ORIGINAL ARTICLE

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

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ABSTRACT

BACKGROUND

Alirocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9), has been shown to reduce low-density lipoprotein (LDL) cholesterol levels in patients who are receiving statin therapy. Larger and longer-term studies are needed to establish safety and efficacy.

METHODS

We conducted a randomized trial involving 2341 patients at high risk for cardiovascular events who had LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or more and were receiving treatment with statins at the maximum tolerated dose (the highest dose associated with an acceptable side-effect profile), with or without other lipid-lowering therapy. Patients were randomly assigned in a 2:1 ratio to receive alirocumab (150 mg) or placebo as a 1-ml subcutaneous injection every 2 weeks for 78 weeks. The primary efficacy end point was the percentage change in calculated LDL cholesterol level from baseline to week 24.

RESULTS

At week 24, the difference between the alirocumab and placebo groups in the mean percentage change from baseline in calculated LDL cholesterol level was −62 percentage points (P<0.001); the treatment effect remained consistent over a period of 78 weeks. The alirocumab group, as compared with the placebo group, had higher rates of injection-site reactions (5.9% vs. 4.2%), myalgia (5.4% vs. 2.9%), neurocognitive events (1.2% vs. 0.5%), and ophthalmologic events (2.9% vs. 1.9%). In a post hoc analysis, the rate of major adverse cardiovascular events (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was lower with alirocumab than with placebo (1.7% vs. 3.3%; hazard ratio, 0.52; 95% confidence interval, 0.31 to 0.90; nominal P=0.02).

CONCLUSIONS

Over a period of 78 weeks, alirocumab, when added to statin therapy at the maximum tolerated dose, significantly reduced LDL cholesterol levels. In a post hoc analysis, there was evidence of a reduction in the rate of cardiovascular events with alirocumab. (Funded by Sanofi and Regeneron Pharmaceuticals; ODYSSEY LONG TERM ClinicalTrials.gov number, NCT01507831.)

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Monoclonal antibodies to proprotein convertase subtilisin–kexin type 9 (PCSK9) have been shown to reduce low-density lipoprotein (LDL) cholesterol levels in patients who are being treated with statins. In phase 2 studies lasting 8 to 12 weeks, the PCSK9 inhibitor alirocumab lowered LDL cholesterol levels by 40 to 70% when added to background statin therapy.[1-3] However, this new treatment needs to be evaluated in larger populations for longer periods of follow-up to establish its safety and efficacy.[4-7]

We conducted a 78-week trial comparing alirocumab (150 mg every 2 weeks) with placebo in 2341 patients at high risk for cardiovascular events who were receiving treatment with statins at the maximum tolerated dose (the highest dose associated with an acceptable side-effect profile), with or without other lipid-lowering therapy. The trial, which was entitled Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM), was designed to obtain longer-term data on safety and reduction in LDL cholesterol levels. We also collected data on prespecified adjudicated cardiovascular outcomes and performed a post hoc analysis of the composite end point of major adverse cardiovascular events.

Methods

Study Design and Oversight

The ODYSSEY LONG TERM trial was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multinational study, which was conducted at 320 sites in 27 countries throughout Africa, Europe, and North and South America. The study was funded by Sanofi and Regeneron Pharmaceuticals.

The sponsors and the steering committee designed the trial protocol, which is available with the full text of this article at NEJM.org. The protocol was approved by the institutional review board at each participating center. The sponsors collected, managed, and analyzed the data under the supervision of the steering committee. The first draft of the manuscript was prepared by the first author and was thereafter critically reviewed and revised by all the authors. The sponsors provided comments on an early draft. Editorial assistance was provided by Prime Medica, funded by Sanofi and Regeneron Pharmaceuticals. The academic authors had unrestricted access to the data and vouch for the accuracy and completeness of the data and all analyses, as well as for the fidelity of this report to the trial protocol.

Study Population

Adult patients (≥18 years of age) with heterozygous familial hypercholesterolemia (as determined by genotyping or clinical criteria) or with established coronary heart disease or a coronary heart disease risk equivalent (as defined in Table 1) were eligible for inclusion if they had an LDL cholesterol level of 70 mg per deciliter (1.8 mmol per liter) or more at the time of screening. All patients were required to be receiving either high-dose statin therapy (as defined in Table 1) or statin therapy at the maximum tolerated dose, with or without other lipid-lowering therapy, for at least 4 weeks before screening (6 weeks for fenofibrate); this lipid-lowering regimen was continued throughout the study. Full eligibility criteria are listed in the Supplementary Appendix, available at NEJM.org. All participants provided written informed consent.

