Regional variations in alirocumab dosing patterns during an open-label extension study in patients with heterozygous familial hypercholesterolaemia

Gisle Langslet,¹ G Kees Hovingh,² John R Guyton,³ Marie T Baccara-Dinet,⁴ Alexia Letierce,⁵ Garen Manvelian,⁶ Michel Farnier⁷

¹*Lipid Clinic, Oslo University Hospital, Oslo, Norway;* ²*Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands;* ³*Duke University Medical Center, Durham, North Carolina, USA;* ⁴*Clinical Development, R&D, Sanofi, Montpellier, France;* ⁵*Sanofi, Chilly-Mazarin, France;* ⁶*Regeneron Pharmaceuticals, Inc., Tarrytown, New York, USA;* ⁷*Lipid Clinic, Point Médical and Department of Cardiology, CHU Dijon-Bourgogne, Dijon, France*

Background

- Patients with heterozygous familial hypercholesterolaemia (HeFH) are characterised by elevated levels of low-density lipoprotein cholesterol (LDL-C).¹⁻³
 - In clinical practice, many patients do not reach their LDL-C treatment goals, remaining at high risk of atherosclerotic cardiovascular disease (ASCVD).⁴⁻⁷
- Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) with the fully human monoclonal antibody alirocumab significantly reduced LDL-C levels in ODYSSEY Phase 3 trials versus placebo, including in HeFH patients over double-blind periods of 78 weeks (FH I,⁸ FH II,⁸ LONG TERM⁹ and HIGH FH trials¹⁰).
- The alirocumab open-label extension study ODYSSEY OLE (NCT01954394) included patients diagnosed with HeFH who had completed previous Phase 3 parent studies⁸⁻¹⁰ and was designed to assess the long-term safety and efficacy of alirocumab (2.5 years median alirocumab exposure during OLE).¹¹
 - Alirocumab was administered subcutaneously in two dosages (75 mg or 150 mg every 2 weeks [Q2W]), with dose adjustment per physician's clinical judgement.
- The aim of this *post-hoc* analysis was to examine the regional differences in physician dosing decisions during OLE.

Methods

- Patients with HeFH were eligible to enter OLE if they had completed one of four parent studies; the current analyses only include data from patients who received alirocumab 75 mg Q2W at OLE entry (patients from FH I,⁸ FH II⁸ and LONG TERM⁹ studies).
 - These patients received alirocumab 75 mg Q2W at OLE entry irrespective of treatment (alirocumab or placebo) or alirocumab dose received during the parent studies.
- The OLE study included a treatment period of up to 168 weeks and an additional 8-week follow-up period for patients who completed the study or discontinued early.
- LDL-C levels were blinded to the patient and physician from Day 1 until Week 8; subsequently, LDL-C values were communicated to physicians. From Week 12, physicians could adjust the dose from alirocumab 75 mg Q2W to 150 mg Q2W, or vice versa, based on their clinical judgement and the patient's LDL-C level.
- Throughout the treatment period patients received, if possible, the same stable maximally tolerated statin dose ± other lipid-lowering therapies (LLTs) as during the parent study.
- Adherence to alirocumab treatment was assessed according to patient's diary data; percent adherence was defined as 100 – (percent of days with below-planned dosing + percent of days with above-planned dosing).
- Data were assessed in four regions: Western Europe, North America, Eastern Europe and the rest of the world (ROW).
 - The interpretation of ROW data is limited as this category includes countries not related geographically (Figure 1).

Figure 1. Regional distribution of patients in ODYSSEY OLE included in current analysis (safety population)

Results

Baseline characteristics

- The regional distribution of patients (n=909) is presented in Figure 1; just over half (50.6%) were from Western Europe.
- Baseline characteristics are shown in Table 1, both overall and according to region.
 - Overall, 46.9% of patients had ASCVD and 50.1% were at very-high cardiovascular risk (defined as patients with CHD or CHD risk equivalents, according to European Society of Cardiology/European Atherosclerosis Society 2016 guidelines).⁴
 - Baseline mean LDL-C levels were higher in ROW and North America (3.5 and 3.4 mmol/L [133.4 and 132.1 mg/dL], respectively) compared with Western Europe and Eastern Europe (3.1 and 2.4 mmol/L [120.2 and 93.6 mg/dL], respectively).

