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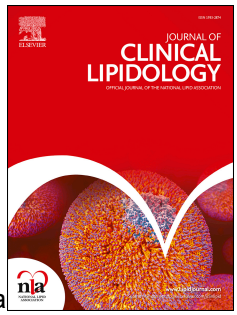

Efficacy of alirocumab in 1191 patients with a wide spectrum of mutations in genes causative for familial hypercholesterolemia

Joep C. Defesche, PhD, Claudia Stefanutti, MD, PhD, Gisle Langslet, MD, Paul N. Hopkins, MD, MSPH, Werner Seiz, MD, PhD, Marie T. Baccara-Dinet, MD, MSc, Sara C. Hamon, MA, PhD, Poulabi Banerjee, PhD, John J.P. Kastelein, MD, PhD, FESC

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Efficacy of alirocumab in 1191 patients with a wide spectrum of mutations in genes causative for familial hypercholesterolemia

Joep C. Defesche, PhD, Claudia Stefanutti, MD, PhD, Gisle Langslet, MD, Paul N. Hopkins, MD, MSPH, Werner Seiz, MD, PhD, Marie T. Baccara-Dinet, MD, MSc, Sara C. Hamon, MA, PhD, Poulabi Banerjee, PhD, John J.P. Kastelein, MD, PhD, FESC*

Department of Clinical Genetics, Academic Medical Centre, Amsterdam, the Netherlands (Dr Defesche); Department of Molecular Medicine, 'Sapienza' University of Rome, Umberto I Hospital, Rome, Italy (Dr Stefanutti); Lipid Clinic, Oslo University Hospital, Oslo, Norway (Dr Langslet); School of Medicine, University of Utah, Salt Lake City, UT, USA (Dr Hopkins); Translational Medicine and Early Development, Sanofi, Frankfurt, Germany (Dr Seiz); Sanofi, Montpellier, France (Dr Baccara-Dinet); Precision Medicine, Regeneron Pharmaceuticals, Inc., New York, NY, USA (Drs Hamon and Banerjee); Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands (Prof Kastelein).

***** Corresponding author:

Professor John J. P. Kastelein, Department of Vascular Medicine, Academic Medical Center, Meibergdreef 9, Room F4–159.2, 1105 AZ, Amsterdam, Netherlands.

Tel: +31 20 566 6612; Fax: +31 20 566 9343; Email: j.j.kastelein@amc.uva.nl

Abstract

BACKGROUND: Mutation(s) in genes involved in the LDL receptor pathway are typically the underlying cause of familial hypercholesterolemia (FH).

OBJECTIVE: Examine the influence of genotype on treatment responses with alirocumab.

METHODS: Patients from 6 trials (n=1191, including 758 alirocumab-treated; Clinicaltrials.gov identifiers: NCT01266876; NCT01507831; NCT01623115; NCT01709500; NCT01617655; NCT01709513) were sequenced for mutations in *LDLR*, *APOB*, *PCSK9*, *LDLRAP1*, and *STAP1* genes. New mutations were confirmed by Sanger sequencing.

RESULTS: One or more specific gene mutations were found in 898 patients (75%): 387 and 437 patients had heterozygous *LDLR* defective and negative mutations, respectively; 46 had a heterozygous *APOB* defective mutation; 8 patients had a heterozygous *PCSK9* gain-of-function mutation; 293 (25%) had no identifiable mutation in the genes investigated. LDL-C reductions at Week 24 were generally similar across genotypes: 48.3% (n=131) and 54.3% (n=89) in *LDLR* defective heterozygotes with alirocumab 75 mg Q2W (with possible increase to 150 mg at Week 12) and 150 mg Q2W, respectively; 49.7% (n=168) and 60.7% (n=88) in *LDLR* negative heterozygotes; 54.1% (n=20) and 50.1% (n=5) in *APOB* defective heterozygotes; 60.5% (n=5) and 90.1% (n=1) in *PCSK9* heterozygotes; and 44.9% (n=85) and 55.4% (n=69) in patients with no identified mutations. Overall rates of treatment-emergent adverse events were similar for alirocumab versus controls (placebo in 5 trials, ezetimibe control or atorvastatin calibrator arm in 1 trial), with only a higher rate of injection-site reactions with alirocumab.

CONCLUSIONS: In this large patient cohort, individuals with a wide spectrum of mutations in genes underlying FH responded substantially and similarly to alirocumab treatment.

Key words: hypercholesterolemia, genetics, cardiovascular, PCSK9, clinical trial, LDLR, APOB.

