Durability of Alirocumab Effect: Data from an Open-Label Extension to the ODYSSEY Program for Patients with Heterozygous Familial Hypercholesterolemia

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INTRODUCTION

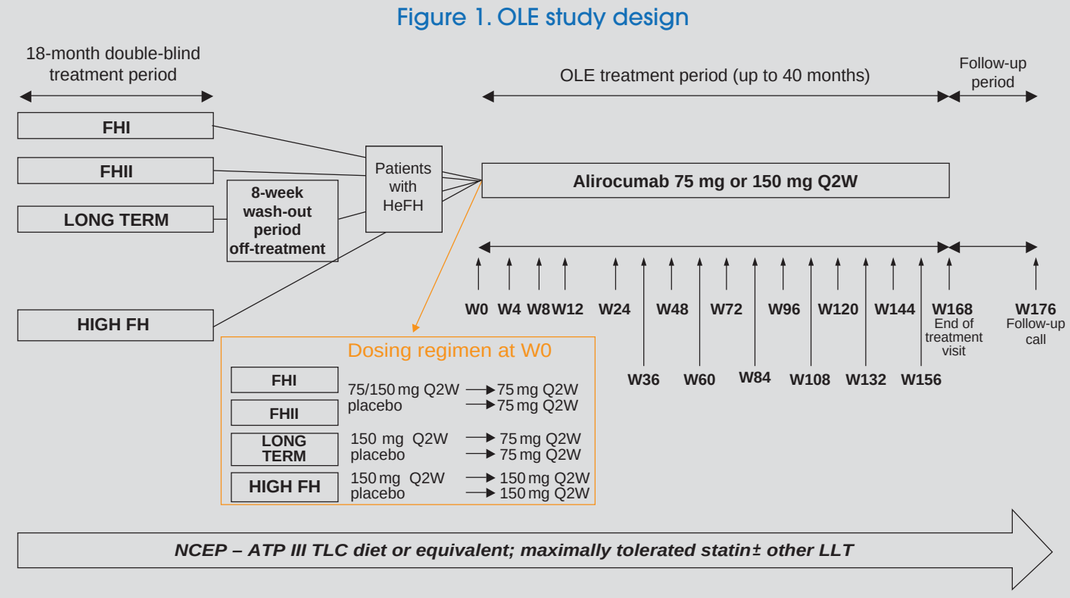
- In clinical practice, a large proportion of patients with HeFH do not reach their LDL-C treatment goals and remain at increased risk of ASCVD as a result.[1,2]
- Alirocumab, a fully human monoclonal antibody against PCSK9, significantly improved levels of LDL-C and other lipids versus placebo in patients with or without HeFH.[3–6]
- The ongoing ODYSSEY OLE study (NCT01954394) of four Phase 3 trials (FH I,[3] FH II,[3] LONG TERM,[4] and HIGH FH[5]) is assessing the long-term efficacy and safety of alirocumab in patients with HeFH for up to 40 months.
- The aim of this analysis was to assess the overall durability of effect of alirocumab in patients with HeFH using data from ODYSSEY OLE.

ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; OLE, open-label extension; PCSK9, proprotein convertase subtilisin/kexin type 9.

METHODS

- Patients were eligible to enter OLE if they had a diagnosis of HeFH and had completed the parent studies.
- Patients entered OLE and received alirocumab 75 mg (FH I, FH II and LONG TERM patients) or 150 mg (HIGH FH patients) Q2W regardless of the treatment regimen received at completion of the parent study (**Figure 1**).
  - The alirocumab starting dose of 75 mg Q2W for patients from FH I, FH II, and LONG TERM studies was chosen because for many patients the magnitude of effect observed with alirocumab 150 mg Q2W may not have been needed to achieve their pre-defined LDL-C goals. However, patients from HIGH FH had high baseline LDL-C (≥160 mg/dL). So the higher starting dose of alirocumab 150 mg Q2W was considered more appropriate.
- The end of the parent studies corresponded with Day 1 of OLE, except for LONG TERM (8-week wash-out period off-treatment prior to OLE, during which patients did not receive alirocumab).
- From Week 12, dose adjustment of alirocumab was allowed as per investigator's clinical judgement and each patient's LDL-C level.
- Throughout the treatment period, patients received, as far as possible, the same stable maximally tolerated statin dose with or without other lipid-lowering therapies as during the parent study.

