

CLAIMS

What is claimed:

1. ~~—A method for treating, reducing, or preventing atherosclerosis in a patient in need thereof comprising administering to the patient an LPA RNAi construct at a dose from about 9 mg to about 675 mg at a dosing interval of at least 8 weeks, wherein the LPA RNAi construct comprises a sense strand comprising the sequence of SEQ ID NO: 1, an antisense strand comprising the sequence of SEQ ID NO: 2, and a targeting moiety comprising an asialoglycoprotein receptor ligand, wherein the targeting moiety is covalently attached to the 5' end of the sense strand.~~

2. ~~—A method for reducing serum or plasma Lp(a) levels in a patient in need thereof comprising administering to the patient an LPA RNAi construct at a dose from about 9 mg to about 675 mg at a dosing interval of at least 8 weeks, wherein the LPA RNAi construct comprises a sense strand comprising the sequence of SEQ ID NO: 1, an antisense strand comprising the sequence of SEQ ID NO: 2, and a targeting moiety comprising an asialoglycoprotein receptor ligand, wherein the targeting moiety is covalently attached to the 5' end of the sense strand.~~

3. ~~—The method of claim 2, wherein the patient is diagnosed with or at risk of a cardiovascular disease.~~

4. ~~—The method of claim 3, wherein the cardiovascular disease is coronary artery disease, carotid artery disease, peripheral artery disease, myocardial infarction, cerebrovascular disease, stroke, aortic valve stenosis, stable or unstable angina, atrial fibrillation, heart failure, hyperlipidemia, heterozygous familial hypercholesterolemia, or homozygous familial hypercholesterolemia.~~

5. ~~—The method of claim 2, wherein the patient is diagnosed with chronic kidney disease.~~

6. ~~—The method of claim 2, wherein the patient has a history of myocardial infarction.~~

7. ~~—The method of claim 2, wherein the patient is diagnosed with acute coronary syndrome.~~

8. ~~—A method for treating, reducing, or preventing a cardiovascular disease in a patient in need thereof comprising administering to the patient an LPA RNAi construct at a dose from about 9 mg to about 675 mg at a dosing interval of at least 8 weeks, wherein the LPA RNAi construct comprises a sense strand comprising the sequence of SEQ ID NO: 1, an antisense strand comprising the sequence of SEQ ID NO: 2, and a targeting moiety comprising an asialoglycoprotein receptor ligand, wherein the targeting moiety is covalently attached to the 5' end of the sense strand.~~

9. ~~—The method of claim 8, wherein the cardiovascular disease is coronary artery disease, carotid artery disease, peripheral artery disease, myocardial infarction, cerebrovascular disease, stroke, aortic valve stenosis, stable or unstable angina, atrial fibrillation, heart failure, hyperlipidemia, heterozygous familial hypercholesterolemia, or homozygous familial hypercholesterolemia.~~

10. ~~—A method for reducing the risk of a cardiovascular event in a patient with atherosclerotic cardiovascular disease comprising administering to the patient an LPA RNAi construct at a dose from about 9 mg to about 675 mg at a dosing interval of at least 8 weeks, wherein the LPA RNAi construct comprises a sense strand comprising the sequence of SEQ ID NO: 1, an antisense strand comprising the sequence of SEQ ID NO: 2, and a targeting moiety comprising an asialoglycoprotein receptor ligand, wherein the targeting moiety is covalently attached to the 5' end of the sense strand.~~

11. ~~—The method of claim 10, wherein the cardiovascular event is cardiovascular death, myocardial infarction, stroke, and/or coronary revascularization.~~

12. ~~—The method of claim 10 or 11, wherein the patient has a history of coronary revascularization, a history of coronary artery bypass grafting, a diagnosis of coronary artery disease, a diagnosis of atherosclerotic cerebrovascular disease, a diagnosis of peripheral artery disease, and/or a history of myocardial infarction.~~

13. —The method of any one of claims 10 to 12, wherein the patient has experienced a myocardial infarction within 1 year prior to the first administration of the LPA RNAi construct.

14. —The method of any one of claims 10 to 12, wherein the patient is hospitalized for acute coronary syndrome or unstable angina.

15. —The method of any one of claims 1 to 14, wherein the patient has a serum or plasma Lp(a) level of about 70 nmol/L or greater prior to the first administration of the LPA RNAi construct.

16. —The method of any one of claims 1 to 14, wherein the patient has a serum or plasma Lp(a) level of about 100 nmol/L or greater prior to the first administration of the LPA RNAi construct.

17. —The method of any one of claims 1 to 14, wherein the patient has a serum or plasma Lp(a) level of about 125 nmol/L or greater prior to the first administration of the LPA RNAi construct.