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Highlights

- 1191 patients sequenced to assess influence of genotype on response to alirocumab
- Mutations in FH genes (*LDLR*, *APOB*, *PCSK9*) found in 75% sequenced patients
- LDL-C reduced substantially and similarly across genotypes
- Alirocumab generally well tolerated in this FH population

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Introduction

Heterozygous familial hypercholesterolemia (HeFH) and homozygous familial hypercholesterolemia (HoFH) are characterized by high levels of plasma low-density lipoprotein cholesterol (LDL-C) and an increased risk of developing premature coronary heart disease .[1] The prevalence of HeFH and HoFH has been estimated to be 1:200 to 1:250 and 1:160,000 to 1:300,000, respectively.[2,3] If untreated, total cholesterol levels in individuals with HeFH and HoFH are typically in the range of 8–15 mmol/L (310–580 mg/dL) and 12–30 mmol/L (460–1160 mg/dL), respectively.[1]

Mutations in genes involved in the LDL receptor (LDLR) pathway (including the *LDLR* gene and apolipoprotein B [*APOB*], proprotein convertase subtilisin/kexin type 9 [*PCSK9*], and LDLR adaptor protein 1 [*LDLRAP1*] genes) are typically associated with FH.[4,5] The LDLR mediates uptake of ApoB-containing lipoproteins (such as LDL-C) from the circulation. The bound complex is subsequently endocytosed via interaction with LDLRAP1 and, following endocytosis, LDL-C is targeted for degradation in the lysosome while LDLR is recycled to the cell membrane.[1,2,6] PCSK9 binds to LDLR on the surface of the hepatocyte, promoting LDLR degradation via endocytosis and prevents LDLR from recycling to the membrane.[2,6] Loss-of-function mutations in *LDLR*, *APOB,* or *LDLRAP1*, or gain-of-function mutations in *PCSK9*, can therefore result in increased circulating LDL-C levels. Mutations in the signal-transducing adaptor protein 1 (*STAP1*) gene have also been associated with the FH phenotype.[7]

Alirocumab is a fully human monoclonal antibody to PCSK9, approved in the United States for lowering LDL-C levels in adults with HeFH or clinical atherosclerotic disease as add on to maximally tolerated dose of statin, and in Europe for the

treatment of adults with primary hypercholesterolemia or mixed dyslipidemia, as add on to maximally tolerated dose of statin or alone or in combination with other lipid-lowering therapies in patients with statin intolerance.[8,9] Alirocumab inhibits PCSK9, thus preventing LDLR degradation and promoting the removal of LDL-C from the circulation.[6]

As the alirocumab mode of action is via the LDLR pathway, mutations in the LDLR pathway genes could alter the response to alirocumab treatment. We sequenced patients with a diagnosis of FH from 6 clinical trials of alirocumab (as well as patients with no recorded diagnosis but very high baseline LDL-C from one study) for one or more causative mutation(s) in 5 FH genes using next-generation sequencing and assessed response to alirocumab in terms of lipid reductions.

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Methods

Patients with elevated LDL-C and FH diagnosis from 6 studies were included in the analysis: 1 Phase 2 study (12 weeks' duration) and 5 studies from the Phase 3 ODYSSEY program (24–78 weeks' duration) (Supplementary Figure 1). Diagnosis of FH in the studies was by previous genotyping or clinical criteria. However, the patients' original genotyping results were not captured in the case report forms for the trials. Clinical diagnosis of FH was based on the Simon Broome criteria for definite FH, the World Health Organization/Dutch Lipid Network criteria (score >8 points).[10-12] As well as including patients from the ALTERNATIVE study who had a confirmed diagnosis of FH, some additional patients from ALTERNATIVE who did not have a recorded diagnosis of FH were included in the sequencing analysis, as they had very high baseline LDL-C levels (defined as >5.0 mmol/L, >193 mg/dL, as per FH diagnosis criteria).

In the Phase 2 study, patients received 1 of 4 alirocumab doses (150 mg every 2 weeks [Q2W], 150 mg every 4 weeks [Q4W], 200 mg Q4W, 300 mg Q4W) or placebo.[13] In 3 Phase 3 trials (FH I [NCT01623115, FH II [NCT0709500], and ALTERNATIVE [NCT01709513]), the initial alirocumab dose was 75 mg Q2W; dosing was increased to 150 mg Q2W at Week 12 if pre-defined risk-based LDL-C goals were not achieved at Week 8.[14,15] In the 2 remaining Phase 3 trials (LONG TERM [NCT01507831] and HIGH FH [NCT01617655]), alirocumab dose was 150 mg Q2W.[16-18] The comparator arm in all studies was placebo, with the exception of the ALTERNATIVE study (conducted in individuals with statin intolerance) which compared alirocumab with ezetimibe 10 mg/day and also used an atorvastatin 20 mg/day calibrator arm (for purposes of statin rechallenge and safety only).[15]

LDL-C levels were calculated (Friedewald equation[19]). In this post-hoc analysis, a clinically meaningful response to alirocumab was defined as a reduction in LDL-C of ≥15% in at least one of the available timepoints (Weeks 12, 24, or 52) post treatment. The ≥15% cut off was chosen based on documentation provided by the US Food and Drug Administration, where "for absorbable agents, demonstration of at least a 15% reduction from baseline in LDL-cholesterol, in the absence of unfavorable alterations in other lipid parameters, is generally required for drug approval".[20] A separate analysis also defined patients as poor responders based on a <15% reduction in LDL-C at Week 12.[21]

Serum total cholesterol, triglycerides, and high-density lipoprotein cholesterol levels were determined using Centers for Disease Control and Prevention National Heart Lung Blood Institute Lipid Standardization Program assays. Lipoprotein(a) levels were determined using an immunoturbidimetric assay as described previously.[22] Serum levels of alirocumab were measured by using specific validated enzyme-linked immunosorbent assay (Regeneron Pharmaceuticals, Inc, Tarrytown, NY).[23]

To determine if there was a significant difference between mutational groups linear regression, linear regression was performed at week 12, where LDL-C was the response variable, mutational class (*LDLR* defective, *LDLR* deficient and *APOB*) were the explanatory variables and statin dose and alirocumab dose were the covariates.

