TITLE

[0001] FIXED DOSE COMBINATIONS AND FORMULATIONS COMPRISING ETC1002 AND EZETIMIBE AND METHODS OF TREATING OR REDUCING THE RISK OF CARDIOVASCULAR DISEASE

BACKGROUND

Field of the invention

[0002] This application relates to methods and compositions useful for treating cardiovascular conditions or reducing the risk of cardiovascular conditions. Statins are the cornerstone of prevention and treatment of cardiovascular disease, but can produce statin-associated muscle symptoms in 5% to 29% of patients. Muscle symptoms including pain, stiffness, cramping, or weakness, usually without serum creatine kinase (CK) elevations, are the primary manifestation of statin intolerance. This application relates to methods and compositions comprising fixed doses of ETC-1002 and Ezetimibe for the treating or reducing the risk of cardiovascular disease.

[0003] 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

[0004] This application relates to methods and compositions comprising fixed doses of ETC-1002 and Ezetimibe for the treating or reducing the risk of cardiovascular disease.

[0005] ETC-1002 is an agent that 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. The present application discloses on a method using fixed dose combination of ETC-1002 and Ezetimibe based on results from studies, disclosed herein, that compared the efficacy and safety of ETC-1002 monotherapy (120 mg or 180 mg daily) and ETC-1002 combined with Ezetimibe 10 mg (EZE) versus EZE monotherapy among hypercholesterolemic patients with or without a history of statin-related muscle symptoms.

[0006] Ezetimibe is a compound which lowers cholesterol levels in the body by decreasing cholesterol absorption in the small intestine. It can be used alone or in combination with statin therapy. Although effective for lowering the overall cholesterol count in a patient, clinical results have never shown Ezetimibe could have a statistically significant impact on major cardiovascular event outcomes, for example those associated with a heart attack or stroke. Moreover, Ezetimibe has not been shown effective for reducing atherosclerosis.

[0007] The inventors have found that both Ezetimibe and ETC-1002 directly affect a lower LDL-C level (within 2 weeks) in patients which are statin-tolerant and in patients which are statin-intolerant. Additionally, the inventors find that combining these two therapies leads to cooperative activity, even lower LDL-C levels, and a favorable clinical treatment. Accordingly, the present invention is directed toward cholesterol-lowering compositions comprising Ezetimibe and ETC-1002. These compositions lead to further reductions in total cholesterol, and specifically LDL-C, in patients.

[0008] The present application also discloses a method of lowering cholesterol using fixed dose combination of ETC-1002 and Ezetimibe. Based on observations in on-going studies, combination therapy with ETC-1002 and a fixed dosage of Ezetimibe has comparable efficacy and safety to that of ETC-1002 alone, or combined with a fixed, low to medium dosage of one or more statins. Of course, combination therapy with a fixed dosage ETC-1002 and Ezetimibe 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.

[0009] In one aspect, methods and compositions of present invention even lower cholesterol (LDL-C, and other markers for example: triglycerides, ApoB, hsCRP, non-HDL-C, HDL-C, LDL particle number, ApoA1, and lower the risk of cardiovascular disease and

any AEs) in patients with persistently elevated LDL-C, despite stable statin therapy at high of a dosages from 10mg to 80 mg of statins.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0010] 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:

[0011] **FIGURE 1: Disposition of Patients.** *One patient who was statin tolerant was randomized but discontinued before receiving study drug. EZE = Ezetimibe; mITT = modified intent-to-treat; Pop. = population.

[0012] **FIGURE 2: Percent Changes from Baseline in LDL-C, Stratified by Statin Tolerance.** Week 12 or last observation carried forward is the end-of-study endpoint and differs slightly from week 12 value; p-values versus EZE monotherapy were determined by an analysis of covariance model with terms for treatment and statin intolerance and baseline value as a covariate. *$p \leq 0.05$ versus EZE; †$p \leq 0.01$ versus EZE; ‡$p < 0.0001$ versus EZE. EZE = Ezetimibe.

[0013] **FIGURE 3: Percent Changes from Baseline in LDL-C by Treatment Group and Time.** P-values vs. EZE at week 12 endpoint are shown. Week 12 or last observation carried forward is the end-of-study endpoint and differs slightly from week 12 value; p-values versus EZE monotherapy were determined by an analysis of covariance model with terms for treatment and statin intolerance and baseline value as a covariate. EZE = Ezetimibe

DETAILED DESCRIPTION

Advantages and utility

[0014] 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 Ezetimibe 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 Ezetimibe and ETC-1002 than when patients are treated with either Ezetimibe or ETC-1002 alone. As described above, Statins are the cornerstone of prevention and treatment of cardiovascular disease, but can produce statin-associated muscle symptoms in 5% to 29% of patients. Statin-associated muscle symptoms are an important

clinical problem because statin discontinuation in hypercholesterolemic patients increases cardiovascular risk. Patients who discontinue statin treatment because of intolerance show a trend toward decreased 8-year survival compared with patients who continue statin therapy. Hence, there is a significant need for cardiovascular therapies for patients that exhibit muscle-related statin intolerance

Definitions

[0015] Terms used in the claims and specification are defined as set forth below unless otherwise specified.

[0016] 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.

[0017] 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.

[0018] 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, C^{14}, P^{32} and S^{35} 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.

[0019] 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.

[0020] 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.

[0021] The term "*in vivo*" refers to processes that occur in a living organism.

[0022] 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.

[0023] 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.

[0024] 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.

[0025] 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.

[0026] "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.

[0027] "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.

[0028] "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.

[0029] 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.

[0030] 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, ± 100% in some aspects ± 50%, in some aspects ± 20%, in some aspects ± 10%, in some aspects ± 5%, in some aspects ±1%, in some aspects ± 0.5%, and in some aspects ± 0.1% from the specified amount, as such variations are appropriate to perform the disclosed methods or employ the disclosed compositions.

[0031] 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.

[0032] Herein any and all heteroaryl and heterocycloalkyl substituents may contain up to four heteroatoms selected from the group consisting of: O, N, and S.

[0033] 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).

[0034] 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.

[0035] 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:

[0036] AE is an abbreviation for adverse event

[0037] CK in an abbreviation for creatine kinase

[0038] EZE = is an abbreviation for Ezetimibe

[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 administrating a fixed-dose combination of a fixed dose of ETC-1002 or an analog thereof and a fixed dose of Ezetimibe 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 Ezetimibe is administered at a fixed dose of 10 mg.

