Atherosclerosis xxx (2018) 1–9

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study

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ARTICLE INFO

Article history:
Received 1 May 2018
Received in revised form
1 June 2018
Accepted 5 June 2018
Available online xxx

Keywords:
Cardiovascular disease
Hyperlipidemia
ETC-1002
Low-density lipoprotein cholesterol
Prevention
Statin-associated muscle symptoms
Statin intolerance

ABSTRACT

Background and aims: Patients with hyperlipidemia who are unable to tolerate optimal statin therapy are at increased cardiovascular risk due to ongoing elevations in low-density lipoprotein cholesterol (LDL-C). The objective of CLEAR Tranquility (NCT03001076) was to evaluate the efficacy and safety of bempedoic acid when added to background lipid-modifying therapy in patients with a history of statin intolerance who require additional LDL-C lowering.

Methods: This phase 3, multicenter, randomized, double-blind, placebo-controlled study enrolled patients with a history of statin intolerance and an LDL-C $\geq$100 mg/dL while on stable lipid-modifying therapy. After a 4-week ezetimibe 10 mg/day run-in period, patients were randomized 2:1 to treatment with bempedoic acid 180 mg or placebo once daily added to ezetimibe 10 mg/day for 12 weeks. The primary endpoint was the percent change from baseline to week 12 in LDL-C.

Results: The study population comprised 269 patients (181 bempedoic acid, 88 placebo). Bempedoic acid added to background lipid-modifying therapy that included ezetimibe reduced LDL-C by 28.5% more than placebo ($p < 0.001$; −23.5% bempedoic acid, +5.0% placebo). Significant reductions in secondary endpoints, including non-high-density lipoprotein cholesterol (−23.6%), total cholesterol (−18.0%), apolipoprotein B (−19.3%), and high-sensitivity C-reactive protein (−31.0%), were observed with bempedoic acid *vs.* placebo ($p < 0.001$). Bempedoic acid was well tolerated; rates of treatment-emergent adverse events, muscle-related adverse events, and discontinuations were similar in the bempedoic acid and placebo treatment groups.

Conclusions: Bempedoic acid may provide an oral therapeutic option complementary to ezetimibe in statin intolerant patients who require additional LDL-C lowering.

1. Introduction

Statins have established their role as a first-line option for low-density lipoprotein cholesterol (LDL-C) lowering through demonstrated efficacy and event risk reduction. Absolute cardiovascular (CV) risk reduction with lipid-lowering therapies depends on the patient's baseline CV risk and the extent of LDL-C reduction [1]. However, some patients are unable to tolerate statin doses necessary to optimally lower LDL-C, most commonly due to muscle-related side effects [2,3]. Whereas aggregate data from randomized controlled trials indicate low rates of myalgia, myositis, and rhabdomyolysis with statin therapy [4–6], observational and

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https://doi.org/10.1016/j.atherosclerosis.2018.06.002

patient-report data suggest an incidence of statin-associated muscle complaints as high as 29% in clinical practice [7–9]. Statin intolerance has been linked to a lower likelihood of achieving LDL-C goals, increased risk for non-fatal CV events, and higher healthcare costs [10,11]. Statin intolerance ranges from "complete intolerance" of any statin at any dose to the more frequent scenario of inability to tolerate statins at doses that provide optimal reductions of LDL-C. Many statin intolerant individuals are at extreme or very high CV risk and, therefore, merit intensive intervention to reduce LDL-C [11–13]. Although ezetimibe and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can be used in this situation, additional LDL-C lowering and/or less expensive alternatives may still be required to reduce CV risk and reach guideline-recommended LDL-C treatment goals.

Bempedoic acid (ETC-1002) is an oral, once-daily, first-in-class, small-molecule cholesterol synthesis inhibitor in development for the treatment of hyperlipidemia. As an adenosine triphosphate (ATP)-citrate lyase inhibitor, bempedoic acid acts upstream of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase to inhibit cholesterol biosynthesis and increase LDL receptor expression [14,15]. In phase 2 clinical trials, bempedoic acid significantly reduced LDL-C, decreased atherogenic lipid levels, reduced high-sensitivity C-reactive protein (hsCRP) concentrations, and was well tolerated [16–20]. Improvements in lipid parameters were observed when bempedoic acid was administered as monotherapy or in addition to other lipid-modifying therapies. These studies encompassed a broad mix of primary and secondary prevention populations, including patients with primary hyperlipidemia or mixed dyslipidemia, some of whom also had a history of type 2 diabetes mellitus, coronary heart disease, and/or statin intolerance [16–20]. Doses of bempedoic acid ranging from 40 to 240 mg/day were evaluated in phase 2 studies. The favorable efficacy and safety profile supported use of the 180 mg/day dose in phase 3 clinical trials [16–20].