Study Procedures

After a 3-week screening period, eligible patients were randomly assigned, in a 2:1 ratio, to receive alirocumab (150 mg) or placebo, in a double-blind fashion, every 2 weeks for 78 weeks (in addition to their statin therapy, with or without other lipid-lowering therapy; see Fig. S1 in the Supplementary Appendix). Both alirocumab and placebo were administered as a single 1-ml subcutaneous injection, which was provided in a prefilled syringe. All patients were instructed to follow a stable Therapeutic Lifestyle Changes diet, as outlined by the Adult Treatment Panel III of the National Cholesterol Education Program, or an equivalent diet for the duration of the study.

Patients were to return to the study site during the double-blind study period at weeks 0 (baseline), 4, 8, 12, 16, 24, 36, 52, 64, and 78, and again 8 weeks after the end of the double-blind period (i.e., at week 86) for a safety assessment. Further details on randomization, assessment of adherence and exposure to the study drug, and laboratory assessments are provided in the Supplementary Appendix.

Table 1. Baseline Characteristics of All Randomly Assigned Patients.*

Characteristic	Alirocumab (N=1553)	Placebo (N=788)
Demographic variables		
Age — yr	60.4±10.4	60.6±10.4
Male sex — no. (%)	983 (63.3)	474 (60.2)
White race — no. (%)†	1441 (92.8)	730 (92.6)
Cardiovascular history and risk factors		
Body-mass index‡	30.2±5.7	30.5±5.5
Heterozygous familial hypercholesterolemia — no. (%)§	276 (17.8)	139 (17.6)
Coronary heart disease — no. (%)	1055 (67.9)	552 (70.1)
Coronary heart disease risk equivalent — no. (%)¶	639 (41.1)	323 (41.0)
Type 2 diabetes — no. (%)	542 (34.9)	267 (33.9)
Current smoker — no. (%)	325 (20.9)	159 (20.2)
Lipid-modifying medications — no. (%)		
Any statin	1552 (>99.9)	787 (99.9)
High-dose statin‖	727 (46.8)	368 (46.7)
Other lipid-lowering therapy	437 (28.1)	220 (27.9)
Ezetimibe	216 (13.9)	118 (15.0)
Lipid and lipoprotein levels — mg/dl		
Calculated LDL cholesterol**		
Mean	122.7±42.6	121.9±41.4
Range	39–424	19–404
Non-HDL cholesterol	152.6±46.6	152.0±45.8
Apolipoprotein B	101.9±27.7	101.4±27.3
Lipoprotein(a)		
Median	22.2	20.9
Interquartile range	7.6–66.5	6.5–66.8
Fasting triglycerides		
Median	132.0	135.0
Interquartile range	93.8–183.2	94.7–188.5
HDL cholesterol	49.8±12.2	50.0±12.4
Apolipoprotein A1	146.5±25.1	147.3±27.3

* Plus–minus values are means ±SD. The P value for all between-group comparisons was greater than 0.05, indicating no significant differences. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

† Race was self-reported.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Heterozygous familial hypercholesterolemia was diagnosed by means of genotyping in 40.2% of the patients in the two groups combined and by clinical criteria (World Health Organization–Simon Broome diagnostic criteria) in 59.8% of the patients in the two groups combined.

¶ Coronary heart disease risk equivalents were defined as peripheral arterial disease, ischemic stroke, moderate chronic kidney disease (estimated glomerular filtration rate, 30 to <60 ml per minute per 1.73 m^2 of body-surface area), or diabetes mellitus plus two or more additional risk factors (hypertension; ankle–brachial index of ≤0.90; microalbuminuria, macroalbuminuria, or a urinary dipstick result of >2+ protein; preproliferative or proliferative retinopathy or laser treatment for retinopathy; or a family history of premature coronary heart disease).

‖ High-dose statin therapy was defined as a daily dose of 40 to 80 mg of atorvastatin, 20 to 40 mg of rosuvastatin, or 80 mg of simvastatin.

** LDL cholesterol levels were calculated with the use of the Friedewald formula and also measured by means of beta-quantification (see Table S1 in the Supplementary Appendix).

END POINTS

The primary efficacy end point was the percentage change in calculated LDL cholesterol level from baseline to week 24, analyzed with the use of an intention-to-treat approach. Secondary end points included the percentage change in LDL cholesterol level while the study drug was being taken, as well as other lipoprotein variables at weeks 12 and 24 in both the intention-to-treat analysis and the analysis that included only patients who were receiving the study drug. All the efficacy end points are listed in the Supplementary Appendix.

