Original Investigation

Effect of Evolocumab or Ezetimibe Added to Moderate- or High-Intensity Statin Therapy on LDL-C Lowering in Patients With Hypercholesterolemia
The LAPLACE-2 Randomized Clinical Trial

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IMPORTANCE In phase 2 studies, evolocumab, a fully human monoclonal antibody to PCSK9, reduced LDL-C levels in patients receiving statin therapy.

OBJECTIVE To evaluate the efficacy and tolerability of evolocumab when used in combination with a moderate- vs high-intensity statin.

DESIGN, SETTING, AND PATIENTS Phase 3, 12-week, randomized, double-blind, placebo- and ezetimibe-controlled study conducted between January and December of 2013 in patients with primary hypercholesterolemia and mixed dyslipidemia at 198 sites in 17 countries.

INTERVENTIONS Patients (n = 2067) were randomized to 1 of 24 treatment groups in 2 steps. Patients were initially randomized to a daily, moderate-intensity (atorvastatin [10 mg], simvastatin [40 mg], or rosuvastatin [5 mg]) or high-intensity (atorvastatin [80 mg], rosuvastatin [40 mg]) statin. After a 4-week lipid-stabilization period, patients (n = 1899) were randomized to compare evolocumab (140 mg every 2 weeks or 420 mg monthly) with placebo (every 2 weeks or monthly) or ezetimibe (10 mg or placebo daily; atorvastatin patients only) when added to statin therapies.

MAIN OUTCOMES AND MEASURES Percent change from baseline in low-density lipoprotein cholesterol (LDL-C) level at the mean of weeks 10 and 12 and at week 12.

RESULTS Evolocumab reduced LDL-C levels by 66% (95% CI, 58% to 73%) to 75% (95% CI, 65% to 84%) (every 2 weeks) and by 63% (95% CI, 54% to 71%) to 75% (95% CI, 67% to 83%) (monthly) vs placebo at the mean of weeks 10 and 12 in the moderate- and high-intensity statin-treated groups; the LDL-C reductions at week 12 were comparable. For moderate-intensity statin groups, evolocumab every 2 weeks reduced LDL-C from a baseline mean of 115 to 124 mg/dL to an on-treatment mean of 39 to 49 mg/dL; monthly evolocumab reduced LDL-C from a baseline mean of 123 to 126 mg/dL to an on-treatment mean of 43 to 48 mg/dL. For high-intensity statin groups, evolocumab every 2 weeks reduced LDL-C from a baseline mean of 89 to 94 mg/dL to an on-treatment mean of 35 to 38 mg/dL; monthly evolocumab reduced LDL-C from a baseline mean of 89 to 94 mg/dL to an on-treatment mean of 33 to 35 mg/dL. Adverse events were reported in 36%, 40%, and 39% of evolocumab-, ezetimibe-, and placebo-treated patients, respectively. The most common adverse events in evolocumab-treated patients were back pain, arthralgia, headache, muscle spasms, and pain in extremity (all <2%).

CONCLUSIONS AND RELEVANCE In this 12-week trial conducted among patients with primary hypercholesterolemia and mixed dyslipidemia, evolocumab added to moderate- or high-intensity statin therapy resulted in additional LDL-C lowering. Further studies are needed to evaluate the longer-term clinical outcomes and safety of this approach for LDL-C lowering.

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Statin therapy reduces atherosclerotic cardiovascular disease events in proportion to the magnitude of low-density lipoprotein cholesterol (LDL-C) lowering.[1] Based on an extensive body of evidence, statins are considered first-line therapy for reduction of atherosclerotic cardiovascular disease risk.[2-5]

The 2013 US cholesterol treatment guidelines recommend high-intensity statin therapy (anticipated to lower LDL-C levels by approximately ≥50%) for adults at high risk for atherosclerotic cardiovascular disease and moderate-intensity statin therapy (anticipated to lower LDL-C levels by 30%-<50%) if a high-intensity statin is not tolerated.[2] Those with LDL-C levels of 190 mg/dL (4.9 mmol/L) or greater due to a genetic cholesterol disorder should receive a high-intensity statin and may require nonstatin therapy to achieve additional LDL-C lowering. The addition of a nonstatin cholesterol-lowering drug also can be considered for patients with a less than anticipated LDL-C lowering response or for those unable to tolerate the recommended statin intensity. Outside the United States, several guidelines recommend LDL-C goals of less than 100 mg/dL (2.6 mmol/L) or less than 70 mg/dL (1.8 mmol/L) depending on the level of risk.[3-5] Many patients receiving moderate- or high-intensity statin therapy are unable to achieve these recommended goals with statin therapy, and consideration of nonstatin therapy for additional LDL-C lowering has been recommended.[4-8]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce circulating LDL-C levels by preventing the degradation of LDL-C receptors when bound to PCSK9.[9] Evolocumab, a fully human monoclonal antibody against PCSK9, showed robust LDL-C lowering in phase 2 trials,[10-13] including a longer-term study of 52 weeks' duration,[14] and was well tolerated.

The LAPLACE-2 (LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy) study was designed to evaluate the efficacy and safety of evolocumab vs placebo or ezetimibe, the most commonly prescribed nonstatin therapy, in patients randomized to different background moderate- and high-intensity statin therapies.[15]

METHODS

Patients

Briefly, this study enrolled patients aged 18 to 80 years with a screening LDL-C level of 150 mg/dL or greater (to convert to mmol/L, multiply by 0.0259) (no statin at screening), 100 mg/dL or greater (nonintensive statin at screening), or 80 mg/dL or greater (intensive statin at screening) and fasting triglyceride levels of 400 mg/dL or less (to convert to mmol/L, multiply by 0.0113). At screening, intensive statin use was defined as daily atorvastatin (40 mg or greater), rosuvastatin (20 mg or greater), simvastatin (80 mg), or any statin plus ezetimibe. Inclusion/exclusion criteria focused on safety and conditions that could influence efficacy.[15] The study was approved by the institutional review board at each site, and written informed consent was obtained from all participants.

Study Design and Oversight

LAPLACE-2 was a 12-week, randomized, double-blind, placebo- and ezetimibe-controlled, phase 3, multicenter study examining the efficacy and safety of evolocumab in combination with background statin therapy in patients with primary hypercholesterolemia and mixed dyslipidemia. Trial design and baseline patient characteristics have been previously reported.[15]

An independent data monitoring committee reviewed accumulating trial data provided by an independent biostatistical group external to Amgen. Deaths and suspected cardiovascular events were adjudicated by an independent, blinded, clinical events committee. All site personnel, patients, study monitors and Amgen staff were blinded to subcutaneous investigational product and oral ezetimibe or placebo.

Randomization and Intervention

Patients meeting the inclusion criteria received a placebo injection to determine tolerance for subcutaneous administration of study drug. Patients tolerating placebo injection discontinued previous statin and ezetimibe use and were randomized to 1 of 5 open-label, oral treatments with a moderate-intensity statin (atorvastatin [10 mg], rosuvastatin [5 mg], simvastatin [40 mg]) or high-intensity statin (atorvastatin [80 mg], rosuvastatin [40 mg]) (**Figure 1** and **Figure 2**).