18. —The method of any one of claims 1 to 14, wherein the patient has a serum or plasma Lp(a) level of about 150 nmol/L or greater prior to the first administration of the LPA RNAi construct.

19. —The method of any one of claims 1 to 14, wherein the patient has a serum or plasma Lp(a) level of about 175 nmol/L or greater prior to the first administration of the LPA RNAi construct.

20. —The method of any one of claims 1 to 14, wherein the patient has a serum or plasma Lp(a) level of about 200 nmol/L or greater prior to the first administration of the LPA RNAi construct.

21. —The method of any one of claims 1 to 14, wherein the patient has a serum or plasma Lp(a) level of about 225 nmol/L or greater prior to the first administration of the LPA RNAi construct.
22. —The method of any one of claims 1 to 21, wherein the dosing interval is about 12 weeks.
23. —The method of any one of claims 1 to 21, wherein the dosing interval is about 24 weeks.
24. —The method of any one of claims 1 to 21, wherein the LPA RNAi construct is administered to the patient at a dose from about 10 mg to about 225 mg once every 12 weeks.
25. —The method of claim 24, wherein the LPA RNAi construct is administered to the patient at a dose from about 50 mg to about 100 mg once every 12 weeks.
26. —The method of claim 24, wherein the LPA RNAi construct is administered to the patient at a dose from about 150 mg to about 225 mg once every 12 weeks.
27. —The method of claim 24, wherein the LPA RNAi construct is administered to the patient at a dose of about 75 mg once every 12 weeks.
28. —The method of claim 24, wherein the LPA RNAi construct is administered to the patient at a dose of about 150 mg once every 12 weeks.
29. —The method of claim 24, wherein the LPA RNAi construct is administered to the patient at a dose of about 225 mg once every 12 weeks.
30. —The method of any one of claims 1 to 21, wherein the LPA RNAi construct is administered to the patient at a dose from about 225 mg to about 675 mg once every 24 weeks.
31. —The method of claim 30, wherein the LPA RNAi construct is administered to the patient at a dose of about 225 mg once every 24 weeks.

32. — The method of any one of claims 1 to 31, wherein the patient is receiving a lipid-lowering therapy.

33. — The method of claim 32, wherein the lipid-lowering therapy is a statin, ezetimibe, a PCSK9 inhibitor, bempedoic acid, or combinations thereof.

34. — The method of any one of claims 1 to 33, wherein the patient has a serum low-density lipoprotein cholesterol (LDL-C) level of about 100 mg/dL or less prior to the first administration of the LPA RNAi construct.

35. — The method of any one of claims 1 to 33, wherein the patient has a serum low-density lipoprotein cholesterol (LDL-C) level of about 70 mg/dL or less prior to the first administration of the LPA RNAi construct.

36. — The method of any one of claims 1 to 35, wherein the patient has an estimated glomerular filtration rate of about 30 mL/min/1.73 m² or greater prior to the first administration of the LPA RNAi construct.

37. — The method of any one of claims 1 to 36, wherein the patient has an average systolic blood pressure less than about 160 mmHg and an average diastolic blood pressure of less than about 100 mmHg at rest prior to the first administration of the LPA RNAi construct.

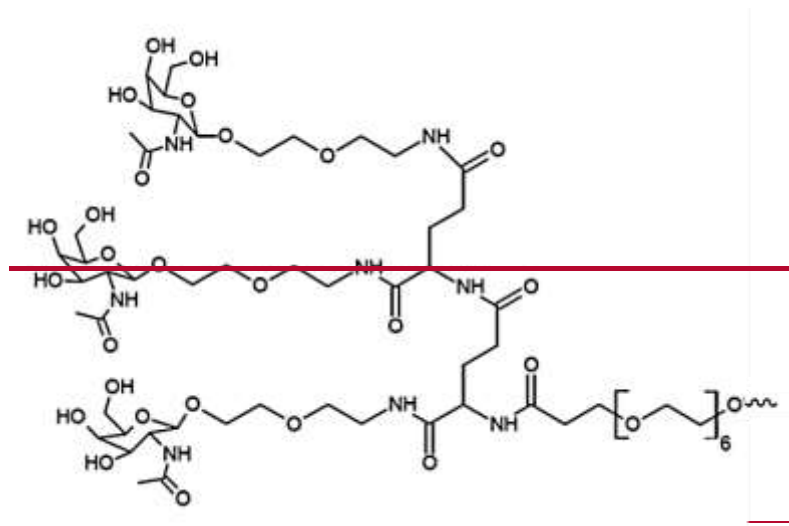
38. — The method of any one of claims 1 to 37, wherein the patient has a glycated hemoglobin A1c level less than about 8.5% prior to the first administration of the LPA RNAi construct.

39. — The method of any one of claims 1 to 38, wherein the patient has a serum triglyceride level of less than about 400 mg/dL prior to the first administration of the LPA RNAi construct.

