Henoch-Schönlein purpura nephritis, systemic lupus erythematosus-associated vasculitis, vasculitis associated with rheumatoid arthritis, immune complex vasculitis, Takayasu's disease, dilated cardiomyopathy, diabetic angiopathy, Kawasaki's disease (arteritis), venous gas embolus (VGE), and restenosis following stent placement, rotational atherectomy, membraneous nephropathy, Guillain-Barre syndrome, and percutaneous transluminal coronary angioplasty (PTCA). In another embodiment, the complement component C5-associated disease is paroxysmal nocturnal hemoglobinuria (PNH). In yet another embodiment, the complement component C5-associated disease is atypical hemolytic uremic syndrome (aHUS).

In one embodiment, the subject is human.

In another embodiment, the methods of the ~~invention~~ disclosure further include administering an anti-complement component C5 antibody, or antigen-binding fragment thereof, to the subject.

In one embodiment, the antibody, or antigen-binding fragment thereof, inhibits cleavage of complement component C5 into fragments C5a and C5b. In another embodiment, the anti-complement component C5 antibody is eculizumab.

In another embodiment, the methods of the disclosure ~~invention~~ further include administering a meningococcal vaccine to the subject.

In one embodiment, eculizumab is administered to the subject weekly at a dose less than about 600 mg for 4 weeks followed by a fifth dose at about one week later of less than about 900 mg, followed by a dose less than about 900 mg about every two weeks thereafter.

In another embodiment, eculizumab is administered to the subject weekly at a dose less than about 900 mg for 4 weeks followed by a fifth dose at about one week later of less than about 1200 mg, followed by a dose less than about 1200 mg about every two weeks thereafter.

In one embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 900 mg for 4 weeks followed by a fifth dose at about one week later of less than about 1200 mg, followed by a dose less than about 1200 mg about every two weeks thereafter.

In another embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 600 mg for 2 weeks followed by a third dose at about one week later of less than about 900 mg, followed by a dose less than about 900 mg about every two weeks thereafter.

In another embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 600 mg for 2 weeks followed by a

third dose at about one week later of less than about 600 mg, followed by a dose less than about 600 mg about every two weeks thereafter.

In yet another embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 600 mg for 1 week followed by a second dose at about one week later of less than about 300 mg, followed by a dose less than about 300 mg about every two weeks thereafter.

In one embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 300 mg for 1 week followed by a second dose at about one week later of less than about 300 mg, followed by a dose less than about 300 mg about every two weeks thereafter.

In another embodiment, the methods of the disclosure ~~invention~~ further include plasmapheresis or plasma exchange in the subject. In one such embodiment, eculizumab is administered to the subject at a dose less than about 600 mg or at a dose less than about 300 mg.

In a further embodiment, the methods of the disclosure ~~invention~~ further include plasma infusion in the subject. In one such 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 one 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 15 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 50 mg/kg.

In another embodiment, dsRNA agent is administered at a dose of about 10 mg/kg to about 30 mg/kg.

In one 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 methods of the disclosure ~~invention~~ further include measuring hemoglobin and/or LDH levels in the subject.

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

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

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

~~In one aspect, t~~The present disclosure also~~invention~~ provides methods of inhibiting complement component C5 expression in a cell. The methods include contacting the cell with a dsRNA agent comprising a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5; and maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a C5 gene, thereby inhibiting expression of the C5 gene in the cell.

In another aspect, the present disclosure provides the double stranded RNAi agent of the disclosure or a pharmaceutical composition of the disclosure for use in inhibiting complement component C5 expression in a cell, wherein the double stranded RNAi agent or pharmaceutical composition is to be contacted with a cell; and wherein the contacted cell is to be maintained 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 another aspect, t~~The present disclosure also~~invention~~ provides methods of inhibiting complement component C5 expression in a cell. The methods include contacting the cell with a dsRNA agent comprising a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23; and maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a C5 gene, thereby inhibiting expression of the C5 gene in the cell.

~~In another aspect, t~~The present disclosure also~~invention~~ provides methods of inhibiting complement component C5 expression in a cell, which includes contacting the cell with a dsRNA agent comprising a sense strand and an antisense strand comprising a region of complementarity, the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15

contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, wherein substantially all of the nucleotides of the antisense strand and substantially all of the nucleotides of the sense strand are modified nucleotides and, wherein the sense strand is conjugated to one or more ligands at the 3'-terminus; and maintaining the cell produced in the first step for a time sufficient to obtain degradation of the mRNA transcript of a C5 gene, thereby inhibiting expression of the C5 gene in the cell.

