

Therapeutic Uses and Doses of Lp(a) Disrupter Compounds

TECHNICAL FIELD

[001] The disclosure relates to therapeutic methods and uses of Lp(a) disrupter compound (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 treatment of cardiovascular disease, elevated Lp(a) levels, individuals with elevated Lp(a) levels at risk for cardiovascular events and atherosclerotic cardiovascular disease. It especially relates to particular doses of the Lp(a) disrupter compound which can be used in the treatment of these conditions.

BACKGROUND

[002] There have been significant advances in treating cardiovascular disease (CVD). Despite treatment advances, patients continue to experience cardiovascular disease events such as angina, myocardial infarction, and stroke, which if untreated, lead to death. Lipid disorder or dyslipidemia remains a major risk factor for CVD. Lipid disorders can be divided into four general risk factors: elevated low-density lipoprotein cholesterol (LDL-c), low high-density lipoprotein cholesterol (HDL-c), elevated triglycerides (TG), and elevated lipoprotein(a) (Lp(a)). There are a variety of treatment regimens targeting elevated LDL-c, low HDL-c, and elevated triglycerides. There are few treatment options for patients with elevated Lp(a) concentrations. In some cases, apheresis may be used to filter the blood to remove LDL and Lp(a); however, the effects are temporary and typically need to be repeated every two weeks. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce Lp(a) by approximately 25% and niacin produces modest reductions in Lp(a), but neither are approved for Lp(a) reduction. There is no pharmaceutical treatment approved to lower Lp(a) levels. The physiological function of Lp(a) is complex; however, it is reported that elevated Lp(a) plasma level is an independent risk factor for CVD.

[003] Lp(a) may exhibit both prothrombotic and antithrombotic properties, atherogenic and atherothrombotic properties. Lp(a) may inhibit fibrinolysis and accumulate in the vascular wall inducing thrombogenesis and atherosclerotic lesions. Plasma levels of Lp(a) vary substantially among individuals. Unlike the other risk

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 OF THE INVENTION

[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 aspect, 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 another aspect, 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 aspect, 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 aspect, 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 aspect, 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 aspect, 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 aspect, 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 aspect, 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 yet a further aspect, there is provided the use of compound 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for 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.

[0016] In yet a further aspect, 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 aspect, 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 the use of compound 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for 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.

[0019] In an embodiment, the individual to be treated has an Lp(a) plasma level greater than or equal to 75 nmol/L prior to treatment. In another embodiment, 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 embodiment, 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 embodiment, the individual to be treated has an Lp(a) plasma level greater than or equal to 30 mg/dL prior to treatment. In another embodiment, 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 embodiment, 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 embodiment, 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 embodiment, the once-daily dose is about 120 mg. In an embodiment, 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 $\pm$ SE percent change relative to placebo Lp(a) concentration versus day profiles on linear scale. Plasma

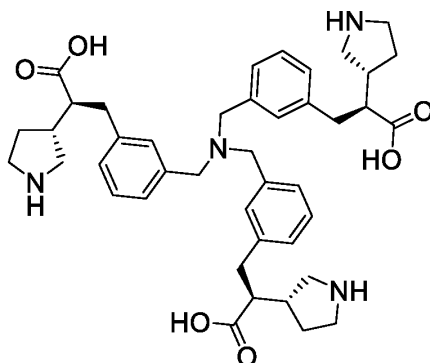
levels of Lp(a) determined using an assay available from Randox Laboratories Ltd (RX SERIES LP 3403).

[0023] Figure 2 – Data from Part B- MAD: Arithmetic mean $\pm$ SE percent change relative to placebo Lp(a) concentration versus day profiles on linear scale. Plasma levels of Lp(a) determined using an assay available from Randox Laboratories Ltd (RX SERIES LP 3403).

[0024] Figure 3 – Data from Phase 2: Least squares mean $\pm$ 1.96 SE percent change relative to baseline versus week profiles. Plasma levels of Lp(a) determined using an assay available from Randox Laboratories Ltd (RX SERIES LP 3403).

DETAILED DESCRIPTION

[0025] The Lp(a) disrupter compound (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 is herein referred to as compound 1. Compound 1 and methods for the preparation of compound 1 are disclosed in WO 2020/247429. Compound 1 has the structure:



An alternate name for this compound is (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(benzene-3,1-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid).

[0026] The present invention provides methods of treating various conditions, disorders and diseases comprising administering once-daily, oral doses of compound 1, or a pharmaceutically acceptable salt thereof, of between 10 mg and 240 mg. The present invention further provides compound 1, or a pharmaceutically acceptable salt thereof, for use in the treatment of various conditions, disorders and diseases, wherein the compound is orally administered at a once-daily dose of between 10 mg and 240 mg.

[0027] In a particular embodiment, the condition, disorder or disease is selected from: cardiovascular disease, elevated Lp(a) levels and ASCVD. In a further embodiment, compound 1, or a pharmaceutically acceptable salt thereof, is administered to individuals with elevated Lp(a) levels at risk for cardiovascular events. Individuals at risk for cardiovascular events or at risk for a cardiovascular event include those with coronary artery disease (CAD), those who have had a stroke, or those with peripheral artery disease or ASCVD risk equivalents (familial hypercholesterolemia or type 2 diabetes).

