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Alirocumab in high-risk patients: Observations from the open-label expanded use program



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KEYWORDS:

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Heterozygous familial hypercholesterolemia;
Coronary heart disease;
LDL-C;
Statin intolerance;
ODYSSEY

BACKGROUND: The alirocumab expanded use program provided open-label access to alirocumab before its commercial availability to patients with severe hypercholesterolemia not controlled with maximally tolerated doses of standard-of-care lipid-lowering therapy.

OBJECTIVE: To describe the safety and lipid-lowering efficacy of alirocumab in high-risk patients who were likely to be early users of proprotein convertase subtilisin/kexin type 9 inhibitors after approval.

METHODS: Patients with heterozygous familial hypercholesterolemia (HeFH) and/or coronary heart disease (CHD) and baseline low-density lipoprotein cholesterol (LDL-C) of ≥ 160 mg/dL on maximally tolerated lipid-lowering therapy were enrolled and received alirocumab 150 mg every 2 weeks for 24 weeks. Patients were permitted use of all available statins; those not taking any dose of statin could also be enrolled.

RESULTS: Of 100 enrolled patients, 93 were white, 62 were women, and overall mean age was 58 years; 61 had HeFH, 3 had unknown type of familial hypercholesterolemia, 66 had CHD, and 30 had both familial hypercholesterolemia and CHD. Sixty-four patients were identified by their providers to have some level of statin intolerance; of these, 47 were not on statin. Alirocumab reduced LDL-C on average from 221 mg/dL at baseline to 102 mg/dL by week 24 (-55%). Treatment-emergent adverse events were experienced in 61% of patients and treatment-emergent adverse events leading to permanent treatment discontinuation in 3% of patients; no deaths occurred.

CONCLUSIONS: Safety and efficacy observations from the open-label alirocumab expanded use program of very high-risk patients with HeFH and/or CHD and baseline LDL-C of ≥ 160 mg/dL uncontrolled by maximally tolerated lipid-lowering therapy were consistent with those in the placebo/ezetimibe-controlled ODYSSEY trials.

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Introduction

Patients with severely elevated low-density lipoprotein cholesterol (LDL-C) levels have increased risk of cardiovascular disease and may require additional

LDL-C-lowering treatment in addition to statin and other nonstatin therapies.¹⁻³ The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor alirocumab has been shown in the ODYSSEY phase 3 clinical trial program to be generally well tolerated and produce significant reductions in LDL-C and other lipid levels in patients with heterozygous familial hypercholesterolemia (HeFH),⁴⁻⁷ statin intolerance,⁸ and high cardiovascular risk.^{7,9,10} The results of the ODYSSEY phase 3 trials supported the approval of alirocumab in July 2015 as adjunct therapy to diet and maximally tolerated statin therapy in patients with HeFH or clinical atherosclerotic cardiovascular disease who need additional LDL-C reduction.¹¹

Before its approval in the US, based on numerous requests for access to alirocumab by health care providers, Sanofi and Regeneron Pharmaceuticals, Inc., implemented an expanded use program for alirocumab in high-risk patients who met stringent eligibility criteria. Based on clinical data from the ODYSSEY phase 3 trials, and in accordance with the US Food and Drug Administration regulations,¹² this program was restricted to patients with HeFH or coronary heart disease (CHD) with severe hypercholesterolemia not controlled with maximally tolerated standard-of-care lipid-lowering therapy.

Safety and lipid-lowering efficacy of alirocumab (150 mg every 2 weeks [Q2W] for 24 weeks) were assessed in very high-risk patients with severe hypercholesterolemia who were likely to be early users of PCSK9 inhibitors after approval. Observations from this program provide insight

into early clinical use of alirocumab in high-risk patients that are complementary to the clinical findings from the ODYSSEY program.

