Efficacy and Safety of Alirocumab in Patients With Autosomal Dominant Hypercholesterolemia Associated With Proprotein Convertase Subtilisin/Kexin Type 9 Gain-of-Function or Apolipoprotein B Loss-of-Function Mutations

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Efficacy and Safety of Alirocumab in Patients With Autosomal Dominant Hypercholesterolemia Associated With Proprotein Convertase Subtilisin/Kexin Type 9 Gain-of-Function or Apolipoprotein B Loss-of-Function Mutations

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Autosomal dominant hypercholesterolemia results from mutations affecting the low-density lipoprotein receptor pathway, including proprotein convertase subtilisin/kexin type 9 (PCSK9) gain-of-function mutations (GoFm) and apolipoprotein B (APOB) loss-of-function mutations (LoFm). This study examined the long-term efficacy and safety of alirocumab in patients with *PCSK9* GoFm and *APOB* LoFm who participated in the open-label extension to a Phase 2 double-blind study (NCT01604824). Of the 23 patients who completed the 14-week double-blind period and 8-week follow-up, 21 opted to continue in the open-label extension (*PCSK9* GoFm, n = 15; *APOB* LoFm, n = 6). Patients received alirocumab 150 mg every 2 weeks from week 32 up to 3 years for *PCSK9* GoFm and 2 years for *APOB* LoFm. Mean duration of alirocumab exposure was 129 weeks (median: 144 weeks). After initiation of alirocumab treatment, low-density lipoprotein cholesterol (LDL-C) decreased in both groups. At week 80, mean percent reduction in LDL-C from baseline was 58.0% and 47.1% for *PCSK9* GoFm and *APOB* LoFm groups, respectively. Treatment-emergent adverse events were reported in 19 patients (90.5%); no patients discontinued treatment due to treatment-emergent adverse events. In patients with autosomal dominant hypercholesterolemia and elevated LDL-C levels despite receiving maximally tolerated lipid-lowering therapies, alirocumab 150 mg every 2 weeks resulted in clinically meaningful reductions in LDL-C, sustained through to 3 years and 2 years for patients with *PCSK9* GoFm and *APOB* LoFm, respectively. Alirocumab was generally well tolerated with no unexpected safety concerns. **(Am J Cardiol 2020;125:880−886)**

Autosomal dominant hypercholesterolemia (ADH)[1] results from mutations affecting the low-density lipoprotein receptor pathway, mainly including LDL-receptor gene mutations but also apolipoprotein B (*APOB*) loss-of-function mutations (LoFm) and, less commonly, proprotein convertase subtilisin/kexin type 9 (*PCSK9)* gain-of-function mutations (GoFm).[2−4] *APOB* LoFm reduce the binding affinity between ApoB and the LDL-receptor,[3,5] whereas *PCSK9* GoFm may result in reduced LDL receptor levels and concomitant elevated LDL-cholesterol (LDL-C) levels due to increased lysosomal degradation of the LDL receptor.[6] Alirocumab, a fully human monoclonal antibody that inhibits PCSK9, is effective for further lowering of LDL-C in statin-treated patients with ADH and is associated with a reduction in cardiovascular risk.[4,7] The mutation underlying ADH may influence the response to alirocumab.[4] The results of the long-term efficacy and safety assessment of alirocumab in patients with *PCSK9* GoFm and *APOB* LoFm who participated in the open-label extension (OLE) of a randomized intervention study[8,9] are presented here.

Methods

This study was an OLE of a Phase 2, randomized, double-blind study to evaluate the pharmacodynamics and safety of alirocumab in patients with ADH, and *PCSK9* GoFm or *APOB* LoFm (ClinicalTrials.gov registration: NCT01604824). The study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization guidelines for Good Clinical Practice and was approved by an appropriately constituted Institutional Review Board or Independent Ethics Committee. All patients provided written informed consent.

The study design is shown in Figure 1. Patients continued to take their prestudy lipid-lowering therapy (LLT) throughout the double-blind and follow-up periods. During the OLE, patients were no longer required to remain on a stable LLT regimen, and the investigator could change the

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See page 885 for disclosure information.