Figure 1. OLE study design



End of treatment visit was to be performed 2 weeks after the last injection for the patients who completed the study or within 5 days after treatment discontinuation. Follow-up call was to be performed 10 weeks after the last injection.
HeFH, heterozygous familial hypercholesterolemia; LLT, lipid-lowering therapy; NCEP – ATP III TLC, National Cholesterol Education Program Adult Treatment Panel III Therapeutic Lifestyle Changes; OLE, open-label extension; Q2W, every 2 weeks; W, week.

- Safety parameters were assessed throughout the study.
- The current analysis was performed after all continuing patients had completed at least 1 year of open-label treatment.

HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; OLE, open-label extension; Q2W, every 2 weeks.

RESULTS

Baseline characteristics

Table 1. Baseline characteristics at OLE entry (safety population)

	Patients who received alirocumab in parent study (n=655)	Patients who received placebo in parent study (n=330)	Total in OLE (n=985)
Age, years, mean (SD)	54.1 (12.1)	54.8 (11.4)	54.4 (11.9)
Male, n (%)	368 (56.2)	182 (55.2)	550 (55.8)
BMI, kg/m^2, mean (SD)	29.3 (5.1)	29.3 (5.2)	29.3 (5.1)
Diabetes (type 1 or 2), n (%)	68 (10.4)	49 (14.8)	117 (11.9)
ASCVD, n (%)	314 (47.9)	174 (52.7)	488 (49.5)
CHD	302 (46.1)	166 (50.3)	468 (47.5)
Ischemic stroke	28 (4.3)	9 (2.7)	37 (3.8)
Peripheral artery disease	20 (3.1)	9 (2.7)	29 (2.9)
Statin therapy, n (%)	648 (98.9)	330 (100)	978 (99.3)
Use of LLTs other than statins, n (%)	409 (62.4)	218 (66.1)	627 (63.7)
Ezetimibe	372 (56.8)	198 (60.0)	570 (57.9)

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHD, coronary heart disease; LLT, lipid-lowering therapy; OLE, open-label extension; SD, standard deviation.

- OLE baseline LDL-C values reflect the 8-week wash-out in LONG TERM and placebo allocation in the other parent studies (no wash-out) **Table 2**.
- Other lipid levels at OLE entry were generally higher in patients who received placebo in the parent studies compared with alirocumab **Table 2**.

Table 2. Lipid parameters at OLE baseline (safety population)

mg/dL, mean (SD)	Patients who received alirocumab in parent study (n=655)	Patients who received placebo in parent study (n=330)	Total in OLE (n=985)
Calculated LDL-C	106.2 (66.9)	158.8 (58.7)	123.9 (68.9)
Calculated LDL-C by parent studies			
FH I†	80.2 (47.7)	155.5 (57.8)	106.7 (62.8)
FH II‡	64.0 (38.7)	136.6 (43.3)	87.3 (52.5)
LONG TERM¶	163.7 (58.3)	167.5 (60.0)	165.0 (58.8)
HIGH FH§	120.5 (79.9)	198.6 (67.8)	146.2 (84.2)
Non-HDL-C	132.6 (74.2)	187.1 (63.4)	150.9 (75.2)
Apolipoprotein B	91.7 (41.7)	124.6 (34.9)	102.8 (42.5)
Lipoprotein (a)#	21.0 (6.0:62.0)	25.0 (8.0:74.0)	23.0 (7.0:65.0)
Total cholesterol	184.6 (72.8)	237.5 (61.0)	202.4 (73.4)

• OLE baseline LDL-C values reflect the 8-week wash-out in LONG TERM and placebo allocation in the other parent studies (no wash-out).
• Other lipid levels at OLE entry were generally higher in patients who received placebo in the parent studies compared with alirocumab.

† n=254, 138, and 392 for alirocumab, placebo and OLE total, respectively; ‡ n=136, 63, and 199 for alirocumab, placebo and OLE total, respectively; ¶ n=214, 104, and 318 for alirocumab, placebo and OLE total, respectively; § n=51, 25, and 76 for alirocumab, placebo and OLE total, respectively; #Lp(a) shown in median Q1:Q3.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OLE, open-label extension; SD, standard deviation.