After a 4-week lipid-stabilization period, patients taking rosuvastatin or simvastatin during the lipid-stabilization phase were then randomized to 1 of 4 treatment groups: evolocumab (140 mg, subcutaneous, every 2 weeks) or matching placebo (subcutaneous, every 2 weeks), or evolocumab (420 mg, subcutaneous, monthly) or matching placebo (subcutaneous, monthly) (Figures 1 and 2).[15]

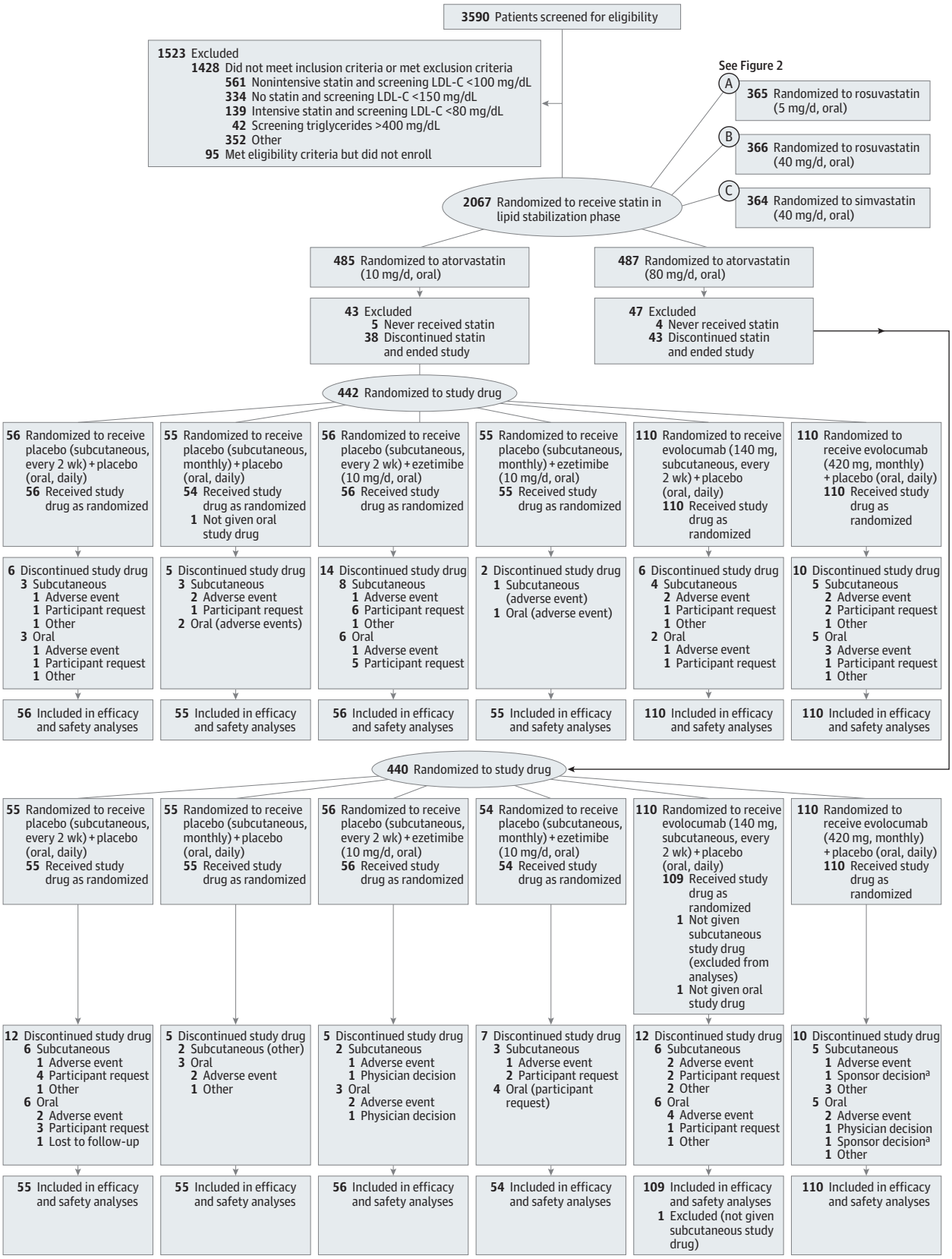
Patients taking atorvastatin during the lipid-stabilization phase were then randomized to 1 of 6 treatment groups: evolocumab (140 mg, subcutaneous, every 2 weeks) and placebo (oral, daily), evolocumab (420 mg, subcutaneous, monthly) and placebo (oral, daily), placebo (subcutaneous, every 2 weeks) and placebo (oral, daily) or ezetimibe (10 mg, oral, daily), or placebo (subcutaneous, monthly) and placebo (oral, daily) or ezetimibe (10 mg, oral, daily).[15] Ezetimibe was evaluated only in patients treated with atorvastatin, the most commonly prescribed statin. Subcutaneous evolocumab and placebo were presented as a sterile, preservative-free solution in a single-use, disposable, mechanical prefilled autoinjector pen for a fixed-dose, subcutaneous injection. Oral ezetimibe and placebo were provided as 10-mg tablets of identical size and color.

No additional prescription lipid-modifying drugs were allowed during the trial.

