Pooled Safety Analysis of Evolocumab in Over 6000 Patients from Double-blind and Open-label Extension Studies

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Abstract

Background: Evolocumab, a fully human monoclonal antibody to PCSK9, markedly reduces LDL-C across diverse patient populations. The objective of this study was to assess the safety and tolerability of evolocumab in a pooled safety analysis from phase 2 or 3 randomized and placebo or comparator-controlled trials (integrated parent trials) and the first year of open-label extension (OLE) trials that included a standard-of-care control group.

Methods: This analysis included adverse event (AE) data from 6026 patients in 12 phase 2 and 3 parent trials, with a median exposure of 2.8 months, and of those patients, from 4465 patients who continued with a median follow-up of 11.1 months in two OLE trials. Adverse events were analyzed separately for the parent and OLE trials. Overall AE rates, serious AEs (SAEs), laboratory assessments, and AEs of interest were evaluated.

Results: Overall AE rates were similar between evolocumab and control in the parent trials (51.1% vs 49.6%) and in Year 1 of OLE trials (70.0% vs 66.0%), as were those for SAEs. Elevations of serum transaminases, bilirubin and creatine kinase were infrequent and similar between groups. Muscle-related AEs were similar between evolocumab and control. Neurocognitive adverse events were infrequent and balanced during the double-blind parent studies (5 events [0.1%], evolocumab groups vs 6 events [0.3%], control groups). In the OLE trials, 27 patients (0.9%) in the evolocumab groups and 5 patients (0.3%) in the control groups reported neurocognitive AEs. No neutralizing anti-evolocumab antibodies were detected.

Conclusions: Overall, this integrated safety analysis of 6026 patients pooled across phase 2/3 trials and 4465 patients who continued in open-label extension trials for 1 year supports a favorable benefit-risk profile for evolocumab.

CLINICAL PERSPECTIVE

- Evolocumab was well tolerated in individual phase 3 studies. This pooled analysis from the PROFICIO program, which included over 6000 patients from 12 phase 2 and 3 trials and the corresponding open-label extension trials, demonstrates that longer-term treatment with evolocumab for up to one year was not associated with discernible differences in adverse events, serious adverse events, or key laboratory assessments compared to control or standard of care. In addition, adverse event rates did not increase among patients attaining very low levels of LDL-C (<25 mg/dL) compared to patients attaining LDL-C levels ≥40 mg/dL.
- Evolocumab is approved for reducing serum levels of LDL-C across diverse patient populations. The present analysis confirms that longer-term treatment with evolocumab, either alone or in combination with other lipid-lowering therapies, may have a favorable benefit-risk profile.

INTRODUCTION

Lowering LDL cholesterol (LDL-C) is an essential component of the therapeutic paradigm to reducing the morbidity and mortality associated with cardiovascular disease in both primary and secondary prevention settings. According to guidelines published around the world, statins are designated as first-line therapy for treating hypercholesterolemia, specifically in patients with high cardiovascular risk.[1-4] However, a sizeable number of patients fail to achieve risk-stratified goal LDL-C levels or percent reductions with statin therapy alone[5, 6] or in combination with ezetimibe.[7] Blocking the interaction of proprotein convertase subtilisin/kexin type 9 (PCSK9) with LDL receptors (LDLR) has emerged as a highly effective therapeutic strategy for lowering LDL-C. Upon binding to LDLR, PCSK9 promotes increased lysosomal LDLR degradation, reduced hepatocyte cell surface expression of LDLR, and increased plasma LDL-C concentrations.[8]

Evolocumab is a subcutaneously (SC)-administered fully human monoclonal IgG2 antibody to PCSK9 that is approved for use in the United States (US) and Europe, among other countries. Regulatory approval was based on review of the comprehensive clinical trial program, Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations (PROFICIO). These trials demonstrated robust reductions of LDL-C with evolocumab treatment compared to placebo or ezetimibe across a broad population of patients with hypercholesterolemia, including those with familial hypercholesterolemia or other high-risk conditions, as well as statin-intolerant patients.[9-18]

The safety of newly emerging anti-hypercholesterolemia agents is of paramount importance. Any such agent will be utilized on a chronic basis and must be both safe and well tolerated to promote optimal adherence. Each of the evolocumab trials showed a favorable safety and tolerability profile of evolocumab when compared to placebo or control regimens.[9-18]

To gain further understanding of the safety profile of evolocumab, as part of the PROFICIO program, we assessed safety and tolerability in a pooled analysis from patients enrolled in the randomized placebo- or ezetimibe-controlled phase 2 and 3 trials and during the Year 1 standard-of-care (SoC)-controlled portion of the OLE trials.

METHODS

Patients

Patients were enrolled in one of twelve phase 2 and 3 evolocumab parent clinical trials (Table 1 and Figure 1).[9-18] All patients provided written informed consent and the individual protocols were approved by each institutional review board. All patients completing a phase 2 or 3 parent trial on study drug were eligible to enroll in SoC-controlled open-label extension trials.

Data Sources

Each parent trial included was a double-blind, placebo-controlled randomized trial of 12 weeks' duration with the exception of one trial of 6 weeks' duration (THOMAS-1; NCT01849497) and one trial of 52 weeks' duration (Durable Effect of PCSK9 Antibody Compared with Placebo Study [DESCARTES]).[9] Dosing regimens and frequencies for evolocumab subcutaneous administration in the phase 2 parent trials were as follows: 70, 105, and 140 mg every 2 weeks (Q2W) and 280, 350, and 420 mg monthly (QM). The phase 3 parent trials utilized evolocumab regimens of 140 mg Q2W and/or 420 mg QM. Five trials included an ezetimibe-treated arm, alone or in combination with placebo.[12, 13, 16-18] A total of 6026 patients were randomized and received at least 1 dose of evolocumab or control in the 12 phase 2 and 3 parent studies. Of these patients, 4465 (74%) enrolled in two ongoing open-label extension studies: Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER)-1, which enrolled patients from the phase 2 trials,[19] and OSLER-2, which enrolled patients from the phase 3 trials. The OSLER

trials included a standard-of-care (SOC)-controlled period for the first year of follow-up, followed by a period during which all patients received evolocumab. Upon enrollment to each OSLER trial, patients were re-randomized 2:1 to receive evolocumab plus SOC or SOC alone.

Adverse event (AE) data were pooled from the 6026 patients in phase 2 and 3 studies (integrated parent studies) and from the 4465 patients after the SOC-controlled 1-year period in the OSLER studies. From these respective datasets, 5942 of 6026 patients and 4417 of 4465 patients had at least 1 postbaseline LDL-C evaluation and were analyzed for safety associated with attainment of postbaseline on-treatment very low LDL-C (<25 mg/dL) in a post-hoc exploratory analysis. Data were compared between patients who never achieved LDL-C <40 mg/dL and patients who ever achieved LDL-C <40 mg/dL. Patients in the latter category were further divided into subgroups of those who ever achieved LDL-C <25 mg/dL and patients who ever achieved LDL-C ≥25 mg/dL to <40 mg/dL. Data cut-off dates were October 1, 2014 for OSLER-1 and April 1, 2015 for OSLER-2; all patients from OSLER-1 had completed Year 1 by October 2014.