Safety end points were adverse events, including symptoms, laboratory abnormalities, vital-sign abnormalities, electrocardiographic abnormalities, and adjudicated cardiovascular events, that occurred after the first injection and up to 10 weeks after the last injection. Adverse events are reported as the number of patients having an event in each category, classified according to the *Medical Dictionary for Regulatory Activities* (MedDRA). The safety of patients with an LDL cholesterol level of less than 25 mg per deciliter (0.6 mmol per liter) at two consecutive measurements was specifically monitored by a dedicated member of the data and safety monitoring committee and an independent physician (see the Supplementary Appendix for details).

We performed a post hoc analysis that compared the rate of positively adjudicated major adverse cardiovascular events between the two study groups, using the composite end point of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. This composite end point was selected because it is the primary end point of the ongoing Study to Evaluate the Effect of Alirocumab on the Occurrence of Cardiovascular Events in Patients Who Have Experienced an Acute Coronary Syndrome (ODYSSEY OUTCOMES).[8] The prespecified definitions of cardiovascular events are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

For the safety assessment, we estimated that a sample of 2100 patients (1400 patients treated with alirocumab and 700 with placebo) would include at least 1000 patients exposed to alirocumab for a minimum of 12 months and approximately 900 patients exposed to alirocumab for 18 months at the study end (assuming dropout rates of 25% and 35% at 12 and 18 months, respectively). This sample size would allow detection of adverse events with a rate of 0.2% or more in the alirocumab group with 95% confidence.

The intention-to-treat analysis that was used for the evaluation of the primary end point included all LDL cholesterol values that were collected, regardless of whether they were obtained while the patient was receiving the study drug or after the study drug was discontinued, up to week 24. We accounted for missing data by using a mixed-effects model for repeated measures. Patients who discontinued the study drug prematurely were asked to return for further clinic visits and assessments until the scheduled final visit.

The assessment of continuous secondary efficacy end points was similar to the assessment of the primary efficacy end point, except in the case of the end points of lipoprotein(a) and triglyceride levels (which were analyzed with the use of multiple imputation, followed by robust regression), and the end point of reaching LDL cholesterol goals (which was analyzed with the use of multiple imputation, followed by logistic regression). A Cox proportional-hazards model was used in the post hoc analysis to compare rates of major adverse cardiovascular events between the two study groups.

The safety population included all randomly assigned patients who received at least one dose or part of a dose of a study drug. Safety data were analyzed descriptively.

RESULTS

PATIENT CHARACTERISTICS AND FOLLOW-UP

A total of 2341 patients were enrolled in the trial, of whom 1553 were assigned to alirocumab and 788 to placebo (Fig. 1). Demographic characteristics and clinical history were well balanced between the two study groups (Table 1). The mean age of the study participants was 60 years, and 37.8% were women. A total of 68.9% of the patients had a history of coronary heart disease, and 17.7% had heterozygous familial hypercholesterolemia. All but 2 patients overall were receiving a statin, and 46.8% of the patients were receiving high-dose statin therapy; 28.1% were also receiving other lipid-lowering therapy. The mean calculated LDL cholesterol level at

baseline was 122 mg per deciliter (3.2 mmol per liter).

The mean study-drug exposure among the 2338 patients included in the safety analysis (1550 in the alirocumab group and 788 in the placebo group) was 70 weeks (Fig. 1), providing 2061 patient-years of exposure to alirocumab at a dose of 150 mg every 2 weeks. The mean rate of adherence to the study drug (i.e., the percentage of days that patients received their injections as per the planned dosing schedule) was 98.0% and 97.6% in the alirocumab group and the placebo group, respectively. The mean duration of follow-up (regardless of adherence to the study drug) in the safety population was 80.9 weeks in the alirocumab group and 80.1 weeks in the placebo group.

The rate of study-drug discontinuation was 28.2% in the alirocumab group and 24.5% in the placebo group. A total of 98.7% of the patients met the criteria for the intention-to-treat population and thus were included in the primary efficacy analysis. At week 24, a total of 144 patients (9.4%) in the alirocumab group and 72 patients (9.2%) in the placebo group had missing LDL cholesterol values (Table S1 in the Supplementary Appendix). These missing values were accounted for with the use of the mixed-effects model for repeated measures.