[0047] In some aspects, 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 10 mg dose of Ezetimibe, and optionally wherein the method treats or reduces the risk of cardiovascular disease in the subject.

[0048] In some aspects, ETC-1002 is administered at a fixed dose of 120 mg or at a fixed dose of 180 mg and Ezetimibe is administered at a fixed dose of 10 mg.

[0049] In some aspects, the subject has hypercholesterolemia, and wherein the method further comprises treating hypercholesterolemia.

[0050] In some aspects, the method treats or reduces the risk of cardiovascular disease in the subject.

[0051] 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 10 mg dose of Ezetimibe.

[0052] 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 10 mg dose of Ezetimibe. 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 10 mg dose of Ezetimibe. 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 10 mg dose of Ezetimibe. 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 a fixed 10 mg dose of Ezetimibe. In some aspects, the method decreases the level of triglycerides 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 10 mg dose of Ezetimibe. 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 10 mg dose of Ezetimibe.

[0053] In some aspects, LDL-C is decreased in the subject by at least 30, 35, 40, 43, 45, 48, or 50% relative to baseline. In some aspects, non HDL-C is decreased in the subject by at least 30, 35, 37, 40, 42, or 45% relative to baseline. In some aspects, hsCRP is decreased in the subject by at least 20, 25, 26, 30, 35, 38, or 40% relative to baseline.

[0054] In some aspects, Ezetimibe and ETC-1002 are each administered orally. In some aspects, Ezetimibe and ETC-1002 are each administered at least once daily. In some aspects, Ezetimibe 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).

[0055] 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/m^2. In some aspects, the subject is statin tolerant. In some aspects, the subject is statin intolerant. In some aspects, the subject is unable to tolerate at least two

statins including one statin at the lowest FDA approved dose due to muscle-related symptoms such as pain, aches, weakness, or cramping that began or increased during statin therapy and resolved when statin therapy was discontinued.

[0056] In some aspects, the subject has a baseline LDL-C level of 130-220 mg/dL. In some aspects, the subject has a baseline triglycerides level of less than or equal to 400 mg/dL.

[0057] In some aspects, Ezetimibe and ETC-1002 are administered simultaneously. In some aspects, Ezetimibe and ETC-1002 are administered separately.

[0058] Also disclosed herein is a method of treating cardiovascular disease or reducing the risk of cardiovascular disease in a subject, comprising administrating a fixed-dose combination of a fixed dose of ETC-1002 or an analog thereof and a fixed dose of Ezetimibe 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 Ezetimibe is administered at a fixed dose of 10 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 10 mg dose of Ezetimibe, and optionally wherein the subject has hypercholesterolemia.

[0059] Also disclosed herein is a pharmaceutical composition comprising ETC-1002 and Ezetimibe, optionally wherein ETC-1002 is present at a fixed dose of 120 mg or 180 mg and Ezetimibe is present at a fixed dose of 10 mg.

[0060] 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 Ezetimibe is present at a fixed dose of 10 mg. In some aspects, the composition is formulated for oral delivery. In some aspects, the composition is formulated for administration once daily.

[0061] 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 10 mg dose of Ezetimibe.

[0062] 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 10 mg dose of Ezetimibe.

[0063] In some aspects, the method increases the level of 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 10 mg dose of Ezetimibe.

[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 10 mg dose of Ezetimibe.

[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 10 mg dose of Ezetimibe.

[0066] In some aspects, , the method decreases the number of very low lipoprotein particles (VLDL) 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 10 mg dose of Ezetimibe.

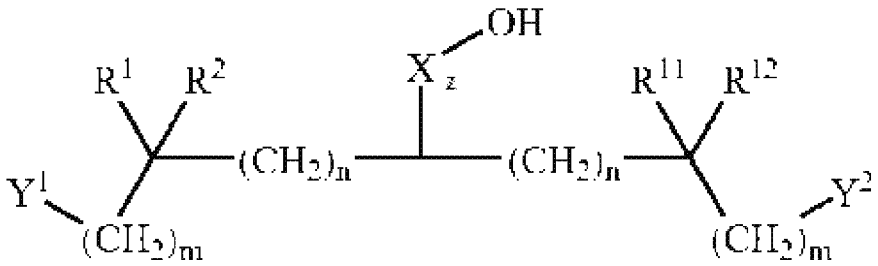
[0067] In some aspects, , the method decreases the size of very low lipoprotein particles (VLDL) in the subject below that of a control subject receiving a placebo, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 10 mg dose of Ezetimibe.

Compounds

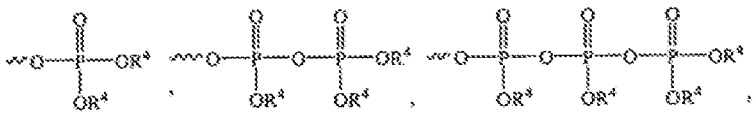
[0068] Combinations of Ezetimibe and ETC-1002 are described herein.

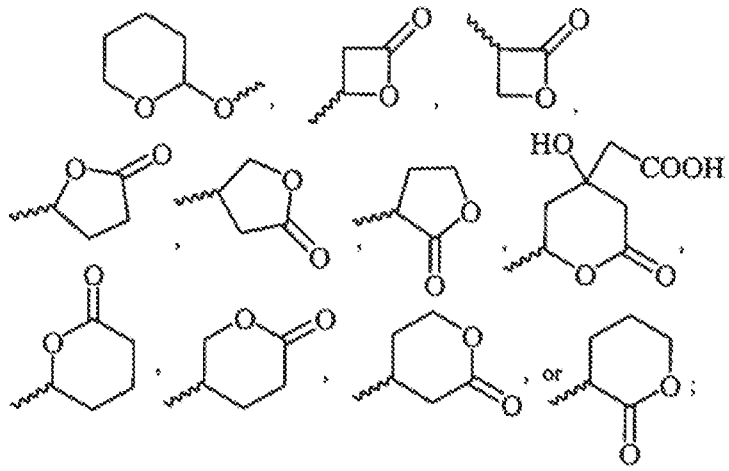
[0069] Formula I below shows ETC-1002 and analogs of ETC-1002.

