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Original Contribution

Use of ETC-1002 to treat hypercholesterolemia in patients with statin intolerance

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Statin intolerance;
ETC-1002;
Muscle complaints;
Hypercholesterolemia

BACKGROUND: Once-daily, oral ETC-1002 reduces low-density lipoprotein cholesterol (LDL-C) and has beneficial effects on other cardiometabolic risk factors but has not been examined in statin intolerant patients.

OBJECTIVES: To study the efficacy and safety of ETC-1002 (a novel LDL-C–lowering agent) in patients with hypercholesterolemia and a history of statin intolerance.

METHODS: Patients intolerant to at least 1 statin were entered into this multicenter, double-blind, 8-week trial. Participants were required to have a history of muscle complaints that developed during statin treatment and resolved within 4 weeks of statin discontinuation. Patients (n = 56) were randomized in a 2:1 ratio to ETC-1002 60 mg daily or placebo. The ETC-1002 dose was increased at 2-week intervals to 120 mg, 180 mg, and 240 mg. The primary end point was the percentage change from baseline to week 8 in calculated LDL-C.

RESULTS: ETC-1002 reduced LDL-C 28.7% more than placebo (95% confidence interval, −35.4 to −22.1; $P < .0001$). ETC-1002 significantly reduced non–high-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein. Triglycerides and high-density lipoprotein cholesterol did not change with ETC-1002 treatment. Sixty-two percent of patients receiving ETC-1002 and none in the placebo group achieved the 2004 National Cholesterol Education Program Adult Treatment Panel III LDL-C goal ($P < .0001$). Muscle-related adverse events occurred with similar frequency in the placebo and ETC-1002 treatment groups, causing no discontinuations in ETC-1002–treated patients.

CONCLUSIONS: ETC-1002 appears to be effective at reducing LDL-C and was well tolerated in patients with statin-associated muscle complaints. Longer and larger studies are required to confirm the absence of muscle side effects.

Introduction

Statins, or 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, are among the most effective interventions for reducing cardiovascular events.[1] In contrast,

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cessation of statin therapy is associated with significantly worse cardiovascular outcomes.[2] Statins can produce muscle complaints ranging from myalgia to rare but life-threatening rhabdomyolysis.[3,4] A recent, large, observational survey reports that statin-associated muscle pain affects 29% of statin users and causes 15% of these individuals to stop statin therapy.[3]

Recent cholesterol management guidelines from the American College of Cardiology and the American Heart Association acknowledge the problem of statin intolerance and offer recommendations for the management of statin-associated muscle symptoms, including the use of other lipid-regulating medications.[1] These guidelines, however, also note the paucity of data to guide treatment of statin intolerant patients and cite the need for randomized clinical trials in this population.[1]

ETC-1002 is a novel low-density lipoprotein cholesterol (LDL-C)–lowering agent in development for the treatment for dyslipidemia. The agent inhibits both sterol and fatty acid synthesis and enhances fatty acid oxidation in preclinical models and produces beneficial effects on proatherogenic lipids.[5,6] These effects are linked to its dual mechanism of action: inhibition of adenosine triphosphate citrate lyase and activation of adenosine monophosphate–activated protein kinase.[6] Once-daily, oral ETC-1002 in patients with hypercholesterolemia reduces LDL-C and improves other cardiometabolic risk factors.[7,8] The present study evaluates the lipid-altering efficacy and safety of 8 weeks of ETC-1002 treatment in patients with hypercholesterolemia and a history of statin intolerance.

Methods

Study design

This was a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial (NCT01751984) conducted at 5 sites in the United States. The trial included a screening phase (weeks −4 to 0) with single-blind placebo run-in (weeks −2 to 0) and an 8-week double-blind treatment phase (weeks 0–8; Fig. 1). During screening, eligible patients underwent a washout of any lipid-regulating drugs and supplements for at least 4 weeks. During the 2-week placebo run-in, patients reporting muscle-related or other clinically significant adverse events (AEs) were excluded. After screening, eligible patients were randomized in a 2:1 ratio to receive either oral ETC-1002 or placebo daily for 8 weeks. Patients in the ETC-1002 group initially received 60 mg daily for 2 weeks. The ETC-1002 dose was increased at 2-week intervals to 120, 180, and 240 mg daily. The escalating dose schedule was designed to characterize the magnitude of LDL-C reduction with increasing ETC-1002 dose and to help select optimum doses for subsequent studies in patients with statin-associated muscle complaints. ETC-1002 was dispensed in white, opaque, size #3, gelatin capsules containing either 20 mg of ETC-1002 with 100-mg microcrystalline cellulose (MCC) filler or 40 mg of ETC-1002 and 80-mg MCC filler. Placebo capsules were dispensed as matching white, opaque, size #3, gelatin capsules containing 120-mg MCC filler. All participants ingested 6 capsules by mouth once daily; the number of capsules ingested daily did not change for the duration of the study in either treatment group. Study visits occurred at weeks −4, −3, −2, 0, 2, 4, 6, 7, and 8.

Informed consent was obtained from patients using documents approved by the local and central institutional review boards.

