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

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Objective—8-Hydroxy-2,2,14,14-tetramethylpentadecanedioic acid (ETC-1002) is a small molecule with a unique mechanism of action shown in nonclinical studies to modulate pathways of cholesterol, fatty acid, and carbohydrate metabolism. In previous phase 2 clinical trials, once daily oral treatment with ETC-1002 significantly reduced low-density lipoprotein-cholesterol in patients with hypercholesterolemia. In this trial, the lipid-lowering efficacy of ETC-1002 was evaluated in patients with type 2 diabetes mellitus and hypercholesterolemia. Additional cardiometabolic biomarkers, including glycemic measures, were also assessed.

Approach and Results—A single-center, double-blind, placebo-controlled trial evaluated 60 patients with type 2 diabetes mellitus and elevated low-density lipoprotein-cholesterol. Patients discontinued all diabetes mellitus and lipid-regulating drugs and were randomized to receive ETC-1002 80 mg QD for 2 weeks followed by 120 mg QD for 2 weeks or placebo for 4 weeks. ETC-1002 lowered low-density lipoprotein-cholesterol levels by 43±2.6% (least squares mean±SE), compared with a reduction of 4±2.5% by placebo at day 29 (P<0.0001; primary end point). Non–high-density lipoprotein-cholesterol and total cholesterol were also significantly lowered by ETC-1002 compared with placebo (P<0.0001). High-sensitivity C-reactive protein was reduced by 41% (median) compared with a placebo reduction of 11% (P=0.0011). No clinically meaningful safety findings were observed.

Conclusions—ETC-1002 lowered low-density lipoprotein-cholesterol and other lipids and demonstrated improvement in high-sensitivity C-reactive protein in patients with type 2 diabetes mellitus and hypercholesterolemia without worsening glycemic control. ETC-1002 was well tolerated in this population.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT# 01607294.

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Key Words: cardiovascular diseases ■ lipid and lipoprotein metabolism ■ low-density lipoprotein-cholesterol ■ risk factors ■ type 2 diabetes mellitus

Patients with type 2 diabetes mellitus (T2DM) are at higher risk for cardiovascular disease (CVD)[1–3] and many fail to achieve their low-density lipoprotein-cholesterol (LDL-C) goal on statin therapy.[4–6] The use of statins in patients with diabetes mellitus is supported by a large body of clinical data demonstrating reduced risk for CVD. However, recently published meta-analyses of clinical studies suggest an increased risk for worsening of glycemic control and new onset diabetes mellitus associated with statin use, which presents a challenge to effective LDL-C lowering for diabetics.[7–12] In 2012, the Food and Drug Administration required that language be added to statin labels reporting increases in hemoglobin A1C and fasting serum glucose.[13] A therapy demonstrating substantial lowering of LDL-C with neutral to beneficial effects on glycemic control and additional CVD risk factors in patients with T2DM is not currently available.

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ETC-1002 (8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid) is currently in phase 2 clinical development to treat hypercholesterolemia, with early evidence for favorable effects on other cardiometabolic biomarkers, such as insulin sensitivity, inflammation, and high blood pressure. Nonclinical studies show that ETC-1002 modulates 2 distinct and complementary molecular targets regulating lipid homeostasis: hepatic ATP-citrate lyase and AMP-activated protein kinase (Figure 1).[14] Inhibition of ATP-citrate lyase by ETC-1002 rapidly reduces levels of acetyl-CoA, the final common

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Nonstandard Abbreviations and Acronyms

BMI	body mass index
CI	confidence interval
CVD	cardiovascular disease
LDL-C	low-density lipoprotein-cholesterol
T2DM	type 2 diabetes mellitus

substrate for both fatty acid and sterol synthesis, at a point in the lipid synthesis pathway upstream of 3-hydroxy-3-methyl-glutaryl-CoA reductase, the molecular target of statins. In addition, ETC-1002–mediated AMP-activated protein kinase activation reduces lipid synthesis, regulates carbohydrate metabolism, and reduces inflammation and adiposity in non-clinical studies.[14,15] Thus, ETC-1002, via effects at multiple points, regulates hepatic lipid homeostasis and has favorable effects on glucose regulation in animal models.[15–18]

A previous phase 2 placebo-controlled trial in 177 patients with hypercholesterolemia (baseline LDL-C between 130 and 220 mg/dL), with or without elevated triglyceride levels, showed a dose-related, statistically significant lowering of LDL-C levels up to 27±2.2% (least squares mean±SE) after 12 weeks of treatment with ETC-1002 compared with a 2.1±2.2% decrease with placebo (P<0.0001).[19] The aim of this phase 2, placebo-controlled, double-blind, parallel group trial was to evaluate the lipid-altering effects of ETC-1002 in patients with both elevated LDL-C (≥100 mg/dL) and T2DM.