Methods

The alirocumab expanded use program was a prospective, multicenter, single arm, open-label, expanded-access program in the US. The program included patients with HeFH and/or CHD and baseline LDL-C of ≥ 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. Unlike most of the ODYSSEY development studies, which required all patients to be taking maximally tolerated doses of simvastatin, atorvastatin, or rosuvastatin, the expanded use program permitted use of all available statins (which were to be at maximal tolerated doses); high-dose statin was defined as the highest dose of each statin. Patients who were documented as being unable to tolerate any dose of statin were included in the program. Diagnosis of HeFH was required to be made either by genotyping or by clinical criteria based on either the Simon Broome criteria (with a diagnosis of “definite familial hypercholesterolemia [FH]”)^{13,14} or the World Health Organization/Dutch Lipid Network criteria (score > 8 points).¹⁴ CHD was defined as one or more of the following: acute myocardial infarction, silent myocardial infarction, unstable angina, coronary revascularization procedure (eg, percutaneous coronary intervention or coronary artery bypass graft

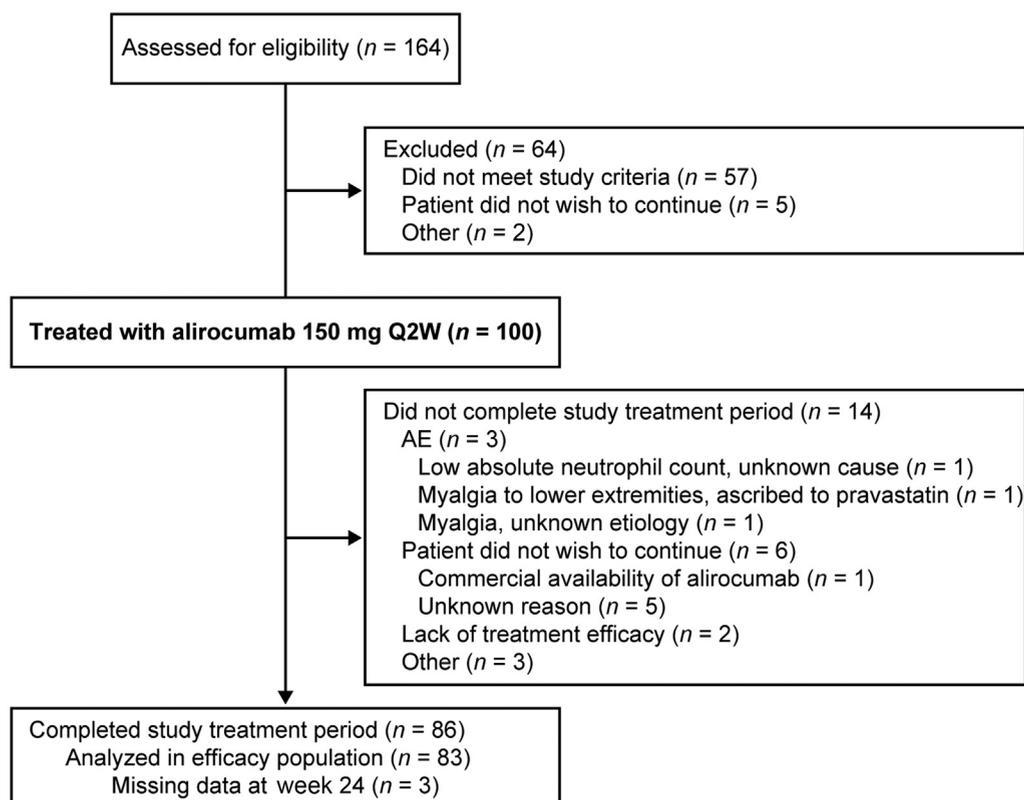


Figure 1 Patient flow through the alirocumab expanded use program. AE, adverse event; Q2W, every 2 weeks.

surgery), or clinically significant CHD diagnosed by invasive or noninvasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging).

Enrollment into the program ended once alirocumab was approved in the US. All participants provided written informed consent. The program protocol was approved by the appropriate institutional review boards, and the program was conducted in accordance with the Declaration of Helsinki and applicable amendments and International Conference on Harmonization guidelines for Good Clinical Practice.

