On-Treatment LDL-C Levels when Alirocumab Dose is Decreased from 150 to 75 mg Every 2 Weeks in Patients with Heterozygous Familial Hypercholesterolemia: Results from ODYSSEY OLE

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Background

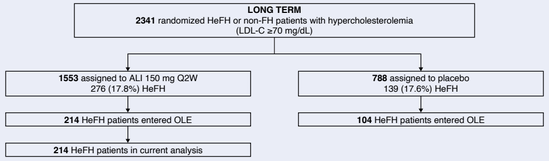
- Patients with heterozygous familial hypercholesterolemia (HeFH) are at increased risk for cardiovascular events due to elevated low-density lipoprotein cholesterol (LDL-C).[1,2]
- HeFH patients unable to reach LDL-C threshold levels on current standard-of-care of treatment may require additional lipid-lowering therapy (LLT).[3,4]
- Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) with the fully human monoclonal antibody alirocumab significantly improved LDL-C levels versus placebo in patients with and without HeFH in ODYSSEY Phase 3 trials with double-blind periods of 78 weeks (FH I,[5] FH II,[5] LONG TERM,[6] and HIGH FH[7]).
- Alirocumab is available in two doses, 75 and 150 mg (to be administered once every 2 weeks [Q2W]).
- ODYSSEY LONG TERM (NCT01507831) was a 78-week double-blind trial of alirocumab 150 mg Q2W versus placebo, as add-on to maximally tolerated statin ± other LLT.[6]
- Patients with HeFH who completed LONG TERM could enter an open-label extension study (ODYSSEY OLE; NCT01954394) following an 8-week off-drug wash-out period. From the start of OLE up to Week 8, all patients received alirocumab 75 mg Q2W (with their existing statin ± other LLT).
- For the first time, this study provides an opportunity to assess on-treatment LDL-C levels when the dose of alirocumab is decreased from 150 to 75 mg Q2W in the same cohort of HeFH patients.

Methods

Study design

- Patients who participated in the FH I,[5] FH II,[5] HIGH FH,[7] and LONG TERM[6] studies were eligible to enter OLE if they had a diagnosis of HeFH and had completed the parent study.
- In the current analysis, only HeFH patients who received alirocumab in the LONG TERM study and subsequently entered OLE are included (Figure 1).

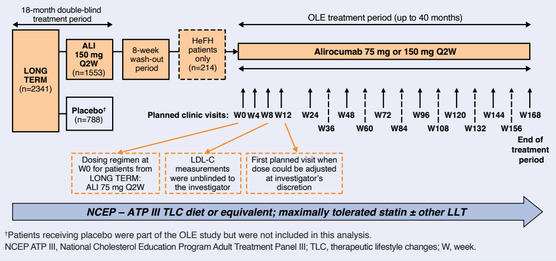
Figure 1. Patient selection: This analysis included patients with HeFH who received alirocumab in the LONG TERM study



ALI, alirocumab; non-FH, non-familial hypercholesterolemia.

- In LONG TERM, patients randomized to alirocumab received a dose of 150 mg Q2W.[6] At entry to OLE (following an 8-week wash-out period), the dose was reduced to 75 mg Q2W (Figure 2).
  - The alirocumab starting dose of 75 mg Q2W was chosen because for many patients the magnitude of effect observed with 150 mg Q2W may not be needed to achieve their pre-defined LDL-C goals.

Figure 2. Study design



†Patients receiving placebo were part of the OLE study but were not included in this analysis.
NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; TLC, therapeutic lifestyle changes; W, week.

- In OLE, LDL-C values were blinded to the physician and patient from Day 1 until Week 8. From Week 8, the LDL-C values were communicated to physicians; from Week 12, physicians could adjust the alirocumab dose based on their clinical judgement and the patient's LDL-C level.
  - For example, if further LDL-C reduction was required, the alirocumab dose could be increased to 150 mg Q2W; however, if the LDL-C value was subsequently felt to be too low, the dose could be decreased from 150 mg Q2W to 75 mg Q2W.
- Throughout OLE, patients received as far as possible, the same stable maximally tolerated statin dose ± other LLTs as they received during LONG TERM.
- Simultaneous adjustments in any LLTs and alirocumab dose were avoided.

Data analyses

- Efficacy data were assessed in an on-treatment, modified intention-to-treat (mITT) analysis, including only patients who were receiving alirocumab. On-treatment LDL-C levels and percent change in LDL-C from baseline were compared in the same cohort of patients at Week 8 of LONG TERM (when all patients received alirocumab 150 mg Q2W) versus Week 8 in OLE (when all patients received alirocumab 75 mg Q2W).
- Safety data were assessed up to the cut-off date for this analysis; at this time, all patients continuing in OLE had completed at least 12 months of treatment with alirocumab.

