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Patrick M. Moriarty, MD*, Paul D. Thompson, MD, Christopher P. Cannon, MD, John R. Guyton, MD, Jean Bergeron, MD, Franklin J. Zieve, MD, PhD, Eric Bruckert, MD, Terry A. Jacobson, MD, Stephen L. Kopecky, MD, Marie T. Baccara-Dinet, MD, Yunling Du, PhD, Robert Pordy, MD, Daniel A. Gipe, MD, for the ODYSSEY ALTERNATIVE Investigators[1]

Division of Clinical Pharmacology, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, USA (Dr Moriarty); Hartford Hospital, Hartford, CT, USA (Dr Thompson); Harvard Clinical Research Institute, Boston, MA, USA; Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, MA, USA (Dr Cannon); Duke University Medical Center, Durham, NC, USA (Dr Guyton); Lipid Clinic, Centre Hospitalier Universitaire de Québec, Laval University, Québec, Canada (Dr Bergeron); McGuire VA Medical Center, Richmond, VA, USA (Dr Zieve); Groupe Hospitalier Pitié–Salpêtrière (Assistance Publique–Hôpitaux de Paris), Paris, France (Dr Bruckert); Department of Medicine, Emory University, Atlanta, GA, USA (Dr Jacobson); Mayo Clinic, Department of Cardiovascular Diseases, Rochester, MN, USA (Dr Kopecky); PCSK9 Development and Launch Unit, Sanofi, Montpellier, France (Dr Baccara-Dinet); Department of Biostatistics, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA (Dr Du); and Department of Clinical Sciences, Cardiovascular & Metabolism Therapeutics, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA (Drs Pordy, and Gipe)

KEYWORDS:
Lipid-lowering drugs;
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PCSK9;
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Monoclonal antibodies

BACKGROUND: Statin intolerance limits many patients from achieving optimal low-density lipoprotein cholesterol (LDL-C) concentrations. Current options for such patients include using a lower but tolerated dose of a statin and adding or switching to ezetimibe or other non-statin therapies.

METHODS: ODYSSEY ALTERNATIVE (NCT01709513) compared alirocumab with ezetimibe in patients at moderate to high cardiovascular risk with statin intolerance (unable to tolerate ≥2 statins, including one at the lowest approved starting dose) due to muscle symptoms. A placebo run-in and statin rechallenge arm were included in an attempt to confirm intolerance. Patients (n = 361) received single-blind subcutaneous (SC) and oral placebo for 4 weeks during placebo run-in. Patients reporting muscle-related symptoms during the run-in were to be withdrawn. Continuing patients were randomized (2:2:1) to double-blind alirocumab 75 mg SC every 2 weeks (Q2W; plus oral placebo), ezetimibe 10 mg/d (plus SC placebo Q2W), or atorvastatin 20 mg/d (rechallenge; plus SC placebo Q2W) for

[1] Study investigators are listed in Supplemental Text 1.

* Corresponding author. Division of Clinical Pharmacology, Department of Internal Medicine, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160, USA.
E-mail address: pmoriart@kumc.edu

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24 weeks. Alirocumab dose was increased to 150 mg Q2W at week 12 depending on week 8 LDL-C values. Primary end point was percent change in LDL-C from baseline to week 24 (intent-to-treat) for alirocumab vs ezetimibe.

RESULTS: Baseline mean (standard deviation) LDL-C was 191.3 (69.3) mg/dL (5.0 [1.8] mmol/L). Alirocumab reduced mean (standard error) LDL-C by 45.0% (2.2%) vs 14.6% (2.2%) with ezetimibe (mean difference 30.4% [3.1%], $P < .0001$). Skeletal muscle-related events were less frequent with alirocumab vs atorvastatin (hazard ratio 0.61, 95% confidence interval 0.38–0.99, $P = .042$).

CONCLUSIONS: Alirocumab produced greater LDL-C reductions than ezetimibe in statin-intolerant patients, with fewer skeletal-muscle adverse events vs atorvastatin.

Introduction

Statins are the treatment of choice for lowering low-density lipoprotein cholesterol (LDL-C),[1,2] producing substantial reductions in cardiovascular morbidity and mortality in primary and secondary prevention.[3] Statins are generally well tolerated, and serious side effects are rare.[4] However, many patients may suffer statin-associated muscle symptoms and are unable to either take any dose or increase the dose sufficiently, even after trying an alternate statin, to achieve long-term reduction of LDL-C and cardiovascular risk.[4–7]

Statin-associated muscle symptoms encompass a wide range of clinical presentations.[8] Symptoms are subjective and, in the absence of a definitive diagnostic test, the prevalence remains unclear.[8] In a meta-analysis of 26 randomized trials, approximately 13% of statin-treated patients reported muscle complaints, most commonly myalgia.[9] This is most likely an underestimate because patients with a history of, or at an increased risk of, intolerance were excluded from many of the trials in this meta-analysis. Observational data suggest a prevalence ranging from 7% to 29%.[5,8] The Effect of Statins on Skeletal Muscle Function and Performance trial investigated the rate of statin intolerance in healthy statin-naïve patients. Overall, muscle complaints occurred in 9.4% of patients on atorvastatin 80 mg vs 4.6% on placebo ($P = .05$), indicating an approximate 5% rate of muscle events with high-dose statin.[10]

Large, well-controlled randomized trials of cholesterol-lowering drugs in statin-intolerant patients are lacking, and there remains a need for an effective non-statin treatment for patients who are intolerant of these medications and remain at cardiovascular risk. Alirocumab is a fully human monoclonal antibody against proprotein convertase subtilisin kexin type 9. Alirocumab reduced LDL-C concentrations by 40% to 70% when given in combination with other lipid-lowering therapies or as monotherapy.[11–19] The ODYSSEY ALTERNATIVE study compared the reduction of LDL-C produced by alirocumab vs ezetimibe after 24 weeks of treatment in patients with primary hypercholesterolemia and well-documented statin intolerance. The study included a placebo run-in period before randomization, during which patients who developed muscle symptoms in the absence of statin exposure were excluded from continuing in the trial. Ezetimibe was selected as the active control as it is a recommended option for LDL-C lowering in statin-intolerant patients due to a favorable safety profile.[20] The trial also sought to determine safety compared with atorvastatin in an at-risk population that had failed multiple attempts to use first-line evidence-based statin therapy. Thus, a blinded statin rechallenge arm was conducted in parallel with blinded alirocumab and ezetimibe arms. An optional open-label treatment period on alirocumab continued after 24 weeks of double-blind treatment.

