Effect of ETC-1002 on Serum Low-Density Lipoprotein Cholesterol in Hypercholesterolemic Patients Receiving Statin Therapy

Christie M. Ballantyne, MD[a,*], James M. McKenney, PharmD[b], Diane E. MacDougall, MS[c], Janice R. Margulies, MS[c], Paula L. Robinson, MS[c], Jeffrey C. Hanselman, MS[c], and Narendra D. Lalwani, PhD, MBA[d]

ETC-1002 is an oral, once-daily medication that inhibits adenosine triphosphate citrate lyase, an enzyme upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, to reduce cholesterol biosynthesis. ETC-1002 monotherapy has demonstrated significant reduction in low-density lipoprotein cholesterol (LDL-C) compared with placebo in phase 2 studies. The objective of this study was to compare the lipid-lowering efficacy of ETC-1002 versus placebo when added to ongoing statin therapy in patients with hypercholesterolemia. This phase 2b, multicenter, double-blind trial (NCT02072161) randomized 134 hypercholesterolemic patients (LDL-C, 115 to 220 mg/dl) on stable background statin therapy to 12 weeks of add-on treatment with ETC-1002 120 mg, ETC-1002 180 mg, or placebo. The primary efficacy end point was the percent change in calculated LDL-C from baseline to week 12. For LDL-C, the least-squares mean percent change ± standard error from baseline to week 12 was significantly greater with ETC-1002 120 mg (−17 ± 4%, p = 0.0055) and ETC-1002 180 mg (−24 ± 4%, p <0.0001) than placebo (−4 ± 4%). ETC-1002 also dose dependently reduced apolipoprotein B by 15% to 17%, non−high-density lipoprotein cholesterol by 14% to 17%, total cholesterol by 13% to 15%, and LDL particle number by 17% to 21%. All these reductions in ETC-1002−treated cohorts were significantly greater than those with placebo. Rates of adverse events (AEs), muscle-related AEs, and discontinuations for AEs with ETC-1002 were similar to placebo. In conclusion, ETC-1002 120 mg or 180 mg added to stable statin therapy significantly reduced LDL-C compared to placebo and has a similar tolerability profile. **(Am J Cardiol 2016;117:1928−1933)**

ETC-1002 (bempedoic acid) is an oral, once-daily therapy that lowers low-density lipoprotein cholesterol (LDL-C) by direct inhibition of adenosine triphosphate (ATP) citrate lyase, an enzyme upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase in the cholesterol biosynthesis pathway. This inhibition leads to reduced cholesterol biosynthesis and increased LDL receptor activity.[1−3] The present phase 2b trial (NCT02072161) evaluated whether add-on ETC-1002 would lead to further reductions in LDL-C in patients with persistently elevated LDL-C, despite stable, ongoing statin therapy.

Methods

Hypercholesterolemic men and women aged 18 through 80 years with a body mass index from 18 to 45 kg/m^2 who were on stable statin therapy were eligible for inclusion. Stable statin therapy was defined as use of atorvastatin (10 or 20 mg), simvastatin (5, 10, or 20 mg), rosuvastatin (5 or 10 mg), or pravastatin (10, 20, or 40 mg) for at least 3 months before screening. Included participants had fasting, calculated LDL-C levels from 115 to 220 mg/dl and a fasting triglyceride level of ≤400 mg/dl after washout of lipid-regulating agents other than the statins listed previously. Patients were excluded if they had a history of clinically significant cardiovascular disease within 12 months of screening, including but not limited to acute coronary syndromes, stroke, transient ischemic attack, carotid or peripheral artery disease, or cardiac arrhythmias; current clinically significant cardiovascular disease including decompensated heart failure, uncontrolled hypertension, or cardiac arrhythmias; a history of liver or muscle enzyme elevation that occurred during statin therapy and resolved after statin discontinuation; type 1 diabetes or uncontrolled type 2 diabetes; a history of long-term muscle symptoms difficult to differentiate from myalgia; current muscle symptoms that may have been due to ongoing statin therapy; uncontrolled hypothyroidism; liver or renal dysfunction; gastrointestinal disorders affecting drug absorption; unexplained creatine kinase elevations; or use of anticoagulants, colchicine, systemic corticosteroids, digoxin, potent cytochrome P450 3A4 inhibitors or inducers, metformin, or thiazolidinediones within 4 weeks of screening.