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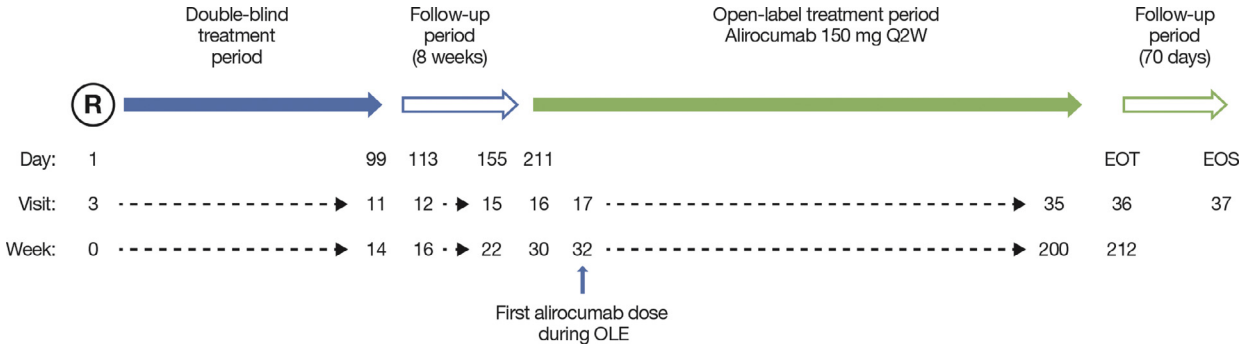

Figure 1. Study design. Notes: Between week 22 and week 32 patients were off-treatment. EOS = end of study (70 days after the last alirocumab dose); EOT = end of treatment; OLE = open-label extension; Q2W = every 2 weeks; R = randomization.

patient's LLT if needed. Further details on study design, key exclusion criteria, laboratory assessments, and statistical analyses are given in the Supplementary Methods.

Patients who completed the follow-up period of the double-blind part of the study were invited to enter the OLE, during which they received alirocumab 150 mg every 2 weeks (Q2W) from week 32 up to 3 years. A total of 21 patients opted to continue in the OLE (*PCSK9* GoFm, n = 15; *APOB* LoFm, n = 6); 2 patients opted not to continue in the OLE (both *PCSK9* GoFm carriers).

Results

All 21 patients completed the OLE treatment period; only 1 patient (4.8%) did not attend the end of study follow-up visit (reason given, "other"). Baseline patient characteristics are summarized separately for patients with *PCSK9* GoFm and *APOB* LoFm, and overall, in Table 1. Study-directed genotyping indicated that patients in the *PCSK9* GoFm group had 4 different variants (Asp374Tyr; Ser127Arg; Leu108Arg; Arg218Ser), while patients in the

Table 1
Summary of patient characteristics by group (proprotein convertase subtilisin/kexin type 9 gain-of-function mutations or apolipoprotein B loss-of-function mutations) and overall at baseline (open-label safety analysis set)