Materials and methods

Study design

ODYSSEY ALTERNATIVE (NCT01709513) was a randomized, double-blind, double-dummy, active-controlled, parallel-group study conducted at 67 sites in 8 countries (Austria, Canada, France, Israel, Italy, Norway, the UK, and the USA), with enrollment from November 2012 to October 2013. The study rationale and methods have been published.[21]

The study was conducted according to the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. The institutional review board and ethics committee at each center approved the protocol; all participants gave written informed consent.

Study population

The population comprised patients (≥18 years) with primary hypercholesterolemia.[21] Patients at moderate or high cardiovascular risk (as defined in Supplemental Text 2) were eligible if they had a calculated serum LDL-C concentration ≥ 100 mg/dL (2.6 mmol/L) at screening; those at very high risk were eligible if they had a calculated serum LDL-C ≥70 mg/dL (1.8 mmol/L).[21] During screening, each patient completed a questionnaire that collected data on history of statin therapies and symptoms. Statin intolerance was defined as the inability to tolerate 2 or more statins because of

unexplained skeletal muscle–related symptoms (eg, pain, aches, weakness, or cramping), other than those due to strain or trauma that began or increased during statin treatment and resolved with statin discontinuation (see Supplemental Text 2). One of the 2 statins had to have been discontinued while at or below the lowest-approved daily starting dose (ie, rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, pitavastatin 2 mg). A full list of the exclusion criteria is available.[21]

Intervention

The study comprised 5 periods: 1-week screening; 2-week washout of ezetimibe, statins (for patients taking a less than lowest-approved daily starting dose or regimen), and red yeast rice; 4-week single-blind placebo run-in to exclude patients with non-statin–related muscle symptoms; 24-week double-blind treatment; and 8-week off-treatment follow-up.[21] See Supplemental Text 2 for details on diet and use of non-statin medications. As an alternative to the 8-week follow-up, patients who successfully completed the double-blind treatment period or discontinued due to a muscle-related adverse event (AE) were offered up to 196 weeks of alirocumab in an open-label treatment period, starting at their planned week 24 visit.

Patients who completed the placebo run-in without experiencing a skeletal muscle–related AE were randomized to alirocumab, ezetimibe, or atorvastatin (2:2:1, respectively, permuted block design), with stratification for history of myocardial infarction or ischemic stroke, to receive subcutaneous (SC) alirocumab 75 mg twice weekly (Q2W) and oral placebo for ezetimibe or atorvastatin daily, or SC placebo Q2W for alirocumab and either oral ezetimibe 10 mg daily or atorvastatin 20 mg daily (statin rechallenge arm). Oral and SC medications were blinded.[21] At week 12 of the 24-week double-blind treatment period, the alirocumab dose was increased to 150 mg Q2W (also in a 1-mL volume) if the patient's week 8 LDL-C concentration remained elevated (≥70 mg/dL [1.8 mmol/L] in very high cardiovascular risk patients or ≥100 mg/dL [2.6 mmol/L] in moderate or high cardiovascular risk patients).

After 24 weeks, all eligible patients could enter the open-label treatment phase of the study and continue alirocumab 75 mg SC Q2W for approximately 3 years (see Supplemental Text 2).

Efficacy outcome measures

The primary efficacy end point was the percent change in calculated LDL-C concentration from baseline to week 24 by intent-to-treat (ITT) approach. Key secondary efficacy end points were changed from baseline to 24 weeks using on-treatment (modified ITT) LDL-C values, and percent change from baseline to 12 and 24 weeks in LDL-C, apolipoprotein B, non–high-density lipoprotein cholesterol (non–HDL-C), total cholesterol, lipoprotein(a), HDL-C, apolipoprotein A1, and fasting triglyceride concentrations. All efficacy end points were assessed for alirocumab vs ezetimibe arms (see Supplemental Text 2). Efficacy comparisons vs atorvastatin were not assessed as this treatment arm was only included as an essential control to define the appropriate patient population.

Safety outcome measures

Safety end points included AEs, irrespective of their possible relationship to the study drug, defined as those that developed, worsened, or became serious during each of the 3 phases of the study: pretreatment, double blind, and open label. All AEs were assessed by both patient self-reports and AE query. Skeletal muscle AEs included a predefined category of AEs (comprising myalgia or myositis, muscle spasms, muscular weakness, musculoskeletal stiffness, and muscle fatigue) that were identified, on the basis of expert opinion, to be closely related to statin intolerance (see Supplemental Text 2).

Statistical analysis

A sample of 42 patients in both the alirocumab and ezetimibe treatment groups would provide 95% power to detect a 20% difference between alirocumab and ezetimibe in least squares (LS) mean percent change from baseline to week 24 in LDL-C, using a 2-sided *t*-test and assuming a common standard deviation (SD) of 25%.[11] The overall study sample size for safety parameters during the double-blind treatment period was planned to be 250 patients, allocating 100 patients to both the alirocumab and ezetimibe arms and 50 patients to the statin arm. With specific attention to study treatment withdrawal due to AEs, 100 patients in both the alirocumab and ezetimibe arms would give a 96% probability of recording at least 1 withdrawal event assuming that the event occurs in approximately 3.3% of the population for each arm, based on product information.[22]

The ITT analysis used for evaluation of the primary end point included all calculated LDL-C values, irrespective of treatment adherence, up to week 24. Missing data were accounted for using a mixed-effect model with repeated measures approach.[23,24] The consistency of the treatment effect for the primary end point was assessed across prespecified subgroups.[21] A P value of ≤.05 was considered to be statistically significant.

