

EP Application No.: 16 852 695.2
Applicant: Arrowhead Pharmaceuticals, Inc.
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NEW CLAIMS

1. An LPA RNA interference (RNAi) agent comprising a sense strand and an antisense strand, wherein the antisense strand comprises the sequence of any one of SEQ ID NO:1280, SEQ ID NO:1282, SEQ ID NO:1246, SEQ ID NO:1242, SEQ ID NO:1244, or SEQ ID NO:1254, and wherein the sense strand comprises a sequence that is complementary to the sequence of the antisense strand.
2. The LPA RNAi agent of claim 1, wherein the sense strand and antisense strand are each 19 to 26 nucleotides in length.
3. The LPA RNAi agent of claim 2, wherein the sense strand and antisense strand are each 21 nucleotides in length.
4. The LPA RNAi agent of any one of claims 1 to 3, wherein the LPA RNAi agent comprises one or two overhangs.
5. The LPA RNAi agent of claim 4, wherein the LPA RNAi agent comprises an overhang at the 3' end of the antisense strand and an overhang at the 3' end of the sense strand.
6. The LPA RNAi agent of any one of claims 1 to 3, wherein the LPA RNAi agent comprises one or two blunt ends.
7. The LPA RNAi agent of claim 6, wherein the LPA RNAi agent comprises two blunt ends.
8. The LPA RNAi agent of any one of claims 1 to 7, wherein the sense strand, the antisense strand, or both the sense and antisense strand comprise one or more modified nucleotides.
9. The LPA RNAi agent of claim 8, wherein the one or more modified nucleotides are independently selected from a 2'-modified nucleotide, a locked nucleotide, an abasic nucleotide, an inverted deoxynucleotide, a morpholino nucleotide, a 2',3'-seco nucleotide mimic, or a nucleotide containing a non-natural base.

10. The LPA RNAi agent of claim 9, wherein the 2'-modified nucleotide is a 2'-O-methyl nucleotide, a 2'-deoxy-2'-fluoro nucleotide, a 2'-deoxynucleotide, a 2'-methoxyethyl nucleotide, a 2'-amino nucleotide, or a 2'-alkyl nucleotide.
11. The LPA RNAi agent of any one of claims 1 to 10, wherein the LPA RNAi agent comprises one or more phosphorothioate internucleoside linkages.
12. The LPA RNAi agent of any one of claims 1 to 11, wherein the LPA RNAi agent further comprises a targeting group, wherein the targeting group comprises an asialoglycoprotein receptor ligand.
13. The LPA RNAi agent of claim 12, wherein the asialoglycoprotein receptor ligand comprises a galactose cluster selected from (C11-PEG3-NAG3), (C6-PEG4-NAG3), (NAG3), (NAG4), (NAG3-AA2), (NAG3-Palm), (NAG13), (NAG18), (NAG24), (NAG25), (NAG25)s, (NAG26), (NAG27), (NAG28), (NAG29), (NAG30), (NAG30)s, (NAG31), (NAG31s), (NAG32), (NAG33), (NAG34), (NAG35), (NAG36), and (NAG37).
14. The LPA RNAi agent of claim 12 or 13, wherein the targeting group is conjugated to the 5' end of the sense strand or the 3' end of the sense strand.
15. The LPA RNAi agent of any one of claims 1 to 14, wherein:
- a) the antisense strand comprises the sequence of SEQ ID NO:1280 and the sense strand comprises the sequence of SEQ ID NO:1284;
 - b) the antisense strand comprises the sequence of SEQ ID NO:1246 and the sense strand comprises the sequence of SEQ ID NO:1247;
 - c) the antisense strand comprises the sequence of SEQ ID NO:1242 and the sense strand comprises the sequence of SEQ ID NO:1243;
 - d) the antisense strand comprises the sequence of SEQ ID NO:1244 and the sense strand comprises the sequence of SEQ ID NO:1245;
 - e) the antisense strand comprises the sequence of SEQ ID NO:1254 and the sense strand comprises the sequence of SEQ ID NO:1255;
 - f) the antisense strand comprises the sequence of SEQ ID NO:1280 and the sense strand comprises the sequence of SEQ ID NO:1260; or
 - g) the antisense strand comprises the sequence of SEQ ID NO:1282 and the sense strand comprises the sequence of SEQ ID NO:1259.

16. The LPA RNAi agent of any one of claims 1 to 15, wherein:

- a) the antisense strand comprises the sequence of SEQ ID NO:188 and the sense strand comprises the sequence of SEQ ID NO:384;
- b) the antisense strand comprises the sequence of SEQ ID NO:156 and the sense strand comprises the sequence of SEQ ID NO:310;
- c) the antisense strand comprises the sequence of SEQ ID NO:164 and the sense strand comprises the sequence of SEQ ID NO:357;
- d) the antisense strand comprises the sequence of SEQ ID NO:164 and the sense strand comprises the sequence of SEQ ID NO:376; or
- e) the antisense strand comprises the sequence of SEQ ID NO:164 and the sense strand comprises the sequence of SEQ ID NO:384.

17. The LPA RNAi agent of any one of claims 1 to 16, wherein:

- a) the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 790 and the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 1189;
- b) the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 637 and the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 1132;
- c) the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 709 and the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 1135;
- d) the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 787 and the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 1191; or
- e) the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 788 and the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 1189.

18. The LPA RNAi agent of claim 17, wherein the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 790 and the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 1189.

19. A pharmaceutical composition comprising the LPA RNAi agent of any one of claims 1 to 18 and a pharmaceutically acceptable excipient.

20. The LPA RNAi agent of any one of claims 1 to 18 for use in a method for inhibiting LPA gene expression in a subject.
21. The LPA RNAi agent of any one of claims 1 to 18 for use in treating cardiovascular disease in a subject in need thereof.
22. The LPA RNAi agent of any one of claims 1 to 18 for use in treating Berger's disease, peripheral artery disease, coronary artery disease, metabolic syndrome, acute coronary syndrome, aortic valve stenosis, aortic valve regurgitation, aortic dissection, retinal artery occlusion, cerebrovascular disease, mesenteric ischemia, superior mesenteric artery occlusion, renal artery stenosis, stable/unstable angina, acute coronary syndrome, heterozygous or homozygous familial hypercholesterolemia, hyperapobetalipoproteinemia, cerebrovascular atherosclerosis, cerebrovascular disease, or venous thrombosis in a subject in need thereof.