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FULL RESEARCH PAPER
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Safety and efficacy of alirocumab in a real-life setting: the ODYSSEY APPRISE study

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Aims To obtain safety and efficacy data of alirocumab, a proprotein convertase subtilisin/kexin type 9 inhibitor, in a real-life setting in high cardiovascular (CV) risk patients with heterozygous familial hypercholesterolaemia (HeFH) or very-high low-density lipoprotein cholesterol (LDL-C) levels despite maximally tolerated dose of statin ± other lipid-lowering therapies (MTD ± LLTs). ODYSSEY APPRISE was a prospective, single-arm, Phase 3b open-label (≥12 weeks to ≤ 30 months) European/Canadian study with alirocumab.

Methods and results Patients received alirocumab 75 or 150 mg every 2 weeks, with dose adjustment based on physician's judgment. In total, 994 patients were enrolled and treated. The mean [standard deviation (SD)] duration of alirocumab exposure was 72.4 (42.5) weeks. Patients with HeFH were younger [mean (SD) age of 53.8 (11.6) vs. 61.6 (10.1) years], more likely to be female (41.7% vs. 29.1%) and had higher baseline LDL-C compared with non-familial hypercholesterolaemia (non-FH) patients [mean (SD) of 5.1 (1.7) vs. 4.1 (1.1) mmol/L]. The overall incidence of treatment-emergent adverse events (TEAEs) was 71.6%; common TEAEs included nasopharyngitis (7.8%), myalgia (7.1%), and headache (6.2%). At Week 12, mean (SD) LDL-C was reduced by 54.8 (20.1)% from baseline [2.6 (1.2) mmol/L], maintained for the trial duration. LDL-C was reduced below 1.8 mmol/L and/or by ≥50% reduction from baseline in 69.1% of patients overall, and for 64.7 and 77.4% of the HeFH and non-FH subgroups, respectively.

Conclusion In a real-life setting in patients with hypercholesterolaemia and high CV risk, alirocumab was generally well tolerated and resulted in clinically significant LDL-C reductions.

Keywords AlirocumabProprotein covertase subtilisin/kexin type 9 • Familial hypercholesterolaemia • LDL cholesterol

Introduction

Hypercholesterolaemia constitutes a major risk for the development of atherosclerosis and coronary heart disease (CHD),[1,2] a leading cause of death worldwide.[3–5] Management of severe hypercholesterolaemia involves modification of cardiovascular (CV) risk factors and the use of lipid-lowering therapies (LLTs).[1,2] Familial hypercholesterolaemia (FH) is characterized by very-high plasma levels of low-density lipoprotein cholesterol (LDL-C) and an increased CV risk.[6,7] Patients with heterozygous FH (HeFH) typically receive maximally tolerated dose of statin (MTD), with or without ezetimibe, as first-line therapy; however, in clinical practice, many patients do not reach their

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guideline-recommended LDL-C treatment goals without additional LLTs.[8–12] Statin intolerance remains an issue in some patients, and discontinuation of statin therapy may cause an increase in CV events.[13]

Recent European guidelines recommend considering the addition of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor for patients at very-high CV risk not achieving their risk-based LDL-C goal while receiving MTD and ezetimibe therapy.[1] Similarly, for adult patients with HeFH and LDL-C ≥ 2.6 mmol/L (≥100 mg/dL) while receiving MTD and ezetimibe, the addition of a PCSK9 inhibitor is recommended for consideration by recent American guidelines.[2] Alirocumab, a monoclonal antibody that inhibits PCSK9, has been shown in randomized controlled trials to significantly lower levels of LDL-C and other atherogenic lipids compared with placebo or ezetimibe in patients with or without HeFH.[14–17]

ODYSSEY APPRISE (NCT02476006) was a European/Canadian prospective study designed with the objective to assess the safety and efficacy of alirocumab in a real-life setting among high CV risk patients with severe hypercholesterolaemia inadequately controlled with MTD ± other LLT (excluding PCSK9 inhibitors). ODYSSEY APPRISE was initiated in 2015, and categorization of patients as being at high CV risk was based on the guidelines available during the design of the study.[18,19] ODYSSEY APPRISE provided patients with severe hypercholesterolaemia access to alirocumab ahead of commercial availability in Canada and 16 European countries. Here, we describe the safety and efficacy results from ODYSSEY APPRISE in the overall study population and according to FH status (HeFH vs. non-FH).