Safety was assessed by treatment-emergent adverse events (TEAEs), defined as events occurring after the first injection and up to 10 weeks after the last injection

of study treatment. TEAEs were classified according to the Medical Dictionary for Regulatory Activities.

All study protocols were approved by the appropriate institutions and all patients provided written, informed consent to participate in the trials. In addition, all patients were required to sign an informed consent form for inclusion in the genotyping analysis.

Mutation sequencing

Patients who had participated in one of the trials, gave consent, and had DNA samples available were sequenced for mutations in *LDLR*, *APOB*, *PCSK9*, *LDLRAP1*, and *STAP1* genes using the SEQPRO LIPO IS NGS kit.[24] All analyses were performed by Progenika Biopharma, Derio, Spain. The SEQPRO LIPO IS NGS kit detects mutations in: *LDLR*, *APOB*, *PCSK9*, *LDRAP1,* and *STAP1,* and also copy number variations in the *LDLR* gene. Exon and exon-intron boundaries of the *LDLR* (18 exons), *PCSK9* (12 exons) *LDLRAP1* (9 exons), *STAP1* (9 exons), and *APOB* (exons 26 and 29) genes were sequenced. (Illumina sequencing by synthesis). For samples in which no variants were identified (single nucleotide variants or copy number variants) capillary electrophoresis sequencing was performed for the *STAP1* exons.

DNA was isolated from a patient's whole blood and two consecutive DNA amplifications performed; the first to amplify the target regions of interest and the second to provide an index to identify the samples. A total of 54 amplicons covering the regions of interest as well as 4 amplicons covering chromosome 21 regions were grouped into 4 separate multiplex polymerase chain reactions (PCRs) which were amplified under the same conditions for both the first and the second PCR. Between

the first and second PCRs a purification step was carried out using ExoSAP (Affymetrix, Santa Clara, CA). Following the 4 PCRs, each sample was pooled, purified, and normalized with SEQUAL PREP normalization plates (Invitrogen, Life Technologies, Carlsbad, CA). After dilution to 3 nM, amplicons were denaturalized and diluted to 15 pM for MiSeq library preparation. Cluster generation as well as the sequencing process was carried out according to the manufacturer's instructions (Illumina, San Diego, CA). Each amplicon underwent bridge amplification on a flow cell, which was then sequenced. Data analysis for alignment and variant detection was performed using the SEQPRO LIPO IS software. Coverage of at least 50 forward and 50 reverse reads was required for high reliability variant calling. Variants were named according to the Human Genome Variation Society nomenclature (http://www.hgvs.org/mutnomen/) and compared to the Progenika Database. New variants that were not present in the Progenika database were analyzed and confirmed using Sanger sequencing and multiplex ligation-dependent probe amplification analysis in the case of large gene rearrangements in the original DNA samples.[25] For copy number variation and large indel detection, proprietary algorithms were applied based on coverage depth. Variants were classified as being: homozygous if the same mutation was present on both homologous chromosomes, compound heterozygous if two different mutations for the same gene were present on homologous chromosomes, double heterozygous if two mutations were on two different genes, or *LDLR* defective (if the mutation resulted in an amino acid change) or negative (if mutations, premature termination codons, splice mutations, and frame shifts were null alleles and resulted in failure to produce protein).

Results

Baseline characteristics

A total of 3574 patients with hypercholesterolemia were randomized in the 6 trials, of whom 1381 met the diagnosis criteria for FH (Supplementary Figure 1). In addition, 60 patients from the ALTERNATIVE study who with no recorded FH diagnosis but who had LDL-C >5.0 mmol/L (>193 mg/dL) were included. DNA sequencing was conducted for 1191 patients (758 treated with alirocumab and 433 treated with control) who gave consent for sequencing and had available DNA samples and clinical data (Table 1, Supplementary Table S1). A total of 57 patients from the Phase 2 study were sequenced (Table 1). For the Phase 3 studies, the analysis included 437 patients who received alirocumab 75 mg Q2W (with possible increase to 150 mg Q2W at Week 12), 275 patients who received alirocumab 150 mg Q2W only, 366 patients who received placebo, and 37 and 19 patients, respectively, who received ezetimibe control or atorvastatin calibrator (in the ALTERNATIVE trial).

Baseline characteristics between the mutation classifications were generally comparable, with the caveat of a small patient population for some mutations (Table 2).