40. — The method of any one of claims 1 to 39, wherein the sense strand of the LPA RNAi construct comprises or consists of the sequence of SEQ ID NO: 3 and the antisense strand of the LPA RNAi construct comprises or consists of the sequence of SEQ ID NO: 4.

41. ~~The method of any one of claims 1 to 40, wherein the sense strand of the LPA RNAi construct comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 5 and the antisense strand of the LPA RNAi construct comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 6.~~

42. ~~The method of any one of claims 1 to 41, wherein the targeting moiety of the LPA RNAi construct has the structure of:~~



43. ~~The method of any one of claims 1 to 42, wherein the LPA RNAi construct is olpasiran.~~

44. ~~The method of any one of claims 1 to 43, wherein administration of the LPA RNAi construct reduces serum or plasma Lp(a) levels in the patient by greater than 50% for at least 12 weeks as compared to the patient's baseline serum or plasma Lp(a) levels.~~

45. ~~The method of any one of claims 1 to 43, wherein administration of the LPA RNAi construct reduces serum or plasma Lp(a) levels in the patient by greater than 80% for at least 12 weeks as compared to the patient's baseline serum or plasma Lp(a) levels.~~

46. ~~The method of any one of claims 1 to 43, wherein administration of the LPA RNAi construct reduces serum or plasma Lp(a) levels in the patient by greater than 90% for at least 12 weeks as compared to the patient's baseline serum or plasma Lp(a) levels.~~

47. —The method of any one of claims 1 to 43, wherein administration of the LPA RNAi construct reduces serum or plasma Lp(a) levels in the patient to about 100 nmol/L or less.

48. —The method of any one of claims 1 to 43, wherein administration of the LPA RNAi construct reduces serum or plasma Lp(a) levels in the patient to about 75 nmol/L or less.

49. —The method of any one of claims 1 to 43, wherein administration of the LPA RNAi construct reduces serum or plasma Lp(a) levels in the patient to about 50 nmol/L or less.

50. —The method of any one of claims 1 to 49, wherein the LPA RNAi construct is administered to the patient in a pharmaceutical composition comprising potassium phosphate and sodium chloride.

51. —The method of any one of claims 1 to 50, wherein the LPA RNAi construct is administered to the patient by subcutaneous injection.

52. —The method of claim 51, wherein the injection volume is about 1 mL or less.

53. —An LPA RNAi construct for use in a method for treating, reducing, or preventing atherosclerosis in a patient in need thereof, wherein the method comprises administering to the patient the LPA RNAi construct at a dose from about 9 mg to about 675 mg at a dosing interval of at least 8 weeks, wherein the LPA RNAi construct comprises a sense strand comprising the sequence of SEQ ID NO: 1, an antisense strand comprising the sequence of SEQ ID NO: 2, and a targeting moiety comprising an asialoglycoprotein receptor ligand, wherein the targeting moiety is covalently attached to the 5' end of the sense strand.

54. —An LPA RNAi construct for use in a method for reducing serum or plasma Lp(a) levels in a patient in need thereof, wherein the method comprises administering to the patient the LPA RNAi construct at a dose from about 9 mg to about 675 mg at a dosing interval of at least 8 weeks, wherein the LPA RNAi construct comprises a sense strand comprising the sequence of SEQ ID NO: 1, an antisense strand comprising the sequence of SEQ ID NO: 2, and a targeting

moiety comprising an asialoglycoprotein receptor ligand, wherein the targeting moiety is covalently attached to the 5' end of the sense strand.

55. — The LPA RNAi construct for use according to claim 54, wherein the patient is diagnosed with or at risk of a cardiovascular disease.

56. — The LPA RNAi construct for use according to claim 55, wherein the cardiovascular disease is coronary artery disease, carotid artery disease, peripheral artery disease, myocardial infarction, cerebrovascular disease, stroke, aortic valve stenosis, stable or unstable angina, atrial fibrillation, heart failure, hyperlipidemia, heterozygous familial hypercholesterolemia, or homozygous familial hypercholesterolemia.

57. — The LPA RNAi construct for use according to claim 54, wherein the patient is diagnosed with chronic kidney disease.

58. — The LPA RNAi construct for use according to f claim 54, wherein the patient has a history of myocardial infarction.

59. — The LPA RNAi construct for use according to claim 54, wherein the patient is diagnosed with acute coronary syndrome.

60. — An LPA RNAi construct for use in a method for treating, reducing, or preventing a cardiovascular disease in a patient in need thereof, wherein the method comprises administering to the patient the LPA RNAi construct at a dose from about 9 mg to about 675 mg at a dosing interval of at least 8 weeks, wherein the LPA RNAi construct comprises a sense strand comprising the sequence of SEQ ID NO: 1, an antisense strand comprising the sequence of SEQ ID NO: 2, and a targeting moiety comprising an asialoglycoprotein receptor ligand, wherein the targeting moiety is covalently attached to the 5' end of the sense strand.