Variable	Patients with *PCSK9* GoFm variants (n = 15)	Patients with *APOB* LoFm variants (n = 6)	All (N = 21)
Age (years), mean ± SD	44.7 ± 12.7	45.5 ± 4.2	44.9 ± 10.8
Sex			
Male	3 (20.0%)	4 (66.7%)	7 (33.3%)
Female	12 (80.0%)	2 (33.3%)	14 (66.7%)
Country			
France	6 (40.0%)	1 (16.7%)	7 (33.3%)
USA	9 (60.0%)	5 (83.3%)	14 (66.7%)
Race			
White	14 (93.3%)	6 (100.0%)	20 (95.2%)
Indian Ocean Islander	1 (6.7%)	0	1 (4.8%)
Body weight (kg), mean ± SD	78.4 ± 15.1	91.0 ± 15.7	82.0 ± 16.0
Height (cm), mean ± SD	164.7 ± 6.4	174.1 ± 10.4	167.4 ± 8.6
BMI (kg/m^2), mean ± SD	29.0 ± 6.3	30.1 ± 5.3	29.3 ± 5.9
HbA1c (%), mean ± SD	5.8 ± 0.6	5.5 ± 0.2	5.7 ± 0.5
PCSK9 GoFm variant*			
Asp374Tyr	9 (60.0%)	0	9 (42.9%)
Ser127Arg	4 (26.7%)	0	4 (19.0%)
Leu108Arg	1 (6.7%)	0	1 (4.8%)
Arg218Ser	1 (6.7%)	0	1 (4.8%)
APOB LoFm variant*			
Arg3500Gln	0	6 (100.0%)	6 (28.6%)
Lipid parameters (mg/dl)			
Total cholesterol, mean ± SD	224.2 ± 86.0	204.2 ± 27.4	218.5 ± 73.8
Measured LDL-C, mean ± SD	154.5 ± 86.8	129.8 ± 31.1	147.5 ± 75.2
Calculated LDL-C, mean ± SD†	146.1 ± 83.2	122.3 ± 27.5	139.3 ± 71.8
HDL-C, mean ± SD	56.7 ± 14.2	64.0 ± 8.1	58.8 ± 13.0
Triglycerides, median (Q1:Q3)	107.0 (55.0:144.0)	79.5 (75.0:98.0)	89.0 (66.0:131.0)
Lipoprotein (a), median (Q1:Q3)	20.8 (10.0:66.6)	111.7 (66.5:188.0)	34.4 (10.9:90.3)

Baseline value is defined as the last available value prior to the first dose in double-blind period. *APOB* = gene encoding apolipoprotein B100; BMI = body mass index; GoFm = gain-of-function mutation; HbA1c = glycated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LoFm = loss-of-function mutation; *PCSK9*, gene encoding proprotein convertase subtilisin/kexin type 9; SD = standard deviation.

* By study-directed genotyping.

† Calculated using the Friedewald formula.

