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A subgroup analysis of the ODYSSEY APPRISE study: Safety and efficacy of alirocumab in the Italian cohort

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Abstract *Background and aims:* ODYSSEY APPRISE trial evaluated efficacy and safety of alirocumab in 994 patients with hypercholesterolemia and high CV risk in a real-life setting. The aim of the present report is to detail on the Italian cohort enrolled and treated in the trial.
Methods and results: The methodology of the of the multinational, single-arm, Phase 3b open-label ODYSSEY APPRISE (Clinicaltrials.gov: NCT02476006) has been previously reported. 255 Italian patients were enrolled and treated according to the trial protocol.

Overall mean exposure to alirocumab was 83.3 ± 27.7 weeks. At week 12, LDL-C decreased by 51.3 ± 23.1% and this reduction was overall maintained for the duration of the study. A similar reduction was observed in patients with and without heterozygous familial hypercholesterolemia (HeFH 50.7% ± 23.9 vs. non-FH, 53.6% ± 19.6).

LDL-C was reduced below 1.8 mmol/L and/or by ≥ 50% reduction from baseline in 62% of patients overall (61% in HeFH and 67% in non-FH).

Alirocumab was similarly well tolerated in the Italian cohort as in the entire study population and the more common treatment emergent adverse events (TEAEs) were influenza, myalgia and nasopharyngitis. The incidence LDL-C levels <25 mg/dl and <15 mg/dl, was 8.2% and 2.9% respectively.
Conclusion: The efficacy and safety of alirocumab in a real-life setting, in the Italian subgroup of patients are consistent with findings in the entire study population and confirm that alirocumab is a beneficial approach to further reduce LDL-C levels in patients at high CV risk on maximally tolerated conventional lipid lowering treatment.
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1. Introduction

Patients with hypercholesterolemia have an increased risk for the development of atherosclerosis and coronary heart disease (CHD) [1,2] a leading cause of death worldwide [3–5].

Several epidemiological studies, Mendelian randomization studies, and randomized controlled trials (RCTs) have consistently proved that low density lipoprotein cholesterol (LDL-C) is a causal risk factor for the development of atherosclerotic cardiovascular disease (ASCVD) and that lowering LDL-C reduces the risk of ASCVD proportionally to the absolute achieved reduction in LDL-C [6].

In addition, Mendelian randomization studies support the concept that the effect of LDL-C on the risk of ASCVD is determined by the absolute magnitude and the total duration of exposure to LDL-C [7].

This concept is more evident in Heterozygous Familial Hypercholesterolemia (HeFH), a common codominant monogenic dyslipidemia characterized by lifelong very-high plasma levels of LDL-C and an increased CV risk [8,9].

The cornerstones of treatment for patients with HeFH typically include therapy with high-intensity statin or maximally tolerated dose of other statins, in most cases in combination with ezetimibe [1,2]. Likewise, hypercholesterolemic patients without FH (non-FH) with CHD, or a CHD risk equivalent, are at very high CV risk and therefore are also candidate to intensive lipid lowering therapies (LLTs) [1,2].

However, in clinical practice, many of HeFH and non-FH patients do not reach their guideline-recommended LDL-C treatment goals [10–12].

European and American guidelines have recently recommended on top of the standard treatment, the addition of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor for non-FH patients at very-high CV risk and for adult HeFH patients not achieving their LDL-C goal while treated with maximum tolerated dose of statin (MTD) and ezetimibe [1,2]. Alirocumab, a monoclonal antibody that inhibits PCSK9, has been shown in randomized controlled trials to significantly lower levels of LDL-C and other atherogenic lipoproteins compared with placebo or ezetimibe in patients with or without HeFH [13–16].

The prospective study ODYSSEY APPRISE (NCT02476006) was aimed to evaluate safety and efficacy of alirocumab in a real-life setting among high CV risk patients with or without HeFH and hypercholesterolemia inadequately controlled with MTD ± other LLT (excluding PCSK9 inhibitors) [17].

ODYSSEY APPRISE provided access to alirocumab ahead of commercial availability in Canada and 16 European countries, including Italy. Alirocumab was generally well tolerated and resulted in clinically significant LDL-C reductions.

