factors, Lp(a) plasma levels do not vary significantly with diet and exercise. Lp(a) plasma levels are primarily determined by genetic predisposition.

[004] Lp(a) resembles LDL-c in that it includes an LDL lipid core with the attendant apolipoprotein B (apoB), but unlike LDL-c, Lp(a) also contains a unique apolipoprotein(a) (apo(a)) bound covalently to the apoB via a disulfide bond. Apo(a) is synthesized in the liver. The assembly of Lp(a) from apo(a) and LDL particles can occur in hepatocytes, on the cell wall or in plasma. Inhibition of the assembly of the LDL particle with apo(a) may reduce Lp(a) levels. Additional treatment options are desired for patients suffering from cardiovascular diseases and, in particular, patients suffering from lipid disorders or dyslipidemia. There is a need for additional treatment options for patients whose cardiovascular risks are not adequately managed using current standard of care therapies, such as, diet, exercise and/or the use of one or more drugs such as statins, fibrates, and niacin. The present invention offers another treatment option for patients suffering from CVD. There is a need for pharmaceutically acceptable compounds and treatment options to reduce plasma Lp(a) levels.

[005] In particular, there is a need for a treatment regimen with optimized doses and dosing regimens with compounds that effectively reduce Lp(a) plasma levels and associated cardiovascular risk, while also preserving an overall acceptable profile of safety and adverse events and tolerability to the individual. In particular, there is a need for doses which reduce the Lp(a) plasma level of an individual to less than 125 nmol/L after 12 weeks of treatment and/or which lower the Lp(a) level of an individual by at least 150 nmol/L after 12 weeks of treatment.

SUMMARY

[006] To address this need, the disclosure describes once-daily, oral doses of (2S)-3-[3-[[bis[[3-[(2S)-2-carboxy-2-[(3R)-pyrrolidin-3-yl]ethyl]phenyl]methyl]amino] methyl]phenyl]-2-[(3R)-pyrrolidin-3-yl]propanoic acid (compound 1), or a pharmaceutically acceptable salt thereof, of between 10 mg and 240 mg.

[007] In an example, there is provided a method of treating cardiovascular disease in an individual, the method comprising: orally administering to the individual in need thereof a once-daily dose of between 10 mg and 240 mg of compound 1, or a pharmaceutically acceptable salt thereof.

[008] In an example, there is provided a method of treating an individual with elevated Lp(a) levels, the method comprising: orally administering to the individual in need thereof a once-daily dose of between 10 mg and 240 mg of compound 1, or a pharmaceutically acceptable salt thereof.

[009] In another example, there is provided a method of treating an individual with elevated Lp(a) levels at risk for cardiovascular events, the method comprising: orally administering to the individual in need thereof a once-daily dose of between 10 mg and 240 mg of compound 1, or a pharmaceutically acceptable salt thereof.

[0010] In another example, there is provided a method of treating atherosclerotic cardiovascular disease (ASCVD), the method comprising: orally administering to the individual in need thereof a once-daily dose of between 10 mg and 240 mg of compound 1, or a pharmaceutically acceptable salt thereof.

[0011] In a further example, there is provided compound 1, or a pharmaceutically acceptable salt thereof, for use in the treatment of cardiovascular disease in an individual, wherein the compound is orally administered at a once-daily dose of between 10 mg and 240 mg.

[0012] In a further example, there is provided compound 1, or a pharmaceutically acceptable salt thereof, for use in the treatment of an individual with elevated Lp(a) levels, wherein the compound is orally administered at a once-daily dose of between 10 mg and 240 mg.

[0013] In a further example, there is provided compound 1, or a pharmaceutically acceptable salt thereof, for use in the treatment of an individual with elevated Lp(a) levels at risk for cardiovascular events, wherein the compound is orally administered at a once-daily dose of between 10 mg and 240 mg.

[0014] In a further example, there is provided compound 1, or a pharmaceutically acceptable salt thereof, for use in the treatment of ASCVD in an individual, wherein the compound is orally administered at a once-daily dose of between 10 mg and 240 mg.

[0015] In an aspect, there is provided use of (2S)-3-[3-[[bis[[3-[(2S)-2-carboxy-2-[(3R)-pyrrolidin-3-yl]ethyl]phenyl]methyl]amino]methyl]phenyl]-2-[(3R)-pyrrolidin-3-yl]propanoic acid, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cardiovascular disease in an individual, wherein the (2S)-3-[3-[[bis[[3-[(2S)-2-carboxy-2-[(3R)-pyrrolidin-3-yl]ethyl]phenyl]methyl]amino]methyl]phenyl]-2-[(3R)-pyrrolidin-3-yl]propanoic acid, or a pharmaceutically acceptable salt thereof, is to be orally administered at a once-daily dose of between 10 mg and 240 mg.

[0016] In yet a further example, there is provided the use of compound 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of an individual with elevated Lp(a) levels, wherein the compound is orally administered at a once-daily dose of between 10 mg and 240 mg.