Methods

ODYSSEY APPRISE (NCT02476006) was a single-arm, Phase 3b, open-label study designed to obtain safety, and efficacy data of alirocumab in a real-life setting among high CV risk patients with severe hypercholesterolaemia not adequately controlled by MTD ± other LLTs (first patient enrolled 23 June 2015; last patient completed 12 April 2019). A complete list of study sites and investigators is available in Supplementary material online.

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The study protocol was approved by the appropriate institutional review boards or independent ethics committee at each study centre. Written informed consent was obtained from all participating individuals prior to their involvement in study-related activities.

Study design

Following a screening period of up to 3 weeks, patients received subcutaneous alirocumab 75 mg or 150 mg every 2 weeks (Q2W). The starting dose was based on the patient's baseline characteristics and goal of therapy, as assessed by the investigator. The open-label treatment period with alirocumab lasted for a minimum of 12 weeks and a maximum of 30 months, and also featured an end-of-study visit at least 2 weeks after the last study treatment injection (Supplementary material online, *Figure S1*). During the study, the dose could be adjusted from 75 mg to 150 mg Q2W, or vice versa, at the investigator's discretion, based on treatment response. Alirocumab was administered on top of background stable MTD ± other LLTs.

An MTD was defined as rosuvastatin 20 or 40 mg/day, atorvastatin 40 or 80 mg/day, or simvastatin 80 mg/day (if already on this dose for >1 year). Patients not able to be on MTD were permitted to be treated with the dose of atorvastatin, rosuvastatin, or simvastatin considered appropriate for them as per the investigator's judgment or concerns. In exceptional and documented cases, use of another statin regimen was permitted. Statin dose and regimen, as well as dose and regimen of other LLTs (if applicable), were kept stable throughout the entire study duration, including the screening period. However, modification of LLTs was allowed under certain conditions after enrolment at the investigator's judgment.

In each country, patient recruitment ended when alirocumab became commercially available (i.e. accessible to the patient as per each country's regulation) and reimbursed. In this case, study treatment could be switched to the commercial product once the patient had completed the minimum 12 weeks of study treatment.

Study population

Patients were eligible for study participation if they were aged ≥18 years, with HeFH or with established CHD or a CHD risk equivalent, and with hypercholesterolaemia not adequately controlled with MTD ± LLT as follows:

- Patients with HeFH with LDL-C ≥4.1 mmol/L (160 mg/dL) despite treatment.
- Patients with HeFH with LDL-C ≥3.4 mmol/L (130 mg/dL) despite treatment, and ≥2 CV risk factors.
- Patients with HeFH with LDL-C ≥3.4 mmol/L (130 mg/dL) despite treatment, and established CHD or other CV disease (CVD), diabetes, or a family history of CHD.
- Non-FH patients with established CHD or other CVD, and with LDL-C ≥3.4 mmol/L (130 mg/dL).
- Patients with progressive CVD (coronary artery disease, or peripheral arterial occlusive disease or cerebrovascular disease as documented clinically or by imaging techniques, with a subsequent CV event despite treatment) and LDL-C ≥2.6 mmol/L (100 mg/dL).

The full inclusion and exclusion criteria can be found in Supplementary material online, *Tables S1* and *S2*.

Study endpoints and assessments

The primary endpoint of the study was to assess safety parameters throughout the study, including adverse events (AEs), AEs of special interest (details provided in Supplementary material online), laboratory data, product complaints, and vital signs.

The main secondary efficacy endpoint was the percent change in calculated LDL-C from baseline to Week 12. Key secondary efficacy endpoints assessed at Week 12 included: the proportion of patients achieving calculated LDL-C < 2.6 mmol/L (100 mg/dL), <1.8 mmol/L (70 mg/dL), or <1.8 mmol/L (70 mg/dL) and/or ≥50% reduction from baseline [if LDL-C ≥ 1.8 mmol/L (70 mg/dL)]; and the percent change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol, HDL-C, and triglyceride levels.

LDL-C was calculated using the Friedewald formula[20] at all analysis time points; however, if triglyceride values were >4.5 mmol/L (400 mg/dL) then the LDL-C values were not included in the current analyses.