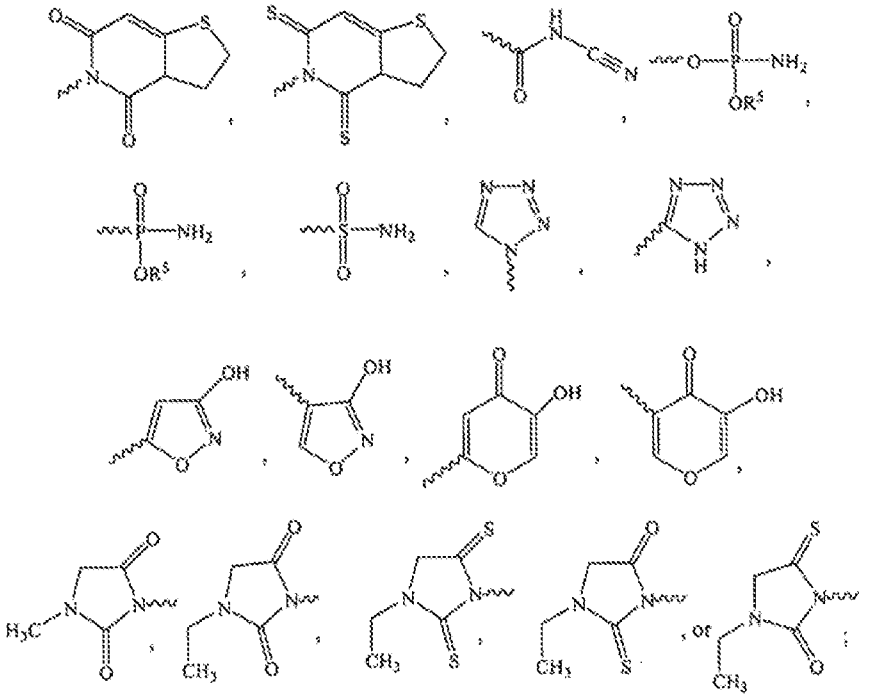
[0070] Formula I:



[0071] wherein 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, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$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 $(C_1$-$C_6)$alkyl, OH, COOH, $COOR^3$, SO_3H,



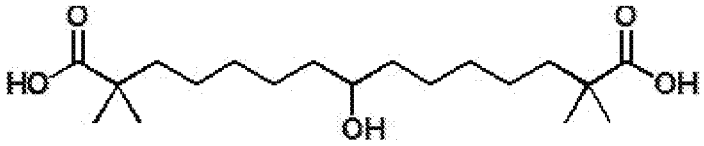




wherein: (i) Y^1 and Y^2 are not each simultaneously $(C_1$-$C_6)$alkyl; (ii) R^3 is $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or

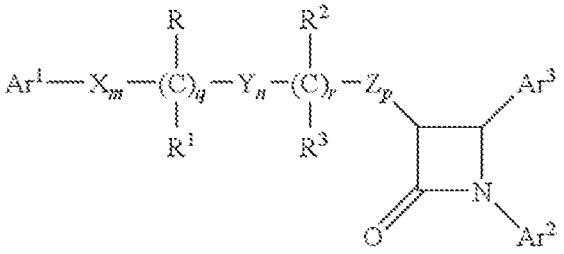
substituted with one or more halo, OH, (C_1-C_6)alkoxy, or phenyl groups, (iii) each occurrence of R^4 is independently H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl and is unsubstituted or substituted with one or two halo, OH, C_1-C_6, alkoxy, or phenyl groups; and (iv) each occurrence of R^5 is independently H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl.

[0072] Structure of ETC-1002:



[0073] ETC-1002 can be referred to as 8-hydroxy-2,2,14,14 tetramethylpentadecanedioic acid.

[0074] Formula (II) below shows Ezetimibe and analogs of Ezetimibe:

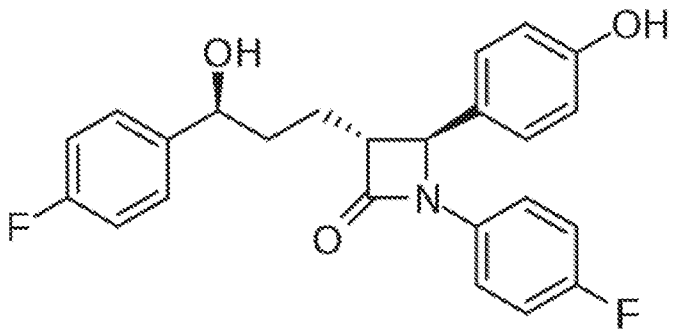


[0075] wherein in Formula (II) above or a salt thereof, wherein: Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl; Ar^3 is aryl or R^5-substituted aryl; X, Y and Z are independently selected from the group consisting of —CH_2—, —CH(lower alkyl)— and —C(dilower alkyl)—; R and R^2 are independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$ and —$O(CO)NR^6\ R^7$; R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl; q is 0 or 1; r is 0 or 1; m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5; R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1\text{-}5}\ OR^6$, —$O(CO)NR^6\ R^7$, —$NR^6R^7$, —$NR^6\ (CO)R^7$, —$NR^6\ (CO)OR^9$, —$NR^6\ (CO)NR^7\ R^8$, —$NR^6\ SO_2\ R^9$, —$COOR^6$, —$CONR^6\ R^7$, —$COR^6$, —$SO_2\ NR^6\ R^7$, $S(O)_{0\text{-}2}\ R^9$, —$O(CH_2)_{1\text{-}10}$—$COOR^6$, —$O(CH_2)_{1\text{-}10}\ CONR^6\ R^7$, —(lower alkylene)$COOR^6$, —CH=CH—$COOR^6$, —$CF_3$, —CN, —$NO_2$ and halogen; R^5 is 1-5

substituents independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}$ OR^6, —$O(CO)NR^6$ R^7, —NR^6 R^7, —NR^6 $(CO)R^7$, —NR^6 $(CO)OR^9$, —NR^6 $(CO)NR^7$ R^8, —NR^6 SO_2 R^9, —$COOR^6$, —$CONR^6$ R^7, —COR^6, —SO_2 NR^6 R^7, $S(O)_{0-2}$ R^9, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}$ $CONR^6$ R^7, —(lower alkylene)$COOR^6$ and —CH=CH—$COOR^6$; R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.

[0076] Ezetimibe can be referred to as 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone; or (3*R*,4*S*)-1-(4-fluorophenyl)-3-[(3*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one.

[0077] The structure of Ezetimibe is:



[0078] 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 ETC-1002 according to Formula II can be used in any of the methods and/or compositions or formulations disclosed herein.