Following a screening period of up to 4 weeks to determine patient eligibility, enrolled patients received alirocumab 150 mg Q2W by subcutaneous injection for a treatment duration of 24 weeks. As an open-label expanded use program, the primary objective was to provide access to alirocumab before its commercial availability in high-risk patients in need of additional LDL-C lowering despite maximally tolerated lipid-lowering therapy. The secondary objectives included the documentation of alirocumab safety and efficacy over the 24-week treatment duration. Safety

endpoints included rates of adverse events (AEs), assessed throughout the duration of the program in the safety population (defined as patients who received at least part of one dose of alirocumab). Investigators were asked to characterize each AE as related or not related to alirocumab. The primary efficacy endpoint of interest was the percentage change of LDL-C from baseline at week 24; percentage changes in other lipids from baseline at week 24 were also assessed. The efficacy population included patients who received at least part of one dose of alirocumab and had an available on-treatment LDL-C value at week 24. This definition of the efficacy population is consistent with that of the modified intention-to-treat population that was used in the ODYSSEY trials, but with one key difference: the modified intention-to-treat population in the ODYSSEY trials allowed missing values at week 24 to be accounted for by using the mixed-effect model repeat measurement statistical approach, whereas the protocol for the alirocumab expanded use program (since it was an open-label single arm study, not a randomized controlled trial) specified that all analyses were descriptive and presented based on observed data

Table 1 Baseline characteristics and lipid levels by FH status and in the overall population

Study parameters, n (%), unless otherwise specified	FH (n = 64)	Non-FH (n = 36)	Overall (n = 100)
Age (y), mean (SD)	55.1 (12.1)	63.8 (10.6)	58.2 (12.2)
<55	32 (50.0)	7 (19.4)	39 (39.0)
55–<65	14 (21.9)	12 (33.3)	26 (26.0)
≥65	18 (28.1)	17 (47.2)	35 (35.0)
Male	23 (35.9)	15 (41.7)	38 (38.0)
White	59 (92.2)	34 (94.4)	93 (93.0)
FH	64 (100.0)	0	64 (64.0)
HeFH	61 (95.3)	0	61 (61.0)
Unknown	3 (4.7)	0	3 (3.0)
CHD	30 (46.9)	36 (100.0)	66 (66.0)
Hypertension	37 (57.8)	29 (80.6)	66 (66.0)
Diabetes	8 (12.5)	2 (5.6)	10 (10.0)
Current smoker	7 (10.9)	5 (13.9)	12 (12.0)
High-dose statin*	26 (41.3)	9 (25.0)	35 (35.0)
Statin intolerant	37 (57.8)	27 (75.0)	64 (64.0)
No statin	26 (41.3)	21 (58.3)	47 (47.0)
Reduced statin dose*	11 (17.5)	6 (16.7)	17 (17.0)
Any nonstatin LLT	24 (37.5)	11 (30.6)	35 (35.0)
Ezetimibe	20 (31.3)	8 (22.2)	28 (28.0)
Baseline lipid levels, mean (95% CI), unless otherwise specified, mg/dL			
LDL-C	227.9 (213.0–242.8)	207.9 (196.5–219.3)	220.7 (210.2–231.2)
Non-HDL-C	264.2 (248.4–279.9)	244.1 (231.9–256.3)	256.9 (245.8–268.0)
Total cholesterol	315.9 (300.1–331.8)	293.7 (281.0–306.4)	307.9 (296.6–319.2)
Triglycerides	173.1 (152.7–193.6)	180.5 (152.7–208.3)	175.8 (159.4–192.2)
Median (Q1:Q3)	147.5 (107.0:217.5)	164.0 (124.5:210.0)	156.5 (110.0:215.0)
HDL-C	51.8 (48.7–54.8)	49.6 (46.2–53.0)	51.0 (48.7–53.3)

CHD, coronary heart disease; CI, confidence interval; FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; non-HDL-C, non-high-density lipoprotein cholesterol; Q1:Q3, interquartile range; SD, standard deviation.