Results

Baseline demographics

- A total of 214 patients with HeFH who received alirocumab during the LONG TERM study entered OLE, of whom 211 were included in the mITT population.
- Demographics and lipid parameters for these patients at OLE baseline are shown in Table 1 and Table 2.

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

	All patients† (n=214)
Age, years, mean (SD)	55.8 (10.7)
Sex, male, n (%)	121 (56.5)
BMI, mean (SD) kg/m²	29.6 (5.4)
ASCVD, n (%)	106 (49.5)
Very high CV risk, n (%)	117 (54.7)
High CV risk, n (%)	97 (45.3)
Hypertension, n (%)	93 (43.5)
Diabetes, n (%)	27 (12.6)

†HeFH patients who received alirocumab in LONG TERM and entered OLE.
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CV, cardiovascular.

Table 2. Baseline lipid profile at entry in OLE (safety population)

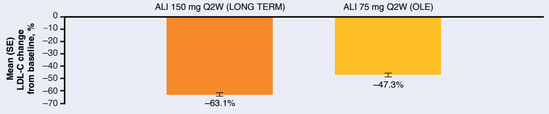
Baseline lipid, mg/dL	All patients† (n=214)
LDL-C, mean (SD)	163.7 (58.3)
Non-HDL-C, mean (SD)	195.3 (70.0)
HDL-C, mean (SD)	49.2 (13.3)
Total cholesterol, mean (SD)	244.5 (68.7)
Fasting TGs, median (Q1:Q3)	126.0 (96.0:180.0)
Lp(a), median (Q1:Q3)	27.0 (10.0:63.0)
ApoB, mean (SD)	125.8 (35.8)
ApoA1, mean (SD)	142.9 (27.6)

†HeFH patients who received alirocumab in LONG TERM and entered OLE. Apo, apolipoprotein; Lp(a), lipoprotein (a).

Efficacy

- In the mITT population, mean (standard deviation [SD]) LDL-C at OLE baseline was 166.6 (59.5) mg/dL, compared with 162.3 (58.6) mg/dL in the same HeFH patient cohort at baseline in the LONG TERM study.
  - Baseline lipid levels in OLE reflect the fact that there was an 8-week wash-out period off-drug between the end of the parent LONG TERM trial and the start of OLE.
- At Week 8 of the LONG TERM study, the mean (SD) LDL-C in this cohort of patients was 61.6 (42.9) mg/dL with alirocumab 150 mg Q2W (63.1% reduction from baseline). For the same cohort of patients in OLE, the mean (SD) LDL-C was 89.6 (54.9) mg/dL at Week 8 with alirocumab 75 mg Q2W (47.3% reduction from baseline; Figure 3).
  - This correlates to absolute LDL-C reductions of 100.7 mg/dL with alirocumab 150 mg Q2W during the first 8 weeks of the LONG TERM study, and 77.0 mg/dL with alirocumab 75 mg Q2W during the first 8 weeks of the OLE study.
- It should be noted that, although the absolute mean LDL-C level at Week 8 was higher in OLE than in LONG TERM (89.6 mg/dL vs 61.6 mg/dL), subsequent alirocumab dose adjustment from 75 to 150 mg Q2W was possible in OLE for patients requiring further reduction in LDL-C levels (performed in approximately 50% of patients in this cohort).

Figure 3. Percent LDL-C reduction from baseline to Week 8 in the parent study (LONG TERM) and OLE study, in the same cohort of patients (mITT population)

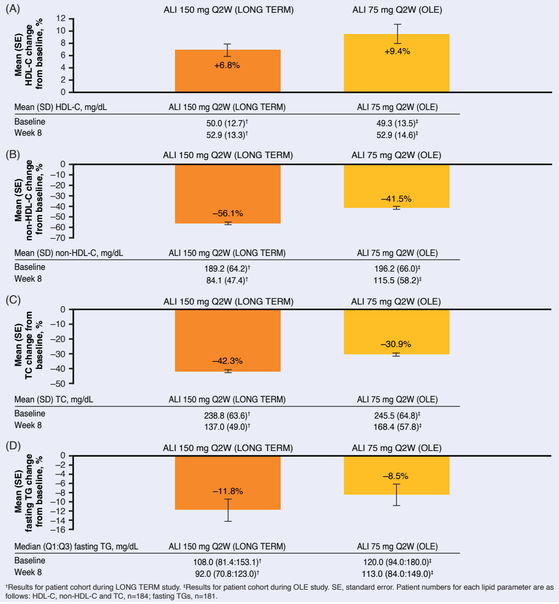


Mean (SD) LDL-C, mg/dL	ALI 150 mg Q2W (LONG TERM)	ALI 75 mg Q2W (OLE)
Baseline	162.3 (58.6)†	166.6 (59.5)‡
Week 8	61.6 (42.9)†	89.6 (54.9)‡

†Results for patient cohort during LONG TERM study (n=179). ‡Results for patient cohort during OLE study (n=179). SE, standard error. As LDL-C is calculated based on the Friedewald equation, patient numbers reflect the availability of different lipid measurements for TC and fasting TG.