Since the clinical trial protocol required an individualized dosing and treatment plan based on physician's judgment, it is worthy to evaluate how patients were managed, and how efficacy and safety outcomes varied according to tailored treatment in different health system settings, as information of this type can be used to implement treatment decisions in real-world clinical practice. The aim of this analysis was to examine the efficacy and safety of alirocumab in the patients enrolled in the ODYSSEY APPRISE in Italy.

2. Methods

The study design of ODYSSEY APPRISE (NCT02476006) has been previously reported [16). Briefly, this prospective, single-arm, Phase 3b open-label European/Canadian study was designed to obtain safety, and efficacy data of alirocumab in a real-life setting among patients with HeFH or with established CHD or a CHD risk equivalent, on top of background of stable MTD ± other LLT and in whom hypercholesterolemia was not adequately controlled [16].

MTD of statin was defined as rosuvastatin 20 mg or 40 mg daily, atorvastatin 40 mg or 80 mg daily or simvastatin 80 mg daily (if already on this dose for >1 year). Patients not able to be on any of the above statin doses were treated with the dose of daily atorvastatin, rosuvastatin or simvastatin which is considered appropriate for the patient as per the investigator's judgment or concerns. In exceptional and well-documented cases with documented medical history of adverse reactions to statins (e.g., rhabdomyolysis, transaminases elevations, muscle symptoms), another statin regimen could be used.

As per protocol, diagnosis of HeFH was documented, either by genotyping or by clinical criteria. For patients who were not genotyped, the clinical diagnosis was based on either the Simon Broome criteria or the WHO/Dutch Lipid Network criteria and the diagnostic must be "definite" [16]. Patients with genetic diagnosis of HeFH were 25.4%.

The open-label treatment period with alirocumab 75 mg or 150 mg every 2 weeks (Q2W) lasted for a minimum of 12 weeks and a maximum of 30 months and the dose could be adjusted from 75 mg to 150 mg Q2W, or vice versa, at the investigator's discretion, based on the patient's baseline characteristics, goal of therapy and treatment response.

The primary endpoint of the study was to assess safety parameters throughout the study. 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 $\geq$ 50% reduction from baseline [if LDL-C $\geq$ 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.

Overall, 994 patients were enrolled and treated in the ODYSSEY APPRISE and 88.3% of them completed the treatment period. 255 patients (25.6% of the entire cohort) were enrolled and treated at Italian study sites.

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 center. Written informed consent was obtained from all participating individuals prior to their involvement in study-related activities.

3. 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.

4. Results

4.1. Patient disposition and baseline characteristics

Main baseline characteristics are presented in Table 1. Most of enrolled patients were HeFH (206, 80.8% *vs* 49, 19.2% non-FH patients). Compared to non-FH, patients with HeFH had higher baseline LDL-C and were younger (Table 1). Median (Q1:Q3) time since diagnosis of dyslipidemia was 20.0 (10.0: 30.0) years and 6.0 (4.5: 17.0) years in the HeFH and non-FH subgroups, respectively. Overall, one third of the enrolled patients were females (86, 33.7%) and among them 76 (29.8%) were HeFH. Established CHD or other ASCVD were nearly twice as

