

[0010] In some instances, the ds RNAi agent can be at a concentration from about 100 mg/mL to about 300 mg/mL. In other instances, the ds RNAi agent can be at a concentration from about 150 mg/mL to about 170 mg/mL, especially about 160 mg/mL, or from about 190 mg/mL to about 210 mg/mL, especially about 200 mg/mL.

[0011] In some instances, the formulations can be at a pH from about 6.0 to about 8.0. In other instances, the formulations can be at a pH of about 7.0.

[0011a] In an aspect, there is provided a pharmaceutical composition comprising:

a double-stranded (ds) RNAi agent or its pharmaceutically acceptable salt thereof at a concentration from about 100 mg/mL to about 300 mg/mL in water (H₂O), wherein the pharmaceutical composition is at a pH from about 6.0 to about 8.0, and wherein the ds RNAi agent comprises:

- (1) a sense strand comprising a nucleotide sequence of SEQ ID NO:1, and
- (2) an antisense strand comprising a nucleotide sequence of SEQ ID NO:2.

[0012] In some instances, the pharmaceutical compositions herein can be preservative free.

[0013] In some instances, the pharmaceutical compositions herein can be diluted with about 0.9% NaCl injection for lower doses.

[0014] In one particular instance, a pharmaceutical composition includes a ds RNAi agent that modulates *LPA* expression, where the ds RNAi agent has a sense strand having a nucleotide sequence of SEQ ID NO:1 and an antisense strand having a nucleotide sequence of SEQ ID NO:2 in H₂O at a concentration from about 150 mg/mL to about 170 mg/mL, especially about 160 mg/mL, at pH 7.0, and where the pharmaceutical composition is preservative free.

[0015] In another instance, a pharmaceutical composition includes a ds RNAi agent that modulates *LPA* expression, where the ds RNAi agent has a sense strand having a nucleotide sequence of SEQ ID NO:1 and an antisense strand having a nucleotide sequence of SEQ ID NO:2 in H₂O at a concentration from about 190 mg/mL to about 210 mg/mL, especially about 200 mg/mL, at pH 7.0, and where the pharmaceutical composition is preservative free.

[0016] In one particular instance, a pharmaceutical composition includes a ds RNAi agent that modulates *LPA* expression, where the ds RNAi agent has a sense strand having a nucleotide sequence of SEQ ID NO:3 and an antisense strand having a nucleotide sequence of SEQ ID NO:4 in H₂O at a concentration from about 150 mg/mL to about 170 mg/mL, especially about 160 mg/mL, at pH 7.0, and where the pharmaceutical composition is preservative free.

[0017] In another particular instance, a pharmaceutical composition includes a ds RNAi agent that modulates *LPA* expression, where the ds RNAi agent has a sense strand having a nucleotide sequence of SEQ ID NO:3 and an antisense strand having a nucleotide sequence of SEQ ID NO:4 in H₂O at a concentration from about 190 mg/mL to about 210 mg/mL, especially about 200 mg/mL, at pH 7.0, and where the pharmaceutical composition is preservative free.

[0018] The disclosure also describes dosing regimens for and methods of attenuating, preventing and/or treating diseases, disorders and/or conditions associated with *LPA*

expression, where such methods include a step of administering to an individual in need thereof a first dose of a ds RNAi agent that modulates *LPA* expression or a pharmaceutical composition thereof such as a formulation herein, where the dose can be from about 4 mg to about 608 mg.

[0019] In some instances, the ds RNAi agent includes a sense strand having a nucleotide sequence of SEQ ID NO:1 and an antisense strand having a nucleotide sequence of SEQ ID NO:2. In other instances, the ds RNAi agent includes a sense strand having a nucleotide sequence of SEQ ID NO:3 and an antisense strand having a nucleotide sequence of SEQ ID NO:4.

[0020] In some instances, the first dose can be about 4 mg, about 12 mg, about 16 mg, about 32 mg, about 64 mg, about 96 mg, about 128 mg, about 160 mg, about 192 mg, about 224 mg, about 256 mg, about 288 mg, about 304 mg, about 320 mg, about 352 mg, about 384 mg, about 400 mg, about 416 mg, about 448 mg, about 480 mg, about 512 mg, about 544 mg, about 576 mg or about 608 mg.

[0021] In some instances, the methods include a step of administering one or more subsequent doses (*i.e.*, second, third, fourth, fifth, *et seq.* dose) about every month (Q1M), about every three months (Q3M), about every six months (Q6M), about every nine months (Q9M) or about every twelve months (Q12M) from the first dose (or from a previous dose for any other subsequent dose), where the one or more subsequent doses can be from about 4 mg to about 608 mg.

