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Long-Term Efficacy and Safety of Evolocumab in Patients With Hypercholesterolemia

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ABSTRACT

BACKGROUND Evolocumab and other anti-PCSK9 antibodies reduced adverse cardiovascular outcomes in clinical trials of high-risk patients over <3 years median treatment duration.

OBJECTIVES The OSLER-1 trial (Open Label Study of Long Term Evaluation Against LDL-C Trial) evaluated longer-term effects of evolocumab during open-label hypercholesterolemia treatment for up to 5 years.

METHODS Patients randomized to standard of care (SOC) or evolocumab 420 mg monthly (evolocumab + SOC) for year 1. After year 1, patients could enter the all-evolocumab period and receive evolocumab + SOC for an additional 4 years. The authors analyzed the persistence of lipid effects and exposure-dependent safety focusing on yearly rates of adverse events (AEs) and anti-drug antibodies over 4.951 patient-years of observation.

RESULTS A total of 1,255 patients (safety analysis population) randomized into the year 1 SOC-controlled period and received ≥1 evolocumab dose (mean ± SD age 57 ± 12 years; 53% female). A total of 1,151 patients (efficacy analysis population) progressed to the all-evolocumab period (year 2 and beyond). Evolocumab + SOC persistently lowered mean ± SE low-density lipoprotein cholesterol (LDL-C) by 56% ± 0.6% (n = 1,071), 57% ± 0.8% (n = 1,001), 56% ± 0.8% (n = 943), and 56% ± 0.8% (n = 803) after approximately 2, 3, 4, and 5 years, respectively, from randomization. Mean baseline LDL-C decreased from 140 to 61 mg/dl on treatment. Yearly serious AE rates during evolocumab + SOC ranged from 6.9% to 7.9%, comparable to the 6.8% rate in SOC patients during year 1. Evolocumab discontinuation due to AEs occurred in 5.7% of patients. Two SOC and 2 evolocumab + SOC patients developed new, transient, binding anti-drug antibodies; no neutralizing antibodies were observed.

CONCLUSIONS The OSLER-1 trial demonstrated consistently excellent LDL-C–lowering efficacy, tolerance, and safety of evolocumab, with no neutralizing antibodies detected, throughout the longest-duration study of a PCSK9 inhibitor reported to date. (Open Label Study of Long Term Evaluation Against LDL-C Trial [OSLER-1]; NCT01439880) (J Am Coll Cardiol 2019;74:2132–46) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Therapeutic monoclonal antibodies directed against proprotein convertase subtilisin/kexin type 9 (PCSK9) have emerged as a highly effective and well-tolerated treatment for lipid disorders (1). Evolocumab, 1 of the 2 PCSK9 antibodies that have received regulatory approval (2), consistently lowers low-density lipoprotein cholesterol (LDL-C) by approximately 60% as monotherapy or in combination with lipid-lowering therapies, such as statins, across diverse patient populations with hypercholesterolemia (3–8). Studies of evolocumab have shown consistently large LDL-C–lowering effects and excellent tolerance of therapy in both men and women, among patients of various ethnicities and racial backgrounds, in populations with or without known pre-existing cardiovascular disease, and in patients with familial hypercholesterolemia or intolerance of statins (3–8). Furthermore, evolocumab and other PCSK9 antibodies produce smaller, but consistently favorable, effects on triglycerides and lipoprotein(a) (Lp[a]) levels (9–11).

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Recently, the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) study became the first large-scale randomized, double-blind clinical trial to demonstrate that the salutary lipid effects of PCSK9 inhibition lead to improved cardiovascular outcomes (12). Over a median treatment of 26 months, evolocumab reduced the risk of the primary composite endpoint of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization by 15% in a high-risk population with atherosclerotic cardiovascular disease and additional cardiovascular risk factors (81% with history of myocardial infarction, 19% with a prior nonhemorrhagic stroke, and 13% with symptomatic peripheral artery disease) (12). The FOURIER trial suggested that the benefits of persistently low lipid levels increase over time. Specifically, evolocumab reduced the risk of cardiovascular death, myocardial infarction, or stroke by 16% in the first year and by 25% thereafter (12). This finding supports other data that show greater relative event reduction with extended LDL-C–lowering treatment due to the time-accrued cardiovascular benefits of lower LDL-C levels (13).

Two other PCSK9 inhibitors—bococizumab and alirocumab—have demonstrated outcome improvements in studies of 12 and 34 months of median drug exposure, respectively (14,15). The SPIRE (The Evaluation of Bococizumab [PF-04950615; RN316] in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects) studies with bococizumab showed that drug-specific characteristics influence the long-term tolerance and efficacy of anti-PCSK9 therapy. In the SPIRE studies, the lipid-lowering effects of bococizumab became attenuated over time, possibly related to the development of anti-drug antibodies (ADAs) (14). The high incidence of ADAs during treatment with bococizumab probably reflects immunogenicity due to the persistent murine elements of bococizumab as compared with the 2 currently approved, fully human anti-PCSK9 antibodies, evolocumab and alirocumab (14). Due to ADA development during long-term treatment, the manufacturer of bococizumab discontinued its clinical development (16).

The OSLER-1 (Open-Label Study of Long-Term Evaluation Against LDL-C Trial), initiated in 2011, has followed patients treated with evolocumab for up to 5 years (17,18). This final report of the OSLER-1 study describes findings from the longest duration of treatment experience with anti-PCSK9 antibodies to date.

ABBREVIATIONS AND ACRONYMS

ADA = anti-drug antibody

AE = adverse event

ApoB = apolipoprotein B

LDL-C = low-density lipoprotein cholesterol

Lp(a) = lipoprotein(a)

PCSK9 = proprotein convertase subtilisin/kexin type 9

SAE = serious adverse event

METHODS

Previous publications have described the design of the OSLER-1 study and have reported year 1 results (17) and preliminary longer-term results (18). The current paper reports the final safety results for the 1,255 patients (of the original 1,324 enrolled) who received at least 1 dose of evolocumab during the

support from Amgen; has received honoraria from Amgen, Amarin, Daiichi-Sankyo, Akcea, Bristol-Myers Squibb, CVS Caremark, and Pfizer. Dr. Langslet has received lecture and Advisory Board fees from Amgen, Sanofi, and Boehringer Ingelheim. Dr. Wiviott has received institutional grants from Amgen, Arena, AstraZeneca, Bristol-Myers Squibb, Daiichi-Sankyo, Eisai, Eli Lilly, Janssen, Merck, and Sanofi; has received consulting fees from Angel Medical Systems, ARENA, AstraZeneca, Allergan, Boehringer Ingelheim, Boston Clinical Research Institute, Bristol-Myers Squibb, Daiichi-Sankyo, Eisai, Eli Lilly, ICON Clinical Research, Janssen, Lexicon, Merck, St. Jude Medical, Servier, and Xoma; and his spouse is an employee of Merck. Drs. Ruzza and Hamer are employees of and own stocks/stock options in Amgen. Dr. Ma is employed as a contractor on behalf of Amgen. Dr. Wasserman is an employee of and holds stocks/stock options in Amgen; and appears on a number of pending patents owned by Amgen relating to evolocumab and PCSK9 inhibition. Dr. Raal has received research grants, honoraria, or consulting fees for professional input and/or delivered lectures from Sanofi, Regeneron, Amgen, and The Medicines Company.

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OSLER-1 study. This report also describes the final efficacy results for the 1,151 patients who entered the all-evolocumab period (year 2 and beyond), and received at least 1 dose of evolocumab during this period and 1 on-treatment laboratory blood draw. The OSLER-1 study provided long-term open-label exposure to evolocumab for up to 5 years.

STUDY DESIGN AND PATIENTS. The OSLER-1 study initially enrolled patients from 1 of 5 eligible phase 2 parent studies of evolocumab from 192 sites in 18 countries. Patients could participate in the OSLER-1 study provided that they did not discontinue treatment due to a serious adverse event (SAE) during their qualifying phase 2 study participation or require unblinded lipid measurements and/or adjustment of background lipid therapy during the first 12 weeks of the OSLER-1 study. The first patient consented to participate in the OSLER-1 study in October 2011. The last patient enrolled in June 2013. Final patient visits occurred in June 2018. This follow-up period includes at least 4 years of possible evolocumab exposure, considering that some patients received SOC only during the first year of their study participation before becoming eligible to receive open-label treatment with evolocumab.

The study randomized patients in a 2:1 ratio, irrespective of their treatment assignments during the phase 2 parent study, to either evolocumab 420 mg subcutaneously every 4 weeks plus standard of care (SOC) or SOC alone. Local investigators determined SOC therapy. Scheduled study visits occurred at 12-week intervals.

