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Treatment with ETC-1002 alone and in combination with ezetimibe lowers LDL cholesterol in hypercholesterolemic patients with or without statin intolerance

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Statin intolerance

BACKGROUND: ETC-1002 is an oral, once-daily, first-in-class medication being developed to treat hypercholesterolemia.

OBJECTIVES: To compare 2 doses of ETC-1002, alone or combined with ezetimibe 10 mg (EZE), vs EZE monotherapy for lowering low-density lipoprotein cholesterol (LDL-C).

METHODS: This phase 2b, multicenter, double-blind trial-evaluated 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-week treatment with ETC-1002 120 mg or ETC-1002 180 mg alone, EZE alone, ETC-1002 120 mg plus EZE, or ETC-1002 180 mg plus EZE.

RESULTS: EZE alone lowered LDL-C by 21%, whereas ETC-1002 monotherapy with 120 mg or 180 mg reduced LDL-C by 27% ($P = .0008$ vs EZE) and 30% ($P < .0001$ vs EZE), respectively. The combination of ETC-1002, 120 mg or 180 mg plus EZE reduced LDL-C by 43% and 48%, respectively (both $P < .0001$ vs EZE). ETC-1002 alone or combined with EZE also reduced non–high-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, LDL particle number, and high-sensitivity C-reactive protein compared with EZE alone. Across all treatment groups, statin-intolerant patients reported more muscle-related adverse events than did statin-tolerant patients. ETC-1002 was safe and well tolerated, and rates of muscle-related adverse events were similar in all treatment groups.

CONCLUSIONS: In patients with and without statin intolerance, daily treatment with ETC-1002 120 mg and 180 mg alone or with EZE reduced LDL-C more than EZE alone and had a similar tolerability profile (NCT01941836).

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Statins are the cornerstone of prevention and treatment of cardiovascular disease but can produce statin-associated muscle symptoms in 5% to 29% of patients.[1–4] There is no universally accepted definition for statin intolerance. The National Lipid Association Statin Intolerance Panel defines it as a patient's inability to tolerate ≥2 statins, at least 1 at the lowest approved daily dose and another at any daily dose.[1] Muscle symptoms including pain, stiffness, cramping, or weakness, usually without serum creatine kinase (CK) elevations, are the primary manifestations of statin intolerance.[1,4,5]

Statin-associated muscle symptoms are an important clinical problem because statin discontinuation in hypercholesterolemic patients increases cardiovascular risk.[4] Patients who discontinue statin treatment because of intolerance show a trend toward decreased 8-year survival compared with patients who continue statin therapy (log-rank *P* value, .08).[5] The challenge of muscle-related statin intolerance and the need for research into therapies for this population are recognized in the latest American College of Cardiology/American Heart Association cholesterol management guidelines,[6] the National Lipid Association's Statin Safety Task Force recommendations,[1] and the European Atherosclerosis Society Consensus Panel statement on statin-associated muscle symptoms.[4]

ETC-1002 is a first-in-class, once-daily, oral 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.[7–9] ETC-1002 in doses from 120 mg to 240 mg daily reduced LDL-C by 27% to 43% in phase 2a clinical trials of various hypercholesterolemic patient populations, including patients with type 2 diabetes mellitus and patients with muscle-related statin intolerance.[10–12] The present phase 2b study (NCT01941836) compared the efficacy and safety of ETC-1002 monotherapy (120 mg or 180 mg daily) and ETC-1002 combined with ezetimibe 10 mg (EZE) vs EZE monotherapy among hypercholesterolemic patients with or without a history of statin-related muscle symptoms.

Methods

Study objectives

The primary objective was to assess the LDL-C–lowering effect of ETC-1002 monotherapy (120 mg or 180 mg daily) vs 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).

Study population

Medically stable, hypercholesterolemic men and women aged 18 through 80 years with a body mass index between 18 and 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 (ie, 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 (including acute coronary syndromes, stroke, transient ischemic attack, carotid or peripheral artery disease, decompensated heart failure, uncontrolled hypertension, or cardiac arrhythmias); 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.

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, single-blind 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.

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