A hierarchical testing procedure was used to control type I error and handle multiplicity for analyzing the key secondary end points.[21] The first secondary end point was an on-treatment (modified ITT) analysis. Further secondary end points, in order of hierarchical testing, included percent change in LDL-C from baseline to week 12 (ITT and on-treatment), the percent change in other lipid parameters, and the proportion of patients reaching their cardiovascular-risk-based LDL-C goal at week 24 in both the ITT and on-treatment analyses (see also

Supplemental Table 1). The modified ITT population included all randomized and treated patients with a baseline LDL-C measurement and at least 1 measurement after 4 to 24 weeks of treatment, as long as the patient was on study treatment. For this analysis, all available measurements from weeks 4 to 24 within the on-treatment time window were used in the mixed-effect model with repeated measures model. Binary efficacy end points were analyzed using the multiple imputation approach followed by logistic regression; continuous efficacy end points anticipated to have a non-normal distribution (ie, triglycerides and lipoprotein[a]) were analyzed using the same multiple imputation approach followed by robust regression. The analysis was performed using SAS version 9.2 software.

Results

Patients and intervention

Of the 519 patients screened, 361 met the eligibility criteria (and entered the placebo run-in), and 314 (87.0%) completed the placebo run-in and were randomized to 1 of the 3 treatment arms: 126 to alirocumab, 125 to ezetimibe, and 63 to atorvastatin (Fig. 1). Of the 47 patients who failed to complete the placebo run-in, 25 had skeletal muscle–related symptoms as defined by exclusion criteria, and 23 of 47 (48.9%) had at least 1 skeletal muscle–related AE according to a predefined category of AEs, of which the most common was myalgia (9 of 47; 19.1%) and muscle spasms

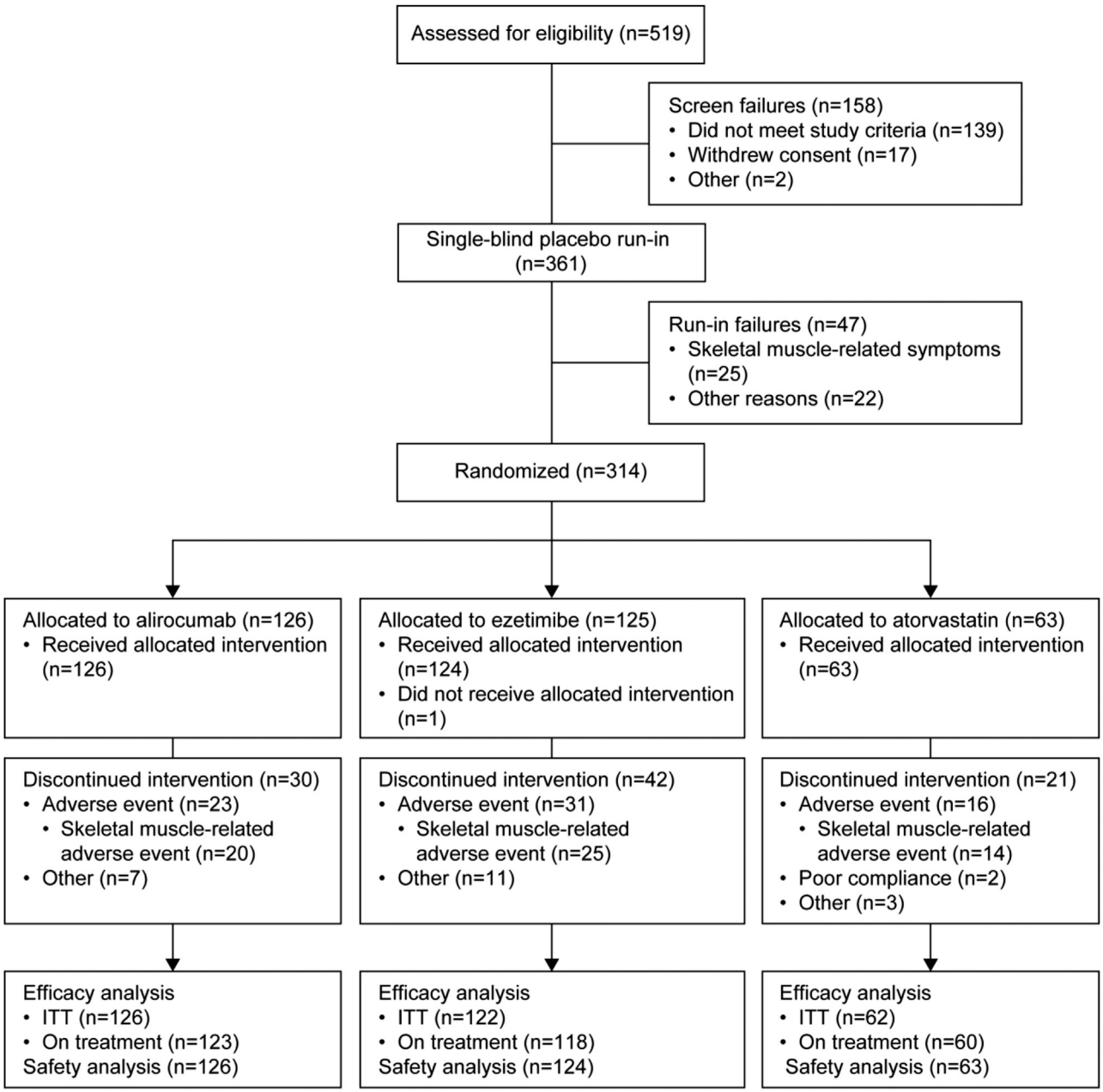


Figure 1 Flow chart. ITT, intent-to-treat.