An independent ethics committee or institutional review board approved the protocol before study procedures at all sites. All patients provided written informed consent before enrollment into the extension study.

SAFETY AND EFFICACY ENDPOINTS. The primary objective of the OSLER-1 study was to characterize the safety and tolerability of long-term exposure to evolocumab (subject incidence of adverse events [AEs], SAEs, and events leading to evolocumab discontinuation). Other safety endpoints included the incidence of evolocumab ADAs. Analyses of events of special interest evaluated the incidence of new-onset diabetes, injection-site reactions, neurocognitive events, and adjudicated cardiovascular events.

The annualized safety analyses for patients exposed to evolocumab included 1,255 patients who received at least 1 dose of evolocumab during the OSLER-1 study. These analyses excluded 69 patients (5.2%) of the initial cohort of 1,324 who randomized to the SOC arm but did not advance to the all-evolocumab phase starting in year 2 and never received evolocumab. Safety analyses calculated exposure-adjusted yearly event rates to evaluate a possible time-dependent relationship between evolocumab exposure and the event.

Secondary study objectives characterized yearly changes in lipid levels compared with baseline levels measured before parent study participation. These parameters included LDL-C, non–HDL-C, apolipoprotein B (ApoB), total cholesterol/HDL-C ratios, and ApoB/apolipoprotein A-1 (ApoA1) ratios. Changes in Lp(a) were assessed as part of the exploratory endpoints. Lipid samples obtained at 52 weeks (year 1) determined the efficacy of evolocumab plus SOC versus SOC alone. Summed measurements from laboratory samples obtained during study weeks 100, 160, 208, and 260 determined year-end values reported for years 2, 3, 4, and 5, respectively, during the all-evolocumab period.

An independent clinical events committee adjudicated cardiovascular events (death, myocardial infarction, hospitalization for unstable angina, revascularization, cerebrovascular event [transient ischemic attack, ischemic stroke, hemorrhagic stroke], and hospitalization for heart failure) for exploratory analysis. An independent data monitoring committee regularly reviewed data from all ongoing randomized evolocumab studies, prepared by an external biostatistical group. Amgen assumed safety monitoring for open-label evolocumab studies as of March 2015 at the request of the data monitoring committee.

LABORATORY METHODS. Plasma lipids were measured from samples obtained after a fast of ≥9 h. Reported calculated LDL-C levels used the Friedewald formula. Previous reports have described the laboratory methods, including binding and neutralizing anti-evolocumab antibody assays, in detail (17). Assessment of anti-evolocumab binding antibodies used an electrochemiluminescence-based immunoassay. Patients who tested positive underwent subsequent evaluation for anti-evolocumab neutralizing antibodies. Surveillance testing for binding ADAs occurred every 12 weeks during the first year of the OSLER-1 study and at weeks 52, 100, 160, and 208, and at the end-of study visits. Testing for neutralizing antibodies followed all positive tests for binding ADAs.

STATISTICAL ANALYSIS. For baseline characteristics and efficacy endpoints during SOC-controlled year 1, data summaries analyzed all enrolled patients on the

basis of their randomized treatment group. During the year 2 to year 5 all-evolocumab period, data were combined by year of exposure to evolocumab and summarized for the patients who entered this period and received ≥1 dose of evolocumab. Lipid endpoint assessments, performed as "on-treatment" analyses, combined data from patients' blood samples obtained within 5 weeks of their last dose of evolocumab. Safety data analyses included all enrolled patients using descriptive statistics.

Adverse events coding used the *Medical Dictionary for Regulatory Activities* (MedDRA) version 21.0. AEs were reported by preferred term and tabulated for the SOC-alone group for the first year and by year of evolocumab exposure to evaluate a possible time-dependent relationship between evolocumab exposure and AEs. Summary statistics for continuous variables included the number of patients, mean, median, SD or SE, 25th percentile, 75th percentile, minimum, and maximum. For categorical variables, the frequency and percentages were presented. All data analyses used observed values.

We present both mean and median values for lipid endpoints. A nonparametric analysis of the Wilcoxon signed rank test was used for the comparison of percent change from baseline at week 52 between the evolocumab plus SOC group and the SOC-alone group.

Analyses of evolocumab discontinuation used Cox proportional hazards regression models. Factors included age, sex, diabetes status, coronary artery disease, high cardiovascular risk as defined by the European Society of Cardiology and National Cholesterol Education Program scoring criteria; baseline statin intensity; and baseline lipid panel parameters, including LDL-C, total cholesterol, triglycerides, and Lp(a). Parameters were tested separately in univariate Cox models and then in a multivariate stepwise selection procedure. The proportional hazard assumption of the Cox regression model was examined through graphic diagnosis on Kaplan-Meier curves for categorical predictor variables and found to be satisfied. All statistical tests used a 2-sided 0.05 significance level without multiplicity adjustment. An annualized evolocumab discontinuation rate was estimated using total patient exposure years based on exponential distribution. All statistical analyses performed used SAS version 9.3 (SAS Institute, Cary, North Carolina). Statisticians employed by the sponsor performed requested data analyses. Independent investigators had access to the data and could request queries of the database. Qualified researchers may request data from Amgen clinical studies.

RESULTS

Total exposure to evolocumab during the OSLER-1 study was 4,951 patient-years. A total of 1.324 patients initially enrolled in the OSLER-1 study and randomized into the 52-week SOC-controlled period (882 evolocumab plus SOC; 442 SOC alone) (**Figure 1**). A total of 1,151 patients (87% of patients who initially enrolled) completed the year 1 SOC-controlled portion of the OSLER-1 study, entered the all-evolocumab period (years 2–5), and received ≥1 dose of evolocumab followed by an "on-treatment" lipid measurement (efficacy population) (**Figure 1**). The safety population set included 1,255 patients who received ≥1 dose of evolocumab during the study. This population includes 881 patients who received ≥1 dose of evolocumab during year 1 and 374 patients initially randomized to SOC who received their first dose of evolocumab in year 2 (374 of 442 or 85% of the patients initially randomized to SOC) (**Figure 1**). A total of 659 patients had more than 4 years of exposure to evolocumab. Safety results include data from all patients participating in the study at a given time point. Lipid results reflect on-treatment analyses.

Table 1 provides summary demographic characteristics for the study population. Baseline demographics compared similarly between the safety (n = 1,255) and efficacy (n = 1,151) analysis populations and were balanced between patients initially randomized to the evolocumab plus SOC and the SOC-only groups.

Of the 1,255 patients who received at least 1 dose of evolocumab, 887 patients (71%) used statins at the time of receiving their first open-label dose of evolocumab; 253 (20%) received high-intensity, 393 (31%) moderate-intensity, and 223 (18%) low-intensity statin treatment. Of the 1,255 patients who received at least 1 dose of evolocumab, 168 patients (13%) decreased statin intensity, 123 (10%) stopped statins, and 49 (4%) either started (20 [2%]) or increased (29 [2%]) statin intensity. All patients receiving ezetimibe at the beginning of evolocumab treatment (171 [14%]) continued receiving ezetimibe during their study participation. Twelve patients (1%) added ezetimibe to their treatment during the course of the study. In the all-evolocumab efficacy set, 393 patients achieved an LDL-C value <40 mg/dl on 2 consecutive occasions, and 91 achieved an LDL-C value <25 mg/dl on 2 consecutive occasions.