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

	HeFH (N = 206)	Non-FH (N = 49)	Overall (N = 255)
Age (years), mean (SD)	53.8 (11.7)	60.8 (10.7)	55.1 (11.8)
Gender, male, n (%)	130 (63.1%)	39 (79.6%)	169 (66.3%)
Race [n (%)]			
White/Caucasian	203 (98.5%)	47 (95.9%)	250 (98.0%)
Black	1 (0.5%)	1 (2.0%)	2 (0.8%)
Asian/Oriental	1 (0.5%)	0 (0.0%)	1 (0.4%)
Multiracial	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	1 (0.5%)	1 (2.0%)	2 (0.8%)
Ethnicity [n (%)]			
Hispanic	19 (9.2%)	2 (4.1%)	21 (8.2%)
Not Hispanic	187 (90.8%)	47 (95.9%)	234 (91.8%)
Body Mass Index (kg/m^2)			
Mean (SD)	27.0 (4.9)	27.7 (4.8)	27.2 (4.9)
Medical history, *n* (%)			
CHD or other CVD[a]	92 (44.7)	41 (83.7)	133 (52.2)
CHD risk equivalents[b]	28 (13.6)	13 (26.5)	41 (16.1)
Cerebrovascular disease	15 (7.3)	11 (22.4)	26 (10.2)
Any CV risk factors	135 (65.5%)	43 (87.8%)	178 (69.8%)
Hypertension	85 (41.3%)	35 (71.4%)	120 (47.1%)
Type 1 diabetes mellitus	1 (0.5%)	1 (2.0%)	2 (0.8%)
Type 2 diabetes mellitus	23 (11.2%)	11 (22.4%)	34 (13.3%)
Family history of premature CHD[b]	80 (38.8%)	14 (28.6%)	94 (36.9%)
Lipids (mmol/L)			
Total cholesterol, mean (SD)	6.8 (1.4)	5.8 (1.0)	6.6 (1.4)
LDL-C, mean (SD)	4.8 (1.4)	3.7 (0.8)	4.6 (1.4)
HDL-C, mean (SD)	1.2 (0.3)	1.3 (0.3)	1.2 (0.3)
Non-HDL-C, mean (SD)	5.4 (1.4)	4.4 (1.0)	5.2 (1.4)
Triglycerides, median (Q1:Q3)	1.3 (0.9:1.8)	1.3 (0.9:2.0)	1.3 (0.9: 1.7)
Concomitant LLT, *n* (%)			
Any LLT	202 (98.1%)	46 (93.9%)	248 (97.3%)
Statins	191 (92.7%)	41 (83.7%)	232 (91.0%)
High-intensity statins[c]	148 (71.8%)	28 (57.1%)	176 (69.0)
Other than statins	162 (78.6%)	34 (69.4%)	196 (76.9%)
Ezetimibe	155 (75.2%)	30 (61.2%)	185 (72.5%)

CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; 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 (>2þ 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.

high more prevalent in the non-FH group compared to the HeFH group.

4.2. Alirocumab compliance and dose adjustment

Overall mean exposure to alirocumab was 83.3 ± 27.7 weeks with a median (Q1:Q3) duration of 82.1 (64.4:108.6) weeks. Among the 255 treated patients, 235 (92.2%) completed the treatment period and 20 (7.8%) of patients did not. The most common reason cited for discontinuation was unwillingness of continue treatment for personal reason [13/20 patients (65%)]. Exposure >48 weeks was 92.7% among HeFH (191/206 safety population) and 95.9% among non-FH patients (47/49 safety population).

The initial alirocumab dose (75 or 150 mg Q2W) and up or down titration, were decided by the physicians' based on clinical judgment and based mainly on LDL goals and on treatment response. The baseline LDL-C in patients treated with initial dose of 75 mg of alirocumab [196/255 (76.9%)] was 174.6 ± 53.7 mg/dl (4.5 ± 1.4 mmol/L); for patients initially treated with alirocumab 150 mg [59/255 (23.1%)] baseline LDL-C was 199.5 ± 53.2 mg/dl (5.2 ± 1.4 mmol/L). The initial dose of alirocumab 150 mg was more frequently administered to HeFH patients [54/206 (26.2%) vs 5/49 (10.2%) of non-FH patients].

Among the 188 patients whose initial dose of alirocumab 75 mg (mITT population with at least 12 weeks of follow-up), 59 (31.4%) had at least one dose increase to alirocumab 150 mg Q2W; the median time to first dose increase was 23.7 (Q1:Q3-12.1:36.1) weeks. In most cases (98.3%), dose adjustment was motivated by the need of managing inadequate lipid values. Most of patients who required an up titration to alirocumab 150 mg Q2W were HeFH [50/59 (84.7%)] and the median time to first dose increase was much shorter than in non-FH (13.0 weeks; Q1:Q3 - 12.1: 35.4).

