Efficacy and Safety of Longer-Term Administration of Evolocumab (AMG 145) in Patients With Hypercholesterolemia

52-Week Results From the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) Randomized Trial

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Background—Evolocumab (AMG 145), a monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9), significantly reduced low-density lipoprotein cholesterol (LDL-C) in phase 2 studies of 12 weeks' duration. The longer-term efficacy and safety of PCSK9 inhibition remain undefined.

Methods and Results—Of 1359 randomized and dosed patients in the 4 evolocumab phase 2 parent studies, 1104 (81%) elected to enroll into the Open-Label Study of Long-term Evaluation Against LDL-C (OSLER) study. Regardless of their treatment assignment in the parent study, patients were randomized 2:1 to receive either open-label subcutaneous evolocumab 420 mg every 4 weeks with standard of care (SOC) (evolocumab+SOC, n=736) or SOC alone (n=368). Ninety-two percent of patients in the evolocumab+SOC group and 89% of patients in the SOC group completed 52 weeks of follow-up. Patients who first received evolocumab in OSLER experienced a mean 52.3% [SE, 1.8%] reduction in LDL-C at week 52 (P<0.0001). Patients who received 1 of 6 dosing regimens of evolocumab in the parent studies and received evolocumab+SOC in OSLER had persistent LDL-C reductions (mean reduction, 50.4% [SE, 0.8%] at the end of the parent study versus 52.1% [SE, 1.0%] at 52 weeks; P=0.31). In patients who discontinued evolocumab on entry into OSLER, LDL-C levels returned to near baseline levels. Adverse events and serious adverse events occurred in 81.4% and 7.1% of the evolocumab+SOC group patients and 73.1% and 6.3% of the SOC group patients, respectively.

Conclusion—Evolocumab dosed every 4 weeks demonstrated continued efficacy and encouraging safety and tolerability over 1 year of treatment in the largest and longest evaluation of a PCSK9 inhibitor in hypercholesterolemic patients to date.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT01439880.

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Key Words: cholesterol, LDL ■ hypercholesterolemia ■ randomized controlled trial ■ serine proteases

Multiple clinical trials over 2 decades, mostly with statins, have shown that progressively more aggressive lowering of low-density lipoprotein cholesterol (LDL-C) leads to lower rates of vascular disease complications.[1] This success has generated interest in developing novel therapies that address the limitations of currently available hypercholesterolemia treatments and explore the effects of reducing serum LDL-C levels below those achievable with statin therapy alone.

Clinical Perspective on p 243

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition has emerged as a promising new approach for treating hypercholesterolemia.[2] Monoclonal antibodies against PCSK9 have been shown to reduce LDL-C substantially, either with or without concomitant statin therapy.[3–10] Evolocumab, a fully human monoclonal antibody against PCSK9, reduced LDL-C

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up to 65% and showed an encouraging safety and tolerability profile in 4 randomized, placebo-controlled, phase 2 clinical trials in >1300 hypercholesterolemic patients.[4,5,7,10] To date, the only report evaluating an anti-PCSK9 inhibitor for >12 weeks involved 8 patients with homozygous familial hypercholesterolemia.[11] No previous reports have comprehensively evaluated the efficacy and safety of any PCSK9 inhibitor through 1 year or in a large and diverse patient population.

To provide such data on evolocumab, patients completing any of the 4 phase 2 trials could participate in the Open-Label Study of Long-term Evaluation Against LDL-C (OSLER), a global, multicenter, randomized, controlled, open-label extension trial in which investigators could adjust background standard-of-care (SOC) therapy, including medications, after 12 weeks. The present analysis reports the efficacy and safety results for hypercholesterolemic patients treated in OSLER for 1 year.

Methods

Study Design and Patients

OSLER was a global study conducted at 156 study centers that participated in 1 or more of the 4 phase 2 studies (Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels [MENDEL], monotherapy; LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy–Thrombolysis in Myocardial Infarction 57 [LAPLACE-TIMI 57], combination therapy with statins with or without ezetimibe; Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects [GAUSS], statin-intolerant patients; and Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder [RUTHERFORD], patients with heterozygous familial hypercholesterolemia) between October 2011 and June 2012. Details of the parent trials have been published previously.[4,5,7,10,12] Patients completing any evolocumab phase 2 parent study could enroll in OSLER provided that they did not experience a treatment-related serious adverse event (AE) that led to discontinuation of investigational product in the phase 2 parent study or were anticipated to require unblinded lipid measurements and/or adjustment of background lipid-regulating therapy during the first 12 weeks of OSLER participation. An independent ethics committee or institutional review board approved the protocol, and all patients provided written informed consent before enrollment in the extension study.

Schedule of Events

Randomization of eligible patients occurred ideally at or within 3 days of the phase 2 parent end-of-study visit. Patients were randomized in a 2:1 fashion to 1 of 2 treatment groups, regardless of their treatment assignments during the phase 2 parent study: either evolocumab 420 mg SC every 4 weeks plus SOC (evolocumab+SOC; n=736) or SOC alone (n=368). The SOC-only group served as the control arm (Figure 1). SOC was based on local guidelines for the treatment of hypercholesterolemia. After the first 12 weeks, central laboratory lipid results were unblinded, and investigators could adjust SOC therapies in both arms. Downtitration of statins continued from a phase 2 parent study was prohibited if the decision was based on unblinded LDL-C values obtained after week 12.

Study visits occurred every 4 weeks for patients randomized to evolocumab+SOC. After their week 4 visits, patients randomized to SOC returned to the study center only for quarterly visits thereafter (weeks 12, 24, 36, 48, and 52); all other interval visits (every 4 weeks) were conducted over the phone. Sites collected blood samples at week 4 and at the quarterly visits.