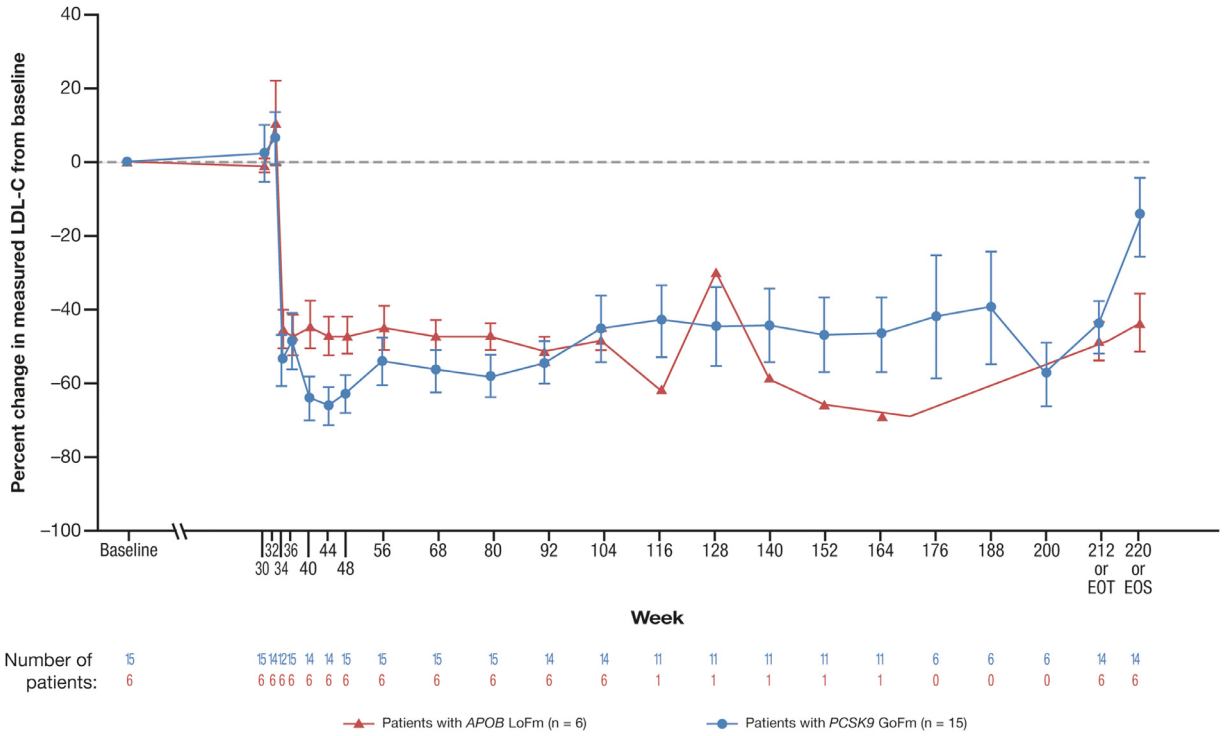

Figure 2. Mean percent change from baseline in measured LDL-C (±SE) during the OLE period, separately for patients with *PCSK9* GoFm and *APOB* LoFm (open-label safety analysis set). Notes: All patients received alirocumab for approximately 3 years or until alirocumab became commercially available, whichever came first, resulting in a reduction in patient numbers from week 116 through to week 200. Baseline value is defined as the last available value prior to the first dose in double-blind period. *APOB* = gene encoding apolipoprotein B100; EOS = end of study; EOT = end of treatment; GoFm = gain-of-function mutation; LDL-C = low-density lipoprotein cholesterol; LoFm = loss-of-function mutation; OLE = open-label extension; *PCSK9* = gene encoding proprotein convertase subtilisin/kexin type 9; SE = standard error.

APOB LoFm group all had the same variant (Arg3500Gln). The pathogenicity of the variants included in this study was verified based on genetic and molecular evidence from the literature.[5,10] The proportion of female patients was greater in the *PCSK9* GoFm group (80%) compared with the *APOB* LoFm group (33%). There was a difference in body weight between the 2 groups, possibly due to the greater proportion of females in the *PCSK9* GoFm group; however, mean body mass index was similar in the 2 groups. Mean baseline calculated LDL-C was higher in the *PCSK9* GoFm group (146 mg/dl) compared with the *APOB* LoFm group (122 mg/dl).

Adherence with alirocumab was high during the OLE; patients received their alirocumab injections on 99% of planned occasions. The mean duration of alirocumab exposure was 129 weeks (range 82 to 180 weeks; median, 144 weeks). Overall, 100% of patients were exposed to alirocumab for ≥72 weeks, 57.1% for ≥132 weeks, and 28.6% for ≥179 weeks.

The mean percent change from baseline in measured LDL-C during the OLE is shown in Figure 2 for the *PCSK9* GoFm and *APOB* LoFm groups. In both groups, LDL-C decreased following initiation of alirocumab treatment at week 32 and remained below baseline throughout the duration of the study. At week 44 (12 weeks after the start of the OLE period) mean ± standard deviation (SD) percent reduction from baseline in measured LDL-C was 66.0% ± 19.0% in patients with *PCSK9* GoFm variants and 47.0% ± 12.3% in patients in the *APOB* LoFm group.

The mean percent reduction in LDL-C in patients with *PCSK9* GoFm variants was greater than that observed in patients with *APOB* LoFm variants at all timepoints up to week 80; the mean ± SD percent reduction in LDL-C was 58.0% ± 22.5% and 47.1% ± 8.5% at week 80 in the 2 groups, respectively. Note that only 1 patient from the *APOB* LoFm group continued the study after study week 104. At the EOT visit the mean ± SD percent reduction from baseline in measured LDL-C was 44.6% ± 26.5% and 48.3% ± 12.7% in the *PCSK9* GoFm and *APOB* LoFm patients, respectively.

