

TITLE

[0001] Fixed Dose Combinations And Formulations Comprising ETC1002 And One Or More Statins And Methods Of Treating Or Reducing The Risk Of Cardiovascular Disease

CROSS REFERENCE TO RELATED APPLICATIONS

[0002] This application claims the benefit of U.S. Provisional Application No. 62/133,739 filed March 16, 2015 and U.S. Provisional Application No. 62/277,403 filed January 11, 2016, each of which is hereby incorporated in its entirety by reference.

BACKGROUND

Field of the invention

[0003] This application relates to methods and compositions useful for treating cardiovascular conditions or reducing the risk of cardiovascular conditions. Statins are a cornerstone of prevention and treatment of cardiovascular disease, however, cardiovascular disease remains amongst the top leading causes of death in the United States and other countries around the world. Millions of people, in the United States alone, suffer from a cardiovascular disease or disorder.

[0004] Low-density lipoprotein cholesterol (LDL-C) is a well-established risk factor for cardiovascular disease. However, many patients, for example those with hypercholesterolemia, fail to reduce LDL-C to desired levels with traditional therapies. Existing residual cardiovascular risk, especially observed in high-cholesterol patients, and despite the advances of new cholesterol-reducing drugs, has encouraged a search for new, non-traditional pharmaceuticals. New pharmaceutical drugs have been developed and are effective at reducing cholesterol levels in the human body. Unfortunately, these drugs also induce negative side-effects. Many of the compounds which have shown to be potent for inhibiting the enzymes of cholesterol biosynthesis are also systemically toxic. Thus, there is a need for new pharmaceutical formulations which are both effective and safe for reducing cholesterol.

SUMMARY

[0005] This application relates to methods and compositions comprising fixed doses of ETC-1002 and statins for the treating or reducing the risk of cardiovascular disease.

[0006] ETC-1002 (bempedoic acid) is an oral, once-daily therapy which lowers cholesterol by inhibiting adenosine triphosphate (ATP) citrate lyase (ATPCL). ATPCL is farther upstream than HMG-CoA reductase in the cholesterol biosynthetic pathway.

[0007] ETC-1002 lowers low-density lipoprotein cholesterol (LDL-C) by direct inhibition of hepatic adenosine triphosphate citrate lyase, leading to reduced de novo cholesterol synthesis and increased LDL receptor expression. ETC-1002 administered in doses from 120 mg to 240 mg daily reduced LDL-C by 27% to 43% in phase 2a clinical trials of various hypercholesterolemic populations including patients with type 2 diabetes mellitus and patients with muscle-related statin intolerance.

[0008] The general class of "statins" are compounds which lower cholesterol levels in the body by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and concomitantly, the pathway for synthesizing cholesterol in the liver. Examples of compounds which are part of the "stain" class include, but are not limited to, atorvastatin, simvastatin, rosuvastatin, and pravastatin. Treatments usually administer from about 2 mg to 80 mg of a statin compound.

[0009] The inventors have found that HMG-CoA reductase inhibition leads to an increase in LDL receptor activity. Additionally, the inventors find that combining these two therapies leads to cooperative activity and favorable clinical treatment. Accordingly, the present invention is directed toward cholesterol-lowering compositions comprising statins and ETC-1002. These compositions lead to further reductions in total cholesterol, and specifically LDL-C, in patients.

[0010] The present application also discloses a method of lowering cholesterol using fixed dose combination of ETC-1002 and one or more statins. Based on observations in on-going studies, combination therapy with ETC-1002 and a fixed, high dosage of one or more statins has comparable efficacy and safety to that of ETC-1002 combined with a fixed, low to medium dosage of one or more statins. Of course combination therapy with ETC-1002 and a fixed, high dosage of one or more statins is also significantly greater versus statin or ETC-1002 monotherapy (120 mg or 180 mg daily) in patients with or without a history of statin-related muscle symptoms. The combination therapy shows a significantly greater efficacy and safety profile even in acute hypercholesterolemic patients.

[0011] In one aspect, methods and compositions of present invention even lower cholesterol in patients with persistently elevated LDL-C, despite stable statin therapy at this high of a dosage.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0012] These and other features, aspects, and advantages of the present invention will become better understood with regard to the following description, and accompanying drawings, where:

[0013] **FIGURE 1: Disposition of Patients.** *One patient was randomized but discontinued before receiving study drug. AE = adverse event; mITT = modified intent to-treat.

[0014] **FIGURE 2: Mean Percent Change in LDL-C from Baseline to Week 12.**

These data are from the modified intent-to-treat population. LDL-C = low-density lipoprotein cholesterol; LS= least-squares. *p = 0.0055 vs placebo; †p < 0.0001 vs placebo. Error bars represent standard error.

DETAILED DESCRIPTION

Advantages and utility

[0015] Briefly, and as described in more detail below, described herein are compositions, methods of making the said compositions and methods for treating cardiovascular disease or reducing the risk of cardiovascular disease using fixed-dose combinations of one or more statins and ETC-1002. The advantages for this approach are numerous and include, but are not limited to, increased reduction of cholesterol and low density lipoprotein levels in patients treated with the fixed-dose combinations of one or more statins and ETC-1002 than when patients are treated with either statins or ETC-1002 alone. As described above, statins are the cornerstone of prevention and treatment of cardiovascular disease, but can produce unwanted side effects in many patients. Such side effects include, but are not limited to, increased concentrations of liver enzymes, muscle problems, and an increased risk of diabetes. Statin-associated muscle symptoms are an important clinical problem because statin discontinuation in hypercholesterolemic patients increases cardiovascular risk. Hence, there is a significant need for cardiovascular therapies for patients that exhibit muscle-related statin intolerance.

Definitions

[0016] Terms used in the claims and specification are defined as set forth below unless otherwise specified.

[0017] Terms used in the claims and specification are defined as set forth below unless otherwise specified. Further, if any term or symbol used herein is not defined as set forth below, it shall have its ordinary meaning in the art.

[0018] As used herein and in the appended claims, singular articles such as “a,” “an” and “the” and similar referents in the context of describing the elements (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, including the upper and lower bounds of the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein, is intended merely to better illuminate the embodiments and does not pose a limitation on the scope of the claims unless otherwise stated. No language in the specification should be construed as indicating any non-claimed element as essential.

[0019] Generally, reference to a certain element such as hydrogen or H is meant to include all isotopes of that element. For example, if an R group is defined to include hydrogen or H, it also includes deuterium and tritium. Compounds comprising radioisotopes such as tritium, C¹⁴, P³² and S³⁵ are thus within the scope of the present technology. Procedures for inserting such labels into the compounds of the present technology will be readily apparent to those skilled in the art based on the disclosure herein.

[0020] The term “ameliorating” refers to any therapeutically beneficial result in the treatment of a disease state, e.g., an inflammatory disease state, including lessening in the severity or progression, remission, or cure thereof. In some embodiments, “ameliorating” includes prophylaxis of a disease state.

[0021] The term “*in vitro*” refers to processes that occur in a living cell growing separate from a living organism, e.g., growing in tissue culture.

[0022] The term “*in vivo*” refers to processes that occur in a living organism.

[0023] The term “mammal” as used herein includes both humans and non-humans and include but is not limited to humans, non-human primates, canines, felines, murines, bovines, equines, and porcines.

[0024] The term “sufficient amount” means an amount sufficient to produce a desired effect, e.g., an amount sufficient to modulate protein aggregation in a cell.

[0025] The term “therapeutically effective amount” is an amount that is effective to ameliorate a symptom of a disease. A therapeutically effective amount can, in some

embodiments, be a “prophylactically effective amount” as prophylaxis can be considered therapy.

[0026] The compounds of the present technology can exist as solvates, especially hydrates. Hydrates may form during manufacture of the compounds or compositions comprising the compounds, or hydrates may form over time due to the hygroscopic nature of the compounds. Compounds of the present technology can exist as organic solvates as well, including DMF, ether, and alcohol solvates among others. The identification and preparation of any particular solvate is within the skill of the ordinary artisan of synthetic organic or medicinal chemistry.

[0027] “Subject” refers to a mammalian organism treated using a compound of the present invention. The “subject” can be a human or non-human mammalian organism.

[0028] “Tautomer” refer to alternate forms of a compound that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring NH moiety and a ring =N moiety such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

[0029] “Treating” or “treatment” of a disease or disorder in a subject refers to 1) preventing the disease or disorder from occurring in a subject that is predisposed or does not yet display symptoms of the disease or disorder; 2) inhibiting the disease or disorder or arresting its development; or 3) ameliorating or alleviating the cause of the regression of the disease or disorder.