Table 1 Characteristics by randomized treatment*

Characteristic	Alirocumab† (n = 126)	Ezetimibe‡ (n = 125)	Atorvastatin§ (n = 63)
Age, mean (SD), y	64.1 (9.0)	62.8 (10.1)	63.4 (8.9)
Male gender, n (%)	70 (55.6)	67 (53.6)	35 (55.6)
Race, n (%)‖			
White	117 (92.9)	116 (92.8)	62 (98.4)
Black or African American	5 (4.0)	7 (5.6)	0
Other	4 (3.2)	2 (1.6)	1 (1.6)
Body mass index, mean (SD), kg/m^2	29.6 (6.6)	28.4 (4.9)	29.7 (5.4)
HbA_{1c}, mean (SD), %	5.86 (0.66)	5.73 (0.55)	5.87 (0.72)
Creatine kinase, mean (SD), ULN	0.7 (0.5)	0.7 (0.4)	0.8 (0.6)
Current smoker, n (%)	11 (8.7)	5 (4.0)	5 (7.9)
Selected medical history, n (%)			
Abdominal aortic aneurysm	3 (2.4)	2 (1.6)	3 (4.8)
Acute myocardial infarction	21 (16.7)	15 (12.0)	7 (11.1)
Carotid artery occlusion >50% without symptoms	10 (7.9)	6 (4.8)	6 (9.5)
Carotid endarterectomy or carotid artery stent procedure	6 (4.8)	3 (2.4)	2 (3.2)
Chronic kidney disease (eGFR 30–<60 $mL/min/1.73\ m^2$)	6 (4.8)	8 (6.4)	2 (3.2)
Coronary heart disease	64 (50.8)	54 (43.2)	28 (44.4)
Diabetes mellitus (type 2)	36 (28.6)	24 (19.2)	15 (23.8)
Hypertension	85 (67.5)	77 (61.6)	35 (55.6)
Ischemic stroke	4 (3.2)	5 (4.0)	5 (7.9)
Transient ischemic attack	9 (7.1)	7 (5.6)	4 (6.3)
Peripheral artery disease	1 (0.8)	2 (1.6)	3 (4.8)
Renal artery stenosis or renal artery stent procedure	0	2 (1.6)	0
Cardiovascular risk level			
Moderate¶	19 (15.1)	14 (11.2)	10 (15.9)
High#	29 (23.0)	47 (37.6)	13 (20.6)
Very high**	73 (57.9)	62 (49.6)	35 (55.6)
Lipid parameters, mean (SD) or median (quartile 1, quartile 3)			
LDL-C (Friedewald formula), mg/dL	191.1 (72.7)	193.5 (70.9)	187.3 (59.5)
Range (min:max)	91:577	81:427	86:382
LDL-C (beta-quantification method), mg/dL	179.4 (71.3)	188.1 (72.7)	181.8 (60.9)
Min:max	99:584	87:443	76:370
Apolipoprotein B, g/L	141.7 (39.5)	138.2 (37.4)	139.1 (34.7)
Total cholesterol, mg/dL	278.9 (79.5)	280.5 (83.3)	274.9 (63.2)
Non–HDL-C, mg/dL	230.0 (80.4)	229.8 (82.7)	223.8 (64.8)
Lipoprotein(a), mg/dL	18.0 (8.0, 47.0)	14.0 (7.0, 43.0)	12.0 (6.0, 50.0)
Triglycerides (fasting), mg/dL	164.0 (114.0, 233.0)	140.0 (95.0, 218.0)	158.0 (119.0, 246.0)
HDL-C, mg/dL	48.9 (15.3)	50.7 (14.1)	51.1 (12.5)
Apolipoprotein A1, mg/dL	149.4 (25.0)	150.0 (24.2)	154.2 (24.8)
LMT (other than statin) at randomization, n (%)	47 (37.3)	55 (44.0)	34 (54.0)
LMT (other than nutraceutical) at randomization, n (%)	41 (32.5)	48 (38.4)	31 (49.2)
Nutraceutical	7 (5.6)	17 (13.6)	6 (9.5)

LMT (other than statins) during double-blind treatment period, n (%)	49 (38.9)	56 (45.2)	36 (57.1)
Bile acid sequestrant	4 (3.2)	13 (10.5)	5 (7.9)
Fenofibrate	5 (4.0)	3 (2.4)	6 (9.5)
Nicotinic acid	8 (6.3)	12 (9.7)	7 (11.1)
Omega-3 fatty acids (excluding nutraceuticals; ≥1000 mg/d)	3 (2.4)	5 (4.0)	4 (6.3)

eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin A_{1c}; HDL-C; high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LMT, lipid-modifying treatment; SD, standard deviation; ULN, upper limit of normal.

To convert cholesterol measurements to mmol/L, multiply by 0.02586; to convert triglycerides measurements to mmol/L, multiply by 0.01129.

*All between-group comparisons were $P > .05$.

†Alirocumab 75 mg subcutaneous every 2 weeks (Q2W) with a dose increase to 150 mg Q2W at week 12 depending on week 8 LDL-C values.

‡10 mg/d oral ezetimibe.

§20 mg/d oral atorvastatin (statin rechallenge arm).

‖Race was self-reported.

¶10-y fatal cardiovascular risk Systematic Coronary Risk Evaluation (SCORE) between ≥1% and <5%.

#10-y fatal cardiovascular risk SCORE ≥ 5%; moderate chronic kidney disease; diabetes mellitus without target organ damage; or familial hypercholesterolemia.

**Documented history of coronary heart disease, ischemic stroke, peripheral artery disease, transient ischemic attack, abdominal aortic aneurysm, or carotid artery occlusion >50% without symptoms; carotid endarterectomy or carotid artery stent procedure; renal artery stenosis or renal artery stent procedure; or diabetes mellitus with target organ damage.

(7 of 47; 14.9%) (Supplemental Table 2). Others excluded from entering the double-blind treatment period did so for reasons such as withdrawal of consent and unstable dose of concomitant medicine.

