Journal of Clinical Lipidology (2016) 10, 556–567

Journal of Clinical Lipidology

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

**Paul D. Thompson, MD*, Diane E. MacDougall, MS, Roger S. Newton, PhD, Janice R. Margulies, MS, Jeffrey C. Hanselman, MS, David G. Orloff, MD[1], James M. McKenney, PharmD, Christie M. Ballantyne, MD**

*Department of Cardiology, Hartford Hospital, Hartford, CT, USA (Dr Thompson); Esperion Therapeutics Inc., Ann Arbor, MI, USA (Drs MacDougall, Newton, Margulies, Hanselman); Medpace Inc., Cincinnati, OH, USA (Dr Orloff); School of Pharmacy, Virginia Commonwealth University and National Clinical Research Inc., Richmond, VA, USA (Dr McKenney); and Baylor College of Medicine and Houston Methodist DeBakey Heart and Vascular Center, Houston, TX, USA (Dr Ballantyne)*

**KEYWORDS:**
ETC-1002;
Ezetimibe;
Hypercholesterolemia;
Myalgia;
Statin-associated muscle symptoms;
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).



[1] Deceased.

* Corresponding author. Department of Cardiology, Hartford Hospital, 80 Seymour Street, Hartford, CT 06102, USA.
E-mail address: paul.thompson@hhchealth.org

Submitted October 22, 2015. Accepted for publication December 22, 2015.


http://dx.doi.org/10.1016/j.jacl.2015.12.025

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

weeks −6, −5, −3, −1, 0, 2, 4, 8, and 12. A contract laboratory (Medpace Inc., Cincinnati, OH), performed all clinical laboratory tests. LDL-C was calculated using the Friedewald equation. Phlebotomy was performed after a minimum 12-hour fast (water was allowed) and only if the patient took their dose of study drug the previous day.

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.

## Efficacy endpoints

The primary endpoint was the percent change from baseline to week 12 in calculated LDL-C in patients treated with ETC-1002 monotherapy vs those treated with EZE alone. Secondary endpoints included the dose-response relationship between ETC-1002 and the percent change in LDL-C from baseline to week 12, the percent change in LDL-C from baseline to week 12 in patients treated with ETC-1002 plus EZE vs those treated with EZE alone, and the percent change from baseline to week 12 for all treatment groups in LDL particle number, apolipoprotein B, total cholesterol, non–high-density lipoprotein cholesterol (non–HDL-C), HDL-C, HDL particle number, apolipoprotein A-I, triglycerides, very low-density lipoprotein (VLDL) particle number, and high-sensitivity C-reactive protein (CRP). Lipoprotein particle number was measured using nuclear magnetic resonance imaging.

## Safety endpoints

The safety of ETC-1002 was assessed using treatment-emergent AEs; hematology, serum chemistry, and urinalysis laboratory values; 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 16.0, and evaluated by the investigator for severity and relation to study drug. 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 from this system organ class after database lock and before unblinding.

## Statistical plan and analyses

The study was designed to include 322 patients: 92 patients in each monotherapy group and 23 patients in each combination therapy group. Sample size calculations were performed using nQuery Advisor, version 7.0 (Statistical Solutions, Cork, Ireland). The sample size of 92 patients per monotherapy group was expected to provide 90% power to detect a difference of 10% in the absolute percent change from baseline to week 12 in LDL-C between either ETC-1002 treatment groups and the EZE monotherapy group. This calculation was based on a 2-sided *t* test at the 5% level of significance and assumed a common standard deviation of 15% in the statin-tolerant patients and 22% in the statin-intolerant patients with a dropout rate of 15%.

Efficacy analyses were performed on the modified intent-to-treat population, which consisted of randomized patients who had a baseline assessment, received at least 1 dose of study medication, and had at least 1 on-treatment assessment, excluding assessments taken >2 days after a dose of study drug. Safety analyses were performed on the safety population, which included randomized patients who received at least 1 dose of study drug. Baseline patient characteristics were summarized for the safety population by treatment group and statin-tolerance subgroup.

An analysis of covariance was used to compare each ETC-1002 treatment group with EZE monotherapy for each of the efficacy endpoints. The primary model included the effects of treatment and statin intolerance and the baseline value as a covariate. Baseline was defined as the mean of values from weeks −1 and 0 for LDL-C, non–HDL-C, total cholesterol, HDL-C, and triglycerides. For all other lipid and biomarker measures, 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. When LDL-C could not be calculated (ie, triglycerides >400 mg/dL), beta-quantification measurements were used to determine LDL-C values. Least-square (LS) means and standard errors were obtained for each treatment group; differences in LS means and *P* values were obtained for the treatment comparisons. Graphical methods (eg, normal probability plot and histogram of residuals, plot of residuals vs predicted values) or analytical methods (eg, Shapiro–Wilk test), or both, were used to assess the model assumptions. Because of departures from normality observed in the parameters of triglycerides, CRP, and VLDL particle number, nonparametric analyses were performed for these measures, with *P* values obtained from the Wilcoxon rank-sum test and median values presented.