Efficacy and Safety Evaluations

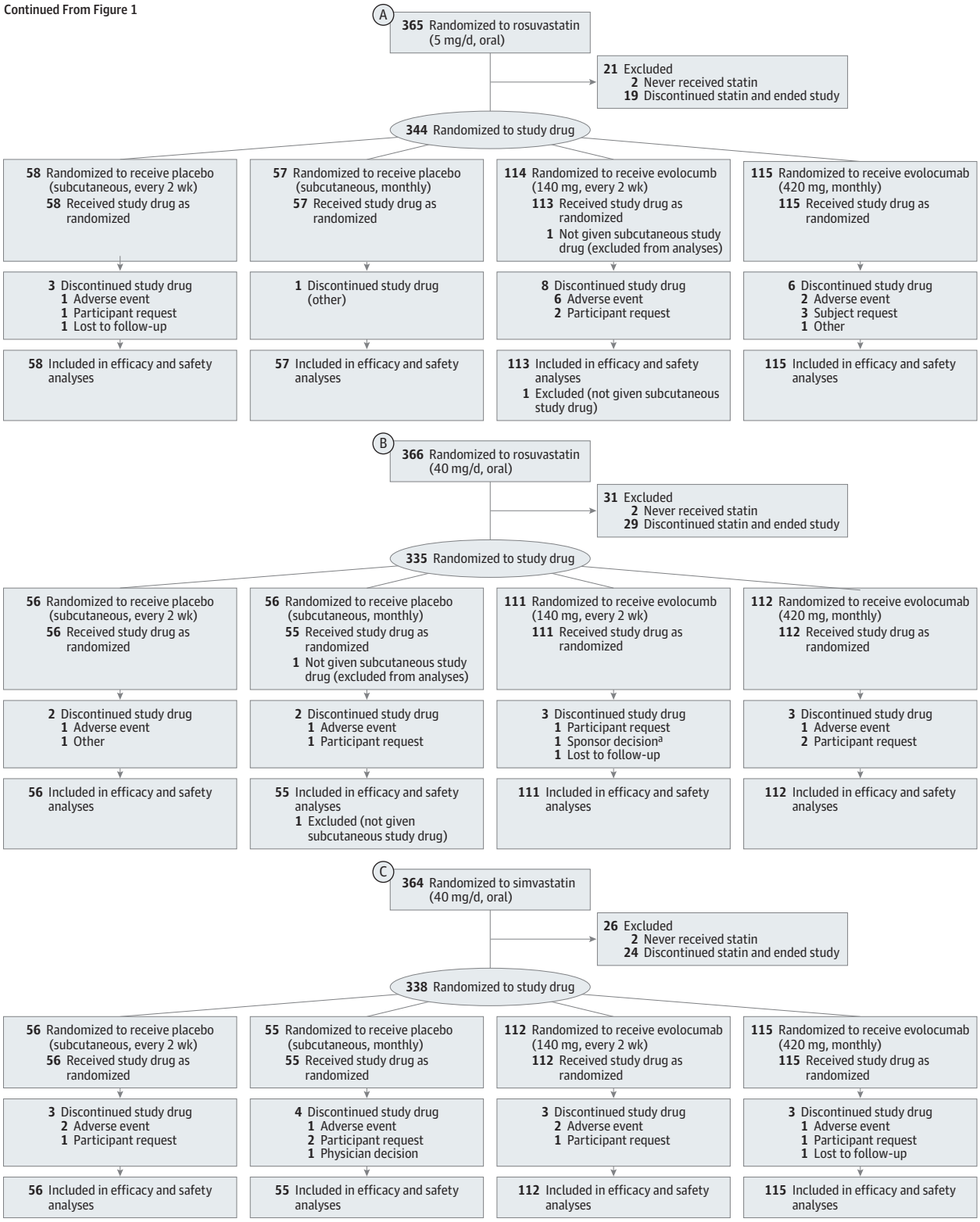
Coprimary end points were the percent change from baseline in LDL-C level at the mean of weeks 10 and 12 and at week 12. The averaging of weeks 10 and 12 better reflects average LDL-C reduction with monthly dosing. Level of LDL-C was determined by the Friedewald formula, unless calculated LDL-C was less than 40 mg/dL or triglyceride levels were greater than 400 mg/dL; then the LDL-C level was measured by preparative ultracentrifugation. Secondary end points included the mean at weeks 10 and 12 and at week 12 for the change from baseline in LDL-C level, the percent change from baseline in additional lipid parameters, and the proportion of patients achieving LDL-C levels less than 70 mg/dL. Baseline lipid parameters

Figure 1. Trial Design and Patient Disposition, Atorvastatin Groups



[a] Sponsor decision because of other reason.

Figure 2. Trial Design and Patient Disposition, Rosuvastatin and Simvastatin Groups



[a] Patient removed from study because of eligibility deviation (participated in previous evolocumab study).

were measured after the lipid-stabilization period and before administration of the first dose of study drug.

Key safety end points included incidence of adverse events, serious adverse events, and antievolocumab antibodies. Safety laboratory studies included measurement of transaminase, bilirubin, and creatine kinase levels. Adjudicated cardiovascular events included cardiovascular death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, and hospitalization for heart failure. Neurocognitive events were not prespecified as key safety end points in the protocol but were documented if reported at clinical visits; no formal assessments of cognitive function were performed.

Statistical Analyses

Efficacy and safety analyses were conducted for all patients randomized to investigational product and who received at least 1 dose of study drug. For coprimary and secondary efficacy end points within each dose frequency and statin dose cohort, a repeated-measures linear effects model was used, which included stratification factor(s) (study entry statin intensity and simvastatin contraindicated concomitant medication group for patients randomized to simvastatin), treatment, visit, and treatment by visit terms. There was no imputation of missing data because the repeated-measures model accounts for missing data. A patient was determined to have achieved an LDL-C level less than 70 mg/dL if a postbaseline LDL-C value was less than 70 mg/dL. If the value was missing, the patient was considered to have not achieved the target LDL-C level. Mean achievement of LDL-C less than 70 mg/dL at weeks 10 and 12 was defined using the mean of nonmissing LDL-C values at those 2 time points. Achievement end points were assessed using Cochran-Mantel-Haenszel tests accounting for the stratification factor(s).

Comparisons were made between evolocumab and each matched dose frequency (every 2 weeks; monthly) comparator within a statin dose cohort. Significance testing was 2-sided. Because the study was designed to assess the efficacy of each evolocumab regimen given each statin dose cohort, a total significance level of .05 was allocated for comparisons between treatment and control within each dose frequency and statin cohort. The significance level was split to .01 vs placebo and .04 vs ezetimibe within each atorvastatin dose cohort and dose frequency, because of lower assumed power vs ezetimibe. The significance level split led to similar power calculations vs placebo and vs ezetimibe for atorvastatin dose cohorts.

The overall sample size was chosen to ensure a sufficient safety database size. However, power calculations were conducted to verify sufficient power given the planned allocation of 100 patients to each evolocumab treatment group and 50 patients to each control treatment group. The lowest calculated power for any coprimary end point test was 92% for testing vs ezetimibe in either atorvastatin dose cohort. This calculation assumed a treatment effect of 16.5% vs ezetimibe with a common SD of 23% (10% of patients missing all data).

To control for testing multiple primary and secondary end points within each dose frequency and statin dose cohort, testing was conducted sequentially and with *P*-value adjustments.[16,17] Testing was first conducted for the coprimary end points of percent change from baseline in LDL-C. Given statistical significance of the coprimary end points, a protocol-prespecified first set of cosecondary end points were tested at a significance level of .005 using a Hochberg adjustment. Additional testing on a second prespecified set of cosecondary end points was conducted using a Hochberg adjustment with the remainder of the significance level not spent from the prior tests.

Subgroup analyses were conducted using the same model and included the stratification factors age (<65 years, ≥65 years), race, region, baseline LDL-C level (split by median), screening LDL-C level (<130 mg/dL, ≥130 mg/dL), body mass index (<25, 25-<30, ≥30), glucose tolerance status, hypertension, smoking status, having 2 or more baseline coronary heart disease risk factors, family history of premature coronary heart disease, baseline PCSK9 level (split by median), baseline triglyceride level (split by median: <150 mg/dL, ≥150 mg/dL, <200 mg/dL, ≥200 mg/dL), and National Cholesterol Education Program high risk. Interaction tests were conducted using the subgroup analyses to help identify possible patient factors with differing treatment effects.

Descriptive statistics were used to summarize results of the safety analyses.[15] Adverse events were coded using the most recent version of MedDRA (MedDRA MSSO) (version 16.1). All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc).

Results

Patient Characteristics

Patients were recruited from 198 study sites in Australia, Belgium, Canada, the Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, Italy, the Netherlands, Russia, Spain, Sweden, Switzerland, the United Kingdom, and the United States. The first patient was screened on January 15, 2013; the last patient completed the study on December 4, 2013. Of 3590 participants screened at 164 sites, 1899 were randomized to 1 of 24 different study-drug treatment groups and included in efficacy and safety analyses (Figures 1 and 2). In total, 1896 patients received at least 1 dose of study drug; 3 patients did not receive any study drug and were subsequently excluded from all analyses (Figures 1 and 2). In total, 1826 patients (96%) completed the study.

