TITLE

METHODS FOR REDUCING THE RISK OF DIABETES IN PATIENTS BEING TREATED FOR HIGH CHOLESTEROL-RELATED ILLNESSES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/722,766 filed August 24, 2018 and U.S. Provisional Application No. 62/751,404 filed October 26, 2018, the contents of each of which are incorporated herein by reference.

BACKGROUND

Field of the invention

[0002] This application relates to methods and compositions useful for treating diabetes or reducing the risk of diabetic conditions. Low-density lipoprotein cholesterol (LDL-C) and well-established indicator for cardiovascular diseases, as well as a risk factor for diabetes. Similar, hemoglobin A1c (HbA_{1C}) level is a well-known biomarker for diabetes and new-onset diabetes. A common and cornerstone treatment for managing LDL-C level for patients who are either diabetic, at risk of developing new-onset diabetes or at risk of cardiovascular diseases is the administration of statins. However, many patients, for example those with hypercholesterolemia, fail to reduce LDL-C to desired levels with traditional statin therapies. 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 been 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, improving hemoglobin A1c levels, and reducing the risk of developing cardiovascular diseases and diabetic conditions.

SUMMARY

[0002a] In an aspect of the present disclosure, there is provided a use of ETC-1002 in the manufacture of a medicament for decreasing the likelihood of new-onset diabetes in a subject or decreasing the likelihood of worsening existing diabetes in a subject, wherein ETC-1002 is to be administered with ezetimibe, and one or more statins.

[0003] This application relates to compositions comprising fixed doses of any one of ETC-1002, ezetimibe and statins, and methods for treating or reducing the risk of diabetes comprising the administration of ETC-1002, or ETC-1002 and ezetimibe, in the presence or absence of statin treatment.

[0004] ETC-1002 (bempedoic acid) is a typically oral, typically once-daily therapeutic which lowers cholesterol by inhibiting adenosine triphosphate (ATP) citrate lyase (ATPCL). ATPCL is farther upstream than HMG-CoA reductase in the cholesterol biosynthetic pathway.

[0005] 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 about 120 mg to about 240 mg daily reduced LDL-C by about 27% to about 43% in phase 2a clinical trials of various hypercholesterolemic populations including patients with type 2 diabetes mellitus and patients with muscle-related statin intolerance.

[0006] 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.

[0007] 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.

[0008] 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. Furthemore 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 (about 120 mg or about 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 example, the methods and compositions described in the present disclosure lower cholesterol in patients with persistently elevated LDL-C, despite receiving high dosages of statin therapy.

[0010] It is well known in the art that the chronic use of statin therapies in patients lead to an increase in HbA_{1C} level, a biomarker for diabetes. Such increase in HbA_{1C} level often times lead to a worsening of existing diabetic conditions, as well as increases the likelihood of developing new-onset diabetes in patients receiving high dosages of statin therapy.

[0011] Thus, the present application also discloses a method of improving HbA_{1C} level in patients with diabetes, or in patients who are at risk of developing new-onset diabetes.

BRIEF DESCRIPTION OF THE FIGURES

[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** depicts current understanding of the mechanism of action of bempedoic acid.

[0014] **FIGURE 2** depicts the observed change in HbA_{1C} levels in patients treated with bempedoic acid or placebo, at 12 and 52 weeks, where the patients have a medical history of diabetes and where the patients are receiving the maximal tolerated dose of statin (50% high intensity).

[0015] **FIGURE 3** depicts the change in fasting glucose levels over time for the same patients described in **Fig. 2**.

[0016] **FIGURE 4** depicts the observed change in HbA_{1C} levels in patients treated with bempedoic acid or placebo, at 12 and 24 weeks, where the patients have a medical history of diabetes, are statin-intolerant, and are being treated with low doses of statin (8% very low dose statin).

[0017] **FIGURE 5** depicts the change in fasting glucose levels over time for the same patients described in **Fig. 4**.

[0018] **FIGURE 6** depicts the observed change in HbA_{1C} levels in statin-intoleratnt patients treated with bempedoic acid or placebo for 12 weeks, where the patients are on a background level of ezemetibe, have a medical history of diabetes, and where 31% of the patients are on low or very low doses of statin.

CLAIMS

What is claimed:

1. Use of ETC-1002 in the manufacture of a medicament for decreasing the likelihood of new-onset diabetes in a subject or decreasing the likelihood of worsening existing diabetes in a subject, wherein ETC-1002 is to be administered in combination with ezetimibe, and one or more statins.

2. The use of claim 1, wherein the subject has diabetes.

3. The use of claim 1 or 2, wherein said diabetes is selected from the group consisting of Type 1 diabetes, Type 2 diabetes, Type 3 diabetes, gestational diabetes, latent autoimmune diabetes in adults, maturity onset diabetes of the young, double diabetes, steroid-induced diabetes, brittle diabetes, secondary diabetes, diabetes insipidus, and Juvenile diabetes.

4. The use of claim 1 or 2, wherein the subject has a history of Type 2 diabetes for 6 months or greater.

5. The use of any one of claims 1-4, wherein the subject has been taking stable diabetes medication for three months.

6. The use of any one of claims 1-5, wherein the subject has a HbA_{1c} level between 5% and 10%, or between 7% and 10%.

7. The use of any one of claims 1-6, wherein the subject has a fasting calculated LDL-C level of greater than 70 mg/dL.

8. The use of any one of claims 1-7, wherein the subject has a fasting calculated LDL-C level of between 100 and 220 mg/dL.

9. The use of claim 8, wherein the subject has had a washout of all lipid-modifying therapy (LMT).

10. The use of claim 1, wherein the subject has risk factors for Type 2 diabetes.

11. The use of claim 10, wherein the said risk factors are selected from the group consisting of overweight or obesity, 45 years of age or older, family history of diabetes, high blood pressure, a low level of high-density lipoprotien cholesterol, a high level of triglycerides, a history of gestational diabetes, heart disease or stroke, polycystic ovary syndrome, and acanthosis nigricans.

12. The use of claim 1, wherein the subject is to receive maximally tolerated statin therapy.

13. The use of any one of claims 1-12, wherein ETC-1002 is to be administered in an amount of about 120 mg.

14. The use of any one of claims 1-12, wherein ETC-1002 is to be administered in an amount of about 180 mg.

15. The use of any one of claims 1-14, wherein ezetimibe is to be administered in an amount of about 10 mg.

16. The use of any one of claims 1-15, wherein the subject is a human.

17. The use of claim 16, wherein the subject is identified as a subject with diabetes or with an increased risk of diabetes relative to normal, and an amount of bempedoic acid, or ezetimibe, or a combination of bempedoic acid and ezetimibe is to be administered to said subject.

18. The use of claim 17, wherein the amount of bempedoic acid or ezetimibe or both is effective to reduce LDL-C in said subject.

19. The use of claim 17 or 18, wherein the increased risk of diabetes is the result of ongoing or expected statin therapy.