[a]Department of Medicine, Baylor College of Medicine and Houston Methodist DeBakey Heart and Vascular Center, Houston, Texas; [b]Virginia Commonwealth University and National Clinical Research Inc., Richmond, Virginia; and [c]Clinical Development, Esperion Therapeutics, Inc., Ann Arbor, Michigan; [d]Research and Development, Esperion Therapeutics, Inc., Ann Arbor, Michigan. Manuscript received December 1, 2015; revised manuscript received and accepted March 18, 2016.

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*Corresponding author: Tel: (713) 798-5034; fax: (713) 798-7885.

E-mail address: cmb@bcm.edu (C.M. Ballantyne).

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This was a double-blind, parallel-group, placebo-controlled, multicenter, phase 2b trial consisting of a 6-week screening and washout phase and a 12-week treatment phase. Patients were randomized in a 1:1:1 ratio to ETC-1002 120 mg, ETC-1002 180 mg, or matching placebo once daily for 12 weeks in addition to ongoing statin therapy. Participants were stratified by history of statin intolerance, defined as discontinuation of ≥1 statins at any dose because of muscle-related symptoms. Patients supplied background statin therapy from their usual source and ingested study drug and statin once daily. Study visits occurred every 2 weeks through week 8, with a final visit at week 12. Clinical laboratory assessments and basic fasting lipid blood tests (total cholesterol, calculated LDL-C, high-density lipoprotein cholesterol [HDL-C], and triglycerides) were performed at screening and at all treatment-phase study visits; all other fasting lipid and biomarker measurements were performed at week 0 (day 1) and week 12. Adverse events (AEs) were monitored throughout the study, beginning with the first screening visit, and were observed until resolution or for 30 days after the last dose of study drug.

The primary efficacy end point was the percent change in calculated LDL-C from baseline to week 12 in patients treated with ETC-1002 versus those treated with placebo. Secondary efficacy end points included the percent change from baseline to week 12 in apolipoprotein B, non−HDL-C, total cholesterol, LDL particle number, HDL-C, HDL particle number, apolipoprotein A-1, triglycerides, very-low-density lipoprotein particle number, and high-sensitivity C-reactive protein (CRP).

Safety assessments included reported or observed treatment-emergent AEs, clinical laboratory tests (hematology, serum chemistry, coagulation, urinalysis), physical examination findings, vital sign measurements, electrocardiogram readings, weight, and ankle and waist circumference measurements. AEs were coded using the *Medical Dictionary for Regulatory Activities* version 16.1, and the severity and relation to study drug was assessed by the investigator. Muscle-related AEs were defined as those from the system organ class of musculoskeletal and connective tissue disorders, except for those that were not obviously muscle related. Terms included in the muscle-related AE analysis were selected after database lock and before unblinding; excluded terms were arthralgia, back pain, bursitis, joint swelling, rotator cuff syndrome, and tendonitis.

The planned sample size was 44 patients per treatment group, which provided 90% power to detect a difference of 15% in the percent change in calculated LDL-C from baseline to week 12 between at least 1 ETC-1002 treatment group and the placebo group. This calculation was based on a 2-sided *t* test at the 5% level of significance and assumed a common standard deviation of 20% and a dropout rate of 10%.

Efficacy analyses were performed on the modified intent-to-treat (mITT) population, which consisted of all randomized patients who received at least 1 dose of study drug, had a baseline assessment, and at least 1 postbaseline assessment, excluding any assessment taken more than 2 days after a dose of study drug. Safety analyses were performed on the safety population, which consisted of all randomized patients who received at least 1 dose of study drug.

For LDL-C, non−HDL-C, total cholesterol, HDL-C, and triglycerides, baseline was defined as the mean of the values from the last screening visit (day −10 to −7) and day 1. For all other efficacy measurements, baseline was defined as the last value before the first dose of study drug. Missing values at week 12 were imputed using the last-observation-carried-forward procedure.