[0030] As used herein, the terms “prevent,” “preventing,” “prevention,” “prophylactic treatment” and the like refer to reducing the probability of developing a disease, disorder, or condition in a subject, who does not have, but is at risk of or susceptible to developing a disease, disorder, or condition. Thus, in some embodiments, an agent can be administered prophylactically to prevent the onset of a disease, disorder, or condition, or to prevent the recurrence of a disease, disorder, or condition.

[0031] For the purposes of this specification and appended claims, unless otherwise indicated, all numbers expressing amounts, sizes, dimensions, proportions, shapes, formulations, parameters, percentages, parameters, quantities, characteristics, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term “about” even though the term “about” may not expressly appear with the value, amount or range. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are not and need not be exact, but may be approximate and/or larger or smaller as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to

those of skill in the art depending on the desired properties sought to be obtained by the presently disclosed subject matter. For example, the term “about,” when referring to a value can be meant to encompass variations of, in some aspects, $\pm 100\%$ in some aspects $\pm 50\%$, in some aspects $\pm 20\%$, in some aspects $\pm 10\%$, in some aspects $\pm 5\%$, in some aspects $\pm 1\%$, in some aspects $\pm 0.5\%$, and in some aspects $\pm 0.1\%$ from the specified amount, as such variations are appropriate to perform the disclosed methods or employ the disclosed compositions.

[0032] Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this invention belongs.

[0033] Herein any and all heteroaryl and heterocycloalkyl substituents may contain up to four heteroatoms selected from the group consisting of: O, N, and S.

[0034] It is understood that in all substituted groups defined above, polymers arrived at by defining substituents with further substituents to themselves (e.g., substituted aryl having a substituted aryl group as a substituent which is itself substituted with a substituted aryl group, etc.) are not intended for inclusion herein. In such cases, the maximum number of such substituents is three. That is to say that each of the above definitions is constrained by a limitation that each functional group is substituted (at from one to three positions) and that any and all of those substituent groups may be substituted one more time (at from one to three positions).

[0035] It is understood that the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluoro groups). Such impermissible substitution patterns are well known to the skilled artisan.

[0036] Throughout this application, the text refers to various embodiments of the present compounds, compositions, and methods. The various embodiments described are meant to provide a variety of illustrative examples and should not be construed as descriptions of alternative species. Rather, it should be noted that the descriptions of various embodiments provided herein may be of overlapping scope. The embodiments discussed herein are merely illustrative and are not meant to limit the scope of the present technology.

Abbreviations

[0037] AE is an abbreviation for adverse event

[0038] CK is an abbreviation for creatine kinase

[0039] HDL-C is an abbreviation for high-density lipoprotein cholesterol

[0040] CRP = is an abbreviation for high-sensitivity C-reactive protein

[0041] LDL-C is an abbreviation for low-density lipoprotein cholesterol

[0042] LS is an abbreviation for least-squares

[0043] NCEP ATP-III is an abbreviation for National Cholesterol Education Program Adult Treatment Panel III

[0044] non-HDL-C is an abbreviation for non-high-density lipoprotein cholesterol

[0045] VLDL is an abbreviation for very-low-density lipoprotein

Therapy

[0046] Disclosed herein is a method comprising administering a fixed-dose combination of a fixed dose of ETC-1002 or an analog thereof and a fixed dose of one or more statins or an analog thereof to a subject in need thereof, optionally wherein ETC-1002 is administered at a fixed dose of 180 mg or at a fixed dose of 120 mg and each one of the one or more statins is administered at a fixed dose from 2 to 80 mg, optionally wherein the method decreases the level of low density lipoprotein cholesterol (LDL-C) in the subject below that of a control subject receiving a placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed dose between 2 to 80 mg of each one of the one or more statins, and optionally wherein the method treats or reduces the risk of cardiovascular disease in the subject.

[0047] In some aspects, ETC-1002 is administered at a fixed dose of 180 mg or at a fixed dose of 120 mg and each one of the one or more statins is administered at a fixed dose from 2 to 80 mg.

[0048] In some aspects, the subject has hypercholesterolemia, and wherein the method further comprises treating hypercholesterolemia.

[0049] In some aspects, the method treats or reduces the risk of cardiovascular disease in the subject.

[0050] In some aspects, the method decreases the level of cholesterol in the subject below that of a control subject receiving a placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed dose from 2 to 80 mg dose of each one of the one or more statins.

[0051] In some aspects, the method decreases the level of LDL-C in the subject below that of a control subject receiving a placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed dose from 2 to 80 mg dose of each one of the one or more statins. In some aspects, the method decreases the level of C-reactive protein (hsCRP) in the subject below that of a control subject receiving a placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed dose from 2 to 80 mg dose of each one of

the one or more statins. In some aspects the reduction of C-reactive protein is up to 20% or 30% or more relative to baseline. In some aspects, the method decreases the level of apolipoprotein B (ApoB) in the subject below that of a control subject receiving a placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed dose from 2 to 80 mg dose of each one of the one or more statins. In some aspects, the method decreases the level of non-high density lipoprotein-cholesterol in the subject below that of a control subject receiving a placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or fixed dose from 2 to 80 mg for each one of the one or more statins. In some aspects, the method decreases the LDL particle number in the subject below that of a control subject receiving a placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed dose from 2 to 80 mg for each one of the one or more statins.

[0052] In some aspects, the method dose dependently reduces apolipoprotein B by 15% to 17% or more, non-high-density lipoprotein cholesterol by 14% to 17% or more, total cholesterol by 13% to 15% or more, and LDL particle number by 17% to 21% or more.

[0053] In some aspects, LDL-C is decreased in the subject up to 24% or more relative to baseline. In some aspects, non HDL-C is decreased in the subject by at least 30, 35, 37, 40, 42, or 45% or more relative to baseline. In some aspects, hsCRP is decreased in the subject by at least 20, 25, 26, 30, 35, 38, or 40% or more relative to baseline.

[0054] In some aspects, non-HDL-C is decreased in the subject by at least 30, 35, 40, 43, 45, 48, or 50% or more relative to baseline. In other aspects, HDL-C is decreased in the subject relative to baseline.

[0055] In some aspects, Statin and ETC-1002 are each administered orally. In some aspects, one or more statins and ETC-1002 are each administered at least once daily. In some aspects, one or more statins and ETC-1002 are each administered at least once daily for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 week(s).

[0056] In some aspects, the subject has dyslipidemia. In some aspects, the subject has hypercholesterolemia. In some aspects, the subject is obese, optionally wherein the BMI of the subject is 18-45 kg/m². In some aspects, the subject is statin tolerant. In some aspects, the subject is statin intolerant. In some aspects, the subject experiences an adverse event when on one or more statins at the lowest FDA approved dose, said adverse events being selected from the group consisting of muscle-related pain, aches, weakness, and cramping. The inventors have observed that such muscle-related adverse events that began or increased during statin therapy could be significantly lowered or even resolved when treatment with add on ETC-1002 therapy to statin therapy was employed.

[0057] In some aspects, the subject has a baseline LDL-C level of 115-220 mg/dL. In some aspects, the subject has a baseline triglycerides level of less than or equal to 400 mg/dL.

[0058] In some aspects, one or more statins and ETC-1002 are administered simultaneously. In some aspects, one or more statins and ETC-1002 are administered separately.

[0059] Also disclosed herein is a method of treating cardiovascular disease or reducing the risk of cardiovascular disease in a subject, comprising administering a fixed-dose combination of a fixed dose of ETC-1002 or an analog thereof and a fixed dose of one or more statins or an analog thereof to a subject in need thereof, optionally wherein ETC-1002 is administered at a fixed dose of 120 mg or at a fixed dose of 180 mg and each one of the one or more statins is administered at a fixed dose of between 2-80 mg, optionally wherein the method decreases the level of low density lipoprotein cholesterol (LDL-C) in the subject below that of a control subject receiving a placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose of each one of one or more statins, and optionally wherein the subject has hypercholesterolemia.

[0060] Also disclosed herein is a pharmaceutical composition comprising ETC-1002 and one or more statins, optionally wherein ETC-1002 is present at a fixed dose of 120 mg or 180 mg and each one of the one or more statins is present at a fixed dose between 2-80 mg.