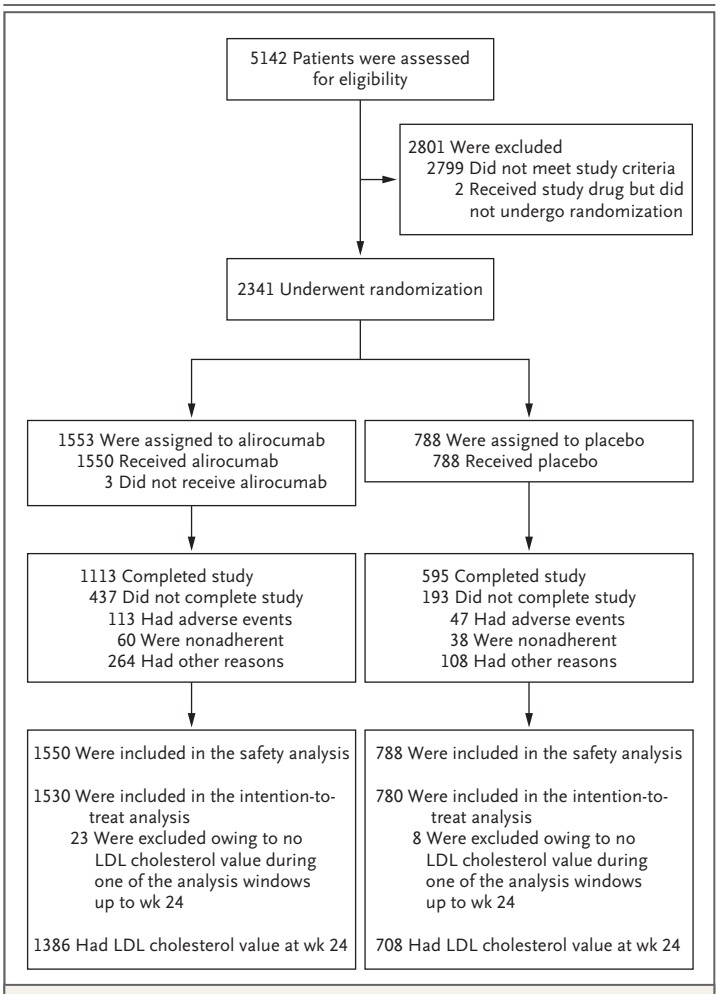

Figure 1. Randomization and Treatment.

The intention-to-treat population included all randomly assigned patients who had both a baseline calculated low-density lipoprotein (LDL) cholesterol value and at least one calculated LDL cholesterol value during one of the analysis windows up to week 24. The three patients in the alirocumab group who underwent randomization but did not receive treatment are included in the intention-to-treat population. Completion of the study was defined, as per the electronic case-report form, in the following way: the last study-drug injection was received (week 76), and the end-of-treatment visit (week 78) occurred within 21 days after the last injection and at least 525 days after randomization.

EFFICACY

The mean percentage change in calculated LDL cholesterol level from baseline to week 24 was −61.0% with alirocumab versus 0.8% with placebo, for a difference of −61.9 percentage points (P<0.001) (Table 2 and Fig. 2). The mean absolute LDL cholesterol level at week 24 was 48 mg per deciliter (1.2 mmol per liter) in the alirocumab group and 119 mg per deciliter (3.1 mmol per liter) in the placebo group, corresponding to a mean absolute change from baseline of −74 mg per deciliter (−1.9 mmol per liter) and −4 mg per deciliter (−0.1 mmol per liter), respectively. The goal of an LDL cholesterol level of less than 70 mg per deciliter at week 24 was met by 79.3% of the patients in the alirocumab group versus 8.0% of the patients in the placebo group (P<0.001). A consistent reduction in LDL cholesterol level from baseline was observed from week 4 to week 78 in the alirocumab group (Fig. 2). Results of measured LDL cholesterol levels were consistent with those of calculated LDL cholesterol levels (Table S2 in the Supplementary Appendix).

The percentage decrease in LDL cholesterol level in the alirocumab group was slightly lower at week 78 (52.4%) than at week 24 (61.0%) in the intention-to-treat analysis (Table 2); this observation was influenced by levels obtained after premature discontinuation of treatment. The 58.0% reduction in LDL cholesterol level at week 78 in the analysis that included only patients

Table 2. Primary Efficacy End Point and Selected Secondary Efficacy End Points in the Intention-to-Treat Population.*