Statistical analyses

The safety population included patients who received at least one dose or partial dose of alirocumab. Safety parameters were explored through descriptive statistics (no formal statistical comparisons were made as this was a single-arm open-label study).

The efficacy analysis was performed on the modified intention-to-treat (mITT) population, which included all patients who received at least one dose or partial dose of alirocumab, had baseline LDL-C data available, and had at least one LDL-C measurement within the analysis window associated with Week 12.

Results

Patient disposition and baseline characteristics

Overall, 994 patients were enrolled and treated; mean [standard deviation (SD)] exposure to alirocumab was 72.4 (42.5) weeks [median (Q1:Q3) duration of 72 (28:120) weeks]. Among the 994 treated patients, 88.3% completed the treatment period; 11.7% of patients did not complete the study treatment period, and the most common reason cited for discontinuation was AEs (41 patients; Supplementary material online, *Figure S2*). Baseline characteristics are presented in *Table 1*. Compared with non-FH patients, patients with HeFH were younger, more likely to be female, and had higher baseline LDL-C (*Table 1*). Additionally, the proportion of patients with CHD or other CVD was nearly twice as high in the non-FH group than in the HeFH group. Median (Q1:Q3) time since diagnosis of hyperlipoproteinaemia was 20 (9:30) years and 10 (5:18) years in the HeFH and non-FH subgroups, respectively.

Concomitant lipid-lowering therapies

During the study, 873/994 (87.8%) of the overall population were receiving concomitant LLTs (*Table 1*). Patients with HeFH were more likely than non-FH patients to be concomitantly taking any form of LLT (93.7% vs. 77.4%), statins (87.3% vs. 56.7%), or ezetimibe (69.3% vs. 41.3%; *Table 1*). Of the 712 patients receiving concomitant statins, 126 patients (17.7%) temporarily, or permanently discontinued statins during the trial.

Alirocumab dose adjustment

The initial alirocumab dose (75 or 150 mg Q2W) was selected by the physician based on an individual patient's characteristics and their LDL-C therapy goals. For patients whose initial dose of alirocumab was 75 mg (687/994; 69.1%) mean (SD) baseline LDL-C was 4.4 (1.3) mmol/L ($n = 684$; safety population); for patients whose initial dose of alirocumab was 150 mg (307/994; 30.9%) mean (SD) baseline LDL-C was 5.3 (1.8) mmol/L ($n = 306$; safety population).

During the study, the alirocumab dose could be adjusted from 75 to 150 mg Q2W, or vice versa, according to the physicians' clinical judgment, based on treatment response and individual patient characteristics. In the subgroup whose initial dose of alirocumab was 75 mg ($n = 634$; mITT population), 265 (41.8%) patients had at least one dose increase to alirocumab 150 mg Q2W (patients with at least 12 weeks of follow-up); the median (Q1:Q3) time to first dose increase was 12.1 (8.1:24.1) weeks. In most cases (96.6%), the reason given for the first dose increase was lipid values. For those patients who received only a single dose increase during the study ($n = 239$; 90.2%), mean (SD) LDL-C decreased from 3.3 (1.5) mmol/L to 2.4 (1.5) mmol/L following alirocumab dose increase.

In the subgroup whose starting dose of alirocumab was 150 mg ($n = 287$; mITT population), 49 (17.1%) patients had at least one dose decrease to alirocumab 75 mg Q2W; the median (Q1:Q3) time to first dose decrease was 9.0 (4.6:24.1) weeks. The main reason cited for alirocumab dose decrease was lipid values (71.4% of cases). For those patients who received only a single dose decrease from 150 to 75 mg Q2W during the study ($n = 38$; 77.6%), the mean (SD) LDL-C values increased from 1.4 (1.1) mmol/L to 2.0 (1.2) mmol/L following alirocumab dose decrease.