Materials and Methods

Materials and Methods are available in the online-only Supplement.

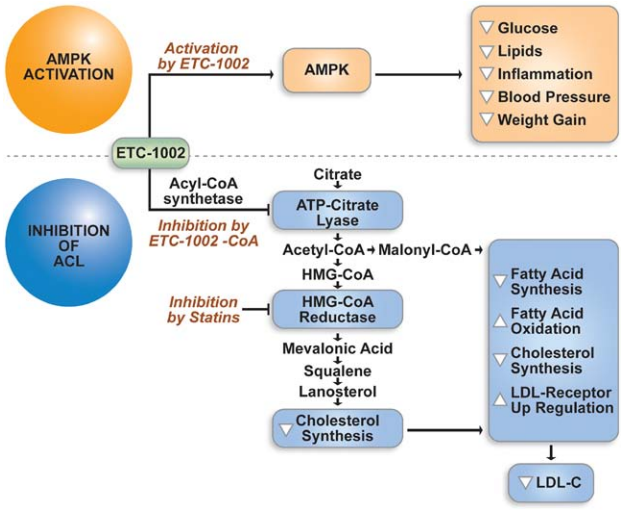

Figure 1. Dual mechanism of action of ETC-1002 AMP-activated protein kinase (AMPK) activation and ATP-citrate lyase (ACL) inhibition. ETC-1002 inhibits ACL to reduce cholesterol synthesis resulting in the reduction of low-density lipoprotein-cholesterol (LDL-C). ETC-1002 also activates AMPK. This pathway has known effects on glucose, lipids, inflammation, blood pressure, and weight gain. Adapted from Pinkosky et al[14] with permission of the publisher. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. HMG-CoA indicates 3-hydroxy-3-methyl-glutaryl-CoA reductase.

Table 1. Demographic, Baseline, and Disease Characteristics

Parameter	ETC-1002 (n=30)	Placebo (n=30)
Age, y, mean (SD)	55.3 (6.9)	56.0 (9.9)
Sex, n (%), men	17 (56.7)	20 (66.7)
Race, n (%), white	29 (96.7)	28 (93.3)
Ethnicity, n (%), Hispanic, or Latino	30 (100)	29 (96.7)
Weight, kg,† mean (SD)	82.6 (14.6)	80.3 (10.0)
Height, cm, mean (SD)	163.6 (10.2)	165.7 (8.4)
Body mass index, kg/m^2, mean (SD)	30.6 (3.0)	29.2 (3.0)
Body mass index, ≥30 kg/m^2, n (%)	19 (63.3)	12 (40.0)
Baseline fasting lipid parameters		
Calculated LDL-C, mg/dL,*† mean (SD)	125.2 (27.5)	128.4 (28.5)
Total cholesterol, mg/dL,† mean (SD)	206.3 (36.1)	206.7 (34.1)
HDL-C, mg/dL,† mean (SD)	43.7 (10.1)	47.4 (11.8)
Triglyceride, mg/dL,† median (min, max)	181.5 (86, 572)	152.0 (81, 248)
Inflammation biomarker		
hsCRP, mg/L,‡ median (min, max)	2.3 (0.2, 12.5)	2.2 (0.4, 13.1)
Baseline fasting glycemic parameters		
Plasma glucose, mg/dL,† mean (SD)	185.9 (27.4)	198.1 (32.1)
Insulin, μIU/mL,† mean (SD)	11.7 (6.1)	12.9 (11.9)
Fructosamine,‡ mean (SD)	351.8 (43.5)	348.4 (45.5)
HbA1C, %,§ mean (SD)	8.0 (0.73)	8.2 (0.91)
Baseline blood pressure measurements		
Cuff SBP, mm Hg,†‖ mean (SD)	117.0 (9.6)	119.7 (13.1)
Cuff DBP, mm Hg,†‖ mean (SD)	76.9 (5.8)	77.5 (5.9)
Hypertension as ongoing medical history		
Hypertension at baseline, n (%)	8 (26.7)	8 (26.7)
Diabetes mellitus characteristics		
Diabetes mellitus duration, y, median (min, max)	7.0 (2.5, 31.6)	7.45 (2.0, 12.6)
Diabetes mellitus duration categories, n (%)		
0–5 y	7 (23.3)	9 (30.0)
>5–10 y	13 (43.3)	14 (46.7)
>10 y	10 (33.3)	7 (23.3)
No. of prior diabetes mellitus therapies, n (%)		
0	0	2 (6.7)
1	30 (100)	28 (93.3)
Type of prior diabetes mellitus therapies, n (%)		
Metformin	29 (96.7)	28 (93.3)
Sulfonylurea	1 (3.3)	0
No prior therapies indicated	0	2 (6.7)

DBP indicates diastolic blood pressure; HbA1C, hemoglobin A1C; HDL-C, high-density lipoprotein-cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein-cholesterol; and SBP, systolic blood pressure.