End Point	Alirocumab (N=1530)	Placebo (N=780)	Alirocumab vs. Placebo		
			Least-Squares Mean Difference	95% CI	P Value
Primary efficacy end point: calculated LDL cholesterol					
Baseline level — mg/dl					
Mean†	122.8±42.7	122.0±41.6			
Range	39–424	19–404			
Absolute level at wk 24 — mg/dl	48.3±0.9	118.9±1.2			
Absolute change from baseline to wk 24 — mg/dl	−74.2±0.9	−3.6±1.2			
Percentage change from baseline to wk 24	−61.0±0.7	0.8±1.0	−61.9±1.3	−64.3 to −59.4	<0.001
Selected secondary efficacy end points					
Proportion of patients who reached prespecified calculated LDL cholesterol levels by wk 24 — %‡					
<70 mg/dl in patients at very high risk or <100 mg/dl in patients at high risk	80.7	8.5			<0.001
<70 mg/dl regardless of risk	79.3	8.0			<0.001
Percentage change from baseline to wk 78 in calculated LDL cholesterol	−52.4±0.9	3.6±1.3	−56.0±1.6	−59.1 to −52.8	<0.001§
Percentage change from baseline to wk 24 in secondary lipid variables					
Non-HDL cholesterol	−51.6±0.6	0.7±0.9	−52.3±1.1	−54.4 to −50.2	<0.001
Apolipoprotein B	−52.8±0.7	1.2±1.0	−54.0±1.2	−56.3 to −51.7	<0.001
Total cholesterol	−37.8±0.5	−0.3±0.7	−37.5±0.8	−39.1 to −35.9	<0.001
Lipoprotein(a)¶	−29.3±0.7	−3.7±1.0	−25.6±1.3	−28.1 to −23.1	<0.001
Fasting triglycerides¶	−15.6±0.8	1.8±1.2	−17.3±1.4	−20.1 to −14.6	<0.001
HDL cholesterol	4.0±0.4	−0.6±0.5	4.6±0.7	3.3 to 5.9	<0.001
Apolipoprotein A1	4.0±0.4	1.2±0.6	2.9±0.7	1.6 to 4.2	<0.001

* Plus–minus values are least-squares means ±SE, unless otherwise indicated. Primary and secondary efficacy analyses were performed with the use of an intention-to-treat approach, which included patients with a baseline calculated LDL cholesterol value and at least one calculated LDL cholesterol value during or after receipt of the study drug within one of the analysis windows up to week 24. A prespecified analysis that included only patients who were receiving the study drug was also performed (Table S3 in the Supplementary Appendix). Least-squares means (±SE) and P values were calculated with the use of a mixed-effects model with repeated-measures analysis (except for end points noted in the footnotes below). The P values are significant according to the fixed hierarchical approach used to ensure control of the overall type I error rate at the 0.05 level. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. CI denotes confidence interval.

† Plus–minus values are means ±SD.

‡ The analysis of this end point was performed with the use of multiple imputation, followed by logistic regression. The combined estimate of the proportion of patients was obtained by calculation of the average of all the imputed proportions of patients meeting the level of interest.

§ The P value has not been adjusted for multiple testing and is provided for descriptive purposes only.

¶ The percentage change in levels of lipoprotein(a) and triglycerides was analyzed with the use of multiple imputation, followed by robust regression. A combined estimate for adjusted mean (±SE) is shown.

who were receiving the study drug was more consistent with the 62.8% reduction at week 24 (Table S3 in the Supplementary Appendix). Analysis of the primary end point with the use of a pattern-mixture model yielded results that were similar to those of the analysis in which a mixed-effects model for repeated measures was used (Table S4 in the Supplementary Appendix).

The difference between the alirocumab and placebo groups in the percentage change in LDL cholesterol level from baseline to week 24 was similar in patients with heterozygous familial

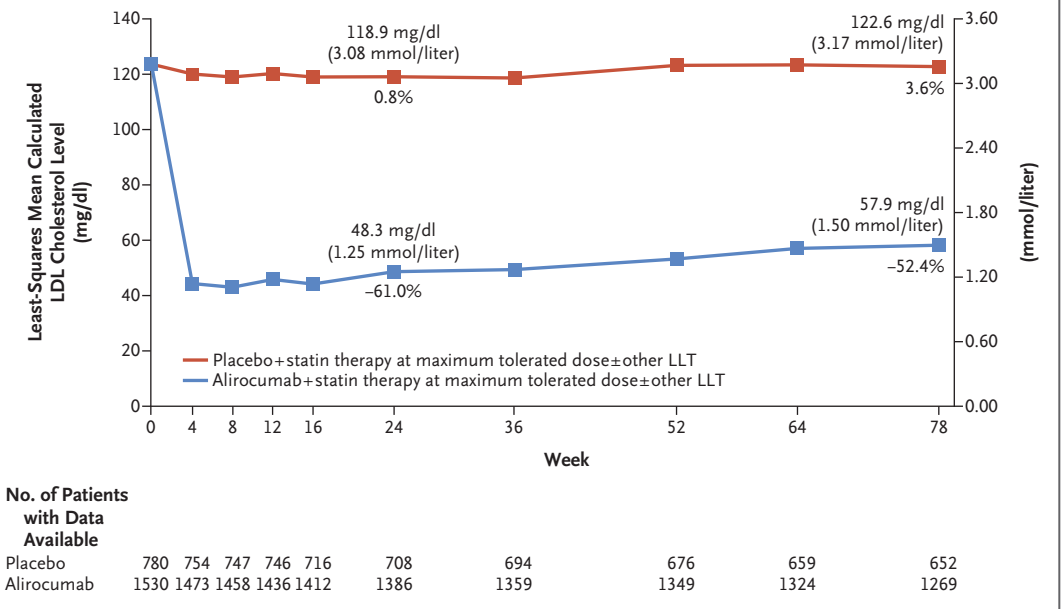

Figure 2. Calculated LDL Cholesterol Levels over Time (Intention-to-Treat Analysis).