[0021a] In another aspect, there is provided use of a double-stranded (ds) RNAi agent that modulates *LPA* expression in the manufacture of a medicament for attenuating, preventing and/or treating a disease, disorder and/or condition associated with apolipoprotein(a) gene (*LPA*) expression, wherein the ds RNAi agent comprises:

- (i) a sense strand comprising SEQ ID NO:1, and
- (ii) an antisense strand comprising SEQ ID NO:2; and wherein
 - (a) a first dose of the ds RNAi agent from about 4 mg to about 608 mg is to be administered; and
 - (b) one or more subsequent doses of the ds RNAi agent is to be administered at an interval selected from the group consisting of about every month (Q1M), about every three months (Q3M), about every six months (Q6M), about every nine months (Q9M) and about every twelve months (Q12M) from the first dose or from a previous dose, wherein the one or more subsequent doses are from about 4 mg to about 608 mg.

[0022] In some instances, the one or more subsequent doses can be about 4 mg, about 12 mg, about 16 mg, about 32 mg, about 64 mg, about 96 mg, about 128 mg, about 160 mg, about 192 mg, about 224 mg, about 256 mg, about 288 mg, about 304 mg, about 320 mg, about 352 mg, about 384 mg, about 400 mg, about 416 mg, about 448 mg, about 480 mg, about 512 mg, about 544 mg, about 576 mg or about 608 mg.

[0023] In some instances, the one or more subsequent doses can be the same as the first dose. In other instances, the one or more subsequent doses can be different from the first dose. In yet other instances, a second dose can be the same as the other subsequent doses (but all different from the first dose). In yet other instances, the second dose can be different from the other subsequent doses (but not all are necessarily different from the first dose).

[0024] In one particular instance, the second dose can be administered about 1 month, about 3 months, about 6 months, about 9 months or about 12 months after the first dose, and any other subsequent doses (*i.e.*, third, fourth, fifth, *et seq.* dose) can be administered about Q6M,

peripheral vascular events and CV mortality. In other instances, the individual can be an adult with elevated Lp(a) and established CV disease. In yet other instances, the individual can be an adult at risk for a first CV event and optionally with elevated Lp(a).

[0034] In any of the above methods, the diseases, disorders and/or conditions associated with *LPA* expression include atherosclerosis, calcific aortic valve stenosis (CAVS), cardiometabolic diseases, cardiovascular events including coronary revascularization, CV mortality, cerebrovascular disease, chronic kidney disease, coronary heart disease, dyslipidemia, heart failure, MI and stroke, and/or peripheral vascular disease.

[0034a] In another aspect, there is provided use of a double-stranded (ds) RNAi agent that modulates *LPA* expression in the manufacture of a medicament for reducing apolipoprotein(a) gene (*LPA*) expression in an individual having a high lipoprotein(a) (Lp(a)) level, wherein the ds RNAi agent comprises:

- (i) a sense strand comprising SEQ ID NO:1, and
- (ii) an antisense strand comprising SEQ ID NO:2, and

wherein a first dose of the ds RNAi agent from about 4 mg to about 608 mg is to be administered,

whereby the Lp(a) level of the individual is to be reduced by about 90% within about 14 days from the first dose.

[0034b] In another aspect, there is provided use of an oligonucleotide that modulates *LPA* expression in the manufacture of a medicament for reducing the risk of a major adverse cardiovascular event (MACE) in an individual, wherein:

(a) a first dose of the oligonucleotide from about 4 mg to about 608 mg is to be administered; and

(b) one or more subsequent doses of the oligonucleotide is to be administered at an interval selected from the group consisting of about every month (Q1M), about every three months (Q3M), about every six months (Q6M), about every nine months (Q9M) and about every twelve months (Q12M) from the first dose or from a previous dose, wherein the one or more subsequent doses are from about 4 mg to about 608 mg, wherein the individual is at risk for a first cardiovascular event.

[0035] In any of the above methods, the individual can have a Lp(a) level of at least about ≥ 75 nmol/L. In some instances, the individual can have a Lp(a) level of at least about 100

nmol/L, about 125 nmol/L, about 150 nmol/L, about 175 nmol/L or about 200 nmol/L prior to administering the first dose.