*n=30 except for LDL-C in which 1 patient from the ETC-1002 group had no baseline.

†Baseline is defined as the mean of the values from days −1 to 1.

‡Baseline is defined as the value from day 1.

§Baseline is defined as the value from day −1.

‖Blood pressure was measured in triplicate with the first measurement dropped and the mean of the second 2 calculated.

Table 2. Percentage Change From Baseline to Day 29 in Additional Secondary Fasting Lipid Parameters

Treatment Group	n	Baseline,* Mean (SE)	Day 29,† Mean (SE)	LS Mean Percentage Change‡ (SE)	Difference From Placebo (95% CI)	*P* Value
Primary end point–LDL-C, mg/dL						
ETC-1002	29§	125.2 (5.1)	71.9 (4.7)	−42.9 (2.6)	−39.0 (−46.2, −31.7)	<0.0001
Placebo	30	128.4 (5.2)	121.6 (4.9)	−4.0 (2.5)	…	…
Secondary end points						
Non–HDL-C, mg/dL						
ETC-1002	30	162.9 (6.3)	111.0 (6.0)	−32.0 (2.3)	−31.4 (−38.0, −24.8)	<0.0001
Placebo	30	159.8 (6.1)	157.7 (6.2)	−0.5 (2.3)	…	…
Total cholesterol, mg/dL						
ETC-1002	30	206.3 (6.6)	154.2 (5.9)	−25.1 (1.9)	−24.6 (−29.9, −19.4)	<0.0001
Placebo	30	206.7 (6.2)	204.8 (6.5)	−0.5 (1.9)	…	…
HDL-C, mg/dL						
ETC-1002	30	43.7 (1.8)	43.2 (1.9)	−1.2 (1.8)	−1.8/(−6.9, 3.4)	0.4965
Placebo	30	47.4 (2.2)	47.1 (2.0)	0.5 (1.8)	…	…

All analyses were performed in the mITT population. CI indicates confidence interval; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LS, least squares; and mITT, modified intent to treat.

*Baseline is defined as the mean of the values from days −1 to 1.

†Missing values at day 29 were imputed using the last observation carried forward procedure (only postbaseline values were carried forward).

‡LS mean percentage change from baseline to day 29 based on ANCOVA model with effect of treatment and baseline value as a covariate.

§One patient from the ETC-1002 group had no baseline LDL-C value (because of an error processing the sample with triglyceride >400 mg/dL) and was excluded from the mITT population for that end point but was included in the mITT population for other efficacy end points.

Results

Baseline, Demographic, and Disease Characteristics

Baseline and demographic characteristics were generally similar between the 2 groups. The mean body mass index (BMI) was slightly higher in the ETC-1002 group than in the placebo group (30.6 versus 29.2 kg/m^2), corresponding to a greater number of patients with BMI ≥30 kg/m^2 (19 versus 12; Table 1). Nearly all patients were receiving diabetes mellitus therapy (97%) before the trial, most commonly metformin monotherapy (95%). Hypertension was the most frequently reported additional medical condition, occurring in 8 patients in each group.

Mean baseline lipid parameters for fasting calculated LDL-C were similar between the 2 groups (ETC-1002, 125.2 mg/dL and placebo, 128.4 mg/dL). Median fasting triglyceride was higher in the ETC-1002 group than in the placebo group (181.5 versus 152.0 mg/dL; Table 1). The median high-sensitivity C-reactive protein levels were similar in the ETC-1002 and the placebo groups. Comparison of baseline glycemic parameters showed a lower mean fasting plasma glucose level in the ETC-1002 group compared with placebo (185.9 versus 198.1 mg/dL). The baseline mean values were similar between the 2 groups for the other fasting glycemic markers tested, including insulin, hemoglobin A1C, and fructosamine.

Table 3. Percentage Change From Baseline to Day 29 in Primary and Secondary Fasting Lipid Parameters

Treatment Group	n	Baseline* Median	Day 29† Median	Median Percentage Change‡	*P* Value
Triglycerides, mg/dL					
ETC-1002	30	181.5	168.0	−1.0	0.1219
Placebo	30	150.2	171.5	8.0	…
Free fatty acids, mEq/L					
ETC-1002	30	0.430	0.395	−2.0	0.1013
Placebo	30	0.450	0.455	2.5	…

All analyses were performed in the modified intent-to-treat population.