Treatment adherence

- Mean overall treatment adherence to alirocumab was high across all regions, ranging from 97.7% to 98.7% (Figure 2); overall, 99.2% of patients were ≥80% treatment adherent.
- Overall, 21.9% of patients had a change in their background statin medication during OLE, including interruptions (8.0%), discontinuations (3.7%), change in statin type (4.4%), and dose increases (4.3%) or dose decreases (10.0%).
 - There were fewer changes in background statin medication in Eastern Europe (13.3%) compared with other regions (Western Europe, 23.7%; North America, 21.0%; ROW, 23.2%).
- Similarly, 20.7% of patients had a change in their background non-statin LLTs: interruptions, 5.2%; discontinuations, 11.3%; change in LLT type, 5.8%; dose increases, 0.6% and dose decreases, 1.2%.
 - There were fewer changes in non-statin LLTs in Eastern Europe and ROW (12.4% and 13.1%, respectively) compared with North America and Western Europe (24.4% and 23.9%, respectively).

Table 1. Baseline characteristics at OLE baseline according to region (safety population)

	North America (n=176)	Western Europe (n=460)	Eastern Europe (n=105)	ROW (n=168)	All (n=909)
Age, years, mean (SD)	53.1 (12.3)	54.7 (11.3)	54.7 (12.7)	55.9 (11.6)	54.6 (11.7)
Male, n (%)	111 (63.1)	267 (58.0)	56 (53.3)	76 (45.2)	510 (56.1)
Race, n (%)					
White	160 (90.9)	454 (98.7)	105 (100)	148 (88.1)	867 (95.4)
Black or African American	3 (1.7)	0	0	0	3 (0.3)
Asian	3 (1.7)	4 (0.9)	0	1 (0.6)	8 (0.9)
Ethnicity, n (%)					
Hispanic or Latino	12 (6.8)	17 (3.7)	0	5 (3.0)	34 (3.7)
Not Hispanic or Latino	164 (93.2)	437 (95.0)	105 (100)	163 (97.0)	869 (95.6)
Unknown	0	6 (1.3)	0	0	6 (0.7)
BMI, kg/m ² , mean (SD)	29.8 (5.3)	28.8 (4.7)	29.1 (4.5)	30.3 (6.0)	29.3 (5.1)
ASCVD, ^a n (%)	93 (52.8)	209 (45.4)	49 (46.7)	75 (44.6)	426 (46.9)
CHD ^b	90 (51.1)	200 (43.5)	42 (40.0)	73 (43.5)	405 (44.6)
Very-high CV risk, ^c n (%)	99 (56.3)	221 (48.0)	52 (49.5)	83 (49.4)	455 (50.1)
High CV risk, ^d n (%)	77 (43.8)	239 (52.0)	53 (50.5)	85 (50.6)	454 (49.9)
Calculated LDL-C, mmol/L, mean (SD)	3.4 (1.7)	3.1 (1.7)	2.4 (1.6)	3.5 (1.8)	3.2 (1.7)

^aASCVD defined as CHD, ischaemic stroke or peripheral artery disease. ^bCHD defined according to the items pre-listed in the e-CRF of the parent study, based on medical history and also including adverse events observed during the parent study and during the pre-treatment period of the OLE study. ^cVery-high CV risk defined as patients with CHD or CHD risk equivalents according to 2016 ESC/EAS Guidelines.⁴ ^dHigh CV risk defined as all other patients. ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHD, coronary heart disease; CV, cardiovascular; e-CRF, electronic case report form; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol; ROW, rest of world; SD, standard deviation.

Figure 2. Mean overall alirocumab treatment adherence by region during OLE (safety population)

LDL-C levels used by physicians for alirocumab dose decisions

- Mean LDL-C values used by physicians for the decision to increase the dose from alirocumab 75 mg Q2W to 150 mg Q2W were higher in Eastern Europe and ROW (3.7 and 3.8 mmol/L [144.0 and 145.2 mg/dL], respectively) compared with Western Europe and North America (3.1 and 3.3 mmol/L [118.6 and 126.6 mg/dL], respectively; Table 2).