The first of the completed phase 3 studies, CLEAR Tranquility (NCT03001076), evaluated the efficacy and safety of bempedoic acid 180 mg daily when added to background therapy with ezetimibe 10 mg daily in patients with a history of not tolerating at least one statin and who required additional LDL-C lowering.

2. Patients and methods

2.1. Study population

The study population included men and women ages 18 years and older who had a history of statin intolerance, were on no more than low-dose statin therapy (which could also include no statin), and required additional LDL-C lowering. Patients were required to have fasting LDL-C ≥100 mg/dL (2.6 mmol/L) at screening. Low-dose statin therapy was defined as an average daily dose of rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg, which represents the lowest approved dose for each of these statins in the United States. Average daily doses less than these were considered very low-dose statin therapy. Patients with a recent history of clinically significant cardiovascular disease (CVD), including uncontrolled hypertension; a planned revascularization procedure; New York Heart Association class IV heart failure; or any one of the following within 3 months of screening: myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary artery bypass graft surgery, stroke, transient ischemic attack, cerebrovascular event, symptomatic coronary artery disease, symptomatic peripheral arterial disease, or arrhythmia requiring medical intervention, were not eligible for study participation. Additional reasons for study exclusion included body mass index (BMI) > 50 kg/m^2; fasting triglycerides ≥500 mg/dL; glycosylated hemoglobin (HbA_{1c}) ≥10%; uncontrolled hypothyroidism; liver disease or dysfunction; renal dysfunction (estimated glomerular filtration rate <30 mL/min) or glomerulonephritis; gastrointestinal conditions or procedures that may affect drug absorption; hematologic or coagulation disorders; active malignancy; unexplained creatine kinase elevation >3 times the upper limit of normal (ULN) any time prior to randomization; or use of cholestin or red yeast rice–containing products within 2 weeks prior to screening, statin doses exceeding low dose within 4 weeks prior to screening, mipomersen, lomitapide, apheresis, probenecid, or cyclosporine within 3 months prior to screening, or a PCKS9 inhibitor within 4 months prior to screening.

2.2. Study design

This phase 3, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 90 sites in the United States, Canada, and Europe from November 29, 2016, to January 11, 2018. The study comprised 3 phases: a 1-week screening period; a 4-week, single-blind run-in period; and a 12-week, double-blind treatment period (Fig. 1). During the run-in phase, patients received open-label ezetimibe 10 mg once daily and single-blind placebo to confirm tolerance to ezetimibe and compliance with protocol-directed therapy. Patients with poor adherence to ezetimibe or placebo (i.e. ingesting <80% of planned doses) during the run-in phase or who experienced an ezetimibe–related adverse event (AE) were not eligible for randomization. At the end of the screening phase, patients were randomized 2:1 to double-blind treatment with oral bempedoic acid 180 mg or placebo once daily for 12 weeks. Randomization for treatment assignments was determined using an interactive web response system; patients, investigators, pharmacists, and study personnel remained blinded to treatment group assignments through the duration of the study. Random allocation sequences were generated by dynamic allocation using Rave Balance (Medidata Solutions, New York, New York). Stable background lipid-modifying therapy (inclusive of a low-dose or very low-dose statin and/or permitted non-statin agents) and study-provided open-label ezetimibe 10 mg once daily were maintained throughout the study.

The study protocol and informed consent documents received appropriate institutional review board/independent ethics committee approval, and the study was conducted in accordance with ethical principles established by the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

2.3. Assessments and endpoints

Basic fasting lipid levels (LDL-C, total cholesterol, high-density

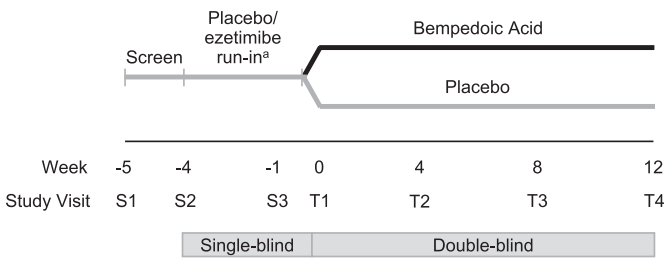

Fig. 1. Study design.
[a]Patients with ≤80% adherence and/or who experienced a study drug-related adverse event during the placebo and ezetimibe run-in period did not proceed to randomization.

Please cite this article in press as: C.M. Ballantyne, et al., Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study, Atherosclerosis (2018), https://doi.org/10.1016/j.atherosclerosis.2018.06.002