Study participants

Eligible patients were men and postmenopausal or surgically sterile women aged 18 to 80 years with hypercholesterolemia and a history of intolerance to ≥1 statins, which was defined as the development of new myalgia, muscle cramps, muscle aches, or muscle weakness during statin treatment and resolution or marked improvement of muscle symptoms within 4 weeks of statin cessation. In those patients taking lipid-lowering therapy at screening (visit, 1; week, −4), hypercholesterolemia was defined as a fasting, calculated LDL-C between 100 and 220 mg/dL and triglycerides <350 mg/dL. In those patients not taking lipid-lowering therapy at screening visit 1, hypercholesterolemia was defined as an LDL-C between 115 and 270 mg/dL and triglycerides <400 mg/dL. Patients were required to have a body mass index between 18 and 40 kg/m^2. Patients with controlled type II diabetes mellitus were eligible to participate provided they were not taking exclusionary medications metformin or thiazolidinediones, which were excluded because appropriate drug interaction and safety studies have not yet been completed.

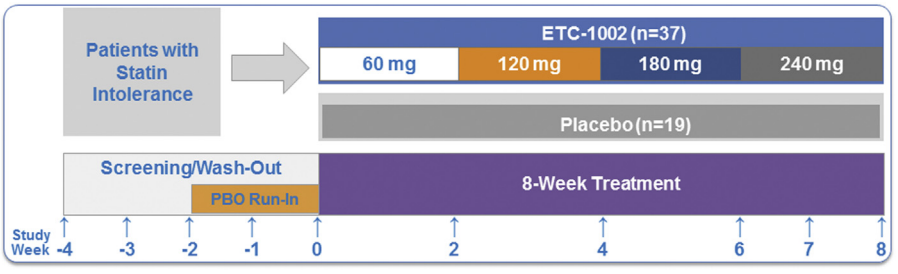

Figure 1 Study design. PBO, placebo.

Patients were excluded from the study if they had type I diabetes mellitus; a history of major cardiovascular events within 12 mo; a systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg; a history of chronic arthritis or arthralgia that could not be differentiated from myalgia; uncontrolled hypothyroidism; liver dysfunction, including elevations in alanine aminotransferase (ALT), aspartate aminotransferase, or total bilirubin >1.5 times the upper limit of normal (ULN), or a history of unexplained elevation in ALT or aspartate aminotransferase >2 times ULN; renal dysfunction, including a calculated creatinine clearance <60 mL/min at screening visit 1; or unexplained creatine kinase (CK) elevations >3 times ULN.

Efficacy end points

The primary end point was the percent change from baseline to week 8 in calculated LDL-C. Secondary end points included the percent change in non–high-density lipoprotein cholesterol (HDL-C), total cholesterol, HDL-C, triglycerides, apolipoprotein (apo) B, apo A1, lipoprotein(a), free fatty acids, and high-sensitivity C-reactive protein (hsCRP). Additional secondary end points were the number of patients achieving their National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) 2004 goal for LDL-C and the percent change in lipids from baseline to weeks 2, 4, 6, and 8 in the respective completer populations for those weeks.

Laboratory methods

Blood samples for efficacy laboratory measures were obtained after a ≥12-h fast. Clinical laboratory tests were performed by Medpace, Inc (Cincinnati, OH).

Triglycerides and cholesterol were measured with enzymatic colorimetric tests using the Olympus AU2700 or AU5400 Analyzer (Center Valley, PA), following Centers for Disease Control and Prevention calibration and reference procedures. HDL-C was measured after dextran sulfate precipitation of apo B–containing lipoproteins.[9] The formula by Friedewald et al[10] was used to calculate LDL-C, unless triglycerides were >400 mg/dL, in which case, LDL-C was measured after preparative ultracentrifugation (beta quantification).[11] Apo A1, apo B, lipoprotein(a), and hsCRP were measured by rate immunonephelometry using the Dade Behring BNII nephelometer (Siemens Healthcare Diagnostics, Deerfield, IL). Free fatty acids were measured using an enzymatic photometry assay purchased from Wako Chemicals USA, Inc, Richmond, VA, adapted to a Randox Daytona (Crumlin, UK) instrument. Homocysteine, a biomarker of interest, was measured on an Olympus analyzer using an enzymatic photometry assay purchased from Diazyme Laboratories, Poway, CA.

Safety end points

Safety and side effects were determined from reports of treatment-emergent AEs (TEAEs), including muscle-related AEs, as well as laboratory test results, findings at physical examination, vital sign measurements, electrocardiographic measurements, waist and ankle circumference measurements, and body weight. Blood pressure was measured twice (only the second value was used) in patients seated quietly for at least 5 min. AEs were coded using the *Medical Dictionary for Regulatory Activities* version 15.1. TEAEs were defined as those events that began or worsened in severity after the first dose of study medication and for up to 30 days after the last dose of study medication. The intensity of AEs was graded as "mild," "moderate," or "severe" by the study investigator, and the relation to study drug was judged by the investigator as "not related," "possible," "probable," or "definite." A post hoc analysis was performed of muscle-related AEs commonly associated with statin intolerance. These were defined as all AEs coded as preferred terms in the Musculoskeletal and Connective Tissue Disorders organ class excluding the AEs of arthralgia, back pain, bursitis, joint stiffness, joint swelling, plantar fasciitis, or spinal osteoarthritis (as these AEs are not typically associated with statin intolerance).