[0028] What is considered to be the normal range for Lp(a) levels varies depending on the ethnicity of the individual as described in European Heart Journal (2022) 43, 3925–3946. Elevated Lp(a) levels are levels which are above the normal range for that individual in view of their ethnicity. In a particular embodiment, elevated Lp(a) levels refers to Lp(a) plasma levels greater than or equal to 75 nmol/L, greater than or equal to 125 nmol/L, or greater than or equal to 175 nmol/L. In a particular embodiment, elevated Lp(a) levels refers to Lp(a) plasma levels greater than or equal to 30 mg/dL, greater than or equal to 50 mg/dL, or greater than or equal to 70 mg/dL. Both nmol/L and mg/dL are widely recognized and used measurement units for Lp(a) plasma levels.

[0029] In an embodiment, there is provided a method of treating or preventing coronary artery 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.

[0030] In an embodiment, there is provided a method of preventing cardiovascular death, myocardial infarction, urgent coronary revascularization, all-cause death or ischemic stroke in 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.

[0031] In an embodiment, there is provided a method of treating acute coronary syndrome 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.

[0032] In an embodiment, there is provided a method of reducing cardiovascular events in an individual with ASCVD and 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.

[0033] In an embodiment, 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, wherein the individual has an Lp(a) plasma level greater than or equal to 175 nmol/L prior to treatment. In a particular embodiment, the Lp(a) plasma level of the individual is less than 125 nmol/L after 12 weeks of treatment. In a further embodiment, the Lp(a) level of the individual is lowered by at least 150 nmol/L after 12 weeks of treatment.

[0034] In an embodiment, 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, wherein the individual has an Lp(a) plasma level greater than or equal to 175 nmol/L prior to treatment. In a particular embodiment, the Lp(a) plasma level of the individual is less than 125 nmol/L after 12 weeks of treatment. In a further embodiment, the Lp(a) level of the individual is lowered by at least 150 nmol/L after 12 weeks of treatment.

[0035] In an embodiment, 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, wherein the individual has an Lp(a) plasma level greater than or equal to 175 nmol/L prior to treatment. In a particular embodiment, the Lp(a) plasma level of the individual is less than 125 nmol/L after 12 weeks of treatment. In a further embodiment, the Lp(a) level of the individual is lowered by at least 150 nmol/L after 12 weeks of treatment.

[0036] In an embodiment, there is provided a method of treating ASCVD 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, wherein the individual has an Lp(a) plasma level greater than or equal to 175 nmol/L prior to treatment. In a particular embodiment, the Lp(a) plasma level of the individual is less than 125 nmol/L after 12 weeks of treatment. In a further

embodiment, the Lp(a) level of the individual is lowered by at least 150 nmol/L after 12 weeks of treatment.

[0037] In an embodiment, there is provided a method of treating an individual with elevated Lp(a) levels, the method comprising the steps of:

- i. measuring the Lp(a) plasma level of the individual;
- ii. if the individual has an Lp(a) plasma level of greater than or equal to 175 nmol/L, orally administering to the individual a once-daily dose of between 10 mg and 240 mg of compound 1, or a pharmaceutically acceptable salt thereof.

[0038] In an embodiment, there is provided compound 1, or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of coronary artery disease in an individual, wherein the compound is orally administered at a once-daily dose of between 10 mg and 240 mg.

[0039] In an embodiment, there is provided compound 1, or a pharmaceutically acceptable salt thereof, for use in the prevention of cardiovascular death, myocardial infarction, urgent coronary revascularization, all-cause death or ischemic stroke in 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.

[0040] In an embodiment, there is provided compound 1, or a pharmaceutically acceptable salt thereof, for use in the treatment of acute coronary syndrome in an individual, wherein the compound is orally administered at a once-daily dose of between 10 mg and 240 mg.

[0041] In an embodiment, there is provided compound 1, or a pharmaceutically acceptable salt thereof, for use in the reduction of cardiovascular events in an individual with ASCVD and elevated Lp(a) levels, wherein the compound is orally administered at a once-daily dose of between 10 mg and 240 mg.

[0042] In an embodiment, 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 and wherein the individual has an Lp(a) plasma level greater than or equal to 175 nmol/L prior to treatment. In a particular embodiment, the Lp(a) plasma level of the individual is less than 125 nmol/L after 12 weeks of treatment. In a further embodiment,

the Lp(a) level of the individual is lowered by at least 150 nmol/L after 12 weeks of treatment.

[0043] In an embodiment, 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 and wherein the individual has an Lp(a) plasma level greater than or equal to 175 nmol/L prior to treatment. In a particular embodiment, the Lp(a) plasma level of the individual is less than 125 nmol/L after 12 weeks of treatment. In a further embodiment, the Lp(a) level of the individual is lowered by at least 150 nmol/L after 12 weeks of treatment.

[0044] In an embodiment, 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 and wherein the individual has an Lp(a) plasma level greater than or equal to 175 nmol/L prior to treatment. In a particular embodiment, the Lp(a) plasma level of the individual is less than 125 nmol/L after 12 weeks of treatment. In a further embodiment, the Lp(a) level of the individual is lowered by at least 150 nmol/L after 12 weeks of treatment.