*High-dose statin was defined as the highest dose of each available statin, and reduced statin dose included all other statin doses. One patient declined to take statin. At baseline, using statin intensity categories as defined per the ACC/AHA guideline,¹⁵ 29 patients (29.0%) were on high-intensity statin and 23 patients (23.0%) were on moderate-/low-intensity statin.

only (in other words, statistical approaches such as mixed-effect model repeat measurement to account for missing data at week 24 were not used). Descriptive statistics used to analyze endpoints included number, mean, median, interquartile range (Q1 and Q3), maximum, and standard deviation and 95% confidence intervals.

Results

Baseline characteristics

Twenty-five clinical sites in the US screened 164 patients and enrolled 100 patients (Fig. 1). Of the 100 enrolled patients, 86 completed alirocumab treatment for up to 24 weeks, 83 of whom had available data at week 24. Of the 14 patients who did not complete the program (Fig. 1), 13 were statin intolerant, and 1 was not statin intolerant. Three of the 14 patients discontinued due to AEs (see Safety), and 6 patients did not wish to continue (1 of whom discontinued because US approval provided access to commercial alirocumab without repeated clinic visits and blood draws) (Fig. 1). Two patients discontinued due to lack of treatment efficacy (per investigators' judgment; 1 was likely due to lack of compliance, and the other was due to an unknown reason), and 3 patients did not complete the program for other unspecified reasons (Fig. 1).

The baseline characteristics of the 100 enrolled patients are shown in Table 1. The majority of patients were white (93%) and female (62%), with a mean age of 58 years. Sixty-four patients had FH (61 patients had

confirmed HeFH, and 3 had unknown type of FH), 66 had CHD, and 30 had both FH and CHD; baseline characteristics by FH status are also shown in Table 1. Sixty-six patients had hypertension, 10 had diabetes, and 12 were smokers.

Of the 100 enrolled patients in the expanded use program, 35 were on high-dose statin at baseline. One patient declined to take statin. Sixty-four patients were statin intolerant as reported by the investigators; 47 of these 64 patients were not on a statin and 17 were on reduced statin dose at baseline. Thirty-five were on nonstatin lipid-lowering therapy; of these, 28 were receiving ezetimibe (Table 1).

Safety

Rates of treatment-emergent AEs are shown in Table 2. Serious AEs were experienced by 6 (6%) patients (Table 2).

As mentioned previously, 3 patients discontinued due to AEs (Table 2 and Fig. 1). Two patients discontinued due to myalgia (1 in the lower extremities ascribed to pravastatin, and the other due to unknown etiology [this patient was not on statin]). One patient discontinued due to low neutrophil count, indicated by low white blood cell count, of unknown cause and of moderate intensity (this patient was on statin); the patient did not receive any corrective treatment and recovered from the event without sequelae.

No deaths occurred, and there was one case of an AE of special interest (cognitive disorder), which was nonserious in nature consisting of recent memory disorders and

Table 2 Safety analysis

Patients with at least 1 TEAE	Overall (N = 100)	
	All, n (%)	Potentially related*, n (%)
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

AE, adverse event; TEAE, treatment-emergent adverse event; SAE, serious adverse event.

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

†AEs of special interest included increase in alanine aminotransferase (ALT) $\geq 3 \times$ upper limit of normal (ULN; if baseline ALT < ULN) or ALT ≥ 2 times the baseline value (if baseline ALT \geq ULN); allergic events (including local injection-site reactions that are allergic in nature) requiring consultation with another physician; pregnancy occurring in a female participant or the partner of a male participant; symptomatic overdose (accidental or intentional) with alirocumab; neurologic events requiring additional examinations/procedures and/or consultation with a specialist; and neurocognitive events.

thinking disorders of moderate intensity that did not require treatment discontinuation or corrective treatment; this patient had a known medical history of similar cognitive impairment symptoms on statin therapy and was therefore recommended by the investigator to be observed without neurologist consultation (the patient recovered from the event without sequelae).