Approximately 50% to 60% of the LDL-C measurements in the overall evolocumab group were measured by ultracentrifugation in patients treated with a moderate-intensity statin; approximately 70% to 80% were measured by ultracentrifugation in the high-intensity statin groups. The majority (≥90%) of ultracentrifugation LDL-C values were provided because calculated LDL-C was less than 40 mg/dL.

Prior to enrollment, intensive statin therapy was used by 29% of patients, nonintensive statin by 41%, and 30% were using no statin. In the total treatment population, the mean age was 60 (SD, 10) years, 46% were women, 23% had coronary artery disease, 10% had other atherosclerotic cardiovascular disease, and 16% had diabetes mellitus. Following the lipid stabilization period, the mean LDL-C level was 109.1 (SD, 41.1) mg/dL (**Table 1**).[15] A detailed description of patient baseline characteristics by treatment group is provided in eTables 1 and 2 in Supplement). At the time of randomization to study drug, mean LDL-C levels were 109 to 127 mg/dL in the moderate-intensity statin groups (atorvastatin [10 mg],

Table 1. Baseline Characteristics

Characteristic	Overall		
	Placebo (n = 558)	Ezetimibe (n = 221)	Evolocumab (n = 1117)
Age, mean (SD), y	59.9 (10.2)	60.8 (9.3)	59.6 (9.9)
Women, No. (%)	267 (47.8)	109 (49.3)	492 (44.0)
Race, No. (%)			
White	531 (95.1)	204 (92.3)	1047 (93.7)
Black or African American	16 (2.9)	10 (4.5)	49 (4.4)
Other[a]	11 (2.0)	7 (3.2)	21 (1.9)
Cardiac risk factors, No. (%)			
Coronary artery disease	123 (22.0)	38 (17.2)	266 (23.8)
Peripheral arterial disease or cerebrovascular disease	55 (9.9)	19 (8.6)	124 (11.1)
Type 2 diabetes mellitus	74 (13.3)	44 (19.9)	175 (15.7)
Baseline lipid parameters, mean (SD), mg/dL[b]			
LDL-C	107.7 (40.2)	109.4 (37.3)	109.7 (42.3)
Total cholesterol	187.9 (44.3)	188.2 (43.3)	190.4 (47.5)
HDL-C	54.5 (16.5)	51.8 (14.8)	53.4 (15.7)
Non-HDL-C	133.5 (43.4)	136.4 (41.7)	137.0 (46.5)
VLDL-C, median (Q1, Q3)	23.0 (17.0, 30.0)	25.0 (18.0, 32.0)	23.0 (17.0, 32.0)
ApoB	87.8 (25.1)	90.1 (25.0)	89.5 (26.9)
Triglycerides, median (Q1, Q3)	114.0 (85.0, 154.0)	123.0 (89.0, 158.0)	116.0 (86.0, 160.0)
Lp(a), median (Q1, Q3), nmol/L	34.0 (12.0, 149.0)	34.5 (10.0, 178.0)	34.5 (11.0, 164.0)
Free PCSK9, mean (SD), ng/mL	352.7 (114.4)	351.2 (112.3)	355.1 (110.6)

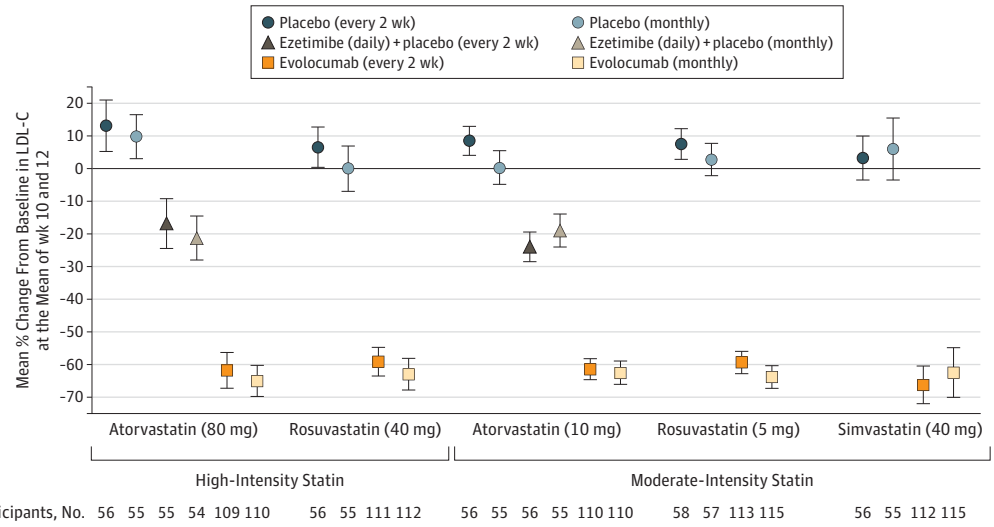
Abbreviations: ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL-C,very low-density lipoprotein cholesterol.

SI conversion factors: To convert LDL-C, total cholesterol, HDL-C, and NonHDL-C values to mmol/L, multiply by 0.0259; triglyceride values to mmol/L, multiply by 0.0113.

[a] Other includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, or Mixed Race.

[b] Baseline was measured after the lipid stabilization period and before administration of first dose of study drug.

Figure 3. Mean Percent Change From Baseline in LDL-C at the Mean of Weeks 10 and 12



Baseline was measured after the lipid-stabilization period and prior to administration of first dose of study drug. Error bars indicate 95% confidence intervals. To convert low-density lipoprotein cholesterol (LDL-C) values to mmol/L, multiply by 0.0259.

rosuvastatin [5 mg], and simvastatin [40 mg]), and 77 to 103 mg/dL in the high-intensity statin groups (atorvastatin [80 mg] and rosuvastatin [40 mg]).

LDL-C Reduction

Significant lowering of LDL-C occurred in all evolocumab-treated statin groups at the mean of weeks 10 and 12 (**Figure 3**; **Table 2**, **Table 3**, **Table 4**; eTable 3 and eTable 4 in Supplement), and at week 12 (eFigure 1 and eTable 5 in Supplement). The mean of week 10 and 12 results are presented below, with week-12 results available in the eAppendix in Supplement.

At the mean of weeks 10 and 12, percent reduction from baseline in LDL-C was 59% to 66% with every-2-weeks dosing and 62% to 65% with monthly dosing (Tables 2 and 3). These reductions corresponded to changes vs placebo of 66% to 75%