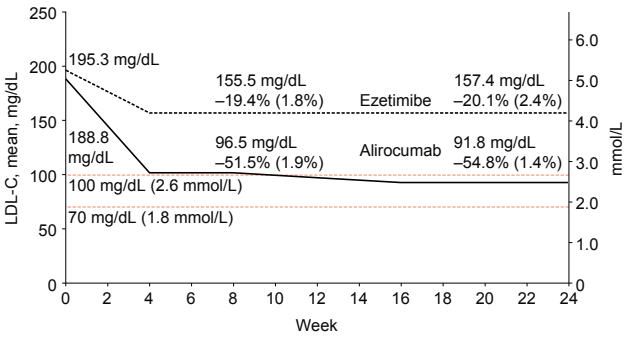
Patient baseline characteristics and lipid parameters were evenly distributed across the study arms (Table 1). Overall mean (SD) age was 63.4 (9.5) years, 54.8% were men, 93.9% were white, and mean (SD) baseline LDL-C was 191.3 (69.3) mg/dL (range 81.0–577.0 mg/dL; 5.0 [1.8] mmol/L, range 2.1–14.9 mmol/L). Rates of coronary heart disease and cardiovascular risk factors were high. All patients with known data had reported the development of muscle symptoms since starting the most recent statin therapy before entering the study (Supplemental Table 3). In most cases, symptoms were new, bilateral, and constant.

During the double-blind treatment period, 141 (45.0%) patients received lipid-modifying therapy with bile acid sequestrants, nicotinic acid, fenofibrate, or omega-3 fatty acids (Table 1). In this population of patients with very high baseline LDL-C, half of the patients (n = 54, 49.5%) in the alirocumab arm required a dose increase from 75 to 150 mg Q2W per protocol.

Ninety-six (76.2%) patients in the alirocumab arm, 82 (65.6%) in the ezetimibe arm, and 42 (66.7%) in the atorvastatin arm remained on treatment throughout the double-blind treatment period (Fig. 1). The primary reason for treatment discontinuation was the occurrence of an AE. A total of 281 patients (89.5% of those randomized) who completed the double-blind period entered the ongoing open-label treatment period with alirocumab, 117 of 126 (92.9%) from the alirocumab arm, 105 of 124 (84.7%) from the ezetimibe arm, and 59 of 63 (93.7%) from the atorvastatin arm.

Efficacy

For the primary ITT efficacy analysis, LS mean (standard error [SE]) change in LDL-C concentrations from baseline to week 24 were −45.0% (2.2%) for alirocumab and −14.6% (2.2%) for ezetimibe, with a difference between groups of −30.4% (3.1%; $P < .0001$). For the on-treatment analysis, the LS mean (SE) change from baseline was −52.2% (2.0%) for alirocumab and −17.1% (2.0%) for ezetimibe (LS mean difference of −35.1% [2.8%], $P < .0001$). A substantial reduction in LDL-C concentration occurred over the first 4 weeks, which was greater in the alirocumab arm (Fig. 2) and persisted throughout the 24-week treatment period. The on-treatment values demonstrate a durable treatment effect. The distribution of baseline and achieved LDL-C values for alirocumab and ezetimibe at 24 weeks is shown in Figure 3. At week 24, 52 (41.9%) patients on alirocumab and 5 (4.4%) of those on ezetimibe ($P < .0001$; ITT analysis) reached an LDL-C goal of <70 mg/dL (1.8 mmol/L) in very high cardiovascular risk patients or <100 mg/dL (<2.6 mmol/L) in moderate-to-high-risk patients. Corresponding results in the on-treatment population were



No. Pts.	Baseline	Week 12	Week 24
Alirocumab	123	109	90
Ezetimibe	118	95	78

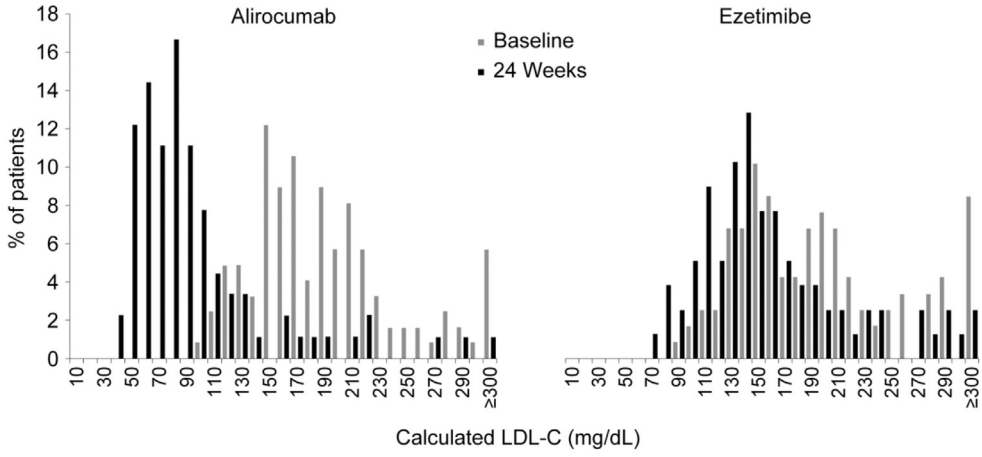
Figure 2 LDL-C concentrations vs study time points (on-treatment analysis using raw data). Values at week 12 and week 24 data points indicate achieved LDL-C concentration and LS mean (SE) percent change from baseline. In a post-hoc ITT analysis, the mean (SD) change in LDL-C concentration in the atorvastatin arm was −31.9% (25.1%) at week 24. ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least squares; Pts, patients; SD, standard deviation; SE, standard error.

51.2% and 5.6% ($P < .0001$). The greater effect of alirocumab relative to ezetimibe on LDL-C-lowering from baseline to week 24 was consistent across most of the prespecified subgroups in the ITT population (Supplemental Fig. 1). In addition, reductions in apolipoprotein B, non–HDL-C, total cholesterol and lipoprotein(a) concentrations were greater for alirocumab vs ezetimibe (all $P < .0001$; Table 2). There were no statistically significant differences between the 2 groups in changes in triglyceride, HDL-C, and apolipoprotein A1 concentrations.