[0045] In an embodiment, 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 and wherein the individual has an Lp(a) plasma level greater than or equal to 175 nmol/L prior to treatment. In a particular embodiment, the Lp(a) plasma level of the individual is less than 125 nmol/L after 12 weeks of treatment. In a further embodiment, the Lp(a) level of the individual is lowered by at least 150 nmol/L after 12 weeks of treatment.

[0046] In an embodiment, there is provided a compound 1, or a pharmaceutically acceptable salt thereof, for use in the treatment of an individual with elevated Lp(a) levels, wherein the treatment comprises the steps of:

- i. measuring the Lp(a) plasma level of the individual;
- ii. if the individual has an Lp(a) plasma level of greater than or equal to 175 nmol/L, orally administering to the individual a once-daily dose of between 10 mg and 240 mg of compound 1, or a pharmaceutically acceptable salt thereof.

[0047] In an embodiment, the once-daily oral dose is between 30 mg and 150 mg, particularly 60 mg and 150 mg, particularly between 60 mg and 120 mg, more particularly between 80 mg and 120 mg. In a further embodiment, the once-daily dose is between 100 mg and 240 mg, particularly between 100 mg and 180 mg.

[0048] In an embodiment, the once-daily oral dose is about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg or about 240 mg. In a particular embodiment, the once-daily oral dose is about 30 mg. In a particular embodiment, the once-daily oral dose is about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg or about 150 mg. In a particular embodiment, the once-daily oral dose is about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg or about 120 mg. In a particular embodiment, the once-daily oral dose is about 80 mg, about 90 mg, about 100 mg, about 110 mg or about 120 mg. In a particular embodiment, the once-daily oral dose is about 80 mg. In a particular embodiment, the once-daily oral dose is about 100 mg. In a particular embodiment, the once-daily oral dose is about 120 mg.

[0049] In the methods of treatment and therapeutic uses disclosed herein, compound 1, or a pharmaceutically acceptable salt thereof, may be administered in a pharmaceutical composition formulated for oral administration. Pharmaceutical compositions may be formulated as a tablet or capsule for oral administration or as a solution for oral administration. In a preferred embodiment, the pharmaceutical composition is formulated as a tablet.

[0050] Also provided herein are pharmaceutical compositions comprising compound 1, or a pharmaceutically acceptable salt thereof, in a dose of between 10mg and 240 mg and at least one pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition is suitable for oral administration. In an embodiment, the dose is between 60 mg and 150 mg, preferably between 60 mg and 120 mg, more preferably between 80 mg and 120 mg. In a further embodiment, the dose is between 100 mg and 240 mg, preferably between 100 mg and 180 mg, more preferably about 120 mg. Pharmaceutical compositions may be formulated as a tablet or capsule for oral administration or as a

solution for oral administration. In a preferred embodiment, the pharmaceutical composition is formulated as a tablet.

[0051] As used herein, “about” means within a statistically meaningful range of a value or values such as, for example, a stated concentration, length, molecular weight, pH, sequence identity, time frame, temperature or volume. Such a value or range can be within an order of magnitude typically within 20%, more typically within 10%, and even more typically within 5% of a given value or range. The allowable variation encompassed by “about” will depend upon the particular system under study, and can be readily appreciated by one of skill in the art.

[0052] As used herein, “dose” or “doses” means a quantity of the compound which is administered to an individual in a discrete amount at a particular point in time.

[0053] As used herein, “individual in need thereof” means a mammal, such as a human, with a condition, disease, disorder or symptom requiring treatment or therapy, including for example, those listed herein. In particular, the preferred individual to be treated is a human.

[0054] The term “pharmaceutically acceptable salt” as used herein refers a salt of a compound that is acceptable for clinical and/or veterinary use. Examples of pharmaceutically acceptable salts and common methodology for preparing them can be found in “Handbook of Pharmaceutical Salts: Properties, Selection and Use” P. Stahl, *et al.*, 2nd Revised Edition, Wiley-VCH, 2011 and S.M. Berge, *et al.*, “Pharmaceutical Salts”, *Journal of Pharmaceutical Sciences*, 1977, 66(1), 1-19. Salt formation can occur upon the addition of a pharmaceutically acceptable acid to form the acid addition salt or by the addition of a pharmaceutically acceptable base to form a base addition salt. Salts can also form simultaneously upon deprotection of a nitrogen or oxygen, *i.e.*, removing the protecting group. Examples, reactions and conditions for salt formation are known to the skilled artisan.

[0055] As used herein, “treat,” “treating,” “to treat” and the like mean restraining, slowing, stopping or reversing the progression or severity of an existing condition, disease, disorder or symptom.

[0056] Plasma levels of Lp(a) may be determined using a commercially available immunoturbidimetric assay, for example, the assay available from Randox Laboratories Ltd (RX SERIES LP 3403). Agglutination occurs due to an antigen-antibody reaction

between Lp(a) in a sample and anti-Lp(a) antibody adsorbed to latex particles. This agglutination is detected as an absorbance change at 700 nm proportional to the concentration of Lp(a) in the sample.