Efficacy and Safety End Points

The primary efficacy objective was to characterize the effects of longer-term administration of evolocumab as assessed by LDL-C,

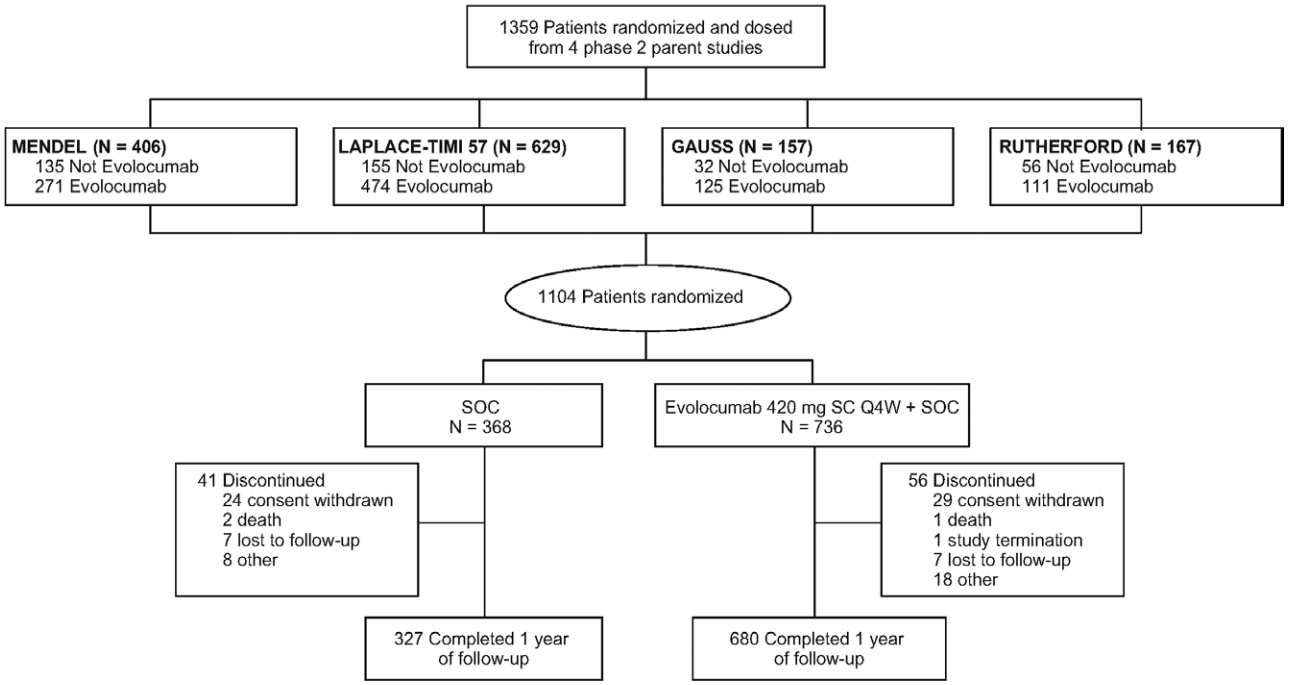

Figure 1. The Open-Label Study of Long-term Evaluation Against LDL-C (OSLER): patient disposition. GAUSS indicates Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects; LAPLACE-TIMI 57, LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy–Thrombolysis in Myocardial Infarction 57; MENDEL, Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels; Q4W, every 4 weeks; RUTHERFORD, Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder; SC, subcutaneous; and SOC, standard of care.

non–high-density lipoprotein cholesterol (non–HDL-C), apolipoprotein (Apo) B, ratio of total cholesterol to HDL-C, and ApoB/ApoA1 ratio in patients with hypercholesterolemia. The primary safety objective was to characterize the safety and tolerability of longer-term administration of evolocumab. Safety end points included the incidence of AEs, serious AEs, and AEs leading to discontinuation of investigational product. Other safety end points included the incidence of creatine kinase and liver function test abnormalities and the incidence and percentage of patients who developed anti-evolocumab antibodies (binding or neutralizing). Clinical events were adjudicated by an independent Clinical Events Committee and included cardiovascular and muscle-related events (see the Appendix in the online-only Data Supplement). An independent Data Monitoring Committee regularly reviewed data from this and other ongoing evolocumab studies, prepared by an external biostatistical group.

Laboratory Methods

Plasma lipids, ApoA1, ApoB, and lipoprotein(a) were measured after a fast of ≥9 hours on day 1 of open-label treatment (end-of-study visit for phase 2 parent study), at week 4, and every 12 weeks (weeks 12, 24, 36, 48, 52) for 1 year. LDL-C values with preparative ultracentrifugation[13] were obtained on day 1 and at 12-week intervals. All LDL-C values reported are based on the preparative ultracentrifugation method except those at week 4. Safety laboratory tests were performed by Covance Laboratories (Indianapolis, IN, or Geneva, Switzerland) and included serum chemistry, hematology, urinalysis, high-sensitivity C-reactive protein, and hemoglobin A_{1c}.

Analyses of serum lipids [total cholesterol, HDL-C, LDL-C, non–HDL-C, triglycerides, ApoB, ApoA1, and lipoprotein(a)] were performed by a central laboratory, Medpace Reference Laboratories (Cincinnati, OH, and Leuven, Belgium). LDL-C and very-low-density lipoprotein cholesterol were measured after preparative ultracentrifugation (β quantification).[14] LDL-C was also calculated with the Friedewald formula.[15] Binding and neutralizing anti-evolocumab antibodies were assayed as reported previously.[3] Additional details of laboratory methods are included in the Appendix in the online-only Data Supplement.

Statistical Analysis

For all end points, data were summarized for patients by the randomized treatment group. Patients were further categorized according to whether they were randomized to evolocumab in the phase 2 parent studies. AEs were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 16.0. Summary statistics for continuous variables included the number of patients, mean, median, standard deviation or standard error, 25th percentile, 75th percentile, minimum, and maximum. For categorical variables, the frequency and percentage were presented. All data analyses were based on observed values.

For continuous analyses, a 1-sample *t* test or Wilcoxon signed rank test was used for the comparisons with parent baseline and a 2-sample t test or Wilcoxon rank sum test was used for between-group comparisons. For categorical analyses, a χ^2 test was used to compare between treatment groups. All statistical tests were based on a 2-sided significance level of 0.05 without multiplicity adjustment. All statistical analyses were performed with SAS version 9.3.