Synthesis of ETC-1002 and Ezetimibe

[0079] ETC-1002 and the process of synthesis of ETC-1002 is 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.

[0080] Ezetimibe and the process of synthesis of Ezetimibe is disclosed in the issued U.S. Patent No. 5,631,365. The details of this process can be found in the specification, beginning on page 4 right column, line 43 through page 11 right column, line 65, each of which is herein incorporated by reference.

[0081] Any other synthetic modifications for any analogs of these two organic compounds, which may include for example unique or alternative aromatic substituent groups for the Ezetimibe, 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 or even heteroaryl ring systems into a final Ezetimibe analog 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

[0082] 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.

[0083] 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.

[0084] 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.

[0085] The present invention further provides methods for altering lipid metabolism in a patient, e.g., reducing LDL in the blood of a patient, reducing free triglycerides 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

[0086] 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 Ezetimibe and ETC-1002. The fixed dose combination of Ezetimibe and ETC-1002 can be formulated in pharmaceutical compositions. These compositions can comprise, a pharmaceutically acceptable excipient, carrier, buffer, stabiliser 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.

[0087] 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.

[0088] 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.

[0089] 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 Ezetimibe at a fixed dose of 10 mg.

[0090] 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.

[0091] 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.

[0092] A composition can be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated.

EXAMPLES

[0093] 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.

[0094] 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).

[0095] 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.

[0096] 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.

Methods

[0097] **Brief description of clinical study and results.** A phase 2b, multicenter, double-blind trial evaluated 348 hypercholesterolemic patients (LDL-C, 130 to 220 mg/dL) with (n = 177) or without (n = 171) muscle-related intolerance to ≥2 statins; 1 at lowest approved dose. Subjects were randomized to 12 weeks of treatment with ETC-1002 120 mg or ETC-1002 180 mg (both alone), EZE alone, ETC-1002 120 mg plus EZE, or ETC-1002 180 mg plus EZE. The percent change in LDL-C at week 12 in each of the 4 ETC-1002 treatment groups was compared with that in the EZE monotherapy group.

[0098] Of 690 patients screened, 341 were excluded, mainly for failure to satisfy inclusion criteria (Figure 1). Of the 349 randomized patients (177 statin intolerant and 172 statin tolerant), 309 patients completed the study. The 40 who discontinued participation did so most commonly because of AEs. A higher percentage of statin-tolerant patients (93%) than statin-intolerant patients (84%) completed the study. The safety population included 348 patients as 1 statin-tolerant patient discontinued before receiving any study drug.

[0099] Most patients were non-Hispanic Caucasians with similar numbers of men and women (Table 1). Mean age, baseline lipid values, and National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III risk category were slightly higher in statin-intolerant patients. The most common prestudy statin-associated muscle complaints were bilateral calf and thigh pain (data not shown). Most statin-intolerant patients historically experienced the onset of statin-associated muscle symptoms within 1 to 2 weeks of statin initiation and most had resolution of symptoms within 1 to 2 weeks of discontinuation.

[00100] **Study Objectives**. The primary objective was to assess the LDL-C–lowering effect of ETC-1002 monotherapy (120 mg or 180 mg daily) versus EZE monotherapy in hypercholesterolemic patients with or without statin intolerance. Secondary objectives were to characterize the dose response of ETC-1002, evaluate the impact of treatment on other lipid and cardiometabolic biomarkers, compare the LDL-C–lowering effect of ETC-1002 plus EZE combination therapy with EZE monotherapy, and characterize the safety and tolerability of the treatment regimens, including muscle-related adverse events (AEs).

[00101] **Study Population**. Medically stable, hypercholesterolemic men and women aged 18 through 80 years with a body mass index between 18 to 45 kg/m^2 were included in the study. Eligible patients had fasting, calculated LDL-C values between 130 and 220 mg/dL and a fasting triglyceride level ≤400 mg/dL after washout of lipid-regulating drugs. The study population included both statin-tolerant and statin-intolerant participants. Statin intolerance was defined as the inability to tolerate ≥2 statins because of muscle-related symptoms such as

pain, weakness, or cramping that began or increased during statin therapy and resolved on statin discontinuation. At least 1 statin must have been administered at the lowest approved daily dose, defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg. Treatment with less than the lowest approved daily dose of a statin (i.e., skipping days) was considered equivalent to not tolerating 1 statin at the lowest approved daily dose. Patients were excluded if they had clinically significant cardiovascular disease; type 1 diabetes mellitus; uncontrolled type 2 diabetes mellitus; non-statin related musculoskeletal complaints; uncorrected hypothyroidism; liver or renal dysfunction; unexplained CK elevations off statin treatment >3 times the upper limit of normal; ingested <80% of drug during single-blind run-in; or used anticoagulants, systemic corticosteroids, cyclosporine, metformin, or thiazolidinediones within 3 months of screening.

[00102] **Overall Study Design And Plan.** This phase 2b, randomized, double-blind, active comparator-controlled, parallel-group study was conducted at 70 sites in the United States from September 16, 2013 to August 7, 2014 and consisted of a 6-week screening phase (week -6 to week 0) and a 12-week double-blind treatment period (week 0 to week 12). Patients underwent a 5-week washout of all lipid-regulating drugs and dietary supplements and abstained from these drugs and supplements throughout the study. Patients also underwent a 5-week patient-only-blinded placebo run-in during the screening period (week -5 to week 0). This single-blind placebo run-in period was used to eliminate patients with muscle-related AEs during placebo treatment. Patients reporting new or worsening, unexplained muscle-related AEs during this run-in period were excluded from the study.

[00103] Patients were stratified (1:1) by history of statin intolerance and randomized at week 0 in a 4:4:4:1:1 ratio to once-daily treatment with capsules containing ETC-1002 120 mg, ETC-1002 180 mg, EZE, ETC-1002 120 mg plus EZE, or ETC-1002 180 mg plus EZE. Patients were seen at weeks -6, -5, -3, -1, 0, 2, 4, 8, and 12. A contract laboratory (Medpace Inc., Cincinnati, Ohio), performed all clinical laboratory tests. LDL-C was calculated using the Friedewald equation. Phlebotomy was performed after a minimum 12-hour fast (water was allowed) and only if the patient took their dose of study drug the previous day.

[00104] Individual institutional review boards approved the clinical study protocol and informed consent documents. Written informed consent was obtained from all participants before any study-related procedures.