[0061] In some aspects, the composition further comprises a pharmaceutically acceptable vehicle. In some aspects, ETC-1002 is present at a fixed dose of 120 mg or 180 mg and each one of the one or more statins is present at a fixed dose between 2-80 mg. In some aspects, the composition is formulated for oral delivery. In some aspects, the composition is formulated for administration once daily.

[0062] In some aspects, the method decreases the level of apolipoprotein B (ApoB) in the subject below that of a control subject receiving a placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.

[0063] In some aspects, the method decreases the level of apolipoprotein A1 (ApoA1) in the subject below that of a control subject receiving a placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.

[0064] In some aspects, the method does not change the level of ApoA1 in the subject compared to that of a control subject receiving a placebo, a fixed 120 mg dose of ETC-1002,

a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.

[0065] In some aspects, the method decreases the ratio of ApoB to ApoA1 in the subject above that of a control subject receiving a placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.

[0066] In another aspect, the method decreases the number of drug-related AEs by at least 25%, by 35%, 45% or by 50% or more. In another aspect, the method decreases the number of muscle-related AEs by at least 50%, by 65%, 75% or by 85% or more.

[0067] In another aspect, methods disclosed herein significantly reduce the risk of a cardiovascular event in a subject. In some aspects this risk is reduced by up to 35% or more.

[0068] In some aspects, the methods herein provide for treating cardiovascular disease and/or reducing the risk of cardiovascular disease in a subject comprising administering an amount of a composition comprising ETC-1002 which is rapidly absorbed having a T_{max} at less than 4 hours.

[0069] In some aspects, the methods herein provide for treating cardiovascular disease and/or reducing the risk of cardiovascular disease in a subject comprising administering an amount of a composition comprising ETC-1002 which do not prolong QTc or QT/QTc (TQT study). In one aspect, the add-on ETC-1002 therapy does not affect subject heart rate and PR and QRS intervals.

[0070] In some aspects, the methods herein provide for treating cardiovascular disease and/or reducing the risk of cardiovascular disease in a subject comprising administering an amount of a composition comprising ETC-1002 which systemic exposure, $AUC_{tau,ss}$, occurs with $t_{1/2}$ approximately 15 to 27 hours.

[0071] In some aspects, the methods herein provide for treating cardiovascular disease and/or reducing the risk of cardiovascular disease in a subject comprising administering an amount of a composition comprising ETC-1002 as add-on therapy to statin therapy which provides exposure measures AUC and/or C_{max} indicating that the 2 regimens have no appreciable drug interaction. In one embodiment, neither the one or more statin(s) nor ETC-1002 exposure measures are outside safe values as established by confidence intervals.

[0072] In one aspect, the composition includes one or more statins as defined by the fixed dosages of atorvastatin (10 mg or 20 mg), simvastatin (5 mg, 10 mg, or 20 mg), rosuvastatin (5 mg or 10 mg), and/or pravastatin (10 mg, 20 mg, or 40 mg). In another aspect, the method includes one or more statins as defined by the fixed dosages of atorvastatin (10 mg or 20 mg), simvastatin (5 mg, 10 mg, or 20 mg), rosuvastatin (5 mg or 10 mg), and/or pravastatin (10

mg, 20 mg, or 40 mg). In yet another aspect, any combination of atorvastatin (10 mg or 20 mg), simvastatin (5 mg, 10 mg, or 20 mg), rosuvastatin (5 mg or 10 mg), and/or pravastatin (10 mg, 20 mg, or 40 mg) may be used in any embodiment or aspect disclosed herein.

[0073] In one aspect, the composition includes one or more statins as defined by the fixed dosages of Table 1 below:

Table 1.

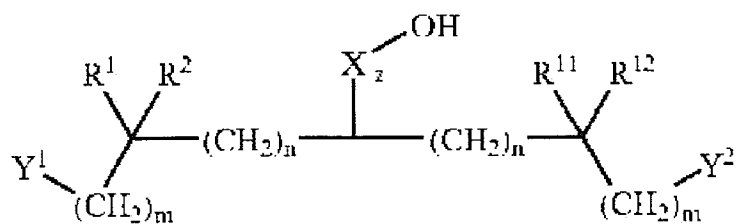
High Intensity Statins	Moderate Intensity Statins	Low Intensity Statins
• Atorvastatin 40-80 mg	• Atorvastatin 10-20 mg	• Simvastatin 10 mg
• Rosuvastatin 20-40 mg	• Rosuvastatin 5-10 mg	• Pravastatin 10-20 mg
• Simvastatin 80 mg [†]	• Simvastatin 20-40 mg	• Lovastatin 20 mg
	• Pravastatin 40-80 mg	• Fluvastatin 20-40 mg
	• Lovastatin 40 mg	• Pitavastatin 1 mg
	• Fluvastatin XL 80 mg	
	• Fluvastatin 40 mg twice daily	
	• Pitavastatin 2-4 mg	

Compounds

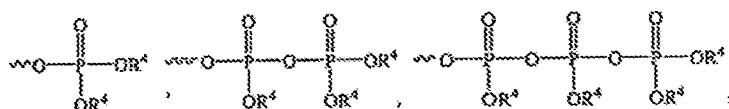
[0074] Combinations of one or more statins and ETC-1002 are described herein. In one aspect, one or more or all of the statins are natural products isolated from a natural source such as Penicillium and Aspergillus fungi. In another aspect, one or more or all of the statins are synthetic, meaning they are made by advancing petrochemical starting material via organic synthesis to the desired statin compound.

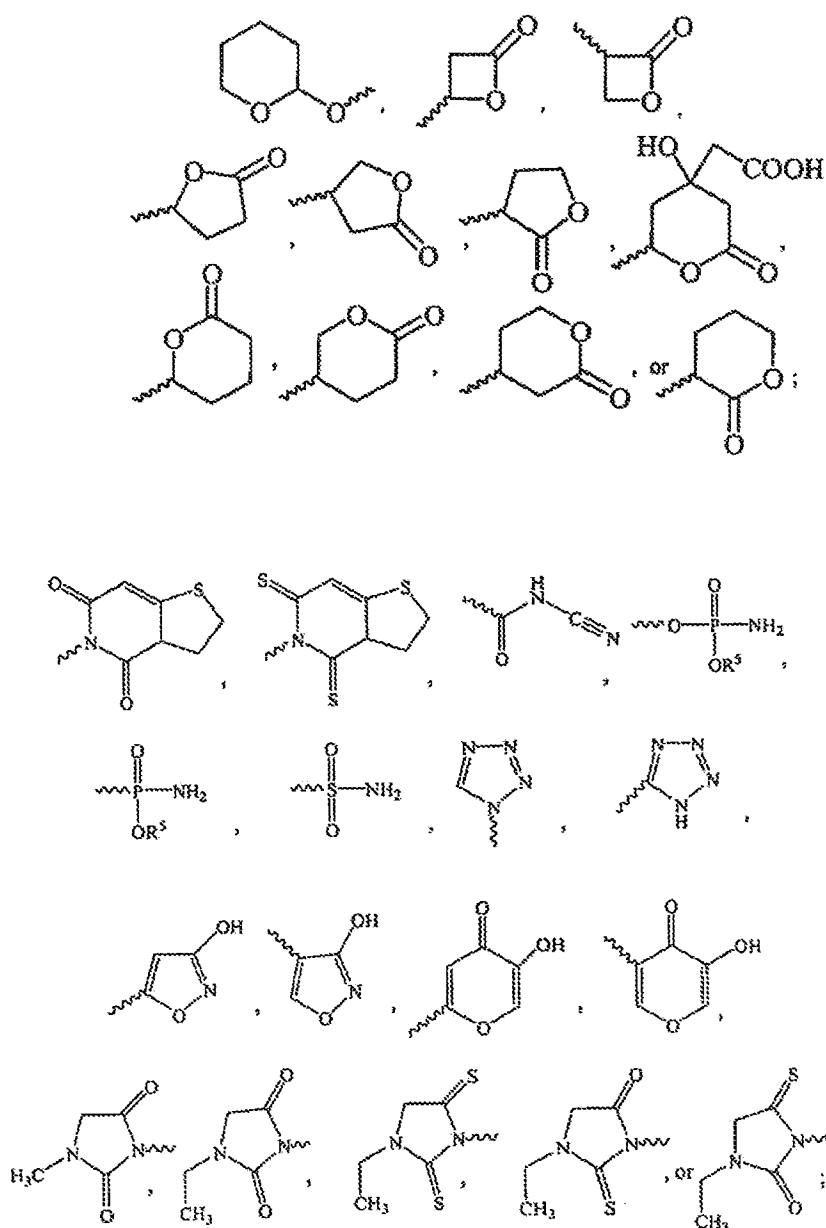
[0075] Formula I below shows ETC-1002 and analogs of ETC-1002.

