Safety of Very Low Low-Density Lipoprotein Cholesterol Levels With Alirocumab
Pooled Data From Randomized Trials

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ABSTRACT

BACKGROUND Proprotein convertase subtilisin/kexin type 9 monoclonal antibodies can reduce low-density lipoprotein cholesterol (LDL-C) to very low levels when added to background lipid-lowering therapy.

OBJECTIVES The safety of alirocumab was evaluated in patients with at least 2 consecutive LDL-C values <25 or <15 mg/dl in the ODYSSEY program, with follow-up as long as 104 weeks.

METHODS Pooled data from 14 trials were analyzed (double-blind treatment 8 to 104 weeks; n = 3,340 alirocumab, n = 1,894 control [placebo or ezetimibe]; representing 4,029 [alirocumab] and 2,114 [control] double-blind patient-years’ exposure).

RESULTS In alirocumab-treated patients, 839 (25.1%) achieved 2 consecutive LDL-C values <25 mg/dl, and 314 (9.4%) achieved <15 mg/dl. Baseline LDL-C was lower (mean 100.3 vs. 134.3 mg/dl) in patients with LDL-C <25 versus ≥25 mg/dl. Similar rates of adverse events occurred in patients achieving LDL-C <25 and <15 mg/dl (72.7% and 71.7%, respectively), compared with 76.6% in those who did not achieve LDL-C <25 mg/dl. Neurological and neurocognitive events were similar among the 3 groups. In a propensity score analysis, the rate of cataracts was higher in patients with LDL-C <25 mg/dl (2.6%) versus ≥25 mg/dl (0.8%; hazard ratio: 3.40; 95% confidence interval: 1.58 to 7.35). However, no difference in cataract incidence was observed between pooled alirocumab and control groups.

CONCLUSIONS LDL-C levels <25 or <15 mg/dl on alirocumab were not associated with an increase in overall treatment-emergent adverse event rates or neurocognitive events, although cataract incidence appeared to be increased in the group achieving LDL-C levels <25 mg/dl. (Pooled analyses of already reported trials; NCT01288443, NCT01288469, NCT01266876, NCT01812707, NCT01507831, NCT01617655, NCT01644175, NCT01644188, NCT01709513) © 2017 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/).
The safety of pharmacological treatment to very low levels of low-density lipoprotein cholesterol (LDL-C) is becoming increasingly important as new lipid-lowering drugs become available. Post hoc studies of statin trials suggest that cardiovascular risk can be safely reduced in patients achieving LDL-C <50 mg/dl (1,2). However, in a post hoc analysis of the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial, in which patients with LDL-C <130 mg/dl were randomized to a high-intensity statin, those achieving LDL-C <30 mg/dl (n = 767) experienced increases (p < 0.05) in physician-reported diabetes, hematuria, hepatobiliary disorders, and insomnia (3). More recently, in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), patients treated with simvastatin plus ezetimibe achieved a mean LDL-C level of 54 mg/dl and further reduction in cardiovascular events compared with those receiving simvastatin alone (mean LDL-C 70 mg/dl) (4). No differences in adverse events between the 2 treatment groups were reported.

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Monoclonal antibodies (mAbs) to proprotein convertase subtilisin/kexin type 9 (PCSK9) are now approved in the United States and Europe to treat patients who require additional reduction in LDL-C beyond that achieved with maximally tolerated statins and other lipid-lowering therapies (LLTs). PCSK9 mAbs lower LDL-C by an additional 45% to 65% compared with placebo when added to background LLT, with mean achieved LDL-C levels of 33 to 51 mg/dl in high-risk patients (5–7).

Theoretical areas of concern with very low levels of LDL-C include effects on metabolic functions reliant upon cholesterol such as gonadal hormones and adrenal function, as well as transport of fat-soluble vitamins as observed in some genetic disorders with very low LDL-C levels (8).

The large alirocumab phase 2 and 3 trial program provides an opportunity for evaluating the safety of low levels of LDL-C attained through pharmacological treatment. We pooled data from 14 randomized controlled studies (including 5,234 patients treated for up to 2 years) and examined the occurrence of adverse events as well as laboratory values in patients who achieved 2 or more consecutive calculated LDL-C values of <25 or <15 mg/dl. An LDL-C level of 25 mg/dl was selected as a basis for examining the effects of low LDL-C because this was previously suggested to be a sufficient level for normal cell function (9,10).