Statistical methods

Descriptive statistics were calculated for continuous data, and the number and percentage of patients in each category were provided for categorical data. Missing values for efficacy end points at their primary time point for analysis were imputed using the last-observation-carried-forward procedure. Only on-treatment values were carried forward. Statistical testing of efficacy end points was 2-sided, and 5% was used as the level of significance with no adjustment for multiple end points. Safety end points were not tested for statistical significance.

The modified intent-to-treat (mITT) population was used for the efficacy analyses and consisted of randomized patients who had a baseline assessment, received ≥1 dose of study medication, and had ≥1 on-treatment measurement (excluding assessments taken >2 days after a dose of study medication). Baseline was defined as the value from week 0. Completer populations for weeks 2, 4, 6, and 8 consisted of patients in the mITT population with an assessment at the specified time point. Like the mITT population, the composition of a completer population could change depending on the parameter being analyzed. The safety population consisted of all randomized patients who received ≥1 dose of study medication.

Demographic and baseline clinical characteristics were summarized by treatment group for the safety population. Baseline comparability between treatment groups was examined using a *t* test for continuous parameters (except hsCRP, for which a Wilcoxon rank-sum test was used) and a Fisher's exact or Fisher-Freeman-Halton test for categorical parameters.

Analysis of covariance (ANCOVA) was used to compare ETC-1002 with placebo for the percent change from

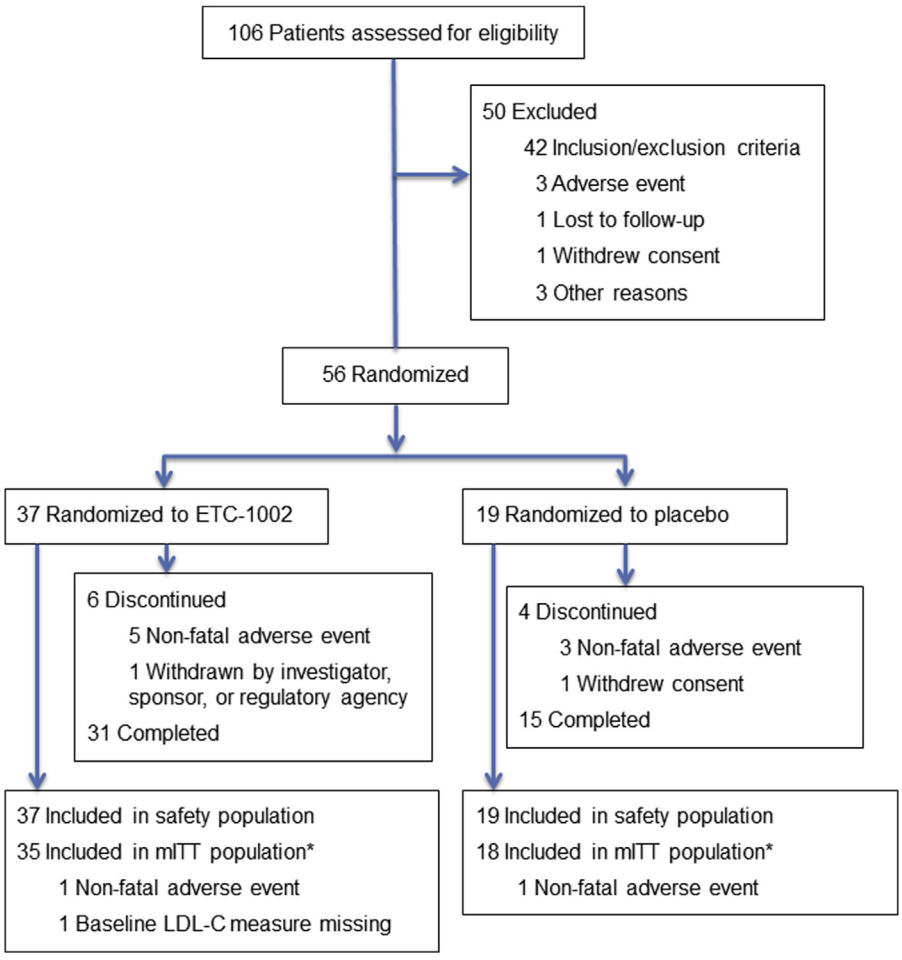

Figure 2 Patient disposition. Asterisk, based on low-density lipoprotein cholesterol (LDL-C). mITT, modified intent to treat.

baseline to week 8 in efficacy end points. The primary model included the effect of treatment and the baseline value as a covariate. Least square (LS) means and standard errors were provided for each treatment group, as well as the difference in LS means, corresponding 2-sided 95% confidence interval (CI), and *P* value for the treatment comparison. Because of skewed distributions of lipoprotein(a), free fatty acids, and hsCRP values, nonparametric analyses were performed for these parameters; *P* values were obtained from the Cochran-Mantel-Haenszel test in rank ANCOVA, and median values were reported. A nonparametric analysis of triglycerides was performed as a post hoc sensitivity analysis. Secondary analyses of the percent change in lipid measures from baseline to weeks 2, 4, 6, and 8 were performed with separate ANCOVA models that used the procedure described previously in the completer populations for each of those weeks.