Safety Endpoints

Safety endpoints of the trials included the incidence of AEs, serious AEs, AEs of interest, laboratory values, and anti-evolocumab antibodies. Adverse events in this integrated analysis were coded using version 18.0 of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events in the individual parent trials were coded using the most current version of MedDRA at the time of database lock. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0[20] when applicable. The immunogenicity of evolocumab was evaluated using an electrochemiluminescent bridging immunoassay for the detection of binding anti-drug antibodies. For patients whose sera tested positive in the immunoassay, an in vitro biological assay was performed to detect neutralizing antibodies.

Statistical Analysis

Safety analyses were conducted using descriptive statistics. Safety data were reported as observed. All analyses were performed with SAS/STAT, version 9.2 (SAS Institute, Cary, NC, USA). Patient incidences of AEs were summarized for all AEs, serious AEs, and AEs of interest. Adverse events were tabulated and reported separately for the parent studies and the OLE studies; an identical AE occurring in a patient in both the parent study and the OLE study was therefore recorded twice and reported separately as occurring in each dataset. Incidences of AEs were tabulated by system organ class, preferred term, and grade. Summaries of AEs occurring in at least 2% of the patients by preferred term in any treatment arm in parent or extension studies were provided in descending order of frequency. Descriptive statistics were provided for actual values and changes from baseline of laboratory parameters. Patient incidences of creatine kinase (CK) and liver function test abnormalities were summarized. The incidence of patients who developed anti-evolocumab antibodies at any time was tabulated. The studies were not powered for safety endpoints; therefore, no inferential statistical analyses with associated P values were conducted.

RESULTS

Baseline Characteristics

The phase 2 and 3 parent evolocumab studies included in this analysis are summarized in Table 1. Trials included patients with primary hyperlipidemia, familial hypercholesterolemia, and statin intolerance. Comparator therapies included placebo and ezetimibe. Background therapies included no therapy, statin, or statin combined with ezetimibe. Baseline characteristics of the integrated safety population are summarized in Table 2. In the parent trial population, 49.5% of

patients were men, 83.4% were white, the mean age of participants was 57.5 years, and 73.5% of patients were randomized to receive evolocumab in combination with a statin. In the extension trial population, 50.5% were men, 85.7% were white, and the mean age of participants was 58.0 years. Of the 6026 patients enrolled in the parent studies, 4465 (74.1%) enrolled in the extension trials. Reasons for not continuing in the extension trials are detailed in Supplemental Table 1. Of the 1561 patients who did not enroll, 5.9% discontinued study drug early due to an adverse event in the parent trials. Median (range) evolocumab exposure was 2.8 (0-12.3) months in the parent studies and 11.1 (0-13.1) months in the extension studies. Of the 6026 patients enrolled in the parent studies, 4635 patients (76.9%) had ≥12 months of evolocumab exposure and 610 patients (10.1%) had ≥18 months of evolocumab exposure.

Safety Outcomes According to Randomized Treatment

Overall AE rates were similar between evolocumab and control in the parent studies (51.1% vs 49.6%, respectively) and in the Year 1 SoC-controlled period of the OLE studies (70.0% vs 66.0%, respectively; Table 3). The majority of the difference between arms in the OLE studies is related to the occurrence of injection-site reactions (ISRs), which occurred in 4.4% of patients receiving evolocumab and are not reported for patients in the SoC-control arm, as these patients were not receiving injectable therapy. The majority of AEs were mild to moderate in severity in each treatment group. Serious AEs were also comparable between evolocumab and control, occurring in 2.8% and 2.1%, respectively, during the parent studies and in 7.8% and 7.8%, respectively, during the OLE studies. Adverse events leading to study drug discontinuation in the parent trials occurred in 1.9% of evolocumab-treated patients and 2.3% of control-treated patients; 2.5% of evolocumab-treated patients discontinued drug due to an AE during the Year 1 SoC-controlled period of the OLE studies. Fatal adverse events occurred in 3 patients (0.08%) in the evolocumab arm and 1 patient (0.05%) in the control arm of the parent

trials and in 4 patients (0.13%) in the evolocumab arm and 6 patients (0.40%) in the SoC arm of the OLE trials. Nasopharyngitis was the most common AE among evolocumab-treated patients during both periods (5.9% in the parent studies and 9.4% in the OLE studies; rates in the control- and SoC-treated groups were 4.8% and 9.5%, respectively). Injection-site reactions were observed in 3.3% of evolocumab-treated patients and 3.0% of control-treated patients in the parent trials. Among these patients, 95.4% of evolocumab-associated ISRs were mild in severity and 4.6% were of moderate severity. In the OLE trials, 91.6% of evolocumab-associated ISRs were mild in severity and 8.4% were of moderate severity. Hypersensitivity reactions were observed in 3.2% of evolocumab-treated patients and 2.4% of patients in the control arm of parent trials and in 5.7% of evolocumab-treated patients and 4.3% of SoC-treated patients in the OLE trials. In the parent trials, 73.0% of evolocumab-associated hypersensitivity reactions were mild in severity, 26.2% were of moderate severity, and 1 patient (0.8%) experienced a severe reaction, consisting of worsening urticaria. In the OLE trials, the majority of hypersensitivity reactions were of mild to moderate severity.

Muscle-related AEs (Table 4) were similar in overall frequency and type of event in the evolocumab, control, or SoC groups. Neurocognitive-related AEs (Table 5) were similar with evolocumab (0.1%) compared to control (0.3%) in the blinded phase 2 and 3 parent trials. In the OLE studies, the rate of neurocognitive events was 0.6%, and consisted primarily of amnesia and memory impairment in both treatment groups. Neurocognitive events were observed in 0.9% of patients receiving evolocumab plus SoC and 0.3% of patients receiving SoC alone. There were small increases in amnesia (0.3% vs 0.1%) and in dementia, confusional state, and mental impairment (0.1% vs 0%). The proportion of patients discontinuing study drug for neurocognitive events was <0.1% in each arm of the parent trials and 0.1% of patients receiving evolocumab in the extension study.

Laboratory evaluations (Table 6) revealed that CK and liver enzyme elevations were infrequent and similar between groups. No drug-induced liver injury events were assessed to be associated with evolocumab use. No clinically meaningful changes in renal laboratory parameters occurred over 1 year in the extension studies or during the 52-week, randomized DESCARTES parent trial.