Results

Patients

A total of 1104 patients enrolled in OSLER (81.2% of those randomized and dosed in phase 2 parent studies); most (88.0%) enrolled within 3 days of their last phase 2 parent study visits. Of the 1104 patients, 736 were randomized to receive evolocumab 420 mg every 4 weeks subcutaneously+SOC and 368 were randomized to receive SOC only for 52 weeks (Figure 1). Ninety-two percent of patients in the evolocumab+SOC group completed 52 weeks of follow-up, and 89% of patients in the SOC group completed 52 weeks of follow-up.

Overall, 55.3% of patients were female and 88.0% were white. Mean age was 56 years [SD, 12 years], and 11.4% of patients had a documented history of statin intolerance. Mean LDL-C at baseline of the pooled phase 2 parent studies was 3.6 mmol/L [SD, 1.0 mmol/L] (141.1 mg/dL [SD, 39.4 mg/dL]). OSLER participants included 210 patients (19.0%) with established coronary artery disease, 109 (9.9%) with type 2 diabetes mellitus, 297 (26.9%) with a family history of CHD, and 425 (38.5%) with metabolic syndrome (Table 1 and Table I in the online-only Data Supplement). A total of 691 patients (62.6%) were on statin therapy at baseline, and of those 691 patients, 295 (42.7%) received intensive statin therapy (defined as daily doses of atorvastatin ≥40 mg, rosuvastatin ≥20 mg, simvastatin 80 mg, or any statin plus ezetimibe). The proportion of patients who received statin therapy at baseline was higher in the evolocumab+SOC group (64.9%) compared with the SOC group (57.9%).

Only 4 of 736 patients (<1%) receiving evolocumab either discontinued a statin or switched from an intensive to a non-intensive statin regimen, and only 2 of 368 patients (<1%) in the SOC-only group discontinued statin use. A total of 20 patients (2.7%) in the evolocumab+SOC group and 33 patients (9.0%) in the SOC-only group initiated statin therapy during OSLER. Another 25 patients (6.8%) in the SOC group and 14 patients (1.9%) in the evolocumab+SOC group started taking nonstatin lipid-lowering therapies during OSLER, and 5 patients (1.4%) in the SOC group and 6 patients (0.8%) in the evolocumab+SOC group continued taking nonstatin lipid-lowering therapies during OSLER.

Efficacy Outcomes

Patients not taking evolocumab in the phase 2 parent study had large initial LDL-C reductions determined at 12 weeks after starting evolocumab treatment in OSLER (51.8% [SE, 1.6%] reduction from the parent study baseline; $P<0.0001$ versus baseline), with reductions maintained over the 52-week study period (52.3% [SE, 1.8%] at week 52; $P<0.0001$ versus baseline; Figure 2 and Table II in the online-only Data Supplement). Patients who received 1 of 6 dosing regimens of evolocumab (70, 105, 140 mg every 2 weeks or 280, 350, 420 mg every 4 weeks) in the parent studies and received evolocumab 420 mg every 4 weeks+SOC in OSLER had persistent reductions in LDL-C (compared with baseline, from 50.4% [SE, 0.8%] at the end of the parent study to 52.1% [SE, 1.0%] at 52 weeks; paired *t* test, $P=0.31$). For patients who discontinued evolocumab after random assignment to SOC in OSLER, mean reductions in calculated LDL-C from baseline went from 53.1% [SE, 1.2%] at the start of OSLER to 17.9% [SE, 1.2%] at 4 weeks and then to near baseline levels (5.8% [SE, 1.2%]) within 12 weeks without a rebound effect.

Percentage changes from the phase 2 parent study baseline in other lipid parameters, including ApoB, lipoprotein(a), and triglycerides, are shown in Figure 3 and Table III in the online-only Data Supplement. ApoB and lipoprotein(a) reductions tracked those observed for LDL-C. For HDL-C and ApoA1, patients who continued treatment with evolocumab maintained the observed larger increases for the 52-week treatment period compared with the patients who discontinued

Table 1. Baseline Patient Characteristics

Characteristic	SOC (n=368)	Evolocumab 420 mg Every 4 wk+SOC (n=736)
Age, mean (SD), y	56.7 (11.7)	56.1 (11.9)
Female sex, n (%)	206 (56.0)	404 (54.9)
Race, n (%)		
White	324 (88.0)	648 (88.0)
Asian	11 (3.0)	21 (2.9)
Black	24 (6.5)	55 (7.5)
Other	9 (2.4)	12 (1.6)
Coronary artery disease, n (%)*	57 (15.5)	153 (20.8)
Cardiovascular risk factors, n (%)		
Current cigarette use	49 (13.3)	126 (17.1)
Type 2 diabetes mellitus	37 (10.1)	72 (9.8)
Family history of coronary heart disease†	96 (26.1)	201 (27.3)
Metabolic syndrome‡	134 (36.4)	291 (39.5)
Statin use, n (%)		
Nonintensive	123 (33.4)	273 (37.1)
Intensive§	90 (24.5)	205 (27.9)
Lipid parameters at the parent study baseline		
LDL-C by ultracentrifugation, mean (SD), mmol/L	3.7 (1.0)	3.6 (1.0)
LDL-C, calculated, mean (SD), mmol/L	3.7 (1.1)	3.6 (1.0)
Total cholesterol, mean (SD), mmol/L	5.8 (1.2)	5.6 (1.2)
HDL-C, mean (SD), mmol/L	1.4 (0.4)	1.4 (0.4)
Non–HDL-C, mean (SD), mmol/L	4.4 (1.2)	4.3 (1.1)
Total cholesterol/HDL-C ratio, mean (SD)	4.6 (1.7)	4.4 (1.5)
VLDL-C, median (Q1, Q3), mmol/L	0.6 (0.4, 0.8)	0.6 (0.4, 0.8)
ApoB, mean (SD), g/L	1.1 (0.3)	1.1 (0.3)
ApoA1, g/L, mean (SD)	1.5 (0.3)	1.5 (0.3)
ApoB/ApoA1 ratio, mean (SD)	0.8 (0.2)	0.7 (0.2)
Triglycerides, median (Q1, Q3), mmol/L	1.4 (1.0, 1.9)	1.4 (1.1, 1.9)
Lp(a), median (Q1, Q3), nmol/L	36.0 (11.0, 115.0)	40.0 (12.0, 151.0)
Free PCSK9, mean (SD), nmol/L	5.8 (2.1)	6.1 (2.0)

ApoA1 indicates apolipoprotein A1; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a): lipoprotein(a); PCSK9. proprotein convertase subtilisin kexin 9 Q1, 25th percentile; Q3, 75th percentile; SD, standard deviation; SOC, standard of care; and VLDL-C, very low-density lipoprotein cholesterol.