[0036] In any of the above methods, the individual can have a single-nucleotide polymorphism (SNP) of *LPA* selected from rs10455872 and rs3798220.

[0037] The disclosure further describes a composition herein for use as a medicament.

[0038] The disclosure further describes a composition herein for use in the treatment of diseases, disorders and/or conditions associated with *LPA* expression.

[0039] The disclosure further describes an article of manufacture including a formulation herein. In some instances, the article of manufacture is a single-use vial or a multi-use vial. In some instances, the article of manufacture is a pre-filled syringe. In some instances, the article of manufacture is an automatic injection apparatus. In some instances, the article of manufacture is a pump for continuous perfusion, especially a pump for subcutaneous infusion.

[0040] An advantage of the doses, regimens, methods and uses herein is that they provide a limited duration of exposure, durable treatment effects and fewer adverse events (AEs). Likewise, such doses, regimens, methods and uses have a potential to improve acceptance and compliance in view of their infrequent administration that is required.

DETAILED DESCRIPTION

[0041] *Overview*

[0042] Lp(a) is considered a strong genetic risk factor for coronary heart disease. Genetic variation within *LPA*, which determines the level of Apo(a) production, is strongly associated with both Lp(a) levels in plasma and risk of MI.

CLAIMS

The invention claimed is:

1. A pharmaceutical composition comprising:
a double-stranded (ds) RNAi agent or its pharmaceutically acceptable salt thereof at a concentration from about 100 mg/mL to about 300 mg/mL in water (H₂O), wherein the pharmaceutical composition is at a pH from about 6.0 to about 8.0, and wherein the ds RNAi agent comprises:
 - (1) a sense strand comprising a nucleotide sequence of SEQ ID NO:1, and
 - (2) an antisense strand comprising a nucleotide sequence of SEQ ID NO:2.
2. The pharmaceutical composition of Claim 1, wherein the concentration is from about 150 mg/mL to about 170 mg/mL or from about 190 mg/mL to about 210 mg/mL.
3. The pharmaceutical composition of Claim 2, wherein the concentration is about 160 mg/mL or about 200 mg/mL.
4. The pharmaceutical composition of any one of Claims 1 to 3, wherein the sense strand is SEQ ID NO:3.
5. The pharmaceutical composition of any one of Claims 1 to 4, wherein in the antisense strand is SEQ ID NO:4.
6. The pharmaceutical composition of any one of Claims 1 to 5, wherein the pH is about 7.0.
7. The pharmaceutical composition of any one of Claims 1 to 6, wherein the composition is preservative free.
8. Use of a double-stranded (ds) RNAi agent that modulates *LPA* expression in the manufacture of a medicament for attenuating, preventing and/or treating a disease, disorder

and/or condition associated with apolipoprotein(a) gene (*LPA*) expression, wherein the ds RNAi agent comprises:

- (i) a sense strand comprising SEQ ID NO:1, and
- (ii) an antisense strand comprising SEQ ID NO:2; and wherein

(a) a first dose of the ds RNAi agent from about 4 mg to about 608 mg is to be administered; and

(b) one or more subsequent doses of the ds RNAi agent is to be administered at an interval selected from the group consisting of about every month (Q1M), about every three months (Q3M), about every six months (Q6M), about every nine months (Q9M) and about every twelve months (Q12M) from the first dose or from a previous dose, wherein the one or more subsequent doses are from about 4 mg to about 608 mg.

9. The use of Claim 8, wherein the administration is intravenous (IV) or subcutaneous (SC).

10. The use of Claim 9, wherein the administration is SC.

11. The use of any one of Claims 8 to 10, wherein the sense strand is SEQ ID NO:3.

12. The use of any one of Claim 8 to 11, wherein the antisense strand is SEQ ID NO:4.

13. The use of any one of Claims 8 to 12, wherein the one or more subsequent doses are the same as the first dose.

14. The use of any one of Claims 8 to 12, wherein the one or more of the subsequent doses are not the same as the first dose.

15. The use of any one of Claims 8 to 14, wherein the first dose is selected from the group consisting of about 4 mg, about 12 mg, about 16 mg, about 32 mg, about 96 mg, about 304 mg, about 400 mg and about 608 mg.

16. The use of any one of Claims 8 to 15, wherein the one or more subsequent doses are independently selected from the group consisting of about 4 mg, about 12 mg, about 16 mg, about 32 mg, about 96 mg, about 304 mg, about 400 mg and about 608 mg.

