Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Alirocumab (rch)

Proprietary Product Name: Praluent (Golyra/Eliriduc)

Sponsor: Sanofi-Aventis Australia Pty Ltd

First round: 31 August 2015

Second round: 14 August 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
Apo A-1	apolipoprotein A-1
Apo B	apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
AUC	area under the serum concentration versus time curve to time infinity
AUC_{last}	area under the serum concentration versus time curve from time zero to real time T_{last}
AUC_{0-28}	area under the serum concentration versus time curve from time zero to Day 29
AUC_{0-14}	area under the serum concentration versus time curve from time zero to Day 15
BMI	body mass index
C_{D15}	serum concentration observed on Day 15 (14 days post dose)
C_{D29}	serum concentration observed on Day 29(28 days post dose)
CHD	coronary heart disease
CHMP	Committee for Medicinal Products for Human Use (EU)
CKD	chronic kidney disease
CL/F	apparent total body clearance of drug from serum
C_{max}	maximum serum concentration observed
CSR	clinical study report
CV	cardiovascular
CVD	cardiovascular disease
DMC	data monitoring committee
EOS	end of study

Abbreviation	Meaning
EOT	end of treatment
FAS	full analysis set
GCP	Good Clinical Practice
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
heFH	heterozygous familial hypercholesterolemia
HLT	high level term
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA
HR	hazard ratio
hs-CRP	high-sensitivity C-reactive protein
IMP	investigational medicinal product
ITT	intention-to-treat
LC-MSMS	liquid chromatography with tandem mass spectrometry
LDL	low density lipoprotein
LDL-C	low density lipoprotein cholesterol
LDLR	low density lipoprotein receptor
LLOQ	lower limit of quantification
LMT	lipid-modifying therapy
Lp(a)	lipoprotein (a)
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
MMRM	mixed-effect model with repeated measures
MRT	mean residence time (mean time molecule resides in body)
NMAR	not-missing-at-random
non-FH	non-familial hypercholesterolemia
non-HDL-C	non-high-density lipoprotein cholesterol

Abbreviation	Meaning
PCSK 9	proprotein convertase subtilisin kexin type 9
PD	pharmacodynamics
PFP	pre-filled pen
PFS	pre-filled syringe
PK	pharmacokinetics
POP PK	population pharmacokinetic
PT	preferred term
Q2W	every 2 weeks
Q4W	every 4 weeks
SAE	serious adverse event
SC	subcutaneous
SE	standard error
SMQ	standardised MedDRA query
SOC	system organ class
SREBP-2	sterol regulatory element-binding-protein-2
TEAE	treatment emergent adverse event
TGs	triglycerides
T_{last}	time corresponding to the last concentration above the limit of quantification
T½z	terminal half life
Total-C	total-cholesterol
Vss/F	distribution volume at steady state
Vz/F	distribution volume in the terminal phase

1. Introduction

This is an application to register a new biological entity.

Alirocumab (rch) is a fully human monoclonal antibody (IgG1 isotype) that targets proprotein convertase subtilisin kexin type 9 (PCSK9).

In the submission alirocumab is also referred to as SAR236553 or REGN727.

The proposed indication is:

- Praluent is indicated, as adjunct therapy to diet, for long-term use in adult patients with primary hypercholesterolaemia (non-familial and heterozygous familial) or mixed dyslipidaemia, to reduce low density lipoprotein cholesterol (LDL-C).
- Praluent also decreases other atherogenic lipid parameters, such as total cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides (TG), and lipoprotein (a) [Lp(a)]. Praluent also increases high-density lipoprotein cholesterol (HDL-C).
- Praluent is indicated in combination with a statin (HMG-CoA reductase inhibitor), with or without other lipid-modifying therapy (LMT), in patients not appropriately controlled with a statin.
- Praluent is indicated as monotherapy, or as add-on to other non-statin LMT, in patients who cannot tolerate statins.

