

Claims

1. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Angiopoietin-like 3 (ANGPTL3), wherein the dsRNA agent comprises a sense strand and an antisense strand, and optionally comprises a targeting ligand,
wherein the antisense strand of the dsRNA agent consists of a nucleotide sequence II: 5'-z₁uagaguauaaccuuccz₂-3', wherein z₁ is selected from c, g, a or u, z₂ is a nucleotide sequence IV; wherein, the nucleotide sequence IV is 0-15 nucleotides in length.
2. The dsRNA agent according to claim 1, wherein, z₁ is u; or
the nucleotide sequence IV is selected from a, au, aa, ac, ag, auu, aua, auc, aug, auug, auuu, auua, auuc, auuuu, auuuug, auucuu, auucga, auuuuga, auuuugag, auuuugaga or auuuugagacuucca; or
the nucleotide sequence IV is 1, 2, 3 or 4 nucleotides in length; or
the nucleotide sequence IV is selected from a, au, aa, ac, ag, auu, aua, auc, aug, auug, auuu, auua or auuc.
3. The dsRNA of claim 1, wherein the dsRNA agent comprises at least one modified nucleotide,
optionally, wherein all of the nucleotides of the antisense strand are modified nucleotides,
optionally wherein the at least one modified nucleotide comprises: a 2'-O-methyl nucleotide, 2'-Fluoro nucleotide, 2'-deoxy nucleotide, 2'3'-seco nucleotide mimic, locked nucleotide, unlocked nucleic acid nucleotide (UNA), glycol nucleic acid nucleotide (GNA), 2'-F-Arabino nucleotide, 2'-methoxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide, inverted 2'-Ome nucleotide, inverted 2'-deoxy nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, mopholino nucleotide, and 3'-OMe nucleotide, a nucleotide comprising a 5'-phosphorothioate group, or a terminal nucleotide linked to a

cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2'-amino-modified nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide.

4. The dsRNA agent of claim 3, wherein the dsRNA agent comprises an E-vinylphosphonate nucleotide at the 5' end of the antisense strand,

optionally, wherein the dsRNA agent comprises at least one phosphorothioate internucleoside linkage,

optionally, wherein the sense strand comprises at least one phosphorothioate internucleoside linkage;

optionally, wherein the antisense strand comprises at least one phosphorothioate internucleoside linkage;

optionally, wherein the sense strand comprises 1, 2, 3, 4, 5, or 6, phosphorothioate internucleoside linkages;

optionally, wherein the antisense strand comprises 1, 2, 3, 4, 5, or 6, phosphorothioate internucleoside linkages,

optionally wherein all of the nucleotides of the sense strand and the antisense strand are modified nucleotides.

5. The dsRNA agent of claim 1, wherein the sense strand is complementary to the antisense strand, and the region of complementarity is between 16 and 23 nucleotides in length,

optionally wherein the region of complementarity is 19-21 nucleotides in length,

optionally wherein each strand is no more than 30 nucleotides in length;