*Baseline is defined as the mean of the values from days −1 to 1.

†Missing values at day 29 were imputed using the last observation carried forward procedure (only postbaseline values were carried forward). Least squares mean percentage change from baseline to day 29 based on ANCOVA model with effect of treatment and baseline value as a covariate.

‡Because of the skewed distributions of the triglyceride and free fatty acids values, a nonparametric analysis, the Cochran–Mantel–Haenszel test in rank ANCOVA, was performed.

Primary and Other Efficacy End Points

Lipid End Points

Using prespecified ANCOVA models, significant reductions in LDL-C as well as several other fasting lipid parameters were observed after treatment with ETC-1002 compared with placebo (Tables 2 and 3; Figure 2A). At day 29, LDL-C was reduced by 42.9% (least squares mean percentage change from baseline) for the ETC-1002 group compared with 4.0% for the placebo group. The difference in the reduction for the ETC-1002 group compared with placebo (the primary end point) was 39.0%, which was highly statistically significant (95% confidence interval [CI], −46.2, −31.7; P<0.0001). A similar analysis was performed at day 15, which assessed the effect of the 80 mg QD dosage. The magnitude of LDL-C

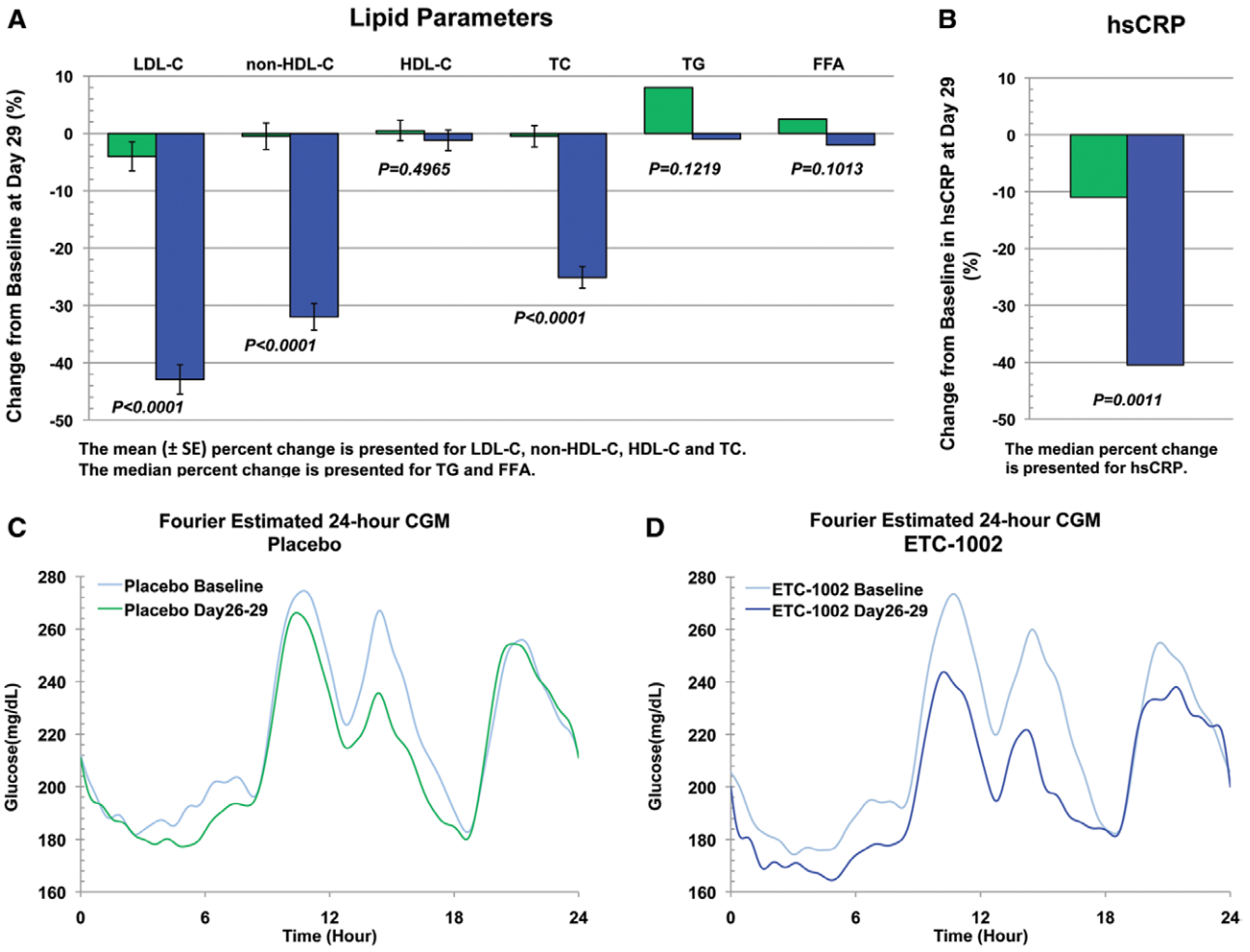

Figure 2. Change from baseline in lipids, high-sensitivity C-reactive protein (hsCRP), and continuous glucose monitoring (CGM) daily peak glucose for ETC-1002–treated and placebo patients. Blue indicates ETC-1002–treated patients (n=30 for all parameters except n=29 for low-density lipoprotein-cholesterol [LDL-C]) and green indicates placebo patients (n=30). The primary end point for this study, LDL-C, was decreased by 43% in the ETC-1002 group compared with 4% for the placebo group (P<0.0001). **A**, Mean (±SE) or median percentage change from baseline to day 29 for various lipid parameters. **B**, Median percentage change from baseline to day 29 for hsCRP. Fourier estimated 24-hour CGM glucose at baseline and day 26 to 29 in (**C**) placebo and (**D**) ETC-1002–treated patients. FFA indicates free fatty acids; HDL-C, high-density lipoprotein-cholesterol; TC, total cholesterol; and TG, triglyceride.