Participants' NCEP ATP-III risk category and associated LDL-C goals were calculated using LDL-C and HDL-C values from week 0 and patients' risk factors.[12] The number and percentage of patients achieving their LDL-C goal at weeks −4, 0, and 8 were summarized by treatment group. Percentages at week 8 were based on those patients who had not achieved their LDL-C goal at week 0. The proportion of patients meeting their LDL-C goal at week 8 was compared between treatment groups using Fisher's exact test. Treatment estimates and differences in proportions were presented with 2-sided 95% CIs constructed using the Clopper-Pearson approximation to the exact binomial proportion[13] for individual estimates within treatment groups and the normal approximation for the difference between treatment groups.

The sample size of 36 patients in the ETC-1002 group and 18 patients in the placebo group was expected to provide more than 95% power to detect a difference of 20% between the study groups in the percent change from baseline to week 8 in LDL-C. This sample size estimate was based on a 2-sided *t* test at the 5% level of significance and assumed a common standard deviation of 15% and a dropout rate of 10%. Sample size calculations were performed using nQuery Advisor version 7.0 (Statistical Solutions, Ltd, Cork, Ireland). All data analyses were generated using SAS version 9.1.3 (SAS Institute, Cary, NC) software under the Microsoft Windows XP operating system (Redmond, Washington). Statistical procedures were finalized before study completion and unblinding.

Table 1 Baseline demographic and clinical characteristics

Parameter	ETC-1002 (n = 37)	Placebo (n = 19)	*P* value
Age, y, mean ± SD	64 ± 5	60 ± 8	.0542
Female, n (%)	17 (46)	11 (58)	.5731
White, n (%)	35 (95)	19 (100)	.5435
Body mass index, kg/m^2, mean ± SD	30 ± 4	29 ± 5	.8064
Hypertension, n (%)	21 (57)	10 (53)	.7843
Tobacco use, n (%)			.4844
Never	19 (51)	9 (47)	
Former	17 (46)	8 (42)	
Current	1 (3)	2 (11)	
NCEP ATP-III Risk Category, n (%)			.6179
Very high	4 (11)	2 (11)	
High	4 (11)	1 (5)	
Moderate	27 (73)	13 (68)	
Low	2 (5)	3 (16)	
Patients at NCEP ATP-III LDL-C goal, n (%)	1 (3)	1 (5)	1
Fasting lipid measures, mg/dL, mean ± SD			
LDL-C	176 ± 37	185 ± 33	.3680
Total cholesterol	263 ± 45	276 ± 43	.2847
HDL-C	51 ± 14	58 ± 18	.0943
Triglycerides	200 ± 172	166 ± 72	.4221
Median hsCRP, mg/L (Q1, Q3)	2.2 (1.1, 4.8)	1.6 (0.4, 4.0)	.2002
History of statin intolerance, n (%)			
Intolerant of ≥2 statins	37 (100)	18 (95)	.3393
Muscle symptoms, n (%)*			
Ache	30 (81)	16 (84)	1
Pain	26 (70)	13 (68)	1
Weakness	20 (54)	12 (63)	.5779
Cramps	17 (46)	7 (37)	.5779
Other	2 (5)	4 (21)	.1652
Location of muscle symptoms (bilateral), n (%)*			
Back	3 (8)	1 (5)	1
Calf	23 (62)	12 (63)	1
Foot	2 (5)	2 (11)	.5981
Forearm	5 (14)	1 (5)	.6522
Hand	2 (5)	1 (5)	1
Neck	2 (5)	2 (11)	.5981
Shoulder	8 (22)	4 (21)	1
Thigh	23 (62)	12 (63)	1
Upper arm	11 (30)	6 (32)	1
Other	5 (14)	5 (26)	.2813
Time to onset after statin initiation, n (%)			.2514
Within 1 wk	15 (41)	6 (32)	
2 wk	12 (32)	8 (42)	
3 wk	6 (16)	1 (5)	
4 wk	0	2 (11)	
>1–6 mo	2 (5)	2 (11)	
>6 mo	2 (5)	0	
Time to resolution after statin discontinuation, n (%)			.2009
1 wk	21 (57)	16 (84)	
2 wk	10 (27)	3 (16)	
3 wk	4 (11)	0	
≥4 wk	2 (5)	0	

HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; NCEP ATP-III, National Cholesterol Education Program Adult Treatment Panel III Risk Category; SD, standard deviation.

NCEP ATP-III was calculated using risk factors for coronary heart disease and LDL-C and HDL-C values at baseline; Q1, first (lower) quartile; Q3, third (upper) quartile.

Baseline is defined as the value from week 0.

*Because participants could be counted in more than one category for these parameters, treatment groups were compared individually for each category.