Formula I:



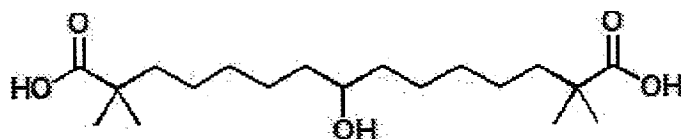
wherein (a) each occurrence of m is independently an integer ranging from 0 to 5; (b) each occurrence of n is independently an integer ranging from 3 to 7; (c) X is (CH_2) , or Ph, wherein z is an integer from 0 to 4 and Ph is a 1,2-, 1,3-, or 1,4 substituted phenyl group; (d) each occurrence of R^1 , R^2 , R^{11} , and R^{12} is independently H, $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_2\text{-C}_6)$ alkenyl, $(\text{C}_2\text{-C}_6)$ alkynyl, phenyl, or benzyl, wherein R^1 , R^2 , R^{11} , and R^{12} are not each simultaneously H; and (e) each occurrence of Y^1 and Y^2 is independently $(\text{C}_1\text{-C}_6)$ alkyl, OH, COOH, COOR³, SO₃H,





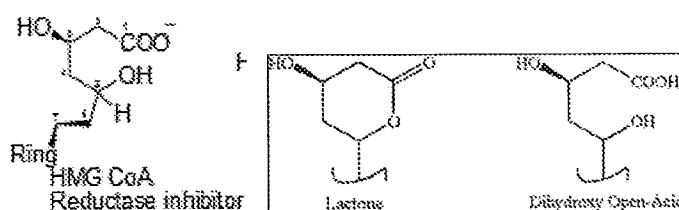
wherein: (i) Y^1 and Y^2 are not each simultaneously (C_1-C_6) alkyl; (ii) R^3 is (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, (C_1-C_6) alkoxy, or phenyl groups, (iii) each occurrence of R^4 is independently H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl and is unsubstituted or substituted with one or two halo, OH, C_1-C_6 , alkoxy, or phenyl groups; and (iv) each occurrence of R^5 is independently H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl.

[0076] Structure of ETC-1002:

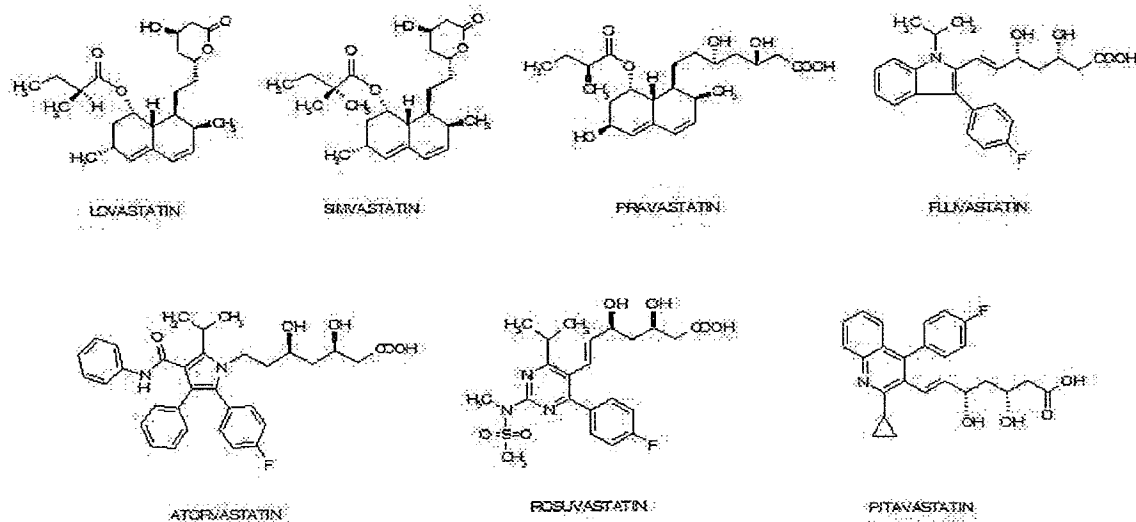


[0077] ETC-1002 can be referred to as 8-hydroxy-2,2,14,14 tetramethylpentadecanedioic acid.

[0078] Statin compounds inhibit HMGR enzymatic activity in the liver. In terms of structure, all statin compounds possess a dihydroxyheptanoic acid group or lactone thereof and a substituted ring system (shown below).



[0079] However, statins do differ with respect to the substituted ring structure. Some statins have a substituted decalin-ring structure while others have substituted aryl and heteroaryl ring systems. The structure of exemplary statin compounds is shown below, however, this list is in no way limiting.



[0080] It is acknowledged that any and all analogs of ETC-1002 according to Formula I can be used in any of the methods and/or compositions or formulations disclosed herein. It is further acknowledged that any and all analogs of statins according to the description above can be used in any of the methods and/or compositions or formulations disclosed herein.

Synthesis of ETC-1002 and Statins

[0081] ETC-1002 and the processes of the synthesis of ETC-1002 are disclosed in the issued U.S. Patent No. 7,335,799. The details of this process can be found in the published U.S. patent publication No. US2005-0043278 A1, in paragraphs [0247] - [0343] of the specification, each of which is herein incorporated by reference.

[0082] The synthesis of statins is known in the art. In a strategic and general disclosure, the synthesis of statins is disclosed in WO2005047276A2 which is herein incorporated by reference. Any other synthetic modifications for statins (or analogs of ETC-1002 for that matter), which may include unique or alternative ring systems, are within the purview of the skilled artisan. For example, the skilled artisan will be able to use synthetic reference texts to incorporate unique or desired substituted-aryl, heteroaryl, and decalin ring systems into the final statin compound. Such references include, but are not limited to: as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley, and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5, and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley, and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley, and Sons, 5th Edition, 2001), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989), T. W. Greene and P.G.M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York, 1999.

Methods of use

[0083] The present invention provides methods for the treatment or prevention of a cardiovascular disease, comprising administering to a subject fixed doses of compounds or a composition comprising compounds of the invention and a pharmaceutically acceptable vehicle. As used herein, the term "cardiovascular diseases" refers to diseases of the heart and circulatory system. These diseases are often associated with dyslipoproteinemias and/or dyslipidemias. Cardiovascular diseases which the compositions of the present invention are useful for preventing or treating include but are not limited to arteriosclerosis; atherosclerosis; stroke; ischemia; endothelium dysfunctions, in particular those dysfunctions affecting blood vessel elasticity; peripheral vascular disease; coronary heart disease; myocardial infarction; cerebral infarction and restenosis.

[0084] The present invention provides methods for the treatment or prevention of a dyslipidemia comprising administering to a subject fixed doses of compounds or a composition comprising compounds of the invention and a pharmaceutically acceptable

vehicle. As used herein, the term "dyslipidemias" refers to disorders that lead to or are manifested by aberrant levels of circulating lipids. To the extent that levels of lipids in the blood are too high, the compositions of the invention are administered to a patient to restore normal levels. Normal levels of lipids are reported in medical treatises known to those of skill in the art. For example, recommended blood levels of LDL, HDL, free triglycerides and others parameters relating to lipid metabolism can be found at the web site of the American Heart Association and that of the National Cholesterol Education Program of the National Heart, Lung and Blood Institute (http://www.americanheart.org/cholesterol/about_level.html and http://www.nhlbi.nih.gov/health/public/heart/chol/hb-c_what.html, respectively). At the present time, the recommended level of HDL cholesterol in the blood is above 35 mg/dL; the recommended level of LDL cholesterol in the blood is below 130 mg/dL; the recommended LDL:HDL cholesterol ratio in the blood is below 5:1, ideally 3.5:1; and the recommended level of free triglycerides in the blood is less than 200 mg/dL.

[0085] Dyslipidemias which the compositions of the present invention are useful for preventing or treating include but are not limited to hyperlipidemia and low blood levels of high density lipoprotein (HDL) cholesterol. In certain embodiments, the hyperlipidemia for prevention or treatment by the compounds of the present invention is familial hypercholesterolemia; familial combined hyperlipidemia; reduced or deficient lipoprotein lipase levels or activity, including reductions or deficiencies resulting from lipoprotein lipase mutations; hypertriglyceridemia; hypercholesterolemia; high blood levels of urea bodies (e.g. .beta.-OH butyric acid); high blood levels of Lp(a) cholesterol; high blood levels of low density lipoprotein (LDL) cholesterol; high blood levels of very low density lipoprotein (VLDL) cholesterol and high blood levels of non-esterified fatty acids.

