Alirocumab in High-Risk Patients with Baseline LDL-C ≥160 mg/dL: Findings from the Compassionate Use Program

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Background

- Patients with severely elevated low-density lipoprotein cholesterol (LDL-C) levels have a higher risk of cardiovascular disease and may require additional LDL-C-lowering treatment in addition to statin and other non-statin therapies.[1–3]
- Alirocumab is a human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9) that has been shown in the ODYSSEY Phase 3 clinical trials to significantly reduce LDL-C levels.[4]
- The alirocumab compassionate use program was an open-label expanded-access program that provided alirocumab to high-risk patients before its commercial availability in the US.
- In accordance with US Food and Drug Administration (FDA) regulations on expanded-access/compassionate use programs, this program was restricted to patients with heterozygous familial hypercholesterolemia (HeFH) and/or coronary heart disease (CHD) with severe hypercholesterolemia that were not controlled with maximally tolerated standard-of-care lipid-lowering therapy.
- We present the baseline patient characteristics, safety, and lipid-lowering efficacy of alirocumab from this program.

Methods

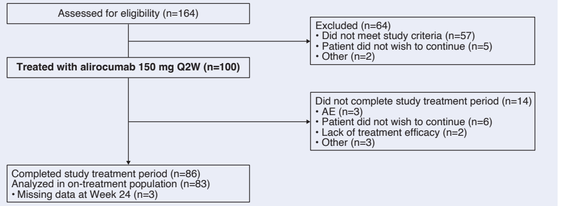
- This prospective, multicenter, single arm, open-label, expanded-access program included patients with HeFH and/or established/documented CHD and baseline LDL-C ≥160 mg/dL (≥4.14 mmol/L) on standard-of-care maximally tolerated lipid-lowering therapy in addition to diet for at least 3 months.
- Following a screening period of up to 4 weeks to determine patient eligibility, enrolled patients received alirocumab 150 mg every 2 weeks (Q2W) via subcutaneous injection for up to 24 weeks.
  - Patient enrollment into this program ended once alirocumab was approved by the FDA.
- Patients unable to tolerate any dose of statin could be enrolled.
- Safety endpoints included rates of adverse events (AEs).
- Efficacy endpoints included percent change from baseline at Week 24 in LDL-C and other lipids.
- All endpoints were analyzed descriptively only (i.e. number, mean, Q1, median, Q3, maximum, standard deviation [SD] and 95% confidence intervals [CI]), as specified in the study protocol.

Results

Baseline characteristics

- Of 164 screened patients, 100 were enrolled and treated at 25 US clinical sites (Figure 1); of the 100 enrolled patients, 86 completed alirocumab treatment for up to 24 weeks.

Figure 1. Patient flow through the alirocumab compassionate use program



- The baseline characteristics of the enrolled patients are shown in Table 1.
  - The majority of patients were white (93%) and female (62%), with an overall mean age of 58 years.
  - Sixty-four patients had FH, 66 had CHD, and 30 had both FH and CHD.
  - Sixty-four patients were statin intolerant as reported by investigator; of these, 47 were not on a statin and 17 were on reduced statin dose.
  - Thirty-six were on non-statin lipid-lowering therapy; of these, 28 were receiving ezetimibe.

Table 1. Baseline characteristics and lipid levels

Study parameters, n (%), unless otherwise specified	Alirocumab 150 mg Q2W (n=100)
Age, years, mean (SD)	58.2 (12.2)
<55	39 (39.0)
55 to <65	26 (26.0)
≥65	35 (35.0)
Male	38 (38.0)
White	93 (93.0)
HeFH†	61 (61.0)
CHD	66 (66.0)
Hypertension	66 (66.0)
Diabetes	10 (10.0)
Statin intolerant	64 (64.0)
Any non-statin LLT	36 (36.0)
Ezetimibe	28 (28.0)
Baseline lipid levels, mean (95% CI), unless otherwise specified, mg/dL	
LDL-C	220.7 (210.2–231.2)
HDL-C	51.0 (48.7–53.3)
Non-HDL-C	256.9 (245.8–268.0)
Total cholesterol	307.9 (296.6–319.2)
Triglycerides	175.8 (159.4–192.2)
Median (Q1:Q3)	156.5 (110.0:215.0)

FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Q1:Q3, interquartile range. †Of 64 patients with FH, 61 had HeFH and three had FH of unknown type.

Safety

- Rates of treatment-emergent AEs (TEAE) and serious AEs (SAEs) are displayed in Table 2 and were consistent with findings from the ODYSSEY program.[4–7]
- SAEs were experienced in 6% of patients, and TEAEs leading to permanent treatment discontinuation were seen in 3% of patients (Table 2); no deaths occurred, and there was one case of an AE of special interest (cognitive disorder).