Actual values, changes from baseline, and percent changes from baseline in calculated LDL-C and secondary lipid and biomarker measures were summarized using descriptive statistics by treatment group and time point. Percent changes from baseline in LDL-C also were summarized by statin-tolerance subgroup. To assess the dose-response relationship for ETC-1002 monotherapy, the primary analysis of covariance model was used for the comparison of ETC-1002 120 mg and ETC-1002 180 mg. Statistical testing of the efficacy endpoints was 2-sided and conducted at the 5% level of significance with no adjustment for multiple comparisons.

For the evaluation of safety, the incidence of AEs was summarized by system organ class and preferred term for each treatment group. Muscle-related AEs also were summarized by statin-tolerance subgroup. Actual values and

changes from baseline in clinical laboratory parameters, vital sign measurements, electrocardiogram tracings, body weight, and ankle and waist circumference measurements were summarized using descriptive statistics by treatment group and time point.

## Results

### Patient disposition and baseline characteristics

Of 690 patients screened, 341 were excluded, mainly for failure to satisfy inclusion criteria (Fig. 1). Of the 349 randomized patients (177 statin intolerant and 172 statin tolerant), 309 patients completed the study. The 40 who discontinued participation did so most commonly because of AEs. A higher percentage of statin-tolerant patients (93%) than statin-intolerant patients (84%) completed the study. The safety population included 348 patients as 1 statin-tolerant patient discontinued before receiving any study drug.

Most patients were non-Hispanic Caucasians with similar numbers of men and women (Table 1). Mean age, baseline lipid values, and National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III risk category were slightly higher in statin-intolerant patients. The most common prestudy statin-associated muscle complaints were bilateral calf and thigh pain (data not shown). Most statin-intolerant patients historically experienced the onset of statin-associated muscle symptoms within 1 to 2 weeks of statin initiation and most had resolution of symptoms within 1 to 2 weeks of discontinuation.

### Efficacy endpoints

ETC-1002 alone or in combination with EZE reduced LDL-C from baseline to week 12 more than EZE monotherapy (Table 2). LDL-C reductions were greatest with the combination of ETC-1002 120 mg (43%) or 180 mg (48%) plus EZE ($P < .0001$ vs EZE alone, both comparisons). The combination treatment effect of ETC-1002 plus EZE was approximately equal to the sum of their individual effects on LDL-C. The LDL-C reduction was slightly, but not significantly, higher with ETC-1002 180 mg alone (30%) than with 120 mg alone (27%) ($P = .15$). The percent reductions in LDL-C with ETC-1002 were similar in statin-intolerant and statin-tolerant patients (Fig. 2). LDL-C reductions were apparent and steady after 2 weeks of treatment (Fig. 3).

ETC-1002 alone or with EZE reduced LDL particle number, apolipoprotein B, total cholesterol, and non–HDL-C more than EZE alone (Table 2). Median values for CRP decreased from baseline to the week 12 endpoint by 30% with ETC-1002 120 mg and 40% with ETC-1002 180 mg. These CRP reductions in the ETC-1002 monotherapy groups were significantly greater ($P < .01$, both comparisons) than the 10% reduction observed with EZE alone (Table 2). ETC-1002 had minimal effect on triglycerides and VLDL particle number (Table 2). HDL-C decreased with ETC-1002 treatment (by 3% to 6%) and increased with EZE alone (by 5%; $P < .0001$ to $P < .05$ for ETC-1002 groups vs EZE alone; Table 2). ETC-1002 did not alter HDL particle number or apolipoprotein A-I vs EZE alone, although apolipoprotein A-I did decrease