Patients who received only a single dose increase of alirocumab during the study (n = 57; 23.3%), the mean LDL-C decreased from 3.4 ± 1.2 mmol/L [131.9 ± 46.7 mg/dl] to 2.6 ± 1.2 mmol/L [98.9 ± 46 mg/dl].

In the subgroup on starting dose of alirocumab 150 mg (n = 57; mITT population), only 1 (1.75%) patient had at least one dose decrease to alirocumab 75 mg Q2W at 72.1 (72.1:72.1) weeks. In this patient, LDL-C levels remained quite comparable after dose decrease (107.3 mg/dl vs 100.8 mg/dl).

4.3. Safety

Overall, treatment-emergent adverse events (TEAEs) were reported in 51.0% of patients (n = 130; Table 3); in the subgroup analysis, TEAEs were reported in 50.5% of HeFH and 53.1% of non-FH patients, respectively. No deaths were occurred during the treatment-emergent adverse event period.

Overall, 7 patients (2.7%) permanently discontinued treatment due to a TEAE; TEAEs leading to permanent treatment discontinuation (with at least one TEAE) were thrombocytopenia, neutropenia, conjunctivitis, injection site hypersensitivity and hypertransaminasaemia [one patient each (0.4%)]. Treatment-emergent SAEs were reported in 33 patients (12.9%) overall (Table 3). One patient (0.4%) experienced seizures and this was a treatment-emergent SAEs considered to be related to alirocumab by the investigator.

TEAEs corresponding to AEs of special interest (prespecified in the study protocol) occurred in 2 patients (0.8%) overall (Table 3).

Other common TEAEs are summarized in Table 3.

The incidence of very low LDL-C levels (<25 mg/dl and <15 mg/dl) at least once during the observational period in the overall mITT population (245 patients) was 8.2% (20) and 2.9% (7) respectively. LDL-C levels <25/mg/dl and <15 mg/dl were recorded in 15 (7.6%) and 6 (3.0%) of HeFH and in 5 (10.4%) < 25 mg/dl and 1 (2.1%) of non-FH. Regardless of the dose at the time of the occurrence of very

Table 2 Changes in lipid parameters from baseline to Week 12 (modified-intention-to-treat population).

Mean (SD)	HeFH (N = 197)	Non-FH (N = 48)	Overall (N = 245)
Total Cholesterol			
Absolute change (mmol/L)	−2.5 (1.4)	−2.1 (1.0)	−2.4 (1.4)
Relative change (%)	−35.8 (18.2)	−35.3 (15.5)	−35.7 (17.7)
LDL-C			
Absolute change (mmol/L)	−2.5 (1.3)	−2.0 (0.9)	−2.4 (1.3)
Relative change (%)	−50.7 (23.9)	−53.6 (19.6)	−51.3 (23.1)
HDL-C			
Absolute change (mmol/L)	0.05 (0.21)	0.026 (0.218)	0.043 (0.215)
Relative change (%)	4.9 (16.6)	3.8 (16.6)	4.7 (16.5)
Non-HDL-C			
Absolute change (mmol/L)	−2.5 (1.4)	−2.0 (0.9)	−2.4 (1.4)
Relative change (%)	−45.1 (23.6)	−45.1 (18.2)	−45.1 (22.6)
Tryglicerides			
Absolute change (mmol/L)	−0.1 (0.5)	−0.2 (0.5)	−0.1 (0.5)
Relative change (%)	−4.1 (36.1)	−4.3 (41.8)	−4.2 (37.2)

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

Table 3 Overview of adverse event profile: treatment-emergent adverse events (safety population).

