Alirocumab Titration Strategy Allows Individualized LDL-C Reduction in a Real-World Setting: Results from ODYSSEY OLE (LONG TERM Cohort)

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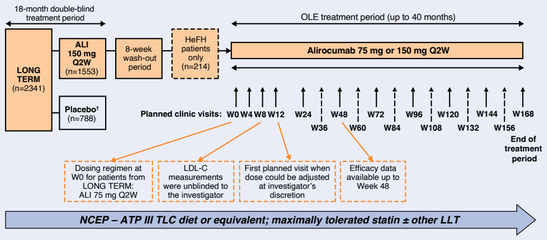
Background

- A large proportion of patients with heterozygous familial hypercholesterolemia (HeFH) do not reach their guideline-recommended target low-density lipoprotein cholesterol (LDL-C) levels on standard-of-care statin therapy (with or without other lipid-lowering therapies [LLTs] such as ezetimibe).[1,2]
- Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) with the fully human monoclonal antibody alirocumab significantly reduced LDL-C levels and enabled a significantly greater proportion of patients with HeFH to achieve LDL-C goals versus placebo in ODYSSEY Phase 3 trials with double-blind periods of 78 weeks.[3–5]
- ODYSSEY OLE (NCT01954394) is an open-label extension (OLE) study of patients with HeFH from four Phase 3 double-blind clinical trials (FH I,[3] FH II,[3] LONG TERM,[4] and HIGH FH[5]) evaluating long-term efficacy and safety of alirocumab over a treatment duration of up to 40 months.
- Alirocumab can be administered at a dose of 75 or 150 mg every 2 weeks (Q2W). In this analysis, we evaluated dose adjustments following investigator judgment in patients with HeFH who completed LONG TERM and entered the open-label ODYSSEY OLE study.
- Patients entering ODYSSEY OLE from LONG TERM all received alirocumab 75 mg Q2W (regardless of whether they previously received alirocumab 150 mg or placebo in the double-blind parent trial). During ODYSSEY OLE, the alirocumab dose could be adjusted to 150 mg following investigator judgement. This strategy differs from the automatic blinded algorithm for dose adjustment used in most previous double-blind studies.[3] Therefore ODYSSEY OLE more closely represents how investigators in a real-world setting may be using alirocumab. We investigated the LDL-C levels in patients enrolled in ODYSSEY OLE.

Methods

- This analysis focuses on 214 patients who received alirocumab 150 mg Q2W (with background statin ± other LLT) in LONG TERM before entering OLE (Figure 1).

Figure 1. Study design



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

- Patients with HeFH who completed the 78-week LONG TERM study were eligible to participate in the OLE study after an 8-week off-drug wash-out period.
- At entry to OLE, all patients received alirocumab at a dose of 75 mg Q2W. The alirocumab starting dose of 75 mg Q2W was chosen as for many patients the magnitude of effect observed with 150 mg Q2W may not be needed to achieve their pre-defined LDL-C goals.
- 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.
- Patients were kept on stable maximally tolerated statin dose ± other LLTs as during the LONG TERM study, and simultaneous adjustments in any LLTs and alirocumab dose were avoided.
- The current analysis was performed after all continuing patients had completed at least 1 year of open-label treatment.
- Efficacy data were available up to Week 48.

Results

- Baseline characteristics and lipid profiles for these 214 HeFH 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, mean (SD) years	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)

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)
Total cholesterol, mean (SD)	244.5 (68.7)
HDL-C, mean (SD)	49.2 (13.3)
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)

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein (a); TGs, triglycerides.

- Overall mean baseline LDL-C in this cohort was very high (163.7 mg/dL), despite patients being on maximally tolerated statins ± other LLTs.
- Alirocumab dose was increased from 75 to 150 mg Q2W in 48.1% of patients (n=103).
  - Reasons for dose adjustment are shown in Table 3.

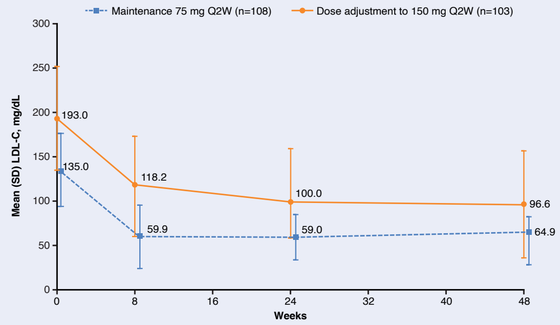
Table 3. Dose adjustment during OLE (safety population)