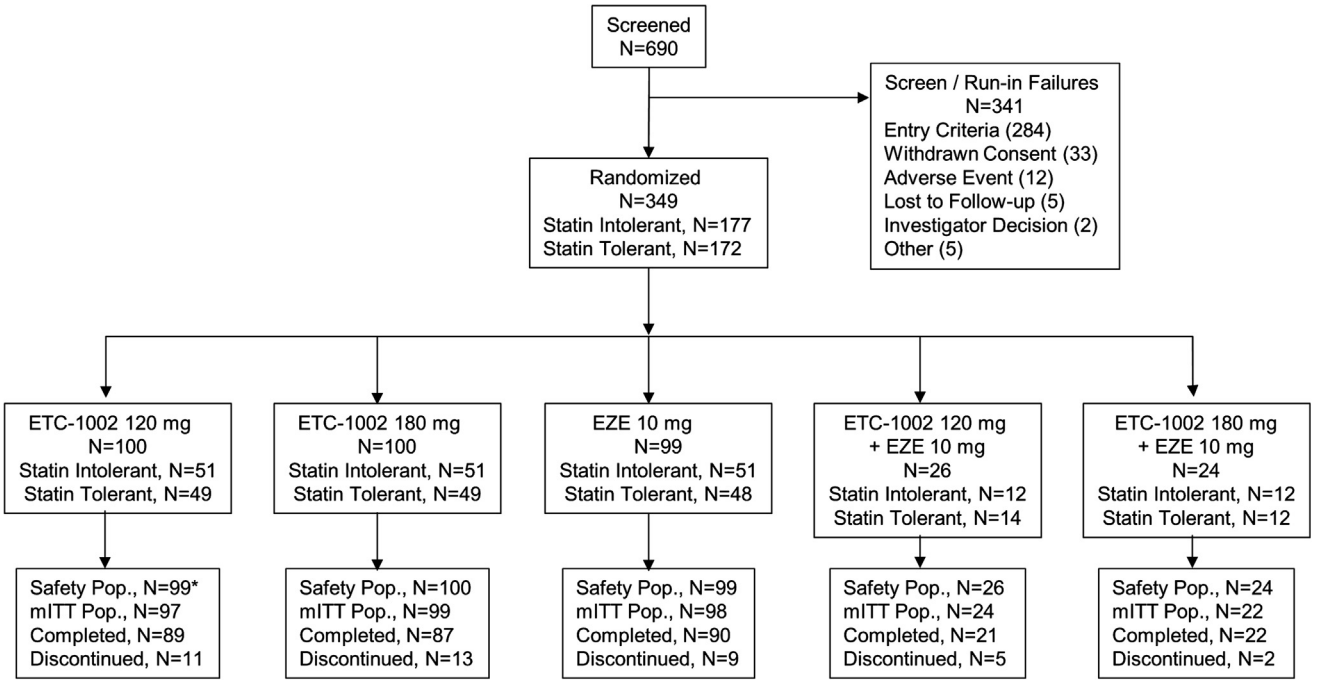


**Figure 1** Disposition of patients. *One patient who was statin tolerant was randomized but discontinued before receiving study drug. EZE, ezetimibe; mITT, modified intent-to-treat; Pop., population.

**Table 1** Baseline demographic and clinical characteristics

| Characteristics | Safety population | | | | | | |
|---|---|---|---|---|---|---|---|
| | Statin intolerant, n = 177 | Statin tolerant, n = 171 | ETC-1002 120 mg, n = 99 | ETC-1002 180 mg, n = 100 | EZE 10 mg, n = 99 | ETC-1002, 120 mg + EZE 10 mg, n = 26 | ETC-1002 180 mg + EZE 10 mg n = 24 |
| Demographic | | | | | | | |
| Age, y | 62 ± 9 | 57 ± 9 | 61 ± 10 | 59 ± 9 | 60 ± 10 | 59 ± 10 | 59 ± 9 |
| Women, % | 57 | 47 | 54 | 51 | 52 | 54 | 54 |
| Caucasian, % | 89 | 91 | 91 | 91 | 88 | 92 | 92 |
| Not Hispanic/Latino, % | 94 | 84 | 92 | 85 | 90 | 92 | 92 |
| NCEP ATP III risk category very high, % | 14 | 3 | 11 | 7 | 8 | 8 | 8 |
| NCEP ATP III risk category high, % | 14 | 9 | 14 | 10 | 11 | 12 | 8 |
| NCEP ATP III risk category moderate, % | 41 | 50 | 38 | 49 | 49 | 42 | 46 |
| NCEP ATP III risk category low, % | 32 | 38 | 36 | 34 | 32 | 39 | 38 |
| Clinical | | | | | | | |
| LDL-C, mg/dL | 169 ± 25 | 160 ± 25 | 164 ± 28 | 166 ± 24 | 165 ± 25 | 162 ± 26 | 162 ± 27 |
| Total cholesterol, mg/dL | 255 ± 33 | 244 ± 31 | 249 ± 31 | 253 ± 33 | 248 ± 32 | 247 ± 35 | 246 ± 32 |
| HDL-C, mg/dL | 53 ± 13 | 51 ± 15 | 54 ± 16 | 52 ± 13 | 49 ± 12 | 51 ± 15 | 52 ± 16 |
| Triglycerides, mg/dL* | 157 (52–365) | 150 (38–434) | 136 (71–375) | 162 (38–371) | 163 (64–434) | 161 (81–332) | 151 (50–343) |
| CRP, mg/L*,† | 1.90 (0.2–31.7) | 2.20 (0.1–22.5) | 1.60 (0.2–19.2) | 2.50 (0.1–20.3) | 2.60 (0.3–31.7) | 1.85 (0.2–19.5) | 1.25 (0.2–4.7) |
| SBP, mm Hg | 124 ± 11 | 126 ± 12 | 126 ± 11 | 125 ± 12 | 126 ± 12 | 126 ± 11 | 119 ± 12 |
| DBP, mm Hg | 77 ± 8 | 78 ± 8 | 77 ± 8 | 78 ± 7 | 78 ± 7 | 77 ± 7 | 76 ± 9 |
| Weight, kg | 86 ± 17 | 88 ± 19 | 87 ± 18 | 89 ± 19 | 85 ± 17 | 88 ± 20 | 83 ± 22 |
| BMI, kg/m$^2$ | 30 ± 5 | 30 ± 5 | 31 ± 6 | 31 ± 5 | 30 ± 5 | 30 ± 5 | 28 ± 5 |

BMI, body mass index; DBP, diastolic blood pressure; EZE, ezetimibe; HDL-C, high-density lipoprotein cholesterol; CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; SBP, systolic blood pressure.

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

*Median values (minimum, maximum).

†Baseline defined as the last value before the first dose of study drug.