*Based on the presence of angina, myocardial infarction, coronary artery bypass graft, or percutaneous coronary intervention.

†Based on presence of coronary heart disease in a first-degree relative male ≤55 years of age or female relative ≤65 year of age.

‡Defined as having 3 or more of the following factors: elevated waist circumference, triglycerides ≥150 mg/dL, low HDL-C (<40 mg/dL in men and <50 mg/dL in women), systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, or hypertension.

§Defined as simvastatin 80 mg/d, atorvastatin ≥40 mg/d, rosuvastatin ≥20 mg/d, or any statin plus ezetimibe.

evolocumab. Median triglyceride levels fell slightly in the evolocumab+SOC groups over 52 weeks (Figure 3).

Evolocumab+SOC patients reached ultracentrifugation LDL-C levels of <2.6 mmol/L (100 mg/dL) or <1.8 mmol/L (70 mg/dL) more frequently than patients on SOC alone. Among the patients who had at least 1 ultracentrifugation LDL-C post baseline value during OSLER, LDL-C <2.6 mmol/L (100 mg/dL) was achieved at least at 1 visit by 96.0% of patients treated with evolocumab+SOC but only 32.4% of patients in the SOC group (P<0.0001; Table 2). Among the patients who had ultracentrifugation LDL-C values at all OSLER visits, LDL-C <2.6 mmol/L (100 mg/dL) was achieved at every visit by 72.1% of patients treated with evolocumab+SOC but only 3.3% of patients in the SOC group (P<0.0001) over 52 weeks. Similarly, LDL-C <1.8 mmol/L (70 mg/dL) was achieved at least at 1 visit by 82.8% of patients treated with evolocumab+SOC but only 3.6% of patients in the SOC group (P<0.0001). Among the patients who had ultracentrifugation LDL-C values at all OSLER visits, LDL-C <1.8 mmol/L (70 mg/dL) was achieved at every visit by 37.8% of patients treated with evolocumab+SOC and no patients in the SOC group (P<0.0001).

Achievement of ultracentrifugation LDL-C levels of <1.3 mmol/L (50 mg/dL) or <0.65 mmol/L (25 mg/dL) at any OSLER visit occurred in 55.6% and 13.3% of evolocumab+SOC patients, respectively. In contrast, only 2 patients (0.5%) in the SOC group reached LDL-C <1.3 mmol/L (50 mg/dL), and none achieved LDL-C <0.65 mmol/L (25 mg/dL). Among the evolocumab+SOC group patients, of those who achieved LDL-C <1.3 mmol/L (50 mg/dL), 76.0% used statins at baseline, and of those who achieved LDL-C <0.65 mmol/L (25 mg/dL), 86.7% took statins. Statin use was 51.1% in patients with LDL-C levels ≥1.3 mmol/L (50 mg/dL). Among SOC patients, 1 of the 2 patients who reached LDL-C <1.3 mmol/L (50 mg/dL) and 57.9% of those with LDL-C ≥1.3 mmol/L (50 mg/dL) were taking statins at baseline.

Safety and Tolerability

Adverse events occurred in 269 patients (73.1%) in the SOC group and 599 patients (81.4%) in the evolocumab+SOC group (Table 3). The 5 most commonly reported AEs in the 2 groups were nasopharyngitis, upper respiratory tract infections, influenza, arthralgia, and back pain. Investigators considered AEs as possibly related to evolocumab in 5.6% of all AEs. Six patients (1.6%) in the SOC group and 13 patients (1.8%) in the evolocumab+SOC group had alanine aminotransferase or aspartate aminotransferase values >3 times the upper limit of normal. One patient (0.3%) in the SOC group and 4 patients (0.5%) in the evolocumab+SOC group experienced an elevation in alanine aminotransferase or aspartate aminotransferase >5 times the upper limit of normal. Serious AEs occurred in 23 SOC patients (6.3%) and 52 patients (7.1%) in the evolocumab+SOC group. No particular serious AEs affected ≥2% of patients in either group or was considered by investigators to be possibly related to evolocumab. Twenty-seven patients (3.7%) had AEs that led to the discontinuation of evolocumab, with low frequencies of specific events (Table IV in the online-only Data Supplement). Injection-site reactions were reported in 38 patients (5.2%) in the evolocumab+SOC group and led to discontinuation of evolocumab in only 1 patient. No patient in the SOC group received evolocumab or placebo injections during the study. No neutralizing antibodies to evolocumab were detected in OSLER. Low-titer binding antibodies were detected