LIPID EFFICACY OUTCOMES. **Figure 2** shows lipid measurements over the course of the study. Of the 1,151 patients in the efficacy (all-evolocumab) analysis set, on treatment LDL-C measurements were

FIGURE 1 **Patient Disposition in the OSLER-1 Study**

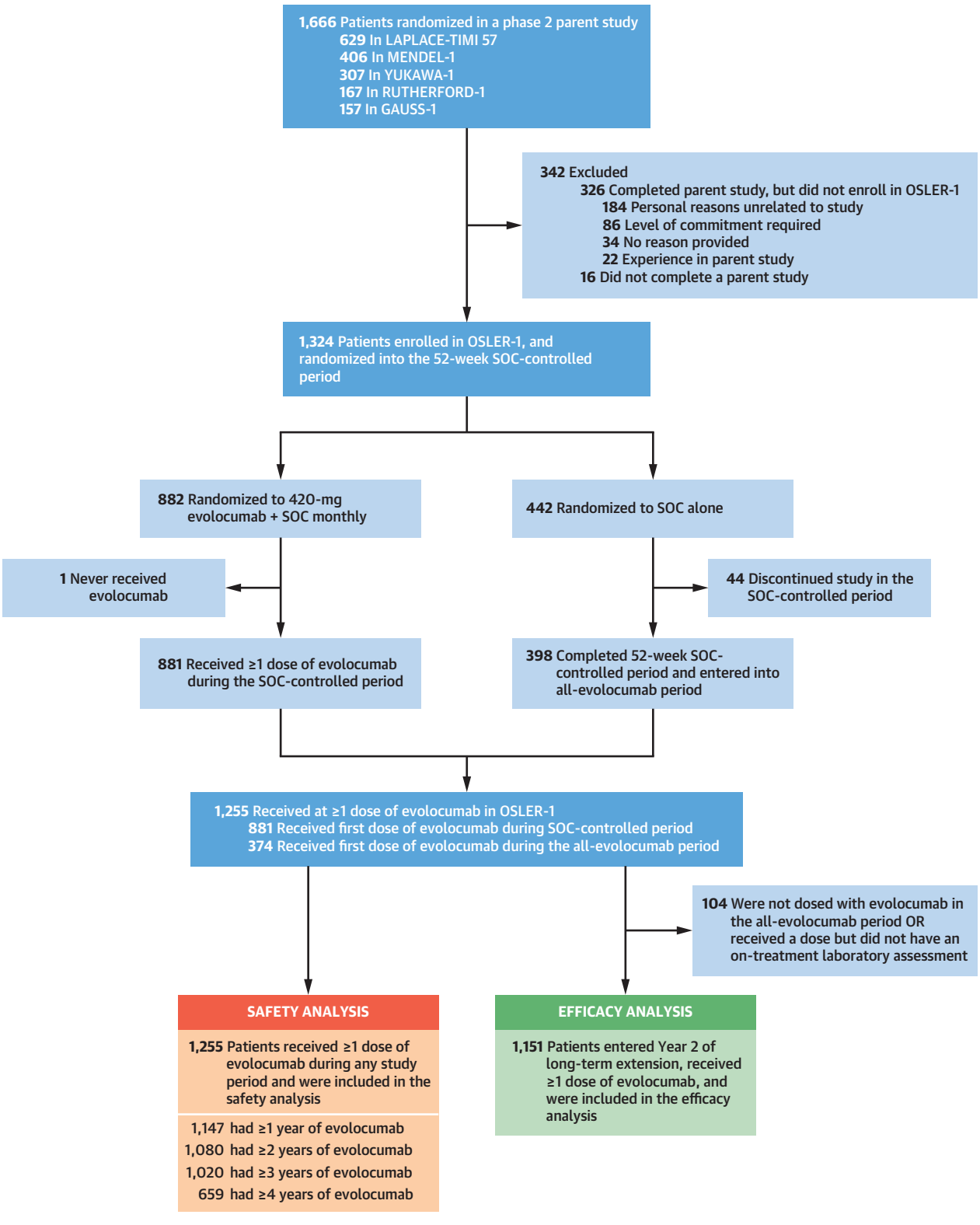

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TABLE 1 Baseline Demographics and Clinical Characteristics

	SOC Patients at 1 Year	Length of Evolocumab Exposure, yrs					All*
		First	Second	Third	Fourth	Fifth	
	(n = 442)	(n = 1,255)	(n = 1,147)	(n = 1,080)	(n = 1,020)	(n = 659)	(n = 1,151)
Age, yrs	57.6 ± 11.5	57.1 ± 11.5	57.2 ± 11.3	57.5 ± 10.9	57.6 ± 10.8	57.4 ± 10.7	57.3 ± 11.2
BMI, kg/m^2	29.1 ± 5.9	29.0 ± 5.9	29.0 ± 5.9	29.0 ± 5.8	28.9 ± 5.7	29.0 ± 5.7	29.0 ± 5.9
Female	241 (54.5)	662 (52.7)	597 (52.0)	554 (51.3)	519 (50.9)	337 (51.1)	600 (52.1)
Race							
White	325 (73.5)	917 (73.1)	838 (73.1)	786 (72.8)	742 (72.7)	481 (73.0)	834 (72.5)
Asian	87 (19.7)	249 (19.8)	234 (20.4)	226 (20.9)	221 (21.7)	140 (21.2)	239 (20.8)
Black	24 (5.4)	74 (5.9)	61 (5.3)	55 (5.1)	46 (4.5)	30 (4.6)	64 (5.6)
Other	6 (1.4)	15 (1.2)	14 (1.2)	13 (1.2)	11 (1.1)	8 (1.2)	14 (1.2)
Coronary artery disease	76 (17.2)	249 (19.8)	229 (20.0)	220 (20.4)	215 (21.1)	156 (23.7)	231 (20.1)
Cardiovascular risk factors							
Current cigarette use	65 (14.7)	224 (17.8)	203 (17.7)	188 (17.4)	178 (17.5)	125 (19.0)	201 (17.5)
Type 2 diabetes mellitus	58 (13.1)	182 (14.5)	167 (14.6)	161 (14.9)	153 (15.0)	102 (15.5)	166 (14.4)
Family history of coronary heart disease	107 (24.2)	304 (24.2)	280 (24.4)	268 (24.8)	258 (25.3)	176 (26.7)	281 (24.4)
Metabolic syndrome	153 (34.6)	461 (36.7)	422 (36.8)	396 (36.7)	369 (36.2)	258 (39.2)	426 (37.0)
Statin therapy intensity per ACC/AHA definition							
High intensity	80 (18.1)	253 (20.2)	232 (20.2)	221 (20.5)	214 (21.0)	150 (22.8)	226 (19.6)
Moderate intensity	130 (29.4)	393 (31.3)	356 (31.0)	338 (31.3)	318 (31.2)	207 (31.4)	356 (30.9)
Low intensity	76 (17.2)	223 (17.8)	207 (18.0)	198 (18.3)	193 (18.9)	127 (19.3)	211 (18.3)
No statin use	156 (35.3)	386 (30.8)	352 (30.7)	324 (29.9)	295 (28.9)	175 (26.6)	358 (31.1)
Lipid parameters at the parent study baseline							
LDL-C by ultracentrifugation, mg/dl	144.6 ± 37.5	141.4 ± 37.2	141.9 ± 37.2	142.4 ± 37.4	142.6 ± 37.3	141.2 ± 38.0	142.1 ± 37.6
LDL-C calculated, mg/dl	143.2 ± 39.0	139.6 ± 38.1	140.1 ± 38.0	140.7 ± 38.2	140.9 ± 38.2	139.0 ± 38.6	140.3 ± 38.5
Total cholesterol, mg/dl	224.8 ± 42.9	220.7 ± 43.1	221.1 ± 42.9	221.8 ± 42.9	222.1 ± 42.9	219.6 ± 43.4	221.5 ± 43.3
HDL-C, mg/dl	54.1 ± 16.5	53.7 ± 16.2	53.5 ± 15.9	53.6 ± 16.0	53.8 ± 16.1	53.0 ± 15.3	53.6 ± 15.9
Non-HDL-C, mg/dl	170.7 ± 43.0	167.0 ± 41.9	167.6 ± 41.7	168.2 ± 41.8	168.3 ± 41.8	166.6 ± 41.9	167.9 ± 42.3
Total cholesterol/HDL-C ratio	4.5 ± 1.6	4.4 ± 1.5	4.4 ± 1.5	4.5 ± 1.5	4.4 ± 1.5	4.4 ± 1.5	4.4 ± 1.5
VLDL-C, mg/dl	22.5 (16.0–31.5)	22.5 (16.5–31.0)	22.5 (16.5–31.5)	22.5 (16.5–31.5)	22.5 (16.0–31.5)	22.5 (16.5–31.0)	22.5 (16.5–31.5)
ApoB, mg/dl	113.2 ± 25.3	111.4 ± 24.5	111.7 ± 24.5	112.1 ± 24.5	112.2 ± 24.4	111.5 ± 24.6	111.9 ± 24.8
ApoA1, mg/dl	154.8 ± 28.1	154.6 ± 28.1	154.5 ± 27.7	154.7 ± 27.6	154.8 ± 27.8	154.2 ± 27.4	154.7 ± 27.6
ApoB/ApoA1	0.8 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
Triglycerides, mg/dl	121.3 (90.5–167.5)	121.5 (92.5–168.5)	122.5 (93.0–169.5)	121.5 (93.0–170.8)	121.0 (92.0–170.3)	125.0 (94.5–172.0)	122.5 (93.0–169.5)
Lp(a), nmol/l	35.0 (12.0–107.0)	37.0 (12.0–127.0)	36.0 (12.0–124.0)	36.0 (12.0–124.0)	37.0 (12.0–125.0)	36.0 (13.0–127.0)	36.0 (12.0–124.0)
PCSK9, ng/ml	417.0 ± 144.8	427.5 ± 141.1	428.4 ± 142.4	430.2 ± 142.4	429.5 ± 141.5	436.9 ± 138.0	426.9 ± 141.8

