Alirocumab Treatment in a Real-World Setting: Safety Update from an Open-Label Treatment Extension to the ODYSSEY Program for Patients with Heterozygous Familial Hypercholesterolemia

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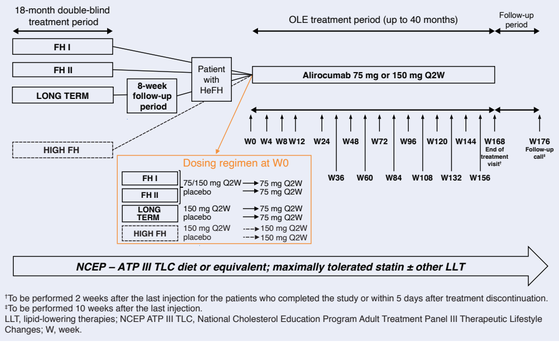
Background

- In clinical practice, a large proportion of patients with familial hypercholesterolemia (FH) do not reach their treatment goals and remain at increased risk of atherosclerotic cardiovascular disease (ASCVD) as a result.[1,2]
- Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) with alirocumab, a fully human monoclonal antibody, significantly improved levels of low-density lipoprotein cholesterol (LDL-C) and other lipids versus placebo or ezetimibe in patients with or without heterozygous FH (HeFH) in double-blind trials of up to 104 weeks.[3–6]
  - Treatment-emergent adverse events (TEAEs) with alirocumab in the individual studies were generally comparable to placebo or ezetimibe.[3–6]
- ODYSSEY OLE (NCT01954394) is an ongoing open-label extension (OLE) study of patients with HeFH from four Phase 3 double-blind trials (FH I,[3] FH II,[3] LONG TERM,[4] and HIGH FH[5])
  - The primary objective of OLE is to assess the long-term safety of alirocumab in patients with HeFH who have completed one of the four parent studies over a treatment duration of up to 40 months.
- In this analysis, we provide an update on the safety of alirocumab using data from OLE.

Methods

- Patients were eligible to enter OLE if they had a diagnosis of HeFH and had completed the parent studies.
- Regardless of the treatment received during the parent studies, patients who had participated in FH I, FH II, and LONG TERM started OLE with alirocumab 75 mg every 2 weeks (Q2W), while those who had participated in HIGH FH received alirocumab 150 mg Q2W at entry to OLE (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 be 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 double-blind treatment period for FH I, FH II, and HIGH FH corresponded with the start of the OLE study; patients who participated in LONG TERM had an 8-week wash-out period off-treatment prior to the start of OLE.

Figure 1. OLE study design



†To be performed 2 weeks after the last injection for the patients who completed the study or within 5 days after treatment discontinuation.
‡To be performed 10 weeks after the last injection.
LLT, lipid-lowering therapies; NCEP ATP III TLC, National Cholesterol Education Program Adult Treatment Panel III Therapeutic Lifestyle Changes; W, week.

- LDL-C values were blinded to the physician and patient from Day 1 until Week 8; however, from Week 8 the LDL-C values were communicated to physicians.
- From Week 12, physicians could adjust the alirocumab dose either from 75 to 150 mg Q2W, or vice versa, based on their clinical judgment and the 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.
- Safety parameters were assessed throughout the study.
- As a secondary analysis, patients who received alirocumab in the parent trials were compared with those who had received placebo in the parent trial.
- The current analysis was performed after all continuing patients had completed at least 1 year of open-label treatment.

Results

Patient disposition and characteristics

- A total of 986 patients with HeFH enrolled into OLE from the parent studies, of whom 985 received treatment during OLE and were analyzed (LONG TERM n=318, FH I n=392, FH II n=199, HIGH FH n=76, Table 1).
  - Of the 985 patients treated during OLE, 330 had received placebo and 655 had received alirocumab in the double-blind treatment period in the parent studies.
  - Baseline characteristics were similar in patients regardless of their treatment allocation in the parent studies.
- During OLE, 56 patients (5.7%) did not complete study period per protocol: 22 (2.2%) due to TEAEs, 10 (1.0%) due to poor compliance, and 24 (2.4%) for other reasons.