61. — The LPA RNAi construct for use according to claim 60, wherein the cardiovascular disease is coronary artery disease, carotid artery disease, peripheral artery disease, myocardial

infarction, cerebrovascular disease, stroke, aortic valve stenosis, stable or unstable angina, atrial fibrillation, heart failure, hyperlipidemia, heterozygous familial hypercholesterolemia, or homozygous familial hypercholesterolemia.

62. — An LPA RNAi construct for use in a method for reducing the risk of a cardiovascular event in a patient with atherosclerotic cardiovascular disease, wherein the method comprises administering to the patient the LPA RNAi construct at a dose from about 9 mg to about 675 mg at a dosing interval of at least 8 weeks, wherein the LPA RNAi construct comprises a sense strand comprising the sequence of SEQ ID NO: 1, an antisense strand comprising the sequence of SEQ ID NO: 2, and a targeting moiety comprising an asialoglycoprotein receptor ligand, wherein the targeting moiety is covalently attached to the 5' end of the sense strand.

63. — The LPA RNAi construct for use according to claim 62, wherein the cardiovascular event is cardiovascular death, myocardial infarction, stroke, and/or coronary revascularization.

64. — The LPA RNAi construct for use according to claim 62 or 63, wherein the patient has a history of coronary revascularization, a history of coronary artery bypass grafting, a diagnosis of coronary artery disease, a diagnosis of atherosclerotic cerebrovascular disease, a diagnosis of peripheral artery disease, and/or a history of myocardial infarction.

65. — The LPA RNAi construct for use according to any one of claims 62 to 64, wherein the patient has experienced a myocardial infarction within 1 year prior to the first administration of the LPA RNAi construct.

66. — The LPA RNAi construct for use according to any one of claims 62 to 64, wherein the patient is hospitalized for acute coronary syndrome or unstable angina.

67. — The LPA RNAi construct for use according to any one of claims 53 to 66, wherein the patient has a serum or plasma Lp(a) level of about 70 nmol/L or greater prior to the first administration of the LPA RNAi construct.

~~68. — The LPA RNAi construct for use according to any one of claims 53 to 66, wherein the patient has a serum or plasma Lp(a) level of about 100 nmol/L or greater prior to the first administration of the LPA RNAi construct.~~

~~69. — The LPA RNAi construct for use according to any one of claims 53 to 66, wherein the patient has a serum or plasma Lp(a) level of about 125 nmol/L or greater prior to the first administration of the LPA RNAi construct.~~

~~70. — The LPA RNAi construct for use according to any one of claims 53 to 66, wherein the patient has a serum or plasma Lp(a) level of about 150 nmol/L or greater prior to the first administration of the LPA RNAi construct.~~

~~71. — The LPA RNAi construct for use according to any one of claims 53 to 66, wherein the patient has a serum or plasma Lp(a) level of about 175 nmol/L or greater prior to the first administration of the LPA RNAi construct.~~

~~72. — The LPA RNAi construct for use according to any one of claims 53 to 66, wherein the patient has a serum or plasma Lp(a) level of about 200 nmol/L or greater prior to the first administration of the LPA RNAi construct.~~

~~73. — The LPA RNAi construct for use according to any one of claims 53 to 66, wherein the patient has a serum or plasma Lp(a) level of about 225 nmol/L or greater prior to the first administration of the LPA RNAi construct.~~

~~74. — The LPA RNAi construct for use according to any one of claims 53 to 73, wherein the dosing interval is about 12 weeks.~~

~~75. — The LPA RNAi construct for use according to any one of claims 53 to 73, wherein the dosing interval is about 24 weeks.~~

~~76. — The LPA RNAi construct for use according to any one of claims 53 to 73, wherein the LPA RNAi construct is administered to the patient at a dose from about 10 mg to about 225 mg once every 12 weeks.~~

~~77. — The LPA RNAi construct for use according to claim 76, wherein the LPA RNAi construct is administered to the patient at a dose from about 50 mg to about 100 mg once every 12 weeks.~~

~~78. — The LPA RNAi construct for use according to claim 76, wherein the LPA RNAi construct is administered to the patient at a dose from about 150 mg to about 225 mg once every 12 weeks.~~

~~79. — The LPA RNAi construct for use according to claim 76, wherein the LPA RNAi construct is administered to the patient at a dose of about 75 mg once every 12 weeks.~~

~~80. — The LPA RNAi construct for use according to claim 76, wherein the LPA RNAi construct is administered to the patient at a dose of about 150 mg once every 12 weeks.~~