In one embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In one embodiment, substantially all of the nucleotides of the sense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, substantially all of the nucleotides of the antisense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, the modified nucleotides are a short sequence of deoxy-thymine (dT) nucleotides. In another embodiment, the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus. In one embodiment, the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus. In yet another embodiment, the sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus.

~~In yet another aspect, t~~The present disclosure also~~invention~~ provides methods of inhibiting complement component C5 expression in a cell. The methods include contacting the cell with a dsRNA agent comprising a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C5, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X'X'X')$_k$-N_b'-Y'Y'Y'-N_b'-(Z'Z'Z')$_l$-N_a'- n_q' 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q' are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

percutaneous transluminal coronary angioplasty (PTCA). In another embodiment, the complement component C5-associated disease is paroxysmal nocturnal hemoglobinuria (PNH). In another embodiment, the complement component C5-associated disease is atypical hemolytic uremic syndrome (aHUS).

In one embodiment, the methods further include contacting the cell with an anti-complement component C5 antibody, or antigen-binding fragment thereof.

In one embodiment, the antibody, or antigen-binding fragment thereof, inhibits cleavage of complement component C5 into fragments C5a and C5b.

In one embodiment, the anti-complement component C5 antibody, or antigen-binding fragment thereof, is eculizumab.

In one embodiment, the methods further include contacting the cell with a meningococcal vaccine.

In one embodiment, the cell is contacted with eculizumab weekly at a dose less than about 600 mg for 4 weeks followed by a fifth dose at about one week later of less than about 900 mg, followed by a dose less than about 900 mg about every two weeks thereafter.

In another embodiment, the cell is contacted with eculizumab weekly at a dose less than about 900 mg for 4 weeks followed by a fifth dose at about one week later of less than about 1200 mg, followed by a dose less than about 1200 mg about every two weeks thereafter.

In another embodiment, the cell is contacted with eculizumab weekly at a dose less than about 900 mg for 4 weeks followed by a fifth dose at about one week later of less than about 1200 mg, followed by a dose less than about 1200 mg about every two weeks thereafter.

In yet another embodiment, the cell is contacted with eculizumab weekly at a dose less than about 600 mg for 2 weeks followed by a third dose at about one week later of less than about 900 mg, followed by a dose less than about 900 mg about every two weeks thereafter.

In one embodiment, the cell is contacted with eculizumab weekly at a dose less than about 600 mg for 2 weeks followed by a third dose at about one week later of less than about 600 mg, followed by a dose less than about 600 mg about every two weeks thereafter.

In another embodiment, the cell is contacted with eculizumab weekly at a dose less than about 600 mg for 1 week followed by a second dose at about one week later of less than about 300 mg, followed by a dose less than about 300 mg about every two weeks thereafter.

In one embodiment, the cell is contacted with eculizumab weekly at a dose less than about 300 mg for 1 week followed by a second dose at about one week later of less than about 300 mg, followed by a dose less than about 300 mg about every two weeks thereafter.

In one embodiment, the cell is within a subject.

In one embodiment, the methods of the ~~invention~~ disclosure further include plasmapheresis or plasma exchange in the subject. In one embodiment, eculizumab is administered to the subject at

a dose less than about 600 mg. In another embodiment, eculizumab is administered to the subject at a dose less than about 300 mg.

In one embodiment, the methods of the disclosure ~~invention~~ 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, the cell is contacted with eculizumab 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, the cell is contacted with eculizumab at a dose of about 5 mg/kg to about 15 mg/kg.

In one embodiment, the cell is contacted with eculizumab at a dose selected from the group consisting of 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 3 mg/kg, 5mg/kg, 7 mg/kg, 10 mg/kg, and 15 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 cell is contacted with the dsRNA agent at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg.

In another embodiment, the cell is contacted with the dsRNA agent at a dose of about 10 mg/kg to about 30 mg/kg.

In one embodiment, the cell is contacted with the dsRNA agent 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 cell is contacted with the dsRNA agent once a week. In another embodiment, the dsRNA agent is administered to the subject twice a week. In another embodiment, the cell is contacted with the dsRNA agent 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 cell is contacted with the dsRNA agent and the eculizumab 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 cell is contacted with the dsRNA agent first for a period of time sufficient to reduce the levels of complement component C5 in the cell, and the cell is subsequrntly contacted with eculizumab at a dose less than about 600 mg.

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

In one embodiment, the cell is contacted with eculizumab at a dose of about 100-500 mg.