The submission proposes registration of the following dosage forms and strengths:

Table 1 Proposed dosage forms and strengths

Active Ingredient	Trade (proprietary) names	Strength	Dosage form	Pack/container
Alirocumab	Praluent	75 mg/mL	Solution for injection	1 (starter pack), 1, 2 and 6 Pre-filled Injection pen
Alirocumab	Praluent	150 mg/mL	Solution for injection	1 (starter pack), 1, 2 and 6 Pre-filled Injection pen
Alirocumab	Praluent	75 mg/mL	Solution for injection	1 (starter pack), 1, 2 and 6 Pre-filled syringe
Alirocumab	Praluent	150 mg/mL	Solution for injection	1 (starter pack), 1, 2 and 6 Pre-filled syringe
Alirocumab	Golyra	75 mg/mL	Solution for injection	1 (starter pack), 1, 2 and 6 Pre-filled Injection pen
Alirocumab	Golyra	150 mg/mL	Solution for injection	1 (starter pack), 1, 2 and 6 Pre-filled Injection pen

Active Ingredient	Trade (proprietary) names	Strength	Dosage form	Pack/container
Alirocumab	Golyra	75 mg/mL	Solution for injection	1 (starter pack), 1, 2 and 6 Pre-filled syringe
Alirocumab	Golyra	150 mg/mL	Solution for injection	1 (starter pack), 1, 2 and 6 Pre-filled syringe
Alirocumab	Eliriduc	75 mg/mL	Solution for injection	1 (starter pack), 1, 2 and 6 Pre-filled Injection pen
Alirocumab	Eliriduc	150 mg/mL	Solution for injection	1 (starter pack), 1, 2 and 6 Pre-filled Injection pen
Alirocumab	Eliriduc	75 mg/mL	Solution for injection	1 (starter pack), 1, 2 and 6 Pre-filled syringe
Alirocumab	Eliriduc	150 mg/mL	Solution for injection	1 (starter pack), 1, 2 and 6 Pre-filled syringe

1.1. Dosage and administration

The proposed PI contains the following proposed dosage and administration instructions:

- The recommended dose for Praluent is 75 mg or 150 mg administered subcutaneously once every 2 weeks. For mean LDL-C reduction achieved with the 75 mg and 150 mg dose in controlled clinical studies see section 7 Clinical efficacy.
- The dose selection should be based on individual patient characteristics and goal of therapy. The dose can be adjusted based on treatment response. Lipid levels may be analysed after 4 weeks, when maximum LDL-C reduction is usually achieved.
- If a dose is missed, the patient should administer the injection as soon as possible and thereafter resume treatment two weeks from the day of the missed dose.
- No dose adjustments are needed for elderly patients or patients based on weight. No dose adjustments are needed for patients with mild or moderate renal or hepatic impairment (see section 4 Pharmacokinetics).

1.1.1. Method of administration

- Praluent is injected as a single subcutaneous injection into the thigh, abdomen or upper arm. It is recommended to rotate the injection site with each injection. Praluent should not be injected into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections.
- The patient may either self-inject Praluent or a caregiver may administer Praluent, after guidance has been provided by a healthcare professional on proper subcutaneous injection technique.

- Praluent must not be co-administered with other injectable medicinal products at the same injection site.
- Praluent is a sterile product and contains no antimicrobial preservatives. Product is for single use in one patient only.
- Before administration, Praluent should be inspected visually for particulate matter and discolouration. If the solution is discoloured or contains particulate matter, the solution should not be used.
- To avoid discomfort, Praluent should be allowed to warm to room temperature (up to 25°C) for 30 to 40 minutes prior to use. Praluent should be used as soon as possible after it has warmed up. Time out of refrigeration should not exceed 24 hours at 25°C.
- After use, place the Praluent pre-filled syringe or pre-filled pen into a puncture resistant container and discard in accordance with local requirements.

2. Clinical rationale

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and disability in the Western world, and an increasing burden in developing countries and in Asia. Hypercholesterolaemia, particularly increased low density lipoprotein cholesterol (LDL-C), constitutes a major risk factor for the development of atherosclerosis and consequently ASCVD, especially coronary heart disease (CHD). LDL-C is identified as the primary target of lipid lowering and has been accepted as a valid surrogate endpoint for CHD risk. Numerous studies have demonstrated that reducing LDL-C levels, mainly via 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibition with statins, reduces the risk of CHD, with a strong direct relationship between LDL-C levels and incidence of CHD events. A large meta-analysis (*Cholesterol Treatment Trialists' Collaborators, 2005*) of 14 randomised trials including 90,056 individuals found that for every 1.0 mmol/L reduction in LDL-C, major vascular events were reduced by about 20%. An update of this meta-analysis (*Cholesterol Treatment Trialists' Collaboration, 2010*) on nearly 170,000 individuals noted that more significant LDL-C reductions provided further CV risk reduction. The authors postulated that a 2-3 mmol/L (77-116 mg/dL) reduction in LDL-C would result in a 40-50% reduction in major vascular events.