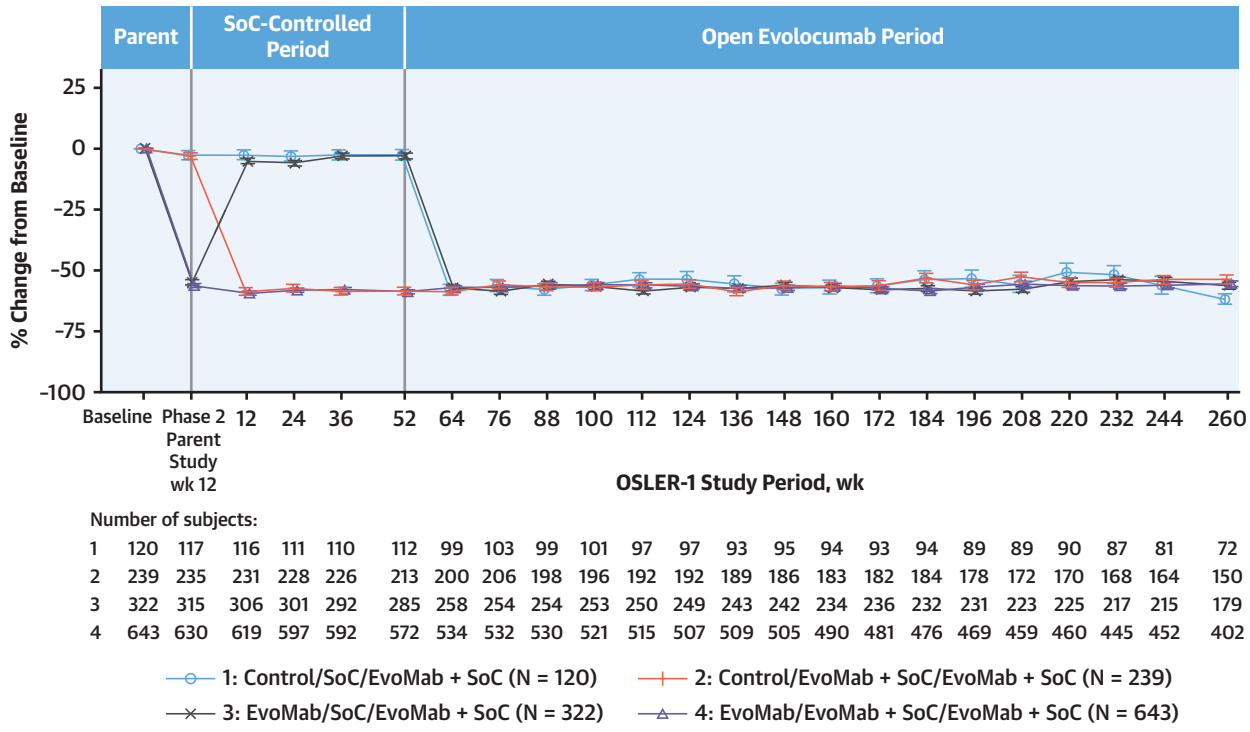
Values are mean ± SD, n (%), or median (interquartile range). *Entered year 2 and received ≥1 dose of evolocumab.

ACC = American College of Cardiology; AHA = American Heart Association; ApoA = apolipoprotein A; ApoB = apolipoprotein B; BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); SOC = standard of care; VLDL-C = very low-density lipoprotein cholesterol.

FIGURE 1 Continued

Patients enrolled into OSLER-1 study from 1 of 5 phase 2 parent studies. Patients randomized 2:1 to receive evolocumab plus SOC or SOC alone for the first 52 weeks (year 1) during the SOC-controlled period. Subsequently, all patients were eligible to receive 420 mg of evolocumab in addition to SOC every month. A total of 659 patients had 4 or more years of follow up on evolocumab; the persistence rate was 64%. GAUSS-1 = Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects; LAPLACE-TIMI = LDL-C Assessment With Proprotein Convertase Subtilisin Kexin Type 9 Monoclonal Antibody Inhibition Combined With Statin Therapy-Thrombolysis In Myocardial Infarction 57; MENDEL-1 = Monoclonal Antibody Against PCSK9 to Reduce Elevated Low-Density Lipoprotein Cholesterol in Adults Currently Not Receiving Drug Therapy for Easing Lipid Levels; OSLER-1 = Open-Label Study of Long-Term Evaluation Against LDL-C Trial; RUTHERFORD-1 = Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder; SOC = standard of care; YUKAWA-1 = Study of LDL-Cholesterol Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk.

FIGURE 2 Effects of Evolocumab on LDL-C Levels Over 5 Years



Calculated LDL-C percentage change (mean ± SE) from the phase 2, parent-study baseline to week 260 of OSLER-1 study. The **error bars** represent SEs. Plot is based on observed data with no imputation for missing values. The mean baseline LDL-C level was 140 mg/dl (3.62 mmol/l). The mean week 260 on-treatment LDL-C level was 61 mg/dl (1.47 mmol/l). The **key** shows parent study assignment/year 1 assignment/long-term open-label assignment. To convert LDL-C to millimoles per liter, multiply by 0.0259. LDL-C = low-density lipoprotein cholesterol; other abbreviations as in Figure 1.

available for 1,071 (93%), 1,001 (87%), 943 (82%), and 803 patients (70%) at 2, 3, 4, and 5 years of follow-up, respectively. Mean baseline LDL-C at the time of parent study enrollment was 140 ± 39 mg/dl. After year 1, mean ± SE percent reduction in LDL-C levels in patients randomized to evolocumab plus SOC was 59 ± 0.8% from baseline compared with 3 ± 1% for those randomized to SOC alone ($p < 0.001$), resulting in mean [interquartile range] LDL-C levels of 57 [35 to 71] mg/dl (1.58 mmol/l) versus 137 [108 to 158] mg/dl (3.54 mmol/l), respectively. Over the next 4 years, OSLER-1 patients who continued therapy maintained their LDL-C percentage reductions and low absolute LDL-C levels. At the end of years 2, 3, 4, and 5, the mean absolute LDL levels for the population were 61, 61, 62, and 61 mg/dl, respectively. Overall, 67.0% of LDL-C measurements in patients receiving evolocumab during all study periods were <70 mg/dl; 87.6% of LDL-C measurements were <100 mg/dl. Online Table 1 shows the percentage of patients who attained LDL-C <70 mg/dl by year of evolocumab exposure.

Evolocumab had favorable and consistent effects on other atherogenic lipoproteins as detailed in Table 2 and Online Table 2. At years 2, 3, 4, and 5, percentage reductions from baseline in mean ApoB were 46%, 45%, 45%, and 43%, respectively. Reductions in median Lp(a) were 31%, 29%, 36%, and 36%, respectively. Mean triglycerides reductions occurred for years 2, 3 and 4 of 5%, 3%, and 1%. Triglycerides increased by 1% at year 5. Mean ApoA1 increased at years 2, 3, 4, and 5 by 7%, 8%, 9% and 9%, respectively. Corresponding increases in mean HDL-C were 11%, 10%, 11%, and 9% at years 2, 3, 4, and 5, respectively. Table 2 provides PCSK9 levels at the end of dose intervals over the course of the study.

SAFETY AND TOLERABILITY. Table 3 and Figure 3 summarize AEs and SAEs that occurred by year of evolocumab exposure. Previous reports compared the rates of AEs and SAEs occurring during the SOC-controlled period and during exposure of up to 4 years (18). The current report reflecting patients with the longest evolocumab exposure indicated no new safety findings. Over the entire study, 1,179 of 1,255

patients (94%) reported ≥1 AE, and 293 patients (23%) reported an SAE. Seventy-one patients overall discontinued evolocumab due to AEs: 36 (2.9%) in year 1, 9 (0.8%) in year 2, 13 (1.2%) in year 3, 10 (1.0%) in year 4, and 1 (0.2%) in year 5. Overall rates of AEs in year 5 (65%) were similar to the previous years of the study (67% to 80%) and to the year 1 SOC control group (74%). The year 5 SAE rate (7%) matches the rates of previous years (7% to 8%) and the year 1 SOC control (7%). Over the 5-year treatment period, rates of AEs of interest, including potential hypersensitivity reactions, potential injection-site reactions, and muscle-related AEs, compare similarly to those of previous years and to the SOC control where applicable (**Table 3**). Further, an analysis of patients who achieved LDL-C levels of <25 or <40 mg/dl on consecutive post-baseline visits did not show a differences in overall rates of AEs compared with patients with LDL-C ≥40 mg/dl.