No neutralizing anti-evolocumab antibodies were detected in the parent or OLE studies. The incidences of binding, non-neutralizing antibodies were 0.2% (9 of 3946 evolocumab-treated patients) during the parent studies and 0.4% (11 of 2976 evolocumab-treated patients) during the OLE. During the OLE, a total of 13 positive binding anti-evolocumab results were observed in the 11 patients. The majority (9 [69.2%]) of the positive results occurred at weeks 12 or 24. One positive result occurred at week 48, in a patient who had prior positive results at weeks 4 and 12, and had received placebo during the parent trials. These data suggest that the development of binding, non-neutralizing anti-evolocumab antibodies does not increase with longer duration of evolocumab administration up to 48 weeks.

No association between time exposure to evolocumab and AEs was observed (Table 7). Among the four quarters of the OLE, AE rates in evolocumab-treated patients ranged from 40.3% in the first quarter to 29.4% in the last quarter. Serious AE rates ranged from 2.2% in the first quarter to 1.8% in the last quarter.

Mean changes from baseline for systolic and diastolic blood pressure were similar among treatment groups over time. In the integrated parent studies, the mean change from baseline to each study time point in systolic and diastolic blood pressure, respectively, ranged from -1.1 to 0.6 mmHg (systolic) and -0.8 to 0.2 mmHg (diastolic) in the any evolocumab group and -1.0 to 1.0 mmHg (systolic) and -0.8 to 0.1 mmHg (diastolic) in the any control group. In the Year 1 SoC-controlled period, the mean change from baseline to each study time point in systolic and diastolic blood pressure, respectively, ranged from -0.9 to 2.1 mmHg (systolic) and -1.5 to 0.8

mmHg (diastolic) in the evolocumab plus SoC group and -0.4 to 2.0 mmHg (systolic) and 0.2 to 0.9 mmHg (diastolic) in the SoC alone group.

Safety Outcomes According to Lowest Achieved LDL-C (Nonrandomized Analysis)

Baseline characteristics of patients according to the lowest level of LDL-C achieved (<25 mg/dL, ≥25 mg/dL to <40 mg/dL, <40 mg/dL, or ≥40 mg/dL) are shown in Supplemental Table 2. Analysis of AEs according to these LDL-C subgroups demonstrated no evidence of increased risk associated with very low LDL levels achieved with evolocumab as monotherapy or in addition to background lipid-lowering therapy (Supplemental Table 3). In the parent trials, AE rates in patients receiving evolocumab who achieved LDL-C of <25 mg/dL or ≥25 mg/dL to <40 mg/dL were 51.4% and 50.4%, respectively. These rates were similar to evolocumab-treated patients whose lowest LDL-C level was ≥40 mg/dL (52.1%). In the OLE trials, AE rates in patients receiving evolocumab who achieved LDL-C of <25 mg/dL or ≥25 mg/dL to <40 mg/dL were 70.2% and 69.2%, respectively. These rates were also consistent with evolocumab-treated patients whose lowest LDL-C level was ≥40 mg/dL (71.1%). No difference in neurocognitive or muscle-related AEs were observed in patients with progressively lower achieved LDL-C levels compared to patients with LDL-C ≥40 mg/dL. There were no discernible differences in key laboratory assessments with evolocumab compared to control or SoC across the lowest LDL-C levels achieved (Supplemental Table 4).

DISCUSSION

This pooled safety analysis from the evolocumab PROFICIO program demonstrates that the overall rates of AEs were similar in the evolocumab and control groups among over 6,000 patients in randomized double-blind and OLE studies. Together with the robust LDL-C lowering observed with evolocumab compared to control across diverse patient populations in these

trials,[9-18] these findings support a positive benefit-risk profile for evolocumab as an addition to the therapeutic armamentarium for LDL-C reduction and form the basis for regulatory approval of evolocumab. The favorable tolerability profile of evolocumab promotes adherence to treatment, and is thus reassuring given the fact that a sizeable number of patients treated with statins alone or in combination with ezetimibe are unable to achieve their risk-stratified goal for LDL-C reduction.[7, 21] The majority of clinical trials in the PROFICIO program were designed to evaluate the addition of evolocumab to statin therapy with or without other lipid-lowering therapies to address this need. Therefore, the tolerability of evolocumab in the setting of polypharmacy in high-risk patients is of paramount importance.

Evolocumab is a monoclonal antibody that binds PCSK9 in the extracellular space and induces steric hindrance so that PCSK9 is no longer able to bind to the LDLR and chaperone the receptor into the lysosome for proteolytic destruction.[8, 22, 23] Due to their size, monoclonal antibodies are unlikely to undergo membrane transport into hepatocytes or other tissues. Due to their high target specificity and extracellular mechanism of action, monoclonal antibodies, like evolocumab, are unlikely to lead to AEs stemming from drug interactions.

Myopathy, including rhabdomyolysis, is known to occur, albeit rarely, in patients receiving statins. This analysis explored the impact of evolocumab on risk for myositis, muscle fatigue, myalgia, elevation in serum levels of CK, and other muscle-related AEs. No evidence of increased risk for these events was observed, despite the inclusion of statin-intolerant patients who had experienced prior myalgia on statin treatment.

Whether statin therapy is associated with an increased risk for neurocognitive deficits and dementia has been evaluated and no definitive evidence for the association exists.[24] In both the Heart Protection Study (HPS) and the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trials, subgroup analyses using neurocognitive testing failed to reveal any increased risk for neurocognitive disorders with statin therapy compared to placebo.[25, 26] In the

integrated 12-week evolocumab parent studies, neurocognitive AEs were similar between evolocumab and control groups. In the open-label integrated extension studies, patients in this analysis were treated for up to 1 year, and neurocognitive AEs were numerically higher in the evolocumab plus SoC group (n=27 [0.9%]) relative to the SoC group (n=5 [0.3%]). The proportion of patients discontinuing study drug for neurocognitive events was low. Similar data were observed with alirocumab in the ODYSSEY LONG TERM study (1.2%, alirocumab vs 0.5%, control).[27] Certain limitations should be considered when interpreting these results. First, the numbers of neurocognitive events are small and are largely based on patient self-reporting. Investigators did not perform formal neurocognitive testing and data specific to neurocognitive events were not systematically collected. Second, the fact that the evolocumab extension studies were open label may have led to responder bias. Third, the length of follow-up is relatively short for identifying neurocognitive deficits. Finally, the population is relatively young (<4% of patients were 75 years of age or older at baseline) with a low rate (<10%) of cerebrovascular disease, suggesting a more favorable baseline neurocognitive status. There is no evidence that either evolocumab or evolocumab-PCSK9 complexes cross the blood-brain barrier to exert neurotoxicity,[28] and preliminary data, albeit modestly powered, from 5777 participants did not support a link of a PCSK9 single-nucleotide polymorphism to cognitive dysfunction in PROSPER.[29] We acknowledge that the neurocognitive safety of antihyperlipidemic agents is an important issue. A more definitive approach to evaluating the impact of evolocumab on neurocognitive function is underway. The Evaluating PCSK9 Binding antibody Influence oN coGnitive HeAlth in High cardiovascular Risk Subjects (EBBINGHAUS [NCT02207634]) trial is a dedicated study of cognition that enrolled over 1900 patients participating in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER; NCT01764633) trial, which in itself has enrolled over 27,000 patients. In EBBINGHAUS, patients who were randomized to receive either evolocumab plus high- or moderate-intensity statin or placebo plus high- or moderate-intensity statin will be