An analysis of covariance was performed on the mITT population to compare each dose of ETC-1002 with placebo for the efficacy end points and evaluated the effects of treatment and history of statin intolerance with the baseline value as a covariate. Least-square means and standard errors were calculated for each treatment group, and differences in least-square means, corresponding 2-sided 95% confidence intervals, and p values were obtained for the treatment comparisons using Wilcoxon rank-sum tests.

Individual institutional review boards approved the clinical study protocol and informed consent documents. Written informed consent was obtained from all participants before any study-related procedures.

Results

Of the 134 randomized patients, 115 (86%) completed the trial and 19 patients (14%) discontinued early, most often for withdrawn consent (Figure 1). Because 1 patient who was randomized did not receive study drug, the safety population included 133 patients. The number of patients included in the mITT population varied according to the end point assessed; 127 patients were included for the primary efficacy end point.

Baseline demographic and clinical characteristics were similar among the treatment groups (Table 1). Overall, 10% of the population reported a history of statin intolerance, defined as a previous discontinuation of at least 1 statin medication because of muscle-related symptoms. The most commonly used protocol-specified background statin medication was simvastatin 20 mg (30%).

ETC-1002 120 and 180 mg added to stable statin therapy reduced mean LDL-C significantly more than placebo, with the greatest reduction observed in patients who received ETC-1002 180 mg (Table 2). The least-square mean ± standard error percent changes from baseline in LDL-C were −4.2 ± 4.2% with placebo, −17.3 ± 4.0% with ETC-1002 120 mg ($p = 0.0055$ vs placebo), and −24.3 ± 4.2% with ETC-1002 180 mg ($p < 0.0001$ vs placebo; Figure 2). LDL-C reductions in the ETC-1002 treatment groups were significantly greater than in the placebo group by week 2 and remained significantly greater through week 12. The reduction in LDL-C was not significantly different in patients treated with ETC-1002 180 and 120 mg (difference in least-square mean percent change, 7.0%; $p = 0.14$).

Compared with placebo, treatment with ETC-1002 added to statin therapy also significantly reduced apolipoprotein B, non−HDL-C, total cholesterol, and LDL particle number (Table 2). Median CRP values were reduced by 22% with ETC-1002 120 mg ($p = 0.26$ vs placebo) and by 30% with ETC-1002 180 mg ($p = 0.08$ vs placebo). ETC-1002 did not significantly affect triglyceride levels or very-low-density lipoprotein particle number. All treatment groups