lowering seemed to be dose related and the difference from placebo remained highly significant (difference, −26.6% [95% CI, −32.5, −20.7; P<0.0001]).

Reductions in LDL-C at day 29 occurred in all ETC-1002 patients across a broad range of individual baseline LDL-C and triglyceride values (Figure 3). Twenty-five of 29 patients (86%) treated with ETC-1002 had a 30% or greater reduction in LDL-C, whereas 9 patients (31%) had a 50% or greater reduction.

The ETC-1002–treated group also showed significant mean percentage reductions versus placebo at day 29 in non–high-density lipoprotein-cholesterol (difference, −31.4 [95% CI, −38.0, −24.8; P<0.0001]) and total cholesterol (difference, −24.6 [95% CI, −29.9, −19.4; P<0.0001]; Tables 2 and 3; Figure 2A). Levels of triglyceride, high-density lipoprotein-cholesterol, and free fatty acids did not change significantly with ETC-1002-treatment (Tables 2 and 3; Figure 2A). ETC-1002 treatment reduced high-sensitivity C-reactive protein by 40.5% (median percentage reduction from baseline) compared with 11.0% with placebo at day 29 (P=0.0011; Figure 2B).

Glycemic End Points

ETC-1002 treatment did not result in a worsening of glycemic control. A nonsignificant reduction of all prespecified glycemic markers was observed at day 29 with ETC-1002 treatment compared with placebo (Table 4). These included fasting plasma glucose concentrations (mean change compared with placebo, −8.5 mg/dL) and postprandial measures; 15-hour weighted mean plasma glucose (−14.3 mg/dL) and morning postprandial plasma glucose area under the concentration–time curve from time 0 to 4 hours after the glucose meal tolerance test standardized meal (−79.2 mg·h/dL). A 24-hour continuous glucose monitoring assessment showed a nonsignificant trend of improved glycemic control with ETC-1002 treatment, particularly associated with reduced postprandial meal peaks compared with placebo (Figure 2C and 2D).