optionally, wherein each strand is no more than 25 nucleotides in length; and

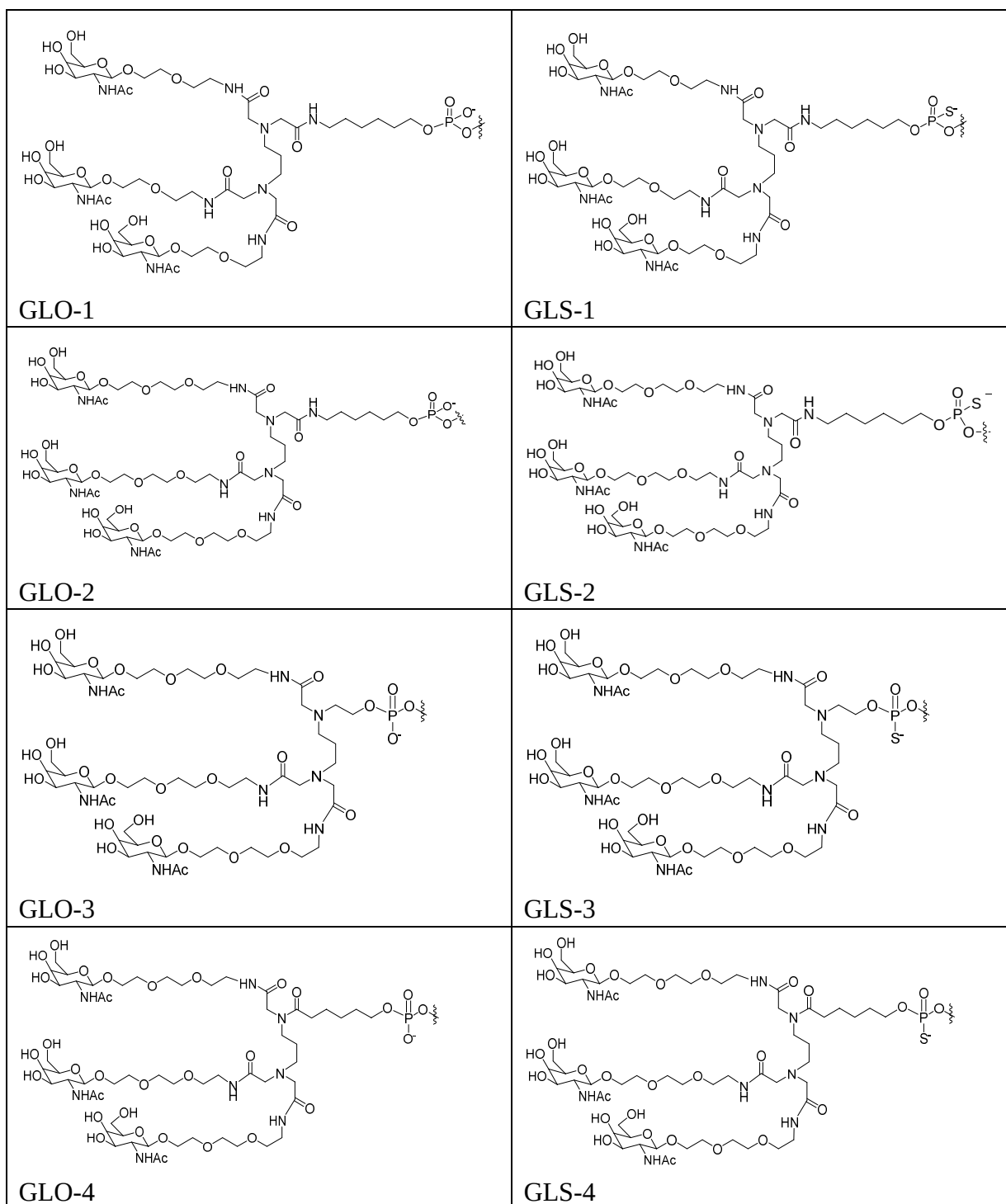
optionally, wherein each strand is no more than 23 nucleotides in length.