In one aspect, the present disclosure ~~invention~~ provides methods of inhibiting the expression of C5 in a subject. The methods include administering to the subject a therapeutically effective amount of a dsRNA agent comprising a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, thereby inhibiting the expression of C5 in the subject.

~~In another aspect, t~~The present disclosure also~~invention~~ provides methods of inhibiting the expression of C5 in a subject. The methods include administering to the subject a therapeutically effective amount of a dsRNA agent comprising a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23, thereby inhibiting the expression of C5 in the subject.

~~In another aspect, t~~The present disclosure also~~invention~~ provides methods of inhibiting complement component C5 expression in a subject which include administering to the subject a therapeutically effective amount of a dsRNA agent comprising a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, wherein substantially all of the nucleotides of the antisense strand and substantially all of the nucleotides of the sense strand are modified nucleotides and, wherein the sense strand is conjugated to one or more ligands at the 3'-terminus, thereby inhibiting expression of the C5 gene in the subject.

In one embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In one embodiment, the administration is subcutaneous administration.

In one embodiment, substantially all of the nucleotides of the sense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, substantially all of the

nucleotides of the antisense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, the modified nucleotides are a short sequence of deoxy-thymine (dT) nucleotides. In another embodiment, the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus. In one embodiment, the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus. In yet another embodiment, the sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus.

~~In another aspect, t~~The present disclosure also~~invention~~ provides methods of inhibiting the expression of C5 in a subject. The methods include administering to the subject a therapeutically effective amount of a dsRNA agent comprising a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C5, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q' are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each n_p, n_p', n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and

wherein the sense strand is conjugated to at least one ligand, thereby inhibiting the expression of C5 in the subject.

In one embodiment, the methods further include administration of an anti-complement component C5 antibody, or antigen-binding fragment thereof, to the subject.

In one embodiment, the anti-complement component C5 antibody, or antigen-binding fragment thereof, is eculizumab.

In one embodiment, the antibody, or antigen-binding fragment thereof, inhibits cleavage of complement component C5 into fragments C5a and C5b.

In one embodiment, the methods of the disclosure ~~invention~~ further include administering a meningococcal vaccine to the subject.

In one embodiment, eculizumab is administered to the subject weekly at a dose less than about 600 mg for 4 weeks followed by a fifth dose at about one week later of less than about 900 mg, followed by a dose less than about 900 mg about every two weeks thereafter.

In another embodiment, eculizumab is administered to the subject weekly at a dose less than about 900 mg for 4 weeks followed by a fifth dose at about one week later of less than about 1200 mg, followed by a dose less than about 1200 mg about every two weeks thereafter.

In one embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 900 mg for 4 weeks followed by a fifth dose at about one week later of less than about 1200 mg, followed by a dose less than about 1200 mg about every two weeks thereafter.

In another embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 600 mg for 2 weeks followed by a third dose at about one week later of less than about 900 mg, followed by a dose less than about 900 mg about every two weeks thereafter.

In one embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 600 mg for 2 weeks followed by a third dose at about one week later of less than about 600 mg, followed by a dose less than about 600 mg about every two weeks thereafter.

In another embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 600 mg for 1 week followed by a second dose at about one week later of less than about 300 mg, followed by a dose less than about 300 mg about every two weeks thereafter.

In yet another embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 300 mg for 1 week followed by a second dose at about one week later of less than about 300 mg, followed by a dose less than about 300 mg about every two weeks thereafter.

In one embodiment, the methods further includeplasmapheresis or plasma exchange in the subject. In one embodiment, eculizumab is administered to the subject at a dose less than about 600 mg. In another embodiment, eculizumab is administered to the subject at a dose less than about 300 mg.

91. The pharmaceutical composition of claim 89, wherein the lipid formulation comprises a MC3.

92. ~~A method of inhibiting complement component C5 expression in a cell, the method comprising:~~

~~(a) contacting the cell with t~~The double stranded RNAi agent of any one of claims 1, 2, 6, 24, and 70-75 or a pharmaceutical composition of any one of claims 83-91 for use in inhibiting complement component C5 expression in a cell, wherein the double stranded RNAi agent or pharmaceutical composition is to be contacted with a cell; and wherein the contacted cell is to be maintained

~~(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.

93. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of claim 92, wherein said cell is within a subject.

94. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of claim 93, wherein the subject is a human.

95. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of any one of claims 91-93, wherein the complement component C5 expression is inhibited by at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98% or about 100%.