Mutation analysis

In total, 285 different mutations were identified in 898 of 1191 (75%) patients (Table 2). Of the 898 patients with identifiable mutations, 387 patients (43%) had heterozygous *LDLR* defective mutations, and 437 patients (49%) had heterozygous *LDLR* receptor negative mutations in *LDLR*, respectively. Ten patients (1.1%) were compound heterozygotes in *LDLR* (i.e. had a different mutation in each gene copy).

One patient was a *LDLR*/*LDLR* defective homozygote. Forty-six patients (5%) had a single mutation in *APOB*; 8 patients (0.9%) had single gain-of-function mutations in *PCSK9*; 2 patients (0.2%) were homozygous for mutations in *LDLRAP1*; 6 patients (0.7%) were double heterozygotes for mutations in both *APOB* and *LDLR*; and 1 patient (0.1%) was a double heterozygote with a mutation in *LDLR* and *PCSK9*. No mutations in *STAP1* were identified. A total of 80 new mutations were identified in the analysis; all but one (*LDLRAP1*) were in the *LDLR* gene (Supplementary Table S2). Mutations were identified in 6 of the 60 hypercholesterolemia patients from ALTERNATIVE who were not originally recorded as FH.

Effect of mutations on LDL-C reduction

In the Phase 3 studies, LDL-C reductions at Week 24 were generally similar across the genotypes and in patients without identifiable mutations: 48.3% and 54.3% in LDLR defective heterozygotes with alirocumab 75 mg Q2W (with possible increase to 150 mg at Week 12) and 150 mg Q2W, respectively; 49.7% and 60.7% in LDLR negative heterozygotes; 54.1% and 50.1% in APOB defective heterozygotes; 60.5% and 90.1% in PCSK9 heterozygotes; 44.9% and 55.4% in patients with no identified mutations (Figure 1). Findings were similar at Week 12 (Figure 1). However, the number of patients in certain mutation types was small (n=1 in some cases; Figure 1). Various alirocumab dosing regimens were used in the Phase 2 study, therefore data from this study is not included in the efficacy analysis.

At Week 12, there was no significant difference (p=0.65) among the three major genotypic groups (*LDLR* negative, *LDLR* defective and *APO*B defective) in terms of LDL-C percent reduction in the alirocumab-treated individuals. Statin dose and

alirocumab dose were used as covariates in the model and the result remained non-significant regardless of whether the covariates were included or not.

Reductions in non-high-density lipoprotein cholesterol, Apo B, lipoprotein (a), and triglycerides were also broadly similar across the different mutation types (Supplementary Table S3).

In studies using the dose increase scheme, approximately half the patients heterozygous for *LDLR* defective or negative mutations (mean baseline LDL-C ~150 mg/dL) required a dose increase from 75 to 150 mg Q2W, and 25% of the group with heterozygous *APOB* mutations (mean baseline LDL-C 122 mg/dL) had their dose increased (Supplementary Table S4).

LDL-C reductions in individual patients are shown in Figure 2 (at Week 24) and Supplementary Figure 2 (at Week 12). Regardless of mutation status, 700 out of 758 patients (92.3%) who received alirocumab achieved an LDL-C reduction of ≥15% at Week 12, and 732 patients (96.6%) had an LDL-C reduction ≥15% for at least 1 time point in Weeks 12, 24, and 52. Among the 26 patients (3.4%) who had an LDL-C reduction of <15% at any of those time points, 13 were found to have non-compliance with alirocumab (based on pharmacokinetic measurements) and/or discontinued study treatment early (i.e. prior to Week 12). This left 13 patients (1.7%) with no explanation for having a <15% LDL-C reduction with alirocumab; of these 13 patients, 9 had mutations also seen in the patients with ≥15% LDL-C reduction (Supplementary Table S5), and 4 had no identified mutations. The 13 patients with no explanation for <15% LDL-C reduction were also sequenced for loss of function mutations in the *PCSK9* gene, however none of the patients had the R46L variant or other known loss of function variants in *PCSK9*, e.g. Y142X, L253F, A443T, or

C679X.

Safety

Overall rates of TEAEs were similar for patients who received alirocumab (82.9%) versus controls (83.3%) (Table 3). For TEAEs occurring in ≥5% of patients, the incidence of injection-site reactions was higher for alirocumab (11.4%) versus controls (8.8%), as was influenza (10.9% vs. 7.9%) (Table 3).

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Discussion

Of the 285 different mutations identified in the four genes underlying FH (*LDLR*, *APOB*, *PCSK9*, and *LDLRAP1*), the vast majority of the mutations were in *LDLR* (n=206 in our cohort), as expected based on previous reports.[26] Overall, the proportion of patients for whom no mutation was identified through this analysis was 24.6%. This is consistent with previous reports that 10–40% of patients with a clinical diagnosis of FH do not have a detectable causal monogenic mutation,[1,27,28] suggesting that other as yet unidentified genes and lifestyle factors may be involved in the FH phenotype.[1,29] However, we would like to emphasise that LDL-C is the key determinant of cardiovascular risk and primary treatment target,[30] rather than the genotype.