**Table 2** Percent changes from baseline to week 12 in lipids and CRP

| Endpoint | mITT population | | | | |
|---|---|---|---|---|---|
| | ETC-1002 120 mg, n = 97 | ETC-1002 180 mg, n = 99 | EZE 10 mg, n = 98 | ETC-1002 120 mg + EZE 10 mg, n = 24 | ETC-1002 180 mg + EZE 10 mg, n = 22 |
| Primary | | | | | |
| LDL-C, mg/dL | −27.5 ± 1.3[b] | −30.1 ± 1.3[a] | −21.2 ± 1.3 | −43.1 ± 2.6[a] | −47.7 ± 2.8[a] |
| Secondary | | | | | |
| LDL particle number, nmol/L | −21.8 ± 1.7[b] | −24.6 ± 1.8[a] | −12.7 ± 1.7 | −35.0 ± 3.7[a] | −37.0 ± 3.6[a] |
| Apolipoprotein B, mg/dL | −19.3 ± 1.3‡ | −21.3 ± 1.3† | −15.2 ± 1.2 | −32.7 ± 2.7[a] | −35.2 ± 2.6[a] |
| Total cholesterol, mg/dL | −19.3 ± 0.9[b] | −20.7 ± 0.9[a] | −14.3 ± 0.9 | −30.6 ± 1.9[a] | −34.3 ± 2.0[a] |
| Non–HDL-C, mg/dL | −23.2 ± 1.2[b] | −25.3 ± 1.1[a] | −18.7 ± 1.2 | −37.4 ± 2.3[a] | −42.4 ± 2.4[a] |
| HDL-C, mg/dL | −5.8 ± 1.4[a] | −4.8 ± 1.4[a] | 5.0 ± 1.4 | −3.1 ± 2.8[c] | −3.7 ± 3.0[b] |
| HDL particle number, μmol/L | 5.0 ± 1.3 | 6.2 ± 1.4 | 6.7 ± 1.3 | 7.3 ± 2.9 | 5.1 ± 2.8 |
| Apolipoprotein A-I, mg/dL | −0.2 ± 1.1 | 0.1 ± 1.2 | 2.0 ± 1.1 | −2.8 ± 2.4 | −4.1 ± 2.4[c] |
| Triglycerides, mg/dL*,† | 0.0 (41.6) | −2.7 (46.2) | −7.0 (34.9) | −18.9 (25.5) | −12.2 (36.5) |
| VLDL particle number, nmol/L* | −2.7 (68.5) | 15.3 (80.5) | −12.6 (63.4) | −11.7 (80.1) | 12.0 (78.1) |
| CRP, mg/L*,†,‡ | −30.1 (55.4)[b] | −40.2 (53.3)[b] | −10.5 (59.0) | −38.1 (83.2) | −25.6 (37.2)[c] |

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

Values are least-squares mean ± SE, unless otherwise indicated.

Baseline defined as the mean of the values from weeks −1 and 0 unless otherwise indicated. Week 12 endpoint is the week 12 value or last observation carried forward.

[a] $P < .0001$.

[b] $P \leq .01$.

[c] $P \leq .05$ vs EZE alone using an analysis of covariance model with terms for treatment and statin intolerance and baseline value as a covariate, unless otherwise indicated.

*Median (interquartile range) values.

†Non-parametric analysis vs EZE using Wilcoxon rank-sum test.

‡Baseline defined as the last value before the first dose of study drug.

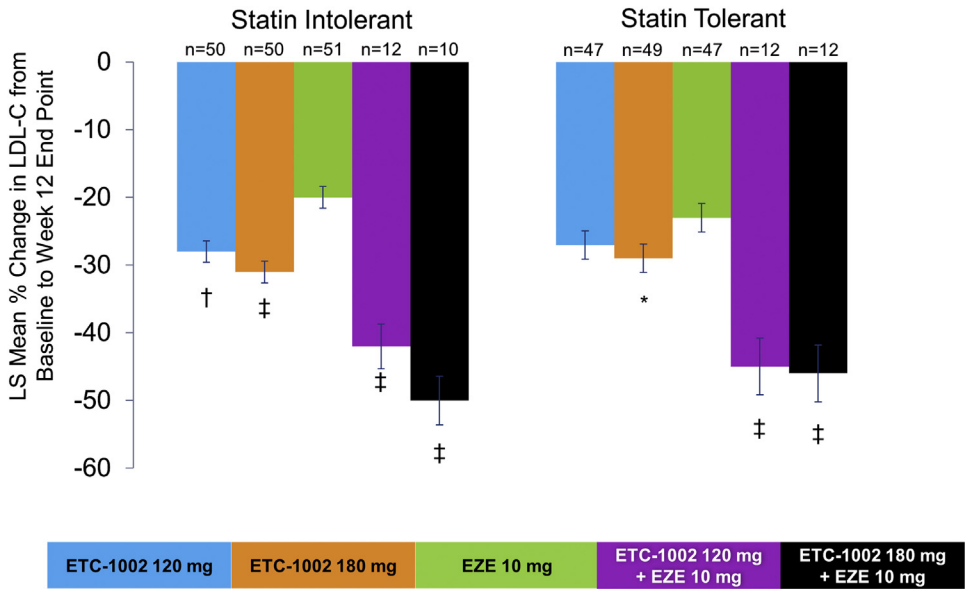


**Figure 2** Percent changes from baseline in LDL-C, stratified by statin tolerance. Week 12 or last observation carried forward is the end-of-study endpoint and differs slightly from week 12 value; *P* values vs EZE monotherapy were determined by an analysis of covariance model with terms for treatment and statin intolerance and baseline value as a covariate. $^{*}P \leq .05$ vs EZE; $^{\dagger}P \leq .01$ vs EZE; $^{\ddagger}P < .0001$ vs EZE. EZE, ezetimibe; LS, least square. Error bars represent standard error.

more with ETC-1002 180 mg plus EZE than with EZE alone.