N (%) of patients	Overall (N = 255)	HeFH (N = 206)	Non-FH (N = 49)
Any TEAE	130 (51.0%)	104 (50.5%)	26 (53.1%)
Treatment emergent SAE	33 (12.9%)	23 (11.2%)	10 (20.4%)
SAEs occurring in >2 patients (in overall group)			
Angina pectoris	2 (0.8%)	1 (0.5%)	1 (2.0%)
Unstable angina	2 (0.8%)	0 (0.0%)	2 (4.1%)
Coronary artery disease	2 (0.8%)	2 (1.0%)	0 (0.0%)
AEs of special interest			
Increase in ALT	2 (0.8%)	2 (1.0%)	0 (0.0%)
Allergic event that requires consultation with another physician -	0 (0.0%)	0 (0.0%)	0 (0.0%)
Local injection-site reaction that is allergic in nature	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pregnancy	3 (1.2%)	3 (1.5%)	0 (0.0%)
Symptomatic overdose with alirocumab	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neurologic event that requires additional examination/procedures and/or referral to a specialist	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neurocognitive event[a]	2 (0.8%)	1 (0.5%)	1 (2.0%)
TEAEs occurring in ≥ 2% of patients (in overall group)			
Nasopharyngitis	5 (2.0%)	2 (1.0%)	3 (6.1%)
Myalgia	7 (2.7%)	5 (2.4%)	2 (4.1%)
Influenza	16 (6.3%)	14 (6.8%)	2 (4.1%)
TEAEs leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAEs leading to permanent treatment discontinuation	7 (2.7%)	5 (2.4%)	2 (4.1%)

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.

low LDL-C value (either 150 mg or 75 mg) no action was taken towards the treatment and in none of the patients the dose was modified.

4.4. Efficacy

Overall, LDL-C decreased by 2.4 ± 1.4 mmol/L [93.6 ± 53.1 mg/dl] from baseline to Week 12 (−51.3% mITT population; Table 2); this reduction was maintained for the duration of the study (Fig. 2). 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 (50.7% vs. 53.6%, respectively; Table 2 and Fig. 2). At 96 and 120 weeks the LDL-C mean reduction was slightly less pronounced in non-FH subgroup compared to the HeFH group (48% vs 53% and 43% vs 53%).

The proportion of patients HeFH and non-FH achieving pre-defined low-density lipoprotein cholesterol goals at week 12 are shown in Fig. 1.

In the overall study population, 42.0%, and 62.0% of patients [95% confidence intervals (CIs): 35.4−48.1, and 55.6−68.1] achieved 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 (Fig. 1). Overall, 29.4% of patients (95% CIs: 23.8−35.5%) achieved LDL-C < 1.4 mmol/l (<55 mg/dl) (Fig. 1) and HeFH patients, were less likely to achieve the goal (24% *vs* 50% of non-FH patients).

Changes in other lipid parameters, both for the overall population and HeFH vs. non-FH subgroups, are summarized in Table 2.

4.5. Concomitant lipid-lowering therapies

During the study, 248/255 (97.3%) 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 (98.1% vs. 93.9%), statins (92.7% vs. 83.7%), or ezetimibe (75.2% vs. 61.2%) (Table 1). Patients with HeFH were more likely than non-FH patients to be on high intensity statins [148/206 (71.8%) and 28/49 (57.1%) respectively] and ezetimibe (155/206, 75.2% *vs* 30/49, 61.2%) (Table 1). Of the 223 patients receiving concomitant statins, 31 patients (26 HeFH and 5 non-FH patients) (13.9%) temporarily, or permanently discontinued statins during the trial (26/197 - 14,21% of HeFH *vs* 5/48 -12.50% of non-FH patients).

11 patients (21.52%) temporarily, or permanently discontinued statins during the trial; 5 out 11 patients, up titrated before statin discontinuation alirocumab from 75 mg to 150 mg and 6 out of 11 patients were on stable dose of alirocumab 150 mg.

5. Discussion

Hypercholesterolemic patients with or without HeFH at very high CV risk are difficult to manage in the real world setting with standard lipid lowering therapies (LLTs) including intensive treatment with high-intensity statins in combination with ezetimibe [9−12].