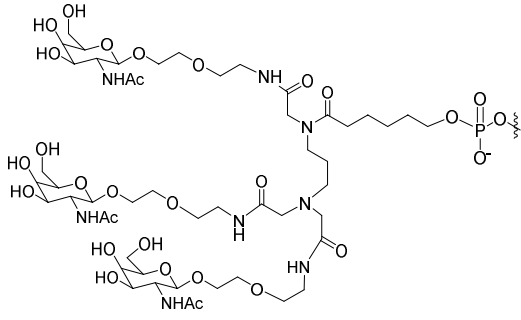
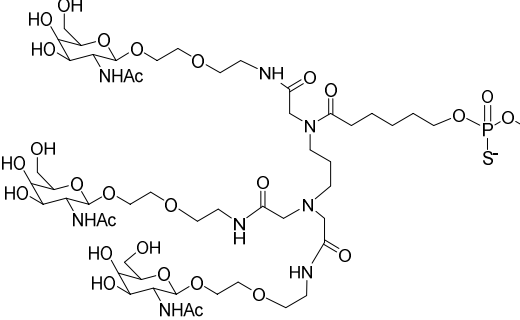
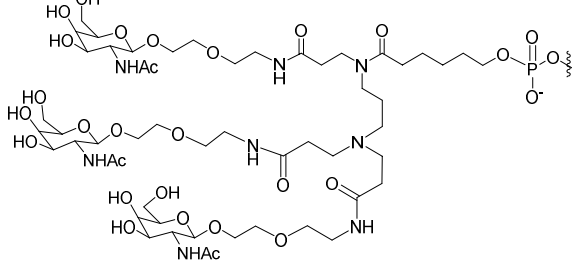
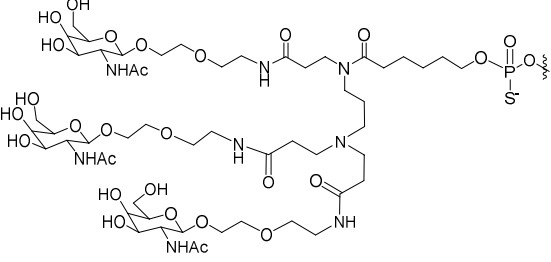
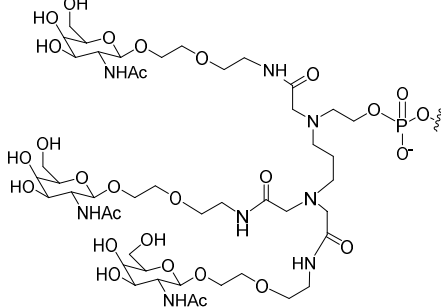
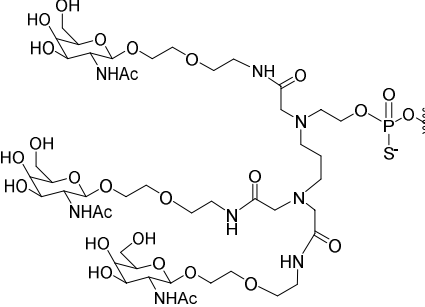
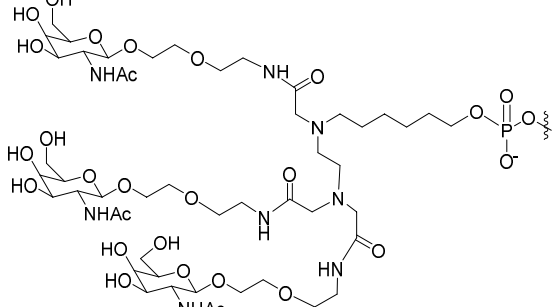
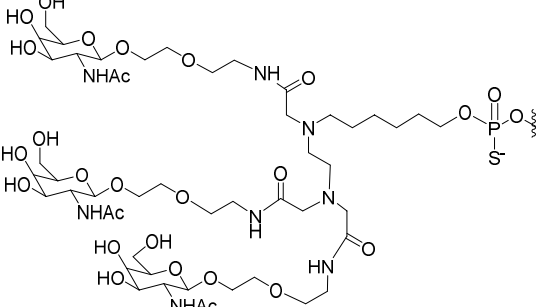
6. The dsRNA agent of claim 1, wherein the dsRNA agent comprises at least one modified nucleotide and further comprises one or more targeting groups or linking groups;