In patients heterozygous for *LDLR* defective or negative mutations or *APOB* defective mutations, alirocumab treatment resulted in LDL-C reductions of 48.3-60.7%, in the same range as reported for the overall alirocumab-treated populations in the Phase 3 trials included in this analysis (mean LDL-C reductions from baseline to Week 24: FH I, 48.8%; FH II, 48.7%; ALTERNATIVE, 45.0%; LONG TERM, 61.0%; and HIGH FH, 45.7%[14-17]). Among patients with PCSK9 gain-of-function mutations who received alirocumab 75 mg Q2W (with possible dose increase to 150 mg Q2W), a mean LDL-C reduction of 60.5% was observed at Week 24, however only one patient with a PCSK9 gain-of-function mutation received alirocumab 150 mg Q2W from the trial outset – this patient had an LDL-C reduction of 90.1%, however interpretation of this finding is limited. In a previous trial involving 13 patients with *PCSK9* gain-of-function mutations, the mean LDL-C reduction was 73% after 8 weeks of treatment with alirocumab 150 mg Q2W.[31]

Of the alirocumab-treated patients who were included in the analysis (n=758), the majority (96.6%) achieved an LDL-C reduction of ≥15% during treatment (i.e. at at least 1 time point from Weeks 12, 24, or 52). These results are in agreement with a previous report for another PCSK9 inhibitor,[21] although the present study includes a larger number of patients. In total, 26 patients had an LDL-C reduction <15% with alirocumab treatment at the timepoints studied here for various reasons (i.e. Weeks 12, 24, or 52). Early study discontinuation or non-compliance with alirocumab can explain why 13 of these patients had an LDL-C reduction of <15% with alirocumab; however, it is not clear why the remaining 13 patients did not have a response to alirocumab: 9 of these patients had the same mutations as other patients who responded to alirocumab, suggesting that the identified mutation was not related to the lack of response, and no mutation was identified in the other 4 patients. There may therefore have been other unidentified mutations involved or other factors that were not assessed.

Study limitations include the following. Genotyping was conducted only for a set of 5 genes associated with FH (*LDLR*, *APOB*, *PCSK9*, *LDLRAP1*, and *STAP1*), and hence potentially relevant mutations in other genes will have been missed. The impact of some mutations may be reported as deleterious but may not have been functionally determined.[32 31] Most patients enrolled in these studies were Caucasian, and analysis of mutations and response to alirocumab in other ethnic groups would be of interest.

In conclusion, in this large cohort of patients, individuals with a wide spectrum of mutations in genes underlying FH responded substantially and similarly to alirocumab treatment, and alirocumab was generally well-tolerated.

Author contributions

Joep C. Defesche: Interpretation of data.

Claudia Stefanutti: Interpretation of data.

Gisle Langslet: Acquisition of data (trial investigator), interpretation of data.

Paul N. Hopkins: Interpretation of data.

Werner Seiz: Concept/design, interpretation of data.

Marie T. Baccara-Dinet: Concept/design, interpretation of data.

Sara Hamon: Concept/design, statistical analysis, interpretation of data.

Poulabi Banerjee: Concept/design, interpretation of data.

John J.P. Kastelein: Concept/design, acquisition of data (trial investigator), interpretation of data.

All authors were involved in critical review of manuscript drafts and approved the final article for submission.

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This analysis was funded by Sanofi and Regeneron Pharmaceuticals, Inc., who were involved in the study design, collection, analysis and interpretation of data. The authors had unrestricted access to study data, were responsible for all content and editorial decisions, and made the final decision to submit the manuscript for publication.

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Disclosures

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Marie T. Baccara-Dinet: Employee of and stockholder in Sanofi.

Sara Hamon: Employee of and stockholder in Regeneron Pharmaceuticals, Inc.

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Figure 1. Mean percentage reduction from baseline in LDL-C level according to mutation status at (A) Week 12 and (B) Week 24

LDL-C data analyzed for Phase 3 trials only. No patients from the Phase 2 trial were included due to the different doses/dosing schedules. Data were not available for all patients in the Phase 3 trials at all timepoints. Control was placebo in all trials except for the ALTERNATIVE trial (which had an ezetimibe control arm and an atorvastatin calibrator arm).

*Alirocumab 75 mg Q2W with possible increase to 150 mg Q2W at Week 12. In panel A (Week 12), all patients in this group were receiving 75 mg.

APOB, apolipoprotein B; GOF, gain-of-function; LDL-C, low-density lipoprotein cholesterol; *LDLR*, low-density lipoprotein receptor; *PCSK9*, proprotein convertase subtilisin/kexin type 9; SE, standard error; Q2W, every 2 weeks.

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Figure 2. Percentage change in LDL-C at Week 24 for all subjects receiving (A) alirocumab 75 mg Q2W (with possible dose increase to 150 mg) and (B) 150 mg Q2W according to mutation status

LDL-C data analyzed for Phase 3 studies only. No patients from the Phase 2 study were included due to the different doses/dosing schedules.