METHODS

In a prospectively defined, pooled, individual-level analysis of patients with LDL-C <25 and <15 mg/dl, data from 14 phase 2 and 3 studies (double-blind periods of 8 to 104 weeks) were evaluated (Figure 1).

STUDY DESIGNS. The largest study, the ODYSSEY LONG TERM (Long-Term Safety and Tolerability of Alirocumab [SAR236553/REGN727] Versus Placebo on Top of Lipid-Modifying Therapy in High Cardiovascular Risk Patients With Hypercholesterolemia) trial, randomized 2,341 patients at high cardiovascular risk with LDL-C ≥70 mg/dl on LLT to either placebo or alirocumab 150 mg every 2 weeks (Q2W) in a 1:2 ratio. This study was designed to explore the effects of reducing LDL-C to low values with alirocumab and included laboratory tests for parameters that rely on cholesterol metabolism and could potentially be affected by low LDL-C levels: gonadal hormones, fat-soluble vitamins, and adrenal function (these parameters were not measured in the other studies) (5).

The other phase 3 studies mainly recruited patients with either heterozygous familial hypercholesterolemia (HeFH) or high cardiovascular risk non-familial hypercholesterolemia who had LDL-C ≥70 or ≥100 mg/dl, depending on history of coronary heart disease or risk equivalents. In these trials, the starting alirocumab dose of 75 mg Q2W was increased to 150 mg Q2W at week 12 if pre-defined LDL-C levels were not achieved at week 8. The exception was...
Patients with heFH and LDL-C >190 mg/dl or >160 mg/dl with CHD risk equivalents). Maximally tolerated statin dose was decreased as tolerated to the level of ef"
therapy (except for the ODYSSEY MONO [Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe in Patients With Hypercholesterolemia] and ODYSSEY ALTERNATIVE [Study of Alirocumab (REGN727/SAR236553) in Patients With Primary Hypercholesterolemia and Moderate, High, or Very High Cardiovascular (CV) Risk, Who Are Intolerant to Statins] groups, in which background statin was not allowed); background statin therapy was described as maximally tolerated in 6 studies (Figure 1).

Phase 2 studies recruited patients with LDL-C >100 mg/dl on statins, and a range of alirocumab doses were used; only the 75 and 150 mg Q2W doses are included here, to permit pooling with phase 3 data. Blood samples for lipid measurements were collected after an overnight fast, and analyses were conducted by a central laboratory using standardized methods (Medpace Reference Laboratories in all studies, except Covance Central Laboratories were used in the ODYSSEY LONG TERM study). LDL-C levels were calculated (Friedewald equation) at baseline and at weeks 4, 12, 24, 36, 52, 64, 78, 88, and 104 in the phase 3 studies (depending on study duration) and at baseline and every 2 or 4 weeks in the phase 2 studies. In the phase 3 trials, LDL-C was also determined using beta quantification if triglycerides were >400 mg/dl, but LDL-C values determined using this method were not included in the present analyses of safety.

SAFETY ASSESSMENTS. Safety data were collected on an ongoing basis. Treatment-emergent adverse events (TEAEs) occurred in the period from first to last dose of study treatment plus 70 days. For patients with 2 consecutive calculated LDL-C measurements <25 or <15 mg/dl, only TEAEs that occurred, worsened, or became serious following the first such value
are included. LDL-C values are considered as consecutive if $\geq 21$ days apart.

A dedicated data monitoring committee member and independent physician were provided access to unblinded LDL-C data to monitor patients who achieved 2 consecutive calculated LDL-C values $< 25$ mg/dl. Hemolytic anemia was assessed using specific algorithms in most studies. See further details in the Online Appendix.