- At the time of analysis, 938 patients (95.2%) had completed ≥1 year of treatment and 56 (5.7%) had discontinued treatment (22 (2.2%) due to adverse events).

Efficacy

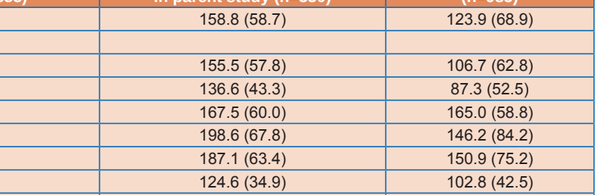
- Mean LDL-C level at baseline of parent studies was 151.7 mg/dL.
- Of those who started OLE on 75 mg Q2W dose, 537/909 (59.1%) were maintained on that dose throughout.
- At Week 48 of OLE, the mean LDL-C was 79.7 mg/dL (n=918), a mean reduction of 46.9% compared with baseline levels of the parent studies **(Figure 2)**.
- Reduction in LDL-C levels was maintained throughout the study (up to Week 72; **Figure 3**).

Figure 2. Percentage change in LDL-C from parent study baseline to OLE Weeks 8 and 48 (mITT population)

• At Week 48 of OLE, the mean LDL-C was 79.7 mg/dL, a mean reduction of 46.9% compared with baseline levels of the parent studies; reductions were independent of the treatment received during the parent study.

LDL-C, low-density lipoprotein cholesterol; mITT, modified intention-to-treat; OLE, open-label extension; SE, standard error.

Figure 3. LDL-C levels over time in OLE (up to Week 72; mITT population)

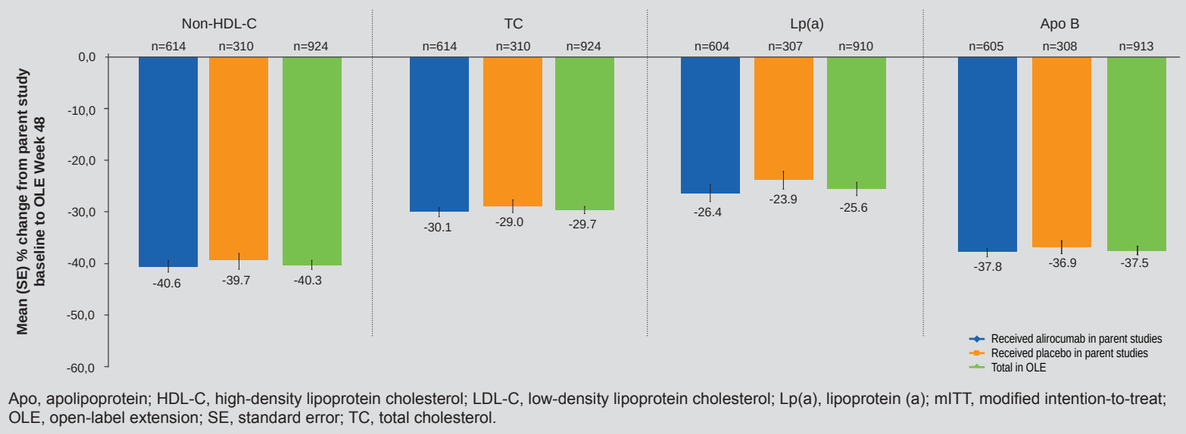


• At the time of analysis, reductions in LDL-C levels was maintained throughout the study (up to Week 72).

† Data from all exposed patients (safety population) in OLE.
LDL-C, low-density lipoprotein cholesterol; mITT, modified intention-to-treat; OLE, open-label extension; SE, standard error.

- Reductions in other lipids at Week 48 are shown in **Figure 4**.

Figure 4. Percentage change in other lipids from parent study baseline to OLE Week 48 (mITT population)



Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); mITT, modified intention-to-treat; OLE, open-label extension; SE, standard error; TC, total cholesterol.

Safety

- Overall safety profile was comparable between patients treated with alirocumab or placebo in the parent studies **Table 3**.