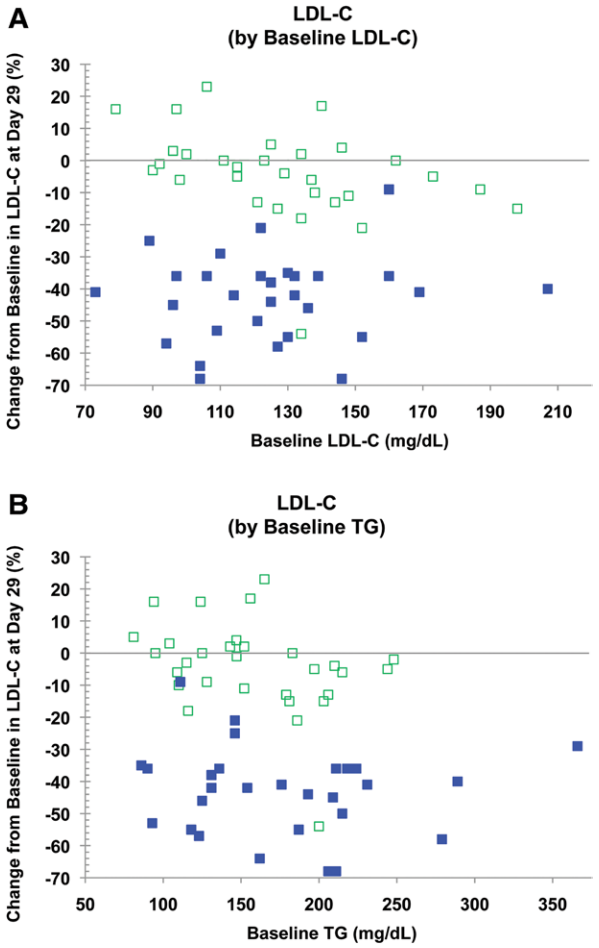

Figure 3. Reductions in low-density lipoprotein-cholesterol (LDL-C) in individual patients with ETC-1002 treatment. Blue-solid indicates ETC-1002–treated patients (n=29) and green-open indicates placebo patients (n=30). Reductions in LDL-C were observed in all ETC-1002-treated patients regardless of (**A**) baseline LDL-C or (**B**) baseline triglyceride (TG) levels.

Post hoc analysis showed a significant reduction of daily peak glucose with ETC-1002 treatment compared with placebo (−24.4 mg/dL) between the hours of 6 AM and 12 PM (with breakfast; 95% CI, −46.3, −2.5; *P*=0.0295). Nonsignificant trends were also observed in peak glucose between the hours of 12 PM to 6 PM (with lunch; difference, −15.6 mg/dL) and 6 PM to 12 AM (with dinner; difference, −19.5 mg/dL).

Further post hoc analysis of the 5 measured glycemic end points in obese patients (BMI≥30 kg/m^2) showed a similar nonsignificant trend toward improvement with ETC-1002 treatment as was seen in the overall patient population (Table II in the online-only Data Supplement). This reached statistical significance for mean reduction in postprandial plasma glucose area under the concentration–time curve from time 0 to 4 hours in the ETC-1002 group compared with placebo group after a glucose meal tolerance test (difference, −157.0 mg·h/dL [95% CI, −292.3, −21.6; *P*=0.0246]).

Blood Pressure

Most patients had well-controlled blood pressure at baseline, as uncontrolled blood pressure (systolic blood pressure, ≥150 mm Hg or diastolic blood pressure, ≥100 mm Hg) was an exclusion criteria. Overall 24-hour ambulatory blood pressure monitoring showed no differences between treatment groups in mean changes from baseline to day 28 (Table III in the online-only Data Supplement).

A post hoc analysis of a subgroup of patients with mild elevation in diastolic blood pressure at baseline (>80 mm Hg) showed that treatment with ETC-1002 (n=5) decreased diastolic blood pressure compared with placebo (n=4) on day 28 (difference, −7.3 mm Hg [95% CI, −14.6, −0.1; *P*=0.0474]). In a similar post hoc analysis of patients with mild elevation in systolic blood pressure at baseline (>120 mm Hg), treatment with ETC-1002 (n=13) trended toward a decrease in systolic blood pressure compared with placebo (n=17) on day 28 (difference, −2.4 mm Hg [95% CI, −7.3, 2.5; *P*=0.3271]).

Safety

ETC-1002 was generally safe and well tolerated in this trial. The number of adverse events reported and the percentage of patients with adverse events in the ETC-1002 group (45 events in 14 patients [47%]) were lower than those in the placebo group (52 events in 21 patients [70%]; Table 5). The most frequently reported adverse event was hyperglycemia, a potential consequence of discontinuation of diabetes mellitus medications before dosing, which occurred in almost twice the number of patients in the placebo group compared with the ETC-1002 group (10 versus 6 patients). Other adverse events, occurring more frequently in the ETC-1002–treated group compared with placebo, were headache (in 6 and 3 patients, respectively) and constipation (in 2 and no patients, respectively). Of note, no patient dosed with ETC-1002, or with placebo, reported myalgia. The majority of adverse events were mild in severity and all adverse events were resolved by the end of the trial. One patient in the placebo group discontinued because of myocardial infarction (Table I in the online-only Data Supplement).

Mean changes from baseline to day 29 in most clinical chemistry or hematology parameters were similar for the ETC-1002 and placebo groups, with the exception of the following changes with ETC-1002 treatment: mild to moderate mean increases in uric acid and homocysteine and mild decreases in alkaline phosphatase and hemoglobin (Table IV in the online-only Data Supplement). No clinical sequelae or interventions were associated with these laboratory findings. Evaluation of clinical chemistry laboratory parameters of particular interest to LDL-C–lowering drugs (alanine transaminase, aspartate aminotransferase, total bilirubin, creatinine, and creatine kinase) showed no clinically meaningful changes compared with baseline (Table IV in the online-only Data Supplement). Abnormal liver function tests of >3× the upper limit of normal or creatine kinase levels of >5× upper limit of normal were not observed in patients treated with ETC-1002.