Table 2. Efficacy at the Mean of Weeks 10 and 12, High-Intensity Statin Groups

	Atorvastatin (80 mg)						Rosuvastatin (40 mg)			
	Placebo + Placebo		Ezetimibe + Placebo		Evolocumab + Placebo		Placebo		Evolocumab	
LDL-C, mg/dL[a]	Every 2 wk + Daily (n = 55)	Monthly + Daily (n = 55)	Daily + Every 2 wk (n = 56)	Daily + Monthly (n = 54)	Every 2 wk + Daily (n = 109)	Monthly + Daily (n = 110)	Every 2 wk (n = 56)	Monthly (n = 55)	Every 2 wk (n = 111)	Monthly (n = 112)
Day-1 (post LS period), mean (SD)[b]	100.3 (36.2)	94.7 (31.9)	98.7 (34.0)	92.3 (19.3)	94.2 (34.8)	93.8 (32.3)	77.4 (20.9)	102.9 (49.3)	88.5 (31.5)	88.5 (31.3)
Achieved at mean of wk 10 and 12, mean (SD)[b]	109.5 (45.7)	100.1 (37.0)	85.6 (66.7)	72.1 (26.2)	35.3 (21.2)	34.8 (31.4)	81.6 (27.5)	96.6 (45.9)	37.5 (27.0)	33.0 (28.3)
Change from baseline to mean of wk 10 and 12, mean (95% CI)	11.0 (1.1 to 21.0)	5.5 (−1.7 to 12.8)	−13.0 (−22.7 to −3.3)	−21.3 (−28.6 to −14.0)	−58.8 (−65.7 to −51.9)	−60.1 (−65.3 to −54.9)	3.4 (−2.5 to 9.4)	−4.8 (−13.0 to 3.4)	−52.3 (−56.6 to −48.0)	−55.3 (−61.0 to −49.6)
LS mean % change from baseline to mean wk 10 and 12, mean (95% CI)[c]	13.1 (5.3 to 21.0)	9.8 (3.1 to 16.5)	−16.9 (−24.5 to −9.2)	−21.3 (−28.0 to −14.5)	−61.8 (−67.3 to −56.3)	−65.1 (−69.8 to −60.3)	6.6 (0.4 to 12.7)	0 (−7.0 to 6.9)	−59.1 (−63.5 to −54.7)	−62.9 (−67.8 to −58.1)
<70 mg/dL at mean of weeks 10 and 12, % (95% CI)	13.7 (6.8 to 25.7)	9.3 (4.0 to 19.9)	50.9 (38.1 to 63.6)	62.3 (48.8 to 74.1)	94.4 (88.4 to 97.4)	92.5 (85.9 to 96.2)	38.9 (27.0 to 52.2)	28.8 (18.3 to 42.3)	93.5 (87.1 to 96.8)	94.5 (88.6 to 97.5)

Abbreviations: LDL-C, low-density lipoprotein cholesterol; LS, lipid stabilization.

SI conversion factor: To convert LDL-C values to mmol/L, multiply by 0.0259.

[a] LDL-C was determined by the Friedewald formula with reflexive testing via ultracentrifugation when calculated LDL-C was less than 40 mg/dL (1.0 mmol/L) or triglyceride levels were greater than 400 mg/dL (3.9 mmol/L).

[b] Observed values.

[c] Coprimary end point.

Table 3. Efficacy at the Mean of Weeks 10 and 12, Moderate-Intensity Statin Groups

	Atorvastatin (10 mg)						Simvastatin (40 mg)				Rosuvastatin (5 mg)			
	Placebo + Placebo		Ezetimibe + Placebo		Evolocumab + Placebo		Placebo		Evolocumab		Placebo		Evolocumab	
LDL-C, mg/dL[a]	Every 2 wk + Daily	Monthly + Daily	Daily + Every 2 wk	Daily + Monthly	Every 2 wk + Daily	Monthly + Daily	Every 2 wk (n = 56)	Monthly (n=55)	Every 2 wk (n=112)	Monthly (n=115)	Every 2 wk (n=58)	Monthly (n=57)	Every 2 wk (n=113)	Monthly (n=115)
Day-1 (post LS period), mean (SD)[b]	123.0 (46.6)	123.7 (47.9)	126.8 (49.6)	119.3 (28.1)	124.2 (43.4)	126.1 (50.4)	110.3 (28.0)	108.6 (30.9)	114.9 (34.5)	123.7 (48.5)	115.6 (39.8)	119.9 (39.1)	118.7 (40.9)	122.9 (42.0)
Achieved at mean of wk 10 and 12, mean (SD)[b]	126.2 (41.6)	123.6 (51.4)	95.0 (36.7)	94.2 (29.8)	47.9 (28.1)	46.6 (25.5)	111.8 (27.9)	114.4 (40.7)	39.0 (18.2)	48.4 (42.8)	121.6 (44.4)	121.5 (39.7)	48.9 (38.9)	43.3 (25.3)
Change from baseline to mean wk 10 and 12, mean (95% CI)	6.8 (-0.4 to 14.1)	-0.4 (-9.1 to 8.2)	-32.4 (-39.9 to -24.9)	-25.1 (-33.6 to -16.6)	-76.8 (-82.0 to -71.5)	-80.1 (-86.1 to -74.1)	-5.7 (-15.9 to 4.5)	1.7 (-11.0 to 14.5)	-83.8 (-92.7 to -75.0)	-78.4 (-88.5 to -68.3)	6.5 (-0.4 to 13.3)	0.1 (-8.2 to 8.4)	-68.9 (-73.9 to -64.0)	-77.8 (-83.6 to -71.9)
LS mean % change from baseline to mean wk 10 and 12, mean (95% CI)[c]	8.5 (4.1 to 13.0)	0.4 (−4.8 to 5.5)	−23.9 (−28.5 to −19.3)	−19.0 (−24.0 to −13.9)	−61.4 (−64.6 to −58.2)	−62.5 (−66.1 to −58.9)	3.3 (−3.4 to 10.0)	6.0 (−3.5 to 15.5)	−66.2 (−72.0 to −60.4)	−62.4 (−70.0 to −54.9)	7.6 (2.8 to 12.3)	2.8 (−2.1 to 7.7)	−59.3 (−62.8 to −55.9)	−63.8 (−67.3 to −60.3)
<70 at mean of wk 10 and 12, % (95% CI)	5.7 (1.9 to 15.4)	5.6 (1.9 to 15.1)	20.0 (11.2 to 33.0)	16.7 (9.0 to 28.7)	88.1 (80.7 to 92.9)	85.8 (78.0 to 91.2)	1.9 (0.3 to 9.8)	3.9 (1.1 to 13.2)	93.6 (87.3 to 96.9)	88.5 (81.3 to 93.2)	7.0 (2.8 to 16.7)	5.3 (1.8 to 14.4)	88.7 (81.2 to 93.4)	89.9 (82.8 to 94.3)

Abbreviations: LDL-C, low-density lipoprotein cholesterol; LS, lipid stabilization.

SI conversion factor: To convert LDL-C values to mmol/L, multiply by 0.0259.

[a] LDL-C was determined by the Friedewald formula with reflexive testing via ultracentrifugation when calculated LDL-C was less than 40 mg/dL (1.0 mmol/L) or triglyceride levels were greater than 400 mg/dL (3.9 mmol/L).

[b] Observed values.

[c] Coprimary end point.

for every-2-weeks dosing and 63% to 75% for monthly dosing (Table 4 and eTable 6 in Supplement). Percent reductions were similar across the statin groups for evolocumab administered every 2 weeks and monthly.

In patients treated with atorvastatin (10 mg or 80 mg), the addition of ezetimibe resulted in reductions in LDL-C values of 17% to 24% from baseline (eTables 1 and 3 in Supplement; Figure 3 and **Figure 4**) compared with the addition of evolocumab administered every 2 weeks, which reduced LDL-C values by 61% to 62% (treatment differences vs placebo and ezetimibe both significant [$P < .001$]; Tables 2, 3, and 4; eTables 1, 3, and 6 in Supplement; Figures 3 and 4). The addition of monthly evolocumab reduced LDL-C values by 62% to 65% from baseline (treatment differences vs placebo and ezetimibe both significant [$P < .001$]).