Table 3. Overview of TEAEs (safety population)

n (%)	Patients who received alirocumab in parent study (n=655)	Patients who received placebo in parent study (n=330)	Total in OLE (n=985)
Any TEAE	516 (78.8)	246 (74.5)	762 (77.4)
Treatment-emergent SAE	93 (14.2)	47 (14.2)	140 (14.2)
TEAE leading to death	2 (0.3)	2 (0.6)	4 (0.4)
TEAE leading to permanent treatment discontinuation	15 (2.3)	7 (2.1)	22 (2.2)
Cardiovascular events confirmed by adjudication	14 (2.1)	9 (2.7)	23 (2.3)
TEAEs in ≥5% of total population			
Nasopharyngitis	73 (11.1)	42 (12.7)	115 (11.7)
Influenza	55 (8.4)	27 (8.2)	82 (8.3)
Upper respiratory tract infection	56 (8.5)	22 (6.7)	78 (7.9)
Back pain	44 (6.7)	19 (5.8)	63 (6.4)
Arthralgia	33 (5.0)	22 (6.7)	55 (5.6)
Diarrhea	39 (6.0)	13 (3.9)	52 (5.3)

OLE, open-label extension; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

- The rates of TEAEs of special interest are presented in **Table 4**.

Table 4. TEAEs of special interest (safety population)

n (%)	Patients who received alirocumab in parent study (n=655)	Patients who received placebo in parent study (n=330)	Total in OLE (n=985)
Local injection-site reaction	23 (3.5)	26 (7.9)	49 (5.0)
General or local allergic events	62 (9.5)	32 (9.7)	94 (9.5)
Neurological events	13 (2.0)	7 (2.1)	20 (2.0)
Neurocognitive disorders	5 (0.8)	5 (1.5)	10 (1.0)
Hepatic disorders	24 (3.7)	8 (2.4)	32 (3.2)
Ophthalmological disorders	8 (1.2)	3 (0.9)	11 (1.1)
Diabetes mellitus and diabetic complications	18 (2.7)	7 (2.1)	25 (2.5)

OLE, open-label extension; TEAE, treatment-emergent adverse event.
• Injection-site reactions were reported by 49 patients (5.0%); one patient discontinued treatment due to an ISR.

CONCLUSIONS

- **In this OLE study of patients with HeFH, alirocumab demonstrated a durable and robust treatment effect, yielding a 47% reduction in LDL-C at Week 48 compared with baseline levels.**
- **During ODYSSEY OLE (at least 12 months of open-label treatment following 18 months of double-blind treatment), alirocumab was generally well-tolerated in patients with HeFH.**
  - **The safety profile observed in this real world setting is consistent with previous data reported in the double-blind studies.[3-5]**

HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; OLE, open-label extension.

DISCLOSURES

- Michel Farnier has received research support from Sanofi/Regeneron Pharmaceuticals, Inc., Amgen, and Merck and Co. He has served as a consultant for Sanofi/Regeneron Pharmaceuticals, Inc., Pfizer, Amgen, Merck and Co, Eli Lilly, AstraZeneca, Kowa, and Akcea/Ionis, and has received speaker fees from Sanofi/Regeneron Pharmaceuticals, Inc., Abbott, Amgen, Merck and Co, Pfizer, and Mylan.
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- Robert Dufour has received research support from Sanofi, Regeneron Pharmaceuticals, Inc., Amgen, Orion, Pfizer, and Ionis. He has served as a consultant for Sanofi, Regeneron Pharmaceuticals, Inc., Amgen, Janssen, and Aegerion, and has received speaker fees from Amgen and Sanofi.
- Marie T. Baccara-Dinet is a stockholder and an employee of Sanofi.
- Chantal Din-Bell is a stockholder and an employee of Sanofi.
- Garen Manvelian is a stockholder and an employee of Regeneron Pharmaceuticals, Inc.
- John R. Guyton has received research support from Sanofi, Regeneron Pharmaceuticals, Inc., Amgen, and Amarin. He has served as a consultant for Amgen and the Familial Hypercholesterolemia Foundation.

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REFERENCES: *1. Huijgen R.* et al. PLoS One. *2010;5:e9220. 2. Pijlman AH* et al. Atherosclerosis. *2010;209:189–194. 3. Kastelein JJ* et al. Eur Heart J. *2015;36:2996–3003. 4. Robinson JG* et al. N Engl J Med. *2015;372:1489–1499. 5. Ginsberg HN* et al. Cardiovasc Drugs Ther. *2016;30:473–483. 6. Cannon CP* et al. Eur Heart J. *2015;36:1186–1194.*