## Safety endpoints

The incidence of AEs in each ETC-1002 monotherapy group was similar to EZE alone (Table 3). Most AEs were mild or moderate in severity. AEs deemed possibly, probably, or definitely related to study drug were least common with ETC-1002 120 mg and most frequent with ETC-1002 180 mg plus EZE. The frequency of AEs resulting in study discontinuation was similar between the ETC-1002 treatment groups and EZE. More statin-intolerant patients (n = 17) experienced AEs resulting in discontinuation than did statin-tolerant patients (n = 3). Four serious AEs were reported (Table 3), 3 of which were unrelated to study drug and did not result in discontinuation (hemothorax with ETC-1002 120 mg, pancreatitis relapse with ETC-1002 180 mg, and transient ischemic attack with EZE). One sudden death of unknown cause in a patient taking ETC-1002 120 mg was deemed possibly related to study drug as a temporal relationship could not be excluded.

Muscle AEs were less frequent and caused fewer discontinuations with ETC-1002 monotherapy than with EZE. In the entire study population, myalgia was the most common muscle-related AE, occurring in 3% of patients treated with ETC-1002 120 mg, 1% with ETC-1002 180 mg, 6% with EZE alone, 8% with ETC-1002 120 mg plus EZE, and 4% with ETC-1002 180 mg plus EZE. Muscle-related AEs were more common among statin-intolerant than statin-tolerant patients (Table 4). The most common muscle-related AE in statin-intolerant patients was myalgia, which was least frequent in the ETC-1002 monotherapy groups.

Overall, no clinically meaningful, dose-related trends in laboratory changes or abnormalities were observed. There also were no clinically meaningful changes in physical examination findings, vital sign measurements, electrocardiogram readings, weight, or waist or ankle circumference measurements. Alanine aminotransferase or aspartate aminotransferase, or both, increased >3 times the upper limit of normal at any measurement in 1 patient treated with ETC-1002 120 mg, 2 patients with ETC-1002 180 mg, 1 patient with EZE, and 1 patient with ETC-1002 120 mg

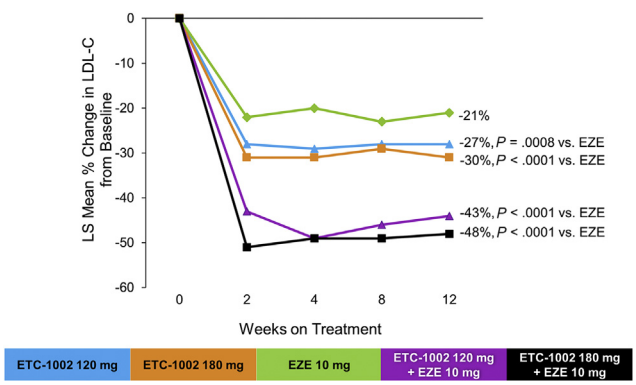


**Figure 3** Percent changes from baseline in LDL-C by treatment group and time. *P* values vs EZE at week 12 endpoint are shown. Week 12 or last observation carried forward is the end-of-study endpoint and differs slightly from week 12 value; *P* values vs EZE monotherapy were determined by an analysis of covariance model with terms for treatment and statin intolerance and baseline value as a covariate. EZE, ezetimibe; LS, least square.

**Table 3** Safety overview: treatment-emergent adverse events

| Adverse events | Safety population | | | | |
|---|---|---|---|---|---|
| | ETC-1002 120 mg, n = 99 | ETC-1002 180 mg, n = 100 | EZE 10 mg, n = 99 | ETC-1002 120 mg + EZE 10 mg, n = 26 | ETC-1002 180 mg + EZE 10 mg, n = 24 |
| Overview | | | | | |
| Any AE(s) | 50 (51) | 55 (55) | 53 (54) | 14 (54) | 17 (71) |
| Serious AE(s)* | 2 (2) | 1 (1) | 1 (1) | 0 | 0 |
| Study drug-related AEs† | 13 (13) | 18 (18) | 19 (19) | 5 (19) | 10 (42) |
| Discontinuation due to AEs | 3 (3) | 6 (6) | 8 (8) | 2 (8) | 1 (4) |
| Most common‡ | | | | | |
| Constipation | 3 (3) | 1 (1) | 1 (1) | 0 | 2 (8) |
| Nasopharyngitis | 3 (3) | 5 (5) | 4 (4) | 0 | 2 (8) |
| Upper respiratory tract infection | 6 (6) | 6 (6) | 1 (1) | 1 (4) | 0 |
| Urinary tract infection | 0 | 4 (4) | 6 (6) | 0 | 1 (4) |
| ALT increased | 0 | 0 | 1 (1) | 2 (8) | 0 |
| AST increased | 0 | 0 | 0 | 2 (8) | 0 |
| Blood CK increased | 1 (1) | 4 (4) | 1 (1) | 2 (8) | 0 |
| Arthralgia | 4 (4) | 1 (1) | 4 (4) | 2 (8) | 1 (4) |
| Back pain | 1 (1) | 1 (1) | 8 (8) | 0 | 0 |
| Myalgia | 3 (3) | 1 (1) | 6 (6) | 2 (8) | 1 (4) |
| Headache | 3 (3) | 2 (2) | 1 (1) | 4 (15) | 0 |

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; EZE, ezetimibe.