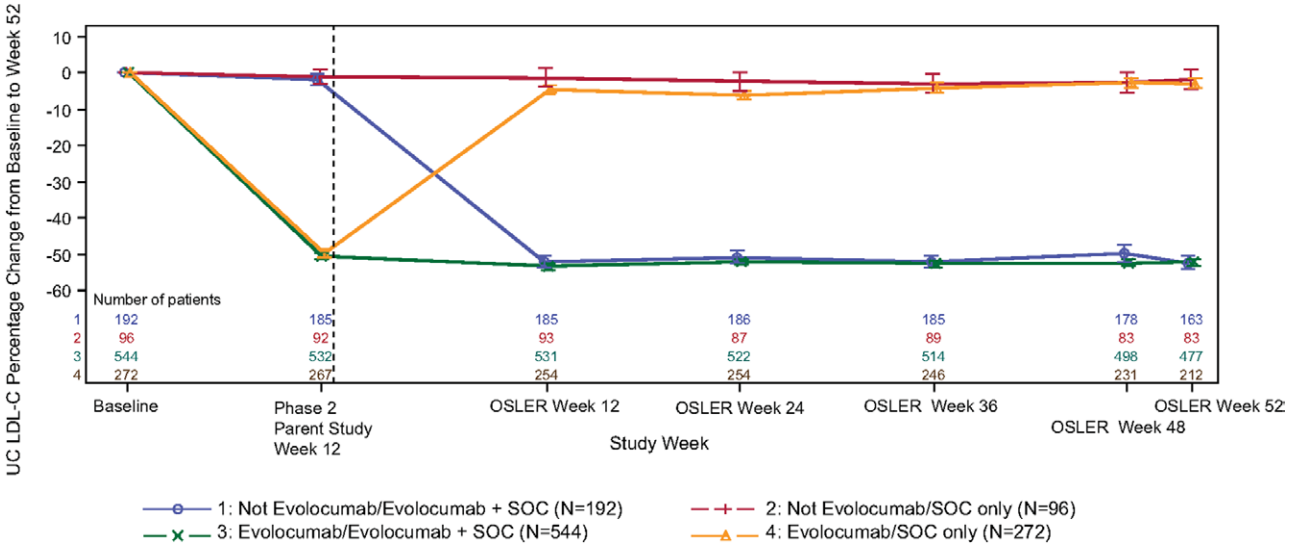

Figure 2. Ultracentrifugation low-density lipoprotein cholesterol (UC LDL-C) percentage change from the phase 2 parent study baseline to week 52. Dashed vertical line indicates time between phase 2 parent and Open-Label Study of Long-term Evaluation Against LDL-C (OSLER) studies. Error bars represent standard error. Plot is based on observed data, and no imputation was used for missing values. SOC indicates standard of care.

at week 4 of OSLER in 2 patients in the SOC group who had received evolocumab in the phase 2 parent study; results at subsequent time points were negative for binding antibodies.

A total of 411 patients (99.5% of whom were receiving evolocumab) achieved LDL-C <1.3 mmol/L (50 mg/dL), and 98 patients (all of whom were receiving evolocumab) achieved LDL-C <0.65 mmol/L (25 mg/dL), whereas 682 patients (47.4% of whom were receiving evolocumab) had LDL-C levels ≥1.3 mmol/L (50 mg/dL). Overall AEs, serious AEs, elevations in creatine kinase, and elevations in aminotransferases were not appreciably greater in those who achieved low LDL-C (Table 4 and Table V in the online-only Data

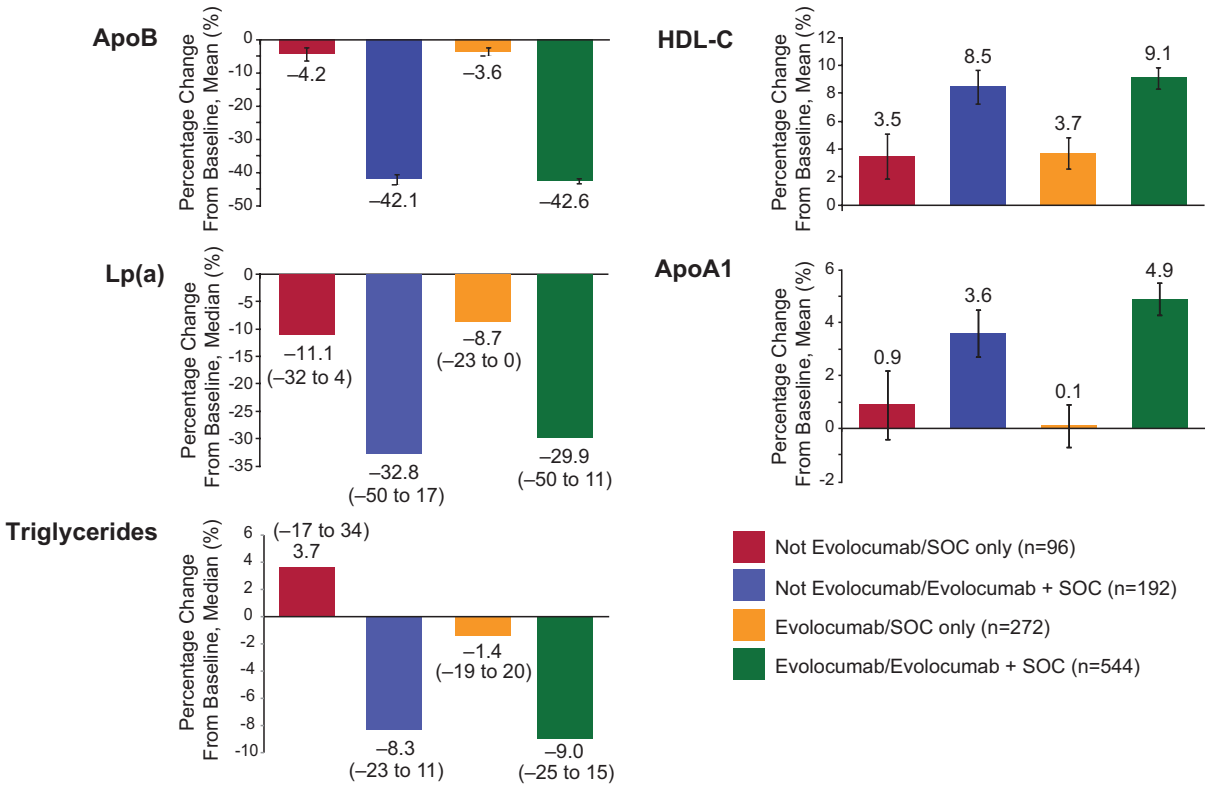

Figure 3. Percentage change from phase 2 parent study baseline at week 52 in apolipoprotein B (ApoB), lipoprotein(a) [Lp(a)], triglycerides, high-density lipoprotein cholesterol (HDL-C), and apolipoprotein A1 (ApoA1). The changes in lipid parameters from baseline in patients receiving evolocumab were all statistically significant ($P<0.0001$, except for the changes in triglycerides which were $P<0.05$). The reductions in lipid parameters were greater for patients receiving evolocumab+SOC vs. SOC alone ($P\leq0.0002$). Error bars represent standard error. SOC indicates standard of care. Data in parentheses represent interquartile ranges.