**STATISTICAL ANALYSIS.** Patient characteristics and safety profile were described in each LDL-C subgroup using descriptive statistics. To account for differences in baseline characteristics between the post-randomization subgroups (i.e., patients with 2 consecutive low LDL-C levels and patients without), a propensity analysis was performed, similar to the analysis conducted for JUPITER (3). This analysis adjusts the risk that a patient will develop a particular adverse event of interest using a propensity score based on that patient’s baseline risk factors for developing LDL-C $< 25$ or $< 15$ mg/dl compared with patients who did not achieve these low LDL-C values (further details are provided in the Online Appendix). The propensity analysis included data from phase 3 studies only, because not all parameters were available from phase 2 studies. The propensity analysis was limited by: 1) the inclusion of only observed baseline factors; and 2) the subgroup sample size.

A correlation analysis was performed to compare LDL-C values derived by the calculated (Friedewald) and measured (beta quantification) methods.

**RESULTS**

**EXPOSURE TO STUDY TREATMENT AND DURATION OF LDL-C $< 25$ mg/dl.** In the pooled analysis of 14 trials ($n = 3,340$ of $5,234$ on alirocumab), 839 alirocumab patients (25.1%) achieved LDL-C $< 25$ mg/dl on at least 2 consecutive visits; 314 alirocumab patients (9.4%) achieved LDL-C $< 15$ mg/dl in at least 2 consecutive visits (Central Illustration). Most patients with LDL-C $< 25$ mg/dl (72.0%) started on an alirocumab dose of 150 mg Q2W (Online Table 1). LDL-C $< 25$ mg/dl was reported in 14.9% of patients starting on 75 mg, compared with 34.4% starting on 150 mg; of 406 alirocumab patients uptitrated from 75 to 150 mg, 33 (8.1%) had LDL-C $< 25$ mg/dl following dose increase. One patient in the control group (who received ezetimibe) achieved LDL-C $< 25$ mg/dl. The mean on-treatment LDL-C value for patients treated with alirocumab was 58.8 mg/dl and for the control group was 117.7 mg/dl (Figure 2).

Median exposure to randomized treatment was 78 weeks in both the control and alirocumab groups, as well as in those with LDL-C $< 25$ and $< 15$ mg/dl (Table 1). The median time to the first LDL-C
TABLE 1  Baseline Characteristics of Patients Included in This Analysis (Pooled Safety Population)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pooled Control (n = 1,894)</th>
<th>Overall Alirocumab (n = 3,340)</th>
<th>LDL-C ≤25 mg/dl† (n = 2,501)</th>
<th>LDL-C &gt;25 mg/dl‡ (n = 839)</th>
<th>LDL-C &gt;35 mg/dl§ (n = 314)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of overall alirocumab group</td>
<td>NA</td>
<td>100</td>
<td>74.9</td>
<td>25.1</td>
<td>9.4</td>
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<tr>
<td>Median exposure (weeks)</td>
<td>78.0</td>
<td>78.0</td>
<td>78.0</td>
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<td>78.0</td>
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<td>Age, yrs</td>
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<tr>
<td>Male</td>
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<td>Race, white</td>
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<td>BMI, kg/m²</td>
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<td>Calculated LDL-C, mg/dl</td>
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<td>Non-HDL-C, mg/dl</td>
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<td>Apo B, mg/dl</td>
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<td>Lp(a), mg/dl</td>
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<td>Fasting TGs, mg/dl</td>
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<td>Baseline HbA1c, %</td>
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<td>Medical history (pool of phase 3)</td>
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<td>CHD§</td>
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<td>CHD risk equivalents†</td>
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<td>Type 2 diabetes‡</td>
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<td>HeFH</td>
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<td>High-intensity statin**</td>
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<tr>
<td>Other lipid-lowering therapy†</td>
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</table>

Values are mean ± SD, % (n), or median (interquartile range). *p < 0.05 for comparison of LDL-C ≤25 vs. >25 mg/dL groups in pooled phase of study 3. †Patients who did not have 2 or more consecutive LDL-C values <25 mg/dL during treatment. ‡Patients with at least 2 consecutive LDL-C values <25 mg/dL during treatment. Values are considered consecutive if spaced out by at least 21 days. §Patients with at least 2 consecutive LDL-C values <15 mg/dL during treatment. (Excludes phase 2 studies. TCHD defined as acute MI, silent MI, unstable angina, coronary revascularization procedure, or other clinically significant CHD. CHD risk equivalents varied depending on study and included ischemic stroke, peripheral arterial disease, moderate chronic kidney disease, history of diabetes mellitus (type 1 or 2), and additional risk factors. Difference between LDL-C ≤25 vs. >25 mg/dL groups was tested by history of MI or ischemic stroke. ¶Difference between LDL-C ≤25 and >25 mg/dL groups was tested by history of type 1 and 2 diabetes. **Atorvastatin 40 to 80 mg, rosvastatin 20 to 40 mg, and simvastatin 80 mg per day. ††Excluding nutraceuticals.