For patients receiving a moderate-intensity statin, evolocumab administered every 2 weeks reduced LDL-C values from a baseline mean of 115 to 124 mg/dL to an on-treatment mean of 39 to 49 mg/dL, and 88% to 94% achieved an LDL-C level less than 70 mg/dL (Table 3, eTables 3 and 4 in Supplement; Figure 4);

Table 4. Treatment Difference (vs Placebo or Ezetimibe) at the Mean of Weeks 10 and 12 and at Week 12

	Mean (95% CI)[a]													
	High-Intensity Statin						Moderate-Intensity Statin							
	Atorvastatin (80 mg)				Rosuvastatin (40 mg)		Atorvastatin (10 mg)				Simvastatin (40 mg)		Rosuvastatin (5 mg)	
	vs Placebo		vs Ezetimibe		vs Placebo		vs Placebo		vs Ezetimibe		vs Placebo		vs Placebo	
LDL-C	Every 2 wk	Monthly	Every 2 wk	Monthly	Every 2 wk	Monthly	Every 2 wk	Monthly	Every 2 wk	Monthly	Every 2 wk	Monthly	Every 2 wk	Monthly
% change at wk 12	−76.3 (−86.9 to −65.7)	−70.5 (−79.8 to −61.2)	−47.2 (−57.5 to −36.9)	−38.9 (−48.2 to −29.6)	−68.3 (−77.0 to −59.6)	−55.0 (−65.3 to −44.7)	−71.4 (−77.6 to −65.3)	−59.2 (−65.9 to −52.4)	−39.6 (−45.8 to −33.4)	−41.1 (−47.8 to −34.4)	−70.6 (−76.7 to −64.4)	−60.4 (−69.1 to −51.7)	−68.2 (−74.7 to −61.7)	−64.5 (−70.8 to −58.1)
% change at mean of wk 10 and 12	−74.9 (−84.5 to −65.4)	−74.8 (−83.0 to −66.6)	−44.9 (−54.3 to −35.6)	−43.8 (−52.1 to −35.6)	−65.7 (−73.2 to −58.1)	−62.9 (−71.4 to −54.5)	−70.0 (−75.4 to −64.5)	−62.8 (−69.1 to −56.6)	−37.5 (−43.0 to −32.0)	−43.5 (−49.7 to −37.3)	−69.4 (−74.9 to −64.0)	−68.5 (−76.7 to −60.2)	−66.9 (−72.7 to −61.1)	−66.6 (−72.6 to −60.6)
Change at wk 12, mg/dL	−71.7 (−84.4 to −59.0)	−61.8 (−71.6 to −52.0)	−49.0 (−61.5 to −36.6)	−35.3 (−45.2 to −25.5)	−57.2 (−65.1 to −49.4)	−44.6 (−55.9 to −33.4)	−85.5 (−95.2 to −75.9)	−75.8 (−86.8 to −64.9)	−46.8 (−56.6 to −37.1)	−51.7 (−62.6 to −40.9)	−79.0 (−87.5 to −70.4)	−71.9 (−83.8 to −60.0)	−77.1 (−86.2 to −67.9)	−75.8 (−86.3 to −65.3)
Change at mean of wk 10 and 12, mg/dL	−69.9 (−81.9 to −57.8)	−65.6 (−74.5 to −56.7)	−45.8 (−57.7 to −33.9)	−38.8 (−47.8 to −29.9)	−55.8 (−63.1 to −48.4)	−50.6 (−60.6 to −40.6)	−83.6 (−92.6 to −74.6)	−79.7 (−90.2 to −69.2)	−44.4 (−53.4 to −35.3)	−55.0 (−65.4 to −44.6)	−78.1 (−86.2 to −70.0)	−80.1 (−91.7 to −68.6)	−75.4 (−83.9 to −67.0)	−77.9 (−88.0 to −67.8)

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

SI conversion factor: To convert LDL-C values to mmol/L, multiply by 0.0259.

[a] Adjusted $P < .05$ for all treatment differences.

24.5% of these patients achieved an LDL-C value less than 25 mg/dL on 2 consecutive occasions. In patients treated with monthly evolocumab added to a moderate-intensity statin, LDL-C values were reduced from a baseline mean of 123 to 126 mg/dL to an on-treatment mean of 43 to 48 mg/dL, and 86% to 90% of patients achieved an LDL-C value less than 70 mg/dL; an LDL-C value less than 25 mg/dL on 2 consecutive occasions was achieved by 17.9% of these patients.

For patients receiving a high-intensity statin, evolocumab administered every 2 weeks reduced LDL-C values from a baseline mean of 89 to 94 mg/dL to an on-treatment mean of 35 to 38 mg/dL, and 94% achieved an LDL-C value less than 70 mg/dL (Table 2; eTables 3 and 4 in Supplement; Figure 4); 42.3% of these patients achieved an LDL-C value less than 25 mg/dL on 2 consecutive occasions. In patients treated with monthly evolocumab added to a high-intensity statin, evolocumab reduced LDL-C values from a baseline mean of 89 to 94 mg/dL to an on-treatment mean of 33 to 35 mg/dL, and 93% to 95% achieved an LDL-C level less than 70 mg/dL; 42.3% of patients achieved LDL-C levels less than 25 mg/dL on 2 consecutive occasions. In pairwise comparisons between moderate- and high-intensity statins, mean differences between treatment groups receiving evolocumab every 2 weeks ranged from 1.5 (95% CI, 7.7 to −4.7) to 12.6 (95% CI, −6.0 to 19.3) mg/dL, and for monthly evolocumab ranged from 8.6 (95% CI, 0.9 to 16.2) to 15.4 (95% CI, −5.8 to 24.9) (Figure 4).

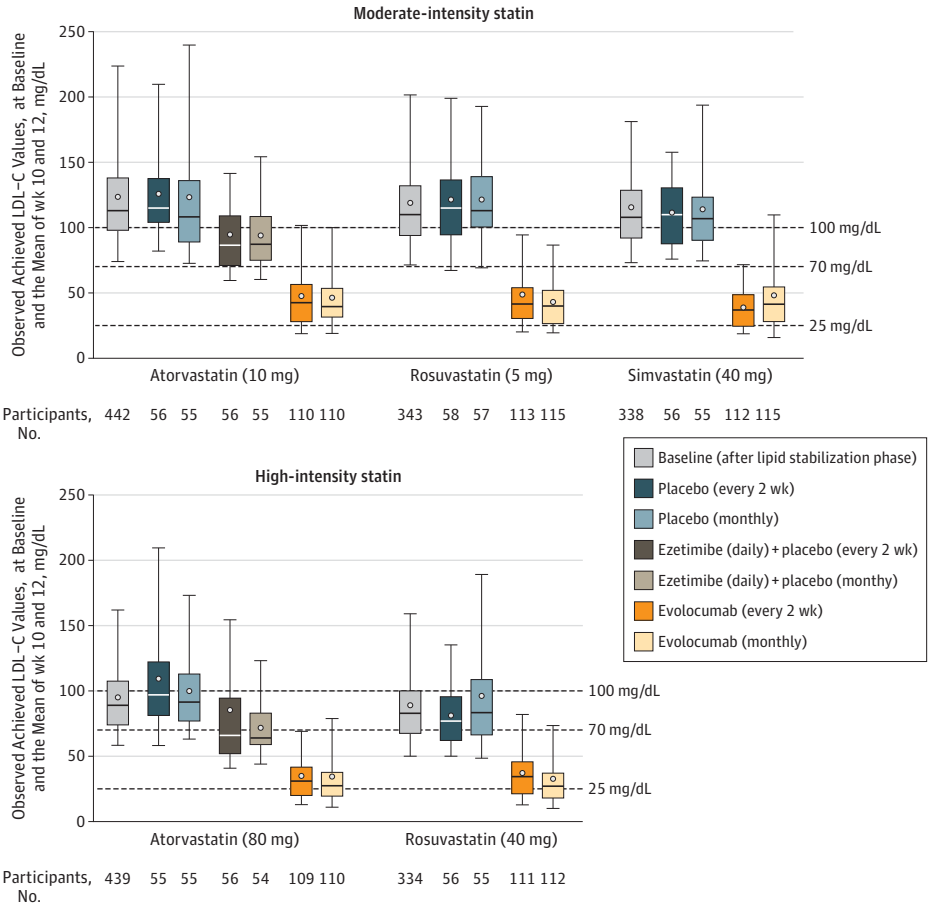
In atorvastatin-treated patients, the addition of ezetimibe resulted in achievement of an LDL-C level less than 70 mg/dL in 17% to 20% of patients receiving moderate-intensity statins and 51% to 62% of those receiving high-intensity statins (eTables 3 and 4 in Supplement; Figure 4). In contrast, an LDL-C level less than 70 mg/dL was achieved by 86% to 94% of evolocumab-treated patients receiving background atorvastatin therapy (Figure 4).