Patients with dose adjustment to alirocumab 150 mg Q2W, n (%)	103 (48.1)
Time from first study treatment to first dose adjustment to 150 mg Q2W, weeks, mean (SD) [median (min:max)]	23.4 (17.2) [12.9 (10:72)]
Reasons for first dose adjustment to 150 mg Q2W,† n (%)	
LDL-C value too high as per investigator judgement	103 (100)
Any dose adjustment from 150 mg Q2W to 75 mg Q2W,‡ n (%)	2 (1.9)
Time from first study treatment to first dose adjustment from 150 mg Q2W to 75 mg Q2W, weeks, mean (SD) [median (min:max)]	30.3 (8.3) [30.3 (24:36)]
Reasons for first dose adjustment from 150 mg Q2W to 75 mg Q2W,† n (%)	
LDL-C value too low as per investigator judgement	1 (50)
Other§	1 (50)

†A patient can be counted in several categories. ‡For those who had previously had dose increase. §Investigator wanted to test reaction to lower doses.

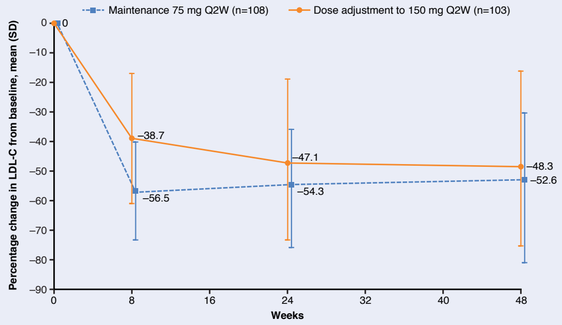
- In patients who underwent dose increase, mean (SD) baseline LDL-C was 193.0 (58.6) mg/dL, while the mean on-treatment LDL-C level at Week 8 (when all patients were still receiving 75 mg Q2W) was 118.2 mg/dL (38.7% reduction from baseline). Upon dose increase, the mean LDL-C level decreased further to 96.6 mg/dL (48.3% reduction from baseline; absolute mean LDL-C reduction of 96.2 mg/dL; Figures 2 and 3) at Week 48.
- Among patients who remained on alirocumab 75 mg Q2W (n=108), mean (SD) baseline LDL-C was 135.0 (41.7) mg/dL, Week 8 LDL-C was 59.9 mg/dL (56.5% reduction from baseline), and Week 48 LDL-C was 64.9 mg/dL (52.6% reduction from baseline; absolute mean LDL-C reduction of 69.2 mg/dL; Figures 2 and 3).

Figure 2. Mean (SD) LDL-C over time (mITT population)



mITT, modified intention-to-treat.

Figure 3. Mean (SD) percentage change in LDL-C from baseline over time (mITT population)



Safety

- Alirocumab was generally well-tolerated. Common treatment-emergent adverse events (TEAEs) were influenza (11.2%), nasopharyngitis (10.7%), back pain (7.0%), diarrhea (6.5%), and upper respiratory tract infection (6.5%; Table 4).
- This alirocumab dosing strategy resulted in a lower number of patients with LDL-C <25 mg/dL; only 2.8% of patients had two consecutive (≥21 days apart) LDL-C values <25 mg/dL in OLE, compared with 16.8% of patients in the same cohort during the parent LONG TERM study (150 mg Q2W only).

Table 4. Safety summary (safety population)

n (%)	All patients (n=214)
Any TEAE	164 (76.6)
Treatment-emergent SAE	38 (17.8)
TEAE leading to death	2 (0.9)
TEAE leading to permanent treatment discontinuation	3 (1.4)
Adverse events in ≥5% of patients	
Influenza	24 (11.2)
Nasopharyngitis	23 (10.7)
Back pain	15 (7.0)
Upper respiratory tract infection	14 (6.5)
Diarrhea	14 (6.5)
Hypertension	13 (6.1)
Bronchitis	12 (5.6)
Arthralgia	12 (5.6)
Myalgia	12 (5.6)

SAE, serious adverse event.

Conclusions

- Patients with HeFH who had their alirocumab dose increased had higher baseline values of LDL-C.
- In a real-world setting, an alirocumab dose adjustment from 75 to 150 mg Q2W provided LDL-C-lowering individualized according to each patient's baseline LDL-C in a cohort of patients with HeFH from the LONG TERM study.
- The occurrence of LDL-C <25 mg/dL was reduced following this dosing strategy, compared with the same cohort during the parent LONG TERM study, an important consideration for individualizing LDL-C levels achieved.
- Alirocumab was generally well-tolerated.

References

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