Calculated LDL cholesterol levels are shown in milligrams per deciliter (left axis) and millimoles per liter (right axis). Values above the data points indicate least-squares mean absolute LDL cholesterol levels, and values below the data points indicate least-squares mean percentage changes from baseline. Values below the chart indicate the number of patients with LDL cholesterol values available for the intention-to-treat analysis at each time point; these include levels measured while the study drug was being taken and, in the case of patients who discontinued the study drug but returned to the clinic for assessments, after the study drug was discontinued. Missing data were accounted for with the use of a mixed-effects model with repeated measures. For statin therapy, the maximum tolerated dose was the highest dose associated with an acceptable side-effect profile. LLT denotes lipid-lowering therapy.

hypercholesterolemia and those without it (Fig. S2A in the Supplementary Appendix). Across four subgroups defined according to baseline LDL cholesterol level, alirocumab reduced the LDL cholesterol level by 59.5 to 62.0%; the difference between the alirocumab and placebo groups in the percentage change from baseline to week 24 was smaller among patients who had higher LDL cholesterol levels at baseline (Fig. S2B in the Supplementary Appendix). The between-group difference in the percentage change in LDL cholesterol level from baseline to week 24 was greater among those with PSCK9 levels at or above the median than among those with levels below the median, with this finding driven mostly by larger within-group differences observed in the placebo group (Fig. S3A in the Supplementary Appendix). Mild heterogeneity of treatment effect was observed for some other subgroup characteristics such as sex (Fig. S3B in the Supplementary Appendix) and geographic region (Fig. S4 in the Supplementary Appendix). Nonetheless, an additional reduction in LDL cholesterol level of approximately 50 to 65 percentage points was observed across various subgroups defined by demographic and baseline characteristics including race, age, presence or absence of diabetes status, and background statin therapy (Fig. S4 in the Supplementary Appendix).

Results for other lipid variables are shown in Table 2. As compared with the placebo group, the alirocumab group had greater reductions from baseline to week 24 in levels of non–high-density lipoprotein (HDL) cholesterol (difference [alirocumab minus placebo], −52.3 percentage points), apolipoprotein B (difference, −54.0 percentage points), total cholesterol (difference, −37.5 percentage points), lipoprotein(a) (difference, −25.6 percentage points), and triglycerides (difference, −17.3 percentage points) and had a modest increase in levels of HDL cholesterol (difference, 4.6 percentage points) and apolipoprotein A1 (difference, 2.9 percentage points) ($P<0.001$ for all comparisons).

SAFETY

The percentage of patients with any adverse event was similar in the two study groups (81.0% with alirocumab and 82.5% with placebo) (Table 3). Adverse events leading to study-drug discontinuation occurred in 7.2% of the patients who received alirocumab and 5.8% of the patients who received placebo. With regard to specific adverse events, the alirocumab group had higher rates than the placebo group of injection-site reactions (5.9% vs. 4.2%), myalgia (5.4% vs. 2.9%), neurocognitive events (1.2% vs. 0.5%), and ophthalmologic events (2.9% vs. 1.9%) (Table 3, and Table S5 in the Supplementary Appendix). Neurocognitive events included amnesia, memory impairment, and confusional state (Table 3, and Table S6 in the Supplementary Appendix). No cases of hemolytic anemia were reported. Rare and sometimes serious cases of neurologic and general allergic events were reported in both study groups (Table S7 in the Supplementary Appendix).

Among patients without a medical history of diabetes at baseline, 1.8% of the patients who received alirocumab and 2.0% of the patients who received placebo had at least one adverse event identified by the custom MedDRA query "diabetes" (which identified a set of adverse events selected by the study sponsors as being related