The mean percent change from baseline in LDL-C during the OLE period is shown separately for each *PCSK9* GoFm or *APOB* LoFm variant in Figure 3. For all variants, LDL-C decreased after initiation of alirocumab treatment. In the patient with the *PCSK9*: Leu108Arg variant, LDL-C level returned to near baseline level by week 56. In the group with the *PCSK9*: Asp374Tyr variant, there was a gradual decrease in mean percent change in measured LDL-C from week 92.

Median percent changes in lipoprotein (a) are shown in Figure 4 for *PCSK9* GoFm and *APOB* LoFm variants separately; reductions from baseline were observed for both groups.

The incidence of treatment-emergent adverse events (TEAEs) during the OLE is summarized in Table 2. TEAEs were reported in 19 patients (90.5%); no deaths occurred, and no patients discontinued treatment due to TEAEs. The most frequently reported TEAEs (>10%) were viral upper

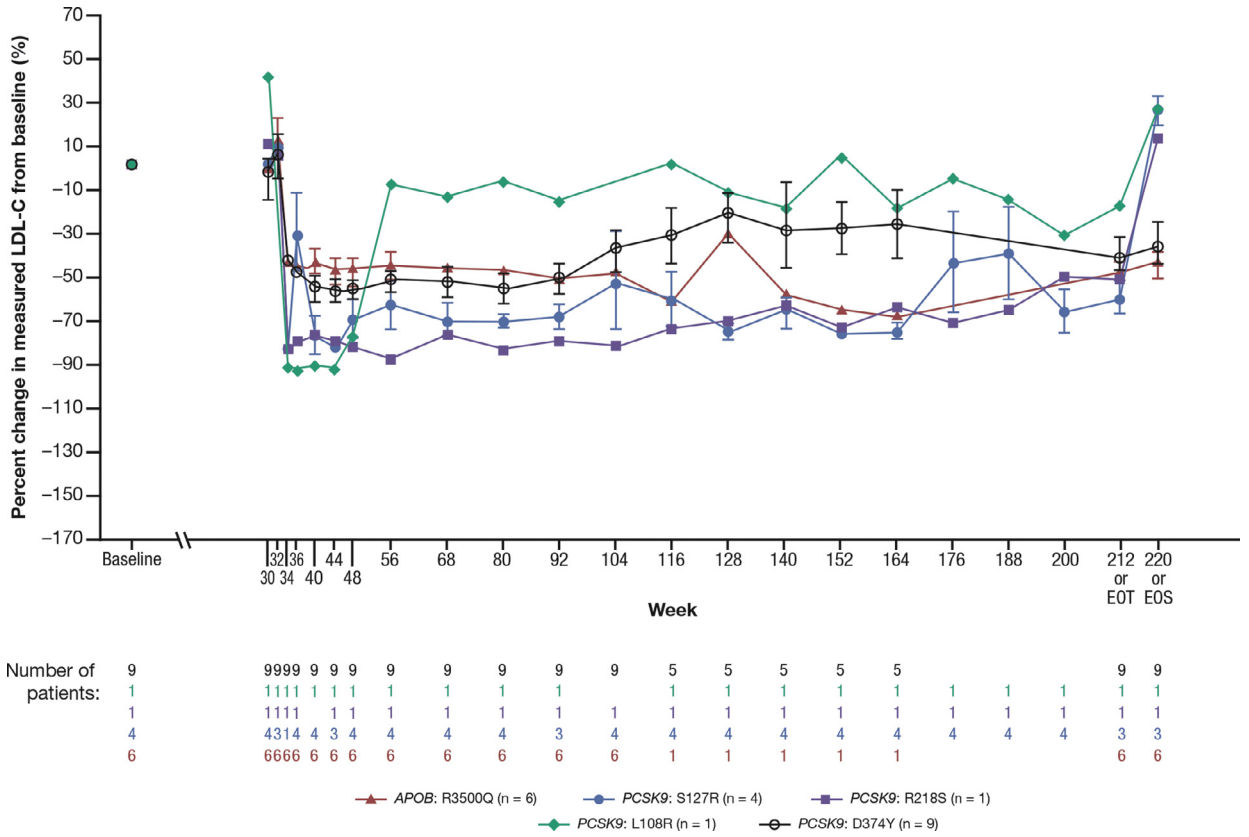

Figure 3. Mean percent change from baseline in measured LDL-C (±SE) during the OLE period, separately for each *PCSK9* GoFm or *APOB* LoFm variant. Notes: Baseline value is defined as the last available value prior to the first dose in double-blind period. *APOB* = gene encoding apolipoprotein B100; GoFm = gain-of-function mutation; LDL-C = low-density lipoprotein cholesterol; LoFm = loss-of-function mutation; OLE = open-label extension; *PCSK9* = gene encoding proprotein convertase subtilisin/kexin type 9; SE = standard error.

respiratory tract infection (28.6%; 6 patients with *PCSK9* GoFm), and upper respiratory tract infection (14.3%; 2 patients with *PCSK9* GoFm, and 1 patient with *APOB* LoFm). Three patients (14.3% overall; all *PCSK9* GoFm) experienced treatment-emergent serious adverse events, including 2 cardiac disorders (unstable angina and myocardial infarction), 1 gastrointestinal disorder (salivary gland disorder), 1 general disorder (chest pain), and 1 metabolism and nutrition disorder (obesity); none were considered by the investigator to be related to study drug. No patient had a positive treatment-emergent ADA response in the OLE.

Discussion