EXAMPLES

[0057] PHASE 1 STUDY: PART A - SINGLE ASCENDING DOSE (SAD) AND PART B MULTIPLE ASCENDING DOSE (MAD)

[0058] Example 1: Part A - SAD Study

[0059] Study was designed to evaluate the safety, tolerability and pharmacokinetics (PK) of compound 1 in healthy individuals. The SAD study was a randomized, investigator- and participant-blind, placebo-controlled, single-dose, dose-escalation study conducted in healthy individuals.

[0060] The following orally administered doses, as well as placebo, were studied: 1 mg, 10 mg, 30 mg, 100 mg, 200 mg, 400 mg and 800 mg.

[0061] PD analyses: absolute values and change from baseline are calculated from concentrations of the following PD markers: Lp(a), triglycerides, cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, ApoB, plasminogen, high-sensitivity C-reactive protein (hs-CRP), plasminogen activator inhibitor-1, tissue plasminogen activator antigen and alpha-2 antiplasmin.

[0062] Safety analyses: Safety parameters assessed during the study included: AEs, laboratory parameters, physical examinations, vital signs, ECGs and Body Weight.

[0063] PK analyses: plasma concentrations of compound 1 were measured pre-dose and at 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours, 48 hours, 72 hours, 168 hours (Day 8), 336 hours (Day 15), 504 hours (Day 22), 1008 hours (Day 43), 1512 hours (Day 64), 2016 hours (Day 85) and 2520 hours (Day 106) post-dose. The plasma concentrations are used to determine PK parameters using standard non-compartmental methods in a validated software program (Phoenix WinNonlin Version 8.1). The PK parameters determined include: $AUC_{0-\infty}$, CL/F , C_{max} , $t_{1/2}$, and t_{max} .

[0064] Oral administration of compound 1 at single doses to healthy individuals of 1 mg to 800 mg reduced Lp(a) levels relative to placebo starting from Day 2 of treatment. The largest reduction as a percent change relative to placebo was seen for the 400 mg

compound dose level with a maximum reduction relative to placebo of approximately 27% on Day 4 in healthy individuals. The Lp(a) levels returned to baseline by Day 8 for the 10 mg dose level. For the other dose levels (1 mg, 30 mg, 100 mg, 200 mg, 400 mg, and 800 mg) the Lp(a) levels were still reduced on Day 15. The percent change in Lp(a) concentration through to day 15 are shown in Figure 1.

[0065] For the lipoprotein panel (including HDL cholesterol, LDL cholesterol, triglycerides, cholesterol, and ApoB) and the other PD biomarkers (hs-CRP, plasminogen, plasminogen activity, plasminogen activator inhibitor-1, tissue plasminogen activator antigen, and alpha-2 antiplasmin), there was considerable inter-subject variability within a treatment and no consistent pattern was recognizable. Given the wide range of values obtained at each time point, and considering baseline values and values obtained postdose, the data seem to indicate that there are no dose-dependent changes versus baseline identified in any of the compound 1 treatments as compared to placebo, although numerical changes (either decreases or increases) were observed.

[0066] The SAD study indicates that single, oral doses of 1 mg, 30 mg, 100 mg, 200 mg, 400 mg, and 800 mg of compound 1 are well tolerated. Most TEAEs were mild in severity. 6 moderate TEAEs were reported. 7 drug-related TEAEs were reported. The most frequently reported TEAEs were headache, back pain and fatigue. There was no clear relation between dose and the number of TEAEs reported or the number of individuals reporting TEAEs.

Dose (mg)	PK Parameter					
	C _{max} (ng/mL)	t _{max} (hr) ^a	AUC _{0-∞} (ng*h/mL)	t _{1/2} (hr)	CL/F (L/hr)	V _z /F (L)
1 (N=2) ^b	1.86	5.00				
10 (N=6) ^c	3.72	4.00				
30 (N=6)	16.0	4.00	311	12.1	96.5	1689
100 (N=6)	45.5	5.00	964	31.7	104	4742
200 (N=5)	52.3	4.00	997	33.9	201	9808
400 (N=6)	64.0	4.00	1696	26.9	236	9136
800 (N=6)	152	2.00	3802	67.0	210	20347

Data is shown as geometric mean unless otherwise stated; N = number of individuals

^a t_{max} is presented as a median

^b For the 1 mg dose level only C_{max} and t_{max} are reported for 2 individuals because there are insufficient values above the lower limit of quantitation (LLOQ) to calculate all parameters.

^c For the 10 mg dose level C_{max} and t_{max} are reported for all individuals. The AUC_{0-∞} could only be calculated for 1 individual due to insufficient values above the LLOQ in the terminal phase to calculate a reliable t_{1/2}. As N=1 no summary statistics are reported.

[0067] Summary:

[0068] Single oral doses of 1 mg to 800 mg of compound 1 were safe and generally well tolerated by healthy individuals. There were no overall trends or clinically relevant changes observed in clinical laboratory parameters, vital signs, ECGs, physical examinations and body weight. The mean C_{max} of compound 1 was reached between 2 hours and 6 hours. Mean t_{1/2} after single oral administration in healthy individuals ranged from 12.1 hours to 67.0 hours and increased with increasing dose. Following single oral doses of compound 1 in the range of 30 mg to 800 mg, exposures increased with dose, but the results of dose proportionality analysis suggest that the increase in C_{max} and AUC_{0-∞} was less than dose proportional. Following single oral administration of compound 1, a reduction in Lp(a) levels was observed over the duration of the treatment course with a maximum reduction relative to placebo of up to approximately 27% after a single dose.