[0086] The present invention further provides methods for altering lipid metabolism in a patient, e.g., reducing LDL in the blood of a patient, increasing the ratio of HDL to LDL in the blood of a patient, and inhibiting saponified and/or non-saponified fatty acid synthesis, said methods comprising administering to the patient a compound or a composition comprising a compound of the invention in an amount effective alter lipid metabolism.

Pharmaceutical compositions

[0087] Methods for treatment of cardiovascular diseases are also encompassed by the present invention. Said methods of the invention include administering a therapeutically effective amount of one or more statins and ETC-1002. The fixed dose combination of one or more statins and ETC-1002 can be formulated in pharmaceutical compositions. These

compositions comprise a pharmaceutically acceptable excipient, carrier, buffer, stabilizer or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material can depend on the route of administration, e.g. oral, intravenous, cutaneous or subcutaneous, nasal, intramuscular, intraperitoneal routes.

[0088] Pharmaceutical compositions for oral administration can be in tablet, capsule, pill, powder or liquid form. A tablet or pill can include a solid carrier such as gelatin or an adjuvant. Liquid pharmaceutical compositions generally include a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol can be included.

[0089] In one aspect, pharmaceutical compositions of the present invention are created from one or more of the compounds disclosed herein and are in the form of a pill.

[0090] In another aspect, herein provided is a method for lowering cholesterol or the associated markers disclosed herein (HDL-C, ApoA1, etc.) or for the treatment or prevention of a cardiovascular disease or dyslipoproteinemias and/or dyslipidemias, comprising administering to a subject a pharmaceutical composition in the form of a pill comprising ETC-1002 at a fixed dose of 120 mg or 180 mg and or a fixed dose from 2 to 80 mg dose of each one of one or more statins.

[0091] For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives can be included, as required.

[0092] Whether it is a small molecule or other pharmaceutically useful compound according to the present invention that is to be given to an individual, administration is preferably in a "therapeutically effective amount" or "prophylactically effective amount" (as the case can be, although prophylaxis can be considered therapy), this being sufficient to show benefit to the individual. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of protein aggregation disease being treated. Prescription of treatment, e.g. decisions on dosage etc, is within the responsibility of general practitioners and other medical doctors, and typically takes account of the disorder to

be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 16th edition, Osol, A. (ed), 1980.

[0093] A composition can be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated.

[0094] In one aspect the present disclosure provides for a method of treating cardiovascular disease or reducing the risk of cardiovascular disease in a subject, comprising administering a fixed-dose combination of a fixed dose of ETC-1002 or an analog thereof and a fixed dose of one or more statins or an analog thereof to a subject in need thereof, optionally wherein ETC-1002 is administered at a fixed dose of 120 mg or at a fixed dose of 180 mg and each of the one more statins is administered at a fixed dose between 2-80 mg, and optionally wherein the method treats or reduces the risk of cardiovascular disease in the subject.

[0095] In one aspect the present disclosure provides for a method wherein the level of total cholesterol and non-HDL-C in the subject is below that of a control subject receiving placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.

[0096] In one aspect the present disclosure provides for a method wherein the level of low density lipoprotein (LDL) in the subject is below that of a control subject receiving placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.

[0097] In one aspect the present disclosure provides for a method wherein the number of LDL particles in the subject is below that of a control subject receiving placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.

[0098] In one aspect the present disclosure provides for a method wherein the level of apolipoprotein B (ApoB) in the subject is less than that of a control subject receiving placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.

[0099] In one aspect the present disclosure provides for a method wherein the level of apolipoprotein A-1 (ApoA1) in the subject is less than that of a control subject receiving placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.

[00100] In one aspect the present disclosure provides for a method wherein the ratio of apolipoprotein B (ApoB) to apolipoprotein A-1 (ApoA1) in the subject is below that of a control subject receiving placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.

[00101] In one aspect the present disclosure provides for a method wherein the subject has hypercholesterolemia.

[00102] In one aspect the present disclosure provides for a method wherein the subject is human.

[00103] In one aspect the present disclosure provides for a therapeutic composition of comprising a therapeutic amount of a fixed dose of ETC-1002 and a fixed dose for each one of one or more statins.

[00104] In one aspect the present disclosure provides for a composition wherein the amount is a 120 or 180 mg dose of ETC-1002 and a fixed 2-80 mg dose for each one of one or more statins.

EXAMPLES

[00105] Below are examples of specific embodiments for carrying out the present invention. The examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental error and deviation should, of course, be allowed for.

[00106] The practice of the present invention will employ, unless otherwise indicated, conventional methods of protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art. Such techniques are explained fully in the literature. See, e.g., T.E. Creighton, *Proteins: Structures and Molecular Properties* (W.H. Freeman and Company, 1993); A.L. Lehninger, *Biochemistry* (Worth Publishers, Inc., current addition); Sambrook, et al., *Molecular Cloning: A Laboratory Manual* (2nd Edition, 1989); *Methods In Enzymology* (S. Colowick and N. Kaplan eds., Academic Press, Inc.); *Remington's Pharmaceutical Sciences*, 18th Edition (Easton, Pennsylvania: Mack Publishing Company, 1990); Carey and Sundberg *Advanced Organic Chemistry 3rd Ed.* (Plenum Press) Vols A and B(1992).

[00107] Any terms not directly defined herein shall be understood to have the meanings commonly associated with them as understood within the art of the invention. Certain terms are discussed herein to provide additional guidance to the practitioner in describing the

compositions, devices, methods and the like of aspects of the invention, and how to make or use them. It will be appreciated that the same thing may be said in more than one way. Consequently, alternative language and synonyms may be used for any one or more of the terms discussed herein. No significance is to be placed upon whether or not a term is elaborated or discussed herein. Some synonyms or substitutable methods, materials and the like are provided. Recital of one or a few synonyms or equivalents does not exclude use of other synonyms or equivalents, unless it is explicitly stated. Use of examples, including examples of terms, is for illustrative purposes only and does not limit the scope and meaning of the aspects of the invention herein.

[00108] It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise.

EXAMPLE 1

1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACL	Adenosine triphosphate-citrate lyase
ACS	Acyl-CoA synthetase
ADR	Adverse drug reaction
AE	Adverse event
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
apoA1	Apolipoprotein A1
apoB	Apolipoprotein B
aPTT	Activated partial thromboplastin time
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
AUC ₀₋₂₄	Area under the curve during 24 hours

Abbreviation or Specialist Term	Explanation
AUC _{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration
BLQ	Below the limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C ₂₄	Concentration in sample collected 24 hours post-dose, or prior to the next dose
Ca	Calcium
C _{avg}	Average plasma concentration over the dosing interval
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
Cl	Chloride
CL/F	Apparent oral clearance
C _{max}	Observed maximum plasma concentration
C _{min}	Minimum plasma concentration
CMV	Cytomegalovirus
CoA	Acetyl-coenzyme A
CO ₂	Carbon dioxide
CrCL	Creatinine clearance
CRF	Case report form
CT	Computed tomography
CYP	Cytochrome P450
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
eGFR	Estimated glomerular filtration rate
EOS	End of study
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
FPFV	First patient first visit
FSH	Follicle-stimulating hormone

Abbreviation or Specialist Term	Explanation
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA _{1C}	Glycosylated hemoglobin, Type A _{1C}
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HR	Heart rate
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IWRS	Interactive web response system
IVRS	interactive voice response system
K	Potassium
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LFT	Liver function test
LOCF	Last observation carried forward
LPLV	Last patient last visit
LSM	Least squares means
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of diet in renal disease

Abbreviation or Specialist Term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MED ID	Medication identification
mITT	Modified intent-to-treat
Na	Sodium
NLA	National Lipid Association
NOAEL	No-observed-adverse-effect level
non-HDL-C	Non-high-density lipoprotein cholesterol
OLA	Open-label atorvastatin
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PE	Physical exam
PK	Pharmacokinetic(s)
PPAS	Per Protocol Analysis Set
PT	Prothrombin time
QD	Once daily
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SE	Standard error
SP	Safety population
$t_{1/2}$	Terminal elimination half-life
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
t_{max}	Time of observed maximum plasma concentration
TSH	Thyroid-stimulating hormone
TQT	Thorough QT/QTc
ULN	Upper limit of normal
USA	United States of America
WBC	White blood cell

Background on ETC-1002

Mechanism of Action

[00109] ETC-1002 is a small molecule inhibitor of adenosine triphosphate (ATP)-citrate lyase (ACL), an enzyme upstream of hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase (molecular target of statins) in the cholesterol biosynthesis pathway. ETC-1002 can mediate competitive inhibition of ACL. Inhibition of ACL decreases cholesterol synthesis in liver leading to increased LDLR expression and LDL particle clearance from the blood. Therefore, inhibition of ACL by ETC-1002 is via the same pathway as HMG-CoA reductase inhibition by statins.