Values are n (%).

*Serious AEs included 1 patient with hemothorax and 1 patient with sudden death (ETC-1002,120 mg), pancreatitis relapse (ETC-1002 180 mg), and transient ischemic attack (EZE).

†AEs were categorized as drug related if relationship to study drug was deemed possible, probable, or definite, or if relationship to study drug was not recorded. The most common drug-related AEs were muscle spasms (3%), peripheral edema (2%), myalgia (2%), and muscle weakness (2%) with ETC-1002 120 mg; upper respiratory tract infection (2%), abnormal liver function test (2%), and pruritus (2%) with ETC-1002 180 mg; myalgia (6%), arthralgia (4%), and muscle spasms (3%) with EZE; and increased ALT (8%), increased AST (8%), and myalgia (8%) in the ETC-1002 120 mg plus EZE combination group. No drug-related AE was experienced by $>1$ patient treated with ETC-1002 180 mg plus EZE.

‡Most common AEs were those occurring in $\geq 5\%$ patients/group.

**Table 4** Safety overview: muscle-related treatment-emergent adverse events

| | Safety population | | | | |
|---|---|---|---|---|---|
| Muscle-related AEs by subgroup | ETC-1002 120 mg | ETC-1002 180 mg | EZE 10 mg | ETC-1002 120 mg + EZE 10 mg | ETC-1002 180 mg + EZE 10 mg |
| Statin-intolerant patients | (n = 51) | (n = 51) | (n = 51) | (n = 12) | (n = 12) |
| Overview of muscle-related AEs | | | | | |
| Any muscle-related AE | 7 (14) | 6 (12) | 9 (18) | 2 (17) | 2 (17) |
| Leading to discontinuation | 1 (2) | 2 (4) | 5 (10) | 0 | 0 |
| Muscle-related AEs by MedDRA preferred term* | | | | | |
| Muscle spasms | 3 (6) | 2 (4) | 1 (2) | 0 | 0 |
| Muscular weakness | 2 (4) | 1 (2) | 1 (2) | 0 | 0 |
| Musculoskeletal chest pain | 0 | 1 (2) | 0 | 0 | 0 |
| Musculoskeletal stiffness | 0 | 0 | 1 (2) | 0 | 0 |
| Myalgia | 2 (4) | 1 (2) | 6 (12) | 2 (17) | 1 (8) |
| Pain in extremity | 1 (2) | 1 (2) | 3 (6) | 0 | 1 (8) |
| Sensation of heaviness | 0 | 0 | 1 (2) | 0 | 0 |
| Statin-tolerant patients | n = 48 | n = 49 | n = 48 | n = 14 | n = 12 |
| Overview of muscle-related AEs | | | | | |
| Any muscle-related AE | 1 (2) | 0 | 3 (6) | 0 | 1 (8) |
| Leading to discontinuation | 0 | 0 | 1 (2) | 0 | 0 |
| Muscle-related AEs by MedDRA preferred term* | | | | | |
| Muscle spasms | 0 | 0 | 2 (4) | 0 | 1 (8) |
| Musculoskeletal pain | 0 | 0 | 1 (2) | 0 | 0 |
| Myalgia | 1 (2) | 0 | 0 | 0 | 0 |

AE, adverse event; EZE, ezetimibe; MedDRA, *Medical Dictionary for Regulatory Activities*, version 16.0.

Values are n (%).

*Prespecified analysis of all musculoskeletal and connective tissue disorders AE terms except arthralgia, back pain, bone pain, bunion, bursitis, groin pain, intervertebral degeneration, intervertebral disc protrusion, joint stiffness, joint swelling, neck pain, osteoarthritis, plantar fasciitis, rotator cuff syndrome, and synovial cyst.

plus EZE. One patient treated with ETC-1002 120 mg plus EZE experienced a CK level >10 times the upper limit of normal, which occurred after heavy physical exertion and was accompanied by myalgia.

## Discussion

In this phase 2b study, ETC-1002 alone reduced LDL-C up to 30%, which was significantly greater than the reduction achieved with EZE monotherapy. The greatest mean reductions in LDL-C, which reached 43% and 48%, occurred with the combination of ETC-1002 120 mg or 180 mg with EZE, respectively. The decreases in LDL-C with ETC-1002, EZE, and the combination occurred within 2 weeks of treatment and were maintained throughout the study. LDL-C reductions in statin-intolerant patients appeared similar to those in statin-tolerant patients. This finding is noteworthy considering that statin-intolerant patients had a higher baseline risk for cardiovascular disease than did statin-tolerant patients, with 28% vs 12% classified as "high" or "very high" risk per NCEP ATP III criteria, respectively.

ETC-1002 alone or with EZE also reduced secondary lipid endpoints including non–HDL-C, total cholesterol, apolipoprotein B, and LDL particle number significantly more than EZE alone. CRP decreased more with ETC-1002 alone and ETC-1002 180 mg plus EZE than with EZE alone. There were no significant differences between ETC-1002 and EZE for triglycerides, HDL particle number, and VLDL particle number, but ETC-1002 did reduce HDL-C slightly.