[0017] In yet a further example, there is provided the use of compound 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of an individual with elevated Lp(a) levels at risk for cardiovascular events, wherein the compound is orally administered at a once-daily dose of between 10 mg and 240 mg.

[0018] In yet a further aspect, there is provided use of (2S)-3-[3-[[bis[[3-[(2S)-2-carboxy-2-[(3R)-pyrrolidin-3-yl]ethyl]phenyl]methyl]amino]methyl]phenyl]-2-[(3R)-pyrrolidin-3-yl]propanoic acid, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of atherosclerotic cardiovascular disease in an individual, wherein the (2S)-3-[3-[[bis[[3-[(2S)-2-carboxy-2-[(3R)-pyrrolidin-3-yl]ethyl]phenyl]methyl]amino]methyl]phenyl]-2-[(3R)-pyrrolidin-3-yl]propanoic acid, or a pharmaceutically acceptable salt thereof, is to be orally administered at a once-daily dose of between 10 mg and 240 mg.

[0019] In an example, the individual to be treated has an Lp(a) plasma level greater than or equal to 75 nmol/L prior to treatment. In another example, the individual to be treated has an Lp(a) plasma level greater than or equal to 125 nmol/L prior to treatment. In a further example, the individual to be treated has an Lp(a) plasma level greater than or equal to 175 nmol/L prior to treatment.

[0020] In an example, the individual to be treated has an Lp(a) plasma level greater than or equal to 30 mg/dL prior to treatment. In another example, the individual to be treated has an Lp(a) plasma level greater than or equal to 50 mg/dL prior to treatment. In a further example, the individual to be treated has an Lp(a) plasma level greater than or equal to 70 mg/dL prior to treatment.

[0021] In an example, the once-daily dose is between 60 mg and 150 mg, preferably between 60 mg and 120 mg, more preferably between 80 mg and 120 mg. In an example, the once-daily dose is about 120 mg. In an example, the once-daily dose is about 10 mg, about 60 mg or about 240 mg.

BRIEF SUMMARY OF THE FIGURES

[0022] Figure 1 – Data from Part A – SAD: Arithmetic mean +/- SE percent change relative to placebo Lp(a) concentration versus day profiles on linear scale. Plasma

CLAIMS

The invention claimed is:

1. Use of (2S)-3-[3-[[bis[[3-[(2S)-2-carboxy-2-[(3R)-pyrrolidin-3-yl]ethyl]phenyl]methyl]amino]methyl]phenyl]-2-[(3R)-pyrrolidin-3-yl]propanoic acid, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cardiovascular disease in an individual, wherein the (2S)-3-[3-[[bis[[3-[(2S)-2-carboxy-2-[(3R)-pyrrolidin-3-yl]ethyl]phenyl]methyl]amino]methyl]phenyl]-2-[(3R)-pyrrolidin-3-yl]propanoic acid, or a pharmaceutically acceptable salt thereof, is to be orally administered at a once-daily dose of between 10 mg and 240 mg.

2. The use of claim 1, wherein the individual has elevated Lp(a) plasma levels.

3. The use of claim 1 or claim 2, wherein the once daily dose is about 120 mg.

4. The use of claim 1 or claim 2, wherein the once-daily dose is between 60 mg and 150 mg.

5. The use of claim 4, wherein the once-daily dose is between 60 mg and 120 mg.

6. The use of claim 5, wherein the once-daily dose is between 80 mg and 120 mg.

7. Use of (2S)-3-[3-[[bis[[3-[(2S)-2-carboxy-2-[(3R)-pyrrolidin-3-yl]ethyl]phenyl]methyl]amino]methyl]phenyl]-2-[(3R)-pyrrolidin-3-yl]propanoic acid, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of atherosclerotic cardiovascular disease in an individual, wherein the (2S)-3-[3-[[bis[[3-[(2S)-2-carboxy-2-[(3R)-pyrrolidin-3-yl]ethyl]phenyl]methyl]amino]methyl]phenyl]-2-[(3R)-pyrrolidin-3-yl]propanoic acid, or a pharmaceutically acceptable salt thereof, is to be orally administered at a once-daily dose of between 10 mg and 240 mg.

8. The use of claim 7, wherein the individual has elevated Lp(a) plasma levels.

9. The use of claim 7 or claim 8, wherein the once-daily dose is about 120 mg.

10. The use of claim 7 or claim 8, wherein the once-daily dose is between 60 mg and 150 mg.

11. The use of claim 10, wherein the once-daily dose is between 60 mg and 120 mg.

12. The use of claim 11, wherein the once-daily dose is between 80 mg and 120 mg.

13. The use according to any one of claims 1 to 12, wherein the individual has an Lp(a) plasma level greater than or equal to 75 nmol/L prior to treatment.

14. The use according to claim 13, wherein the individual has an Lp(a) plasma level greater than or equal to 125 nmol/L prior to treatment.

15. The use according to claim 14, wherein the individual has an Lp(a) plasma level greater than or equal to 175 nmol/L prior to treatment.