[00110] An important differentiating feature of ETC-1002 is that, unlike statins, it does not inhibit cholesterol synthesis in skeletal muscle. Therefore, ETC-1002 is not expected to cause the adverse effects associated with inhibition of the cholesterol biosynthesis pathway in skeletal muscle.

Nonclinical Experience

[00111] The primary pharmacology of ETC-1002 was evaluated in several well-characterized and predictive rodent models of dyslipidemia. In these studies, ETC-1002 lowered LDL-C and triglycerides (TGs) and increased high-density lipoprotein cholesterol (HDL-C).

[00112] Results of the safety pharmacology studies did not identify any significant risks for patients over the range of exposures intended for clinical studies.

[00113] In toxicology studies, evaluations of ETC-1002 in mice, rats, and monkeys in oral studies up to 12 months in duration have been completed. No significant central nervous system, respiratory, or cardiovascular liabilities have been identified. Target organs identified in repeat-dose studies were liver and kidney in rats and monkeys, and changes were reversible following cessation of treatment. Changes in clinical laboratory parameters indicative of hepatic and renal function were observed in animals at doses lower than those associated with frank toxicity. Routine clinical laboratory parameters will continue to be monitored carefully in clinical trials.

[00114] ETC-1002 is non-mutagenic and non-clastogenic in both in-vitro and in-vivo genetic toxicology assays.

[00115] In the pivotal 6-month rat study, the no-observed-adverse-effect level (NOAEL) dose was 30 mg/kg/day in male and female rats and the corresponding area under the curve during 24 hours (AUC₀₋₂₄) values of the sum of ETC-1002 and ESP15228 were up to 528 µg·hr/mL. In the pivotal 12-month monkey study, the NOAEL dose was 60 mg/kg/day and

the corresponding AUC₀₋₂₄ value of the sum of ETC-1002 and ESP15228 was up to 4478 µg·hr/mL.

[00116] In vitro studies indicated that ETC-1002 is neither an inhibitor nor inducer of major cytochrome P450 (CYP) enzymes at clinically relevant plasma concentrations. In addition, ETC-1002 does not appear to inhibit major drug transporters.

Previous Human Experience

[00117] The entire clinical program for ETC-1002 (conducted between 2009 and 2015) has included approximately 1000 subjects and patients, with approximately 700 receiving ETC-1002 doses ranging from 2.5 up to 240 mg/day (multiple doses) for up to 12 weeks. There are 15 completed clinical studies (nine Phase 1 and six Phase 2), and integrated data summaries are based on the 6 completed Phase 2 studies.

[00118] An integrated analysis of six Phase 2 studies resulted in placebo-adjusted LS means for percent change from baseline of approximately 32% with ETC-1002 180 mg monotherapy, 50% with ETC-1002 180 mg + ezetimibe 10 mg, and 22% for 180 mg on top of stable statin therapy. Reduced LDL-C with ETC-1002 treatment was consistently accompanied by corresponding reductions in non-HDL-C, TC, LDL particle number and apoB. Notably, a pattern of hsCRP lowering across studies was also seen with a range of 20%-40% median change from baseline. The effect of ETC-1002 on HDL-C and TGs has been generally neutral.

[00119] PK data indicate that ETC-1002 is rapidly absorbed, with T_{max} occurring at less than 4 hours for ETC-1002 and 7 hours for ESP15228. The C_{max} of ETC-1002 and ESP15228 increase in proportion to increasing dose. However, systemic exposure, AUC_{tau,ss}, shows a slightly more than dose-proportional increase with increasing dose up to 120 mg daily and linear from 140 to 220 mg daily doses. Mean t_{1/2} is approximately 15 to 27 hours. The metabolite, ESP15228, attains systemic exposure of 20%-40% of the parent, with the higher percentage observed at the lower doses; mean t_{1/2} is slightly longer than that of the parent, with values of 20-33 hours.

[00120] No drug interaction was demonstrated with the combination of ETC-1002 and metformin or Ortho-Novum 1/35, a combined oral contraceptive. A food-effect/bioequivalence study demonstrated that ETC-1002 can be taken without regard to food. The capsule and tablet formulations produce similar PK results.

[00121] The effect of ETC-1002 on the PK of atorvastatin was assessed in Study 1002-007. In this study, all patients received atorvastatin 10 mg/day during a 28-day run-in (statin stabilization) period followed by a treatment period during which patients received

atorvastatin 10 mg/day plus a daily dose of ETC-1002 for 8 weeks. All patients started ETC-1002 at a dose of 60 mg/day, which was up-titrated every 2 weeks to 120 mg/day, then 180 mg/day, then 240 mg/day. For determination of a drug interaction between ETC-1002 and atorvastatin, the PK parameters of atorvastatin and ortho-hydroxy atorvastatin on Day 1 (at the end of the statin stabilization period; reference) were compared with corresponding PK parameters at Week 4 (at which time the ETC-1002 dose was 120 mg/day; Test 1) and Week 8 (at which time the ETC-1002 dose was 240 mg/day; Test 2). For atorvastatin and ortho-hydroxy atorvastatin, if the 90% confidence interval (CI) of the ratio of the exposure measures (AUC and/or C_{max}) fell between 80% and 125%, the 2 regimens would be considered similar with no drug interaction.

[00122] The results of the drug interaction evaluations show that a daily regimen of 10 mg atorvastatin plus 120 mg ETC-1002 provides an approximately 60% higher exposure to atorvastatin and ortho-hydroxy atorvastatin than daily doses of 10 mg atorvastatin alone. The higher dose of ETC-1002 (240 mg) administered with atorvastatin also gave higher exposure to the atorvastatin and ortho-hydroxy atorvastatin than administration of atorvastatin alone. The increases with 120 and 240 mg are similar with regard to AUC and C_{max} increases for atorvastatin and metabolite. This study showed a transient increase in the exposure of atorvastatin ($1.4\times$ to $2.0\times$) when given in combination with ETC-1002. Importantly, ETC-1002 in combination with atorvastatin 10 mg was safe and well tolerated and resulted in incremental LDL-C lowering beyond atorvastatin alone.

[00123] The effect of steady-state ETC-1002 on the single-dose PK of simvastatin, pravastatin, and rosuvastatin was evaluated in Study 1002-012. In this study, healthy subjects were assigned to 1 of 3 statin cohorts and received a single oral dose of either simvastatin 20 mg (Cohort 1), pravastatin 40 mg (Cohort 2), or rosuvastatin 10 mg (Cohort 3) on the morning of Day -5. Serial PK blood samples were collected through the morning of Day -3. Starting on Day 1, all subjects received oral ETC-1002, 240 mg, once daily for 16 days. On the morning of Day 12, in addition to ETC-1002, subjects received a single dose of a statin drug, based on their cohort assignment; serial PK blood samples were collected.

[00124] The results of this study showed that plasma concentrations and PK parameters of ETC-1002 and its metabolite ESP15228 after the 12th daily 240-mg dose of ETC-1002 in combination with a single dose of simvastatin 20 mg, pravastatin 40 mg, or rosuvastatin 10 mg were consistent with those in previous monotherapy studies and a multiple-dose study of ETC-1002 in combination with atorvastatin.

[00125] Simvastatin and simvastatin exposure (AUC_{0-inf}) were increased by 29% and 91%, respectively, in the presence of steady-state ETC-1002 as compared to simvastatin alone. Simvastatin C_{max} did not appear to be affected by co-administration with ETC-1002, whereas simvastatin C_{max} was increased by 43% for simvastatin in combination with daily ETC-1002 relative to simvastatin alone. The magnitude of the observed geometric mean ratios for test (simvastatin with ETC-1002) to reference (simvastatin alone) AUC for the active metabolite simvastatin were consistent with a <2-fold increase; results showed that the magnitude of the interaction was lower for the prodrug parent compound (simvastatin).