Guidelines for the management of dyslipidaemias have evolved over time in light of evidence from statin trials, and recommend a strategy of treating to specific LDL-C goals based on patients' CV risk level. European and US guidelines both recommend high intensity treatment in patients at very high CV risk:

Europe: in patients at high cardiovascular disease (CVD) risk, an LDL-C goal< 2.6 mmol/L (< 100 mg/dL) should be considered, and in patients at very high CVD risk, the recommended LDL-C target is < 1.8 mmol/L (< 70 mg/dL) or a ≥ 50% LDL-C reduction when the target level cannot be reached (*Reiner et al, 2011* and *Perk et al, 2012*)

USA: in the most recent guidelines, the use of high intensity statins is recommended in all high CV risk patients rather than specific LDL-C targets, to achieve a ≥ 50% LDL-C reduction, regardless of the LDL-C level (*Stone et al, 2014*)

Despite the use of statins, the LDL-C targets suggested in guidelines are often not achieved and additional lipid-modifying therapies (LMTs) are needed. These are most needed for patients requiring substantial reductions in their LDL-C level, such as patients with familial hypercholesterolemia, or individuals at the highest risk of ASCVD. In addition, some patients suffer from statin side effects that limit their ability to take a statin or a high enough dose of statin to reach their LDL-C goal. Non-statin therapies include ezetimibe, nicotinic acid, bile acid sequestrants, fibrates, and high-dose omega-3 fatty acids. These medications have less LDL-C lowering efficacy compared to statins (typically provide only about a 15 to 20% reduction in

LDL-C) and their actions on cardiovascular outcomes have not yet been convincingly demonstrated. There is a need for additional therapies that can have more profound effects on LDL-C, and provide corresponding CV benefit, particularly for patients who do not meet their LDL-C goals even on the highest tolerated doses of statins.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dosser documented a full clinical development program of pharmacology, efficacy and safety studies.

The submission contained the following clinical information:

- 13 x clinical pharmacology studies, including 10 that provided pharmacokinetic data and 3 that provided pharmacodynamic data.
- 3 x population pharmacokinetic analyses (POH400, POH377, POH394)
- 3 x dose-finding studies (DFI11565, R727-CL-1003)
- 10 x pivotal efficacy/safety studies (EFC12492, R727-CL-1112, EFC12732, EFC11568, EFC11569, EFC11716, R727-CL-1118, R727-CL-1119, LTS11717)
- 3 x other efficacy/safety studies (DFI11566, R727-CL-1032, DFI12361)
- 1 Integrated Summary of Efficacy and Integrated Summary of Safety (tables only)
- 6 x efficacy / safety studies of which only the protocol was submitted. These studies are stated to be ongoing or planned. As there are no study reports these protocols were not evaluated (EFC13786, R727-CL-1308, PDY13670, LTS13463, EFC13672, and EFC11570).

3.2. Paediatric data

The submission did not include paediatric data. Paediatric development programs are ongoing for Praluent and plans have been agreed with both the FDA (PSP) and the EMA (PIP).

3.3. Good clinical practice

The submission states that all studies were conducted in compliance with Good Clinical Practice (GCP), the requirements of the Declaration of Helsinki, standard operating procedures for clinical investigations and documentation of the sponsor, all applicable international laws and regulations as well as national laws and regulations of the country(ies) in which the studies were performed. Clinical study protocols and amendments were subject to Health Authority and Ethics Committee approvals prior to initiation as applicable and adverse events (AEs) were reported according to local laws.

Non-compliance with GCP was identified at 3 sites (2 in USA and 1 in Russia) which affected three of the pivotal studies. The sites were terminated and health authorities notified. The patients were discontinued from the study and sensitivity analysis was conducted to test for effect on the results. The non-compliance and analyses are detailed and discussed in each study.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The following table shows the studies relating to each pharmacokinetic topic:

Table 2. Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Primary aim
PK in healthy adults	General PK - Single dose	PKD12010	Tolerability
		PKD12011	Tolerability
		PKD12275	Injection site tolerability
		R727-CL-0902	Tolerability IV
		R727-CL-0904	Safety
		TDU12190	Safety in Japanese
	Bioavailability - sites	BDR13362	BA
		PKD12010	Tolerability
		PKD12011	Tolerability
		PKD12275	Injection site tolerability
PK in special populations	Target population[1] - Multi-dose	R727-CL-1001 PKD12910	Safety PD/PK
	Hepatic impairment	POP12671	PK
	Dose finding	R727-CL-1003 DFI11565 DFI12361	Dose finding Dose finding Efficacy/Safety
PK Interactions	Atorvastatin	R727-CL-1001	Interaction
	Ezetimibe and fenofibrate	PKD12910	PD/PK
Population PK analyses	Healthy subjects and Target population	POH400 POH377 POH394	PD PK PK/PD

[1] Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Physicochemical characteristics of the active substance

Alirocumab is a recombinant human antibody (IgG1 isotype) consisting of 2 disulfide-bonded human heavy chains, each covalently linked through a disulfide bond to a human kappa light chain. The molecular weight based on primary sequence (without heavy chain C-terminal Lys448) is 145,983.8 Da (in the absence of N-linked glycosylation).