Safety

Overall, treatment-emergent adverse events (TEAEs) were reported in 71.6% of patients ($n = 712$; *Table 2*); in the subgroup analysis, TEAEs were reported in 66.7% of HeFH and 80.4% of non-FH patients, respectively. A total of four deaths were reported during the on-study period, including two deaths (0.2%) during the TEAE period: death from lung adenocarcinoma and death by suicide (not considered related to alirocumab by the investigator; both patients were in the HeFH subgroup). In addition, three deaths occurred post-study. The other two on-study deaths occurred after the TEAE period: one death occurred from five serious adverse events (SAEs; acute myeloid leukaemia, aplasia, sepsis, cardiac failure, and malnutrition) and the other death occurred from two SAEs (pulmonary oedema and myocardial infarction). Overall, 45 patients (4.5%) permanently discontinued treatment due to a TEAE; TEAEs leading to permanent treatment discontinuation (those with more than two patients at the preferred-term level) were thrombocytopenia, myalgia, and asthenia [three patients each (0.3%)]. Treatment-emergent SAEs were reported in 161 patients (16.2%) overall (*Table 2*). Nine patients (0.9%) had treatment-emergent SAEs considered to be related to alirocumab by the investigator; these were liver abscess, lung adenocarcinoma with bone metastasis, anaemia, diabetes mellitus, seizure, chronic hepatitis, hepatocellular injury, maculopapular rash, and increase in transaminases (Supplementary material online, *Table S3*).

TEAEs corresponding to AEs of special interest (pre-specified in the study protocol) occurred in 34 patients (3.4%) overall (*Table 2*). Common TEAEs are summarized in *Table 2*.

Efficacy

Overall, mean (SD) LDL-C decreased by 2.6 (1.2) mmol/L from baseline to Week 12 (54.8%; mITT population; *Table 3*); this reduction was maintained for the duration of the study (Supplementary material online, *Figure S3*). The subgroup analysis showed that, at Week 12, the mean reduction in LDL-C from baseline was similar between the HeFH and non-FH groups (53.4% vs. 57.6%, respectively; *Table 3* and Supplementary material online, *Figure S3*).

In the overall study population, 74.6%, 50.2%, and 69.1% of patients [95% confidence intervals (CIs): 71.7–77.4, 46.9–53.4, and 66.0–72.0] achieved LDL-C <2.59 mmol/L (100 mg/dL), LDL-C <1.81 mmol/L (70 mg/dL), and LDL-C <1.81 mmol/L (70 mg/dL) and/or by ≥50% reduction from baseline at Week 12, respectively (*Figure 1*). LDL-C was reduced to <2.59 mmol/L (100 mg/dL), <1.81 mmol/L (70 mg/dL), and <1.81 mmol/L (70 mg/dL) and/or by ≥50% reduction from baseline at Week 12, by the following proportions (95% CI) in the HeFH vs. non-FH subgroups, respectively: 69.0% (65.1–72.7) vs. 85.2% (80.8–88.9), 43.6% (39.6–47.7) vs. 62.6% (57.0–67.9), and 64.7% (60.7–68.5) vs. 77.4% (72.4–81.8; *Figure 1*).

Changes in other lipid parameters, both for the overall population and HeFH vs. non-FH subgroups, are summarized in *Table 3*.

Discussion

This analysis explored the safety and efficacy of alirocumab (75 mg and 150 mg Q2W) in patients with severe hypercholesterolaemia who were at high and very-high risk of CV events.

Table 1 Baseline characteristics overall and according to familial hypercholesterolaemia status (safety population)