APOB, apolipoprotein B; GOF, gain-of-function; LDL-C, low-density lipoprotein cholesterol; *LDLR*, low-density lipoprotein receptor; *LDLRAP1*, LDL receptor adaptor protein 1; *PCSK9*, proprotein convertase subtilisin/kexin type 9.

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Table 1. Breakdown of sequenced cohort according to study and treatment group

	Alirocumab[‡]	Control[‡]	Total
R727-CL-1003 Phase 2[*]	46	11	57
ALTERNATIVE, total (FH diagnosis)[†]	31 (7)	56 (20)	87 (27)
FH I	264	146	410
FH II	142	72	214
HIGH FH	58	28	86
LONG TERM	217	120	337
Total	758	433	1191

*Patients were randomized to 1 of several alirocumab doses in the Phase 2 study (see Supplementary Figure S1). By alirocumab dose, the number of patients sequenced was as follows: 150 mg Q2W; n=10, 150 mg Q4W; n=11, 200 mg Q4W; n=12, 300 mg Q4W; n=13.

[†]Some patients from ALTERNATIVE were included in the sequencing analysis although they did not have a recorded diagnosis of FH, as they had very high baseline LDL-C levels (>5.0 mmol/L, ~193 mg/dL). The numbers of patients who did have an FH diagnosis are shown in brackets.

[‡]Control was placebo in all trials except ALTERNATIVE (which had an ezetimibe control arm and an atorvastatin calibrator arm).

FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks.

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Table 2. Baseline patient demographics (sequenced cohort)*

	APOB defective	*APOB* defective/ *LDLR* defective	*APOB* defective/ *LDLR* negative	*LDLR* defective	*LDLR* defective/ *LDLR* defective	*LDLR* defective/ *LDLR* negative	*LDLR* negative	*LDLR* negative/ *PCSK9* GOF	*LDLRAP1* null	*PCSK9* GOF	No known mutation
Number of patients	46	3	3	387	8	3	437	1	2	8	293
R727-CL-1003[†]	1	0	0	16	1	0	20	1	0	0	7
ALI 75/150 mg Q2W[‡]	21	2	1	137	0	2	175	0	1	6	92
ALI 150 mg Q2W	4	0	1	88	3	0	100	0	0	0	79
Control[§]	20	1	1	146	4	1	142	0	1	2	115
% of total cohort	3.9	0.25	0.25	32.5	0.67	0.25	36.7	0.08	0.17	0.67	24.6
Age years, mean (SD)	55.2 (12.8)	56.7 (11.2)	55.7 (4.9)	51.9 (12.1)	44.4 (12.3)	51.3 (14.2)	51.6 (12.5)	54.0	42.0 (4.2)	48.6 (11.9)	57.6 (10.2)
Male, n (%)	18 (39.1)	1 (33.3)	0 (0)	195 (50.4)	6 (75.0)	1 (33.3)	278 (63.6)	1 (100)	1 (50.0)	6 (75.0)	131 (44.7)
BMI kg/m^2, mean (SD)	27.7 (5.3)	31.3 (12.3)	22.4 (3.1)	28.8 (4.8)	29.0 (5.7)	27.0 (2.8)	29.0 (4.6)	27.9	23.4 (3.9)	30.5 (7.2)	29.5 (5.5)

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Statin use, n (%)	46 (100)	3 (100)	3 (100)	378 (97.7)	8 (100)	3 (100)	427 (97.7)	1 (100)	2 (100)	7 (87.5)	234 (79.9)
Ezetimibe use, n (%)	26 (56.5)	3 (100)	2 (66.7)	209 (54.0)	4 (50.0)	3 (100)	325 (74.4)	1 (100)	2 (100)	6 (75.0)	46 (15.7)
Calculated LDL-C mg/dL, mean (SD)	138.3 (48.6)	201.0 (77.3)	206.0 (78.2)	160.7 (58.9)	217.0 (80.2)	149.0 (30.3)	158.4 (61.7)	136.0	140.7 (0.9)	186.9 (93.4)	154.4 (58.9)
ApoB mg/dL, mean (SD)	158.2 (50.3)	219.0 (85.0)	236.7 (86.1)	185.2 (62.8)	237.8 (78.9)	171.3 (39.9)	184.5 (72.0)	168.0	152.5 (4.9)	215.0 (90.3)	188.7 (64.9)
Non-HDL-C mg/dL, mean (SD)	105.7 (26.9)	132.3 (31.4)	151.0 (46.6)	122.5 (33.9)	146.8 (27.9)	116.3 (26.4)	122.9 (36.3)	151.0	105.0 (7.1)	136.6 (40.2)	120.8 (35.8)
TG mg/dL, median (Q1:Q3)	21.5 (5.4: 50.0)	38.0 (25.0: 91.0)	50.0 (1.5:99.0)	27.4 (10.6: 74.6)	74.5 (21.0: 146.5)	54.0 (1.5:8 6.0)	29.0 (8.0: 88.0)	218.0	36.5 (2.0: 71.0)	10.0 (7.0: 92.5)	21.6 (9.0: 62.0)
Lp(a) mg/dL, median (Q1:Q3)	81.5 (66.0: 104.0)	73.0 (61.0: 137.0)	138.0 (120.0: 198.0)	110.0 (79.0: 145.0)	97.3 (78.2: 122.5)	104.0 (61.0: 169.0)	107.1 (84.0: 149.0)	159.0	58.7 (43.0: 74.3)	108.5 (77.5: 172.0)	149.0 (110.0: 227.0)

*Baseline characteristics shown for pool of alirocumab and control groups. Data from six studies: Phase 2 study R727-CL-1003, and Phase 3 ODYSSEY studies FH I, FH II, HIGH FH, LONG TERM, and ALTERNATIVE.