~~81. — The LPA RNAi construct for use according to claim 76, wherein the LPA RNAi construct is administered to the patient at a dose of about 225 mg once every 12 weeks.~~

~~82. — The LPA RNAi construct for use according to any one of claims 53 to 73, wherein the LPA RNAi construct is administered to the patient at a dose from about 225 mg to about 675 mg once every 24 weeks.~~

~~83. — The LPA RNAi construct for use according to claim 82, wherein the LPA RNAi construct is administered to the patient at a dose of about 225 mg once every 24 weeks.~~

~~84. — The LPA RNAi construct for use according to any one of claims 53 to 83, wherein the patient is receiving a lipid lowering therapy.~~

85. —The LPA RNAi construct for use according to claim 84, wherein the lipid-lowering therapy is a statin, ezetimibe, a PCSK9 inhibitor, bempedoic acid, or combinations thereof.

86. —The LPA RNAi construct for use according to any one of claims 53 to 85, wherein the patient has a serum low-density lipoprotein cholesterol (LDL-C) level of about 100 mg/dL or less prior to the first administration of the LPA RNAi construct.

87. —The LPA RNAi construct for use according to any one of claims 53 to 85, wherein the patient has a serum low-density lipoprotein cholesterol (LDL-C) level of about 70 mg/dL or less prior to the first administration of the LPA RNAi construct.

88. —The LPA RNAi construct for use according to any one of claims 53 to 87, wherein the patient has an estimated glomerular filtration rate of about 30 mL/min/1.73 m² or greater prior to the first administration of the LPA RNAi construct.

89. —The LPA RNAi construct for use according to any one of claims 53 to 88, wherein the patient has an average systolic blood pressure less than about 160 mmHg and an average diastolic blood pressure of less than about 100 mmHg at rest prior to the first administration of the LPA RNAi construct.

90. —The LPA RNAi construct for use according to any one of claims 53 to 89, wherein the patient has a glycated hemoglobin A1c level less than about 8.5% prior to the first administration of the LPA RNAi construct.

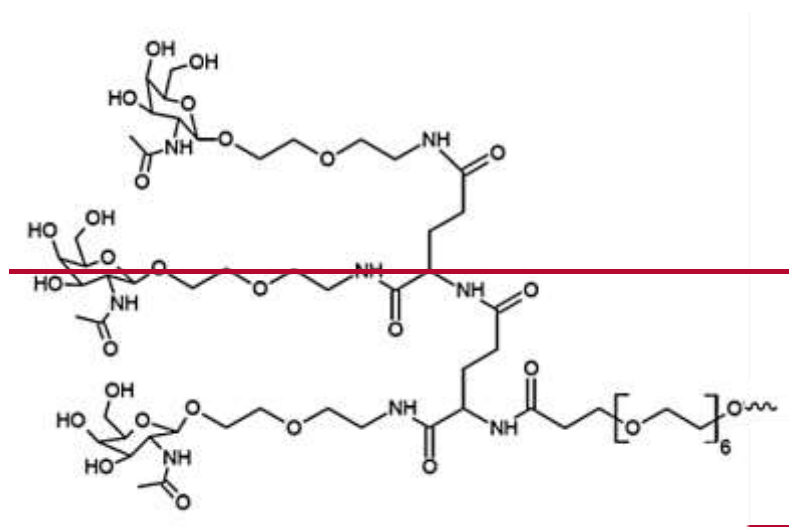
91. —The LPA RNAi construct for use according to any one of claims 53 to 90, wherein the patient has a serum triglyceride level of less than about 400 mg/dL prior to the first administration of the LPA RNAi construct.

92. —The LPA RNAi construct for use according to any one of claims 53 to 91, wherein the sense strand of the LPA RNAi construct comprises or consists of the sequence of SEQ ID NO: 3

and the antisense strand of the LPA RNAi construct comprises or consists of the sequence of SEQ ID NO: 4.

93. — The LPA RNAi construct for use according to any one of claims 53 to 92, wherein the sense strand of the LPA RNAi construct comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 5 and the antisense strand of the LPA RNAi construct comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 6.

94. — The LPA RNAi construct for use according to any one of claims 53 to 93, wherein the targeting moiety of the LPA RNAi construct has the structure of:



95. — The LPA RNAi construct for use according to any one of claims 53 to 94, wherein the LPA RNAi construct is olpasiran.

96. — The LPA RNAi construct for use according to any one of claims 53 to 95, wherein administration of the LPA RNAi construct reduces serum or plasma Lp(a) levels in the patient by greater than 50% for at least 12 weeks as compared to the patient's baseline serum or plasma Lp(a) levels.

97. — The LPA RNAi construct for use according to any one of claims 53 to 95, wherein administration of the LPA RNAi construct reduces serum or plasma Lp(a) levels in the patient by

greater than 80% for at least 12 weeks as compared to the patient's baseline serum or plasma Lp(a) levels.