The ODYSSEY APPRISE trial was designed to investigate the safety and efficacy of alirocumab (75 mg and 150 mg

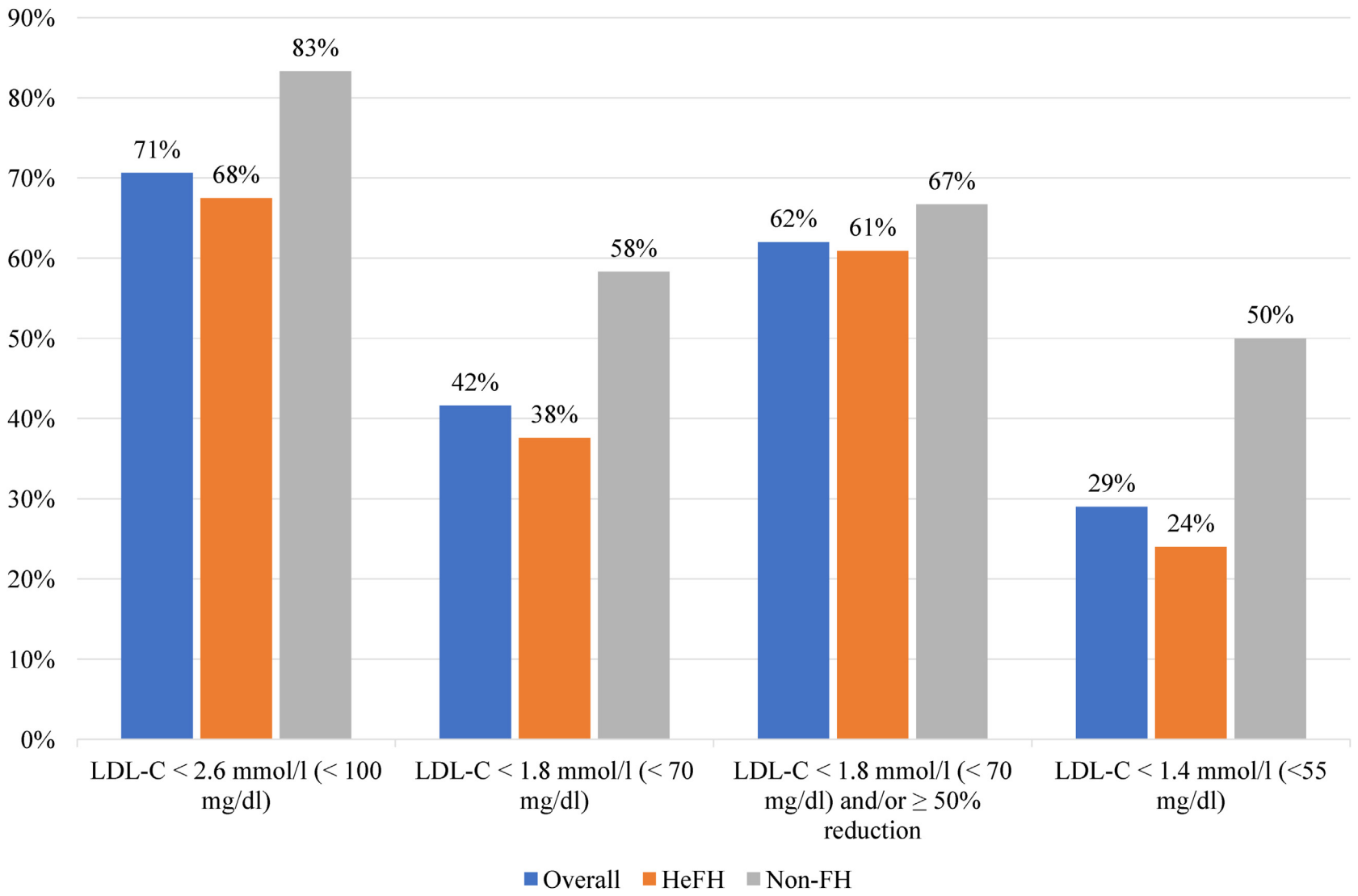

Figure 1 Proportion of patients achieving pre-defined low-density lipoprotein cholesterol goals at Week 12, both overall and according to familial hypercholesterolemia status (modified intention-to-treat population). FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia;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