	HeFH (*n*=636)	Non-FH (*n*=358)	Overall (*N*=994)
Age (years), mean (SD)	53.8 (11.6)	61.6 (10.1)	56.6 (11.7)
Gender, male, *n* (%)	371 (58.3)	254 (70.9)	625 (62.9)
Race, *n* (%)			
White/Caucasian	622 (97.8)	347 (96.9)	969 (97.5)
Black	6 (0.9)	4 (1.1)	10 (1.0)
Asian/Oriental	5 (0.8)	1 (0.3)	6 (0.6)
Multiracial	1 (0.2)	0 (0.0)	1 (0.1)
Other	2 (0.3)	6 (1.7)	8 (0.8)
Ethnicity, *n* (%)			
Hispanic	30 (4.7)	8 (2.2)	38 (3.8)
Not Hispanic	606 (95.3)	350 (97.8)	956 (96.2)
Body mass index (kg/m^2)			
Mean (SD)	27.8 (4.9)	28.3 (4.8)	28.0 (4.9)
HbA1c (%), mean (SD)	5.2 (1.2)	5.8 (1.2)	5.4 (1.2)
Fasting plasma glucose (mmol/L), mean (SD)	5.49 (1.15)	6.28 (2.05)	5.77 (1.58)
CPK (IU/L), mean (SD)	138.2 (86.6)	144.6 (106.7)	140.5 (94.3)
ALT (IU/L), mean (SD)	30.0 (16.2)	30.7 (17.2)	30.2 (16.6)
eGFR (mL/min/1.73 m^2), mean (SD)	89.6 (25.9)	84.9 (31.0)	87.9 (27.9)
Medical history, *n* (%)			
CHD or other CVD[a]	306 (48.1)	325 (90.8)	631 (63.5)
CHD risk equivalents[b]	117 (18.4)	118 (33.0)	235 (23.6)
Cerebrovascular disease	51 (8.0)	61 (17.0)	112 (11.3)
Any CV risk factors	472 (74.2)	283 (79.1)	755 (76.0)
Hypertension	273 (42.9)	247 (69.0)	520 (52.3)
Type 1 diabetes mellitus	7 (1.1)	6 (1.7)	13 (1.3)
Type 2 diabetes mellitus	51 (8.0)	90 (25.1)	141 (14.2)
Family history of premature CHD[b]	347 (54.6)	84 (23.5)	431 (43.4)
Lipids (mmol/L)			
Total cholesterol, mean (SD)	7.1 (1.8)	6.2 (1.2)	6.8 (1.6)
LDL-C, mean (SD)	5.1 (1.7)	4.1 (1.1)	4.7 (1.6)
HDL-C, mean (SD)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)
Non-HDL-C, mean (SD)	5.7 (1.8)	4.9 (1.4)	5.4 (1.7)
Triglycerides, median (Q1:Q3)	1.4 (1.1:1.9)	1.7 (1.2:2.3)	1.5 (1.1:2.1)
Concomitant LLT, *n* (%)			
Any LLT	596 (93.7)	277 (77.4)	873 (87.8)
Statins	555 (87.3)	203 (56.7)	758 (76.3)
High-intensity statins[c]	436 (68.6)	144 (40.2)	580 (58.4)
Other than statins	474 (74.5)	183 (51.1)	657 (66.1)
Ezetimibe	441 (69.3)	148 (41.3)	589 (59.3)

ALT, alanine aminotransferase; CHD, coronary heart disease; CPK, creatine phosphokinase; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; SD, standard deviation.

[a]CHD or other CVD includes acute myocardial infarction, silent myocardial infarction, unstable angina, coronary revascularization procedures, other clinically significant CHD (diagnosed by invasive or non-invasive testing), transient ischaemic attack, carotid artery stenosis ≥50%, or aortic abdominal aneurysm.

[b]CHD risk equivalents were defined according to items pre-listed in the electronic case report form, including: peripheral arterial disease, ischaemic stroke, chronic kidney disease, known history of type 1 or type 2 diabetes mellitus type and two or more additional risk factors, hypertension, microalbuminuria or macroalbuminuria or proteinuria (>2+ at screening), diabetic retinopathy, or known history of premature CHD (before 55 years of age in male or 65 years of age in female first-degree relatives).

[c]Defined in the electronic case report form as atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg, or simvastatin 80 mg daily.

Table 2 Overview of adverse event profile: treatment-emergent adverse events (safety population)