Incidence rates in the evolocumab plus SOC group at year 5 versus SOC alone during year 1 of exposure were 2.7% versus 4.3% for new-onset diabetes and 0.4% versus 0% for neurocognitive events (**Table 3**). Additionally, fasting plasma glucose and glycosylated hemoglobin levels remained stable over time (Online Table 3).

Four patients tested positively for binding ADAs during the OSLER-1 study follow-up: 1) at week 4 while on SOC for a patient who received evolocumab 70 mg every 2 weeks during the parent study, which resolved at week 12 and thereafter; 2) at week 4 while on SOC for a patient who received evolocumab 420 mg every 4 weeks during the parent study, which resolved at week 12 and thereafter; 3) at weeks 4, 12, and 48 on evolocumab during the OSLER-1 study for a patient who received placebo during the parent study, which resolved at week 52 and thereafter; and 4) at day 1 of the OSLER-1 study for a patient who received placebo during the parent study, which resolved at week 4 and thereafter. None of the 4 patients experienced a loss in treatment efficacy. Two patients who transiently tested positively for ADAs during parent studies (1 on evolocumab; 1 on placebo) remained negative for ADAs throughout the OSLER-1 study. No patient tested positive for binding ADAs in the all-evolocumab period. No neutralizing ADAs were detected for any patients over the course of 5 years.

DISCONTINUATION AND PERSISTENCE. Of the 1,255 patients in the safety analysis set, 344 patients (27%) discontinued evolocumab over the 5-year period. The annualized discontinuation rate was 6.7% (95% confidence interval: 6.0% to 7.4%). **Table 4** shows the summary for the analysis of persistence with evolocumab therapy. Of predefined baseline factors, patients with a higher cardiovascular risk defined by European Society of Cardiology/European Atherosclerosis Society risk categories, on high- or moderate-intensity statin therapy at baseline, from regions other than North America, of male sex, or with coronary artery disease were more likely to continue to receive treatment with evolocumab over the trial period.

ADJUDICATED CARDIOVASCULAR EVENTS. Adjudicated cardiovascular events occurred in 10 of 442 patients (2.3%) in the SOC arm during the year 1 of the SOC-controlled period as compared with 12 of 1,255 patients (1.0%) during the first year of evolocumab exposure. Cardiovascular event rates during extended exposure to evolocumab remained low, with a by-year incidence of cardiovascular events during years 2, 3, 4, and 5 of evolocumab exposure of 1.2%, 1.3%, 1.9%, and 1.7%, respectively. In total, 63 patients (5%) had ≥1 adjudicated event during the OSLER-1 study.

DISCUSSION

The final report of the OSLER-1 study adds valuable information about treating patients with hypercholesterolemia using evolocumab over an extended timeframe. Over the course of the clinical trial, nearly 1,000 patients received active treatment for 4 years or longer, making this study the longest duration follow-up of a PCSK9 inhibitor to date (**Central Illustration**). During this extended exposure, LDL-C reduction persisted without attenuation. For patients who remained on evolocumab plus SOC during long-term treatment (with lipid levels measured within 5 weeks of a dose), calculated LDL-C levels dropped, on average, from 140 to 61 mg/dl, assessed at both 2 and 5 years after baseline. This consistent efficacy over time provides reassurance, especially given the expressed concerns about overcoming possible tendencies for less aggressive background pharmacotherapy and diet following the initiation of anti-PCSK9 therapy.

Administration of monoclonal antibodies, particularly during repeated treatments, may lead to both immune and nonimmune adverse reactions. These AEs can include minor reactions, such as flu-like symptoms or injection-site erythema, or more significant problems reflecting immunogenicity, such as loss of drug efficacy or anaphylaxis (19). Assays identifying ADAs to monoclonal antibodies usually classify them as either binding or neutralizing (19).

TABLE 2 Summary of Lipid Parameters and PCSK9 by Scheduled Visit

	All OSLER-1 Patients (N = 1,324)			
	SOC in SOC-Controlled Period/ Evolocumab + SOC in Open Evolocumab Period (n = 442)			
Visit	n	Observed	% Change From Baseline	
LDL-C, mg/dl				
Baseline	442	143.2 ± 1.9	NA	NA
Week 24	412	134.7 ± 2.1	−5.2 ± 1.0	−6.0 (−16.3 to 4.7)
Year 1	397	137.0 ± 2.0	−2.9 ± 1.1	−2.4 (−15.2 to 9.3)
Year 2	354	62.3 ± 1.8	−56.4 ± 1.1	−59.9 (−70.8 to −44.5)
Year 3	328	61.2 ± 2.1	−57.3 ± 1.3	−62.2 (−72.2 to −48.0)
Year 4	312	61.8 ± 2.3	−57.1 ± 1.4	−61.4 (−71.0 to −47.7)
Year 5	251	59.5 ± 1.8	−57.9 ± 1.2	−58.7 (−71.0 to −46.4)
ApoB, mg/dl				
Baseline	442	113.2 ± 1.2	NA	NA
Week 24	416	107.9 ± 1.3	−4.0 ± 0.8	−4.2 (−14.1 to 4.9)
Year 1	401	109.5 ± 1.3	−2.3 ± 0.9	−2.5 (−12.0 to 7.4)
Year 2	356	60.8 ± 1.2	−45.8 ± 0.9	−48.5 (−57.5 to −36.8)
Year 3	336	61.4 ± 1.4	−46.0 ± 1.1	−49.0 (−59.0 to −37.6)
Year 4	319	61.3 ± 1.4	−45.6 ± 1.1	−49.5 (−58.1 to −36.8)
Year 5	255	62.6 ± 1.4	−44.7 ± 1.0	−46.3 (−56.7 to −34.0)
Lp(a), nmol/l				
Baseline	441	35.0 (12.0 to 107.0)	NA	NA
Week 24	416	37.0 (11.0 to 95.0)	2.6 ± 1.5	0.0 (−16.7 to 13.6)
Year 1	401	32.0 (10.0 to 87.0)	−3.7 ± 1.5	−5.4 (−22.6 to 9.6)
Year 2	356	20.0 (6.0 to 65.6)	−30.4 ± 1.3	−32.1 (−50.0 to −11.2)
Year 3	336	16.5 (7.0 to 60.5)	−26.8 ± 3.2	−30.0 (−51.2 to −7.7)
Year 4	319	18.0 (7.0 to 57.0)	−34.6 ± 1.5	−37.6 (−54.6 to −14.5)
Year 5	255	16.0 (7.0 to 65.0)	−34.4 ± 1.8	−38.5 (−54.6 to −15.7)
PCSK9, ng/ml				
Baseline	437	417.0 ± 6.9	NA	NA
Week 24	416	441.6 ± 8.1	8.9 ± 1.8	4.4 (−14.0 to 24.6)
Year 1	401	424.8 ± 8.2	5.3 ± 1.7	0.9 (−17.1 to 20.6)
Year 2	357	241.5 ± 8.1	−42.9 ± 1.6	−44.7 (−63.7 to −26.5)
Year 3	337	186.5 ± 7.1	−55.3 ± 1.6	−59.1 (−75.4 to −36.3)
Year 4	319	180.1 ± 7.1	−56.2 ± 1.7	−58.1 (−78.1 to −39.4)
Year 5	253	221.5 ± 8.9	−48.3 ± 1.9	−50.8 (−69.3 to −35.7)

Values are n, mean ± SE, or median (interquartile range). *Entered year 2 and received ≥1 dose of evolocumab.

IQR = interquartile range; NA = not applicable (based on study design); OSLER-1 = Open-Label Study of Long-term Term Evaluation Against LDL-C Trial; other abbreviations as in Table 1.

Continued on the next page

Binding ADAs can bind to the biological therapeutic agent without impacting the function of the molecule. Neutralizing ADAs, by contrast, can interfere with the primary function of the therapeutic agent (19).

Studies of patients treated with bococizumab, a humanized monoclonal antibody with persistent murine elements, have reported a high degree of immunogenicity resulting in a loss of efficacy (14). In the SPIRE studies, nearly one-half of bococizumab patients had high-titer ADAs, often neutralizing, which reduced the magnitude and durability of the LDL-C-lowering effect of the agent. In addition, 10.4% of patients treated with bococizumab versus 1.3% of placebo patients reported injection-site reactions (14).