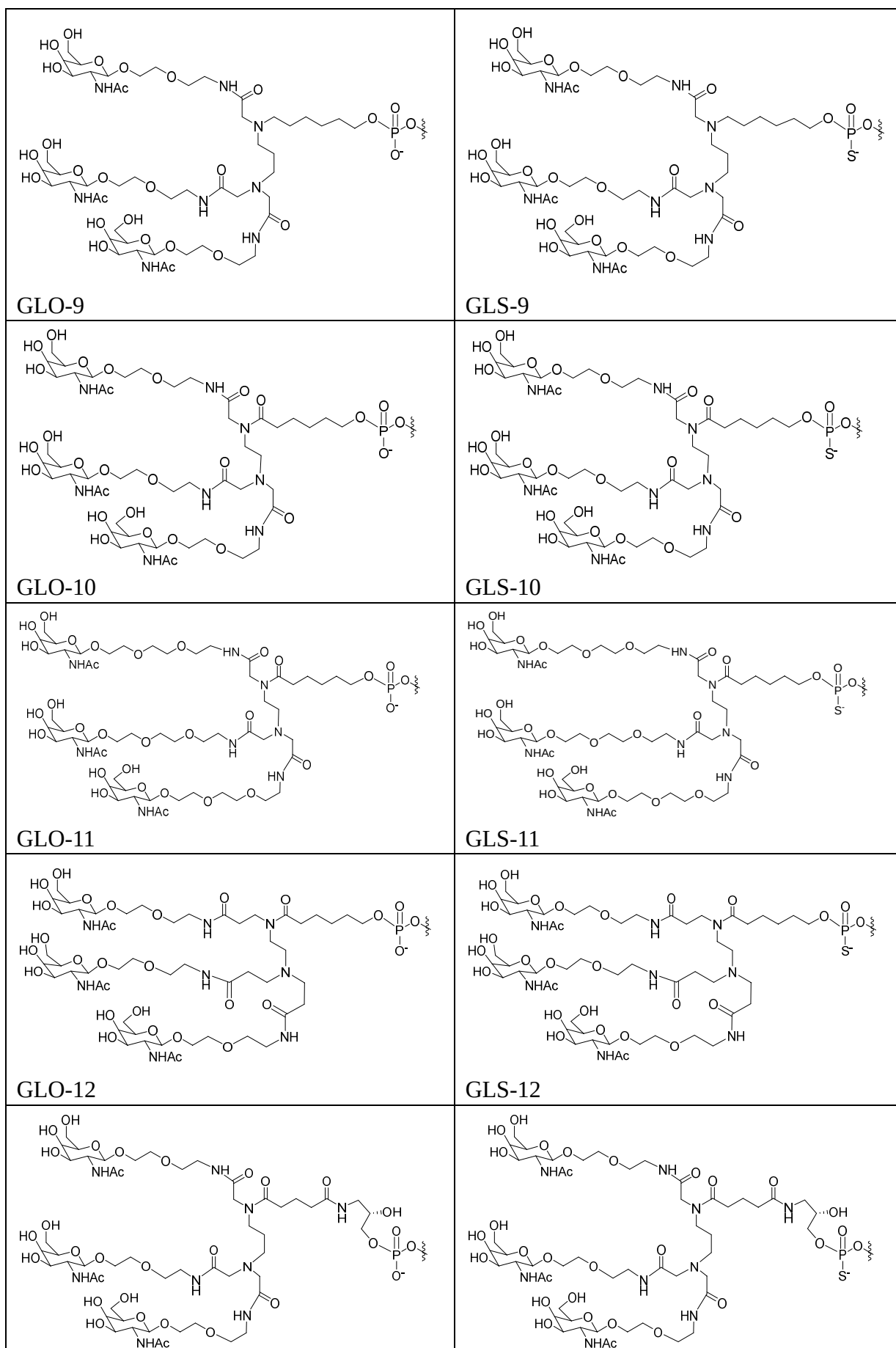
optionally, wherein the one or more targeting groups or linking groups are conjugated to the sense strand,