Table 2. Safety analysis

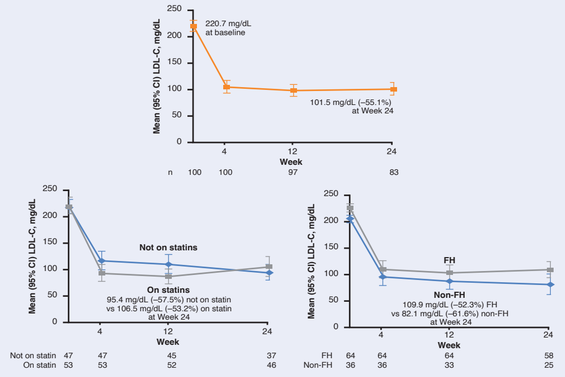
	Alirocumab 150 mg Q2W (n=100)	
n (%) of patients with at least one TEAE	All	Related†
Any TEAE	61 (61.0)	26 (26.0)
Any treatment-emergent SAE	6 (6.0)	0
Cellulitis	1 (1.0)	0
Non-Hodgkin's lymphoma	1 (1.0)	0
Pancreatitis	1 (1.0)	0
Peptic ulcer	1 (1.0)	0
Upper gastrointestinal hemorrhage	1 (1.0)	0
Non-cardiac chest pain	1 (1.0)	0
Any TEAE leading to permanent treatment discontinuation	3 (3.0)	2 (2.0)
Myalgia	2 (2.0)	1 (1.0)
Neutrophil count decreased	1 (1.0)	1 (1.0)
Any TEAE leading to death	0	0
Any AEs of special interest	1 (1.0)	0
Cognitive disorder	1 (1.0)	0

†AEs considered by the investigator to be potentially related to study medication.

Efficacy

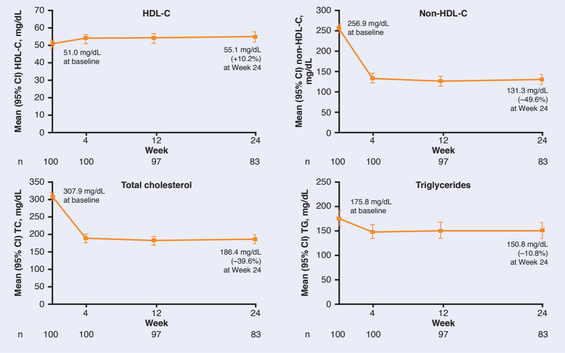
- Alirocumab reduced LDL-C on average from 221 mg/dL at baseline to 105 mg/dL by Week 4 (–54%), and LDL-C reductions were maintained over 24 weeks (Week 24 reduction of –55%; Figure 2).

Figure 2. Changes over time in LDL-C levels from baseline to Week 24 on alirocumab. Top panel is for the overall population, and the bottom panel compares levels based on statin co-medication status (left panel) and compares levels based on FH status (right panel)



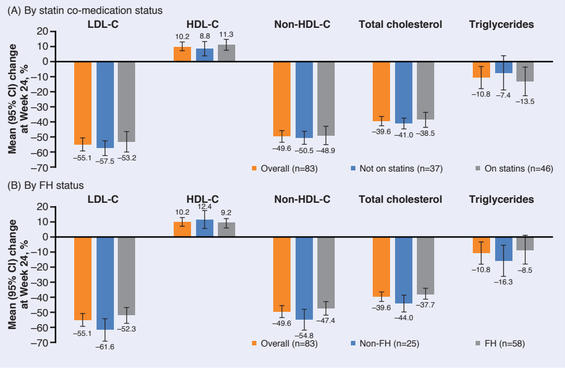
- Alirocumab reduced non-HDL-C (–50%), total cholesterol (–40%) and triglycerides (–11%), and increased HDL-C (+10%), from baseline to Week 24 (Figure 3).

Figure 3. Changes over time in levels of other lipids on alirocumab treatment



- Percent changes in lipid levels on alirocumab treatment were similar in patients on and not on statin (Figure 4A); percent reductions on alirocumab were also similar in patients with and without FH (Figure 4B), consistent with findings from the ODYSSEY HIGH FH[6] and LONG TERM[7] studies.

Figure 4. Percent changes from baseline at Week 24 in LDL-C and other lipid levels on alirocumab based on (A) statin co-medication status and (B) FH status (on-treatment population)



Conclusions

- Results from the alirocumab compassionate use program, which included patients with HeFH and/or CHD with baseline LDL-C ≥160 mg/dL, provide insight into the characteristics of patients not meeting LDL-C goals despite maximally tolerated standard-of-care lipid-lowering therapy.
- Safety and efficacy observations with alirocumab in this program in the real-world setting were consistent with those in the ODYSSEY clinical trials.[4–7]

References

1. Bays HE et al. National Lipid Association Annual Summary of Clinical Lipidology 2016. *J Clin Lipidol.* 2016;10:S1–43.
2. Lloyd-Jones DM et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll Cardiol.* 2016;68:92–125.
3. Catapano AL et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J.* 2016;37:2999–3058.
4. Roth EM. Alirocumab for hyperlipidemia: ODYSSEY Phase III clinical trial results and US FDA approval indications. *Future Cardiol.* 2016;12:115–128.
5. Jones PH et al. Safety of Alirocumab (A PCSK9 Monoclonal Antibody) from 14 Randomized Trials. *Am J Cardiol.* 2016;118:1805–1811.
6. Ginsberg HN et al. Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia and LDL-C of 160 mg/dl or Higher. *Cardiovasc Drugs Ther.* 2016;30:473–483.
7. Robinson JG et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med.* 2015;372:1489–1499.

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