Table 2 Percent change from baseline to week 8 in fasting lipid parameters and other biomarkers (mITT population)

Parameter	Mean (SE) N	Baseline (mg/dL)*	End point (mg/dL)†	LS mean (SE) change from baseline (%)‡	Difference from placebo, % (95% CI)	*P* value
LDL-C						
ETC-1002	35	176.4 (6.2)	119.0 (4.6)	−32.0 (1.9)	−28.7 (−35.4, −22.1)	<.0001
Placebo	18	183.7 (7.8)	174.7 (6.7)	−3.3 (2.7)	—	—
Non–HDL-C						
ETC-1002	36	212.9 (6.7)	156.9 (5.3)	−25.4 (2.0)	−20.9 (−28.0, −13.9)	<.0001
Placebo	18	216.7 (9.5)	204.6 (8.1)	−4.4 (2.9)	—	—
Total cholesterol						
ETC-1002	36	263.7 (7.5)	203.9 (5.6)	−22.2 (1.6)	−18.4 (−24.2, −12.7)	<.0001
Placebo	18	275.4 (10.5)	260.3 (8.7)	−3.7 (2.3)	—	—
HDL-C						
ETC-1002	36	50.9 (2.4)	46.9 (2.7)	−8.2 (2.5)	−5.8 (−14.5, 2.9)	.1892
Placebo	18	58.7 (4.2)	55.7 (3.2)	−2.4 (3.5)	—	—
Triglycerides						
ETC-1002	36	201.9 (29.0)	202.6 (21.5)	11.2 (6.3)	18.7 (−3.5, 40.8)	.0962
Placebo	18	165.4 (17.5)	149.7 (14.8)	−7.4 (9.0)	—	—
Apolipoprotein B						
ETC-1002	29	127.3 (3.9)	102.1 (4.6)	−19.7 (2.6)	−15.3 (−24.6, −6.0)	.0019
Placebo	14	132.1 (6.0)	124.7 (5.6)	−4.4 (3.8)	—	—
Apolipoprotein A1						
ETC-1002	29	147.6 (4.1)	142.1 (4.5)	−4.2 (2.0)	−4.2 (−11.7, 3.2)	.2555
Placebo	14	164.5 (8.7)	160.2 (6.9)	0.1 (3.0)	—	—

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LS, least squares; mITT, modified intent to treat; SE, standard error.

*Baseline is defined as the value from week 0.

†Missing values at week 8 end point were imputed using the last-observation-carried-forward procedure.

‡LS mean percent change from baseline to week 8 based on analysis of covariance model with effect of treatment and baseline value as a covariate.

Results

Patient disposition and characteristics

Of 106 patients assessed for eligibility, 50 were excluded (Fig. 2). Of the 7 patients excluded during the placebo run-in phase, 1 patient was excluded for myalgia. A total of 56 patients were randomized and treated. All 56 patients were included in the safety population; 3 patients were not included in the mITT population. Five patients (14%) treated with ETC-1002 and 3 patients (16%) receiving placebo discontinued the study because of an AE.

At screening, before washout of lipid-lowering drugs and randomization, 15 patients in total (11 of 37 patients in the ETC-1002 group and 4 of 19 patients in the placebo group) were taking a statin. At baseline, there were no statistically significant differences in demographic and clinical characteristics between the treatment groups (Table 1). Most patients reported a history of intolerance to 2 or more statins, with onset of associated muscle symptoms within 3 wk of statin initiation and general resolution of muscle symptoms within 3 wk of statin discontinuation (Table 1). Reported statin-associated muscle symptoms were commonly muscle aches and muscle pains in the bilateral calf and thigh.

Efficacy end points

ETC-1002 reduced LDL-C from baseline to week 8 compared with placebo ($P < .0001$; Table 2; Fig. 3). Similarly, ETC-1002 reduced LDL-C from baseline to weeks 2, 4, 6, and 8 in the completer populations for each time point,

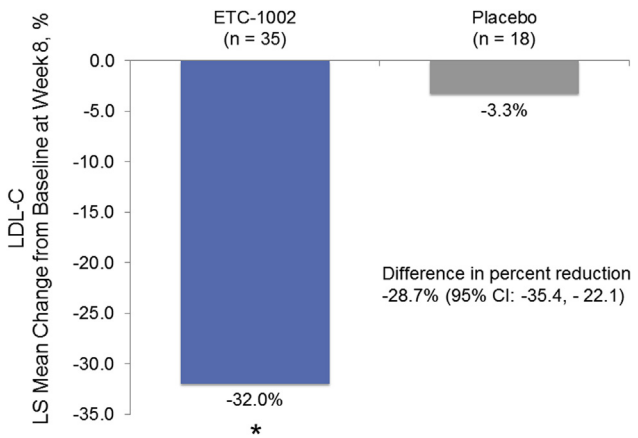

Figure 3 Least squares (LS) mean percent change from baseline to week 8 in calculated low-density lipoprotein cholesterol (LDL-C) (primary end point). Asterisk, $P < .0001$ based on analysis of covariance model with effect of treatment and baseline value as a covariate. CI, confidence interval.