Table 3. Adverse Events of Interest and Laboratory Values: Safety Analysis.*

Event	Alirocumab (N=1550)	Placebo (N=788)	P Value†
Summary of adverse events — no. of patients (%)			
Any adverse event	1255 (81.0)	650 (82.5)	0.40
Serious adverse event	290 (18.7)	154 (19.5)	0.66
Adverse event leading to study-drug discontinuation	111 (7.2)	46 (5.8)	0.26
Adverse event leading to death	8 (0.5)	10 (1.3)	0.08
Cardiovascular adverse events of interest — no. of patients (%)			
Death from coronary heart disease, including death from unknown cause	4 (0.3)	7 (0.9)	0.26
Nonfatal myocardial infarction	14 (0.9)	18 (2.3)	0.01
Fatal or nonfatal ischemic stroke	9 (0.6)	2 (0.3)	0.35
Unstable angina requiring hospitalization	0	1 (0.1)	0.34
Congestive heart failure requiring hospitalization	9 (0.6)	3 (0.4)	0.76
Ischemia-driven coronary revascularization procedure	48 (3.1)	24 (3.0)	1
Positively adjudicated cardiovascular events, including all cardiovascular adverse events listed above	72 (4.6)	40 (5.1)	0.68
Adjudicated major adverse cardiovascular events in post hoc analysis‡	27 (1.7)	26 (3.3)	0.02
Other adverse events of interest			
General allergic reaction — no. of patients (%)	156 (10.1)	75 (9.5)	0.71
Local injection-site reaction — no. of patients (%)	91 (5.9)	33 (4.2)	0.10
Myalgia — no. of patients (%)	84 (5.4)	23 (2.9)	0.006
Neurologic event — no. of patients (%)§	65 (4.2)	35 (4.4)	0.83
Neurocognitive disorder — no. of patients (%)¶	18 (1.2)	4 (0.5)	0.17
Amnesia	5 (0.3)	0	0.17
Memory impairment	4 (0.3)	1 (0.1)	0.67
Confusional state	4 (0.3)	1 (0.1)	0.67
Ophthalmologic event — no. of patients (%)‖	45 (2.9)	15 (1.9)	0.65
Hemolytic anemia — no. of patients	0	0	NC
Diabetes in patients with no history of diabetes — no. of patients/total no. (%)**	18/994 (1.8)	10/509 (2.0)	0.84
Worsening of diabetes in patients with history of diabetes — no. of patients/total no. (%)**	72/556 (12.9)	38/279 (13.6)	0.83

Table 3. (Continued.)

Event	Alirocumab (N=1550)	Placebo (N=788)	P Value†
Laboratory values of interest — no. of patients/total no. (%)			
Alanine aminotransferase >3× ULN	28/1533 (1.8)	16/779 (2.1)	0.75
Aspartate aminotransferase >3× ULN	22/1533 (1.4)	18/779 (2.3)	0.13
Creatine kinase >3× ULN	56/1507 (3.7)	38/771 (4.9)	0.18

* Adverse events were defined as those that developed, worsened, or became serious after the first injection and up to 10 weeks after the last injection. NC denotes not calculated, and ULN upper limit of the normal range.

† P values were calculated with the use of Fisher's exact test and have not been adjusted for multiple testing. They are provided for descriptive purposes only.

‡ The post hoc analysis was not specified in the study protocol. It included the following cardiovascular event categories, which also comprise the end point in the Study to Evaluate the Effect of Alirocumab on the Occurrence of Cardiovascular Events in Patients Who Have Experienced an Acute Coronary Syndrome (ODYSSEY OUTCOMES): death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalization.[8] "Unstable angina requiring hospitalization" is limited to the unstable angina events with definite evidence of progression of the ischemic condition (strict criteria). Congestive heart failure requiring hospitalization and ischemia-driven coronary revascularization procedure were not included in the post hoc analysis.

§ The selection of preferred terms is based on a standardized *Medical Dictionary for Regulatory Activities* (MedDRA) query including "demyelination" (broad and narrow terms), "peripheral neuropathy" (broad and narrow terms), and "Guillain–Barré syndrome" (broad and narrow terms), excluding the preferred terms "acute respiratory distress syndrome," "asthenia," "respiratory arrest," and "respiratory failure."

¶ Neurocognitive events were selected with the use of a custom MedDRA query that was based on the following five High-Level Group Terms: "deliria (including confusion)," "cognitive and attention disorders and disturbances," "dementia and amnestic conditions," "disturbances in thinking and perception," and "mental impairment disorders." See also Table S6 in the Supplementary Appendix.

‖ The selection of preferred terms is based on a standardized MedDRA query that included "optic nerve disorders" (broad and narrow terms), "retinal disorders" (narrow term), and "corneal disorders" (narrow term).

** The selection of preferred terms is based on the custom MedDRA query "diabetes," which includes the High-Level Group Term "diabetes complications," the High-Level Term "diabetes mellitus," and the High-Level Term "carbohydrate tolerance analyses (including diabetes)" (excluding the preferred terms "blood glucose decreased" and "hyperglycemia"). A full list of preferred terms is provided in the Supplementary Appendix.

to newly diagnosed diabetes or worsening of preexisting diabetes; see the Supplementary Appendix) (Table 3). Abnormal levels of aminotransferases or creatine kinase were uncommon and occurred at similar rates in the two study groups (Table 3).