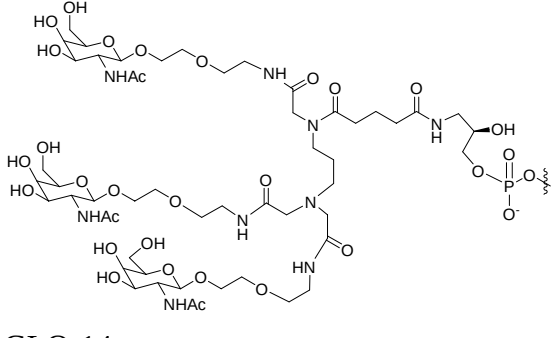
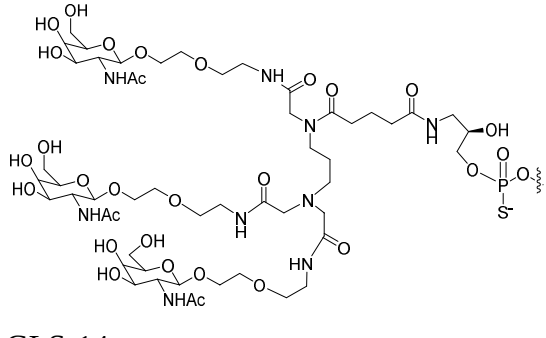
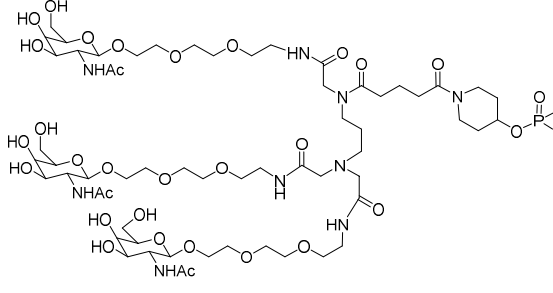
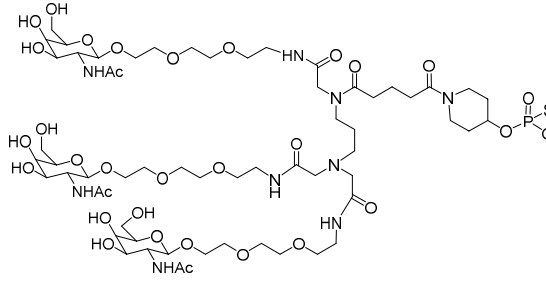
optionally, wherein the targeting group or linking group comprises N-acetyl-galactosamine (GalNAc); and

optionally wherein the targeting group has a structure:



 GLO-5	 GLS-5
 GLO-6	 GLS-6
 GLO-7	 GLS-7
 GLO-8	 GLS-8



GLO-13	GLS-13
	
GLO-14	GLS-14
	
GLO-16	GLS-16.

7. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a targeting group that is conjugated to the 5'-terminal end of the sense strand, and/or
the dsRNA agent comprises a targeting group that is conjugated to the 3'-terminal end of the sense strand.
8. The dsRNA agent of claim 1, wherein the antisense strand comprises one inverted abasic residue at 3'-terminal end,
optionally, wherein the sense strand comprises one or two inverted abasic residues at 3' or/and 5' terminal end.

9. The dsRNA agent of claim 1, wherein the dsRNA agent has two blunt ends; or
wherein at least one strand comprises a 3' overhang of at least 1 or 2 nucleotides.

10. The dsRNA agent according to claim 1, wherein the dsRNA agent comprises a
sequence selected from the group consisting of duplex sequences set forth in SEQ ID
NO: 278 and SEQ ID NO: 328;

SEQ ID NO: 546 and SEQ ID NO: 576;

SEQ ID NO: 547 and SEQ ID NO: 577;

SEQ ID NO: 548 and SEQ ID NO: 578;

SEQ ID NO: 550 and SEQ ID NO: 580;

SEQ ID NO: 551 and SEQ ID NO: 581;

SEQ ID NO: 552 and SEQ ID NO: 582;

SEQ ID NO: 553 and SEQ ID NO: 583;

SEQ ID NO: 554 and SEQ ID NO: 584;

SEQ ID NO: 555 and SEQ ID NO: 585;

SEQ ID NO: 556 and SEQ ID NO: 586;