The baseline characteristics of patients included in this analysis (pooled safety population) are shown in Table 1. Despite significant differences in the baseline characteristics of patients with LDL-C <25 and ≥25 mg/dL, no imbalances in age, sex, race, BMI, or other baseline characteristics were observed. Patients with baseline LDL-C ≤25 mg/dL were more often male, had cardiovascular disease or type 2 diabetes, and had higher baseline triglycerides, low-density lipoprotein cholesterol levels, and higher glycated hemoglobin levels (Table 1). These characteristics (except for glycated hemoglobin and type 2 diabetes) were also associated with LDL-C <25 mg/dL in multivariate analysis (Online Table 2). Similar characteristics were identified for the 15 mg/dL threshold (Online Table 3). Conversely, in those with LDL-C ≥25 mg/dL, the proportion of patients with HeFH was lower (although this was not seen in the multivariate analysis), and lipoprotein(a) levels were lower. Baseline use of high-intensity statins or other LLT was not associated with LDL-C >25 mg/dL.

**TEAEs in Patients with LDL-C <25 mg/dL.** In the pooled analysis of phase 2 and 3 studies, overall rates of TEAEs, serious TEAEs, deaths, and discontinuations appeared similar for patients with LDL-C <25 mg/dL compared with those with LDL-C ≥25 mg/dL (Table 2). TEAEs appeared similar in those with <15 mg/dL and when compared with the overall pooled alirocumab and control populations (Table 2). Individual TEAEs occurring in ≥1% in any pooled group are shown in Online Table 4. Despite significant differences in the baseline characteristics of patients with LDL-C <25 mg/dL compared with those with LDL-C ≥25 mg/dL, no imbalances in age, sex, race, BMI, or other baseline characteristics were observed.
TEAE rates were identified among patients with LDL-C < 25 or < 15 mg/dl compared with those who did not achieve those LDL-C levels for neurocognitive, neurological (including peripheral neuropathy), musculoskeletal, ophthalmological, and hepatic events (Table 2).

A numerically higher incidence (rate per 100 patient-years) of cataracts was observed in patients with LDL-C < 25 mg/dl versus those with higher LDL-C values (2.0 vs. 0.6) (Table 2). In the propensity analysis, when controlling for baseline factors predictive of developing LDL-C < 25 mg/dl, the rate of cataracts remained higher in patients with LDL-C < 25 mg/dl (2.6%) versus ≥ 25 mg/dl (0.8%; hazard ratio: 3.40; 95% confidence interval: 1.58 to 7.35) (Table 3). However, there was no difference between the overall alirocumab and control groups for cataracts (Table 2).

A slight imbalance was observed in TEAEs related to diabetes mellitus or diabetic complications in those with LDL-C < 25 and < 15 mg/dl and baseline diabetes. Patients with diabetes also tended to have lower baseline LDL-C levels: in the propensity analyses, when controlling for baseline factors predictive of developing LDL-C < 25 mg/dl (including baseline LDL-C), no excess risk for diabetes adverse events was observed among patients with LDL-C < 25 mg/dl and diabetes.