Table 2. Percentage of Patients Who Achieved Ultracentrifugation LDL-C Goals at Follow-Up OSLER Visits

Category (n with evaluable LDL-C measurement in SOC and in evolocumab 420 mg every 4 wk+SOC)	<2.6 mmol/L (100 mg/dL), n (%)		<1.8 mmol/L (70 mg/dL), n (%)	
	SOC	Evolocumab 420 mg Every 4 wk+SOC	SOC	Evolocumab 420 mg Every 4 wk+SOC
At parent EOS (359, 717)	231 (64.4)	491 (68.5)	151 (42.1)	302 (42.1)
At week 12 (347, 716)	60 (17.3)	621 (86.7)	1 (0.3)	443 (61.9)
At week 24 (341, 708)	59 (17.3)	613 (86.6)	3 (0.9)	431 (60.9)
At week 36 (335, 699)	47 (14.0)	598 (85.6)	5 (1.5)	430 (61.5)
At week 48 (314, 676)	43 (16.7)	580 (85.8)	2 (0.6)	415 (61.4)
At week 52 (295, 640)	47 (15.9)	552 (86.3)	3 (1.0)	400 (62.5)
Met target goal at any post baseline visit† (361, 732)	117 (32.4)	703 (96.0)	13 (3.6)	606 (82.8)
Met target goal at all post baseline visits‡ (269, 606)	9 (3.3)	437 (72.1)	0 (0.0)	229 (37.8)
By baseline statin use				
Any statin use				
Met target goal at any post baseline visit† (209, 476)	82 (39.2)	458 (96.2)	6 (2.9)	418 (87.8)
Met target goal at all post baseline visits‡ (163, 399)	8 (4.9)	301 (75.4)	0 (0.0)	179 (44.9)
No statin use				
Met target goal at any post baseline visit† (152, 256)	35 (23.0)	245 (95.7)	7 (4.6)	188 (73.4)
Met target goal at all post baseline visits‡ (106, 207)	1 (0.9)	136 (65.7)	0 (0.0)	50 (24.2)

EOS indicates end of study; LDL-C, low-density lipoprotein cholesterol; OSLER, Open-Label Study of Long-term Evaluation Against LDL-C; and SOC, standard of care. $P<0.0001$ for all comparisons (except at parent EOS) between SOC and evolocumab 420 mg every 4 weeks+SOC.

†Based on the patients who had at least 1 nonmissing post baseline value.

‡Based on the patients who had nonmissing values at all post baseline visits in OSLER.

Supplement). Headaches, dizziness, insomnia, and back pain tended to occur with greater frequency in those with lower LDL-C. A total of 2.2% of patients in the SOC group and 1.2% patients in the evolocumab+SOC group experienced an adjudicated cardiovascular clinical event (Table 5). Three deaths were reported during the 52-week study. Two patients died in the SOC group: a 53-year-old man who did not receive evolocumab in the phase 2 parent study died of unknown causes at 7.3 months, and a 40-year-old woman who received evolocumab in a parent study died of a pulmonary embolism at 9.8 months. A 45-year-old man in the evolocumab+SOC group who also received evolocumab in the phase 2 parent study and was known to have significant coronary artery disease and a ventricular aneurysm was found to be deceased during month 5 of OSLER.

Discussion

As the first large longer-term evaluation of a PCSK9 inhibitor, findings from the OSLER trial extend the understanding of a novel therapy and provide insight into the efficacy, safety, and tolerability of evolocumab treatment in hypercholesterolemic patients. Evolocumab reduced LDL-C on average by ≈50% beyond the reduction achieved with optimal SOC in various hypercholesterolemic patient populations. The reductions in lipid levels achieved after 12 weeks were stable over the course of the study without evidence of attenuation. Conversely, discontinuation of evolocumab led to a fairly rapid return to baseline levels, although importantly, without a rebound phenomenon.

OSLER enrolled a heterogeneous group of participants recruited from phase 2 studies of hypercholesterolemic patients on a statin,[4] not on a statin,[5] intolerant to statins,[10] and with heterozygous familial hypercholesterolemia.[7] This heterogeneity in the population provides a broad view of how a novel therapy may affect a spectrum of patients. For example, we found that 72.1% of evolocumab-treated patients reached LDL-C levels <2.6 mmol/L (100 mg/dL) at all lipid measurements over 52 weeks compared with 3.3% of the SOC group patients, even though SOC patients could have their therapy adjusted after 12 weeks into the study.

As healthcare quality assessments shift toward measured outcomes, the predictability of achieving lipid treatment targets as demonstrated in OSLER will likely take on additional importance. Anti-PCSK9 antibodies, if deployed strategically, may lead to greater numbers within a treated population reaching and maintaining stable goals for LDL-C and other lipoproteins. Challenging patients such as those who fail to reach current lipid goals despite maximum doses of highly effective statin agents or those with well-documented statin intolerance are thus logical populations for treatment with PCSK9 inhibitors.