Efficacy

Alirocumab 150 mg Q2W reduced LDL-C on average from 221 mg/dL at baseline to 102 mg/dL (−55%) at week 24 (Fig. 2). Ninety-seven participants completed 12 weeks of treatment; of these, 35 (36.1%) and 56 (57.7%) patients achieved LDL-C of <70 mg/dL and <100 mg/dL at week 12, respectively. Eighty-three subjects completed 24 weeks of treatment; of these, at week 24, 25 (30.1%) and 53 (63.9%) patients achieved LDL-C of <70 mg/dL and <100 mg/dL, respectively, and 54 (65.1%) patients had LDL-C reductions $\geq 50\%$ at week 24.

In the overall population, alirocumab reduced non-high-density lipoprotein cholesterol (−50%), total cholesterol (−40%), and triglycerides (−11%) and increased high-density lipoprotein cholesterol (+10%), from baseline to week 24 (Fig. 2). The percent reductions in LDL-C and other lipid levels on alirocumab at week 24 by FH status and by statin comedication status are shown in Figure 2A, B, respectively. Of the 64 statin-intolerant patients enrolled in this program, 51 completed the study; 12 (23.5%) and 31 (60.8%) of whom had LDL-C levels of <70 mg/dL and <100 mg/dL at week 24, respectively.

Discussion and conclusions

In the alirocumab expanded use program, treatment with alirocumab 150 mg Q2W reduced LDL-C levels in patients with HeFH and/or CHD with baseline LDL-C of ≥ 160 mg/dL on average from 221 mg/dL at baseline to