Safety and tolerability

Overall rates of treatment-emergent and serious AEs were generally similar between treatment arms, and there were no deaths in the study (Table 3). Discontinuations due to treatment-emergent AEs trended lower in the alirocumab treatment arm. Myalgia was the most common AE in all groups. Muscle spasms occurred in 4.0% of alirocumab patients vs 7.3% of ezetimibe patients and 11.1% of atorvastatin patients. One case of myositis occurred in the atorvastatin arm. The rate of skeletal muscle–related AEs was significantly lower with alirocumab vs atorvastatin (hazard ratio [HR] 0.61, 95% confidence interval (CI) 0.38 to 0.99, $P = .042$; Fig. 4). A similar trend was observed for alirocumab vs ezetimibe (HR 0.71, 95% CI 0.47–1.06, $P = .096$), but it did not reach statistical significance. The difference in the rate of skeletal muscle–related AEs was seen soon after study drug initiation (Fig. 4). The rate of study treatment discontinuation due to skeletal muscle–related AEs was nonsignificantly different for alirocumab vs atorvastatin (HR 0.67, 95% CI 0.34–1.32, $P = .24$) or ezetimibe (HR 0.78, 95% CI 0.43–1.41, $P = .41$).

Treatment-emergent AEs that occurred in ≥2% of any treatment group are detailed in Supplemental Table 4. Briefly, those occurring in ≥5% of patients were myalgia (24.6%), nasopharyngitis (6.3%), upper respiratory tract infection (5.6%), and arthralgia (5.6%) in the alirocumab



Mean (SD) LDL-C, mg/dL	Alirocumab	Ezetimibe
Baseline	n = 123 188.8 (67.4)	n = 118 195.3 (72.0)
Week 24	n = 90 91.8 (63.4)	n = 78 157.4 (65.2)
% change from baseline	–54.8 (13.7)	–20.1 (21.3)

Figure 3 Distribution by 10-mg/dL increments of LDL-C concentration at baseline and week 24 in patients on alirocumab (left panel) or ezetimibe (right panel; modified ITT population using raw data). Comparison between week 24 and baseline is descriptive and exploratory, as 24-week data were not available for all patients. ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; SE, standard error.

Table 2 Percent change from baseline in LDL-C and in selected key secondary lipid parameters in prespecified hierarchical testing order

End point	Alirocumab*	Ezetimibe†	Alirocumab* vs ezetimibe†		
			LS mean difference (SE), %	95% CI	*P* value
Primary end point: LDL-C (baseline–wk 24, ITT)	n = 126	n = 122			
Baseline LDL-C, mean (SD), mg/dL	191.1 (72.7)	194.2 (71.2)	—	—	—
LS mean (SE) change from baseline, %	−45.0 (2.2)	−14.6 (2.2)	−30.4 (3.1)	−36.6 to −24.2	<.0001
First key secondary end point: LDL-C (baseline to wk 24, on treatment)	n = 123	n = 118			
Baseline LDL-C, mean (SD), mg/dL	188.8 (67.4)	195.3 (72.0)	—	—	—
Min:max	91:577	81:427	—	—	—
LS mean (SE) change from baseline, %	−52.2 (2.0)	−17.1 (2.0)	−35.1 (2.8)	−40.7 to −29.5	<.0001
Key secondary lipid parameters, mean (SE)	n = 126	n = 122			
LDL-C (baseline–wk 12, ITT)	−47.0 (1.9)	−15.6 (2.0)	−31.5 (2.7)	−36.9 to −26.1	<.0001
Apolipoprotein B (baseline–wk 24, ITT)	−36.3 (1.7)	−11.2 (1.7)	−25.1 (2.4)	−29.8 to −20.4	<.0001
Apolipoprotein B (baseline–wk 24, on-treatment)	−42.6 (1.3)	−14.4 (1.4)	−28.2 (1.9)	−32.1 to −24.4	<.0001
Non–HDL-C (baseline–wk 24, ITT)	−40.2 (1.7)	−14.6 (1.7)	−25.6 (2.4)	−30.4 to −20.8	<.0001
Non–HDL-C (baseline–wk 24, on treatment)	−46.9 (1.4)	−17.1 (1.5)	−29.8 (2.0)	−33.9 to −25.8	<.0001
Total cholesterol (baseline–wk 24, ITT)	−31.8 (1.4)	−10.9 (1.4)	−20.8 (1.9)	−24.7 to −17.0	<.0001
Lipoprotein(a) (baseline–wk 24, ITT)	−25.9 (2.4)	−7.3 (2.5)	−18.7 (3.5)	25.5 to −11.8	<.0001
HDL-C (baseline–wk 24, ITT)‡	7.7 (1.7)	6.8 (1.7)	0.9 (2.4)	−3.8 to 5.6	.70
Fasting triglycerides (baseline–wk 24, ITT)	−9.3 (2.7)	−3.6 (2.8)	−5.7 (3.9)	−13.3 to 1.9	.14
Apolipoprotein A1 (baseline–wk 24, ITT)	4.8 (1.2)	2.9 (1.2)	1.9 (1.7)	−1.5 to 5.3	.28

CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least squares; SD, standard deviation; SE, standard error.

*Alirocumab 75 mg subcutaneous every 2 weeks (Q2W) with a dose increase to 150 mg Q2W at week 12 depending on week 8 LDL-C values.

†10 mg/d oral ezetimibe.

‡Hierarchical testing terminated at the end point of HDL-C (baseline–week 24, ITT), and this statistical comparison and all subsequent ones were not considered statistically significant.

arm; myalgia (23.4%), nasopharyngitis (8.1%), arthralgia (7.3%), muscle spasms (7.3%), and back pain (5.6%) in the ezetimibe arm; and myalgia (27.0%), muscle spasms (11.1%), arthralgia (7.9%), fatigue (7.9%), back pain (7.9%), headache (6.3%), muscular weakness (6.3%), paresthesia (6.3%), and vomiting (6.3%) in the atorvastatin arm. One nonfatal myocardial infarction occurred in the alirocumab arm.

None of the patients experienced 2 consecutive LDL-C measurements of <25 mg/dL (<0.6 mmol/L). Fourteen of the 16 patients with myalgia in the atorvastatin arm discontinued treatment, of which 13 entered the open-label treatment period (including the patient on atorvastatin who developed myositis) and were further monitored.