evaluated for prospective changes in neurocognitive function using the Cambridge Neuropsychological Test Automated Battery (CANTAB). This study will provide a rigorous evaluation of the effects of evolocumab in combination with a statin on neurocognitive impairment compared with statin therapy alone. The effect of anti-PCSK9 antibodies on cognitive function will also be monitored in ongoing phase 3 studies with other antibodies such as the alirocumab ODYSSEY OUTCOMES study.[30]

No evidence emerged that evolocumab is associated with an increased risk for acute renal injury or renal failure and no impact on blood pressure was observed. Drug-induced liver injury events were not assessed to be associated with evolocumab use in this analysis. No association between time exposure to evolocumab and AE rates were identified during the OLE. Finally, to date, neutralizing anti-evolocumab antibodies have not been detected.

A post-hoc exploratory analysis according to achieved LDL-C levels revealed no evidence of differences in risk of AEs in patients achieving very low LDL-C levels (<25 mg/dL). This analysis is limited by the postbaseline definition of subgroups according to on-treatment LDL-C rather than randomized groups. As such, imbalances among groups can occur that can confound safety results. Additionally, small numbers of patients per subgroup precludes the ability to perform meaningful comparisons between evolocumab and control.

CONCLUSIONS

The PROFICIO integrated safety analysis of evolocumab included 6026 patients pooled across phase 2 and 3 trials and 4465 patients that continued in open-label extension trials. With median evolocumab exposures of 2.8 months (phase 2 and 3 trials) and 11.1 months (extension studies), the findings support a positive benefit-risk profile for evolocumab. Injection-site reactions associated with evolocumab were mild-moderate in severity. Evolocumab therapy was

not associated with significant risk for hepatotoxicity, muscle-related AEs, or neurocognitive events.

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Figure Legends

Figure 1. Studies included in pooled analysis. Patients from 12 phase 2 and 3 studies and the 2 emanating open-label extension studies were included in the pooled analysis. *YUKAWA-2 was analyzed after integration for this analysis and was not included. AI/Pen, autoinjector pen; AMD, automated mini-doser; EZE, ezetimibe; HeFH, heterozygous familial hypercholesterolemia; OLE, open-label extension; PBO, placebo; PFS, pre-filled syringe; Q2W, every two weeks; QM, monthly; SoC, standard of care

Table 1. Phase 2 and 3 Parent Evolocumab Studies

Study Name	N	Trial Population and Baseline Fasting LDL-C	Background Lipid Therapy	Endpoint (Weeks)	Dosing
Phase 2					
LAPLACE-TIMI 57[10]	629	FH and NFH ≥2.2 mmol/L (85 mg/dL)	Statin (± ezetimibe)	12	70, 105, 140 mg Q2W; 280, 350, 420 mg QM
RUTHERFORD[14]	167	HeFH ≥2.6 mmol/L (100 mg/dL)	Statin (± ezetimibe)	12	350, 420 mg QM
GAUSS[18]	157	Statin-intolerant (FH and NFH) ≥2.6 mmol/L (100 mg/dL)	Non-ezetimibe lipid-lowering therapy*	12	280, 350, 420 mg QM
MENDEL[13]	406	FH and NFH	None	12	70, 105, 140 mg

		≥2.6 mmol/L (100 mg/dL)			Q2W; 280, 350, 420 mg QM
YUKAWA[11]	307	FH and NFH ≥3.0 mmol/L (115 mg/dL)	Statin (± ezetimibe)	12	70 and 140 mg Q2W; 280 and 420 mg QM
Phase 3					
LAPLACE-2[16]	1896	FH and NFH ≥3.9 mmol/L (150 mg/dL) – no statin ≥2.6 mmol/L (100 mg/dL) – nonintensive statin ≥2.1 mmol/L (80 mg/dL) – intensive statin	Statins[†]	12	140 mg Q2W 420 mg QM
RUTHERFORD-2[15]	329	HeFH ≥2.6 mmol/L (100 mg/dL)	Statin (± ezetimibe)	12	140 mg Q2W 420 mg QM

GAUSS-2[17]	307	Intolerant to ≥2 statins FH and NFH ≥ NCEP ATPIII LDL-C goal	Non-ezetimibe lipid-lowering therapy*	12	140 mg Q2W 420 mg QM
MENDEL-2[12]	614	FH and NFH ≥2.6 mmol/L (100 mg/dL)	None	12	140 mg Q2W 420 mg QM
DESCARTES[9]	901	Various levels of CV risk FH and NFH ≥1.9 mmol/L (75 mg/dL)	Diet ± atorvastatin ± ezetimibe‡	52	420 mg QM
THOMAS-1 (NCT01849497)	149	FH and NFH ≥2.2 mmol/L (85 mg/dL)	Statin (± ezetimibe)	6	140 mg Q2W
THOMAS-2 (NCT01879319)	164	FH and NFH ≥2.2 mmol/L (85 mg/dL)	Statin (± ezetimibe)	Mean of 10 and 12	420 mg QM

*At screening, low or atypical dose statin permitted: weekly doses of ≤70 mg atorvastatin; ≤140 mg simvastatin, pravastatin, lovastatin; ≤35 mg rosuvastatin; ≤280 mg fluvastatin.

†Patients randomized to 1 of 5 background statin doses: moderate intensity (atorvastatin 10 mg, simvastatin 40 mg, or rosuvastatin 5 mg daily) or high intensity (atorvastatin 80 mg or rosuvastatin 40 mg daily).

‡Patients assigned background lipid-lowering therapy according to screening LDL-C and NCEP ATP III risk category: diet alone, diet plus atorvastatin 10 mg orally daily, diet plus atorvastatin 80 mg orally daily, or diet plus atorvastatin 80 mg orally daily and ezetimibe 10 mg orally daily.