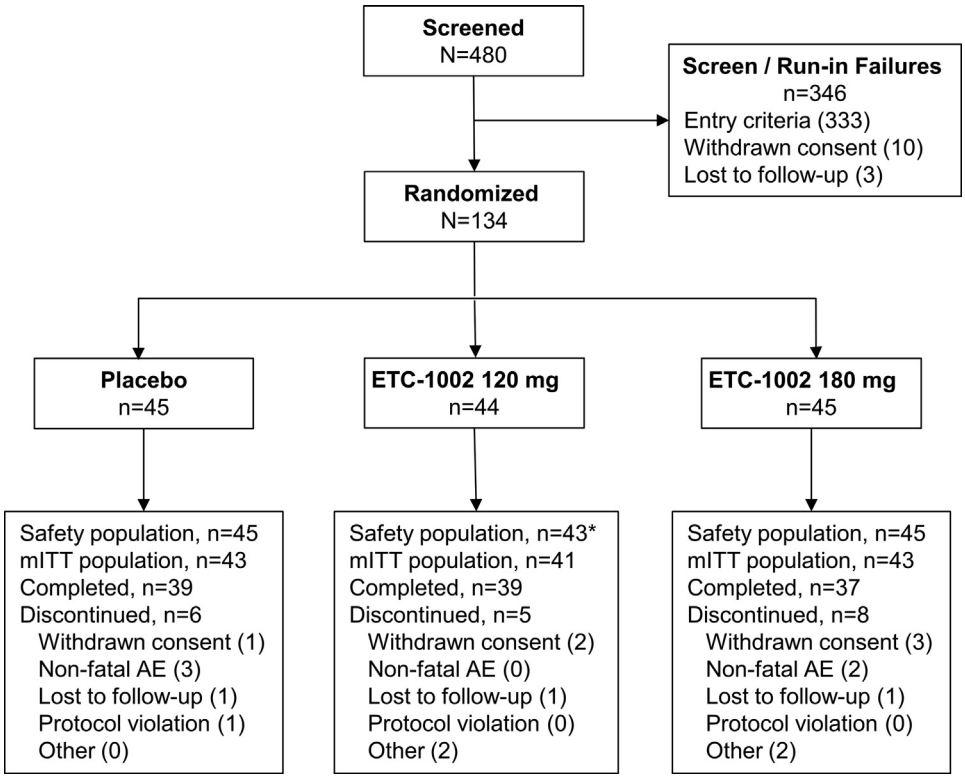

Figure 1. Patient disposition. *One patient was randomized but discontinued before receiving study drug.

demonstrated slight decreases in HDL-C and apolipoprotein A-1 levels, which were not significantly different between ETC-1002 and placebo. Both ETC-1002 treatment groups demonstrated small increases in HDL particle number; the difference in least-square mean percent change in HDL particle number was significant between ETC-1002 180 mg and placebo (10.1% increase vs 1.6% decrease; $p = 0.0004$).

The overall incidence of AEs and drug-related AEs was similar between ETC-1002 180 mg and placebo and lowest with ETC-1002 120 mg (Table 3). The percent of patients discontinuing because of AEs was not different between placebo (3 patients; 1 with dizziness and headache, 1 with cholelithiasis, 1 with constipation) and ETC-1002 180 mg (2 patients; 1 with rash, 1 with abdominal distention) or ETC-1002 120 mg (no patients discontinued for AEs). Most AEs were mild or moderate in severity. Serious AEs included 1 patient with noncardiac-related chest pain and 1 patient with cholelithiasis in the placebo group and 1 patient with ovarian adenoma who was treated with ETC-1002 180 mg; all were determined unrelated to study drug. No specific drug-related AE was reported by more than 1 patient in either of the ETC-1002 treatment groups. Muscle-related AEs were less frequent with ETC-1002 (2% to 5%) than with placebo (13%) and caused no study discontinuations (Table 3). Myalgia was reported in 2 placebo-treated patients, 1 patient treated with ETC-1002 120 mg, and no patients treated with ETC-1002 180 mg.

No clinically important, dose-related trends in laboratory changes were noted. No laboratory abnormality was considered a serious AE or resulted in study drug discontinuation. One patient treated with ETC-1002 180 mg experienced a single increase in aspartate aminotransferase >3 times the upper limit of normal (ULN) at week 12, whereas alanine aminotransferase remained <2 times ULN; there were no other instances of liver enzyme elevations >3 times ULN and no instances of creatine kinase elevations >10 times ULN in any treatment group. No clinically important differences were noted among the treatment groups with respect to mean changes in physical examination findings, vital sign measurements, electrocardiogram readings, weight, or ankle or waist circumference measurements from baseline to week 12.

Discussion

In patients with elevated LDL-C levels despite stable statin therapy, add-on treatment with ETC-1002 decreased LDL-C levels, with both doses (120 and 180 mg) demonstrating superior LDL-C lowering over placebo. In this study, LDL-C was incrementally reduced up to 24% beyond statin therapy in patients treated with ETC-1002. The present trial is the first study of the effects of ETC-1002 added on to a range of stable background statin medications.