[00105] **Efficacy Endpoints.** The primary endpoint was the percent change from baseline to week 12 in calculated LDL-C in patients treated with ETC-1002 monotherapy versus those

treated with EZE alone. Secondary endpoints included the dose-response relationship between ETC-1002 and the percent change in LDL-C from baseline to week 12, the percent change in LDL-C from baseline to week 12 in patients treated with ETC-1002 plus EZE versus those treated with EZE alone, and the percent change from baseline to week 12 for all treatment groups in LDL particle number, apolipoprotein B, total cholesterol, non–high-density lipoprotein cholesterol (non–HDL-C), HDL-C, HDL particle number, apolipoprotein A-I, triglycerides, very-low-density lipoprotein (VLDL) particle number, and high-sensitivity C-reactive protein (CRP). Lipoprotein particle number was measured using nuclear magnetic resonance imaging.

[00106] **Safety Endpoints.** The safety of ETC-1002 was assessed using treatment-emergent AEs; hematology, serum chemistry, and urinalysis laboratory values; physical examination findings; vital sign measurements; electrocardiogram (ECG) readings; weight; and ankle and waist circumference measurements. AEs were coded using the *Medical Dictionary for Regulatory Activities* version 16.0 and evaluated by the investigator for severity and relation to study drug. Muscle-related AEs were defined as those from the system organ class of musculoskeletal and connective tissue disorders, except for those that were not obviously muscle related. Terms included in the muscle-related AE analysis were selected from this system organ class after database lock and before unblinding.

[00107] **Statistical Plan And Analyses.** The study was designed to include 322 patients: 92 patients in each monotherapy group and 23 patients in each combination therapy group. Sample size calculations were performed using nQuery Advisor® version 7.0 (Statistical Solutions, Cork, Ireland). The sample size of 92 patients per monotherapy group was expected to provide 90% power to detect a difference of 10% in the absolute percent change from baseline to week 12 in LDL-C between either ETC-1002 treatment group and the EZE monotherapy group. This calculation was based on a 2-sided *t* test at the 5% level of significance and assumed a common standard deviation of 15% in the statin-tolerant patients and 22% in the statin-intolerant patients with a dropout rate of 15%.

[00108] Efficacy analyses were performed on the modified intent-to-treat population, which consisted of randomized patients who had a baseline assessment, received at least 1 dose of study medication, and had at least 1 on-treatment assessment, excluding assessments taken more than 2 days after a dose of study drug. Safety analyses were performed on the safety population, which included randomized patients who received at least 1 dose of study drug. Baseline patient characteristics were summarized for the safety population by treatment group and statin-tolerance subgroup.

[00109] An analysis of covariance was used to compare each ETC-1002 treatment group with EZE monotherapy for each of the efficacy endpoints. The primary model included the effects of treatment and statin intolerance and the baseline value as a covariate. Baseline was defined as the mean of values from weeks -1 and 0 for LDL-C, non–HDL-C, total cholesterol, HDL-C, and triglycerides. For all other lipid and biomarker measures, baseline was defined as the last value before the first dose of study drug. Missing values at week 12 were imputed using the last-observation-carried-forward procedure. When LDL-C could not be calculated (i.e., triglycerides >400 mg/dL), beta-quantification measurements were used to determine LDL-C values. Least-squares (LS) means and standard errors were obtained for each treatment group; differences in LS means and p-values were obtained for the treatment comparisons. Graphical methods (e.g., normal probability plot and histogram of residuals, plot of residuals vs. predicted values) or analytical methods (e.g., Shapiro-Wilk test), or both, were used to assess the model assumptions. Because of departures from normality observed in the parameters of triglycerides, CRP, and VLDL particle number, nonparametric analyses were performed for these measures, with p-values obtained from the Wilcoxon rank-sum test and median values presented.

[00110] Actual values, changes from baseline, and percent changes from baseline in calculated LDL-C and secondary lipid and biomarker measures were summarized using descriptive statistics by treatment group and time point. Percent changes from baseline in LDL-C also were summarized by statin-tolerance subgroup. To assess the dose-response relationship for ETC-1002 monotherapy, the primary analysis of covariance model was used for the comparison of the ETC-1002 120 mg and ETC-1002 180 mg. Statistical testing of the efficacy endpoints was 2-sided and conducted at the 5% level of significance with no adjustment for multiple comparisons.

[00111] For the evaluation of safety, the incidence of AEs was summarized by system organ class and preferred term for each treatment group. Muscle-related AEs also were summarized by statin-tolerance subgroup. Actual values and changes from baseline in clinical laboratory parameters, vital sign measurements, electrocardiogram tracings, body weight, and ankle and waist circumference were summarized using descriptive statistics by treatment group and time point.

Example 1: ETC-1002 alone or in combination with EZE reduced LDL-C from baseline to week 12 more than EZE monotherapy.

[00112] LDL-C reductions were greatest with the combination of ETC-1002 120 mg (43%) or 180 mg (48%) plus EZE ($p < 0.0001$ vs. EZE alone, both comparisons) (Table 2).

The combination treatment effect of ETC-1002 plus EZE was approximately equal to the sum of their individual effects on LDL-C. The LDL-C reduction was slightly, but not significantly, higher with ETC-1002 180 mg alone (30%) than with 120 mg alone (27%) ($p = 0.15$). The percent reductions in LDL-C with ETC-1002 were similar in statin-intolerant and statin-tolerant patients (Figure 2). LDL-C reductions were apparent and steady after 2 weeks of treatment (Figure 3). ETC-1002 alone reduced LDL-C up to 30%, which was significantly greater than the reduction achieved with EZE monotherapy. The greatest mean reductions in LDL-C, which reached 43% and 48%, occurred with the combination of ETC-1002 120 mg or 180 mg with EZE, respectively. The decreases in LDL-C with ETC-1002, EZE, and the combination occurred within 2 weeks of treatment and were maintained throughout the study. LDL-C reductions in statin-intolerant patients appeared similar to those in statin-tolerant patients. This finding is noteworthy considering that statin-intolerant patients had a higher baseline risk for cardiovascular disease than statin-tolerant patients, with 28% versus 12% classified as "high" or "very high" risk per NCEP ATP III criteria, respectively.

Example 2: . ETC-1002 alone or with EZE reduced LDL particle number, apolipoprotein B, total cholesterol, and non–HDL-C more than EZE alone.