More broadly, the emergence of anti-PCSK9 therapies may provide a means to help answer the long-debated clinical question of how low to reduce LDL-C in patients at risk. Several lines of evidence suggest that further clinical benefits could accrue from lowering LDL-C to levels below those currently advocated. This evidence includes Mendelian randomization analyses showing that genetic variations that produce very low levels of LDL-C confer high levels of protection against atherosclerotic complications without known offsetting morbidity or mortality.[16,17] Observations from statin clinical trials provide another compelling argument for aggressive treatment. In these trials, cohorts with the lowest LDL-C levels consistently experienced the fewest

Table 3. Adverse Events and Laboratory Results

Adverse Events	SOC (n=368), n (%)	Evolocumab 420 mg Every 4 wk+SOC (n=736), n (%)
Any	269 (73.1)	599 (81.4)
Serious	23 (6.3)	52 (7.1)
Leading to discontinuation of investigational product (evolocumab)	NA	27 (3.7)
Deaths	2 (0.5)	1 (0.1)
Most common adverse events		
Nasopharyngitis	36 (9.8)	90 (12.2)
Upper respiratory tract infection	28 (7.6)	57 (7.7)
Influenza	19 (5.2)	52 (7.1)
Arthralgia	16 (4.3)	51 (6.9)
Back pain	20 (5.4)	48 (6.5)
Muscle related	36 (9.8)	68 (9.2)
Injection-site reactions	NA*	38 (5.2)
Laboratory results		
ALT or AST >3×ULN at any post baseline visit	6 (1.6)	13 (1.8)
ALT or AST >5×ULN at any post baseline visit	1 (0.3)	4 (0.5)
Creatine kinase >5×ULN at any post baseline visit	7 (1.9)	7 (1.0)
Creatine kinase >10×ULN at any post baseline visit	2 (0.5)	2 (0.3)

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable; SOC, standard of care; and ULN, upper limit of normal.

*Patients in the SOC group did not receive injections.

adverse clinical outcomes, and patients with LDL-C levels <1.3 mmol/L (50 mg/dL) seemed to fare best.[18,19]

OSLER demonstrated that the vast majority of patients treated with evolocumab can achieve LDL-C levels significantly below current guidelines. The high percentage of OSLER patients with LDL-C <1.3 mmol/L (50 mg/dL), especially those with coadministered statin therapy, suggests that future cardiovascular outcomes trials with evolocumab may be useful to explore the benefit of LDL-C reductions beyond current targets. These studies may also help to define whether clinical gains accrue from the further therapeutic upregulation of LDL receptors, a mechanism of action that PCSK9 inhibition shares with statin therapy.

In terms of tolerability, the high participation rate (81%) from the phase 2 parent evolocumab studies reflects good tolerance of the parenteral therapy, as reported in the short-term studies.[4,5,7,10] Moreover, the low rate of patients who discontinued evolocumab due to AEs (3.7%) also indicates excellent ongoing acceptance of the therapy. Overall, AEs were approximately balanced between the evolocumab+SOC and SOC groups over a year of treatment despite more frequent on-site contact in the evolocumab+SOC group. Injection-site reactions occurred in 5.2% of patients in the evolocumab+SOC group. Side effects of particular concern such as liver function test abnormalities, muscle symptoms, or laboratory abnormalities occurred no more frequently in evolocumab-treated patients than in those treated with SOC. In addition, the absence of neutralizing antibodies and the rarity of binding antibodies in OSLER provide reassurance about the long-term immunogenicity of evolocumab and are consistent with observations in the short-term evolocumab studies. These findings are important because even small untoward off-target effects of LDL-C–lowering therapy may mask or outweigh the antiatherosclerotic benefits of a lipid-lowering treatment. This phenomenon may have affected outcomes in trials of previously studied agents that have positively affected lipid profiles but have led to negative or neutral clinical results.[20–23]

OSLER also provides information about the safety of treating patients to low and very low levels of LDL-C over 1 year. Overall AE rates, serious AE rates, and elevations in creatine kinase and aminotransferases were not appreciably greater in those who achieved low LDL-C. These data suggest that evolocumab may offer significant gains in additional LDL-C lowering without incurring the increased likelihood of untoward laboratory effects, as seen during dose escalation of statins.[24–26] OSLER patients who reached low and very low LDL-C levels reported slightly higher rates of headache, dizziness, insomnia, and back pain. This slightly higher reported rate of minor, subjective symptoms requires cautious interpretation because it may have resulted from an asymmetry in the protocol design, which required a greater number of face-to-face interactions with site personnel for patients treated with injection therapy. Hemorrhagic stroke, a reported cause of concern related to low levels of LDL-C, was not observed during OSLER, and other forms of neurological dysfunction such as amnesia and memory/mental impairment were reported uncommonly (in ≤1% of patients in any group). Safety observations related to the achievement of low LDL-C levels warrant continued investigation, particularly in studies in which lipid results are blinded.

Several potential limitations of this study should be considered. OSLER included a heterogeneous population who completed phase 2 studies. Although this diversity might be viewed as a strength in terms of the generalizability of the findings, some of the included patients such as the low-risk patients from MENDEL who did not receive statin therapy at baseline may not represent a population that will ultimately receive anti-PCSK9 therapy. Furthermore, it should be noted that 6 dosing regimens of evolocumab were used in the phase 2 parent trials, whereas only the top every-4-weeks dose was used in OSLER. LDL-C measurements were available in 85% of patients at week 52 and imputation was not performed for missing data. However, we do not anticipate that missing data, if observed, would appreciably affect the results or conclusions. OSLER was not designed to rigorously address either the likelihood of LDL-C goal attainment for patients who previously failed to reach lipid goals or to attempt to treat populations to specific targeted levels of LDL-C. Therefore observations made related to these issues should be regarded as exploratory. Finally, the open-label design and more frequent visits for patients allocated to evolocumab limit the interpretation of the relative rates of AEs between the 2 arms.