- Following 8 weeks of alirocumab 150 mg Q2W treatment in LONG TERM, mean percentage changes in other lipid parameters from baseline were 6.8% increase in high-density lipoprotein cholesterol (HDL-C); 56.1% decrease in non-HDL-C; 42.3% decrease in total cholesterol (TC); and 11.8% decrease in fasting triglycerides (TGs). The equivalent mean percentage changes for the same cohort of patients in OLE were 9.4% increase in HDL-C; 41.5% decrease in non-HDL-C; 30.9% decrease in TC; and 8.5% decrease in fasting TGs (Figure 4).

Figure 4. Percent change in A) HDL-C, B) non-HDL-C, C) TC, and D) fasting TGs from baseline to Week 8 in the parent study (LONG TERM) and OLE study, in the same cohort of patients (mITT population)



Mean (SD) TC, mg/dL	ALI 150 mg Q2W (LONG TERM)	ALI 75 mg Q2W (OLE)
Baseline	238.8 (63.6)†	245.5 (64.8)‡
Week 8	137.0 (49.0)†	168.4 (57.8)‡

Median (Q1:Q3) fasting TG, mg/dL	ALI 150 mg Q2W (LONG TERM)	ALI 75 mg Q2W (OLE)
Baseline	108.0 (81.4:153.1)†	120.0 (94.0:180.0)‡
Week 8	92.0 (70.8:123.0)†	113.0 (84.0:149.0)‡

†Results for patient cohort during LONG TERM study. ‡Results for patient cohort during OLE study. SE, standard error. Patient numbers for each lipid parameter are as follows: HDL-C, non-HDL-C and TC, n=184; fasting TGs, n=181.

Safety

- During OLE, 164 patients (76.6%) reported a treatment-emergent adverse event (TEAE) and three patients (1.4%) discontinued due to a TEAE (Table 3).
- Local injection-site reactions were reported by 10 patients (4.7%); rates of other TEAEs of interest are shown in Table 3.

Table 3. Safety summary

n (%)	All patients† (n=214)
Any TEAE	164 (76.6)
Any treatment-emergent SAE	38 (17.8)
Any TEAE leading to death	2 (0.9)
Any TEAE leading to treatment discontinuation	3 (1.4)
Adverse events of interest	
Any injection-site reaction TEAE	10 (4.7)
Any neurological TEAE‡	7 (3.3)
Any neurocognitive disorder TEAE§	2 (0.9)
Any TEAE related to hepatic disorders	4 (1.9)

†HeFH patients who received alirocumab in LONG TERM and entered OLE (all continuing patients had completed up to 12 months of treatment with alirocumab during OLE; safety population). ‡Neurological TEAEs included reports of muscular weakness (n=4), paraesthesia (n=2), and a skin burning sensation (n=1). §Neurocognitive TEAEs included two reports of amnesia and one report of a cognitive disorder.
SAE, serious adverse event.

Conclusions

- In this cohort of patients with HeFH receiving statin ± other LLT, absolute LDL-C reductions from baseline were 77.0 mg/dL (47.3%) with alirocumab 75 mg Q2W during the OLE study, and 100.7 mg/dL (63.1%) with alirocumab 150 mg Q2W during the previous LONG TERM study.
- Both dosages of alirocumab (150 and 75 mg Q2W) provided substantial LDL-C reductions in patients with HeFH.
- These data obtained in a real-world setting are consistent with previous data observed in double-blind clinical trials with alirocumab 75 mg Q2W (with possible dose increase to 150 mg Q2W based on LDL-C level) in patients with HeFH.[5]
- The safety profile is consistent with that observed with alirocumab in randomized double-blind clinical trials.[5–7]

References

1. Huijgen R et al. *PLoS One*. 2010;5:e9220.
2. Pijlman AH et al. *Atherosclerosis*. 2010;209:189–194.
3. Catapano AL et al. *Atherosclerosis*. 2016;253:281–344.
4. Lloyd-Jones DM et al. *J Am Coll Cardiol*. 2016;68:92–125.
5. Kastelein JJ et al. *Eur Heart J*. 2015;36:2996–3003.
6. Robinson JG et al. *N Engl J Med*. 2015;372:1489–1499.
7. Ginsberg HN et al. *Cardivasc Drugs Ther*. 2016;30:473–483.

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