[0069] Example 2: Part B - MAD Study

[0070] The study was designed to evaluate the safety, tolerability and PK of compound 1 in healthy individuals with elevated Lp(a). The MAD study was a randomized, investigator- and participant-blind, placebo-controlled, multiple-ascending dose, single-site study conducted in otherwise healthy individuals with elevated Lp(a) (≥ 75 nM or 30 mg/dL).

[0071] The following orally administered doses, as well as placebo, were studied: 30 mg, 100 mg, 300 mg, 500 mg and 800 mg. The individuals received the study dose once per day for 14 days. The individuals resided in the clinical research unit for the duration of the dosing. Safety follow-up visits were scheduled for 123 days after the last dose.

[0072] PD analyses: absolute values and change from baseline are calculated from concentrations of the following PD markers: Lp(a), triglycerides, cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, ApoB, plasminogen, high-sensitivity C-reactive protein (hs-CRP), plasminogen activator inhibitor-1, tissue plasminogen activator antigen and alpha-2 antiplasmin.

[0073] Safety analyses: Safety parameters assessed during the study included: AEs, laboratory parameters, physical examinations, vital signs, ECGs and Body Weight.

[0074] PK analyses: plasma concentrations of compound 1 were measured at the following time points: on Day 1 predose (0 hour) and 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours postdose, on Day 5, Day 8, and Day 11 only predose, and on Day 14 predose (0 hour) and 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours (Day 15), 96 hours (Day 18), 192 hours (Day 22), 360 hours (Day 29), 696 hours (Day 43), 1200 hours (Day 64), 1704 hours (Day 85), 2208 hours (Day 106), and 2952 hours (Day 137) postdose. The plasma concentrations are used to determine PK parameters using standard non-compartmental methods in a validated software program (Phoenix WinNonlin Version 8.1). The PK parameters determined include: AR_{AUC} , $AUC_{0-\tau}$, CL/F , C_{max} , $t_{1/2}$, and t_{max} .

[0075] Oral administration of multiple doses of compound 1 in healthy individuals with baseline Lp(a) >30 mg/dL across the dose range of 30 mg to 800 mg reduced Lp(a) levels relative to placebo starting from Day 2 of treatment. The largest reduction as a percent change relative to placebo was seen for the 100 mg to 800 mg compound 1 dose levels and with a similar maximum reduction relative to placebo of approximately 62% to 65% on Day 14/Day 15. The Lp(a) levels returned to baseline by Day 29 for the 30 mg dose level, by Day 43 for the 100 mg dose level, and by Day 64 for the 300 mg, 500 mg, and 800 mg dose levels. The percent change in Lp(a) concentration through to day 15 are shown in Figure 2.

[0076] Oral administration of compound 1 at multiple doses of 30 mg to 800 mg reduced plasminogen levels relative to placebo starting from Day 2 of treatment. The largest reduction in plasminogen levels relative to placebo was seen for the 800 mg compound 1 dose level with a maximum reduction of approximately 14% on Day 14. The plasminogen levels returned to baseline by Day 22 for the 30 mg dose level, by Day 43 for the 100 mg, 300 mg, and 500 mg dose levels, and by Day 64 for the 800 mg dose level. The plasminogen changes relative to placebo are not through to be clinically relevant given the literature on people with congenital plasminogen deficiency.

[0077] For the lipoprotein panel (including HDL cholesterol, LDL cholesterol, triglycerides, cholesterol, and ApoB) and the other PD biomarkers (hs-CRP, plasminogen activity, plasminogen activator inhibitor-1, tissue plasminogen activator antigen, and alpha-2 antiplasmin), there was considerable inter-subject variability within a treatment and no consistent pattern was recognizable. Given the wide range of values obtained at

each time point, and considering baseline values and values obtained postdose, the data seem to indicate that there are no dose-dependent changes versus baseline identified in any of the compound 1 treatments as compared to placebo, although numerical changes (either decreases or increases) were observed.

[0078] The MAD study indicates that multiple, oral doses of 30 mg, 100 mg, 300 mg, 500 mg and 800 mg of compound 1 are well tolerated. Most TEAEs were mild in severity. 3 moderate TEAEs were reported. 1 drug-related TEAE was reported. The most frequently reported TEAEs were headache, diarrhea, abdominal pain, nausea and fatigue. There was no clear relation between dose and the number of TEAEs reported or the number of individuals reporting TEAEs.