n (%) of patients	HeFH (*n* =636)	Non-FH (*n* =358)	Overall (*N*=994)
Any TEAE	424 (66.7)	288 (80.4)	712 (71.6)
Treatment-emergent SAE	68 (10.7)	93 (26.0)	161 (16.2)
SAEs occurring in >2 patients (in overall group)			
Angina pectoris	6 (0.9)	9 (2.5)	15 (1.5)
Unstable angina	4 (0.6)	8 (2.2)	12 (1.2)
Coronary artery disease	3 (0.5)	3 (0.8)	6 (0.6)
Coronary artery stenosis	3 (0.5)	3 (0.8)	6 (0.6)
Acute coronary syndrome	2 (0.3)	3 (0.8)	5 (0.5)
Acute myocardial infarction	4 (0.6)	1 (0.3)	5 (0.5)
Atrial fibrillation	2 (0.3)	3 (0.8)	5 (0.5)
Myocardial ischaemia	2 (0.3)	3 (0.8)	5 (0.5)
Vascular stent stenosis	2 (0.3)	2 (0.6)	4 (0.4)
Cardiac failure	1 (0.2)	2 (0.6)	3 (0.3)
Carotid artery stenosis	0	3 (0.8)	3 (0.3)
Diabetes mellitus	1 (0.2)	2 (0.6)	3 (0.3)
Diverticulitis	2 (0.3)	1 (0.3)	3 (0.3)
Myocardial infarction	2 (0.3)	1 (0.3)	3 (0.3)
Osteoarthritis	1 (0.2)	2 (0.6)	3 (0.3)
Pneumonia	1 (0.2)	2 (0.6)	3 (0.3)
Prostate cancer	0	3 (0.8)	3 (0.3)
Syncope	2 (0.3)	1 (0.3)	3 (0.3)
Tendon rupture	1 (0.2)	2 (0.6)	3 (0.3)
TEAEs leading to death	2 (0.3)	0	2 (0.2)
TEAEs leading to permanent treatment discontinuation	21 (3.3)	24 (6.7)	45 (4.5)
AEs of special interest			
Increase in ALT	8 (1.3)	3 (0.8)	11 (1.1)
Allergic event that requires consultation with another physician	1 (0.2)	2 (0.6)	3 (0.3)
Local injection-site reaction that is allergic in nature	0	0	0
Pregnancy	4 (0.6)	0	4 (0.4)
Symptomatic overdose with alirocumab	0	0	0
Neurologic event that requires additional examination/procedures and/or referral to a specialist	1 (0.2)	3 (0.8)	4 (0.4)
Neurocognitive event[a]	8 (1.3)	4 (1.1)	12 (1.2)
TEAEs occurring in ≥5% of patients (in overall group)			
Nasopharyngitis	44 (6.9)	34 (9.5)	78 (7.8)
Myalgia	44 (6.9)	27 (7.5)	71 (7.1)
Headache	43 (6.8)	19 (5.3)	62 (6.2)
Influenza	34 (5.3)	19 (5.3)	53 (5.3)

AE, adverse event; ALT, alanine aminotransferase; CMQ, custom MedDRA query; FDA, US Food and Drug Administration; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Neurocognitive events were defined using both sponsor and FDA CMQ lists.

Table 3 Changes in lipid parameters from baseline to Week 12 (modified-intention-to-treat population)

Mean (SD)	HeFH (*n* =603)	Non-FH (*n* =318)	Overall (*N*=921)
Total cholesterol			
Absolute change (mmol/L)	-2.7 (1.4)	-2.4 (1.0)	-2.6 (1.3)
Relative change (%)	-38.0 (16.1)	-38.8 (13.3)	-38.3 (15.2)
LDL-C			
Absolute change (mmol/L)	-2.7 (1.3)	-2.3 (0.9)	-2.6 (1.2)
Relative change (%)	-53.4 (21.2)	-57.6 (17.4)	-54.8 (20.1)
HDL-C			
Absolute change (mmol/L)	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)
Relative change (%)	4.4 (18.3)	4.4 (15.3)	4.4 (17.3)
Non-HDL-C			
Absolute change (mmol/L)	-2.7 (1.5)	-2.4 (1.3)	-2.6 (1.4)
Relative change (%)	-45.5 (33.1)	-46.7 (40.6)	-45.9 (35.8)
Triglycerides			
Absolute change (mmol/L)	-0.2 (0.6)	-0.3 (0.6)	-0.2 (0.6)
Relative change (%)	-7.2 (34.2)	-10.3 (33.5)	-8.3 (34.0)