As patients with ADH may require long-term treatment with LLTs, the evaluation of the long-term maintenance of the LDL-C lowering efficacy and safety of alirocumab in patients with ADH is of importance; particularly as not all monoclonal antibodies developed for PCSK9 inhibition have demonstrated sustained efficacy.[11] In this study, alirocumab 150 mg Q2W resulted in clinically meaningful LDL-C reductions (mean reduction from baseline to week 80 of 58.0% vs 47.1% for *PCSK9* GoFm vs *APOB* LoFm, respectively), shown to be sustained through to 3 years for patients with *PCSK9* GoFm and 2 years for patients with *APOB* LoFm. It should be noted that baseline LDL-C represents the parent study baseline (i.e., before alirocumab treatment was started); however, as all patients were on statins (or other LLTs), baseline mean LDL-C was relatively low (139.3 mg/dl) for this ADH population.

The long-term maintenance of alirocumab efficacy in patients with ADH observed here agrees with previous alirocumab trials of similar duration conducted in differing patient populations. The ODYSSEY OLE study enrolled patients with heterozygous familial hypercholesterolemia (n = 985), receiving maximally tolerated statins, who had completed 1 of 4 Phase 3 parent studies (all 18 months duration); during ODYSSEY OLE, consisting of an additional 2.5 years median treatment duration, alirocumab reduced mean LDL-C from baseline by 47.9% at week 96.[12] The long-term efficacy of alirocumab has also been investigated in the cardiovascular outcomes trial for alirocumab, ODYSSEY OUTCOMES, which enrolled participants (n = 18,924) with recent (4 to 52 weeks) acute coronary syndrome. Following alirocumab treatment during ODYSSEY OUTCOMES, a reduction in mean LDL-C from baseline of 62.7% (vs placebo) was observed at 4 months, sustained through to 48 months (LDL-C reduction of 54.7% vs placebo; on-treatment analysis).[13]

The mean percent change from baseline in LDL-C with alirocumab in this study was also generally consistent with previously published findings from pooled analyses of shorter studies with alirocumab (12 to 78 weeks' duration) in patients with familial hypercholesterolemia.[4,14]

