[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 disclosure 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.

[0009a] In one aspect, provided herein is use of 120 mg or 180 mg ETC-1002 and 20-80 mg of one or more statins selected from the group consisting of rosuvastatin and atorvastatin in the manufacture of a medicament for treating hypercholesterolemia in a subject in need thereof.

[0009b] In another aspect, provided herein is a fixed-dose combination comprising a therapeutic amount of ETC-1002 and one or more statins selected from the group consisting of rosuvastatin and atorvastatin.

[0009c] In yet another aspect, provided herein is use of 120 mg or 180 mg ETC-1002 and 20-80 mg of one or more statins selected from the group consisting of rosuvastatin and atorvastatin in the manufacture of a medicament for lowering low density lipoprotein-cholesterol (LDL-C) in a subject in need thereof, wherein the subject has hypercholesterolemia.

[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 example, methods and compositions of present disclosure even lower cholesterol in patients with persistently elevated LDL-C, despite stable statin therapy at this high of a dosage.

CLAIMS

What is claimed:

1. Use of 120 mg or 180 mg ETC-1002 and 20-80 mg of one or more statins selected from the group consisting of rosuvastatin and atorvastatin in the manufacture of a medicament for treating hypercholesterolemia in a subject in need thereof.

2. The use of claim 1, wherein the medicament decreases the level of total cholesterol and non-HDL-C in the subject below that of a control subject receiving placebo, a 120 mg dose of ETC-1002, a 180 mg dose of ETC-1002, or a 20-80 mg dose of the one or more statins.

3. The use of claim 1, wherein the medicament decreases the level of low density lipoprotein (LDL) in the subject below that of a control subject receiving placebo, a 120 mg dose of ETC-1002, a 180 mg dose of ETC-1002, or a 20-80 mg dose of the one or more statins.

4. The use of claim 1, wherein the medicament decreases the number of LDL particles in the subject below that of a control subject receiving placebo, a 120 mg dose of ETC-1002, a 180 mg dose of ETC-1002, or a 20-80 mg dose of the one or more statins.

5. The use of claim 1, wherein the medicament decreases the level of apolipoprotein B (ApoB) in the subject below that of a control subject receiving placebo, a 120 mg dose of ETC-1002, a 180 mg dose of ETC-1002, or a 20-80 mg dose of the one or more statins.

6. The use of claim 1, wherein the medicament decreases the level of apolipoprotein A-1 (ApoA1) in the subject below that of a control subject receiving placebo, a 120 mg dose of ETC-1002, a 180 mg dose of ETC-1002, or a 20-80 mg dose of the one or

more statins.

7. The use of claim 1, wherein the medicament decreases the ratio of apolipoprotein B (ApoB) to apolipoprotein A-1 (ApoA1) in the subject below that of a control subject receiving placebo, a 120 mg dose of ETC-1002, a 180 mg dose of ETC-1002, or a 20-80 mg dose of the one or more statins.

8. The use of claim 1, wherein the subject has atherosclerotic cardiovascular disease.

9. The use of claim 1, wherein the subject has familial hypercholesterolemia.

10. The use of claim 1, wherein the subject is human.

11. A fixed-dose combination comprising a therapeutic amount of ETC-1002 and one or more statins selected from the group consisting of rosuvastatin and atorvastatin.

12. The fixed-dose combination of claim 11, wherein the amount of each of the one or more statins is 20-80 mg.

13. The fixed-dose combination of claim 11, wherein the amount of ETC-1002 is 120 mg or 180 mg and the amount of each of the one or more statins is 20-80 mg.

14. Use of 120 mg or 180 mg ETC-1002 and 20-80 mg of one or more statins selected from the group consisting of rosuvastatin and atorvastatin in the manufacture of a medicament for lowering low density lipoprotein-cholesterol (LDL-C) in a subject in need thereof, wherein the subject has hypercholesterolemia.

15. The use of claim 14, wherein the subject has atherosclerotic cardiovascular disease.

16. The use of claim 14, wherein the subject has familial hypercholesterolemia.

17. The use of claim 14, wherein the medicament decreases the level of total cholesterol and non-HDL-C in the subject below that of a control subject receiving placebo, a 120 mg dose of ETC-1002, a 180 mg dose of ETC-1002, or a 20-80 mg dose of the one or more statins.

18. The use of claim 14, wherein the medicament decreases the level of low density lipoprotein (LDL) in the subject below that of a control subject receiving placebo, a 120 mg dose of ETC-1002, a 180 mg dose of ETC-1002, or a 20-80 mg dose of the one or more statins.

19. The use of claim 14, wherein the medicament decreases the number of LDL particles in the subject below that of a control subject receiving placebo, a 120 mg dose of ETC-1002, a 180 mg dose of ETC-1002, or a 20-80 mg dose of the one or more statins.

20. The use of claim 14, wherein the medicament decreases the level of apolipoprotein A-1 (ApoA1) in the subject below that of a control subject receiving placebo, a 120 mg dose of ETC-1002, a 180 mg dose of ETC-1002, or a 20-80 mg dose of the one or more statins.

21. The use of claim 14, wherein the medicament decreases the level of total cholesterol and non-HDL-C in the subject below that of a control subject receiving placebo, a 120 mg dose of ETC-1002, a 180 mg dose of ETC-1002, or a 20-80 mg dose of one or more statins.

22. The use of claim 14, wherein the medicament decreases the ratio of apolipoprotein B (ApoB) to apolipoprotein A-1 (ApoA1) in the subject below that of a control subject receiving placebo, a 120 mg dose of ETC-1002, a 180 mg dose of ETC-1002, or a 20-

80 mg dose of the one or more statins.

23. The use of any one of claims 1-10 and 14-22, wherein the amount of ETC-1002 is 120 mg.

24. The use of any one of claims 1-10, and 14-22, wherein the amount of ETC-1002 is 180 mg.

25. The use of claim 23, wherein the one or more statins is rosuvastatin; and the amount of rosuvastatin is 20-40 mg.

26. The use of claim 24, wherein the one or more statins is rosuvastatin; and the amount of rosuvastatin is 20-40 mg.

27. The use of claim 23, wherein the one or more statins is atorvastatin; and the amount of atorvastatin is 40-80 mg.

28. The use of claim 24, wherein the one or more statins is atorvastatin; and the amount of atorvastatin is 40-80 mg.

29. The fixed-dose combination of any one of claims 11-13, wherein the amount of ETC-1002 is 120 mg.

30. The fixed-dose combination of any one of claims 11-13, wherein the amount of ETC-1002 is 180 mg.

31. The fixed-dose combination of claim 29, wherein the one or more statins is rosuvastatin; and the amount of rosuvastatin is 20-40 mg.

32. The fixed-dose combination of claim 30, wherein the one or more statins is rosuvastatin; and the amount of rosuvastatin is 20-40 mg.

33. The fixed-dose combination of claim 29, wherein the one or more statins is atorvastatin; and the amount of atorvastatin is 40-80 mg.

34. The fixed-dose combination of claim 30, wherein the one or more statins is atorvastatin; and the amount of atorvastatin is 40-80 mg.