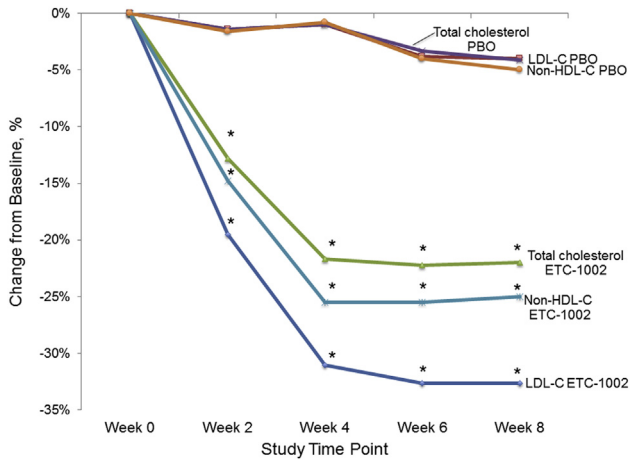

Figure 4 Changes from baseline in low-density lipoprotein cholesterol (LDL-C), non–high-density lipoprotein cholesterol (HDL-C), and total cholesterol by treatment group. Analysis is based on the completer population for each time point. Asterisk, $P \leq .0001$ based on analysis of covariance model with effect of treatment and baseline value as a covariate. PBO, placebo.

and these reductions were significantly greater in ETC-1002–treated patients than placebo-treated patients at all time points ($P < .0001$; Fig. 4). The reduction from baseline in LDL-C with ETC-1002 was 18.0% greater at week 2 than with placebo, and this difference increased to 28.5% and 30.0% at weeks 4 to 8 (Fig. 4).

ETC-1002 decreased non–HDL-C, total cholesterol, and apo B more than placebo (Table 2, Fig. 4), whereas the changes in HDL-C, triglycerides, and apo A1 were no different than placebo. ETC-1002 decreased hsCRP more than placebo, but there were no differences from placebo for lipoprotein(a) and free fatty acids (Table 3). Results from the nonparametric post hoc sensitivity analysis of triglycerides were supportive of those from the primary analysis: changes with ETC-1002 were no different than with placebo (median percent change from baseline to week 8, 7.5 mg/dL for ETC-1002 and −6.0 mg/dL for placebo [$P = .2257$]).

Twenty-one (62%) of the 34 patients in the ETC-1002 treatment arm who were not at LDL-C goal at baseline achieved their LDL-C goal at week 8 or at the end of the study (Fig. 5), whereas no placebo-treated patients reached their LDL-C goal (95% CI for the difference between treatment groups: 45%, 78%; $P < .0001$).

Safety

AEs were reported for 70% of ETC-1002–treated patients and 79% of placebo-treated patients (Table 4). Most AEs were mild or moderate in intensity and all resolved by the end of the study. AEs considered to be possibly or definitely related to study medication were reported for 8 (22%) patients treated with ETC-1002 and 4 (21%) patients receiving placebo (Table 4). The only events assessed as definitely related were tinnitus and nausea in a patient treated with ETC-1002 and muscular weakness in a placebo-treated patient. AEs resulting in discontinuation were reported with similar frequency in both treatment groups: 5 (14%) patients in the ETC-1002 group and 3 (16%) patients in the placebo group. Muscle-related AEs caused all 3 discontinuations in the placebo group and no discontinuations in the ETC-1002 group. None of the events causing discontinuation were reported for more than 1 patient in either treatment group. The only serious AE reported was thyroid cancer in a patient treated with ETC-1002. This was consistent with the patient's medical history and was not considered related to study drug. There were no deaths in the study.

Rates of muscle-related AEs characteristic of statin intolerance were similar between the ETC-1002 and placebo-treatment groups (27% and 32%, respectively) (Table 4). Except for muscle spasms, which occurred in 5 ETC-1002–treated patients and 1 placebo-treated patient,

Table 3 Nonparametric analysis of percent change from baseline to week 8 in lipoproprotein(a), free fatty acids, and high-sensitivity C-reactive protein (mITT population)

		Median (Q1, Q3)			
Parameter	N	Baseline*	End point†	Median (Q1, Q3) change, %	*P* value‡
Lipoprotein(a), mg/dL					
ETC-1002	29	13.0 (6.0, 36.0)	13.0 (6.0, 43.0)	0 (−13.0, 20.0)	.4304
Placebo	14	12.0 (5.0, 26.0)	13.5 (4.0, 33.0)	0 (−16.0, 11.0)	—
Free fatty acids, mmol/L					
ETC-1002	28	0.4 (0.3, 0.6)	0.4 (0.3, 0.6)	11.5 (−33.0, 37.0)	.9531
Placebo	14	0.4 (0.4, 0.5)	0.4 (0.3, 0.6)	16.5 (−14.0, 28.0)	—
hsCRP, mg/L					
ETC-1002	28	1.7 (1.0, 4.3)	1.1 (0.8, 1.6)	−42.0 (−60.0, −16.0)	.0022
Placebo	14	1.0 (0.3, 3.7)	1.1 (0.3, 4.9)	0 (−10.0, 30.0)	—

hsCRP, high-sensitivity C-reactive protein; mITT, modified intent to treat; Q1, first (lower) quartile; Q3, third (upper) quartile.
*Baseline is defined as the value from week 0.
†Missing values at week 8 end point were imputed using the last-observation-carried-forward procedure.
‡*P* values were obtained using the Cochran-Mantel-Haenszel test in rank analysis of covariance.