98. — ~~The LPA RNAi construct for use according to any one of claims 53 to 95, wherein administration of the LPA RNAi construct reduces serum or plasma Lp(a) levels in the patient by greater than 90% for at least 12 weeks as compared to the patient's baseline serum or plasma Lp(a) levels.~~

99. — ~~The LPA RNAi construct for use according to any one of claims 53 to 95, wherein administration of the LPA RNAi construct reduces serum or plasma Lp(a) levels in the patient to about 100 nmol/L or less.~~

100. — ~~The LPA RNAi construct for use according to any one of claims 53 to 95, wherein administration of the LPA RNAi construct reduces serum or plasma Lp(a) levels in the patient to about 75 nmol/L or less.~~

101. — ~~The LPA RNAi construct for use according to any one of claims 53 to 95, wherein administration of the LPA RNAi construct reduces serum or plasma Lp(a) levels in the patient to about 50 nmol/L or less.~~

102. — ~~The LPA RNAi construct for use according to any one of claims 53 to 101, wherein the LPA RNAi construct is administered to the patient in a pharmaceutical composition comprising potassium phosphate and sodium chloride.~~

103. — ~~The LPA RNAi construct for use according to any one of claims 53 to 102, wherein the LPA RNAi construct is administered to the patient by subcutaneous injection.~~

104. — ~~The LPA RNAi construct for use according to claim 103, wherein the injection volume is about 1 mL or less.~~

~~1051~~. Use of an LPA RNAi construct ~~for~~in the preparation of a medicament for treating, reducing, or preventing atherosclerosis in a patient in need thereof, wherein the medicament is to be administered or formulated for administration at a dose from ~~about~~ 9 mg to ~~about~~ 675 mg at a dosing interval of at least 8 weeks, wherein the LPA RNAi construct comprises a sense strand comprising the sequence of SEQ ID NO: 1, an antisense strand comprising the sequence of SEQ ID NO: 2, and a targeting moiety comprising an asialoglycoprotein receptor ligand, wherein the targeting moiety is covalently attached to the 5' end of the sense strand.

~~1062~~. Use of an LPA RNAi construct ~~for~~in the preparation of a medicament for reducing serum or plasma Lp(a) levels in a patient in need thereof, wherein the medicament is to be administered or formulated for administration at a dose from ~~about~~ 9 mg to ~~about~~ 675 mg at a dosing interval of at least 8 weeks, wherein the LPA RNAi construct comprises a sense strand comprising the sequence of SEQ ID NO: 1, an antisense strand comprising the sequence of SEQ ID NO: 2, and a targeting moiety comprising an asialoglycoprotein receptor ligand, wherein the targeting moiety is covalently attached to the 5' end of the sense strand.

~~1073~~. The use of claim ~~1062~~, wherein the patient is diagnosed with or at risk of a cardiovascular disease.

~~1084~~. The use of claim ~~1073~~, wherein the cardiovascular disease is coronary artery disease, carotid artery disease, peripheral artery disease, myocardial infarction, cerebrovascular disease, stroke, aortic valve stenosis, stable or unstable angina, atrial fibrillation, heart failure, hyperlipidemia, heterozygous familial hypercholesterolemia, or homozygous familial hypercholesterolemia.

~~1095~~. The use of claim ~~1062~~, wherein the patient is diagnosed with chronic kidney disease.

~~1106~~. The use of claim ~~1062~~, wherein the patient has a history of myocardial infarction.

~~1117~~. The use of claim ~~1062~~, wherein the patient is diagnosed with acute coronary syndrome.

~~1128~~. Use of an LPA RNAi construct ~~for~~in the preparation of a medicament for treating, reducing, or preventing a cardiovascular disease in a patient in need thereof, wherein the medicament is to be administered or formulated for administration at a dose from ~~about~~ 9 mg to ~~about~~ 675 mg at a dosing interval of at least 8 weeks, wherein the LPA RNAi construct comprises a sense strand comprising the sequence of SEQ ID NO: 1, an antisense strand comprising the sequence of SEQ ID NO: 2, and a targeting moiety comprising an asialoglycoprotein receptor ligand, wherein the targeting moiety is covalently attached to the 5' end of the sense strand.

~~1139~~. The use of claim ~~1128~~, wherein the cardiovascular disease is coronary artery disease, carotid artery disease, peripheral artery disease, myocardial infarction, cerebrovascular disease, stroke, aortic valve stenosis, stable or unstable angina, atrial fibrillation, heart failure, hyperlipidemia, heterozygous familial hypercholesterolemia, or homozygous familial hypercholesterolemia.