96. ~~A method of treating a subject having a disease or disorder that would benefit from reduction in complement component C5 expression, the method comprising administering to the subject a therapeutically effective amount of t~~The dsRNA agent of any one of claims 1, 2, 6, 24, and 70-75 or a pharmaceutical composition of any one of claims 83-91, for use in treating a having a disease or disorder that would benefit from reduction in complement component C5 expression~~thereby treating said subject~~.

97. ~~A method of preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement component C5 expression, the method comprising administering to the subject a prophylactically effective amount of t~~The dsRNA agent of any one of claims 1, 2, 6, 24, and 70-75 or a pharmaceutical composition of any one of claims 83-91 for use in preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement component C5 expression~~, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in C5 expression~~.

98. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of claim 96 or 97, wherein the administration of the dsRNA to the subject causes a decrease in intravascular hemolysis, a stabilization of hemoglobin levels and/or a decrease in C5 protein.

99. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of claim 96 or 97, wherein the disorder is a complement component C5-associated disease.

100. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of claim 99, wherein the complement component C5-associated disease is selected from the group consisting of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), asthma, rheumatoid arthritis (RA); antiphospholipid antibody syndrome; lupus nephritis; ischemia-reperfusion injury; typical or infectious hemolytic uremic syndrome (tHUS); dense deposit disease (DDD); neuromyelitis optica (NMO); multifocal motor neuropathy (MMN); multiple sclerosis (MS); macular degeneration (e.g., age-related macular degeneration (AMD)); hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; thrombotic thrombocytopenic purpura (TTP); spontaneous fetal loss; Pauci-immune vasculitis; epidermolysis bullosa; recurrent fetal loss; pre-eclampsia, traumatic brain injury, myasthenia gravis, cold agglutinin disease, dermatomyositis bullous pemphigoid, Shiga toxin *E. coli*-related hemolytic uremic syndrome, C3 nephropathy, anti-neutrophil cytoplasmic antibody-associated vasculitis, humoral and vascular transplant rejection, graft dysfunction, myocardial infarction, an allogenic transplant, sepsis, Coronary artery disease, dermatomyositis, Graves' disease, atherosclerosis, Alzheimer's disease, systemic inflammatory response sepsis, septic shock, spinal cord injury, glomerulonephritis, Hashimoto's thyroiditis, type I diabetes, psoriasis, pemphigus, autoimmune hemolytic anemia (AIHA), ITP, Goodpasture syndrome, Degos disease, antiphospholipid syndrome (APS), catastrophic APS (CAPS), a cardiovascular disorder, myocarditis, a cerebrovascular disorder, a peripheral vascular disorder, a renovascular disorder, a mesenteric/enteric vascular disorder, vasculitis, Henoch-Schönlein purpura nephritis, systemic lupus erythematosus-associated vasculitis, vasculitis associated with rheumatoid arthritis, immune complex vasculitis, Takayasu's disease, dilated cardiomyopathy, diabetic angiopathy, Kawasaki's disease (arteritis), venous gas embolus (VGE), and restenosis following stent placement, rotational atherectomy, membraneous nephropathy, Guillain-Barre syndrome, and percutaneous transluminal coronary angioplasty (PTCA).

101. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of claim 100, wherein the complement component C5-associated disease is paroxysmal nocturnal hemoglobinuria (PNH).

102. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of claim 100, wherein the complement component C5-associated disease is atypical hemolytic uremic syndrome (aHUS).

103. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of claim 96 or 97, wherein the subject is human.

104. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of any one of claims 96-103, further comprising ~~administering~~ an anti-complement component C5 antibody, or antigen-binding fragment thereof~~, to the subject~~.

105. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of any one of claims 96-104, wherein the dsRNA agent is for administration ~~administered~~ at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg.

106. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of claim 105, wherein the dsRNA agent is for administration ~~administered~~ at a dose of about 10 mg/kg to about 30 mg/kg.

107. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of claim 105, wherein the dsRNA agent is for administration ~~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.

108. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of claim 105, wherein the dsRNA agent is for administration ~~administered~~ to the subject once a week.

109. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of claim 105, wherein the dsRNA agent is for administration ~~administered~~ to the subject twice a week.

110. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of claim 105, wherein the dsRNA agent is for administration ~~administered~~ to the subject twice a month.

111. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of any one of claims 96-110, wherein the dsRNA agent is for administration ~~administered~~ to the subject subcutaneously.

112. The double stranded RNAi agent or pharmaceutical composition ~~method~~ of claim 96 or 97, further comprising measuring hemoglobin and/or LDH levels in said subject.