CV, cardiovascular; FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; NCEP ATPIII, National Cholesterol Education Program Adult Treatment Panel III; NFH, nonfamilial hypercholesterolemia; Q2W, every 2 weeks; QM, monthly

Table 2. Baseline Characteristics

	Integrated Parent Studies		Integrated Interim Extension Studies	
	Control*	**Evolocumab**	**SoC**	**Evolocumab**
	(N=2080)	(N=3946)	(N=1489)	(N=2976)
Age, yr, mean (SD)	57.3 (11.1)	57.7 (11.3)	58.2 (10.9)	57.8 (11.0)
Age group, n (%)				
<65 years	1494 (71.8)	2753 (69.8)	1020 (68.5)	2083 (70.0)
≥ 65 years	586 (28.2)	1193 (30.2)	469 (31.5)	893 (30.0)
≥ 75 years	65 (3.1)	158 (4.0)	62 (4.2)	111 (3.7)
Male sex, n (%)	999 (48.0)	1983 (50.3)	765 (51.4)	1490 (50.1)
Race or ethnicity, n (%)				
White	1754 (84.3)	3270 (82.9)	1267 (85.1)	2559 (86.0)
Asian	184 (8.8)	355 (9.0)	123 (8.3)	231 (7.8)

Black	106 (5.1)	247 (6.3)	72 (4.8)	135 (4.5)
Hispanic	122 (5.9)	202 (5.1)	70 (4.7)	145 (4.9)
NCEP risk categories, n (%)				
High	640 (30.8)	1388 (35.2)	542 (36.4)	1038 (34.9)
Moderately high	189 (9.1)	402 (10.2)	151 (10.1)	294 (9.9)
Moderate	616 (29.6)	1157 (29.3)	428 (28.7)	878 (29.5)
Lower	635 (30.5)	999 (25.3)	368 (24.7)	766 (25.7)
Coronary artery disease, n (%)	350 (16.8)	791 (20.0)	307 (20.6)	589 (19.8)
Cerebrovascular or peripheral arterial disease, n (%)	153 (7.4)	356 (9.0)	141 (9.5)	266 (8.9)
Randomized treatment assignment, n (%)				
Monotherapy	480 (23.1)	651 (16.5)	N/A	N/A
Combination with statins	1466 (70.5)	2965 (75.1)	N/A	N/A

Statin intolerant[†]	134 (6.4)	330 (8.4)	N/A	N/A

[*]Control includes placebo and ezetimibe treatment groups.

[†]Inability to tolerate ≥1 statin at any dose or an increase in dose above weekly maximums of rosuvastatin, 35 mg; atorvastatin, 70 mg; simvastatin, 140 mg; pravastatin, 140 mg; lovastatin, 140 mg; or fluvastatin, 280 mg, because of intolerable myalgia or myopathy (myalgia plus elevated creatine kinase) and having symptom improvement or resolution with statin discontinuation.

N/A, not applicable (patients were randomized to evolocumab plus SoC or SoC alone); NCEP, National Cholesterol Education Program; SoC, standard of care

Table 3. Adverse Events

	Integrated Parent Studies		Integrated Interim Extension Studies Year 1 SoC-controlled Period	
	Control*	**Evolocumab**	**SoC**	**Evolocumab**
	(N=2080)	(N=3946)	(N=1489)	(N=2976)
Any AE, n (%)	1031 (49.6)	2016 (51.1)	982 (66.0)	2084 (70.0)
Grade ≥2†	487 (23.4)	878 (22.3)	593 (39.8)	1211 (40.7)
Grade ≥3†	66 (3.2)	147 (3.7)	125 (8.4)	253 (8.5)
Grade ≥4†	6 (0.3)	24 (0.6)	12 (0.8)	23 (0.8)
AEs occurring in >2% of patients in any treatment arm in parent or extension studies, n (%)				
Nasopharyngitis	99 (4.8)	231 (5.9)	142 (9.5)	281 (9.4)
Upper respiratory tract infection	56 (2.7)	127 (3.2)	74 (5.0)	162 (5.4)

Headache	66 (3.2)	120 (3.0)	32 (2.1)	107 (3.6)
Back pain	57 (2.7)	117 (3.0)	55 (3.7)	126 (4.2)
Myalgia	55 (2.6)	98 (2.5)	43 (2.9)	90 (3.0)
Arthralgia	45 (2.2)	91 (2.3)	48 (3.2)	144 (4.8)
Influenza	41 (2.0)	83 (2.1)	45 (3.0)	108 (3.6)
Nausea	37 (1.8)	81 (2.1)	15 (1.0)	54 (1.8)
Diarrhea	50 (2.4)	79 (2.0)	28 (1.9)	83 (2.8)
Cough	26 (1.3)	78 (2.0)	49 (3.3)	106 (3.6)
Pain in extremity	39 (1.9)	73 (1.8)	35 (2.4)	100 (3.4)
Fatigue	40 (1.9)	71 (1.8)	15 (1.0)	85 (2.9)
Muscle spasms	37 (1.8)	68 (1.7)	30 (2.0)	75 (2.5)
Bronchitis	29 (1.4)	64 (1.6)	56 (3.8)	104 (3.5)
Urinary tract infection	34 (1.6)	60 (1.5)	34 (2.3)	84 (2.8)
Sinusitis	23 (1.1)	54 (1.4)	42 (2.8)	74 (2.5)

Hypertension	26 (1.3)	56 (1.4)	63 (4.2)	114 (3.8)
Musculoskeletal pain	24 (1.2)	43 (1.1)	30 (2.0)	62 (2.1)
Osteoarthritis	9 (0.4)	22 (0.6)	26 (1.7)	74 (2.5)
Injection-site reactions[‡], n (%)	63 (3.0)	131 (3.3)	N/A	131 (4.4)
Grade ≥2[†]	1 (<0.1)	6 (0.2)	N/A	11 (0.4)
Grade ≥3[†]	0	0	N/A	0
Hypersensitivity reactions[§], n (%)	50 (2.4)	126 (3.2)	64 (4.3)	170 (5.7)
Grade ≥2[†]	16 (0.8)	34 (0.9)	23 (1.5)	69 (2.3)
Grade ≥3[†]	0	1 (<0.1)	0	6 (0.2)
Grade ≥4[†]	0	0	0	3 (0.1)
Serious AEs, n (%)	43 (2.1)	110 (2.8)	116 (7.8)	231 (7.8)
AEs leading to study drug discontinuation, n (%)	48 (2.3)	75 (1.9)	N/A	75 (2.5)
Fatal adverse events, n (%)	1 (0.05)	3 (0.08)	6 (0.40)	4 (0.13)

Adverse events are listed in decreasing order of frequency in the evolocumab arm of the parent trials.

[*]Control includes placebo and ezetimibe treatment groups.

[†]Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grade definitions are as follows: grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; grade 2: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living; grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living; grade 4: life-threatening consequences; urgent intervention indicated [20].

[‡]Potential injection site reactions (ISR) were identified using preferred terms consistent with ISRs from the administration site reactions and ISRs high level terms. N/A indicates not applicable because these patients were receiving standard of care and therefore not receiving injections.