Dose (mg) qd	PK Parameter					
	$C_{\max}$ (ng/mL)		$t_{\max}$ (hr) ^a		$t_{1/2}$ (hr)	CL/F (L/hr)
	Day 1	Day 14	Day 1	Day 14	Day 14	Day 14
30 (N=7)	23.0	28.1	5.94	4.00	70.9	65.2
100 (N=8)	46.4	51.0	6.00	4.00	159	143
300 (N=8)	117	114	4.00	4.00	315	162
500 (N=8)	181	169	4.02	4.00	414	177
800 (N=14)	212	203	2.03	2.00	364	250

qd = once daily; N = number of individuals

Data is shown as geometric mean unless otherwise stated

^a $t_{\max}$ is presented as a median

Dose (mg) qd	PK Parameter		
	AUC_{0-24} (ng*h/mL)	$AUC_{0-\tau}$ (ng*h/mL)	AR_{AUC}
	Day 1	Day 14	Day 14
30 (N=7)	350	460	1.41
100 (N=8)	661	698	1.06
300 (N=8)	1846	1848	0.96
500 (N=8)	2968	2819	0.95
800 (N=14)	3005	3194	1.06

qd = once daily; N = number of individuals

Data is shown as geometric mean unless otherwise stated

[0079] Summary:

[0080] Multiple oral doses of 30 mg to 800 mg of compound 1 were safe and generally well tolerated by healthy individuals. There were no overall trends or clinically relevant changes observed in clinical laboratory parameters, vital signs, ECGs, physical examinations and body weight. The mean $C_{\max}$ of compound 1 was reached between 2 hours and 6 hours. Mean $t_{1/2}$ after multiple oral administration in healthy individuals with baseline Lp(a) >30 mg/dL ranged from 70.9 hours to 414 hours and increased with increasing dose. Following multiple oral doses of compound 1 in the range of 30 mg to 800 mg, exposures increased with dose, but the results of dose proportionality analysis suggest that the increase in $C_{\max}$, $AUC_{0-\infty}$, and $AUC_{0-\tau}$ was less than dose proportional. With once daily dosing of 30 to 800 mg for 14 days, there was no relevant accumulation of compound 1 (AR_{AUC} ranging from 0.95 to 1.41). Following multiple oral administration of compound 1, a reduction in Lp(a) levels was observed over the duration of the treatment course with a maximum reduction relative to placebo of up to approximately 62% to 65% after multiple doses of 14 days.

Example 3: Phase 2 Studies

[0081] The purpose of this study is to investigate the impact of various oral doses of compound 1 for 3 months on Lp(a) levels and on safety in a larger population of participants with elevated Lp(a) and high risk for cardiovascular events. It is a parallel, double-blinded, placebo-controlled study. The individuals are assigned to one of the following arms:

- Arm A: 10 mg of compound 1
- Arm B: 60 mg of compound 1
- Arm C: 240 mg of compound 1
- Arm D: placebo

The doses are administered orally, once daily for 12 weeks.

Inclusion Criteria:

Age

1. Participants must be at least 40 years old at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants with Lp(a) ≥ 175 nmol/L at Visit 1, measured at the central laboratory.
3. High risk for cardiovascular events defined as documented coronary artery disease (CAD), stroke, or peripheral artery disease or atherosclerotic cardiovascular disease (ASCVD) risk equivalents (familial hypercholesterolemia or type 2 diabetes).
 - CAD documentation should include at least 1 of the following:
 - a. angiographic evidence of $\geq 50\%$ stenosis of 1 or more major epicardial coronary arteries
 - b. Coronary Artery Calcification Agatston score on computerized tomography (CT) scan of ≥ 300
 - c. history of myocardial infarction documented by positive enzymes, and either symptoms of myocardial ischemia, or electrocardiogram (ECG) changes (Thygesen et al. 2012)
 - d. history of coronary revascularization
 - e. evidence of cardiac ischemia on exercise testing or imaging study.
 - Stroke (an acute episode of focal cerebral, spinal, or visual dysfunction caused by infarction of central nervous system tissue) documentation should include CT scan, magnetic resonance imaging, or other visualization method. Transient ischemic attack or embolic stroke (not of atherosclerotic origin) are not qualifying events.
 - Peripheral artery disease documentation should include intermittent claudication with an ankle-brachial index ≤ 0.90 and/or limb amputation or revascularization due to lower limb ischemia. Thromboangiitis obliterans is not a qualifying event.
4. Participants on the following medications according to local practice must be on a stable regimen for at least 4 weeks prior to Visit 1 and expected to remain on a stable regimen through the end of the post-treatment follow-up period:
 - a. lipid-lowering drugs (e.g., statins, ezetimibe, PCSK9 inhibitors, prescription-dose niacin, fibrates, fish oil, or other products containing omega-3 fatty acids, including over-the-counter [OTC] preparations)
 - b. testosterone, estrogens, anti-estrogens, progestins, selective estrogen receptor modulators, or growth hormone

Weight

5. Have a body mass index within the range 18.5 to 40 kg/m², inclusive.

Sex and Contraceptive/Barrier Requirements

6. Male and/or female

- a. Males who agree to use highly effective or effective methods of contraception may participate in this trial.
- b. Women of childbearing potential (WOCBP) who agree to use highly effective or effective methods of contraception and women not of childbearing potential (WNOCBP) may participate in this trial.

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

7. Capable of giving signed informed consent.

Other Inclusions

8. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures, including willing and able to take four 12-mm round concave tablets of study drug every day for 12 weeks, in the opinion of the investigator.