[00113] ETC-1002 alone or with EZE also reduced secondary lipid endpoints including non–HDL-C, total cholesterol, apolipoprotein B, and LDL particle number significantly more than EZE alone. HDL-C decreased with ETC-1002 treatment (by 3% to 6%) and increased with EZE alone (by 5%) ($p < 0.0001$ to $p < 0.05$ for ETC-1002 groups vs. EZE alone) (Table 2).

Example 3: Median values for CRP decreased from baseline to the week 12 endpoint by 30% with ETC-1002 120 mg and 40% with ETC-1002 180 mg.

[00114] CRP reductions in the ETC-1002 monotherapy groups were significantly greater ($p < 0.01$, both comparisons) than the 10% reduction observed with EZE alone (Table 2).

Example 4: ETC-1002 had a modest effect on triglycerides and VLDL particle number.

[00115] Patients who were administered 120 mg and 180 mg ETC-1002 in combination with EZE had a reduction in triglycerides compared to patients administered ETC-1002 alone or EZE alone (Table 2). VLDL particle number decreased for patients administered 120 mg ETC-1002 and EZE although this effect was not less than the reduction of VLDL particle number in patients who were administered EZE alone.

Example 5: Apolipoprotein A-I is altered in patients administered with ETC-1002 180 mg plus EZE.

[00116] Apoplioprotein A-1 was significantly decreased in patients who were administered 180 mg ETC-1002 in combination with EZE compared to patients administered EZE alone (Table 2).

Example 6: The incidence of AEs in each ETC-1002 monotherapy group was similar to EZE alone.

[00117] Most AEs were mild or moderate in severity. AEs deemed possibly, probably, or definitely related to study drug were least common with ETC-1002 120 mg and most frequent with ETC-1002 180 mg plus EZE. The frequency of AEs resulting in study discontinuation was similar between the ETC-1002 treatment groups and EZE. More statin-intolerant patients (n = 17) experienced AEs resulting in discontinuation than did statin-tolerant patients (n = 3). Four serious AEs were reported (Table 3), 3 of which were unrelated to study drug and did not result in discontinuation (hemothorax with ETC-1002 120 mg, pancreatitis relapse with ETC-1002 180 mg, and transient ischemic attack with EZE). One sudden death of unknown cause in a patient taking ETC-1002 120 mg was deemed possibly related to study drug as a temporal relationship could not be excluded.

Muscle AEs were less frequent and caused fewer discontinuations with ETC-1002 monotherapy than with EZE. In the entire study population, myalgia was the most common muscle-related AE, occurring in 3% of patients treated with ETC-1002 120 mg, 1% with ETC-1002 180 mg, 6% with EZE alone, 8% with ETC-1002 120 mg plus EZE, and 4% with ETC-1002 180 mg plus EZE. Muscle-related AEs were more common among statin-intolerant than statin-tolerant patients (Table 4). The most common muscle-related AE in statin-intolerant patients was myalgia, which was least frequent in the ETC-1002 monotherapy groups.

[00118] Overall, no clinically meaningful, dose-related trends in laboratory changes or abnormalities were observed. There also were no clinically meaningful changes in physical examination findings, vital sign measurements, ECG readings, weight, or waist or ankle circumference. Alanine aminotransferase or aspartate aminotransferase, or both, increased >3 times the upper limit of normal at any measurement in 1 patient treated with ETC-1002 120 mg, 2 patients with ETC-1002 180 mg, 1 patient with EZE, and 1 patient with ETC-1002 120 mg plus EZE. One patient treated with ETC-1002 120 mg plus EZE experienced a CK level >10 times the upper limit of normal, which occurred after heavy physical exertion and was accompanied by myalgia

[00119] 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.

[00120] 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.

TABLE 1 Baseline Demographic and Clinical Characteristics

	Safety Population						
	Statin Intolerant n = 177	**Statin Tolerant n = 171**	**ETC-1002 120 mg n = 99**	**ETC-1002 180 mg n = 100**	**EZE 10 mg n = 99**	**ETC-1002 120 mg + EZE 10 mg n = 26**	**ETC-1002 180 mg + EZE 10 mg n = 24**
Demographics							
Age, years	62 ± 9	57 ± 9	61 ± 10	59 ± 9	60 ± 10	59 ± 10	59 ± 9
Women	57%	47%	54%	51%	52%	54%	54%
Caucasian	89%	91%	91%	91%	88%	92%	92%
Not Hispanic/Latino	94%	84%	92%	85%	90%	92%	92%
NCEP ATP III Risk Category **Very High**	14%	3%	11%	7%	8%	8%	8%
NCEP ATP III Risk Category **High**	14%	9%	14%	10%	11%	12%	8%
NCEP ATP III Risk Category **Moderate**	41%	50%	38%	49%	49%	42%	46%
NCEP ATP III Risk Category **Low**	32%	38%	36%	34%	32%	39%	38%
Clinical characteristics							
LDL-C, mg/dL	169 ± 25	160 ± 25	164 ± 28	166 ± 24	165 ± 25	162 ± 26	162 ± 27
Total cholesterol, mg/dL	255 ± 33	244 ± 31	249 ± 31	253 ± 33	248 ± 32	247 ± 35	246 ± 32
HDL-C, mg/dL	53 ± 13	51 ± 15	54 ± 16	52 ± 13	49 ± 12	51 ± 15	52 ± 16
Triglycerides, mg/dL*	157 (52, 365)	150 (38, 434)	136 (71, 375)	162 (38, 371)	163 (64, 434)	161 (81, 332)	151 (50, 343)
CRP, mg/L*†	1.90 (0.2, 31.7)	2.20 (0.1, 22.5)	1.60 (0.2, 19.2)	2.50 (0.1, 20.3)	2.60 (0.3, 31.7)	1.85 (0.2, 19.5)	1.25 (0.2, 4.7)
SBP, mm Hg	124 ± 11	126 ± 12	126 ± 11	125 ± 12	126 ± 12	126 ± 11	119 ± 12
DBP, mm Hg	77 ± 8	78 ± 8	77 ± 8	78 ± 7	78 ± 7	77 ± 7	76 ± 9

TABLE 1 Baseline Demographic and Clinical Characteristics

Weight, kg	86 ± 17	88 ± 19	87 ± 18	89 ± 19	85 ± 17	88 ± 20	83 ± 22
BMI, kg/m^2	30 ± 5	30 ± 5	31 ± 6	31 ± 5	30 ± 5	30 ± 5	28 ± 5

Values are mean ± SD or %, unless otherwise indicated. Baseline defined as the mean of the values from weeks -1 and 0, unless otherwise indicated. *Median values (min, max). †Baseline defined as the last value before the first dose of study drug.