[§]Potential hypersensitivity reactions were identified using the hypersensitivity standardized MedDRA query (SMQ).

AE, adverse event; N/A, not applicable; SoC, standard of care.

Table 4. Muscle-related Adverse Events

	Integrated Parent Studies		Integrated Interim Extension Studies Year 1 SoC-controlled Period	
	Control*	Evolocumab	SoC	Evolocumab
	(N=2080)	(N=3946)	(N=1489)	(N=2976)
Any musculoskeletal and connective tissue disorder†, n (%)	284 (13.7)	581 (14.7)	315 (21.2)	740 (24.9)
Musculoskeletal and connective tissue disorders occurring in ≥1% in any arm, n (%)				
Back pain	57 (2.7)	117 (3.0)	55 (3.7)	126 (4.2)
Myalgia	55 (2.6)	98 (2.5)	43 (2.9)	90 (3.0)
Arthralgia	45 (2.2)	91 (2.3)	48 (3.2)	144 (4.8)

Pain in extremity	39 (1.9)	73 (1.8)	35 (2.4)	100 (3.4)
Muscle spasms	37 (1.8)	68 (1.7)	30 (2.0)	75 (2.5)
Musculoskeletal pain	24 (1.2)	43 (1.1)	30 (2.0)	62 (2.1)
Osteoarthritis	9 (0.4)	22 (0.6)	26 (1.7)	74 (2.5)
Neck Pain	5 (0.2)	18 (0.5)	6 (0.4)	29 (1.0)

Muscle-related adverse events are listed in decreasing order of frequency in the evolocumab arm of the parent trials.

[*]Control includes placebo and ezetimibe treatment groups.

[†]System organ class and preferred terms.

AE, adverse event; SoC, standard of care.

Table 5. Neurocognitive Adverse Events

	Integrated Parent Studies		Integrated Interim Extension Studies Year 1 SoC-controlled Period	
	Control*	Evolocumab	SoC	Evolocumab
	(N=2080)	(N=3946)	(N=1489)	(N=2976)
Any neurocognitive-related AE†, n (%)	6 (0.3)	5 (0.1)	5 (0.3)	27 (0.9)
Amnesia	0	2 (0.1)	2 (0.1)	8 (0.3)
Disorientation	2 (0.1)	1 (<0.1)	0	1 (<0.1)
Memory impairment	1 (<0.1)	1 (<0.1)	3 (0.2)	7 (0.2)
Delirium	0	1 (<0.1)	0	0
Cognitive disorder	1 (<0.1)	0	0	1 (<0.1)
Dementia with Lewy bodies	1 (<0.1)	0	0	0
Disturbance in attention	1 (<0.1)	0	0	0
Dementia	0	0	0	3 (0.1)
Confusional state	0	0	0	2 (0.1)
Mental impairment	0	0	0	2 (0.1)

Dementia Alzheimer's type	0	0	0	2 (0.1)
Illusion	0	0	0	1 (<0.1)
Transient global amnesia	0	0	0	1 (<0.1)
Neurocognitive-related AEs leading to study drug discontinuation, n (%)	1 (<0.1)	1 (<0.1)	N/A	3 (0.1)

Neurocognitive events are listed in decreasing order of frequency in the evolocumab arm of the parent trials.

*Control includes placebo and ezetimibe treatment groups.

†Neurocognitive events were identified using deliria (including confusion), cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders high-level group terms.

AE, adverse event; N/A, not applicable; SoC, standard of care.

Table 6. Laboratory Investigations for Muscle Injury, Liver Function, and Renal Function

	Integrated Parent Studies		Integrated Interim Extension Studies Year 1 SoC-controlled Period	
	Control*	Evolocumab	SoC	Evolocumab
	(N=2080)	(N=3946)	(N=1489)	(N=2976)
CK				
Number of patients with any post-baseline CK measurement	2055	3892	1472	2962
CK >5 x ULN, n (%)	14 (0.7)	27 (0.7)	17 (1.2)	17 (0.6)
CK >10 x ULN, n (%)	5 (0.2)	9 (0.2)	9 (0.6)	7 (0.2)
Liver function tests				
Number of patients with any post-baseline liver function test measurement	2055	3893	1477	2968
ALT or AST >3 x ULN, n (%)	20 (1.0)	17 (0.4)	18 (1.2)	31 (1.0)
ALT or AST >5 x ULN, n (%)	7 (0.3)	6 (0.2)	3 (0.2)	10 (0.3)
Total bilirubin >2 x ULN, n (%)	3 (0.1)	6 (0.2)	2 (0.1)	8 (0.3)

(ALT or AST >3 x ULN) and (total bilirubin >2 x ULN), n (%)	0	0	0	1 (<0.1)
Renal function tests				
Serum creatinine				
Baseline mean (SD), µmol/L[†]	80.2 (17.7) (n=302[‡])	80.0 (16.5) (n=599[‡])	80.6 (17.6)	80.4 (17.3)
Number of patients evaluated at week 52	273	533	402	833
Mean (SD) change from baseline at week 52, µmol/L[†]	-0.8 (9.0)	0.8 (9.7)	-0.7 (9.6)	-0.8 (10.2)
Blood urea nitrogen				
Baseline mean (SD), mmol/L[§]	5.6 (1.6) (n=302[‡])	5.6 (1.5) (n=599[‡])	5.8 (1.7)	5.8 (1.6)
Number of patients evaluated at week 52	273	533	402	883
Mean (SD) change from baseline at week 52, mmol/L[§]	0.04 (1.2)	0.06 (1.4)	-0.01 (1.3)	0.09 (1.4)

[*]Control includes placebo and ezetimibe treatment groups.

[†]Serum creatinine 88.4 µmol/L = 1 mg/dL

[‡]For the parent trials, week 52 renal function data are available from the DESCARTES study, which enrolled 901 patients (evolocumab plus background therapy, n=599; placebo plus background therapy, n=302).