†Patients were randomized to one of several alirocumab doses in this study.

‡Alirocumab 75 mg Q2W was increased to 150 mg Q2W at Week 12 depending on LDL-C at Week 8. This strategy was used in the studies FH I, FH II, and ALTERNATIVE.

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[§]Control was placebo in all trials except ALTERNATIVE (which had an ezetimibe control arm and an atorvastatin calibrator arm).

ALI, alirocumab; *APOB*, apolipoprotein B; BMI, body mass index; GOF, gain-of-function; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; *LDLR*, low-density lipoprotein receptor; *LDLRAP1*, LDL receptor adaptor protein 1; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9; SD, standard deviation; TG, triglycerides; Q2W, every 2 weeks.

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Table 3. Overall TEAE incidence and selected adverse events of interest (safety population)*

	Sequenced cohort	
	Alirocumab (n = 761)	**Control† (n = 430)**
Any TEAE	82.9 (631)	83.3 (358)
Treatment-emergent SAE	13.3 (101)	12.1 (52)
Deaths during study	0.7 (5)	0.2 (1)
TEAE leading to permanent treatment discontinuation	4.1 (31)	5.8 (25)
TEAEs occurring in ≥5% of patients		
Nasopharyngitis	13.4 (102)	13.3 (57)
Injection site reaction	11.4 (87)	8.8 (38)
Influenza	10.9 (83)	7.9 (34)
Headache	7.0 (53)	7.9 (34)
Myalgia	6.0 (46)	7.7 (33)
Upper respiratory tract infection	6.0 (46)	7.7 (33)
Diarrhea	5.9 (45)	3.0 (13)
Arthralgia	5.4 (41)	7.7 (33)
Back pain	5.4 (41)	5.1 (22)
Urinary tract infection	5.4 (41)	4.9% (21)
Bronchitis	5.3 (40)	5.1 (22)

Data are % (n) of patients.

*Pool of 6 studies: R727-CL-1003, FH I, FH II, HIGH FH, LONG TERM, and ALTERNATIVE.

†Control was placebo in all studies except ALTERNATIVE (which had an ezetimibe control arm and an atorvastatin calibrator arm).

SAE, serious adverse event; TEAE, treatment.

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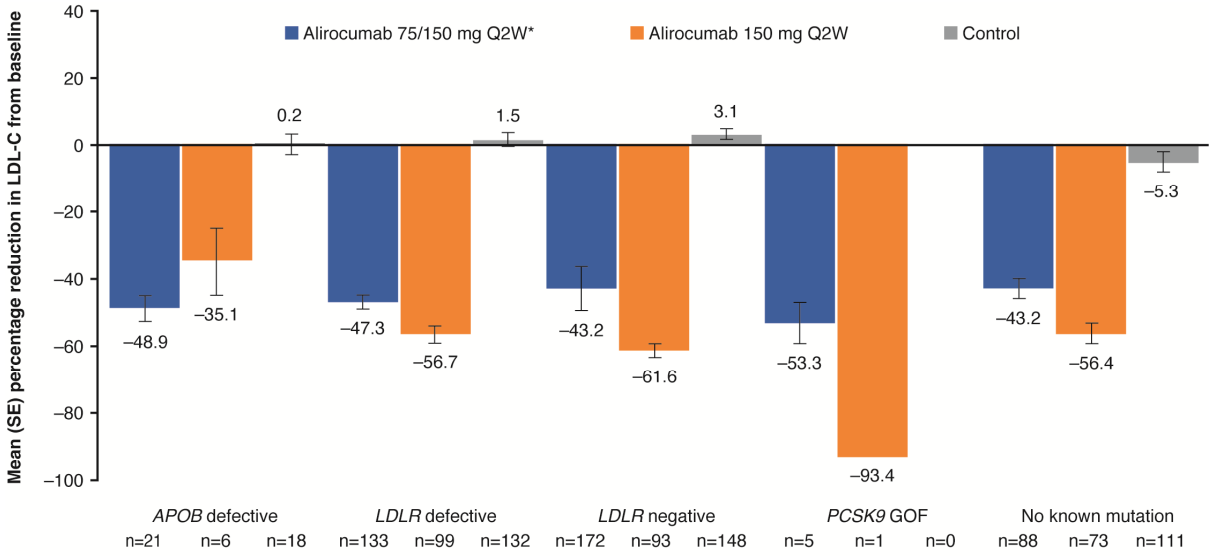