Results for ECGs, vital signs, waist and ankle circumference, and physical examinations showed no dose-limiting, clinically meaningful trends. Interestingly, the mean decreases from baseline in weight and waist circumference were numerically greater in the ETC-1002 group than in the placebo group. The mean (SD) decrease of weight on day 29 was −1.4 kg (1.53) for the ETC-1002 group compared with −0.9 kg (1.07) decrease for the placebo group. A post hoc subgroup analysis

Table 4. Change From Baseline to End Point (Day 28 or 29) in Glycemic Markers

Treatment Group	n	Baseline,* Mean (SE)	End Point,† Mean (SE)	LS Mean Change,‡ (SE)	Difference From Placebo (95% CI)	*P* Value
Fasting plasma glucose, mg/dL						
ETC-1002	30	185.9 (5.0)	171.4 (7.0)	−15.9 (5.7)	−8.5 (−24.9, 8.0)	0.3068
Placebo	30	198.1 (5.9)	189.3 (7.1)	−7.4 (5.7)	…	…
Fasting insulin, μIU/mL						
ETC-1002	30	11.7 (1.1)	12.0 (0.9)	0.1 (1.0)	−2.0 (−4.8, 0.9)	0.1701
Placebo	30	12.9 (2.2)	14.8 (2.2)	2.1 (1.0)	…	…
Fasting fructosamine, μmol/L						
ETC-1002	30	351.8 (8.0)	344.4 (8.6)	−1.8 (1.5)	−3.8 (−8.1, 0.5)	0.0800
Placebo	30	348.4 (8.3)	356.0 (10.0)	2.1 (1.5)	…	…
15-h weighted mean plasma glucose, mg/dL						
ETC-1002	30	223.4 (6.1)	201.2 (8.7)	−23.4 (6.5)	−14.3 (−32.7, 4.2)	0.1265
Placebo	30	233.9 (8.0)	223.5 (8.1)	−9.2 (6.5)	…	…
$AUC_{0\text{-}4\ h}$ after the morning GMTT, mg·h/dL						
ETC-1002	30	1011.7 (31.9)	889.0 (44.8)	−130.3 (34.8)	−79.2 (−177.9, 19.6)	0.1138
Placebo	30	1052.6 (38.7)	993.8 (36.7)	−51.2 (34.8)	…	…

$AUC_{0\text{-}4\ h}$ indicates area under the concentration-time curve from time 0 to 4 hours; CI, confidence interval; GMTT, glucose meal tolerance test; and LS, least squares.

*Baseline is defined as the mean of the values from days −1 and 1 for plasma glucose and insulin, the value from day −1 for 15-hour weighted mean plasma glucose and postprandial plasma glucose $AUC_{0\text{-}4\ h}$, or the value from day 1 for fructosamine.

†The end point was day 29 for plasma glucose, insulin, and fructosamine and was day 28 for 15-hour weighted mean plasma glucose and postprandial plasma glucose $AUC_{0\text{-}4\ h}$. Missing values at end point were imputed using the last observation carried forward procedure (only postbaseline values were carried forward).

‡LS mean change (or mean percentage change for fructosamine) from baseline to end point based on ANCOVA model with effect of treatment and baseline value as a covariate.

showed that in obese patients (BMI≥30 kg/m^2), 10 of 19 (53%) of those treated with ETC-1002 had a 2-kg or greater reduction compared with 1 of 12 (8%) patients in the placebo group.

Table 5. Safety End Points

Parameter	ETC-1002 (n=30)	Placebo (n=30)
Overview of adverse events		
Total number of adverse events	45	52
	No. of patients (%)	
Any adverse event	14 (47)	21 (70)
Discontinuation because of adverse event	0	1 (3)
Common of adverse events* (≥5%)		
Hyperglycemia	6 (20)	10 (33)
Headache	6 (20)	3 (10)
Dry eye	2 (7)	2 (7)
Viral upper respiratory tract infection	2 (7)	2 (7)
Abdominal pain	0	3 (10)
Arthralgia	2 (7)	1 (3)
Pruritus	1 (3)	2 (7)
Constipation	2 (7)	0
Dizziness	0	2 (7)
Nausea	0	2 (7)

*Common adverse events occurred in ≥5% of patients in ≥1 treatment group and are listed in decreasing frequency of the incidence of the adverse event for the total trial population.