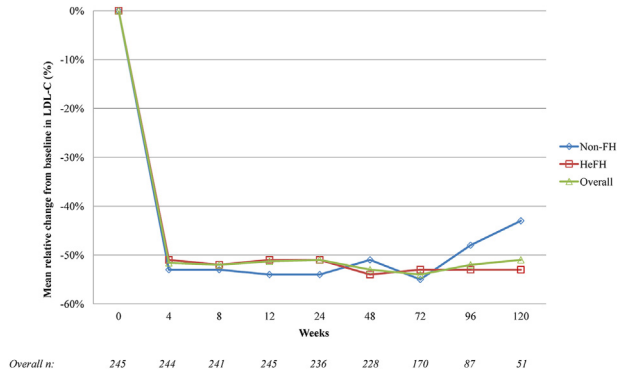

Figure 2 LDL-C reduction from baseline to week 120 for the overall Italian population and according to FH status. FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

Q2W) in this difficult to treat population of patients at high and very-high risk of CV events [17].

The large subset of Italian patients (255/994, 25.6% of the entire cohort) treated in the clinical trial, motivated this analysis with the attempt to highlight any distinctive features in safety and efficacy, increasing the knowledge on the real-world management of patients at high CV risk with inadequate LDL-C levels.

The overall results of the ODYSSEY APPRISE trial showed that the addition of alirocumab to the treatment of high-risk patients with severe hypercholesterolemia receiving MTD ± LLTs is generally well tolerated, and it effectively and sustainably reduces LDL-C of ∼ 50% [17].

In the Italian cohort, patients with HeFH were the 80.8% (206/255) and consistently with the findings of the overall study population, were younger (53.8 vs 60.8 years) and based on clinical history had a lower proportion of CHD or other CVD compared with the non-FH subgroup (44.7% vs 83.7%).

Alirocumab was mostly well tolerated, with 12.9% of patients reporting TEAEs. This is a lower rate compared with reported TEAEs in the complete analysis of the ODYSSEY APPRISE but overall similar to those reported in a pooled analysis of alirocumab clinical studies in both HeFH and non-FH patients [18–21]. Similarly, the incidence of AEs of special interest of any kind were similar to those previously reported in studies with alirocumab [18]. Influenza, myalgia and nasopharyngitis were the most common TEAEs. The incidence of AEs of special interest, including neurocognitive and neurologic events, were like those reported in the ODYSSEY APPRISE overall analysis and in previous studies with alirocumab [17–21].

At week 12, alirocumab reduced LDL-C levels from baseline by 51.3% and a reduction of a similar extent was seen in both the HeFH and non-FH subgroups (50.7% and 53.3% respectively). This magnitude of reduction was attained after 4 weeks of treatment and it was persistent up to 120 weeks. The observed alirocumab efficacy was more pronounced of that observed in a pooled analysis including 4629 patients with high cardiovascular risk from eight ODYSSEY Phase III studies, in particular those with the alirocumab 75-mg Q2W dosing regimen with a possible dose adjustment to 150 mg Q2W at week 12 (44.5% LDL-C reduction) [22]. In non-FH, LDL-C reduction seemed to be less sustained at 120 weeks (43% reduction), but this observation may be related, either to the small number of non-FH patients belonging to this subgroup (12) or to a lower adherence to statins and/or other LLTs although this latter analysis is not available yet.

Effects on other lipid parameters (total cholesterol, non-HDL-C, triglycerides, and HDL-C) in response to alirocumab, were similar in both HeFH and non-FH groups and comparable with that observed in the overall population of the trial [17].

The starting dose of alirocumab 150 mg Q2W was more frequently administered, based on the clinical judgment of physicians, to patients who had a higher baseline LDL-C level and as expected most patients who required an up titration to alirocumab from 75 to 150 mg Q2W were HeFH (50/84.7%). In both groups the main driver for alirocumab dose adjustment was a patient's LDL-C level. Notably, only one patient had at least one dose decrease from alirocumab 150 to 75 mg Q2W.

Although the MTD ± other LLTs should have been the recommend first-line therapy, in the ODYSSEY APPRISE 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). In the Italian subgroup, the proportion of patients on statins was overall high (91%) and 97.3% of patients were taking any LLT. Thus, compared to the overall analysis a lower percentage of HeFH (7.3%) and of non-FH (12.7%), were not receiving concomitant statins. Furthermore, concomitant treatment with ezetimibe was more frequent in the Italian subgroup (75.2% vs 69% of the HeFH and 61.2% vs 41% of the non-FH).