Evolocumab administered every 2 weeks and monthly was effective in all prespecified subgroups relative to placebo and ezetimibe, with no notable differences observed between subgroups. An additional sensitivity analysis of the coprimary end points was conducted using only calculated LDL-C concentrations to support the results obtained using the reflexive approach (eTables 7 and 8 in Supplement). Use of calculated LDL-C can return falsely low values when calculated LDL-C concentrations are less than 40 mg/dL or triglyceride levels are high,[18] thereby resulting in a larger estimated treatment difference in LDL-C percent reduction than that calculated from ultracentrifugation LDL-C values.

Other Lipids

Evolocumab administered every 2 weeks and monthly resulted in significant reductions in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B, and lipoprotein(a) for all statin groups (eTables 3 and 5 and eFigures 2 and 3 in Supplement). For evolocumab every-2-weeks dosing, reductions at the mean of weeks 10 and 12 in non-HDL-C ranged from 52% to 59% (58%-65% vs placebo), reductions in apolipoprotein B from 47% to 56% (51%-59% vs placebo), and reductions in lipoprotein(a) from 24% to 39% (21%-36% vs placebo). For monthly dosing, percent reductions in non-HDL-C, apolipoprotein B, and lipoprotein(a) were comparable to those achieved with every-2-weeks dosing. At the mean of weeks 10 and 12, triglyceride levels were reduced by 12% in patients receiving evolocumab every 2 weeks (12%-23% vs placebo) and by 6% to 16% in patients receiving evolocumab monthly (14%-30% vs placebo) (eTable 3 in Supplement). Lev-

Figure 4. Summary Statistics for Baseline, and Mean of Weeks 10 and 12 LDL-C Values



Horizontal dashed lines represent low-density lipoprotein cholesterol (LDL-C) goals/levels of interest. Boxes indicate 50th and 70th percentiles; error bars indicate 5th and 95th percentiles. Within boxes, dots and horizontal lines indicate mean and median achieved LDL-C levels, respectively.

els of HDL-C were modestly increased by 5% to 10% across both the every-2-weeks and the monthly dose groups (4%-10% vs placebo at the mean of weeks 10 and 12) (eTables 3 and 6 and eFigure 2 in Supplement). Baseline PSCK9 levels were higher in the high-intensity statin groups than in the moderate-intensity statin groups. Reductions in PSCK9 levels were comparable in the high-intensity and moderate-intensity statin groups for every-2-weeks dosing (up to 52% for high intensity vs up to 57% for moderate intensity at the mean of weeks 10 and 12). For monthly dosing, PCSK9 levels were reduced more in the moderate-intensity statin groups (up to 33%) than in the high-intensity statin groups (up to 16%) (eTable 5 in Supplement).

Tolerability and Safety

Adverse events occurred in 36% of evolocumab-treated patients, 40% of ezetimibe-treated patients, and 39% of placebo-treated patients (**Table 5**; eTables 9 and 10 in Supplement). Musculoskeletal symptoms or headache were the most common adverse events (Table 5). Adverse events resulting in study drug discontinuation were 1.9%, 1.8%, and 2.2% in the evolocumab, ezetimibe, and placebo groups. Serious adverse events were reported in 2.1% of evolocumab-treated patients, 0.9% of ezetimibe-treated patients, and 2.3% of placebo-treated patients (Table 5). Elevations in aspartate aminotransferase/alanine aminotransferase levels greater than 3 times the upper limit of normal were uncommon, and creatine kinase elevations greater than 5 times the upper limit of normal were rare among treatment groups. During the 12-week treatment period, positively adjudicated cardiovascular events occurred in 5 evolocumab-treated patients (0.4%), 2 ezetimibe-treated patients (0.9%), and 2 placebo-treated patients (0.4%) (Table 5). One death was reported during the study in a patient receiving rosuvastatin and subcutaneous placebo (Table 5). Neurocognitive adverse events were reported in 1 evolocumab-treated patient (0.1%), 3 ezetimibe-treated patients (1.4%), and 0 placebo-treated patients (Table 5). Injection site reactions were reported in 1.3% of evolocumab-treated patients, 0.9% of ezetimibe-treated patients, and 1.4% of placebo-treated patients (Table 5). Prior to study drug administration, 3 evolocumab-treated patients tested positive for binding antibodies. Of these, 1 patient in the evolocumab (420 mg monthly) (simvastatin [40 mg] background) group had detectable binding antibodies at the end of study; no new cases of binding antibodies posttreatment were reported. Neutralizing antibodies were not detected.

Table 5. Summary of Overall Safety

	No. (%)		
	Any Statin + Placebo (n = 558)	Atorvastatin + Ezetimibe (n = 221)	Any Statin + Evolocumab (n = 1117)
Adverse events[a]	219 (39.2)	89 (40.3)	406 (36.3)
Most common adverse events (top 5 in evolocumab)			
Back pain	14 (2.5)	7 (3.2)	20 (1.8)
Arthralgia	9 (1.6)	4 (1.8)	19 (1.7)
Headache	15 (2.7)	5 (2.3)	19 (1.7)
Muscle spasms	6 (1.1)	6 (2.7)	17 (1.5)
Pain in extremity	7 (1.3)	3 (1.4)	17 (1.5)
Adverse events leading to study drug discontinuation	12 (2.2)	4 (1.8)	21 (1.9)
Serious adverse events	13 (2.3)	2 (0.9)	23 (2.1)
Deaths	1 (0.2)	0[b]	0
Potential injection site reactions[c]	8 (1.4)	2 (0.9)	15 (1.3)
Any postbaseline			
CK >5× ULN	2 (0.4)	0	1 (0.1)
CK >10× ULN	0	0	0
ALT/AST >3× ULN	6 (1.1)	3 (1.4)	4 (0.4)
Total bilirubin >2× ULN	0	0	0
Positively adjudicated cardiovascular events	2 (0.4)	2 (0.9)	5 (0.4)
Neurocognitive adverse events[d]	0	3 (1.4)	1 (0.1)
Disturbance in attention	0	1 (0.5)	0
Cognitive disorder	0	1 (0.5)	0
Disorientation	0	1 (0.5)	1 (0.1)
Any postbaseline binding evolocumab antibodies	NA	NA	1 (0.1)[e]

Abbreviations: ALT/AST, alanine aminotransferase/aspartate aminotransferase; CK, creatine kinase; NA, not applicable; ULN, upper limit of normal.