17. The use of any one of Claims 8 to 12, wherein the first dose is about 304 mg, and wherein the one or more subsequent doses are about 304 mg to be administered about every Q1M, about 304 mg to be administered about every Q3M, about 304 mg to be administered about every Q6M, about 304 mg to be administered about every Q9M or about 304 mg to be administered about every Q12M from the first dose or from the previous dose.

18. The use of any one of Claims 8 to 12, wherein the first dose is about 400 mg, and wherein the one or more subsequent doses are about 400 mg to be administered about every Q1M, about 400 mg to be administered about every Q3M, about 400 mg to be administered about every Q6M, about 400 mg to be administered about every Q9M, or about 400 mg to be administered about every Q12M from the first dose or from the previous dose.

19. The use of any one of Claims 8 to 12, wherein the first dose is about 608 mg, and wherein the one or more subsequent doses are about 608 mg to be administered Q1M, about 608 mg to be administered Q3M, about 608 mg to be administered Q6M, about 608 mg to be administered Q9M, or about 608 mg to be administered Q12M from the first dose or from the previous dose.

20. The use of any one of Claims 8 to 12, wherein the first dose is from about 4 mg to about 608 mg, and wherein the one or more subsequent doses are from about 4 mg to about 608 mg and are to be administered about every Q6M from the first dose or from the previous dose.

21. The use of any one of Claims 8 to 12, wherein the first dose is from about 4 mg to about 608 mg, wherein a second dose is from about 4 mg to about 608 mg and is to be administered about Q6M from the first dose, and wherein the one or more subsequent doses are from about 4 mg to about 608 mg and is to be administered about every Q12M from the second dose or from the previous dose.

22. The use of any one of Claims 8 to 12, wherein the first dose is from about 4 mg to about 608 mg, and wherein the one or more subsequent doses are from about 4 mg to about 608 mg and are to be administered about every Q12M from the first dose or from the previous dose.

23. The use of Claim 8, wherein the disease, disorder and/or condition associated with *LPA* expression is selected from the group consisting of atherosclerosis, calcific aortic valve stenosis (CAVS), cardiometabolic diseases, cardiovascular (CV) events including coronary revascularization, CV mortality, cerebrovascular disease, chronic kidney disease, coronary heart disease, dyslipidemia, heart failure, MI and stroke, and peripheral vascular disease.

24. Use of a double-stranded (ds) RNAi agent that modulates *LPA* expression in the manufacture of a medicament for reducing apolipoprotein(a) gene (*LPA*) expression in an individual having a high lipoprotein(a) (Lp(a)) level, wherein the ds RNAi agent comprises:

- (i) a sense strand comprising SEQ ID NO:1, and
- (ii) an antisense strand comprising SEQ ID NO:2, and

wherein a first dose of the ds RNAi agent from about 4 mg to about 608 mg is to be administered,

whereby the Lp(a) level of the individual is to be reduced by about 90% within about 14 days from the first dose.

25. The use of Claim 24, wherein the sense strand is SEQ ID NO:3.

26. The use of Claim 24 or 25, wherein the antisense strand is SEQ ID NO:4.

27. The use of any one of Claims 24 to 26, wherein

one or more subsequent doses of the ds RNAi agent are to be administered, wherein one or more subsequent doses are from about 4 mg to about 608 mg, and wherein the one or more subsequent doses are to be administered from about every 1 month (Q1M) to about every 12 months (Q12M) from the first dose or from a previous dose,

whereby the Lp(a) level of the individual is to be maintained at the level following the first dose or is to be reduced further beyond the level following the first dose.

28. The use of any one of Claims 24 to 27, wherein the administration is intravenous (IV) or subcutaneous (SC).
29. The method of Claim 28, wherein the administration is SC.
30. The use of any one of Claims 27 to 29, wherein the one or more subsequent doses are the same as the first dose.
31. The use of any one of Claims 27 to 29, wherein the one or more subsequent doses are not the same as the first dose.
32. The use of any one of Claims 24 to 31, wherein the first dose is selected from the group consisting of about 4 mg, about 12 mg, about 16 mg, about 32 mg, about 96 mg, about 304 mg, about 400 mg and about 608 mg.
33. The use of any one of Claims 24 to 32, wherein the one or more subsequent doses are independently selected from the group consisting of about 4 mg, about 12 mg, about 16 mg, about 32 mg, about 96 mg, about 304 mg, about 400 mg and about 608 mg.
34. The use of Claim 27, wherein the first dose is about 304 mg, and wherein the one or more subsequent doses are about 304 mg to be administered about every Q1M, about 304 mg to be administered about every Q3M, about 304 mg to be administered about every Q6M, about 304 mg to be administered about every Q9M, or about 304 mg to be administered about every Q12M from the first dose or from the previous dose.
35. The use of Claim 27, wherein the first dose is about 400 mg, and wherein the one or more subsequent doses are about 400 mg to be administered about every Q1M, about 400 mg to be administered about every Q3M, about 400 mg to be administered about every Q6M, about 400 mg to be administered about every Q9M, or about 400 mg to be administered about every Q12M from the first dose or from the previous dose.