BMI = body mass index; DBP = diastolic blood pressure; EZE = Ezetimibe; HDL-C = high-density lipoprotein cholesterol; CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; NCEP ATPIII = National Cholesterol Education Program Adult Treatment Panel III; SBP = systolic blood pressure.

TABLE 2 Percent Changes from Baseline to Week 12 in Lipids and CRP

	mITT Population				
	ETC-1002 120 mg n = 97	**ETC-1002 180 mg n = 99**	**EZE 10 mg n = 98**	**ETC-1002 120 mg + EZE 10 mg n = 24**	**ETC-1002 180 mg + EZE 10 mg n = 22**
Primary endpoint					
LDL-C, mg/dL	-27.5 ± 1.3†	-30.1 ± 1.3*	-21.2 ± 1.3	-43.1 ± 2.6*	-47.7 ± 2.8*
Secondary endpoints					
LDL particle number, nmol/L	-21.8 ± 1.7†	-24.6 ± 1.8*	-12.7 ± 1.7	-35.0 ± 3.7*	-37.0 ± 3.6*
Apolipoprotein B, mg/dL	-19.3 ± 1.3‡	-21.3 ± 1.3†	-15.2 ± 1.2	-32.7 ± 2.7*	-35.2 ± 2.6*
Total cholesterol, mg/dL	-19.3 ± 0.9†	-20.7 ± 0.9*	-14.3 ± 0.9	-30.6 ± 1.9*	-34.3 ± 2.0*
Non–HDL-C, mg/dL	-23.2 ± 1.2†	-25.3 ± 1.1*	-18.7 ± 1.2	-37.4 ± 2.3*	-42.4 ± 2.4*
HDL-C, mg/dL	-5.8 ± 1.4*	-4.8 ± 1.4*	5.0 ± 1.4	-3.1 ± 2.8‡	-3.7 ± 3.0†
HDL particle number, µmol/L	5.0 ± 1.3	6.2 ± 1.4	6.7 ± 1.3	7.3 ± 2.9	5.1 ± 2.8
Apolipoprotein A-I, mg/dL	-0.2 ± 1.1	0.1 ± 1.2	2.0 ± 1.1	-2.8 ± 2.4	-4.1 ± 2.4‡
Triglycerides, mg/dL§‖	0.0 (41.6)	-2.7 (46.2)	-7.0 (34.9)	-18.9 (25.5)	-12.2 (36.5)
VLDL particle number, nmol/L§	-2.7 (68.5)	15.3 (80.5)	-12.6 (63.4)	-11.7 (80.1)	12.0 (78.1)
CRP, mg/L§‖¶	-30.1 (55.4)†	-40.2 (53.3)†	-10.5 (59.0)	-38.1 (83.2)	-25.6 (37.2)‡

Values are least-squares mean ± SE, unless otherwise indicated. *$p < 0.0001$; †$p \leq 0.01$; ‡$p \leq 0.05$ versus EZE alone using an analysis of covariance model with terms for treatment and statin intolerance and baseline value as a covariate, unless otherwise indicated. Baseline defined as the mean of the values from weeks -1 and 0 unless otherwise indicated. Week 12 endpoint is the week 12 value or last observation carried forward. §Median (interquartile range) values. ‖Non-parametric analysis versus EZE using Wilcoxon rank-sum test. ¶Baseline defined as the last value before the first dose of study drug.

CRP = high-sensitivity C-reactive protein; EZE = Ezetimibe; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mITT = modified intent-to-treat; VLDL = very-low-density lipoprotein.

TABLE 3 Safety Overview: Treatment-Emergent Adverse Events

	Safety Population				
	ETC-1002 120 mg n = 99	**ETC-1002 180 mg n = 100**	**EZE 10 mg n = 99**	**ETC-1002 120 mg + EZE 10 mg n = 26**	**ETC-1002 180 mg + EZE 10 mg n = 24**
Overview of AEs					
Any AE(s)	50 (51%)	55 (55%)	53 (54%)	14 (54%)	17 (71%)
Serious AE(s)*	2 (2%)	1 (1%)	1 (1%)	0	0
Study drug-related AE(s)†	13 (13%)	18 (18%)	19 (19%)	5 (19%)	10 (42%)
Discontinuation due to AE(s)	3 (3%)	6 (6%)	8 (8%)	2 (8%)	1 (4%)
Most common AEs‡					
Constipation	3 (3%)	1 (1%)	1 (1%)	0	2 (8%)
Nasopharyngitis	3 (3%)	5 (5%)	4 (4%)	0	2 (8%)
Upper respiratory tract infection	6 (6%)	6 (6%)	1 (1%)	1 (4%)	0
Urinary tract infection	0	4 (4%)	6 (6%)	0	1 (4%)
ALT increased	0	0	1 (1%)	2 (8%)	0
AST increased	0	0	0	2 (8%)	0
Blood CK increased	1 (1%)	4 (4%)	1 (1%)	2 (8%)	0
Arthralgia	4 (4%)	1 (1%)	4 (4%)	2 (8%)	1 (4%)
Back pain	1 (1%)	1 (1%)	8 (8%)	0	0
Myalgia	3 (3%)	1 (1%)	6 (6%)	2 (8%)	1 (4%)
Headache	3 (3%)	2 (2%)	1 (1%)	4 (15%)	0

Values are n (%). *Serious AEs included 1 patient with hemothorax and 1 patient with sudden death (ETC-1002 120 mg), pancreatitis relapse (ETC-1002 180 mg), and transient ischemic attack (EZE). †AEs were categorized as drug related if relationship to study drug was deemed possible, probable, or definite, or if relationship to study drug was not recorded. The most common drug-related AEs were muscle spasms (3%), peripheral edema (2%), myalgia (2%), and muscle weakness (2%) with ETC-1002 120 mg; upper respiratory tract infection (2%), abnormal liver function test (2%), and pruritus (2%) with ETC-1002 180 mg; myalgia (6%), arthralgia (4%), and muscle spasms (3%) with EZE; and increased ALT (8%), increased AST (8%), and myalgia (8%) in the ETC-1002 120 mg plus EZE combination group. No drug-related AE was experienced by more than 1 patient treated with ETC-1002 180 mg plus EZE. ‡Most common AEs were those occurring in ≥ 5% patients/group.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; EZE = Ezetimibe.