Table 2. Summary of patients with dose adjustment decisions and LDL-C levels used to guide the decisions by dose adjustment status and region (safety population)^a

	North America (n=174)	Western Europe (n=449)	Eastern Europe (n=102)	ROW (n=165)	All (n=890)
Patients with any dose decision to maintain on 75 mg Q2W, %	59.2	74.6	84.3	75.8	72.9
LDL-C at time of decision, mean (SD), mmol/L	1.9 (1.0)	1.7 (0.7)	2.0 (1.1)	1.9 (0.8)	1.8 (0.8)
Patients with any dose decision to increase to 150 mg Q2W, %	56.3	41.2	28.4	44.8	43.4
LDL-C at time of decision, mean (SD), mmol/L	3.3 (1.2)	3.1 (1.3)	3.7 (1.3)	3.8 (1.5)	3.3 (1.3)

^aPatients who had alirocumab dose adjustment due to reasons other than LDL-C values were censored at the time before the corresponding dose adjustment. Dose adjustment from 150 mg Q2W to 75 mg Q2W was also possible during ODYSSEY OLE; however, due to the overall low number of these dose decisions (n/N [%] of 22/367 [6.0] for the overall population), these data are not presented here. LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; ROW, rest of world; SD, standard deviation.

- Similarly, the mean LDL-C value at the time of dose decision to maintain on alirocumab 150 mg Q2W was higher in ROW and Eastern Europe (2.6 and 2.7 mmol/L [100.3 and 102.6 mg/dL], respectively) compared with Western Europe and North America (2.1 and 2.3 mmol/L [82.3 and 87.3 mg/dL], respectively).
 - The proportion of dose decisions to maintain at 150 mg Q2W with LDL-C at the time of decision below 0.6 mmol/L (25 mg/dL) was higher in North America, Western Europe and Eastern Europe (ranging from 3.3% to 4.5%) compared with ROW (1.5%).
- Dose decrease from alirocumab 150 mg Q2W to 75 mg Q2W was also possible, however, as there were only a low number (22 decisions, with maximal LDL-C at time of dose decision of 2.4 mmol/L [93.0 mg/dL] for overall population), there were too few to analyse by region.
- However, irrespective of region, the mean LDL-C at the time of decision to maintain the dose at alirocumab 75 mg Q2W was approximately 1.8 mmol/L (69.3 mg/dL; Table 2).
- When dose decisions were analysed according to ASCVD status, the mean LDL-C value at the time of any dose decision was lower for patients with versus without ASCVD, both overall and across all regions (Figure 3A–C).
 - The proportion of patients with dose adjustment decisions according to ASCVD status at baseline are summarised both overall and by region in Table 3.

Table 3. Summary of patients with dose adjustment decisions by region according to patient ASCVD status at baseline (safety population)

	North America	Western Europe	Eastern Europe	ROW	All
Proportion of patients with any dose decision to maintain on 75 mg Q2W, %					
With ASCVD	57.3	67.4	80.4	76.9	68.4
Without ASCVD	60.0	73.7	79.6	70.0	71.3
Proportion of patients with any dose decision to increase to 150 mg Q2W, %					
With ASCVD	56.3	45.1	15.7	46.2	44.3
Without ASCVD	53.8	35.2	38.9	42.2	40.2

ASCVD, atherosclerotic cardiovascular disease; Q2W, every 2 weeks; ROW, rest of world.

Figure 3. Summary of LDL-C levels used to guide dose decisions by region for A) overall population, B) patients with ASCVD at baseline and C) patients without ASCVD at baseline (safety population)

Safety

- The overall safety of alirocumab in OLE has been previously reported, both for the overall OLE population¹¹ and for the current analysis population.¹²
 - During OLE (median treatment duration of 131.7 weeks for the patients in the current analysis), alirocumab was shown to have no unexpected long-term safety concerns.

Conclusions

- In this ODYSSEY OLE study of patients with HeFH, we observed regional differences in the pattern of physicians' decisions to adjust alirocumab dose; LDL-C values at the time of decision to increase from alirocumab 75 mg to 150 mg Q2W were higher in Eastern Europe and ROW compared with Western Europe and North America.
- The observed variations in clinical treatment decisions suggest that physicians may perceive the severity of HeFH and/or the treatment of HeFH differently depending on their region.
- For HeFH patients with ASCVD, LDL-C values at the time of all alirocumab dose decisions were lower compared with LDL-C values for patients without ASCVD, as expected per guidelines.

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