[§]Blood urea nitrogen 0.36 mmol/L = 1 mg/dL

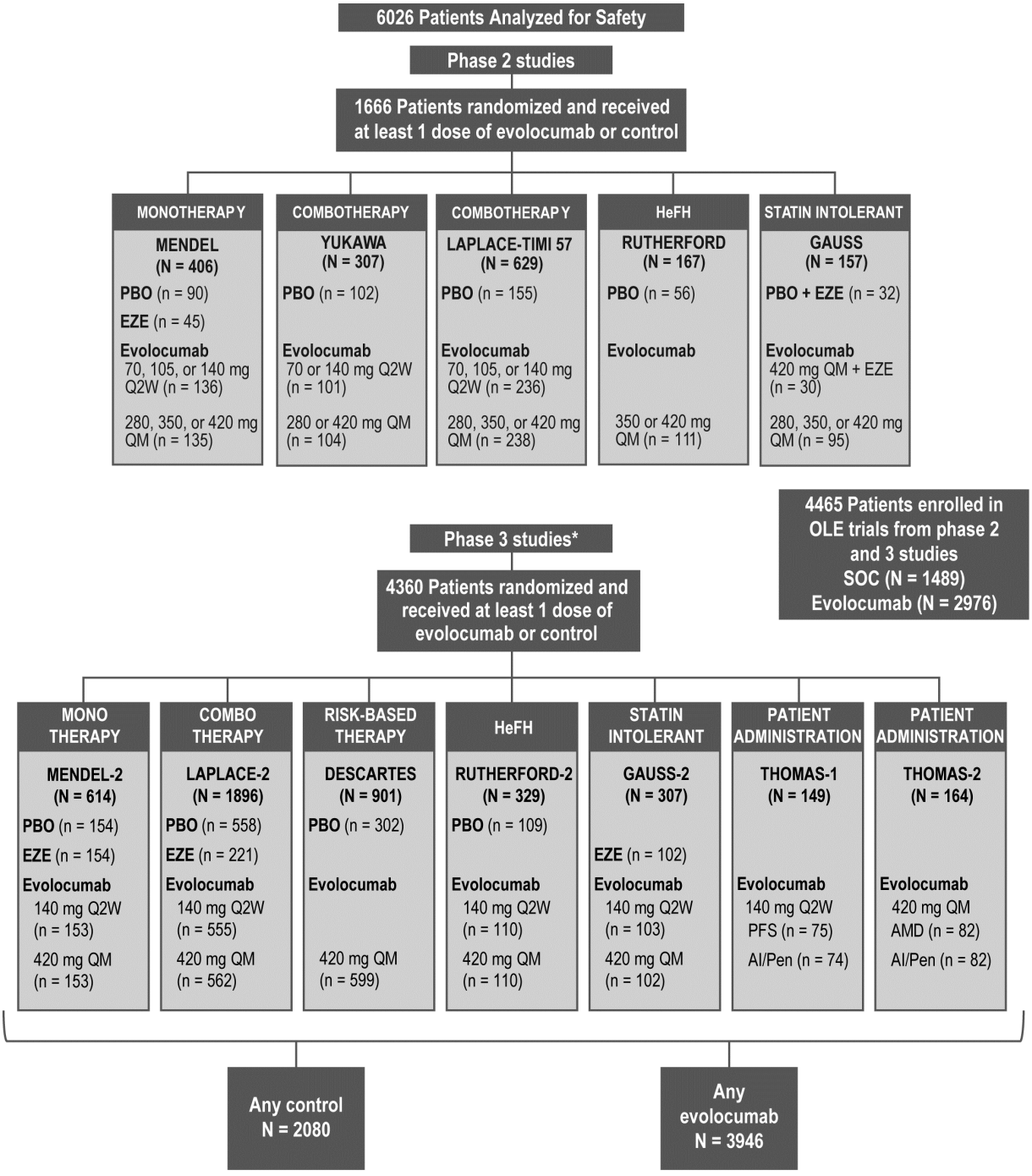
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; SoC, standard of care; ULN, upper limit of normal.

Table 7. Rates of Adverse Events in Evolocumab-treated Patients in the Open-label Extension Study by Treatment Period

		Adverse Events in Evolocumab-Treated Patients	
Open Label Extension Study Period Months	Evolocumab-treated Patients N	Any Adverse Events N (%)	Serious Adverse Events N (%)
≥0 and <3	2976	1198 (40.3)	66 (2.2)
≥3 and <6	2957	974 (32.9)	61 (2.1)
≥6 and <9	2939	932 (31.7)	65 (2.2)
≥9 and <12	2916	857 (29.4)	52 (1.8)

Figures

Figure 1.



A Pooled Safety Analysis of Evolocumab in Over 6000 Patients from Double-blind and Open-label Extension Studies

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Table 1. Reasons for Non-enrollment in Open-label Extension Studies

Reason	Any Control (N=588)	Any Evolocumab (N=973)	Total (N=1561)
	n (%)		
Ended study drug early	**110 (18.7)**	**192 (19.7)**	**302 (19.3)**
Administrative decision	1 (0.2)	7 (0.7)	8 (0.5)
Adverse event	35 (6.0)	57 (5.9)	92 (5.9)
Death	0	2 (0.2)	2 (0.1)
Full consent withdrawn	10 (1.7)	12 (1.2)	22 (1.4)
Lost to follow-up	8 (1.4)	17 (1.7)	25 (1.6)
Other	14 (2.4)	29 (3.0)	43 (2.8)
Physician decision	4 (0.7)	3 (0.3)	7 (0.4)
Pregnancy	0	1 (0.1)	1 (0.1)
Subject request	38 (6.5)	64 (6.6)	102 (6.5)
Completed study drug	**478 (81.3)**	**781 (80.3)**	**1259 (80.6)**
Ended study early	**2 (0.3)**	**7 (0.7)**	**9 (0.6)**
Death	0	1 (0.1)	1 (0.1)
Full consent withdrawn	2 (0.3)	0	2 (0.1)
Lost to follow-up	0	6 (0.6)	6 (0.4)
Did not end study early, and reported intention to roll-over but did not roll over	**121 (20.6)**	**227 (23.3)**	**348 (22.3)**
Did not end study early, and reported intention to not roll over	**351 (59.7)**	**531 (54.6)**	**882 (56.5)**
Due to level of commitment	95 (16.2)	169 (17.4)	264 (16.9)
Due to parent experience	31 (5.3)	30 (3.1)	61 (3.9)
Due to personal reasons	225 (38.3)	332 (34.1)	557 (35.7)
Did not end study early, and unknown intention to roll over	**4 (0.7)**	**16 (1.6)**	**20 (1.3)**