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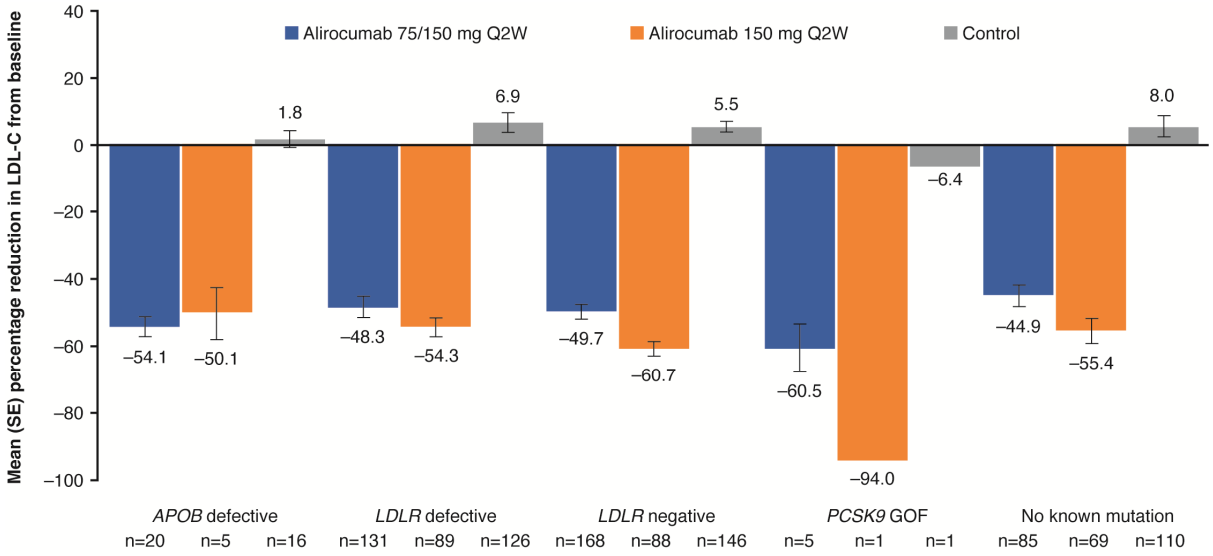

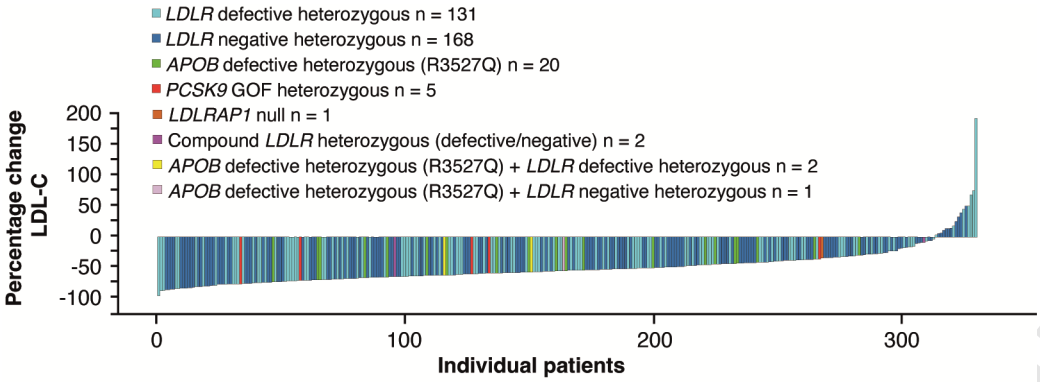

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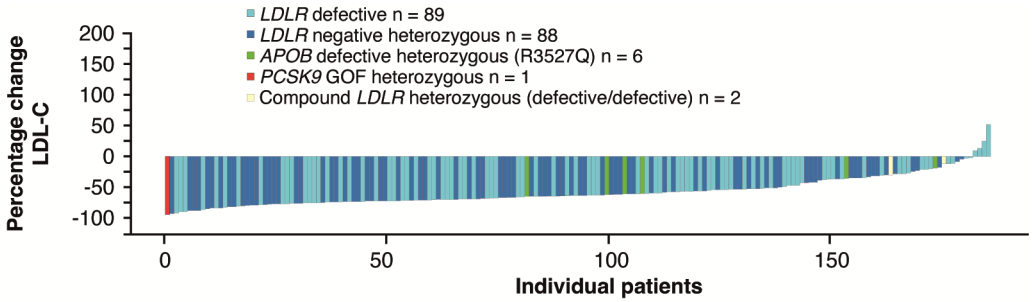

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Highlights

- 1191 patients sequenced to assess influence of genotype on response to alirocumab
- Mutations in FH genes (*LDLR*, *APOB*, *PCSK9*) found in 75% sequenced patients
- LDL-C reduced substantially and similarly across genotypes
- Alirocumab generally well tolerated in this FH population

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