~~11410~~. Use of an LPA RNAi construct ~~for~~in the preparation of a medicament for reducing the risk of a cardiovascular event in a patient with atherosclerotic cardiovascular disease, wherein the medicament is to be administered or formulated for administration at a dose from ~~about~~ 9 mg to ~~about~~ 675 mg at a dosing interval of at least 8 weeks, wherein the LPA RNAi construct comprises a sense strand comprising the sequence of SEQ ID NO: 1, an antisense strand comprising the sequence of SEQ ID NO: 2, and a targeting moiety comprising an asialoglycoprotein receptor ligand, wherein the targeting moiety is covalently attached to the 5' end of the sense strand.

~~11511~~. The use of claim ~~11410~~, wherein the cardiovascular event is cardiovascular death, myocardial infarction, stroke, and/or coronary revascularization.

~~11612~~. The use of claim ~~114 or 11510 or 11~~, wherein the patient has a history of coronary revascularization, a history of coronary artery bypass grafting, a diagnosis of coronary artery disease, a diagnosis of atherosclerotic cerebrovascular disease, a diagnosis of peripheral artery disease, and/or a history of myocardial infarction.

~~117~~13. The use of any one of claims ~~114 to 116~~10 to 12, wherein the patient has experienced a myocardial infarction within 1 year prior to the first administration of the medicament.

~~118~~14. The use of any one of claims ~~114 to 116~~10 to 12, wherein the patient is hospitalized for acute coronary syndrome or unstable angina.

~~119. The use of any one of claims 105 to 118, wherein the patient has a serum or plasma Lp(a) level of about 70 nmol/L or greater prior to the first administration of the medicament.~~

~~120. The use of any one of claims 105 to 118, wherein the patient has a serum or plasma Lp(a) level of about 100 nmol/L or greater prior to the first administration of the medicament.~~

~~121~~15. The use of any one of claims ~~105 to 118~~1 to 14, wherein the patient has a serum or plasma Lp(a) level of about 125 nmol/L or greater prior to the first administration of the medicament.

~~122~~16. The use of any one of claims ~~105 to 118~~1 to 14, wherein the patient has a serum or plasma Lp(a) level of about 150 nmol/L or greater prior to the first administration of the medicament.

~~123~~17. The use of any one of claims ~~105 to 118~~1 to 14, wherein the patient has a serum or plasma Lp(a) level of about 175 nmol/L or greater prior to the first administration of the medicament.

~~124~~18. The use of any one of claims ~~105 to 118~~1 to 14, wherein the patient has a serum or plasma Lp(a) level of about 200 nmol/L or greater prior to the first administration of the medicament.

12519. The use of any one of claims ~~105 to 1181~~ to 14, wherein the patient has a serum or plasma Lp(a) level of about 225 nmol/L or greater prior to the first administration of the medicament.

12620. The use of any one of claims ~~105 to 1251~~ to 19, wherein the dosing interval is about 12 weeks.

12721. The use of any one of claims ~~105 to 1251~~ to 19, wherein the dosing interval is about 24 weeks.

12822. The use of any one of claims ~~105 to 1251~~ to 19, wherein the medicament is to be administered or formulated for administration to the patient at a dose from ~~about~~ 10 mg to ~~about~~ 225 mg once every 12 weeks.

12923. The use of claim 12822, wherein the medicament is to be administered or formulated for administration to the patient at a dose from ~~about~~ 50 mg to ~~about~~ 100 mg once every 12 weeks.

13024. The use of claim 12822, wherein the medicament is to be administered or formulated for administration to the patient at a dose from ~~about~~ 150 mg to ~~about~~ 225 mg once every 12 weeks.

13125. The use of claim 12822, wherein the medicament is to be administered or formulated for administration to the patient at a dose of about 75 mg once every 12 weeks.

13226. The use of claim 12822, wherein the medicament is to be administered or formulated for administration to the patient at a dose of about 150 mg once every 12 weeks.

13327. The use of claim 12822, wherein the medicament is to be administered or formulated for administration to the patient at a dose of about 225 mg once every 12 weeks.

~~13428~~. The use of any one of claims ~~105 to 1251 to 19~~, wherein the medicament is to be administered or formulated for administration to the patient at a dose from ~~about~~ 225 mg to ~~about~~ 675 mg once every 24 weeks.

~~13529~~. The use of claim ~~13428~~, wherein the medicament is to be administered or formulated for administration to the patient at a dose of about 225 mg once every 24 weeks.

~~13630~~. The use of any one of claims ~~105 to 1351 to 29~~, wherein the patient is receiving a lipid-lowering therapy.

~~13731~~. The use of claim ~~13630~~, wherein the lipid-lowering therapy is a statin, ezetimibe, a PCSK9 inhibitor, bempedoic acid, or combinations thereof.