Table 2. Baseline Characteristics According to Lowest LDL-C Level Achieved

Characteristic		Lowest LDL-C Achieved and Treatment Group				
		<25 mg/dL	**≥25 mg/dL and <40 mg/dL**	**All Patients With <40 mg/dL**	**≥40 mg/dL**	
	Initial Parent Trials*	**Any Evolocumab N = 1609**	**Any Evolocumab N = 956**	**Any Evolocumab N = 2565**	**Any Evolocumab N = 1339**	**Any Control† N = 2038**
	OLE‡	**Evolocumab + SoC N = 773**	**Evolocumab + SoC N = 759**	**Evolocumab + SoC N = 1532**	**Evolocumab + SoC N = 1426**	**SoC N = 1459**
Age, yr, mean (SD)	Initial parent trials	58.5 (10.3)	57.8 (11.6)	58.2 (10.8)	56.7 (12.1)	57.3 (11.1)
	OLE	58.9 (10.4)	58.5 (10.1)	58.7 (10.3)	57.0 (11.7)	58.2 (10.9)
Male sex, n (%)	Initial parent trials	953 (59.2)	455 (47.6)	1408 (54.9)	549 (41.0)	972 (47.7)
	OLE	500 (64.7)	394 (51.9)	894 (58.4)	583 (40.9)	749 (51.3)
Race or ethnicity, n (%)						
White	Initial parent trials	1344 (83.5)	779 (81.5)	2123 (82.8)	1113 (83.1)	1716 (84.2)
	OLE	646 (83.6)	644 (84.8)	1290 (84.2)	1252 (87.8)	1238 (84.9)
Asian	Initial parent trials	167 (10.4)	97 (10.1)	264 (10.3)	90 (6.7)	184 (9.0)
	OLE	90 (11.6)	76 (10.0)	166 (10.8)	65 (4.6)	122 (8.4)

Black or African American	Initial parent trials	66 (4.1)	65 (6.8)	131 (5.1)	111 (8.3)	105 (5.2)
	OLE	24 (3.1)	25 (3.3)	49 (3.2)	85 (6.0)	72 (4.9)
Other race	Initial parent trials	32 (2.0)	15 (1.6)	47 (1.8)	25 (1.9)	33 (1.6)
	OLE	13 (1.7)	14 (1.8)	27 (1.8)	24 (1.7)	27 (1.9)
Hispanic	Initial parent trials	75 (4.7)	52 (5.4)	127 (5.0)	71 (5.3)	118 (5.8)
	OLE	36 (4.7)	32 (4.2)	68 (4.4)	77 (5.4)	66 (4.5)
Lipids, mean (SD)						
LDL-C (mg/dL)	Initial parent trials	103.4 (27.0)	122.5 (29.1)	110.5 (29.3)	159.4 (50.1)	126.9 (42.5)
	OLE	108.1 (29.0)	118.2 (30.5)	113.1 (30.1)	143.6 (51.9)	129.1 (45.6)
PCSK9 (ng/mL)	Initial parent trials	415.0 (150.3)	379.1 (139.4)	401.7 (147.3)	356.5 (134.6)	378.4 (141.6)
	OLE	397.8 (137.1)	399.2 (139.0)	398.5 (138.0)	379.3 (145.8)	381.8 (143.6)
Cardiovascular risk factors, n (%)						
NCEP risk category high	Initial parent trials	631 (39.2)	320 (33.5)	951 (37.1)	425 (31.7)	623 (30.6)
	OLE	328 (42.4)	292 (38.5)	620 (40.5)	410 (28.8)	526 (36.1)

Coronary artery disease	Initial parent trials	365 (22.7)	182 (19.0)	547 (21.3)	237 (17.7)	343 (16.8)
	OLE	193 (25.0)	164 (21.6)	357 (23.3)	231 (16.2)	297 (20.4)
Cerebrovascular or peripheral arterial disease	Initial parent trials	149 (9.3)	82 (8.6)	231 (9.0)	122 (9.1)	150 (7.4)
	OLE	86 (11.1)	74 (9.7)	160 (10.4)	103 (7.2)	138 (9.5)

*Median study exposure: 3 months

†Control placebo and/or ezetimibe

‡Year 1 standard of care-controlled period of open-label extension studies; median study exposure: 11 months

OLE, open-label extension; SoC, standard of care

Table 3. Adverse Events According to Lowest LDL-C Level Achieved

AE		Lowest LDL-C Achieved and Treatment Group				
		<25 mg/dL	≥25 mg/dL and <40 mg/dL	All Patients With <40 mg/dL	≥40 mg/dL	
	Initial Parent Trials*	Any Evolocumab N = 1609	Any Evolocumab N = 956	Any Evolocumab N = 2565	Any Evolocumab N = 1339	Any Control† N = 2038
	OLE‡	Evolocumab + SoC N = 773	Evolocumab + SoC N = 759	Evolocumab + SoC N = 1532	Evolocumab + SoC N = 1426	SoC N = 1459
Any AE, %	Initial parent trials	51.4	50.4	51.0	52.1	50.0
	OLE	70.2	69.2	69.7	71.1	66.6
AEs leading to discontinuation of IP	Initial parent trials	1.2	1.0	1.2	3.1	0
	OLE	1.0	1.8	1.4	3.7	N/A§
SAEs	Initial parent trials	2.9	2.4	2.7	2.6	2.0
	OLE	7.8	7.1	7.4	8.2	7.8
Muscle-related AEs, %	Initial parent trials	4.5	3.9	4.2	6.6	4.8
	OLE	5.2	7.1	6.1	6.9	6.2
Neurocognitive AEs, %	Initial parent trials	0.06	0	0.04	0.3	0.3
	OLE	0.5	1.2	0.8	1.0	0.3

*Median study exposure: 3 months

†Control placebo and/or ezetimibe

‡Year 1 standard of care-controlled period of open-label extension studies; median study exposure: 11 months

§Not applicable; standard of care group did not receive investigational drug

AE, adverse event; N/A, not applicable; OLE, open-label extension; SAE, serious AE; SoC, standard of care; IP, investigational product

Table 4. Laboratory Parameters According to Lowest LDL-C Level Achieved

Laboratory Parameter		Lowest LDL-C Achieved and Treatment Group				
		<25 mg/dL	≥25 mg/dL and <40 mg/dL	All Patients With <40 mg/dL	≥40 mg/dL	
	Initial Parent Trials*	Any Evolocumab N = 1609	Any Evolocumab N = 956	Any Evolocumab N = 2565	Any Evolocumab N = 1339	Any Control† N = 2038
	OLE‡	Evolocumab + SoC N = 773	Evolocumab + SoC N = 759	Evolocumab + SoC N = 1532	Evolocumab + SoC N = 1426	SoC N = 1459
CK >5 x ULN, %	Initial parent trials	0.6	0.4	0.5	1.0	0.7
	OLE	0.4	0.9	0.7	0.5	1.1
CK >10 x ULN, %	Initial parent trials	0.2	0.1	0.2	0.3	0.2
	OLE	0.1	0.4	0.3	0.2	0.5
ALT or AST >3 x ULN, %	Initial parent trials	0.4	0.3	0.4	0.5	0.9
	OLE	0.9	0.8	0.8	1.3	1.2
Total bilirubin >2 x ULN, %	Initial parent trials	0.3	0.1	0.2	0	0.1
	OLE	0.4	0.3	0.3	0.1	0.1

*Median study exposure: 3 months

†Control placebo and/or ezetimibe

‡Year 1 standard of care-controlled period of open-label extension studies; median study exposure: 11 months

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; OLE, open-label extension; SoC, standard of care; ULN, upper limit of normal