According to the current European dyslipidemias' guidelines [1], the proportion of patients who achieved the recommended treatment goal of LDL-C level of <1.81 mmol/L (70 mg/dL) and/or at least a 50% reduction in LDL-C from baseline, was 62% of the overall Italian population (60.9% of HeFH patients and 67% of non-FH patients) following treatment with alirocumab.

In the full analysis of the APPRISE [17], the proportion of patients achieving LDL-C <1.4 mmol/L was not available. Our analysis show that overall, in the Italian cohort only 29% of patients were able to achieve LDL-C <1.4 mmol/l (55 mg/dl) and the attainment of this goal was harder in HeFH patients. In a setting of a large HMO (health maintenance organization) in Israel, 38% of patients at very high cardiovascular risk reached LDL-C < 1.4 mmol/l (55 mg/dl) under PCSK9 inhibitors therapy (23). However, subset of Italian patients of the ODISSEY APRRISE showed higher baseline LDL-C (178 mg/dl *vs* 163 mg/dl) and enrolled patients with "definite" FH rather than "possible" FH [23].

Overall mean exposure to alirocumab was 83.3 ± 27.7 weeks with a median duration of 82.1 (Q1:Q3 - 64.4: 108.6) weeks. Among the 255 treated patients, 92.2% completed

the treatment period and 7.8% of patients did not, and the most common reason cited for discontinuation was unwillingness of continue treatment for personal reason [13/20 patients (65%)].

After marketing of PCSK9 inhibitors (alirocumab and evolocumab) a growing number of studies have been designed to evaluate the efficacy and tolerability of these drugs in the current clinical practice in different care settings. Similarly, to the ODISSEY APPRISE, these studies have focused on patients with a history of ASCVD and/or HeFH, who did not achieve adequate LDL-C control despite being treated with maximum tolerated lipid-lowering therapy (23–28).

Overall, in retrospective [23–25] and prospective [16,26–28] real-life studies, treatment either with alirocumab or evolocumab was safe and effectively reduces LDL-C from roughly 40%–60% also in patients with statin intolerance [27]. Data collection in the real-life setting regarding difference in effectiveness between women and men [29], rate of hypo responders [29] and non-adherents to treatment [23,29] need further investigations.

6. Conclusion

The overall safety and efficacy of alirocumab in the Italian patient subgroup of the ODYSSEY APPRISE trial was consistent with that seen in the full study population [16] and in the smaller Belgian sub study sample [30]. With the awareness of the limitations of the study [16] this subanalysis confirms that alirocumab may be a suitable treatment option for patients with hypercholesterolemia, on MTD ± LLTs, at high cardiovascular risk with or without HeFH.

Italian regulatory agency (Agenzia Italiana del Farmaco; AIFA) have defined eligibility criteria for prescribing PCSK9 inhibitors in clinical practice and treatment with PCSK9 inhibitors (alirocumab and evolocumab) can only be initiated and monitored by referral centers. AIFA consider eligible for prescription patients at high and very high CV risk and LDL-C concentration persistently above 130 mg/dl or 100 mg/dL respectively despite the use of maximally tolerated statin dose in combination with ezetimibe (http://www.agenziafarmaco.gov.it).

The patients high and very high CV risk included and treated in the ODYSSEY APPRISE in Italy, were in large proportion on high intensity statins and ezetimibe but still mean LDL-C levels were far from treatment goals recommended by current clinical practice guidelines [1] and they have been eligible based on requested criteria of the Italian regulatory agency.

It is crucial to identify those patients who may benefit the most from more intensive treatment with alirocumab in association with conventional lipid lowering treatment.

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Declaration of competing interest

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KG and GT, Sanofi employee, may hold shares and/or stock options in the company.

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S.N., K.B., R.G., C.B., P.R., S.G., G.M., and M.P. have nothing to disclose.

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