[a] Adverse events are those occurring between the first dose of study drug and the end of study.

[b] One patient died after the end of study and contributes to the positive cardiovascular events count.

[c] Reported using high-level group terms, including injection site rash, inflammation, pruritus, reaction, and urticaria.

[d] Searched high-level group terms: deliria (including confusion); cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; mental impairment disorders.

[e] Binding antibody was present at baseline and at the end of study. No neutralizing antibodies were detected.

Discussion

This 12-week trial examined the safety, tolerability, and LDL-C-lowering efficacy of a PCSK9 inhibitor compared with placebo and ezetimibe in patients with hypercholesterolemia randomized to receive background statin therapy. The statins used in the study include the 3 most commonly prescribed statins globally at doses consistent with the moderate- and high-intensity statin therapy recommended in the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines.[2] Compared with placebo, evolocumab adminstered every 2 weeks (66%-75%) and monthly evolocumab (63% [when added to moderate- or high-intensity statin therapy] to 75%) provided clinically equivalent percent reductions in levels of LDL-C when added to moderate- or high-intensity statin therapy. The additional LDL-C lowering with evolocumab (140 mg every 2 weeks or 420 mg monthly) (up to 66% reduction) was significantly greater than that observed with ezetimibe (10 mg/d) (up to 24% reduction). Evolocumab was well tolerated, with comparable rates of adverse events vs placebo and ezetimibe over the 12-week treatment period. Neurocognitive events were uncommon in this study, and data from an ongoing, longer-term evolocumab extension study reported 1% or less incidence of these events in patients receiving evolocumab.[14]

With the addition of evolocumab to background statin therapy (either moderate or high intensity), most patients (86%-94%) achieved LDL-C levels less than 70 mg/dL at the mean of weeks 10 and 12 and at week 12. In contrast, 17% to 62% of patients receiving background moderate- or high-intensity statin therapy with ezetimibe achieved LDL-C levels less than 70 mg/dL at the mean of weeks 10 and 12 and at week 12.

LAPLACE-2 is to our knowledge the first study to demonstrate that the addition of evolocumab results in similar percent reductions in LDL-C and achieved LDL-C levels regardless of stable baseline statin type, dose, or intensity, across 3 commonly prescribed statins and a broad range of doses. The similarity of achieved LDL-C levels may reflect greater up-regulation of PCSK9 levels with high-intensity statin therapy, as was observed in other evolocumab studies.[19] In this study, patients receiving a moderate-intensity statin and treated with evolocumab had slightly greater mean percent reductions in PCSK9 levels than those receiving a high-intensity statin. The difference in PCSK9 percent reduction between patients receiving every-2-weeks and monthly dosing may have been influenced by the timing of PCSK9 measurement. The week-12 measurement occurred 4 weeks after the last evolocumab dose in the monthly dosing group and 2 weeks after the last dose in the every-2-weeks group, allowing greater time for PCKS9 levels to recover before measurement in the monthly groups. This

effect appears more pronounced when combined with enhanced PCSK9 expression in the intensive statin groups.

According to the 2013 ACC/AHA Cholesterol Guidelines, nonstatin therapy may be considered for individuals with severe hypercholesterolemia, those who are at higher risk but unable to tolerate high-intensity statin therapy, or those in need of additional LDL-C lowering.[2] Nonstatin LDL-C–lowering therapies that have been shown to reduce atherosclerotic cardiovascular disease (CVD) events in randomized, controlled trials are preferred. Atherosclerotic CVD outcomes trials are currently under way for both ezetimibe and evolocumab.[20,21]

The evolocumab outcomes trial is evaluating the effects of evolocumab added to moderate- or high-intensity statins on reduction in atherosclerotic CVD events.[21] Results of this trial will answer at least 3 important questions: (1) Does additional lowering of LDL-C with evolocumab reduce atherosclerotic cardiovascular disease events more than observed with maximal statin therapy? (2) What is the relationship between the magnitude of LDL-C lowering and the relative reduction in atherosclerotic cardiovascular disease risk in the lower ranges of LDL-C (linear, curvilinear, a threshold, or other)? and (3) Is long-term exposure to very low LDL-C safe?

For the second question, LAPLACE-2 provides information on the expected magnitude of LDL-C lowering that may be observed when evolocumab is added to moderate- and high-intensity statin therapy. The Cholesterol Treatment Trialists individual meta-analysis of statin trials reported a 22% reduction in major CVD events for each 39-mg/dL reduction in LDL-C level.[1] This estimate was based largely on trials of moderate-intensity statin therapy. However, high-intensity atorvastatin (80 mg) has been shown to reduce CVD events more than moderate-intensity statins (atorvastatin [10 mg], pravastatin [40 mg], or simvastatin [20-40 mg]) in individuals with coronary heart disease.[6,7,22] Nonetheless, a different relationship between LDL-C lowering and CVD event reduction may exist when additional LDL-C lowering occurs in individuals who have LDL-C levels less than 100 mg/dL or who are already receiving a high-intensity statin.[23,24] Therefore, the results of cardiovascular outcomes trials will be essential for establishing the net benefit (in terms of the further reduction in CVD events vs the excess of adverse events) from the additional LDL-C lowering achieved with evolocumab.

For the third question, about 18% to 25% (moderate-intensity statin) and 42% (high-intensity statin) of patients in the LAPLACE-2 trial had achieved LDL-C levels less than 25 mg/dL on at least 2 consecutive occasions. A longer-term, open-label study has shown that evolocumab added to background atorvastatin therapy was safe and effective; similar rates of adverse effects in patients with LDL-C levels less than 25 mg/dL and less than 50 mg/dL or 50 mg/dL or greater have been observed to date in that trial.[10] Safety continues to be carefully monitored in other ongoing studies in the evolocumab development program.

Limitations of LAPLACE-2 include the 12-week treatment duration for the assessment of safety, tolerability, and atherosclerotic CVD outcomes, the lack of formal neurocognitive assessments, the small sample sizes in some groups, and the absence of information on untreated LDL-C levels prior to prestudy statin therapy. The trial was also designed prior to the publication of the 2013 ACC/AHA guidelines, so study participants were not identified based on the 4 statin benefit groups defined in these guidelines. The study was also not designed to determine whether patients taking nonintensive statin therapy at baseline had a history of statin intolerance.

Conclusions

In this 12-week trial conducted among patients with primary hypercholesterolemia and mixed dyslipidemia, evolocumab added to moderate- or high-intensity statin therapy resulted in additional LDL-C lowering. Further studies are needed to evaluate the longer-term clinical outcomes and safety of this approach for LDL-C lowering.

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