Table 1. Patient characteristics at OLE baseline (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)
Males, 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,† n (%)	68 (10.4)	49 (14.8)	117 (11.9)
ASCVD,‡ n (%)	314 (47.9)	174 (52.7)	488 (49.5)

†As pre-listed in the parent study electronic case report form.
‡Defined as coronary heart disease, ischemic stroke, or peripheral arterial disease.
BMI, body mass index; SD, standard deviation.

- Of the remaining patients, 46 (4.7%) completed the study treatment period, and treatment is ongoing in 883 patients (89.6%).
- Overall mean exposure to alirocumab in OLE was 73.4 weeks.

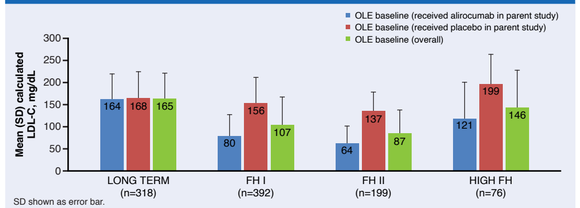
OLE baseline lipid parameters

- Baseline LDL-C values (Figure 2) reflect the 8-week wash-out in LONG TERM and placebo allocation in the other parent studies (no wash-out).
- Other than high-density lipoprotein cholesterol, lipid parameters at OLE baseline were generally higher in patients who received placebo in the parent studies compared with those who received alirocumab (Figure 3).

Safety

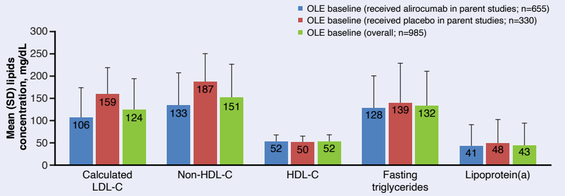
- Overall, 77.4% of patients reported TEAEs and 2.2% discontinued due to a TEAE during OLE (Table 2).

Figure 2. Calculated LDL-C at OLE baseline by parent study (safety population)



SD shown as error bar.

Figure 3. Lipid parameters at OLE baseline (safety population)



SD shown as error bar.

- The proportion of patients who reported any TEAE was similar between those who had received alirocumab (78.8%) and those who had received placebo (74.5%) in the parent studies (Table 2).
  - Overall, the most commonly reported TEAEs were nasopharyngitis (11.7%), influenza (8.3%), and upper respiratory tract infection (7.9%; Table 2).

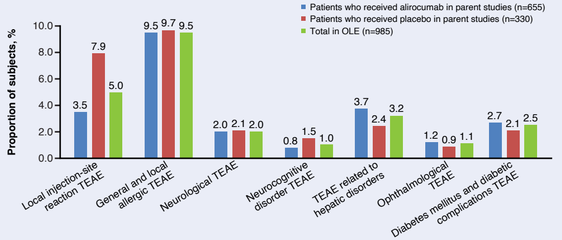
Table 2. Overview of treatment-emergent adverse events (safety population)

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)

SAE, serious adverse event.

- The rates of TEAEs of special interest were similar, regardless of treatment allocation in the parent studies, except for injection-site reactions, of which a lower rate was observed in patients who received alirocumab compared with placebo during the parent studies (Figure 4).
  - One patient (0.1%) discontinued treatment due to an injection-site reaction, one (0.1%) due to a neurocognitive event, and one (0.1%) due to a hepatic event.

Figure 4. TEAEs of special interest† (safety population)



†The categories of TEAE terms defined by the study sponsors based on standard Medical Dictionary for Regulatory Activities categories. These categories of TEAEs were assessed based on identified, potential, and theoretical risks for the new drug class collected during the clinical trial program.

Conclusions

- During ODYSSEY OLE (at least 12 months of open-label treatment following 18 months of double-blind treatment), alirocumab was generally well tolerated with no unexpected safety signals in patients with HeFH.
- The safety profile of alirocumab during OLE was similar regardless of treatment received during the parent trials, and was consistent with data from the 18-month double-blind parent studies.[3–5]

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. *Cardivasc Drugs Ther.* 2016;30:473–483.
6. Cannon CP et al. *Eur Heart J.* 2015;36:1186–1194.

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