Discussion

This was a phase 2 proof-of-concept clinical trial designed to evaluate the lipid-lowering effects of ETC-1002 in hypercholesterolemic patients with T2DM. Significant LDL-C lowering after ETC-1002 120 mg treatment versus placebo was observed at day 29, the primary end point. The magnitude of LDL-C lowering with ETC-1002 treatment at day 29 was 43% compared with a 4% reduction for patients given placebo (P<0.0001). ETC-1002 treatment lowered LDL-C in all patients, the majority of whom (25 of the 29 patients) experienced a 30% or greater drop in LDL-C independent of baseline LDL-C. In addition, a significant LDL-C reduction was also observed with the lower dose, ETC-1002 80 mg, versus placebo at day 15. The reduction of LDL-C was accompanied by corresponding significant reductions in related lipid parameters including non–high-density lipoprotein-cholesterol and total cholesterol compared with placebo (P<0.0001). The inflammatory biomarker, high-sensitivity C-reactive protein, known to be associated with CVD risk, was also significantly reduced with ETC-1002 treatment compared with placebo (41% versus 11%; P=0.0011).

The reduction in LDL-C observed in patients with hypercholesterolemia and T2DM is greater than that observed in a previous placebo-controlled phase 2 trial in hypercholesterolemic patients (n=177) treated for 12 weeks in which ETC-1002 significantly lowered LDL-C by 27% in the 120 mg group compared with 2% in the placebo group.[19] It is

unclear why the magnitude of LDL-C lowering in the current trial was substantially greater than that of the previous trial. In addition to population differences (diabetics versus nondiabetics), other factors that may have contributed to the differences include trial design (inpatient versus outpatient), baseline LDL-C (125 versus 165 mg/dL), and predominance of Hispanic patients in this trial (98%).

The greater weight loss trend observed in this trial in patients treated with ETC-1002 may have been, in part, because of the greater number of obese patients in the ETC-1002 group (19 versus 12 in the placebo group, with a mean BMI of 30.6 versus 29.2 kg/m^2, respectively) and the consequential weight loss because of a healthier lifestyle during the 35 days in the clinic. Future trials with larger numbers of T2DM patients who are not restricted to a clinic, longer treatment duration, and higher doses of ETC-1002 may provide insight to the effects of ETC-1002 on other relevant cardiometabolic measures, including glycemic control, blood pressure reduction, and weight loss.

Assessment of standard safety parameters indicated that ETC-1002 was generally safe and well tolerated in this population of hypercholesterolemic patients with T2DM. Treatment was not associated with dose-limiting adverse events and the majority of adverse events were mild in severity. No patients in the ETC-1002 group had an adverse event that led to withdrawal of trial drug.

Effective lowering of elevated LDL-C in patients with T2DM is a challenging unmet medical need. These patients are at an increased risk of CVD[1,2] and many are unable to achieve LDL-C treatment goals.[3] Furthermore, although statins are widely prescribed for the treatment of hypercholesterolemia in patients with T2DM, increases in hemoglobin A1C and fasting plasma glucose have been reported with statin therapy.[13] The results of this trial suggest that ETC-1002 may offer a potential novel therapeutic approach that is well tolerated and can significantly lower LDL-C and high-sensitivity C-reactive protein in patients with T2DM without worsening glycemic control. The potential beneficial effects of ETC-1002 on LDL-C and other cardiometabolic risk factors, including blood glucose, blood pressure, and body weight, support further clinical investigation in larger clinical trials.

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Dr Rosenberg, Dr Newton, J.C. Hanselman, D.E. MacDougall, and J.R. Margulies are employees of Esperion Therapeutics, Inc. Dr Strange, Dr Milad, and S.J. McBride have consulted for Esperion Therapeutics, Inc. Dr Gutierrez reports no conflicts.

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Significance

8-Hydroxy-2,2,14,14-tetramethylpentadecanedioic acid (ETC-1002) has a novel dual mechanism of action with potential effects on both the reduction of lipids and the control of glucose. The effects of ETC-1002 on low-density lipoprotein-cholesterol and glycemic measures were investigated in a phase 2 trial in patients with type 2 diabetes mellitus and hypercholesterolemia. Significant reduction of low-density lipoprotein-cholesterol by 43% was observed compared with a 4% reduction with placebo ($P<0.0001$). This low-density lipoprotein-cholesterol lowering in patients with type 2 diabetes mellitus was greater than that previously observed in a phase 2 trial in patients without type 2 diabetes mellitus, in which a 25% difference in low-density lipoprotein-cholesterol lowering occurred compared with placebo ($P<0.0001$). Non–high-density lipoprotein-cholesterol and total cholesterol were also significantly lowered and high-sensitivity C-reactive protein was reduced 41% compared with an 11% reduction with placebo ($P=0.0011$). ETC-1002 treatment did not result in a worsening of glycemic measures. Potential effects of ETC-1002 on glycemic and blood pressure control and weight reduction support further study in larger trials.