SEQ ID NO: 557 and SEQ ID NO: 587;

SEQ ID NO: 558 and SEQ ID NO: 588;

SEQ ID NO: 559 and SEQ ID NO: 589;

SEQ ID NO: 560 and SEQ ID NO: 590;

SEQ ID NO: 561 and SEQ ID NO: 591;

SEQ ID NO: 562 and SEQ ID NO: 592;

SEQ ID NO: 563 and SEQ ID NO: 593;

SEQ ID NO: 564 and SEQ ID NO: 594;

SEQ ID NO: 565 and SEQ ID NO: 595;

SEQ ID NO: 566 and SEQ ID NO: 596;

SEQ ID NO: 567 and SEQ ID NO: 597;

SEQ ID NO: 568 and SEQ ID NO: 598;

SEQ ID NO: 569 and SEQ ID NO: 599;

SEQ ID NO: 570 and SEQ ID NO: 600;

SEQ ID NO: 571 and SEQ ID NO: 601;

SEQ ID NO: 572 and SEQ ID NO: 602;

SEQ ID NO: 573 and SEQ ID NO: 603;

SEQ ID NO: 574 and SEQ ID NO: 604; and

SEQ ID NO: 575 and SEQ ID NO: 605.

11. The dsRNA agent according to claim 1, wherein, the dsRNA agent comprises a sequence selected from the group consisting of duplex sequences set forth in SEQ ID NO: 401 and SEQ ID NO: 428; and SEQ ID NO: 606 and SEQ ID NO: 611.

12. A composition comprising a dsRNA agent of any one of claims 1-11, optionally further comprising a pharmaceutically acceptable carrier;
optionally further comprising one or more additional therapeutic agents,
optionally wherein the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial;
optionally, wherein the composition is formulated for subcutaneous administration or is formulated for intravenous (IV) administration.

13. A method of inhibiting the expression of an ANGPTL3 gene in a cell *in vitro*, comprising:
(i) preparing a cell comprising an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-11 or a composition of claim 12,

optionally, further comprising: (ii) maintaining the cell prepared in (i) for a time sufficient to obtain degradation of the mRNA transcript of an ANGPTL3 gene, thereby inhibiting expression of the ANGPTL3 gene in the cell.

14. The double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-11, or the composition of claim 12 for use in treating a disease associated with the presence of ANGPTL3 protein;

optionally, wherein the disease is one or more of: hyperlipidemia, hypertriglyceridemia, abnormal lipid and/or cholesterol metabolism, homozygous and heterozygous familial hypercholesterolemia, statin resistant hypercholesterolemia, cardiometabolic disease, obesity, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, pancreatitis caused by hypertriglyceridemia;

optionally, the composition further comprises one or more ANGPTL3 antisense polynucleotides, or a non-ANGPTL3 dsRNA therapeutic agent;

optionally, the non-ANGPTL3 dsRNA therapeutic agent is one of more of: (i) a statin; (ii) one or more of an antibody, antisense oligonucleotide (ASO), and a PCSK9 siRNA molecule capable of reducing PCSK9 expression; (iii) a therapeutic agent capable of reducing lipid accumulation in a subject, and (iv) a therapeutic agent capable of reducing cholesterol levels and/or accumulation in a subject.

15. The double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-11, or the composition of claim 12 for use in decreasing a level of ANGPTL3 protein in a subject with ANGPTL3-associated disease compared to a baseline pre-treatment level of ANGPTL3 protein in the subject with ANGPTL3-associated disease, or altering a physiological characteristic of an ANGPTL3-associated disease in a subject with ANGPTL3-associated disease compared to a baseline pre-treatment physiological characteristic of the ANGPTL3-associated disease in the subject with ANGPTL3-associated disease;

optionally, the physiological characteristic is one or more of: the subject's serum lipid level, the subject's HDL level, the subjects HDL : LDL ratio, the subject's serum triglyceride level, and the amount of fat in the subject's liver.