~~13832~~. The use of any one of claims ~~105 to 1371 to 31~~, wherein the patient has a serum low-density lipoprotein cholesterol (LDL-C) level of about 100 mg/dL or less prior to the first administration of the medicament.

~~139. — The use of any one of claims 105 to 137, wherein the patient has a serum low-density lipoprotein cholesterol (LDL-C) level of about 70 mg/dL or less prior to the first administration of the medicament.~~

~~140. — The use of any one of claims 105 to 139, wherein the patient has an estimated glomerular filtration rate of about 30 mL/min/1.73 m² or greater prior to the first administration of the medicament.~~

~~141. — The use of any one of claims 105 to 140, wherein the patient has an average systolic blood pressure less than about 160 mmHg and an average diastolic blood pressure of less than about 100 mmHg at rest prior to the first administration of the medicament.~~

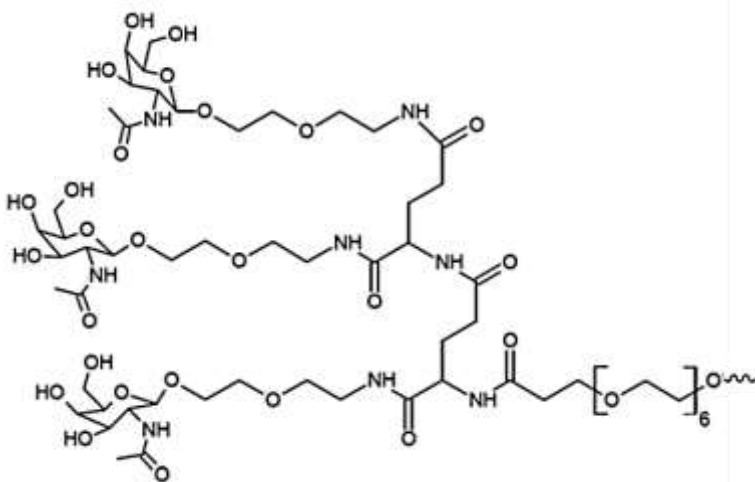
~~142. — The use of any one of claims 105 to 141, wherein the patient has a glycated hemoglobin A1c level less than about 8.5% prior to the first administration of the medicament.~~

~~143.~~ The use of any one of claims ~~105 to 142~~, wherein the patient has a serum triglyceride level of less than about 400 mg/dL prior to the first administration of the medicament.

~~144~~33. The use of any one of claims ~~105 to 143~~1 to 32, wherein the sense strand of the LPA RNAi construct comprises or consists of the sequence of SEQ ID NO: 3 and the antisense strand of the LPA RNAi construct comprises or consists of the sequence of SEQ ID NO: 4.

~~145~~34. The use of any one of claims ~~105 to 144~~1 to 33, wherein the sense strand of the LPA RNAi construct comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 5 and the antisense strand of the LPA RNAi construct comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 6.

~~146~~35. The use of any one of claims ~~105 to 145~~1 to 34, wherein the targeting moiety of the LPA RNAi construct has the structure of:



~~147~~36. The use of any one of claims ~~105-1~~ to 14635, wherein the LPA RNAi construct is olpasiran.

~~148. The use of any one of claims 105 to 147, wherein administration of the medicament reduces serum or plasma Lp(a) levels in the patient by greater than 50% for at least 12 weeks as compared to the patient's baseline serum or plasma Lp(a) levels.~~

~~149. The use of any one of claims 105 to 147, wherein administration of the medicament reduces serum or plasma Lp(a) levels in the patient by greater than 80% for at least 12 weeks as compared to the patient's baseline serum or plasma Lp(a) levels.~~

~~150. The use of any one of claims 105 to 147, wherein administration of the medicament reduces serum or plasma Lp(a) levels in the patient by greater than 90% for at least 12 weeks as compared to the patient's baseline serum or plasma Lp(a) levels.~~

~~151. The use of any one of claims 105 to 147, wherein administration of the medicament reduces serum or plasma Lp(a) levels in the patient to about 100 nmol/L or less.~~

~~152. The use of any one of claims 105 to 147, wherein administration of the medicament reduces serum or plasma Lp(a) levels in the patient to about 75 nmol/L or less.~~

~~153. The use of any one of claims 105 to 147, wherein administration of the medicament reduces serum or plasma Lp(a) levels in the patient to about 50 nmol/L or less.~~

~~154~~37. The use of any one of claims ~~105-1~~ to ~~153~~36, wherein the medicament is to be administered or formulated for administration to the patient in a pharmaceutical composition comprising potassium phosphate and sodium chloride.

~~155~~38. The use of any one of claims ~~105 to 154~~1 to 37, wherein the medicament is to be administered or formulated for administration to the patient by subcutaneous injection.

~~156~~39. The use of claim ~~155~~38, wherein the injection volume is about 1 mL or less.