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.

[0006a] In one aspect, provided herein is use of 120 mg or 180 mg ETC-1002 and 10 mg Ezetimibe in the manufacture of a medicament for treating familial hypercholesteroemlia in a subject in need thereof.

[0006b] In another aspect, provided herein is use of 120 mg or 180 mg ETC-1002 and 10 mg Ezetimibe in the manufacture of a medicament for lowering low density lipoprotein-cholesterol (LDL-C) in a subject in need thereof, wherein the subject has familial hypercholesterolemia.

[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~~disclosure 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~~example, methods and compositions of present ~~invention~~disclosure 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

CLAIMS

What is claimed:

1. ~~A method comprising administrating a fixed dose combination of a fixed dose of~~Use of 120 mg or 180 mg ETC-1002 ~~or an analog thereof~~ and ~~a fixed dose of~~ 10 mg 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~~ in the manufacture of a medicament for treating familial hypercholesterolemia in a subject in need thereof.
2. The ~~method~~ use of claim 1, wherein the medicament decreases 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~~ use of claim 1, wherein the medicament decreases 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~~ use of claim 1, wherein the medicament decreases 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~~ use of claim 1, wherein the medicament increases the level of apolipoprotein A-1 (ApoA1) in the subject ~~is greater than~~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.
6. The ~~method~~ use of claim 1, wherein the medicament does not significantly change 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~~ use of claim 1, wherein the medicament decreases 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~~Use of 120 mg or 180 mg ETC-1002 ~~or an analog thereof~~ and ~~a fixed dose of~~10 mg 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~~in the manufacture of a medicament for lowering low density lipoprotein-cholesterol (LDL-C) in a subject in need thereof, wherein the subject has familial hypercholesterolemia.
9. The ~~method~~ use of claim 8, wherein the ~~method~~ medicament 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~~ use of claim 8, wherein the ~~method~~ medicament 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~~ use of claim 8, wherein the ~~method~~ medicament 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~~ use of claim 8, wherein the ~~method~~ medicament 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~~ use of claim 8, wherein the medicament ~~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~~ use of claim 8, wherein the medicament ~~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~~ use of claim 8, wherein the subject is human.
16. The use of claim 1, wherein the medicament treats or reduces the risk of cardiovascular disease in the subject.
17. The use of claim 8, wherein the medicament treats or reduces the risk of cardiovascular disease in the subject.