Roth et al. (20) assessed ADAs to alirocumab, a fully human monoclonal antibody, and found a lower rate of binding ADAs reported in patients treated with alirocumab (5.1%). Furthermore, Roth et al. reported a low rate of only 1.3% of alirocumab-treated patients with neutralizing antibodies. ADAs with alirocumab also did not appear to significantly reduce the LDL-C-lowering efficacy of the drug at most time points over the relatively shorter duration

TABLE 2 Continued

All OSLER-1 Patients (N = 1,324)				All-Evolocumab Patients (Efficacy Set)* (n = 1,151)			
Evolocumab + SOC in SOC-Controlled Period/ Evolocumab + SOC in Open Evolocumab Period (n = 882)							
n	Observed	% Change From Baseline		n	Observed	% Change From Baseline	
882	137.7 ± 1.3	NA	NA	1,151	140.3 ± 1.1	NA	NA
825	58.3 ± 1.2	−57.9 ± 0.7	−61.5 (−71.3 to −49.1)	NA	NA	NA	NA
785	57.3 ± 1.2	−58.6 ± 0.8	−62.0 (−72.1 to −50.0)	NA	NA	NA	NA
717	60.7 ± 1.2	−56.1 ± 0.8	−59.3 (−71.4 to −45.8)	1,071	61.2 ± 1.0	−56.2 ± 0.6	−59.4 (−71.2 to −45.2)
673	61.0 ± 1.5	−56.3 ± 1.0	−60.0 (−72.8 to −45.8)	1,001	61.1 ± 1.2	−56.6 ± 0.8	−61.1 (−72.7 to −46.4)
631	62.4 ± 1.5	−54.8 ± 1.0	−60.3 (−71.4 to −45.1)	943	62.2 ± 1.2	−55.6 ± 0.80	−60.7 (−71.2 to −45.7)
552	62.2 ± 1.5	−55.1 ± 1.0	−59.4(−70.5 to −43.8)	803	61.4 ± 1.2	−55.9 ± 0.8	−59.2 (−70.6 to −44.5)
882	110.4 ± 0.8	NA	NA	1,151	111.9 ± 0.7	NA	NA
834	60.0 ± 0.8	−45.5 ± 0.6	−48.9 (−57.1 to −37.6)	NA	NA	NA	NA
800	60.0 ± 0.8	−45.5 ± 0.6	−48.3 (−56.9 to −37.4)	NA	NA	NA	NA
727	60.0 ± 0.8	−45.5 ± 0.7	−47.7 (−57.3 to −36.9)	1,083	60.3 ± 0.7	−45.6 ± 0.5	−47.9 (−57.4 to −36.9)
683	60.9 ± 0.9	−45.0 ± 0.8	−47.9 (−58.8 to −35.5)	1,019	61.1 ± 0.8	−45.3 ± 0.6	−48.4 (−58.9 to −36.4)
647	61.9 ± 1.0	−44.1 ± 0.8	−47.2 (−58.5 to −34.0)	966	61.7 ± 0.8	−44.6 ± 0.7	−47.9 (−58.3 to −35.1)
564	63.3 ± 1.0	−42.8 ± 0.8	−46.0 (−56.3 to −32.5)	819	63.1 ± 0.8	−43.4 ± 0.6	−46.1 (−56.4 to −33.3)
878	37.5 (12.0 to 136.0)	NA	NA	1,151	36.0 (12.0 to 124.0)	NA	NA
834	22.0 (6.0 to 86.0)	−26.0 ± 3.5	−28.6 (−47.5 to −11.1)	NA	NA	NA	NA
800	19.0 (6.0 to 78.0)	−31.9 ± 0.9	−32.9 (−50.7 to −13.7)	NA	NA	NA	NA
727	21.0 (6.0 to 74.0)	−30.0 ± 1.0	−30.4 (−50.0 to −9.8)	1,083	21.0 (6.0 to 71.0)	−30.2 ± 0.8	−30.6 (−50.0 to −10.1)
683	19.0 (7.0 to 78.0)	−29.1 ± 1.1	−28.6 (−50.9 to −7.3)	1,019	18.0 (7.0 to 73.0)	−28.3 ± 1.3	−28.6 (−51.0 to −7.7)
647	16.0 (6.0 to 70.0)	−33.6 ± 1.1	−35.3 (−54.0 to −15.9)	966	16.0 (7.0 to 65.0)	−33.9 ± 0.9	−36.3 (−54.3 to −15.9)
564	17.0 (7.0 to 75.0)	−32.4 ± 1.2	−33.9 (−51.9 to −13.1)	819	17.0 (7.0 to 69.0)	−33.0 ± 1.0	−35.9 (−52.9 to −14.3)
871	431.3 ± 4.7	NA	NA	1,151	426.9 ± 4.2	NA	NA
828	246.6 ± 5.1	−41.8 ± 1.1	−44.1 (−64.2 to −25.0)	NA	NA	NA	NA
799	244.9 ± 5.2	−42.5 ± 1.1	−45.9 (−63.7 to −25.7)	NA	NA	NA	NA
726	248.2 ± 5.5	−42.6 ± 1.1	−44.8 (−62.7 to −28.0)	1,083	246.0 ± 4.6	−42.7 ± 0.9	−44.8 (−63.4 to −27.5)
676	198.8 ± 4.9	−53.3 ± 1.1	−58.0 (−74.6 to −36.9)	1,013	194.8 ± 4.0	−54.0 ± 29.2	−57.4 (−76.0 to −36.9)
648	196.8 ± 4.9	−53.9 ± 1.1	−55.6 (−75.4 to −27.7)	967	191.3 ± 4.1	−54.7 ± 0.9	−56.5 (−76.5 to −38.0)
558	225.7 ± 5.9	−47.9 ± 1.3	−49.5(−69.1 to −32.9)	811	224.4 ± 4.9	−48.0 ± 1.1	−49.7 (−69.2 to −33.7)

of 78 weeks of follow-up, though patients with ADAs had more frequent, mostly mild, injection-site reactions (20).

Patients receiving treatment with evolocumab did not develop ADAs over the course of long-term treatment. Although comparative data between PCSK9 inhibitors for an extended duration are not available, the OSLER-1 study results provide reassurance regarding the longer-term safety of PCSK9 inhibition. Only 4 patients in the OSLER-1 study transiently tested positive for ADAs (2 of whom were randomized to SOC and were not receiving evolocumab at the time) and no patients developed positive titers after year 1 during extended follow-up. Further, the present study showed no clinical evidence of increased hypersensitivity with extended evolocumab treatment. For example, the rate of possible injection-site reactions (based on MedDRA search strategies) decreased from a 4.1% annualized rate in the first year of exposure to evolocumab to 0.2% annually in year 4 and beyond, a trend that likely reflects both improved injection skills and the absence of immunogenicity. Potential hypersensitivity events also decreased in frequency over time from 10.2% to 7.3% annually from year 1 to year 5 as compared with 9.3% for SOC patients not receiving injections in the first controlled year of the OSLER-1 study.