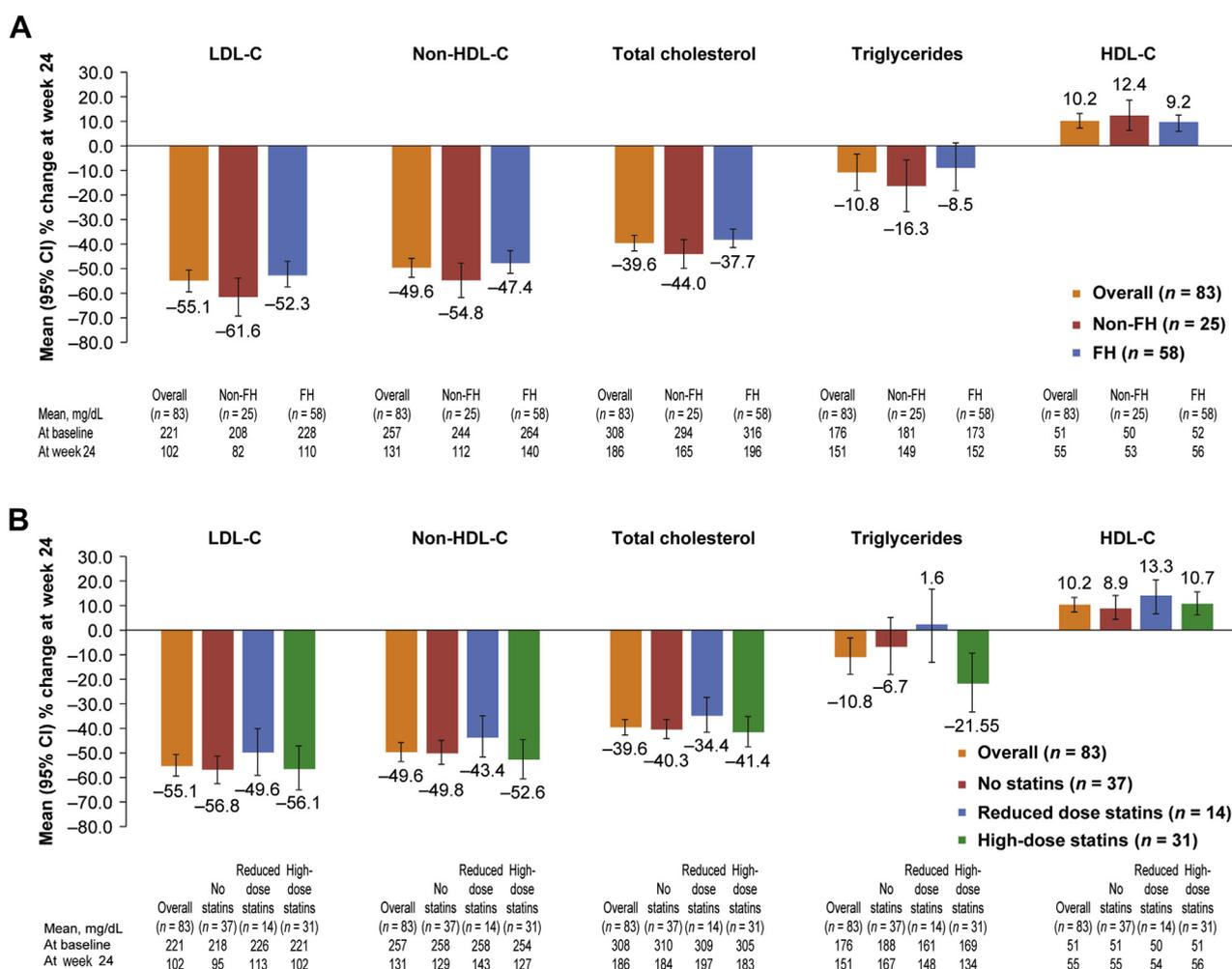


Figure 2 Percent changes from baseline at week 24 in LDL-C and other lipid levels on alirocumab by (A) familial hypercholesterolemia (FH) status and (B) statin comedication status. *N* values represent the number of patients at week 24. The overall population pool included the patient who declined to take statin; this patient was not included in the “no statins” subgroup. CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

102 mg/dL by week 24 (−55%) and allowed the majority of patients to achieve guideline-recommended LDL-C reductions of $\geq 50\%$.³ The percent reductions in LDL-C on alirocumab were similar in patients with and without FH, and regardless of statin dose. The safety and efficacy observations with alirocumab in this open-label program, which included very high-risk and difficult to treat patients with uncontrolled LDL-C who had exhausted other lipid-lowering treatment options, were consistent with those in the ODYSSEY trials^{4,5,7,8,16,17} as well as pooled subanalyses of patients with HeFH⁶ and by statin type and dose.¹⁸

Although this expanded use program required patients to be on maximally tolerated statin therapy as in the majority of ODYSSEY trials, this program was distinct from most ODYSSEY trials (which permitted only simvastatin, atorvastatin, or rosuvastatin) as patients were permitted to use all available statins. Moreover, patients who were documented as being unable to tolerate any dose of statin were included in the program. This distinction in the enrollment criteria, which reflects real-world clinical practice, makes the observations from the expanded use program more relevant for real-world application. The high proportion (64%) of statin-intolerant patients enrolled in this program (who consisted 13 of the 14 patients [93%] that did not complete the 24-week treatment period) highlights statin intolerance as an important real-world clinical-therapeutic challenge, particularly among those with very high levels of LDL-C, though it should be noted that statin intolerance in this program was based on provider and patient judgment and was not systematically assessed. The observations from this program were consistent with analyses of real-world use of PCSK9 inhibitors, which also indicate high rates of statin intolerance and higher LDL-C levels among users of PCSK9 inhibitors.^{19–22}

Although the alirocumab expanded use program started before the approval of alirocumab in the US, the inclusion criteria are similar to the approved indications for alirocumab. Moreover, the characteristics of patients enrolled in this program align with patient characteristics that are highlighted in recent US guidelines/recommendations.^{3,23} Likewise, a retrospective analysis of real-world PCSK9 inhibitor prescribing data from electronic medical records in Accenture's "Predictive Health Intelligence Environment" database showed that alirocumab was mainly prescribed to those with clinical atherosclerotic cardiovascular disease, HeFH, and high baseline LDL-C levels. Furthermore, compared to those without prescriptions for PCSK9 inhibitors, fewer patients with prescriptions for PCSK9 inhibitors were on high-intensity statins, but more were taking ezetimibe, other nonstatin lipid-lowering therapies, or no lipid-lowering therapies.²²