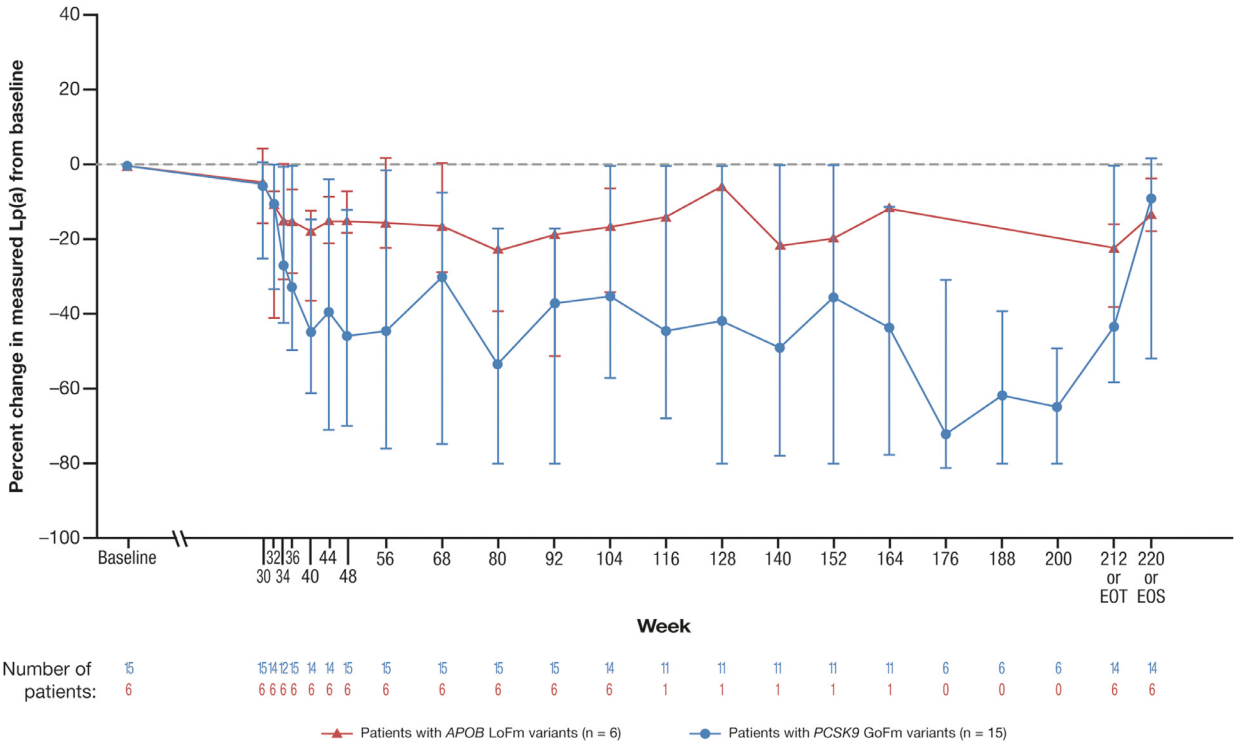

Figure 4. Median (Q1:Q3) percent change from baseline in lipoprotein (a) during the OLE period, separately for patients with *PCSK9* GoFm and *APOB* LoFm (open-label safety analysis set). Notes: All patients received alirocumab for approximately 3 years or until alirocumab became commercially available, whichever came first, resulting in a reduction in patient numbers from week 116 through to week 200. Baseline value is defined as the last available value prior to the first dose in double-blind period. *APOB* = gene encoding apolipoprotein B100; EOS = end of study; EOT = end of treatment; GoFm = gain-of-function mutation; LDL-C = low-density lipoprotein cholesterol; LoFm = loss-of-function mutation; OLE = open-label extension; *PCSK9* = gene encoding proprotein convertase subtilisin/kexin type 9.

The mean percent reduction in LDL-C in patients with *PCSK9* GoFm variants was greater than that observed in patients with *APOB* LoFm variants up to week 80. After that time point, there was a slight decrease in percent LDL-C reduction from baseline over time in the *PCSK9* GoFm group. This decrease was particularly apparent in the patient with *PCSK9:* Leu108Arg variant; although we can confirm this patient was administered study treatment for the duration of the OLE, we are unable to comment on their adherence to other LLTs as this information is not available (further discussion regarding possible causes of variability in LDL-C lowering between the 2 groups is given below). A previous study examined LDL-C reduction with alirocumab in a large cohort of patients (n = 1191) with a wide spectrum of mutations in genes causative for familial hypercholesterolemia.[4] It was observed that LDL-C reduction from baseline was numerically greater in *PCSK9* GoFm variants than *APOB* LoFm; however, this finding was limited by the small numbers of patients with these mutations, particularly *PCSK9* GoFm. The authors concluded that the response to alirocumab was similar across genotypes (*LDLR, LDLRAP1, APOB*, and *PCSK9* variants) at 24 weeks.[4]