FH, familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

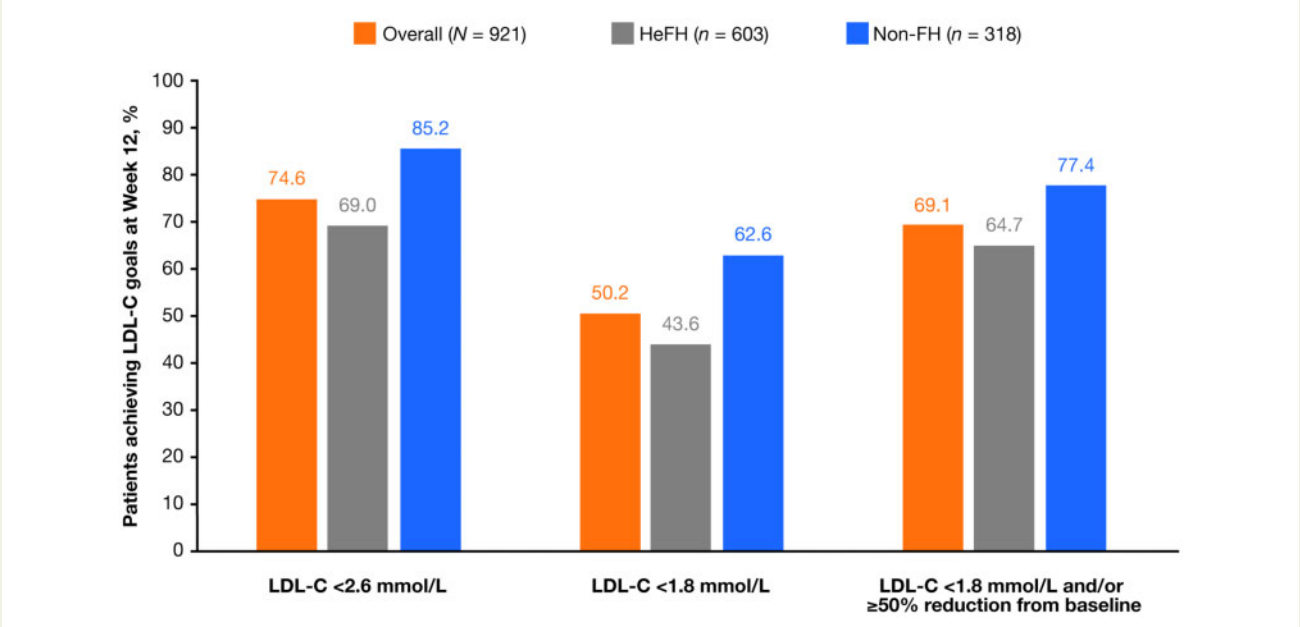

Figure 1 Proportion of patients achieving pre-defined low-density lipoprotein cholesterol goals at Week 12, both overall and according to familial hypercholesterolaemia status (modified intention-to-treat population). FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol.

Safety

Alirocumab was shown to be generally well tolerated with the incidence of TEAEs observed to be similar to those reported in previous alirocumab trials, both from a pooled analysis of Phase 2 and Phase 3 studies[21] and from analyses of patients with HeFH.[22–24] In addition, the incidence of AEs of special interest, including neurocognitive and neurologic events, were similar to those reported in a pooled analysis of previous Phase 2 and Phase 3 studies with alirocumab.[21]

Based on medical history, a higher proportion of CHD or other CVD was observed in the non-FH subgroup compared with the HeFH subgroup (90.8% vs. 48.1%). This could be explained in part by the study selection criteria, the older patient population and the

higher number of males in the non-FH subgroup compared with the HeFH subgroup. These factors could also explain why more TEAEs were reported in non-FH patients compared with patients with HeFH (80.4% vs. 66.7%, respectively). It is of interest to note that, although the mean age of patients with HeFH was 53.8 years, the proportion of HeFH patients with CHD (based on medical history) was relatively low (48.1%). This is lower than expected based on the clinical experience of some of the authors, but agrees with HeFH patient populations from previous Phase 3 clinical studies with alirocumab in which the proportion of HeFH patients with prior CVD ranged from 41.4% to 53.3% across treatment groups and trials.[24]

Efficacy

Alirocumab reduced LDL-C levels by over 50% from baseline to Week 12 in the overall patient population; analysis by subgroup showed that a reduction of a similar magnitude was seen in both the HeFH and non-FH subgroups. Reductions in LDL-C levels from baseline to Week 4 with alirocumab treatment were sustained throughout the study duration (up to 2 years). Additionally, no notable differences between the HeFH and non-FH groups in response to alirocumab were observed for effects on other lipid parameters (total cholesterol, non-HDL-C, triglycerides, and HDL-C). The level of LDL-C reduction in this study is similar to that reported with alirocumab in previous studies with patients with HeFH,[22,23,25] and with another PCSK9 inhibitor, evolocumab, during an open-label extension study with patients with HeFH.[26]

Understandably, patients whose starting dose of alirocumab was 150 mg Q2W had a higher baseline LDL-C level compared with those who started on the lower dose. A greater proportion of patients had at least one dose increase from alirocumab 75 to 150 mg Q2W, compared with those who had at least one dose decrease from alirocumab 150 to 75 mg Q2W. The main driver for alirocumab dose adjustment was a patient's LDL-C level, based on the clinical judgment of the physician.