Data from pool of phase 3 studies (safety populations). LDL-C = low-density lipoprotein cholesterol; Q2W = every 2 weeks.
| TABLE 2 Overall Treatment-Emergent Adverse Event Incidence and Selected Adverse Events of Interest in Patients With at Least 2 Consecutive Low-Density Lipoprotein Cholesterol Values <25 or <15 mg/dl (Pooled Safety Population) |
|---|---|---|---|---|
| AEs of interest | Patients with any TEAEs | Patients with any treatment-emergent SAEs | Patients with any TEAEs leading to permanent treatment discontinuation | Patients with any TEAEs leading to death |
| Neurologic events (CMQ) | 3.7 (71) [3.1] | 4.0 (134) [3.1] | 4.2 (105) [3.4] | 2.4 (20) [1.9] | 2.9 (9) [2.3] |
| Peripheral neuropathy (SMQ) | 3.3 (63) [2.7] | 3.2 (106) [2.4] | 3.4 (84) [2.7] | 1.7 (14) [1.3] | 2.2 (7) [1.8] |
| Neurocognitive disorders (CMQ) | 0.9 (17) [0.7] | 1.0 (32) [0.7] | 1.0 (26) [0.8] | 0.6 (5) [0.5] | 0.3 (1) [0.3] |
| Amnesia (PT) | 0.3 (5) [0.2] | 0.2 (6) [0.1] | 0.2 (5) [0.2] | 0.1 (1) [0.1] | 0 |
| Apathia (PT) | <0.1 (0) [-0.1] | <0.1 (1) [-0.1] | <0.1 (1) [-0.1] | 0.1 (1) [0.1] | 0 |
| Confusional state (PT) | 0.2 (3) [0.1] | 0.2 (8) [0.2] | 0.3 (7) [0.2] | 0.1 (1) [0.1] | 0 |
| Dementia (PT) | 0.1 (2) [0.1] | <0.1 (0) [-0.1] | 0.1 (1) [0.1] | 0 |
| Frontotemporal dementia (PT) | 0 | <0.1 (0) [-0.1] | 0.1 (1) [0.1] | 0.3 (1) [0.3] |
| Musculoskeletal (CMQ) | 17.3 (328) [15.6] | 16.7 (559) [14.1] | 16.5 (413) [14.6] | 13.8 (116) [12.1] | 14.3 (45) [12.9] |
| Myalgia (PT) | 5.0 (95) [4.1] | 5.2 (174) [4.0] | 5.4 (136) [4.4] | 3.1 (26) [2.5] | 3.8 (12) [3.2] |
| Ophthalmological TEAEs (SMQ) | 1.3 (25) [1.1] | 1.9 (64) [1.4] | 1.9 (47) [1.5] | 1.5 (13) [1.2] | 1.6 (5) [1.3] |
| Hepatic disorders (SMQ) | 2.4 (45) [1.9] | 2.8 (95) [2.2] | 3.0 (79) [2.4] | 2.0 (17) [1.6] | 2.2 (7) [1.8] |
| Hepatic steatosis (PT) | 0.6 (11) [0.5] | 0.2 (7) [0.2] | 0.2 (6) [0.2] | 0.1 (1) [0.1] | 0.3 (1) [0.3] |
| Cataract (PT) | 1.0 (19) [0.8] | 1.0 (35) [0.8] | 0.7 (17) [0.5] | 1.9 (16) [1.5] | 2.5 (8) [2.1] |
| Lenticular opacities (PT) | 0 | <0.1 (0) [-0.1] | 0.4 (3) [0.3] | 0.3 (1) [0.3] |
| Cataract nuclear (PT) | <0.1 (0) [-0.1] | 0.1 (5) [0.1] | 0.2 (2) [0.2] | 0 |

TEAEs related to diabetes mellitus or diabetic complications (CMQ), according to baseline diabetes status