[00126] Pravastatin exposure (AUC_{inf} and C_{max}) was increased by 99% and ~2-fold, respectively, in the presence of steady-state ETC-1002 as compared to pravastatin alone. The magnitude of the observed geometric mean ratio for test (pravastatin with ETC-1002) to reference (pravastatin alone) AUC was consistent with a <2-fold increase.

[00127] Rosuvastatin exposure (AUC_{inf} and C_{max}) was increased by 69% and 208%, respectively, in the presence of steady-state ETC-1002 as compared to rosuvastatin alone. The magnitude of the observed geometric mean ratio for test (rosuvastatin with ETC-1002) to reference (rosuvastatin alone) AUC was consistent with a <2-fold increase. As in Study 1002-007, the combination of ETC-1002 and statin therapy was safe and well tolerated.

[00128] The results of the thorough QT/QTc (TQT) study (1002-022) showed no significant change in QTc. Following daily ETC-1002 240 mg for 9 days, ETC-1002 does not prolong QT interval duration and has no clinically significant effect on heart rate and PR and QRS intervals.

[00129] In reviewing the incidence of TEAEs that occurred in ≥ 3 patients in any treatment group in the 6 integrated Phase 2 studies, there did not appear to be any dose-related trends in the frequency of TEAEs in the ETC-1002 treatment groups. The greatest number of patients experiencing at least 1 TEAE among ETC-1002-treated groups occurred in the ETC-1002 40-mg dose group (75.6%); this frequency was similar to the frequency of patients experiencing at least 1 TEAE in the placebo group (74.2%).

[00130] The system organ classes (SOCs) with the highest percentages of patients experiencing at least 1 TEAE in the ETC-1002 treatment groups were infections and infestations, and musculoskeletal and connective tissue disorders, and gastrointestinal disorders.

[00131] In the SOC of infections and infestations, the percent of patients experiencing at least 1 TEAE was highest in the ETC-1002 80 mg group (25.0%). Treatment groups involving ETC-1002 had a frequency of TEAEs in this SOC ranging from 11.6% to 25%,

compared to ezetimibe 10 mg having 23.2%, baseline statins having 14.8%, and placebo having 11.8%. The most frequent TEAEs by preferred term in this SOC (those occurring in ≥ 3 patients in any treatment group) were bronchitis, nasopharyngitis, sinusitis, upper respiratory tract infection (URTI) and urinary tract infection (UTI). All TEAEs by preferred term in the SOC of infections and infestations occurred in $\leq 8\%$ of patients in any treatment group.

[00132] In the SOC of musculoskeletal and connective tissue disorder, the percent of patients experiencing at least 1 TEAE in almost all ETC-1002 treatment groups was equal to or less than the frequency in the placebo group (23.7%), with the exception of the ETC-1002 240 mg group (32.4%). The most frequent TEAEs by preferred term in this SOC (ie, occurred in ≥ 3 patients in any treatment group) were arthralgia, back pain, muscle spasms, muscular weakness, myalgia, and pain in extremity. There were no dose-related trends in the frequency of myalgia in ETC-1002 treatment groups. The most frequent reports of myalgia were in the ETC-1002 120 mg + ezetimibe group (7.7%) and in the ezetimibe 10 mg group (6.1%). There were no reports of rhabdomyolysis. Almost all TEAEs by preferred term in the SOC of musculoskeletal and connective tissue disorder occurred in $< 8\%$ of patients in any treatment group with the exception of arthralgia (9.7% of placebo group), back pain (8.1% of ezetimibe 10 mg group), and muscle spasms (13.5% of ETC-1002 240 mg group).

[00133] A total of 11 SAEs were reported in the 6 integrated Phase 2 studies; 5 (5/579; 0.9%) were in patients receiving ETC-1002, 1 (1/99; 1%) was a patient receiving ezetimibe 10 mg, 2 (2/61; 3.3%) were in patients receiving placebo + baseline statin, and 3 (3/93; 3.2%) were in patients receiving placebo alone. No SAE by preferred term had more than a single patient reporting the event. There were no muscle-related SAEs.

[00134] One patient died with cause unknown. A full narrative for this patient has been provided (18 Aug 2014, SN-0083). The patient, a 55-year-old white male with hyperlipidemia and statin intolerance in the ETC-1002 120 mg treatment group (Study 1002-008), experienced sudden death on Study Day 98. He was found outside by a pool unresponsive and without a pulse. The death certificate did not provide a cause of death. The Investigator considered the event of sudden death (cause unknown) and possibly related to study drug since a temporal relationship could not be ruled out.

[00135] In general other measures of safety including laboratory results showed no clinically significant trends associated with ETC-1002 vs placebo or other comparator agents.

Dose Selection

[00136] Doses of ETC-1002 ranging from 40 to 240 mg/day have been evaluated in the Phase 2 program. Based on data from the integrated analysis of safety and efficacy, observed values and percent change from baseline in the primary efficacy endpoint, LDL-C together with a positive safety profile, support the choice of the 180-mg dose for the Phase 3 studies. An integrated analysis of six Phase 2 studies resulted in placebo-adjusted least squares means (LSM) for percent change from baseline of approximately 32% with ETC-1002 180 mg monotherapy, 50% with ETC-1002 180 mg + ezetimibe 10 mg, and 22% for 180 mg on top of stable statin therapy. The 180-mg dose was noted to have an excellent safety profile. Overall, balancing efficacy and safety the 180-mg dose was chosen for clinical development.

Background Therapy

[00137] ETC-1002 in this study is currently being evaluated as an add-on to high-dose statin (atorvastatin 80 mg) therapy.

Risk Benefit Summary

[00138] To date, the nonclinical and clinical data indicate that ETC-1002 has a favorable risk-benefit profile. The ability of ETC-1002 to achieve clinically meaningful LDL-C-lowering responses while demonstrating a favorable tolerability profile in a variety of patient populations supports continued development of ETC-1002, an oral ACL inhibitor.

EXAMPLE 2

ETC-1002/HIGH-DOSE STATIN FIXED DOSE COMBINATION

[00139] The LDL-C-lowering efficacy of ETC-1002 180 mg versus placebo when added to stable atorvastatin 80 mg background therapy for 28 days in statin-treated patients is evaluated.

[00140] Multiple-dose plasma PK of atorvastatin 80 mg and its active metabolites, ortho-hydroxy atorvastatin and para-hydroxy atorvastatin, alone and in combination with steady-state ETC-1002 180 mg is assessed.

[00141] The inventors contemplate that this add-on therapy is at least as effective as the previous studies and produces the same or better safety profile/ tolerance.

[00142] Without wishing to be bound by theory the inventors believe that ETC-1002 180-mg tablets, when administered in addition to a stable high-dose statin (atorvastatin 80 mg), provides additional LDL-C lowering efficacy relative to atorvastatin alone and safe and is tolerated in statin-treated adult patients. ETC-1002 in combination will show increases in AUC and C_{max} for statins (atorvastatin, rosuvastatin, pravastatin and simvastatin) up to

1.4-fold to 2.0-fold irrespective of structures, physico-chemical properties or doses for the statins and/or their metabolites when given.

[00143] Patients will be randomized in a ratio of 2:1 to receive treatments with either ETC-1002 180-mg tablet or matching placebo tablet in a double-blind fashion as add-on to statin therapy:

[00144] Patients will receive ETC-1002 as an add-on to high intensity statin therapy as shown in Table 3.

Table 3: Statin Dose Categories

High Intensity Statins	Moderate Intensity Statins	Low Intensity Statins
• Atorvastatin 40-80 mg	• Atorvastatin 10-20 mg	• Simvastatin 10 mg
• Rosuvastatin 20-40 mg	• Rosuvastatin 5-10 mg	• Pravastatin 10-20 mg
• Simvastatin 80 mg [†]	• Simvastatin 20-40 mg	• Lovastatin 20 mg
	• Pravastatin 40-80 mg	• Fluvastatin 20-40 mg
	• Lovastatin 40 mg	• Pitavastatin 1 mg
	• Fluvastatin XL 80 mg	
	• Fluvastatin 40 mg twice daily	
	• Pitavastatin 2-4 mg	

[00145] Patients taking simvastatin 80 mg must have history of tolerating simvastatin 80 mg for a minimum of the last 12 months without any evidence of muscle toxicity.

Administration

[00146] Patients take the active tablet or placebo tablet orally once daily.

[00147] Patients will record dosing in diaries to record the time and date of each dose taken, whether they were fasted, and the time of a meal.

Pharmacokinetic Assessments

[00148] Whole blood samples to measure plasma concentrations of statin and active metabolites and ETC-1002 and active metabolites are collected.