Analyses of the secondary efficacy parameters apolipoprotein B, non−HDL-C, total cholesterol, and LDL particle number support the primary end point findings: both doses of ETC-1002 significantly reduced each of these parameters compared with placebo. These results are consistent with those from previous phase 2 trials in which these 4 measures were significantly reduced with ETC-1002 monotherapy compared with placebo[4] and compared with ezetimibe monotherapy.[5] Apolipoprotein B,[6] non−HDL-C,[7] and LDL

Table 1
Baseline demographic and clinical characteristics, safety population

Characteristic	Placebo (n = 45)	ETC-1002 120 mg (n = 43)	ETC-1002 180 mg (n = 45)
Age (years)	56 ± 10	59 ± 9	57 ± 10
Women	22 (49%)	26 (61%)	31 (69%)
White	37 (82%)	37 (86%)	37 (82%)
Not Hispanic/Latino	38 (84%)	33 (77%)	35 (78%)
NCEP ATP III Risk Category			
Very high	6 (13%)	2 (5%)	1 (2%)
High	2 (4%)	3 (7%)	8 (18%)
Moderate	13 (29%)	23 (54%)	22 (49%)
Low	24 (53%)	15 (35%)	14 (31%)
LDL-C (mg/dl)	131 ± 22	134 ± 20	142 ± 28
Total cholesterol (mg/dl)	212 ± 24	216 ± 24	229 ± 29
HDL-C (mg/dl)	54 ± 14	55 ± 15	55 ± 14
Triglycerides (mg/dl) *	119 (82-159)	112 (88-178)	145 (122-196)
High-sensitivity C-reactive protein (mg/l)*†	1.8 (1.10-4.60)	1.8 (0.90-3.10)	1.8 (1.20-4.00)
Systolic blood pressure (mm Hg)	126 ± 12	128 ± 11	129 ± 14
Diastolic blood pressure (mm Hg)	78 ± 7	80 ± 8	78 ± 9
Weight (kg)	90 ± 20	83 ± 20	83 ± 19
Body-mass index (kg/m^2)	31 ± 6	30 ± 6	30 ± 6
History of statin intolerance‡	3 (7%)	6 (14%)	4 (9%)

Values are mean ± SD, unless otherwise indicated. Baseline defined as the mean of the values from weeks −1 and 0, unless otherwise indicated.

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

* Values are median (interquartile range).

† For CRP, baseline defined as the last value before the first dose of study drug; n = 42 for ETC-1002 120 mg.

‡ History of statin intolerance was defined as patient-reported discontinuation of ≥1 statin, at any dose, because of muscle-related symptoms. No patients with a history of statin intolerance were experiencing statin-related AEs at baseline.

particle number[8] have all been shown to have stronger associations with the risk of cardiovascular events than LDL-C. Thus, it is noteworthy that ETC-1002 significantly reduces apolipoprotein B, non−HDL-C, and LDL particle number when used either as monotherapy or in combination with ezetimibe or statins. Although there was no significant change in HDL-C, patients treated with ETC-1002 180 mg demonstrated a modest but significant increase in HDL particle number, which has been shown to be inversely associated with cardiovascular events in patients treated with statin therapy.[9] Previous phase 2 studies with ETC-1002 monotherapy have demonstrated decreases in CRP of 41%[10] to 42%.[11] In the present study, no incremental reduction in CRP was observed for patients in the placebo group (i.e., statin monotherapy), whereas the addition of ETC-1002 120 or 180 mg to stable statin therapy nonsignificantly reduced CRP by 22% and 30% from baseline, respectively.

Table 2
Percent changes in lipid and CRP levels from baseline to week 12, mITT population

	Placebo (n = 43)	ETC-1002 120 mg (n = 41)	ETC-1002 180 mg (n = 43)
Primary end point			
LDL-C (mg/dl)	-4.2 ± 4.2	-17.3 ± 4.0*	-24.3 ± 4.2†
Secondary end points			
Apolipoprotein B (mg/dl)	-5.5 ± 3.4	-15.0 ± 3.3‡	-17.2 ± 3.4*
Non−HDL-C (mg/dl)	-1.8 ± 3.9	-14.3 ± 3.7*	-16.6 ± 3.9*
Total cholesterol (mg/dl)	-3.2 ± 2.9	-12.8 ± 2.7*	-15.3 ± 2.9*
LDL particle number (nmol/l)	-2.3 ± 4.3	-17.4 ± 4.1*	-21.3 ± 4.3*
HDL-C (mg/dl)	-2.0 ± 2.7	-6.1 ± 2.6	-4.0 ± 2.7
HDL particle number (µmol/l)	-1.6 ± 2.8	4.0 ± 2.7	10.1 ± 2.8*
Apolipoprotein A-1 (mg/dl)	-3.7 ± 2.2	-2.0 ± 2.1	-0.1 ± 2.2
Triglycerides (mg/dl)§	-3.0 (37)	-4.8 (28)	-9.1 (47)
VLDL particle number (nmol/l)§	10.9 (76)	10.0 (67)	-8.3 (91)
CRP (mg/l)§	0 (89)	-21.8 (44)	-29.8 (50)