Open-label treatment period

The mean (SD) duration of exposure to alirocumab during the open-label treatment period at the time of this analysis was 41.2 (11.3) weeks (range 2.0–78.1 weeks). Nearly four-fifths (79.0%) of the patients reported experiencing an AE: 4.6% reported an event leading to treatment discontinuation; and 24.2% reported a skeletal muscle–related AE, of which 2.1% discontinued medication as a consequence (Supplemental Table 5). One (0.4%) patient died.

Discussion

In patients at moderate-to-high cardiovascular risk who had reported intolerance to 2 or more statins in the past, self-administered alirocumab reduced LDL-C by 45.0% vs baseline, compared with a reduction of 14.6% for ezetimibe, at 24 weeks of treatment, with a difference between groups of 30.4%. Even greater reductions of LDL-C were observed with alirocumab in the on-treatment analysis owing to the number of patients who discontinued study drug but remained in the study for both treatment arms. Substantially more patients on alirocumab (41.9%) vs ezetimibe (4.4%) reached an LDL-C <70 mg/dL or <100 mg/dL (depending on cardiovascular risk level). Although mean baseline LDL-C concentration was very high (191.3 mg/dL), as anticipated in this population, half of the patients on alirocumab achieved the prespecified LDL-C concentrations without an increase in dose. Alirocumab was associated with a significantly lower rate of musculoskeletal AEs vs atorvastatin.

Statins are currently the most effective treatment for hypercholesterolemia, reducing LDL-C by 30% to 50%[1] vs 15% to 20% with non-statin therapies.[20] However, statin-associated muscle symptoms, estimated to affect between

Table 3 Treatment-emergent AEs* and laboratory parameters (safety population) at 24 weeks

AE category or laboratory parameter	Alirocumab† (n = 126)	Ezetimibe‡ (n = 124)	Atorvastatin§ (n = 63)
Any AE, n (%)	104 (82.5)	100 (80.6)	54 (85.7)
Serious AE,‖ n (%)	12 (9.5)	10 (8.1)	7 (11.1)
AE leading to death, n (%)	0	0	0
AE leading to treatment discontinuation, n (%)	23 (18.3)	31 (25.0)	16 (25.4)
Skeletal muscle–related AE,¶ n (%)	41 (32.5)	51 (41.1)	29 (46.0)
Skeletal muscle–related AE¶ leading to treatment discontinuation, n (%)	20 (15.9)	25 (20.2)	14 (22.2)
Musculoskeletal events occurring in ≥5% of patients in any group, n (%)			
Myalgia	31 (24.6)	29 (23.4)	17 (27.0)
Arthralgia	7 (5.6)	9 (7.3)	5 (7.9)
Back pain	5 (4.0)	7 (5.6)	5 (7.9)
Muscle spasms	5 (4.0)	9 (7.3)	7 (11.1)
Muscular weakness	1 (0.8)	2 (1.6)	4 (6.3)
Injection-site reaction	6 (4.8)	6 (4.8)	1 (1.6)
Adjudicated cardiovascular events,# n (%)	4 (3.2)	1 (0.8)	1 (1.6)
Nonfatal myocardial infarction	1 (0.8)	0	0
Ischemia-driven coronary revascularization procedure	3 (2.4)	1 (0.8)	1 (1.6)
Laboratory parameters, n/N (%)			
Alanine aminotransferase >3 × ULN	0	0	0
Creatine kinase >3 × ULN	3/126 (2.4)	2/123 (1.6)	3/62 (4.8)

AE, adverse event; ULN, upper limit of normal.

*Treatment-emergent AEs are AEs that developed, worsened, or became serious during the AE period (defined as the time from the first dose of double-blind study treatment to the last injection plus 70 days [10 weeks], as residual effect of alirocumab was expected until 10 weeks after last injection).

†Alirocumab 75 mg subcutaneous every 2 weeks (Q2W) with a dose increase to 150 mg Q2W at week 12 depending on week 8 low-density lipoprotein cholesterol values.

‡10 mg/d oral ezetimibe.

§20 mg/d oral atorvastatin (statin rechallenge arm).

‖AE resulting in death, is life threatening, requiring hospitalization, resulting in significant disability or incapacity, resulting in a congenital anomaly or birth defection, or is an important medical event.

¶Predefined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, and muscle fatigue.

#Including coronary heart disease death, nonfatal myocardial infarction, fatal/nonfatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, and ischemia-driven coronary revascularization.

7% and 29% of patients in clinical practice,[5,8] present a major limitation to the management of hypercholesterolemia.[8] The statin-intolerant population comprises a heterogeneous group[9] and the definitions used are variable[8]; hence, the proportion of patients with statin intolerance that is recognizable with blinded, randomized rechallenge is unknown.[6,7] The present study recruited patients with a documented history of intolerance to at least 2 statins (including 1 at the lowest recommended daily starting dose). The presence of intolerance was carefully scrutinized through the novel trial design, which incorporated a placebo run-in phase to exclude patients who experienced symptoms in the absence of statin therapy, and a statin rechallenge arm to document the rate of reproducible statin intolerance.

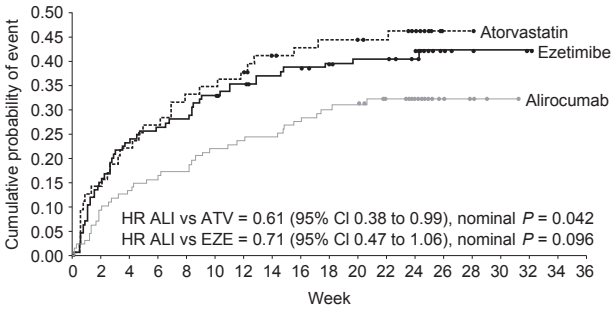


Figure 4 Kaplan–Meier estimates for time to first skeletal muscle–related AE (predefined as myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, or muscle fatigue). AE, adverse event; ALI, alirocumab; ATV, atorvastatin; CI, confidence interval; EZE, ezetimibe; HR, hazard ratio.