ETC-1002 120 mg and ETC-1002 180 mg were well tolerated both alone and combined with EZE 10 mg daily, and safety profiles were similar across all treatment groups. Frequencies of muscle-related AEs were low in all treatment groups and more common in patients with a history of statin intolerance. The greater LDL-C–lowering effect of ETC-1002 vs EZE did not produce more muscle-related AEs. Rather, rates of muscle-related AEs were slightly lower with ETC-1002 monotherapy than with EZE alone.

This is the first clinical study to assess ETC-1002 combined with EZE, the agent most commonly prescribed for patients with statin intolerance.[5] The incremental LDL-C reduction with combination therapy is likely due to the complementary mechanisms of action of the 2 drugs: inhibition of hepatic cholesterol synthesis with ETC-1002[7,8] and inhibition of intestinal cholesterol absorption with EZE.[13] The 43% to 48% reduction in LDL-C with ETC-1002 120 mg or 180 mg plus EZE is comparable to the 42% to 56% LDL-C reduction observed when EZE is combined with moderate-dose statins[13] and to the ≥50% reduction with high-intensity statin monotherapy.[6]

The results from this study are consistent with findings from earlier studies comparing ETC-1002 with placebo. ETC-1002 in doses up to 120 mg daily reduced LDL-C by 27% in patients with hypercholesterolemia treated for 12 weeks[10] and by 43% in diabetic patients with hypercholesterolemia treated for 4 weeks.[11] ETC-1002 was well tolerated in these trials, with an AE profile similar to placebo.[10,11] In a trial of 56 hypercholesterolemic patients with a history of statin-associated muscle complaints treated for 8 weeks, ETC-1002 in doses up to 240 mg daily reduced LDL-C by 32% from baseline ($P < .0001$ compared with placebo).[12] Muscle-related AEs occurred with similar frequency with ETC-1002 and placebo and caused no discontinuations in the ETC-1002–treated patients.[12] Reductions in CRP achieved with ETC-1002 monotherapy in the present study (up to 40%) also were observed in previous studies (41% to 42%).[11,12]

Patients with a history of statin-associated muscle symptoms are difficult to treat. Current recommendations for the management of patients with statin-associated muscle symptoms include the use of maximally tolerated statins combined with nonstatin lipid-lowering therapies as needed.[4,14] EZE has been shown to reduce LDL-C by 16% to 17% in statin-intolerant patients[15,16] and is recommended for statin-intolerant patients, as are bile acid sequestrants, which may be poorly tolerated and fenofibrate.[4,14] Colesevelam[17] and fenofibrate[18] can reduce LDL-C by approximately 20% in hypercholesterolemic patients but have not to our knowledge been studied in patients with statin-associated muscle symptoms. The investigational proprotein convertase subtilisin/kexin type 9 inhibitors may offer a future therapeutic alternative for patients with statin-associated muscle complaints.[4] Evolocumab lowered LDL-C up to 56% after 12 weeks of treatment in statin-intolerant patients,[19] and alirocumab lowered LDL-C by 45% after 24 weeks of treatment in statin-intolerant patients.[20]

There are limitations to the present study. The overall sample size was relatively small, and the combination treatment group was 25% the size of the monotherapy groups. This design was used because the primary goal was to compare LDL-C effects between ETC-1002 (120 mg or 180 mg) and EZE monotherapy. The study did not include a placebo group but used EZE as an active comparator because it is commonly prescribed to statin-intolerant patients. Baseline triglyceride and CRP levels differed among the treatment groups, and the effect of these differences is unknown. Some study participants were statin tolerant, but this diagnosis was not tested with a statin-treatment arm.

## Conclusion

There is a need for alternative oral treatment strategies for hypercholesterolemic patients who cannot sufficiently reduce their LDL-C with available agents, including patients with intolerance to statins.[1,21] The results of this study suggest that ETC-1002 with or without EZE may be a useful treatment in patients with hypercholesterolemia, including those who are unable to tolerate statins because of muscle side effects.

## Acknowledgment

The authors thank all investigators, their staffs, and all patient volunteers. We also thank Medpace Inc., of Cincinnati, OH, for their oversight of patient randomization, clinical laboratory services, statistical analyses, clinical monitoring, data management, clinical programming, and medical writing.

The authors thank Darlene J. Benson, RPh, ELS, and Lamara D. Shrode, PhD, CMPP, of The JB Ashtin Group, Inc., for assistance in preparing this article for publication based on the authors' input and direction.