Exclusion Criteria**Medical Conditions**

- 9. Have a history or presence of an underlying disease, or surgical, physical, medical, or psychiatric condition that, in the opinion of the investigator, would potentially affect participant safety within the study or interfere with participating in or completing the study or with the interpretation of data.
- 10. Any of the following, or other events indicating unstable medical condition in the opinion of the investigator, within 3 months of Visit 1:
 - a. major surgery
 - b. coronary, carotid, or peripheral arterial revascularization
 - c. stroke or transient ischemic attack
 - d. myocardial infarction or unstable angina
 - e. acute limb ischemia.

11. Have, in the 6 months prior to Visit 1, uncontrolled Type 1 or Type 2 diabetes, defined as an episode of ketoacidosis or hyperosmolar state requiring hospitalization, or have a hemoglobin A1c (HbA1c) $\geq 8\%$ at Visit 1.
12. Have uncontrolled hypertension with a resting blood pressure ≥ 160 mm Hg systolic and/or ≥ 100 mm Hg diastolic at Visit 1; a repeat measure is allowed.
13. New York Heart Association Class III or IV heart failure or last known left ventricular ejection fraction $< 30\%$.
14. Active or acute infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Visit 2.
15. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.
16. Recent history of, or current drug or alcohol abuse in the opinion of the investigator.
17. Have 2 or more clinically significant or severe drug allergies, or severe post-treatment hypersensitivity reactions, including, but not limited to
 - a. erythema multiforme major
 - b. linear immunoglobulin A dermatosis
 - c. toxic epidermal necrolysis
 - d. exfoliative dermatitis.
18. Hypersensitivity to the active substance or to any of the excipients.
19. Have a current infection with hepatitis B virus (HBV), that is, positive for hepatitis B surface antigen (HBsAg) and/or PCR positive for HBV deoxyribonucleic acid (DNA).
20. Have a current infection with hepatitis C virus (HCV), that is, positive for HCV ribonucleic acid (RNA).
21. Have human immunodeficiency virus (HIV) infection.

Prior/Concomitant therapy

22. Lipoprotein apheresis within 3 months of Visit 1, or planned during the study.
23. Treatment with another investigational drug, biological agent, or device within 1 month of Visit 1, or 5 half-lives of investigational agent, whichever is longer.
24. Treatment with any investigational oligonucleotide or siRNA within 9 months of Visit 1.

Prior/Concurrent Clinical Study Experience

25. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

Diagnostic Assessments

26. Clinically significant abnormalities in screening laboratory values that would render a participant unsuitable for inclusion in the opinion of the investigator.

27. Any of the following abnormalities:

- a. estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²
- b. alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3.0x upper limit of normal (ULN)
- c. bilirubin > 1.5x ULN, except for participants diagnosed with Gilbert's syndrome

Other Exclusions

28. Are Lilly employees, or are employees of any third party involved in a study that requires exclusion of their employees.

29. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

30. Are pregnant, or intend to become pregnant or to breastfeed during the study.

31. Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.

Optional Pre-Screening:

The study includes an optional pre-screening visit as a simple way for sites to determine whether participants meet Lp(a) criteria, as assessed by a central laboratory assessment, before the full screening activities are initiated at Visit 1. If the participant has not had Lp(a) measured before or is unknown, the prescreening visit should be completed.

Screening:

The screening visit (Visit 1) no more than 3 weeks prior to the first dose. Participants with insufficiently high Lp(a) at Visit 1 will not be eligible for enrollment.

Treatment Period:

All procedures (screening and baseline) need to be completed prior to the first dose. Blood samples will then be taken and clinical observations will be made at 1 week, 2 weeks, 4 weeks, 8 weeks and 12 weeks.

Post Treatment:

There will be a follow-up visit approximately 4 weeks after the final dose.

Percent change in Lp(a) and absolute reduction in Lp(a) was measured from baseline to week 12. The percent change from baseline to week 12 was also measured for other cardiovascular biomarkers ApoB and hsCRP. The lipid profile in response to the administration of compound 1 was measured. The lipid profile includes measurements of LDL, total cholesterol, HDL and triglycerides. At the visits and times specified, blood samples were collected to determine the compound 1 plasma concentrations which were used to determine key PK parameters.

Percent Change in Lp(a):

Treatment	N	CFB (LSM [SE];%)	PBO-Adjusted CFB (LSM [95%CI]; %)	P-value
Primary: Week 12				
Placebo	60	-3.15 (5.342)		
10mg	29	-42.26 (4.477)	-40.38 (-50.45,-28.27)	<.001
60 mg	56	-70.90 (1.669)	-69.95 (-74.23,-64.96)	<.001
240 mg	57	-69.88 (1.676)	-68.90 (-73.27,-63.81)	<.001

Abbreviations: CFB = change from baseline; CI = confidence interval; LSM = least squares mean; N = number of participants in the analysis population with baseline and post-baseline value at the specified time point; PBO = placebo; SE = standard error.