Among the patients who received alirocumab, 575 (37.1%) had a calculated LDL cholesterol level of less than 25 mg per deciliter at two consecutive measurements. Rates of adverse events among these patients were similar to those among the overall alirocumab group (Table S5 in the Supplementary Appendix). A greater number of patients in the alirocumab group than in the placebo group had a level of vitamin E or vitamin K that was below the lower limit of the normal range after baseline; however, there were no clinically meaningful changes. No clinically meaningful effect was observed with respect to changes in levels of other fat-soluble vitamins or cortisol (Table S8 in the Supplementary Appendix).

CARDIOVASCULAR EVENTS

Positively adjudicated cardiovascular adverse events occurred in 4.6% of the patients in the alirocumab group and in 5.1% of the patients in the placebo group (Table 3). In a post hoc analysis that evaluated the prespecified primary end point in the ongoing ODYSSEY OUTCOMES trial (major adverse cardiovascular events: a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization), a lower rate of adjudicated major adverse cardiovascular events was observed in the alirocumab group (27 of 1550 patients [1.7%]) than in the placebo group (26 of 788 patients [3.3%]; hazard ratio, 0.52; 95% confidence interval, 0.31 to 0.90; nominal P=0.02) (Table 3). The cumulative incidence curves diverged progressively over time (Fig. S5 in the Supplementary Appendix).

DISCUSSION

In the ODYSSEY LONG TERM trial, the PCSK9 inhibitor alirocumab, as compared with placebo, reduced LDL cholesterol levels by an additional 62 percentage points in high-risk patients when added to statin therapy at the maximum tolerated dose, with or without other lipid-lowering thera-

py. The effect was consistent over a period of 78 weeks of therapy. The efficacy of alirocumab was similar across various subgroups, including those defined according to the presence or absence of heterozygous familial hypercholesterolemia. There was a reduction of 26 percentage points versus placebo in levels of lipoprotein(a), a finding consistent with that of phase 2 trials.[9] Our findings are similar to those of randomized placebo-controlled or open-label studies of another PCSK9 inhibitor, in which the LDL cholesterol levels decreased by 52 to 57%.[10,11]

Adverse events that occurred more frequently with alirocumab than with placebo included injection-site reactions, myalgia, neurocognitive disorders, and ophthalmologic disorders. Neurocognitive disorders were related primarily to memory. The rare neurologic serious adverse events observed with alirocumab have distinct immunologic or inflammatory causes, so it seems unlikely that they share a common cause such as alirocumab treatment or low LDL cholesterol level. Allergic adverse events observed in the alirocumab group may be related to alirocumab treatment, because allergic reactions have been associated with the use of other monoclonal antibodies. Alirocumab had no untoward effect with respect to the development or exacerbation of diabetes or with respect to levels of aminotransferases or creatine kinase. The frequency of adverse events was similar among patients who had an LDL cholesterol level of less than 25 mg per deciliter at two consecutive measurements and those who did not.

In a post hoc safety analysis, the rate of major adverse cardiovascular events (a composite end point of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was 48% lower among patients who received alirocumab than among those who received placebo during the 80 weeks of follow-up (nominal $P=0.02$). When all adjudicated cardiovascular events were included (i.e., with the addition of congestive heart failure requiring hospitalization and ischemia-driven coronary revascularization), the difference between groups was not significant.

Several limitations of the study should be noted. First, although the ODYSSEY LONG TERM trial followed patients receiving study-drug therapy for a longer period than most other trials of PCSK9 inhibitors, the duration of follow-up is still relatively short for a treatment for a chronic disease, and longer-term studies will be needed. Second, the usefulness of the neurocognitive findings is limited by the lack of formal neurocognitive testing as part of the study design. Third, the number of cardiovascular events was relatively small, which limits the robustness of these data and the confidence that they are not simply a chance finding. ODYSSEY OUTCOMES (ClinicalTrials.gov number, NCT01663402) is an ongoing trial that is intended to provide an assessment of the cardiovascular benefit of alirocumab in approximately 18,000 patients over a period of 5 years.

In conclusion, in the ODYSSEY LONG TERM trial, 2341 high-risk patients were randomly assigned to either the PCSK9 inhibitor alirocumab or placebo. As compared with placebo, alirocumab reduced LDL cholesterol levels by 62 percentage points at 24 weeks, with a consistent reduction over a period of 78 weeks of treatment. In a post hoc analysis, there was evidence of a reduction in cardiovascular events with alirocumab.

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