36. The use of Claim 27, wherein the first dose is about 608 mg, and wherein the one or more subsequent doses are about 608 mg to be administered about every Q1M, about 608 mg to be administered about every Q3M, about 608 mg to be administered about every Q6M, about 608 mg to be administered about every Q9M, or about 608 mg to be administered about every Q12M from the first dose or from the previous dose.

37. The use of Claim 27, wherein the first dose is about 400 mg, and wherein the one or more subsequent doses are about 400 mg and are to be administered about every Q6M from the first dose or from the previous dose.

38. The use of Claim 27, wherein the first dose is about 400 mg, wherein a second dose is about 400 mg and is to be administered about Q6M from the first dose, and wherein any subsequent dose is about 400 mg and is to be administered about every Q12M from the second dose or from the previous dose.

39. The use of Claim 27, wherein the first dose is about 400 mg, wherein the one or more subsequent doses are 400 mg and are to be administered about every Q12M from the first dose or from the previous dose.

40. The use of any one of Claims 24 to 39, wherein the individual has a disease, disorder and/or condition associated with apolipoprotein(a) gene (*LPA*) expression selected from the group consisting of atherosclerosis, calcific aortic valve stenosis (CAVS), cardiometabolic diseases, cardiovascular (CV) events including coronary revascularization, CV mortality, cerebrovascular disease, chronic kidney disease, coronary heart disease, dyslipidemia, heart failure, MI and stroke, and peripheral vascular disease.

41. Use of an oligonucleotide that modulates *LPA* expression in the manufacture of a medicament for reducing the risk of a major adverse cardiovascular event (MACE) in an individual, wherein:

(a) a first dose of the oligonucleotide from about 4 mg to about 608 mg is to be administered; and

(b) one or more subsequent doses of the oligonucleotide is to be administered at an interval selected from the group consisting of about every month (Q1M), about every three months (Q3M), about every six months (Q6M), about every nine months (Q9M) and about every twelve months (Q12M) from the first dose or from a previous dose, wherein the one or more subsequent doses are from about 4 mg to about 608 mg, wherein the individual is at risk for a first cardiovascular event.

42. The use of claim 41, wherein the individual at risk for a first cardiovascular event has a lipoprotein(a) (Lp(a)) level of at least about 75 mmol/L.

43. The use of claim 41, wherein the individual at risk for a first cardiovascular event has a lipoprotein(a) (Lp(a)) level of at least about 100 mmol/L.

44. The use of claim 41, wherein the individual at risk for a first cardiovascular event has a lipoprotein(a) (Lp(a)) level of at least about 125 mmol/L.

45. The use of claim 41, wherein the individual at risk for a first cardiovascular event has a lipoprotein(a) (Lp(a)) level of at least about 150 mmol/L.

46. The use of claim 41, wherein the one or more subsequent doses of the oligonucleotide is at an interval of about every month (Q1M).

47. The use of claim 41, wherein the one or more subsequent doses of the oligonucleotide is at an interval of about every three months (Q3M).

48. The use of claim 41, wherein the one or more subsequent doses of the oligonucleotide is at an interval of about every six months (Q6M).

49. The use of claim 41, wherein the one or more subsequent doses of the oligonucleotide is at an interval of about every twelve months (Q12M).

50. The use of claim 41, wherein the oligonucleotide is a ds RNAi agent.

51. The use of claim 50, wherein the ds RNAi agent comprises:
 - (i) a sense strand comprising SEQ ID NO:1, and
 - (ii) an antisense strand comprising SEQ ID NO:2.
52. The use of claim 50, wherein the ds RNAi agent comprises:
 - (i) a sense strand comprising SEQ ID NO:3, and
 - (ii) an antisense strand comprising SEQ ID NO:4.
53. The use of claim 41, wherein the individual at risk for a first cardiovascular event does not have established atherosclerotic cardiovascular disease.