Values are least-squares mean ± standard error, unless otherwise indicated. Baseline was defined as the mean of the values from weeks −1 and 0 for LDL-C, non−HDL-C, total cholesterol, HDL-C, and triglycerides. Baseline was defined as the last value before the first dose of study drug for apolipoprotein B, LDL particle number, HDL particle number, apolipoprotein A-1, VLDL particle number, and CRP.

CRP = high-sensitivity C-reactive protein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mITT = modified intent-to-treat; VLDL = very-low-density lipoprotein.

* $p < 0.01$ vs placebo.

† $p < 0.0001$ vs placebo.

‡ $p < 0.05$ vs placebo.

§ Values are median (interquartile range); p values vs placebo are from Wilcoxon rank-sum test.

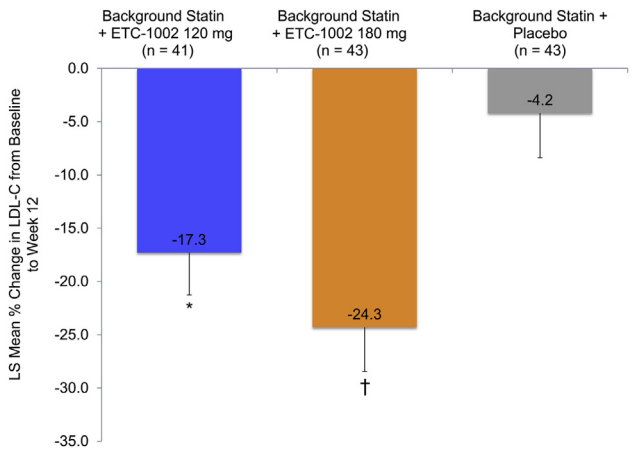

Figure 2. Mean percent change in LDL-C from baseline to week 12. These data are from the modified intent-to-treat population. *p = 0.0055 versus placebo; †p <0.0001 versus placebo. *Error bars* represent standard error. LS = least-squares.

ETC-1002 was safe and well tolerated in the present study, with a similar incidence of AEs between ETC-1002 180 mg and placebo and the lowest incidence observed in patients treated with ETC-1002 120 mg. The incidence of muscle-related AEs during the trial was low, and no patients discontinued because of muscle-related AEs. This

Table 3
Treatment-emergent adverse events, safety population

Characteristic	Placebo (n = 45)	ETC-1002 120 mg (n = 43)	ETC-1002 180 mg (n = 45)
Overview of AEs			
Any AEs	28 (62%)	15 (35%)	28 (62%)
Serious AEs*	2 (4%)	0	1 (2%)
Study-drug related AEs†	9 (20%)	4 (9%)	8 (18%)
Discontinuation due to AEs	3 (7%)	0	2 (4%)
Most common AEs‡			
Constipation	2 (4%)	1 (2%)	0
Nausea	2 (4%)	1 (2%)	1 (2%)
Upper respiratory tract infection	1 (2%)	0	3 (7%)
Urinary tract infection	2 (4%)	3 (7%)	2 (4%)
Arthralgia	2 (4%)	0	0
Dizziness	2 (4%)	0	0
Headache	2 (4%)	1 (2%)	1 (2%)
Rash	0	1 (2%)	2 (4%)
Muscle-related AEs§	6 (13%)	2 (5%)	1 (2%)
Flank pain	0	1 (2%)	0
Muscle spasms	2 (4%)	0	1 (2%)
Muscular weakness	1 (2%)	0	0
Musculoskeletal pain	1 (2%)	0	0
Myalgia	2 (4%)	1 (2%)	0
Neck pain	1 (2%)	0	0

AE = adverse event.