TABLE 3 Summary of AEs*

		Length of Evolocumab Exposure, yrs					
	SOC Patients at 1 Year (n = 442)	First (n = 1,255)	Second (n = 1,147)	Third (n = 1,080)	Fourth (n = 1,020)	Fifth (n = 659)	All (n = 1,255)
Any	327 (74.0)	1,000 (79.7)	849 (74.0)	771 (71.4)	680 (66.7)	430 (65.3)	1,179 (93.9)
Most common AE†							
Nasopharyngitis	64 (14.5)	195 (15.5)	166 (14.5)	139 (12.9)	134 (13.1)	64 (9.7)	411 (32.7)
Arthralgia	18 (4.1)	83 (6.6)	59 (5.1)	54 (5.0)	39 (3.8)	25 (3.8)	216 (17.2)
Upper respiratory tract infection	29 (6.6)	87 (6.9)	68 (5.9)	42 (3.9)	54 (5.3)	28 (4.2)	214 (17.1)
Serious†	30 (6.8)	90 (7.2)	79 (6.9)	85 (7.9)	71 (7.0)	47 (7.1)	293 (23.3)
Osteoarthritis	1 (0.2)	3 (0.2)	3 (0.3)	6 (0.6)	3 (0.3)	2 (0.3)	17 (1.4)
Angina	2 (0.5)	4 (0.3)	2 (0.2)	2 (0.2)	5 (0.5)	1 (0.2)	14 (1.1)
Chest pain	1 (0.2)	4 (0.3)	3 (0.3)	1 (0.1)	1 (0.1)	2 (0.3)	10 (0.8)
Patients who discontinued owing to AEs*	NA	36 (2.9)	9 (0.8)	13 (1.2)	10 (1.0)	1 (0.2)	71 (5.7)
Potential hypersensitivity‡	41 (9.3)	128 (10.2)	95 (8.3)	88 (8.1)	57 (5.6)	48 (7.3)	321 (25.6)
Potential injection-site reactions‡	NA	52 (4.1)	32 (2.8)	23 (2.1)	10 (1.0)	1 (0.2)	95 (7.6)
Muscle related‡	41 (9.3)	104 (8.3)	69 (6.0)	52 (4.8)	40 (3.9)	18 (2.7)	246 (19.6)
New-onset diabetes§	19 (4.3)	51 (4.1)	22 (2.1)	26 (2.8)	38 (4.4)	14 (2.7)	154 (12.3)
Neurocognitive related‖	0 (0.0)	8 (0.6)	3 (0.3)	4 (0.4)	2 (0.2)	2 (0.4)	23 (1.8)
Antibody							
Binding	NA¶	2 (0.16)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.16)
Neutralizing	NA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Values are n (%). *Observed incidence rates. Also, the length of evolocumab plus SOC exposure in OSLER-1 is defined as per patient-year. For discontinuation due to AEs, events were included in the yearly columns only if the AE onset date was in the same year of evolocumab exposure. Thus, some events were not included in the yearly columns but were included in the overall column. †The 3 most common serious AEs are detailed. ‡Based on U.S. Food and Drug Administration broad search terms. §Subjects started to take diabetes-related contaminant medications, or with post-baseline glycosylated hemoglobin value ≥6.5%, or with 2 or more consecutive post-baseline fasting blood glucose ≥126 mg/dl. ‖Based on *Medical Dictionary for Regulatory Activities* search terms. ¶Two incidences of anti-drug antibodies were observed during the SOC-controlled period in patients receiving SOC alone who had received evolocumab during the parent study. No neutralizing antibodies were reported.

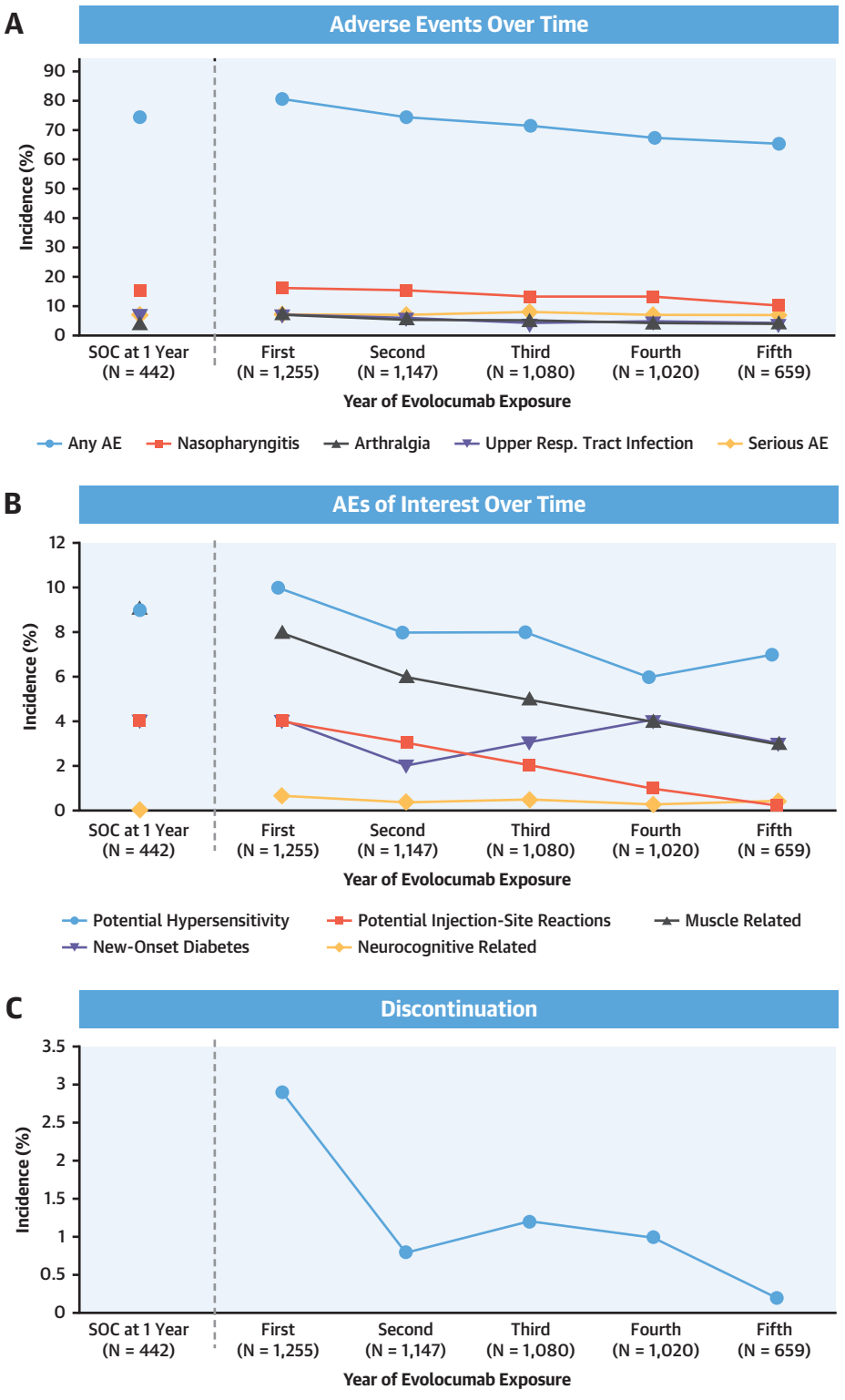
AE = adverse event; other abbreviations as in Tables 1 and 2.

The OSLER-1 study data also extend the safety findings from the FOURIER study and other randomized controlled trials of PCSK9 inhibitors of shorter duration. The study showed that evolocumab lowered LDL-C levels with a favorable safety profile, and without causing an excess of AEs of concern. Specifically, patients maintained at low LDL-C levels did not report an increase in neurocognitive events or new-onset diabetes (21), an indication that the risk of these events does not increase with continued and prolonged treatment with evolocumab. The OSLER-1 study also showed low rates of cardiovascular events over time. Although the design of open-label trials does not allow for a vigorous evaluation of cardiovascular outcomes, the continued low rate of adjudicated cardiovascular events in the OSLER-1 study provides reassurance about the persistence of clinical benefits over longer-term anti-PCSK9 therapy. In total, the OSLER-1 study adds support to previous work that documents the benefits of the clinical strategy of reducing LDL-C to levels generally unachievable before the availability of PCSK9 inhibitors or ezetimibe in combination with statins (12,14,15,22).

STUDY LIMITATIONS. The open-label design of the OSLER-1 study serves as an important limitation to the study's findings. Although reassuring, open-label extension trials do not provide comparative data and can lead to biases related to knowledge of the therapy and because patients who remain on therapy are those most likely to tolerate it well and derive the most benefit. Nevertheless, such trials can provide information on the long-term efficacy and tolerance of a therapy. In open-label trials, knowledge of the therapy received allows patients and their health care providers to mimic the decision-making patterns of clinical practice by choosing to continue a therapy, or not, based on their perception of whether the benefits of treatment outweigh any side effects or inconvenience at any given time. This dynamic differs from that of double-blind studies, in which clinicians and many patients understand that the scientific validity of comparisons requires persistence on an unknown therapy. Further, long-term open-label trials that follow shorter-term randomized, controlled studies provide an opportunity to analyze AEs that may derive from longer-term exposure to a medical therapy against a control group from the same patient population.

Of note, the OSLER-1 study enrolled a diverse representation of patients from 5 different phase 2 evolocumab trials, including GAUSS-1 (Goal

FIGURE 3 Rates of AEs Over 5 Years in the OSLER-1 Trial



Depicts all adverse events in each year of the OSLER-1 study **(A)** and pre-specified adverse events of interest **(B)** with annualized discontinuation rates due to adverse events **(C)**. Annual rates of serious adverse events compared similarly to that of year 1 SOC patients. A total of 5.7% of patients discontinued evolocumab due to AEs. AE = adverse event; other abbreviations as in Figure 1.