Observations from this expanded use program provide insight into the characteristics of high-risk patients who were selected by their health care providers to be early users of PCSK9 inhibitors. In these high-risk patients, a high proportion of whom had some degree of statin intolerance, overall LDL-C levels were reduced by 55%

and the majority of patients achieved the guideline-recommended LDL-C reductions of $\geq 50\%$.³

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Disclosures

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References

- Bays HE, Jones PH, Orringer CE, Brown WV, Jacobson TA. National Lipid Association Annual Summary of Clinical Lipidology 2016. *J Clin Lipidol*. 2016;10:S1–S43.
- Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J*. 2016;37:2999–3058.
- Lloyd-Jones DM, Morris PB, Ballantyne CM, 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: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2016;68:92–125.
- Kastelein JJ, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur Heart J*. 2015;36:2996–3003.
- Ginsberg HN, Rader DJ, Raal FJ, 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.
- Kastelein JJ, Hovingh GK, Langslet G, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 monoclonal antibody alirocumab vs placebo in patients with heterozygous familial hypercholesterolemia. *J Clin Lipidol*. 2017;11:195–203.
- Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1489–1499.
- Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol*. 2015;9:758–769.
- Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *Eur Heart J*. 2015;36:1186–1194.
- Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study. *Am Heart J*. 2015;169:906–915.
- Sanofi-aventis U.S. LLC. Highlights of PRALUENT prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125559s0011b1.pdf. Accessed September 15, 2017.
- US Food and Drug Administration. Expanded Access (Compassionate Use). Available at: https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm#Statutory_Background. Accessed September 15, 2017.
- Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. *BMJ*. 1991;303:893–896.
- Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *Am J Epidemiol*. 2004;160:407–420.
- Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2889–2934.
- Jones PH, Bays HE, Chaudhari U, et al. Safety of alirocumab (a PCSK9 monoclonal antibody) from 14 randomized trials. *Am J Cardiol*. 2016;118:1805–1811.
- Roth EM, Taskinen MR, Ginsberg HN, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized phase 3 trial. *Int J Cardiol*. 2014;176:55–61.
- Catapano AL, Lee LV, Louie MJ, Thompson D, Bergeron J, Krempf M. Efficacy of alirocumab according to background statin type and dose: pooled analysis of 8 ODYSSEY Phase 3 clinical trials. *Sci Rep*. 2017;7:45788.
- Shah P, Glueck CJ, Goldenberg N, et al. Efficacy, safety, Low density lipoprotein cholesterol lowering, and calculated 10-year cardiovascular risk reduction of alirocumab and evolocumab in addition to maximal tolerated cholesterol lowering therapy: a post-commercialization study. *Lipids Health Dis*. 2017;16:19.
- Rane PB, Patel J, Harrison DJ, et al. Patient characteristics and real-world treatment patterns among early users of PCSK9 inhibitors. *Am J Cardiovasc Drugs*. 2017[Epub ahead of print].
- Fairman KA, Davis LE, Sclar DA. Real-world use of PCSK-9 inhibitors by early adopters: cardiovascular risk factors, statin co-treatment, and short-term adherence in routine clinical practice. *Ther Clin Risk Manag*. 2017;13:957–965.
- Karalis D, Mallya U, Elassal J, Ghannam A, Gupta R, Boklage S. Who is today's alirocumab patient? A real world perspective of patients prescribed alirocumab in the United States. *Circulation*. 2016;134:A17012.
- Orringer CE, Jacobson TA, Saseen JJ, et al. Update on the use of PCSK9 inhibitors in adults: Recommendations from an Expert Panel of the National Lipid Association. *J Clin Lipidol*. 2017;11:880–890.