* Serious AEs included 1 patient with noncardiac chest pain and 1 patient with cholelithiasis in the placebo group and 1 patient with ovarian adenoma in the ETC-1002 180-mg group; all were determined to be not related to study drug.

† AEs were considered drug related if relationship to study drug was deemed possible, probable, or definite, or if relationship to study drug was not recorded.

‡ Most common AEs were those occurring in ≥2 patients in any group, excluding muscle-related AEs (which are shown separately, regardless of frequency).

§ Includes AEs from the system organ class musculoskeletal and connective tissue disorders except for arthralgia, back pain, bursitis, joint swelling, rotator cuff syndrome, and tendonitis.

observation of muscle safety with ETC-1002 is supported by findings in previous phase 2 studies in patients with a history of statin-associated muscle symptoms in which the frequency of muscle-related AEs was not different with ETC-1002 monotherapy compared with placebo[11] or ezetimibe monotherapy.[5]

Other nonstatin options used in conjunction with statins for incremental LDL-C lowering include bile acid sequestrants, which further reduce LDL-C by 10% to 20%,[12] and ezetimibe, which incrementally lowers LDL-C by 23% and CRP by 10%.[13] In studies of the newly approved proprotein convertase subtilisin/kexin type 9 inhibitors added to statin therapy, alirocumab has been shown to incrementally reduce LDL-C by 48%[14] to 72%[15] from baseline, with no additional effect on CRP,[16] and evolocumab has shown incremental reductions of up to 66% from baseline.[17] The investigational cholesteryl ester transfer protein inhibitor anacetrapib incrementally lowers LDL-C by 45% and has no incremental effect on CRP when added to statins.[18] It should be noted that important differences in study designs, patient inclusion criteria, baseline LDL-C and cardiovascular risk levels, length of treatment, and concomitant allowed medications in the referenced studies prevent direct comparisons of results.

ETC-1002 inhibits ATP citrate lyase, an enzyme upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase in the cholesterol biosynthesis pathway.[3] Because ETC-1002 and statins target different enzymes in the cholesterol synthesis cascade, the end result is overall decreased cholesterol synthesis. The decreased cholesterol synthesis leads to upregulation of LDL-receptors and subsequent reduction in the circulating levels of LDL-C, suggesting that the mechanism by which both drugs lower LDL-C is identical. Patients who have an inadequate response on maximally tolerated statin therapy represent an unmet need in the clinical management of hypercholesterolemia. Furthermore, it is recognized that residual cardiovascular risk remains in high-risk patients despite optimized statin therapy and that new therapies are needed to address this risk.[19–21] This has inspired further interest in the clinical use of nonstatin agents as add-on therapy for incremental cholesterol reduction and incremental benefit on long-term cardiovascular outcomes. Recent clinical trial evidence with ezetimibe supports the concept that incremental LDL-C lowering in the long-term, beyond statin therapy, is associated with improved cardiovascular outcomes.[22,23] The present study was designed to reflect a typical clinical scenario in which a second lipid-modifying drug is added to ongoing low- or moderate-intensity statin therapy to achieve additional LDL-C lowering, and the efficacy and safety findings in this short-term study demonstrate a potentially promising benefit-risk profile for ETC-1002 in these conditions.

We acknowledge the following study limitations. As a phase 2 trial, the sample size was relatively small and the duration of treatment was only 12 weeks. The safety and efficacy demonstrated in the present study support further evaluation of ETC-1002 as add-on to statins in larger clinical trials in the future. Also, despite the randomized trial design, there were some differences in baseline characteristics among the treatment groups, including gender, level of cardiovascular risk, and levels of LDL-C and triglycerides.

In patients with elevated LDL-C levels despite stable statin therapy, the addition of ETC-1002 120 or 180 mg daily produces significant and clinically relevant incremental LDL-C lowering and is well tolerated. These results indicate that adding once-daily oral ETC-1002 to stable statin therapy may be a useful clinical strategy in the future.

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