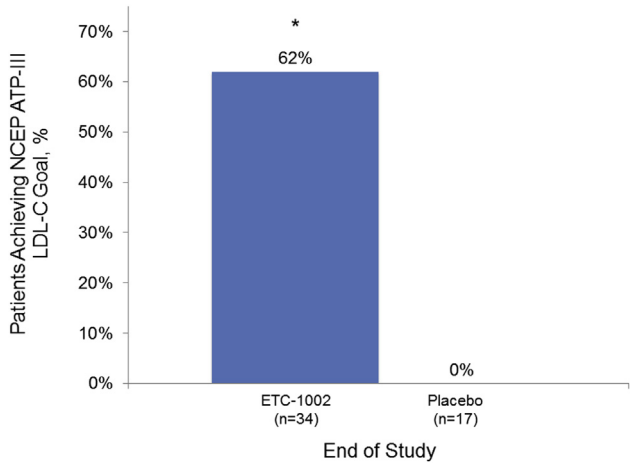

Figure 5 Patients achieving National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) low-density lipoprotein cholesterol (LDL-C) goal at the end of the study. Analysis included patients not at NCEP ATP-III goal at baseline (n = 34, ETC-1002; n = 17, placebo). Missing values at week 8 were imputed using the last-observation-carried-forward procedure. Asterisk, $P < .0001$ compared with placebo at week 8 (end of study) based on the Fisher exact test.

most of the muscle-related complaints were numerically less common in the ETC-1002 group. Myalgia was reported in 5% of patients receiving placebo and 3% of patients treated with ETC-1002. Of the patients who developed a muscle-related AE during the study, 6 patients in the ETC-1002 group were on a statin at screening. No placebo-treated patients who developed a muscle-related AE during the study were on a statin at screening.

Few changes in laboratory parameters were observed. From baseline to week 8, mean uric acid increased 1.2 ± 0.7 mg/dL in the ETC-1002 group but decreased 0.08 ± 0.9 mg/dL with placebo. Homocysteine increased 29.5 ± 15.5% with ETC-1002 and decreased 3.4 ± 9.4% with placebo. Hemoglobin decreased 0.7 ± 0.7 g/dL with ETC-1002 and 0.1 ± 0.6 g/dL with placebo. There was a mean increase in CK of 12.0 ± 46.7 U/L in the ETC-1002 group and 39.3 ± 71.3 U/L in the placebo group. Glucose decreased by 1.7 ± 10.2 mg/dL with ETC-1002 and by 8.4 ± 20.8 mg/dL with placebo (mean glucose values at week 8 were similar between the groups: 93.6 mg/dL with ETC-1002 at the final dose of 240 mg daily, and 94.0 mg/dL with placebo.) Overall, the magnitude of these changes did not suggest any safety concerns. No patient treated with ETC-1002 demonstrated an increase in liver function tests ≥3 times ULN or CK ≥5 times ULN. There were no clinically significant changes in physical findings, vital signs, electrocardiograms, waist and ankle circumference, or weight.

Table 4 Treatment-emergent adverse events

Parameter	Patients, n (%) ETC-1002 (n = 37)	Placebo (n = 19)
Overview of AEs		
Any treatment-emergent AEs	26 (70)	17 (79)
Treatment-related AEs, possible	7 (19)	3 (16)
Treatment-related AEs, definite	1 (3)	1 (5)
Serious AEs	1 (3)*	0
Most common AEs, nonmuscle related†		
Upper respiratory tract infection	1 (3)	4 (21)
Arthralgia	1 (3)	2 (11)
Nausea	3 (8)	0
Urinary tract infection	3 (8)	0
Fatigue	2 (5)	1 (5)
Headache	2 (5)	1 (5)
Dizziness	2 (5)	0
Nasopharyngitis	2 (5)	0
Muscle-related treatment-emergent AEs‡		
Any muscle-related AEs	10 (27)	6 (32)
Assessed as drug related	5 (14)	2 (11)
Resulting in discontinuation	0	3 (16)
Muscle fatigue	1 (3)	1 (5)
Muscle spasms	5 (14)	1 (5)
Muscle tightness	1 (3)	1 (5)
Muscular weakness	1 (3)	2 (11)
Musculoskeletal pain	0	1 (5)
Musculoskeletal stiffness	0	2 (11)
Myalgia	1 (3)	1 (5)
Pain in extremity	2 (5)	1 (5)

AE, adverse event.

*Thyroid cancer, not considered to be related to study drug.

†Occurring in ≥2 patients in either treatment group; excluding AEs assessed in the post hoc analysis of muscle-related AEs.

‡Post hoc analysis of muscle-related AEs characteristic of statin intolerance (all reported musculoskeletal and connective tissue disorders except arthralgia, back pain, bursitis, joint stiffness, joint swelling, plantar fasciitis, and spinal osteoarthritis).

Discussion

This early phase 2 study demonstrates that ETC-1002 reduced LDL-C 28.7% more than placebo in hypercholesterolemic patients with a history of statin-associated muscle complaints. ETC-1002 also decreased non–HDL-C, total cholesterol, apo B, and hsCRP more than placebo. The dose of ETC-1002 was increased by 60 mg daily at 2-week intervals from 60 mg to 240 mg daily. The aforementioned lipid parameters were decreased at the first 2-week interval, but it is not clear whether therapy continuing longer than 2 weeks would produce more lipid reduction nor is it clear whether the 8-week value represents the maximum lipid reduction. These questions will be addressed in future studies, one of which is a larger, 12-week, parallel-group study comparing ETC-1002, 120 mg or 180 mg with ezetimibe 10 mg, alone or in combination, in patients with or without statin intolerance (NCT01941836).