<table>
<thead>
<tr>
<th>Patients with diabetes at baseline, n</th>
<th>559</th>
<th>998</th>
<th>688</th>
<th>310</th>
<th>129</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus or diabetic complications (CMQ)</td>
<td>10.4 (58) [8.7]</td>
<td>10.6 (106) [8.5]</td>
<td>9.0 (62) [7.7]</td>
<td>11.9 (37) [10.1]</td>
<td>11.6 (15) [9.9]</td>
</tr>
<tr>
<td>Diabetes mellitus (PT)</td>
<td>2.5 (14) [2.0]</td>
<td>3.6 (36) [2.8]</td>
<td>3.3 (23) [2.7]</td>
<td>4.2 (13) [3.3]</td>
<td>6.2 (8) [5.1]</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus (PT)</td>
<td>1.6 (9) [1.3]</td>
<td>1.5 (15) [1.1]</td>
<td>1.0 (7) [0.8]</td>
<td>2.3 (7) [1.8]</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes mellitus inadequate control (PT)</td>
<td>2.0 (11) [1.6]</td>
<td>1.5 (15) [1.1]</td>
<td>1.0 (7) [0.8]</td>
<td>2.6 (8) [2.0]</td>
<td>1.6 (2) [1.2]</td>
</tr>
<tr>
<td>Patients without diabetes at baseline, n</td>
<td>1,335</td>
<td>2,342</td>
<td>1,813</td>
<td>529</td>
<td>185</td>
</tr>
<tr>
<td>Diabetes mellitus or diabetic complications (CMQ)</td>
<td>2.5 (33) [2.0]</td>
<td>2.0 (46) [1.5]</td>
<td>1.8 (32) [1.4]</td>
<td>2.3 (12) [1.8]</td>
<td>2.2 (4) [1.8]</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus (PT)</td>
<td>1.2 (16) [1.0]</td>
<td>1.3 (11) [0.7]</td>
<td>1.2 (21) [0.9]</td>
<td>1.7 (9) [1.4]</td>
<td>2.2 (4) [1.8]</td>
</tr>
<tr>
<td>Diabetes mellitus (PT)</td>
<td>0.5 (7) [0.4]</td>
<td>0.4 (9) [0.3]</td>
<td>0.4 (7) [0.3]</td>
<td>0.4 (2) [0.3]</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are % (n) or % (rate per 100 patient-years). TEAEs were encoded as PTs using the MedDRA version 18.0 according to the verbatim entry attached to the investigator. TEAEs were further categorized according to standard MedDRA definitions (HLT, HLGT, and SMQ) or using custom groupings (CMQs) as defined by the study sponsors. Rate per 100 patient-years was calculated as number of patients with events divided by total patient-years. For patients with events, number of patient-years was calculated up to the date of the first event; for patients without events, it was calculated up to the end of the TEAE period. For patients with LDL-C <25 mg/dl, the number of patient-years was calculated from the time of the first such value. *p < 0.0018 for comparison of LDL-C <25 versus <25 mg/dl groups in pool of phase 3 studies. All other comparisons of AEs of interest were not significant (Table 3). Only TEAEs that occurred, worsened, or became serious on the day or after the first of 2 consecutive LDL-C values <25 or <15 mg/dl were considered. Selection of PTs based on MedDRA: “demyelination” (broad + narrow), “peripheral neuropathy” (broad + narrow) and “Guillain-Barre syndrome” (broad + narrow) excluding the following PTs (“acute respiratory distress syndrome,” “asthenia,” “respiratory arrest,” and “respiratory failure”). Selection of PTs is based on the HLGTs “Deliria (including confusion),” “cognitive and attention disorders and disturbances,” “dementia and amnestic conditions,” “disturbances in thinking and perception,” and “mental impairment disorders.” Selection of PTs is based on the SMQs “optic nerve disorders” (broad + narrow), “retinal disorders” (narrow), and “corneal disorders” (narrow). Selection of PTs is based on the HLT “cataract conditions.” Selection of PTs is based on HLGT “diabetic complications,” HLT “diabetes mellitus,” and HLT “carbohydrate tolerance analyses (including diabetes),” excluding PT “blood glucose decreased” and PT “hyperglycemia.” AEs = adverse event; CMQ = Company MedDRA Query; HLGT = high-level group term; HLT = high-level term; LDL-C = low-density lipoprotein cholesterol; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SMQ = Standardized MedDRA Query; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

<25 mg/dl (Table 3). Nor did propensity analyses reveal any differences in the rates of neurocognitive, neurological, ophthalmologic (other than cataracts), or hepatic events in those with LDL-C <25 mg/dl (Table 3).

An analysis of cardiovascular events according to LDL-C values was not performed, because of insufficient numbers (among 839 alirocumab-treated patients who achieved 2 consecutive LDL-C values <25 mg/dl, 16 patients experienced major cardiovascular events).