## Financial disclosure

The design, study conduct, analysis, and financial support of this clinical trial were provided by Esperion Therapeutics, Inc. Esperion participated in the interpretation of data, review, and approval of the publication. All authors contributed to the development of the content; reviewed and approved the article; and maintained control over the final content. Dr Thompson has received research support from Genomas, Sanofi, Regeneron, Esperion, Amarin, and Pfizer. He has served as a consultant for Amgen, Regeneron, Merck, Genomas, Sanofi, Esperion, and Amarin and has received speaker honoraria from Merck, AstraZeneca, Amgen, and Regeneron. In addition, he owns stock in AbbVie Inc., Abbott Labs, General Electric, and Johnson & Johnson. He has also provided expert legal testimony on exercise-related cardiac events and statin myopathy. Dr Orloff has no relationship with industry to declare. Dr McKenney is an employee of National Clinical Research, which has received funding for lipid-modifying research from Sanofi, Regeneron, Esperion Therapeutics, Merck, Amgen, Pfizer, and Lilly and consulting fees from Merck. Dr Ballantyne has received grant and/or research support from Abbott Diagnostic, Amarin, Amgen, Eli Lilly, Esperion Therapeutics, Novartis, Pfizer, Otsuka, Regeneron, Roche Diagnostic, Sanofi-Synthelabo, Takeda, NIH, AHA, and ADA. He has served as a consultant for Abbott Diagnostics, Amarin, Amgen, AstraZeneca, Eli Lilly, Esperion, Genzyme, Matinas BioPharma Inc, Merck, Novartis, Pfizer, Regeneron, Roche, and Sanofi-Synthelabo. Mr Hanselman, Ms MacDougall, Ms Margulies, and Dr Newton are full-time employees of Esperion Therapeutics, Inc.

## References

1. Guyton JR, Bays HE, Grundy SM, Jacobson TA. An assessment by the Statin Intolerance Panel: 2014 update. *J Clin Lipidol*. 2014;8(Suppl 3): S72–S81.
2. Ito MK, Maki KC, Brinton EA, et al. Muscle symptoms in statin users, associations with cytochrome P450, and membrane transporter inhibitor use: a subanalysis of the USAGE study. *J Clin Lipid*. 2014;8: 69–76.
3. Parker BA, Capizzi JA, Grimaldi AS, et al. Effect of statins on skeletal muscle function. *Circulation*. 2013;127:96–103.
4. Stroes ES, Thompson PD, Corsini A, et al. European Atherosclerosis Society Consensus Panel. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J*. 2015;36:1012–1022.
5. Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. *Am Heart J*. 2013;166:597–603.
6. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B): 2889–2934.
7. Pinkosky SL, Filippov S, Srivastava RA, et al. AMP-activated protein kinase and ATP-citrate lyase are two distinct molecular targets for ETC-1002, a novel small molecule regulator of lipid and carbohydrate metabolism. *J Lipid Res*. 2013;54:134–151.
8. Filippov S, Pinkosky SL, Newton RS. LDL-cholesterol reduction in patients with hypercholesterolemia by modulation of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase. *Curr Opin Lipidol*. 2014;25:309–315.
9. Berkhout TA, Havekes LM, Pearce NJ, Groot PH. The effect of (-)-hydroxycitrate on the activity of the low-density-lipoprotein receptor and 3-hydroxy-3-methylglutaryl-CoA reductase levels in the human hepatoma cell line Hep G2. *Biochem J*. 1990;272: 181–186.
10. Ballantyne CM, Davidson MH, MacDougall DE, et al. Efficacy and safety of a novel dual modulator of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase in patients with hypercholesterolemia: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. *J Am Coll Cardiol*. 2013;62:1154–1162.
11. Gutierrez MJ, Rosenberg NL, MacDougall DE, et al. Efficacy and safety of ETC-1002, a novel investigational low-density lipoprotein-cholesterol-lowering therapy for the treatment of patients with hypercholesterolemia and type 2 diabetes mellitus. *Arterioscler Thromb Vasc Biol*. 2014;34:676–683.
12. Thompson PD, Rubino J, Janik MJ, et al. Use of ETC-1002 to treat hypercholesterolemia in patients with statin intolerance. *J Clin Lipidol*. 2015;9:295–304.
13. Ezetimibe (Zetia) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2013.
14. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA. An assessment by the Statin Muscle Safety Task Force: 2014 update. *J Clin Lipidol*. 2014;8(Suppl 3):S58–S71.
15. Stein EA, Ballantyne CM, Windler E, et al. Efficacy and tolerability of fluvastatin XL 80 mg alone, ezetimibe alone, and the combination of fluvastatin XL 80 mg with ezetimibe in patients with a history of muscle-related side effects with other statins. *Am J Cardiol*. 2008; 101:490–496.
16. Saougos VG, Tambaki AP, Kalogirou M, et al. Differential effect of hypolipidemic drugs on lipoprotein-associated phospholipase A2. *Arterioscler Thromb Vasc Biol*. 2007;27:2236–2243.
17. Davidson MH, Dillon MA, Gordon B, et al. Colesevelam hydrochloride (cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. *Arch Intern Med*. 1999;159:1893–1900.
18. Knopp RH, Brown WV, Dujovne CA, et al. Effects of fenofibrate on plasma lipoproteins in hypercholesterolemia and combined hyperlipidemia. *Am J Med*. 1987;83:50–59.
19. Stroes E, Colquhoun D, Sullivan D, et al, GAUSS-2 Investigators. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol*. 2014;63: 2541–2548.

20. Moriarty PM, Thompson PD, Cannon CP, et al. ODYSSEY ALTERNATIVE: efficacy and safety of the proprotein convertase subtilisin/-kexin type 9 monoclonal antibody, alirocumab, versus ezetimibe, in patients with statin intolerance as defined by a placebo run-in and statin rechallenge arm. Presented at: American Heart Association 2014 Scientific Sessions; November 17, 2014; Chicago, IL.
21. Kane JP. New horizons in lipid management. *J Am Coll Cardiol*. 2013; 62:1163–1164.