[00149] Samples are collected and analyzed for basic fasting lipids including the calculated LDL-C, TC, HDL-C, non-HDL-C, TG, apoB, apoA1, and hsCRP.

Table 4: Laboratory Parameters (Lipids)

Clinical Laboratory Test	Clinical Laboratory Test
• <u>Basic Lipid Parameters</u>	• <u>Other Parameters</u>
• Total cholesterol (TC)	• High-sensitivity C-reactive protein (hs-CRP)
• Calculated low-density lipoprotein cholesterol (LDL-C)	• Apolipoprotein B (apoB)
• Calculated non-HDL-C	• Apolipoprotein A1 (apoA1)
• High-density lipoprotein cholesterol (HDL-C)	
• Triglycerides (TG)	

Assessment of Safety Parameters

[00150] Safety information includes the recordation of vital signs, AEs, concomitant medications, and ECG reports.

Vital Signs

[00151] Vital signs will include diastolic and systolic blood pressure as well as heart rate.

Electrocardiogram

[00152] Electrocardiogram collection occurs at designated sample collection points and is assessed using machine readings.

Adverse Events

[00153] An AE is any untoward medical occurrence when a patient is administered a pharmaceutical product, including control, and which does not necessarily have a causal relationship with treatment.

[00154] An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, any new disease or exacerbation of an existing disease, any deterioration in non-protocol-required measurements

of laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from study drug.

[00155] TEAEs are defined as AEs that begin or worsen after the first dose of IMP

Adverse Drug Reaction

[00156] All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction (ADR). “Responses” to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (ie, the relationship cannot be ruled out).

[00157] An unexpected ADR is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

[00158] The severity of the AE is characterized as mild, moderate, or severe according to the following definitions:

[00159] Mild: Events are usually transient and do not interfere with the patient’s daily activities

[00160] Moderate: Events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities

[00161] Severe: Events interrupt the patient’s usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up

[00162] Note: A severe AE need not be serious and an SAE need not, by definition, be severe.

Definition of Serious Adverse Event

[00163] An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

[00164] Results in death

[00165] Is life-threatening

[00166] Requires in-patient hospitalization or prolongation of existing hospitalization

[00167] Results in persistent or significant disability/incapacity, or substantial disruption of the ability to conduct normal life functions

[00168] Is a congenital anomaly/birth defect

[00169] An important medical event

[00170] Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Determination of Sample Size

[00171] For the LDL C-lowering study objective, the sample size of 40 patients in the atorvastatin 80 mg/day + ETC 1002 treatment group and 20 patients in the atorvastatin 80 mg/day + placebo group (60 patients overall) is expected to provide 80% power to detect a difference of 15% in the percent change from baseline to Day 29 in calculated LDL C between atorvastatin 80 mg/day + ETC 1002 and atorvastatin 80 mg/day + placebo. This calculation is based on a 2 sided t test at the 5% level of significance, a common standard deviation of 18% and a dropout rate of 10%. Sample-size calculations were performed using nQuery Advisor®, version 7.0 (Statistical Solutions).

[00172] For the PK drug interaction study objective, the sample size of 36 patients in the atorvastatin 80 mg/day + ETC 1002 treatment group (assuming data from 4 patients will not be included) is expected to provide 79% or greater power for each parameter/analyte, if the expected Test/Reference ratio of exposure measures is 100% (no difference between atorvastatin alone and atorvastatin + ETC 1002) and the acceptance criterion is 80% to 125% for the 90% confidence interval (CI). Thus, 36 patients planned in 1002 035 is anticipated to adequately characterize the effect of ETC 1002 on atorvastatin PK.

[00173] The Per Protocol Analysis Set (PPAS) is defined as the set of patients in the FAS who additionally have all pre-dose PK samples >BLQ (for placebo patients, it is pre-dose atorvastatin PK samples >BLQ; for ETC 1002 patients, it is pre-dose atorvastatin and pre-dose ETC samples >BLQ) and have Day 29 lipid assessments. The PPAS will be used for select sensitivity analyses of the lipid parameters.

Pharmacodynamic Analysis

[00174] Summarization of lipids (LDL-C, TC, HDL-C, non-HDL-C, TG, apoB, apoA1 and hsCRP) over time will be provided. For each parameter, the summary will include the value and the percent change from baseline (for post-baseline time points) in the value.

[00175] The percent change from baseline is calculated for LDL-C and the other parameters.

Pharmacokinetic and Drug Interaction Analysis

[00176] Pharmacokinetic parameters for atorvastatin, ortho-hydroxy atorvastatin, para-hydroxy atorvastatin, ETC 1002, and ESP15228 following multiple-dose administration are derived from the plasma concentration-time profiles as follows:

[00177] C_{max}: Maximum observed plasma concentration

[00178] t_{max}: Time for C_{max}, as observed at the time of first occurrence within the profile

[00179] AUC_{last}: Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}), calculated using the Linear/Log trapezoidal method

[00180] AUC₂₄: Area under the plasma concentration-time profile from time zero to 24 hours, calculated using the Linear/Log trapezoidal method

[00181] CL/F: Apparent oral clearance, calculated from Dose/AUC₂₄, for atorvastatin and ETC 1002 only

[00182] C_{min}: Minimum plasma concentration, as observed prior to drug administration

[00183] C_{avg}: Average plasma concentration, calculated from AUC₂₄ divided by the dosing interval, 24 hours

[00184] C₂₄: Concentration in sample collected 24 hours post-dose, or prior to the next dose

[00185] Standard noncompartmental PK analysis will be used to calculate C_{max}, t_{max}, AUC_{last}, AUC₂₄, C_{min}, C_{avg}, and C₂₄. Pharmacokinetic parameters will be summarized with descriptive statistics by sampling day, and dose of ETC 1002 using the PK parameter population. A different PK parameter population may be used for each analyte.

[00186] Drug Interaction Evaluation from PK Analyses

Safety Assessments

[00187] Safety assessments include AEs, clinical safety laboratories, PEs, vital signs, and ECGs.

[00188] While the invention has been particularly shown and described with reference to a preferred embodiment and various alternate embodiments, it will be understood by persons skilled in the relevant art that various changes in form and details can be made therein without departing from the spirit and scope of the invention.

[00189] All references, issued patents and patent applications cited within the body of the instant specification are hereby incorporated by reference in their entirety, for all purposes.

CLAIMS

What is claimed:

1. A method of treating cardiovascular disease or reducing the risk of cardiovascular disease in a subject, comprising administering a fixed-dose combination of a fixed dose of ETC-1002 or an analog thereof and a fixed dose of one or more statins or an analog thereof to a subject in need thereof, optionally wherein ETC-1002 is administered at a fixed dose of 120 mg or at a fixed dose of 180 mg and each of the one more statins is administered at a fixed dose between 2-80 mg, and optionally wherein the method treats or reduces the risk of cardiovascular disease in the subject.
2. The method of claim 1, wherein the level of total cholesterol and non-HDL-C in the subject is below that of a control subject receiving placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.
3. The method of claim 1, wherein the level of low density lipoprotein (LDL) in the subject is below that of a control subject receiving placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.
4. The method of claim 1, wherein the number of LDL particles in the subject is below that of a control subject receiving placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.
5. The method of claim 1, wherein the level of apolipoprotein B (ApoB) in the subject is less than that of a control subject receiving placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.

6. The method of claim 1, wherein the level of apolipoprotein A-1 (ApoA1) in the subject is less than that of a control subject receiving placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.
7. The method of claim 1, wherein the ratio of apolipoprotein B (ApoB) to apolipoprotein A-1 (ApoA1) in the subject is below that of a control subject receiving placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 2-80 mg dose for each one of one or more statins.
8. The method of claim 1, wherein the one or more statins is selected from the group consisting of rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, fluvastatin, and pitavastatin.
9. The method of claim 1, wherein the subject has hypercholesterolemia.
10. The method of claim 1, wherein the subject is an animal.
11. The method of claim 1, wherein the subject is human.
12. A therapeutic composition comprising a therapeutic amount of a fixed dose of ETC-1002 and a fixed dose for each one of one or more statins.
13. The composition of claim 12, wherein the dose is between 2-80 mg of one statin.
14. The composition of claim 12, wherein the amount is a 120 or 180 mg dose of ETC-1002 and a fixed 2-80 mg dose for each one of one or more statins.
15. The composition of claim 12, wherein the dose is between 40-80 mg of one statin.
16. The composition of claim 12, wherein the one or more statins is selected from the group consisting of rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, fluvastatin, and pitavastatin.