OSLER was not powered or designed as an outcomes study; rather, the ongoing Further Cardiovascular Outcomes

Table 4. Adverse Events by Patient's Lowest Post baseline Ultracentrifugation LDL-C Value

	LDL-C <0.65 mmol/L (<25 mg/dL), n (%)		LDL-C <1.3 mmol/L (<50 mg/dL), n (%)		LDL-C ≥1.3 mmol/L (≥50 mg/dL), n (%)	
Adverse Events	SOC (n=0)	Evolocumab 420 mg Every 4 wk+SOC (n=98)	SOC (n=2)	Evolocumab 420 mg Every 4 wk+SOC (n=409)	SOC (n=359)	Evolocumab 420 mg Every 4 wk+SOC (n=323)
Any	NA	80 (81.6)	0 (0.0)	336 (82.2)	268 (74.7)	262 (81.1)
Serious adverse events	NA	5 (5.1)	0 (0.0)	27 (6.6)	22 (6.1)	25 (7.7)
CK >5×ULN	NA	2 (2.0)	0 (0.0)	2 (0.5)	7 (1.9)	5 (1.5)
CK >10×ULN	NA	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.6)
ALT or AST >3×ULN	NA	1 (1.0)	0 (0.0)	3 (0.7)	6 (1.7)	10 (3.1)
Total bilirubin >2×ULN	NA	2 (2.0)	0 (0.0)	4 (1.0)	1 (0.3)	0 (0.0)
Nervous system disorders	NA	19 (19.4)	0 (0.0)	64 (15.6)	37 (10.3)	44 (13.6)
Headache	NA	9 (9.2)	0 (0.0)	25 (6.1)	10 (2.8)	21 (6.5)
Dizziness	NA	4 (4.1)	0 (0.0)	11 (2.7)	11 (3.1)	5 (1.5)
Migraine	NA	1 (1.0)	0 (0.0)	4 (1.0)	1 (0.3)	7 (2.2)
Amnesia	NA	1 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)
Memory impairment*	NA	0 (0.0)	0 (0.0)	4 (1.0)	0 (0.0)	1 (0.3)
Hepatobiliary disorders	NA	1 (1.0)	0 (0.0)	3 (0.7)	3 (0.8)	1 (0.3)
Psychiatric disorders	NA	5 (5.1)	0 (0.0)	20 (4.9)	12 (3.3)	15 (4.6)
Insomnia	NA	4 (4.1)	0 (0.0)	9 (2.2)	4 (1.1)	4 (1.2)
Depression	NA	1 (1.0)	0 (0.0)	6 (1.5)	5 (1.4)	5 (1.5)
Anxiety	NA	0 (0.0)	0 (0.0)	4 (1.0)	2 (0.6)	5 (1.5)
Renal and urinary disorders	NA	1 (1.0)	0 (0.0)	9 (2.2)	11 (3.1)	8 (2.5)
Musculoskeletal and connective tissue disorders	NA	34 (34.7)	0 (0.0)	135 (33.0)	89 (24.8)	84 (26.0)
Back pain	NA	12 (12.2)	0 (0.0)	31 (7.6)	20 (5.6)	17 (5.3)
Arthralgia	NA	7 (7.1)	0 (0.0)	34 (8.3)	16 (4.5)	17 (5.3)
Pain in extremity	NA	7 (7.1)	0 (0.0)	21 (5.1)	10 (2.8)	15 (4.6)

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; NA, not applicable; SOC, standard of care; and ULN, upper limit of normal.

*Includes memory impairment and mental impairment terms.

Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER; NCT01764633) trial will address this important issue. Nonetheless, it is reassuring that adjudicated cardiovascular clinical events occurred no more frequently in evolocumab-treated patients or in patients who reached low LDL-C levels than in SOC patients treated less aggressively. Although the absence of a safety signal provides support for further development of evolocumab, ongoing trials will ultimately determine the benefits, or lack thereof, derived from treatment to reduce LDL-C levels with PCSK9 inhibitors.

Table 5. Patient Incidence of Adjudicated Cardiovascular Clinical Events

	SOC (n=368), n (%)	Evolocumab 420 mg Every 4 wk+SOC (n=736), n (%)
Patients with any positively adjudicated cardiovascular clinical event	8 (2.2)	9 (1.2)
Death	2 (0.5)	1 (0.1)
Myocardial infarction (fatal and nonfatal)	3 (0.8)	0 (0.0)
Hospitalization for unstable angina	2 (0.5)	2 (0.3)
Revascularization	4 (1.1)	6 (0.8)
Cerebrovascular event	1 (0.3)	3 (0.4)
Transient ischemic attack	1 (0.3)	2 (0.3)
Ischemic stroke	0 (0.0)	1 (0.1)
Hemorrhagic stroke	0 (0.0)	0 (0.0)
Hospitalization for heart failure	1 (0.3)	0 (0.0)

SOC indicates standard of care.

Conclusions

The OSLER trial is the largest and longest efficacy and safety evaluation of an anti-PCSK9 antibody to date. Findings in a diverse patient population during >1000 patient-years of observation suggest a highly effective, consistent, and well-tolerated therapy. Ongoing outcomes trials will further define the clinical utility of evolocumab and other agents in its class as an emerging approach to the treatment of hypercholesterolemia.

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CLINICAL PERSPECTIVE

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a serine protease, impairs low-density lipoprotein cholesterol (LDL-C) clearance from plasma through its pivotal role of signaling the degradation of LDL-C receptors. Evolocumab is a fully human monoclonal antibody targeted against PCSK9. In 4 separate phase 2 dose ranging studies of 12 weeks' duration in patients on statins, with familial hypercholesterolemia, with low risk hypercholesterolemia not on statins, and with statin intolerance, evolocumab reduced LDL-C by up to 65%. The Open-Label Study of Long-term Evaluation Against LDL-C (OSLER), a global clinical trial, included 1104 patients who completed the 4 phase 2 studies and were randomized 2:1, regardless of their phase 2 study assignment, to either open-label subcutaneous evolocumab 420 mg every 4 weeks plus standard of care or standard of care alone. Patients who first received evolocumab in OSLER experienced a 52.3% LDL-C reduction after week 52 ($P<0.0001$) compared with the phase 2 parent study pretreatment baseline. Patients randomized to continue evolocumab after completing phase 2 studies experienced persistent stable reductions in LDL-C. Patients who discontinued evolocumab on entry into OSLER had their LDL-C levels return to near baseline without a rebound effect. Adverse events were largely balanced between groups except for minor injection-site reactions. No neutralizing antidrug antibodies were detected during 52 weeks of follow-up. OSLER, the first large, longer-term evaluation of anti-PCSK9 therapy, shows that evolocumab is well tolerated and demonstrates continued efficacy over 1 year of treatment in a diverse group of patients with hypercholesterolemia.