Factors that may contribute to the variability observed in mean percent LDL-C reduction during the course of the OLE include differences in response to alirocumab between different genetic variants. For example, the lower mean percent LDL-C reduction in patients with *APOB* LoFm compared with *PCSK9* GoFm may be a result of the lower affinity of mutated APOB for the LDL-receptor, thereby leading to reduced clearance of LDL-C particles by hepatic

Table 2
Summary of treatment-emergent adverse events during the open-label extension by group (proprotein convertase subtilisin/kexin type 9 gain-of-function mutations or apolipoprotein B loss-of-function mutations) and overall (open-label safety analysis set)

	Patients with *PCSK9* GoFm variants (n = 15)	Patients with *APOB* LoFm variants (n = 6)	All (N = 21)
Patients with any OLE TEAE	15 (100.0%)	4 (66.7%)	19 (90.5%)
Patients with any OLE treatment emergent SAE	3 (20.0%)	0	3 (14.3%)
Patients with any OLE TEAE leading to death	0	0	0
Patients with any OLE TEAE leading to permanent treatment discontinuation	0	0	0

APOB = gene encoding apolipoprotein B100; GoFm = gain-of-function mutation; LoFm = loss-of-function mutation; OLE = open-label extension; *PCSK9* = gene encoding proprotein convertase subtilisin/kexin type 9; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

uptake through the LDL-receptors.[3,15] In addition, given that patients were no longer required to remain on a stable LLT regimen during the OLE, any changes to the background LLT regimen may also contribute to variability in observed response to alirocumab. However, it should be noted that compliance to background LLT use was not monitored during the OLE. Finally, interindividual variation in biological factors not related to treatment or mutation types may also contribute to observed LDL-C reductions.

No patient in the OLE had a positive treatment-emergent ADA response; therefore, ADAs did not contribute to the variability in mean percent LDL-C reduction over time. Furthermore, alirocumab was well tolerated throughout the duration of the OLE in both the *PCSK9* GoFm and *APOB* LoFm groups.

Limitations of this analysis include the very small sample sizes; therefore, mean percent change from baseline in LDL-C over time should be interpreted with caution. No formal hypothesis testing was performed, instead the results of this study should be seen as hypothesis-forming. In addition, as only 1 patient remained in the *APOB* LoFm group after week 104, no conclusions can be made regarding the efficacy and safety of alirocumab in patients with *APOB* LoFm variants beyond week 104. Furthermore, differences in patient characteristics at baseline existed between the *PCSK9* GoFm and *APOB* LoFm groups, for example, the *PCSK9* GoFm group had a higher proportion of females and higher LDL-C levels.

In summary, the present study demonstrates that in patients with *PCSK9* GoFm and *APOB* LoFm with elevated LDL-C levels despite maximally tolerated LLTs, alirocumab 150 mg Q2W resulted in long-term clinically meaningful LDL-C reductions, with no unexpected long-term safety concerns.

Author Contributions

M.F., P.N.H., E.B., S.L. and S.D. contributed to the analysis and interpretation of the data, and critically reviewed and edited the manuscript. M.K., P.N.H. and E.B. were investigators who contributed to the data acquisition. In addition, S.D. contributed to the concept or study design. Medical writing assistance and editorial support, under the direction of the authors were provided by Rachel Dunn, PhD, of Prime (Knutsford, UK), funded by Sanofi and Regeneron Pharmaceuticals, Inc., according to Good Publication Practice guidelines (http://annals.org/aim/article/2424869/good-publication-practice-communicating-company-sponsored-medical-research-gpp3). Sanofi and Regeneron Pharmaceuticals, Inc., were involved in the study design, collection, analysis and interpretation of data, as well as data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors.

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Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.12.028.

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