TABLE 4 Multivariate Analysis of Variables Contributing to Evolocumab Discontinuation

	n	Patients With Evolocumab Exposure: Discontinued Evolocumab and/or Study (n = 344)	Patients With Evolocumab Exposure: Remained Taking Evolocumab in Study (n = 911)	Hazard Ratio of Drop Out (95% CI)*	p Value*
Age group					
≥65 yrs	361	101 (28.0)	260 (72.0)	Old vs. young: 1.05 (0.83–1.33)	0.68
<65 yrs	894	243 (27.2)	651 (72.8)		
Sex					
Female	662	202 (30.5)	460 (69.5)	F vs. M: 1.3 (1.07–1.65)	0.0092
Male	593	142 (23.9)	451 (76.1)		
Region					
North America	611	228 (37.3)	383 (62.7)	NA vs. other: 2.28 (1.82–2.86)	<0.0001
Other	644	116 (18.0)	528 (82.0)		
Type 2 diabetes					
Yes	182	43 (23.6)	139 (76.4)	Yes vs. no: 0.82 (0.60–1.13)	0.23
No	1,073	301 (28.1)	772 (71.9)		
Coronary artery disease					
Yes	249	50 (20.1)	199 (79.9)	Yes vs. no: 0.64 (0.48–0.87)	0.004
No	1,006	294 (29.2)	712 (70.8)		
ESC/EAS risk categories					
High/very high risk	625	131 (21.0)	494 (79.0)	High vs. low: 0.57 (0.46–0.71)	<0.0001
Moderate/low risk	630	213 (33.8)	417 (66.2)		
NCEP risk categories					
High risk/moderately high risk	570	127 (22.3)	443 (77.7)	High vs. low: 0.66 (0.53–0.82)	0.0002
Moderate/low risk	685	217 (31.7)	468 (68.3)		
Baseline LDL-C, mg/dl					
Mean ± SD		137.2 ± 36.3	140.5 ± 38.7	NA	0.17
Median (interquartile range)		131.3 (111.0–158.0)	133.0 (115.0–155.0)		

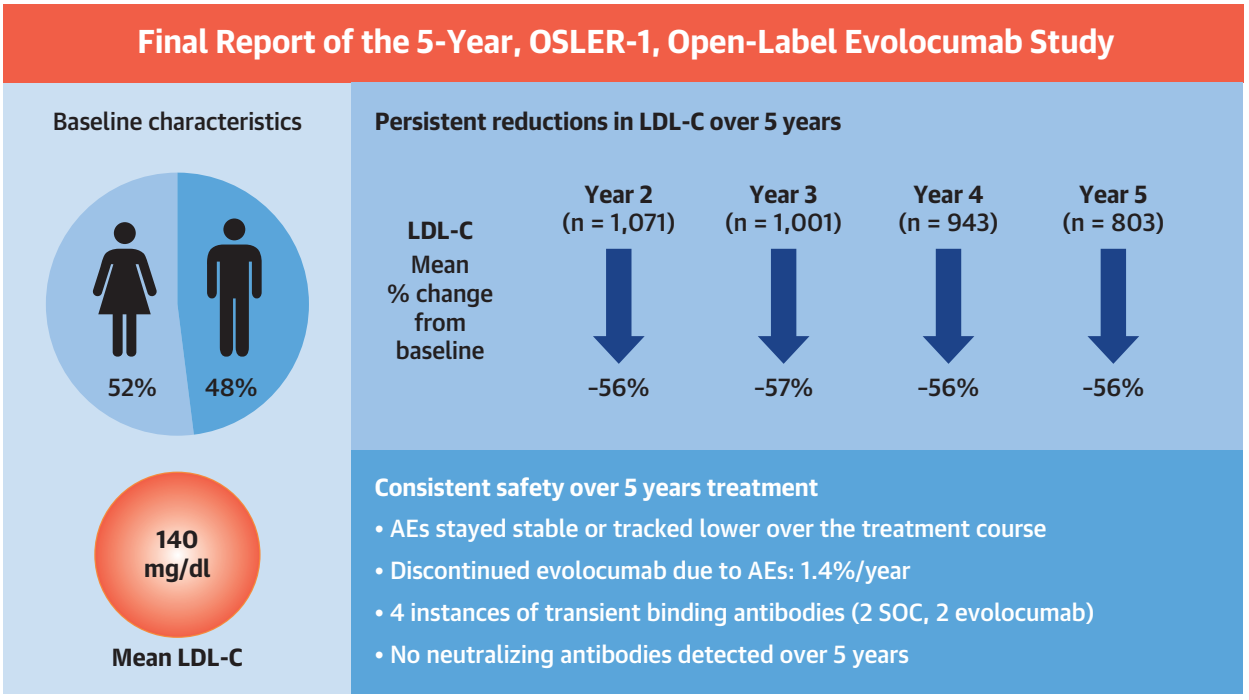
Values are n or n (%) unless otherwise indicated. *Hazard ratio and p values are from multivariate Cox regression model where each baseline factor was fit at a time. SI conversion factors: to convert LDL-C to millimoles per liter, multiply by 0.0259.

CI = confidence interval; EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; NCEP = National Cholesterol Education Program; NS = not significant; SI = systeme internationale (or international system); other abbreviations as in Tables 1 to 3.

Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects) in statin-intolerant patients and MENDEL-1 (Monoclonal Antibody Against PCSK9 to Reduce Elevated Low-density Lipoprotein Cholesterol [LDL-C] in Adults Currently Not Receiving Drug Therapy for Easing Lipid Levels) to assess evolocumab monotherapy in patients not on statins. Further, YUKAWA-1 (Study of LDL-Cholesterol Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk) contributed patients to the OSLER-1 study from Japan where the highest doses of statin therapy, as available in the United States and Europe, are not approved and rarely used. Subsequently, background statin use and intensity varied, with ~20% of patients on concomitant, high-intensity background statin therapy at parent-study baseline. This heterogeneity favors applicability of the efficacy results to more patients, but adds complexity to the analysis of side effects attributable to the attainment of low LDL-C levels compared with side effects attributable to statin or evolocumab use. Nonetheless, patients who achieved an LDL-C <25 or <40 mg/dl on consecutive post-baseline visits experienced comparable overall rates of AEs versus patients with LDL-C ≥40 mg/dl.

The annualized discontinuation rate of 6.7% through year 5 in OSLER-1 study compares favorably to published data for adherence to other lipid therapies, including statins. For mipomersen, an approved injectable treatment for severe forms of hypercholesterolemia, Santos et al. (23) reported that 64 of 141 patients (45.4%) with familial hypercholesterolemia continued open-label therapy in a 2-year clinical trial. Monitoring clinical practice, Perreault et al. (24) reported an overall persistence rate for statin use in a middle-aged hypercholesterolemic population of 71% after 6 months and 45% after 3 years. Corresponding persistence rates for primary prevention patients in this cohort were 65% and 35%, respectively.

CENTRAL ILLUSTRATION **Sustained Efficacy and Long-Term Safety of Evolocumab in Hypercholesterolemia**



Koren, M.J. et al. J Am Coll Cardiol. 2019;74(17):2132–46.

Consistent reductions in LDL-C in each year of the OSLER-1 study and the safety and tolerability profile of evolocumab (no detection of neutralizing antibodies, and an annualized discontinuation rate of 1.4%). AE = adverse event; LDL-C = low-density lipoprotein cholesterol; OSLER-1 = Open-Label Study of Long-Term Evaluation Against LDL-C Trial; SOC = standard of care.

CONCLUSIONS

The OSLER-1 study demonstrated the persistent effectiveness and good tolerance of evolocumab for treating hypercholesterolemia in a diverse patient population for up to 5 years. The yearly incidence of AEs during extended exposure to evolocumab compared similarly to patients randomized to SOC alone for year 1. AE rates did not increase over time and decreased for injection-site reactions. Transient ADAs occurred rarely with none detected after the first year of exposure. Collectively, these data provide reassurance about the long-term safety of evolocumab.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with hypercholesterolemia, including those with severe familial forms, the anti-PCSK9 antibody evolocumab exhibits sustained efficacy without development of drug-neutralizing antibodies or other attenuating factors, and relatively infrequent adverse reactions requiring interruption of treatment.

TRANSLATIONAL OUTLOOK: Similar long-term follow-up studies should include other novel therapies as comparators to better understand the factors that contribute most to sustained benefit over time.

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KEY WORDS evolocumab, LDL-cholesterol, lipoproteins, PCSK9, randomized controlled trial

APPENDIX For supplemental tables, please see the online version of this paper.