**LABORATORY ANALYSES.** In the laboratory analyses performed in ODYSSEY LONG TERM, alirocumab had no clinically meaningful effect on levels of cortisol or gonadal hormones (Online Table 5) or levels of
fat-soluble vitamins A, D, and K (Table 4). An increase in levels of vitamin E adjusted for LDL-C was observed in the alirocumab group (Table 4).

There were no cases of confirmed Hy’s law elevations in hepatic enzymes or hemolytic anemia. Similarly, renal function as assessed by estimated glomerular filtration rate did not appear to be affected by LDL-C <25 or <15 mg/dl (Online Table 6). Nor did LDL-C <25 or <15 mg/dl appear to have an effect on mean glycolated hemoglobin levels over time, regardless of baseline diabetes status (Online Figure 1).

**COMPARISON OF CALCULATED VERSUS MEASURED LDL-C.** In a correlation analysis comparing LDL-C values derived by calculation and beta quantification, only minor differences were observed between the 2 methods. In patients with LDL-C in the range of 15 to <25 mg/dl as measured by beta quantification, there was a median difference of 3.5 mg/dl compared with LDL-C values derived by calculation; in those with measured LDL-C <15 mg/dl, there was a median 3 mg/dl difference (Table 5).

**DISCUSSION**

This analysis included a large population of patients treated with alirocumab (n = 839 [25.1%]) for a median of 18 months who experienced pharmacologically induced LDL-C reductions to levels <25 mg/dl for an average of 10 months (Central Illustration). A substantial proportion of these patients had LDL-C <15 mg/dl (n = 314 [9.4%]). Overall TEAE incidence was similar in alirocumab and control groups and across alirocumab groups according to achieved LDL-C levels. There were no meaningful imbalances between groups in musculoskeletal and neurological conditions (including peripheral neuropathy), neurocognitive events (including those related to memory), and renal or hepatic events. No difference in rates of TEAEs related to diabetes mellitus was observed when controlling for baseline characteristics predictive of achieving LDL-C <25 mg/dl. Previously, the JUPITER trial reported an excess of diabetes as well as events such as insomnia and hepatic steatosis in patients with LDL-C <30 mg/dl, but such events were not found to be associated with LDL-C <25 mg/dl following alirocumab treatment.

The incidence of cataracts was similar between the overall alirocumab and control groups (1.3% and 1.1%, respectively), although there was a numeric excess in alirocumab-treated patients whose LDL-C levels were <25 versus ≥25 mg/dl. Propensity analyses did find an increased incidence of cataracts in patients with LDL-C <25 versus ≥25 mg/dl. Cholesterol needed by the lens is synthesized in situ. In animal toxicity studies, high doses of statins have been shown to inhibit lens cholesterol biosynthesis and promote cataract formation, but these studies have not been duplicated in humans (12). Some studies have shown an increased rate of cataracts or cataract surgery following statin treatment in humans (13-15). An increased rate of cataract formation has also been associated with hyperglycemia and blood pressure (16). It could be that acute LDL-C lowering accelerates underlying aging or metabolic syndrome or diabetes-related changes, contributing to cataracts. The finding of increased cataracts in patients with LDL-C <25 mg/dl requires confirmation in the forthcoming ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) study (17), in which more patients are expected to have exposure to such low LDL-C levels.

Of the possible theoretical risks associated with LDL-C levels <25 mg/dl (e.g., because of effects on cholesterol metabolism or transport), none were confirmed in laboratory tests. This included levels of cortisol and gonadal hormones and levels of fat-soluble vitamins A, D, and K, and the vitamin E/LDL-C ratio.