ETC-1002 was administered for only 8 weeks in the present study, and patients received the highest dose of ETC-1002, 240 mg daily, for only 2 weeks. Nevertheless, the frequency of TEAEs in patients treated with ETC-1002

was similar to that noted in placebo-treated patients. There were no substantial elevations in liver function or CK measurements. Not surprisingly, given the population's history of statin-associated muscle complaints, the most frequently reported AEs were musculoskeletal and connective tissue disorders in both the ETC-1002 and placebo groups. Muscle-related AEs prompted discontinuation of treatment in 3 (16%) placebo-treated patients but no discontinuations occurred in patients treated with ETC-1002.

This is the first study of ETC-1002 in patients with a history of statin-associated muscle complaints. The lipid results of this study are consistent with earlier trials in which ETC-1002 in dosages up to 120 mg daily lowered LDL-C by up to 27% in a general hypercholesterolemic population treated for 12 weeks[7] and by 43% in hypercholesterolemic patients with diabetes treated for 4 weeks.[8] Although ETC-1002 numerically increased triglyceride levels in the present study, ETC-1002 numerically decreased triglyceride levels in the previous phase 2 studies.[7,8] Overall, ETC-1002 does not significantly change triglyceride levels compared with placebo.

Ezetimibe is currently the most commonly prescribed lipid-lowering medication for patients with statin-associated muscle complaints.[14] Results from prospective studies of ezetimibe monotherapy in statin intolerant patients show reductions in LDL-C of 16%[15] to 20%,[16] which are smaller reductions in LDL-C than those observed in the present study with ETC-1002. The proportion of statin intolerant patients achieving their 2004 NCEP ATP-III goal for LDL-C with ezetimibe ranges from 9%[16] to 29%.[15] In the present study, 62% of patients treated with ETC-1002 achieved their LDL-C goal at the end of study. Ezetimibe is approved in Europe for use in patients with statin myopathy, but has been associated with muscle-related AEs in patients with statin-associated muscle symptoms.[15]

Evolocumab, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9) administered subcutaneously, has been studied in statin intolerant patients (Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects [GAUSS and GAUSS-2]). Evolocumab reduced LDL-C by 51% to 56% as monotherapy and by 63% when combined with ezetimibe in statin intolerant patients.[17,18] Myalgia was the most common TEAE in both trials.[17,18] Muscle-related AEs occurred in 12% to 13% of patients treated with evolocumab and 20% of those receiving evolocumab with ezetimibe.[17,18] Discontinuation rates for muscular AEs were 2% to 5% in patients treated with evolocumab, with or without ezetimibe.[17,18] These discontinuation rates for muscle-related events are greater than those in the present report of ETC-1002, but the duration of these studies with evolocumab was 12 weeks, which is longer than the present 8-week ETC-1002 trial.

Mipomersen is another cholesterol-lowering agent that has been evaluated in patients with statin-associated muscle complaints. In a phase 2, double-blind, randomized, controlled trial involving 33 statin intolerant patients, once-weekly mipomersen by subcutaneous injection lowered LDL-C by 47%.[19] However, persistent increases in ALT ≥3 times ULN occurred in 33% of mipomersen-treated patients, and hepatic steatosis was observed in 57% of mipomersen-treated patients.[19] In that 26-week trial by Visser et al,[19] 43% of mipomersen-treated patients and 42% of placebo-treated patients experienced myalgia.

To date, other nonstatin lipid-lowering therapies, including bile acid sequestrants, niacin, and fibrates, are not well studied in patients with statin-associated muscle complaints. Further, the lipid-lowering effects of these agents are modest. In general populations with hyperlipidemia, bile acid sequestrants reduce LDL-C by 15% to 26%[20] and niacin reduces LDL-C by 17% to 22%.[21] Fibrates have minimal effects on LDL-C and are generally reserved for reducing triglyceride levels.[22]

In the present study, ETC-1002 appeared well tolerated vs placebo by patients with a history of statin-associated muscle-related AEs who were treated for 8 weeks. Additional studies with longer treatment duration and direct comparisons between ETC-1002 and other lipid-lowering agents are required to better characterize the tolerability of ETC-1002 in this patient population.

The definition of statin intolerance has evolved since this study was undertaken. Although there is yet no universally accepted definition, the criteria for statin intolerance used in the present investigation is somewhat less rigorous than the provisional definition recently proposed by the National Lipid Association, which, among other things, specifies intolerance to at least 2 statins and at specific dosage intensities.[23] Moreover, 27% of study participants were taking a statin at screening, before washout of lipid-lowering drugs, and thus were not completely statin intolerant. Further study of ETC-1002 in statin intolerant patients is warranted.

Conclusion

Clinically, the search for nonstatin lipid therapies remains vital, and ETC-1002 compares favorably with other nonstatin agents studied in statin intolerant patients. Oral ETC-1002 produces significant reductions in LDL-C compared with placebo in patients with prior statin-associated myalgia, and most patients achieve their 2004 NCEP ATP-III LDL-C goal. There was no difference in muscle complaints or safety parameters between the ETC-1002 and placebo groups during the 8 weeks of the study. ETC-1002 may provide an alternative to statins in patients with statin-associated muscle complaints.

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