Absolute Change in Lp(a):

Treatment	N	CFB (LSM [SE])	PBO-Adjusted CFB (LSM [95%CI])
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Primary: Week 12			
Placebo	60	-7.86 (13.341)	
10mg	29	-105.54 (11.181)	-97.67 (-131.98,-63.37)
60 mg	56	-177.05 (4.169)	-169.18 (-196.74,-141.63)
240 mg	57	-174.50 (4.185)	-166.64 (-194.20,-139.08)

Abbreviations: CFB = change from baseline; CI = confidence interval; LSM = least squares mean; N = number of participants in the analysis population with baseline and post-baseline value at the specified time point; PBO = placebo; SE = standard error.

Safety Results:

Compound 1 was safe and well-tolerated with no identified safety issues in patient population with a high risk for cardiovascular events. Serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs) were balanced across the groups. There was no evidence of an increase in bleeding or diabetes risk. Discontinuation of the study drug due to an adverse event included one placebo patient and six from the 240 mg group. All discontinuations were single cases across various standards of care (SOC) and without any pattern.

Summary:

Compound lowered Lp(a) with a dose response. At a dose of 240 mg, compound 1 showed a week 12 reduction of 69%. Lp(a) lowering plateaus at a point between the 60 mg and 240 mg doses. Compound 1 was safe and well-tolerated with no identified safety issues in patient population with a high risk for cardiovascular events. The phase 2 data shows that doses in the range 10 mg to 240 mg are efficacious and safe.

CLAIMS

The invention claimed is:

1. 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 (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.
2. The method of claim 1, wherein the individual has elevated Lp(a) plasma levels.
3. The method of claim 1 or claim 2, wherein the once daily dose is about 120 mg.
4. The method of claim 1 or claim 2, wherein the once-daily dose is between 60 mg and 150 mg.
5. The method of claim 4, wherein the once-daily dose is between 60 mg and 120 mg.
6. The method of claim 5, wherein the once-daily dose is between 80 mg and 120 mg.
7. 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 (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.
8. The method of claim 7, wherein the individual has an Lp(a) plasma level greater than or equal to 75 nmol/L prior to treatment.
9. The method of claim 8, wherein the individual has an Lp(a) plasma level greater than or equal to 125 nmol/L prior to treatment.

10. The method of claim 9, wherein the individual has an Lp(a) plasma level greater than or equal to 175 nmol/L prior to treatment.
11. The method of any one of claims 7 to 10, wherein the individual is at risk for cardiovascular events.
12. The method of any one of claims 7 to 11, wherein the once daily dose is about 120 mg.
13. The method of any one of claims 7 to 11, wherein the once-daily dose is between 60 mg and 150 mg.
14. The method of claim 13, wherein the once-daily dose is between 60 mg and 120 mg.
15. The method of claim 14, wherein the once-daily dose is between 80 mg and 120 mg.
16. 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 (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.
17. The method of claim 16, wherein the individual has an Lp(a) plasma level greater than or equal to 75 nmol/L prior to treatment.
18. The method of claim 17, wherein the individual has an Lp(a) plasma level greater than or equal to 125 nmol/L prior to treatment.
19. The method of claim 18, wherein the individual has an Lp(a) plasma level greater than or equal to 175 nmol/L prior to treatment.
20. The method of any one of claims 16 to 19, wherein the once-daily dose is about 120 mg.

21. The method of any one of claims 16 to 19, wherein the once-daily dose is between 60 mg and 150 mg.

22. The method of claim 21, wherein the once-daily dose is between 60 mg and 120 mg.

23. The method of claim 22, wherein the once-daily dose is between 80 mg and 120 mg.

24. A method of treating atherosclerotic 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 (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.

25. The method of claim 24, wherein the individual has elevated Lp(a) plasma levels.

26. The method of claim 24 or claim 25, wherein the once-daily dose is about 120 mg.

27. The method of claim 24 or claim 25, wherein the once-daily dose is between 60 mg and 150 mg.

28. The method of claim 27, wherein the once-daily dose is between 60 mg and 120 mg.

29. The method of claim 28, wherein the once-daily dose is between 80 mg and 120 mg.

30. A compound which is (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, 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.

31. A compound which is (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, 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.

32. A compound which is (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, 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.

33. A compound which is (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, for use in the treatment of atherosclerotic cardiovascular disease in an individual, wherein the compound is orally administered at a once-daily dose of between 10 mg and 240 mg.

34. The compound, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 30 to 33, wherein the individual has an Lp(a) plasma level greater than or equal to 75 nmol/L prior to treatment.

35. The compound, or a pharmaceutically acceptable salt thereof, for use according to claim 34, wherein the individual has an Lp(a) plasma level greater than or equal to 125 nmol/L prior to treatment.

36. The compound, or a pharmaceutically acceptable salt thereof, for use according to claim 35, wherein the individual has an Lp(a) plasma level greater than or equal to 175 nmol/L prior to treatment.

37. The compound, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 30 to 36, wherein the once-daily dose is about 120 mg.

38. The compound, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 30 to 36, wherein the once-daily dose is between 60 mg and 150 mg.

39. The compound, or a pharmaceutically acceptable salt thereof, for use according to claim 38, wherein the once-daily dose is between 60 mg and 120 mg.

40. The compound, or a pharmaceutically acceptable salt thereof, for use according to claim 39, wherein the once-daily dose is between 80 mg and 120 mg.