Current European cholesterol guidelines recommend that, for managing elevated lipid levels in patients with a high total CV risk, an achievable treatment goal is a LDL-C level of <1.81 mmol/L (70 mg/dL) and at least a 50% reduction in LDL-C from baseline.[1] Here, 69.1% of the overall population (64.7% of HeFH patients and 77.4% of non-FH patients) achieved the pre-specified goal of LDL-C <1.81 mmol/L and/or ≥50% reduction from baseline following treatment with alirocumab. The current study includes patients at very-high total CV risk, for whom current guidelines recommend an LDL-C target of <1.4 mmol/L (55 mg/dL);[1] however, as ODYSSEY APPRISE was designed prior to these recommendations, the proportion of patients achieving LDL-C <1.4 mmol/L is not available. Additionally, cholesterol guidelines, both current and when the trial was initiated, recommend statins as first-line therapy to manage elevated LDL-C levels for patients at high/very-high CV risk.[1,2,18,19,27] Despite this recommendation, 23.7% of the overall population was not receiving concomitant statins (12.7 and 43.3% of the HeFH and non-FH subgroups, respectively). Although data on statin intolerance are not available, it may be a contributing factor. Furthermore, 31% of the HeFH and 59% of the non-FH subgroups were not receiving concomitant ezetimibe.

Limitations

Limitations of this analysis include the lack of a comparative control and, as a result of the open-label treatment design, the possible introduction of bias. However, the registry was carefully managed to ensure that the highest quality of data was obtained. The selection criteria resulted in a high proportion of patients with HeFH (64%), which may limit the applicability of the findings to other populations. In addition, data on new-onset diabetes and changes in lipoprotein(a) concentrations are not available. Of note, further analyses exploring the effect of concurrent statin intensity on the efficacy and safety of alirocumab are currently in development, as well as an analysis of the effect of treatment adherence.

Conclusion

Addition of alirocumab to the treatment of high-risk patients with severe hypercholesterolaemia receiving MTD ± LLTs is generally well tolerated and may provide an early and substantial reduction in LDL-C of ∼50%, which is sustained for a treatment duration of up to 2 years. This strategy could be of value to achieve the LDL-C levels recommended in contemporary clinical practice guidelines. Although the current analysis provides valuable insight into the management of patients with high/very-high CV risk, future research should focus on the safety and efficacy of alirocumab in real-life populations, without the close monitoring used in controlled registries and clinical trials.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Conflict of interest: D.G. has received research grant support from FH Canada, Aegerion (Novelion Therapeutics), Amgen, Akcea, Esperion, Gemphire, Ionis, Regeneron Pharmaceuticals, Inc., and Sanofi and has

served as a consultant for Amgen, Aegerion, Akcea, Ionis, Regeneron Pharmaceuticals, Inc., and Sanofi. J.L.L.-S. has received grants from Amgen, Pfizer, Bayer, Boehringer Ingleheim, and Sanofi and honoraria from Menarini. M.A. has received grants and personal honoraria for consultancy from Aegerion, Akcea, Ionis, Alfasigma, Amgen, Amryt, Pfizer, Regeneron Pharmaceuticals, Inc., and Sanofi. G.B. is employed by a company that is contracted to Sanofi. M.B. has served on the speakers' bureau and as an advisory board member for Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, Daichii Sankyo, Esperion, Freia Pharmaceuticals, Lilly, KRKA, MSD, Polfarmex, Polpharma, Resverlogix, Sanofi-aventis, Servier, and Valeant and grants from Sanofi and Valeant. A.L., M.L., and I.B. are employees of and stockholders in Sanofi. R.S. and G.S. are employees of stockholders in Regeneron Pharmaceuticals, Inc. P.H. has received a research grant from Amgen; and honoraria for consultancy from Amgen and Sanofi.

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