A higher incidence of neurocognitive events (odds ratio: 2.34; 95% confidence interval: 1.11 to 4.93; p = 0.002) for PCSK9 mAbs versus placebo has been found in a network meta-analysis of data from 6 trials (18). The large majority of neurocognitive events in this analysis occurred in the 2 larger, longer term
Table 5 Correlation Between Low-Density Lipoprotein Cholesterol Determined by Beta Quantification and Calculated by Friedewald Equation

<table>
<thead>
<tr>
<th>LDL-C &lt;15 mg/dl as determined by beta quantification (n = 259)</th>
<th>% Difference vs. Calculated Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Difference vs. Calculated Values (mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>–3.0</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>–6.0 to 0.8</td>
</tr>
<tr>
<td>Minimum/maximum</td>
<td>–14/160</td>
</tr>
<tr>
<td>LDL-C ≥15 to &lt;25 mg/dl as determined by beta quantification (n = 940)</td>
<td></td>
</tr>
<tr>
<td>Absolute Difference vs. Calculated Values (mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>–3.5</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>–7.0 to 0.0</td>
</tr>
<tr>
<td>Minimum/maximum</td>
<td>–24/26</td>
</tr>
</tbody>
</table>

Absolute difference is defined as (calculated LDL-C – measured LDL-C). Percentage difference is defined as (calculated LDL-C – measured LDL-C)/measured LDL-C x 100. Data are pooled from phase 3 studies. LDL-C = low-density lipoprotein cholesterol.

As well as having lower baseline LDL-C levels, most patients who achieved LDL-C <25 mg/dl were receiving the higher (150 mg Q2W) dose of alirocumab. Fewer patients with higher baseline LDL-C levels (including those with HeFH) achieved LDL-C <25 mg/dl. Therefore, patients with the most need for the addition of alirocumab for further LDL-C lowering (i.e., those with high baseline LDL-C levels) are least likely to experience very low LDL-C levels. For physicians concerned about lower LDL-C levels (<25 mg/dl), starting with the 75 mg dose may be desirable.

Some of the concerns regarding the safety of low LDL-C levels arise from patients with abetalipoproteinemia (caused by mutations in microsomal triglyceride transfer protein) or homozygous familial hypobetalipoproteinemia (caused by mutations truncating apolipoprotein B-100 or apolipoprotein B), who have very low concentrations of LDL-C (<30 mg/dl) and triglycerides. Patients with abetalipoproteinemia experience severe symptoms, including fat intolerance and fat-soluble vitamin deficiencies, if not treated, resulting from the body’s inability to produce chylomicrons (particles that capture dietary fats and fat-soluble vitamins). Patients with heterozygous familial hypobetalipoproteinemia (single mutation in APOB) may have LDL-C levels of 20 to 50 mg/dl and are often asymptomatic, although some experience hepatic steatosis due to impaired production of very low density lipoproteins (also seen abetalipoproteinemia). However, as noted previously, no excess of hepatic events (including hepatic steatosis) was observed in alirocumab-treated patients with LDL-C <25 mg/dl. The mechanism for low LDL-C resulting from PCSK9 mutations differs from abetalipoproteinemia or hypobetalipoproteinemia as it involves an increase in uptake and catabolism of apolipoprotein B-containing lipoproteins.
lipoproteins (such as LDL-C) via the LDL receptor (21), rather than loss of lipoprotein production. Notably, patients homozygous for loss-of-function mutations in PCSK9 with LDL-C <20 mg/dl appear to experience no adverse consequences, including 1 woman with 2 healthy children (22–24).

**STUDY LIMITATIONS.** The main limitation of this analysis is that it involved comparisons of post-randomization subgroups that are confounded by the characteristics predisposing patients to low LDL-C levels not controlled by randomization. Other limitations include the sample size and the relatively short duration of treatment. Analysis of diabetes, cataracts, and neurological and neurocognitive TEAEs was limited by the small number of reported events (17).

**CONCLUSIONS**

Low levels of LDL-C (<25 mg/dl) appear to be generally well tolerated over 18 months of alirocumab therapy. The increased incidence of cataracts in those with LDL-C <25 mg/dl may be due to confounding in this comparison of nonrandomized subgroups. Although the consequences of very low LDL-C were not identified in these trials, the long-term effects of very low levels of LDL-C are unknown. Data from large, ongoing cardiovascular outcomes trials should provide important information on the cardiovascular event reduction benefits and adverse effects of long-term exposure to pharmacologically induced low LDL-C levels. Longer term safety of very low LDL-C levels remains to be defined in view of the potential for lifelong therapy.

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KEY WORDS clinical trials, LDL-C, PCSK9, safety

APPENDIX For supplemental methods and tables, please see the online version of this article.