Over the 4-week placebo run-in, 6.4% of the screened patients failed to qualify for the double-blind treatment, suggesting that some patients may experience muscle symptoms because of negative expectations surrounding the potential for statin treatment or for reasons unrelated to statin therapy. During the 24-week double-blind treatment period, 46.0% of patients reported skeletal muscle AEs when rechallenged with atorvastatin 20 mg, a dose judged sufficient to elicit statin-related muscle symptoms, while not preventing patients from consenting to participate in the study,[21] and 22.2% discontinued atorvastatin as a consequence. The discontinuation rate may have increased with more prolonged use, as reported elsewhere.[25] This rate of

discontinuations is consistent with the Cleveland Clinic experience, which reported a rate of 27.5%, in which 72.5% of patients with statin intolerance were able to tolerate a subsequent trial of statin therapy.[26] As such, we have documented in a prospective randomized blinded study that many patients with a history of statin intolerance actually "can" tolerate a statin.

In the present study, alirocumab-treated patients experienced a lower rate of muscle-related AEs vs atorvastatin and showed a trend toward a lower rate vs ezetimibe. The notable rate of skeletal muscle–related AEs in all treatment groups in this study may be related to the novel definition used, namely myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, and muscle fatigue. Although across-trial comparisons have recognized limitations, it is useful to contrast the rates of myalgia (a common Medical Dictionary for Regulatory Activities term) in this population with those from similar studies. The rate of myalgia in alirocumab-treated patients was higher in the present study than in the ODYSSEY MONO study[14] (24.6% vs 3.8%, respectively), with most cases occurring within the first 14 weeks of this 24-week trial; but the rate was also higher with ezetimibe (23.4% vs 3.9%, respectively), a drug that is usually well tolerated.[27] Similarly, the rates of myalgia were higher than in the Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects (GAUSS-2) trial in which patients were randomized to evolocumab or ezetimibe (8% with evolocumab and 18% with ezetimibe).[28] However, the study designs and definitions for statin intolerance differed, and the duration of treatment was significantly shorter in GAUSS-2 (12 vs 24 weeks). Furthermore, the absence of a statin rechallenge arm in GAUSS-2 may have avoided behaviors associated with negative expectations surrounding possible statin treatment.

During the open-label treatment period of this study (mean of 41 weeks), when patients knew that they were not receiving statin therapy, rates of skeletal muscle–related AEs were substantially lower than those during the double-blind period (24.2% vs 32.5%, respectively). Similarly, discontinuations due to skeletal muscle–related AEs were also lower (2.1% vs 15.9%, respectively). Rates of muscle symptoms and muscle-related discontinuations in the open-label treatment period are reasonably consistent with the overall ODYSSEY program (15.1% and 0.4%, respectively). These findings raise the possibility that this statin-intolerant population may have been anticipating the possibility of side effects if rechallenged with a statin during the double-blind period, expressing behavior learned in response to prior statin exposure when reporting muscle symptoms, whether treatment-related or not.

In contrast, the rates of muscle-related AEs in the atorvastatin arm reinforce the challenges clinicians face when diagnosing statin intolerance. One would anticipate that a sizable proportion of statin-intolerant patients would report a recurrence of symptoms when rechallenged with atorvastatin 20 mg. It may be, however, that randomized patients had prior muscle symptoms with a statin other than atorvastatin or at a higher dose; also, the study duration or the dose chosen may have been insufficient for symptoms to manifest in some patients. Furthermore, symptoms in patients who declined to participate may have been more severe than in those who agreed. Our study would suggest that a careful rechallenge of patients with a possible history of statin intolerance would be warranted, and in those who truly do have statin intolerance (either from clear prior documentation or prospective rechallenge), alirocumab would be a powerful means of lowering their LDL-C.

The mean LDL-C concentration at baseline was ≥190 mg/dL, a recognized risk threshold for drug treatment regardless of cardiovascular risk level. As such, these statin-intolerant patients are unlikely, if taking a less than optimal statin dose or less-effective non-statin therapies, to achieve the lipid reductions recommended, or anticipated, in guidelines.[1,20] In the present study, alirocumab was significantly more effective than ezetimibe at reducing LDL-C, total cholesterol, non–HDL-C, apolipoprotein B, and lipoprotein(a). Favorable changes in triglycerides (decrease of 9.3%) and HDL-C (increase of 7.7%) were also seen with alirocumab; they did not, however, differ in comparison to ezetimibe and were within the boundaries expected.[29] The reduction in LDL-C of 31.9% with atorvastatin (although exploratory only) was as expected, given the dropout rate and ITT approach, which included off-treatment data.[17,30]

Study limitations

The study design, which included placebo run-in and statin rechallenge to confirm statin intolerance, may have resulted in hypervigilance by study participants regarding potential statin re-exposure. The definition of statin intolerance differs from those used in other reports, and these results cannot be generalized to all individuals with statin-associated muscle symptoms, particularly those who refuse to be rechallenged with a statin and who may have had even more severe symptoms than the participants. It should also be noted that the study population was predominantly white—an aspect that would benefit from being addressed in future studies. Finally, the study duration was short, and the rate of treatment discontinuation may increase over the longer term.

Cardiovascular outcomes with alirocumab are currently being evaluated in a large ongoing study (http://clinicaltrials.gov/show/NCT01663402)[16] and will be assessed in a pooled analysis from the overall ODYSSEY program.

Conclusions

Alirocumab demonstrated significantly greater LDL-C-lowering vs ezetimibe after 24 weeks of treatment in a population with a history of statin intolerance at moderate to very high cardiovascular risk and with elevated LDL-C

concentrations at baseline. In this population, alirocumab was well tolerated, with significantly lower rates of musculoskeletal AEs compared with atorvastatin and a trend toward lower rates compared with ezetimibe. There was also a trend toward lower rates of muscular events leading to treatment discontinuation when compared with atorvastatin or ezetimibe. More patients achieved LDL-C goals with alirocumab vs ezetimibe. Accordingly, alirocumab may provide a suitable clinical option in the future management of patients who are intolerant of statins.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jacl.2015.08.006.

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