TABLE 4 Safety Overview: Muscle-Related Treatment-Emergent Adverse Events					
	Safety Population				
	ETC-1002 120 mg	ETC-1002 180 mg	EZE 10 mg	ETC-1002 120 mg + EZE 10 mg	ETC-1002 180 mg + EZE 10 mg
Statin-Intolerant Patients	**n = 51**	**n = 51**	**n = 51**	**n = 12**	**n = 12**
Overview of Muscle-Related AEs					
Any muscle-related AE	7 (14%)	6 (12%)	9 (18%)	2 (17%)	2 (17%)
Leading to discontinuation	1 (2%)	2 (4%)	5 (10%)	0	0
Muscle-related AEs by MedDRA Preferred Term*					
Muscle spasms	3 (6%)	2 (4%)	1 (2%)	0	0
Muscular weakness	2 (4%)	1 (2%)	1 (2%)	0	0
Musculoskeletal chest pain	0	1 (2%)	0	0	0
Musculoskeletal stiffness	0	0	1 (2%)	0	0
Myalgia	2 (4%)	1 (2%)	6 (12%)	2 (17%)	1 (8%)
Pain in extremity	1 (2%)	1 (2%)	3 (6%)	0	1 (8%)
Sensation of heaviness	0	0	1 (2%)	0	0
Statin-Tolerant Patients	**n = 48**	**n = 49**	**n = 48**	**n = 14**	**n = 12**
Overview of Muscle-Related AEs					
Any muscle-related AE	1 (2%)	0	3 (6%)	0	1 (8%)
Leading to discontinuation	0	0	1 (2%)	0	0
Muscle-Related AEs by MedDRA Preferred Term*					
Muscle spasms	0	0	2 (4%)	0	1 (8%)
Musculoskeletal pain	0	0	1 (2%)	0	0
Myalgia	1 (2%)	0	0	0	0

TABLE 4 Safety Overview: Muscle-Related Treatment-Emergent Adverse Events

	Safety Population				
	ETC-1002 120 mg	**ETC-1002 180 mg**	**EZE 10 mg**	**ETC-1002 120 mg + EZE 10 mg**	**ETC-1002 180 mg + EZE 10 mg**
Statin-Intolerant Patients	**n = 51**	**n = 51**	**n = 51**	**n = 12**	**n = 12**
Overview of Muscle-Related AEs					
Any muscle-related AE	7 (14%)	6 (12%)	9 (18%)	2 (17%)	2 (17%)
Leading to discontinuation	1 (2%)	2 (4%)	5 (10%)	0	0
Muscle-related AEs by MedDRA Preferred Term*					
Muscle spasms	3 (6%)	2 (4%)	1 (2%)	0	0
Muscular weakness	2 (4%)	1 (2%)	1 (2%)	0	0
Musculoskeletal chest pain	0	1 (2%)	0	0	0
Musculoskeletal stiffness	0	0	1 (2%)	0	0
Myalgia	2 (4%)	1 (2%)	6 (12%)	2 (17%)	1 (8%)
Pain in extremity	1 (2%)	1 (2%)	3 (6%)	0	1 (8%)
Sensation of heaviness	0	0	1 (2%)	0	0
Statin-Tolerant Patients	**n = 48**	**n = 49**	**n = 48**	**n = 14**	**n = 12**
Overview of Muscle-Related AEs					
Any muscle-related AE	1 (2%)	0	3 (6%)	0	1 (8%)
Leading to discontinuation	0	0	1 (2%)	0	0

Values are n (%). *Prespecified analysis of all Musculoskeletal and Connective Tissue Disorders AE terms except arthralgia, back pain, bone pain, bunion, bursitis, groin pain, intervertebral degeneration, intervertebral disc protrusion, joint stiffness, joint swelling, neck pain, osteoarthritis, plantar fasciitis, rotator cuff syndrome, and synovial cyst.

AE = adverse event; EZE = Ezetimibe; MedDRA = *Medical Dictionary for Regulatory Activities*, version 16.0.

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CLAIMS

What is claimed:

1. A method comprising administrating a fixed-dose combination of a fixed dose of ETC-1002 or an analog thereof and a fixed dose of Ezetimibe 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 Ezetimibe is administered at a fixed dose of 10 mg, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 10 mg dose of Ezetimibe, 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 very low density lipoprotein (VLDL) 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 10 mg dose of Ezetimibe.
3. The method of claim 1, wherein the number of VLDL 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 10 mg dose of Ezetimibe.
4. The method of claim 1, wherein the size of VLDL 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 10 mg dose of Ezetimibe.
5. The method of claim 1, wherein the level of apolipoprotein A-1 (ApoA1) in the subject is greater 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 10 mg dose of Ezetimibe.
6. The method of claim 1, wherein the level of apolipoprotein A-1 (ApoA1) in the subject is not significantly changed compared to 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 10 mg dose of Ezetimibe.
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 10 mg dose of Ezetimibe.
8. A method of treating cardiovascular disease or reducing the risk of cardiovascular disease in a subject, comprising administrating a fixed-dose combination of a fixed dose of ETC-1002 or an analog thereof and a fixed dose of Ezetimibe 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 Ezetimibe is administered at a fixed dose of 10 mg, a fixed 120 mg dose of ETC-1002, a fixed 180 mg dose of ETC-1002, or a fixed 10 mg dose of Ezetimibe, and optionally wherein the subject has hypercholesterolemia.

9. The method of claim 8, wherein the method decreases the level of very low density lipoprotein (VLDL) in the subject 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 10 mg dose of Ezetimibe.
10. The method of claim 8, wherein the method decreases the number of VLDL particles in the subject 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 10 mg dose of Ezetimibe.
11. The method of claim 8, wherein the method decreases the size of VLDL particles in the subject 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 10 mg dose of Ezetimibe.
12. The method of claim 8, wherein the method increases the level of apolipoprotein A-1 (ApoA1) in the subject above 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 10 mg dose of Ezetimibe.
13. The method of claim 8, wherein the method does not significantly change the level of apolipoprotein A-1 (ApoA1) in the subject compared to 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 10 mg dose of Ezetimibe.
14. The method of claim 8, wherein the method decreases the ratio of apolipoprotein B (ApoB) to apolipoprotein A-1 (ApoA1) in the subject 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 10 mg dose of Ezetimibe.
15. The method of claim 8, wherein the subject is human.