4.2.2. Pharmacokinetics in healthy subjects and target population

The Phase I studies were conducted in healthy adults with LDL-C >100 mg/dL (2.59 mmol/L) except 2 studies, 1 that enrolled patients with hypercholesterolemia (either familial or non-familial) (Studies CL-1001) and 1 in patients with hepatic failure and matched healthy subjects Study POP12671). Only patients with hypercholesterolaemia were enrolled in the Phase II and Phase III studies. In all studies, except the first Phase I study (CL-0902, IV administration), alirocumab was administered via SC injection.

4.2.2.1. Absorption

IV administration

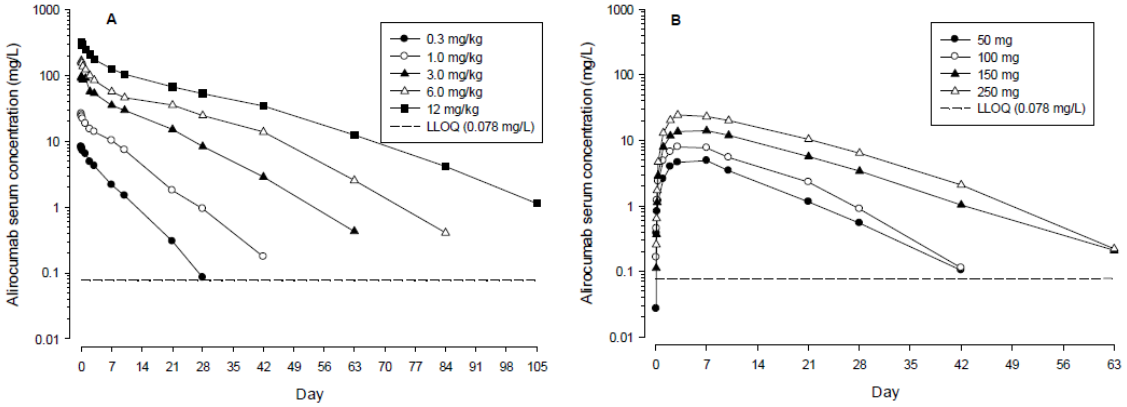
In Study R727-CL-0902 alirocumab was administered via a 1-\ hour infusion in 30 healthy subjects with LDL-C > 100 mg/dL (> 2.59 mmol/L) who were not indicated for statin therapy**.** There were 5 sequential dose cohorts (0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, 6.0 mg/kg, and 12.0 mg/kg) with each dose cohort consisting of 8 subjects (6 subjects on alirocumab and 2 on placebo). Following IV administration, an initial short distribution phase was followed by a beta-elimination phase and a target mediated elimination phase. The mean maximum serum concentration (C_{max}) was dose proportional. The mean AUC_{last} was greater than dose proportional when the dose was increased up to 3 mg/kg, while dose proportional kinetics were generally observed at doses higher than 3 mg/kg. The mean terminal half-life (T½z) was not dose-dependent, and ranged from 4.75 to 7.97 days.

Maximum concentrations of total PCSK9 increased with dose when the dose was increased up to 3 mg/kg. PCSK9 was almost completely bound to alirocumab at the 3 mg/kg dose and above. Concentrations of free PCSK9 were below the LLOQ level when concentrations of alirocumab were above about 10 mg/L, which was also the concentration when the beta-elimination phase was observed and when concentrations of total PCSK9 reached their maximum. The dose-response profile of alirocumab with free and total PCSK9 are consistent with saturation of the target mediated elimination of alirocumab at a dose of 3 mg/kg.

SC administration

After single dose SC administration of 50 mg to 250 mg to healthy subjects, alirocumab C_{max} was observed at a median time of 3 days to 7 days with no apparent dose dependency. In patients at steady state, alirocumab C_{max} was observed with a median time of 3 days at 75 mg and 150 mg every 2 weeks (Q2W) (Study POH0377).

Figure 1. Mean alirocumab serum concentrations versus nominal day after IV (A) and SC (B) single administration in healthy subjects - semi-logarithmic scale



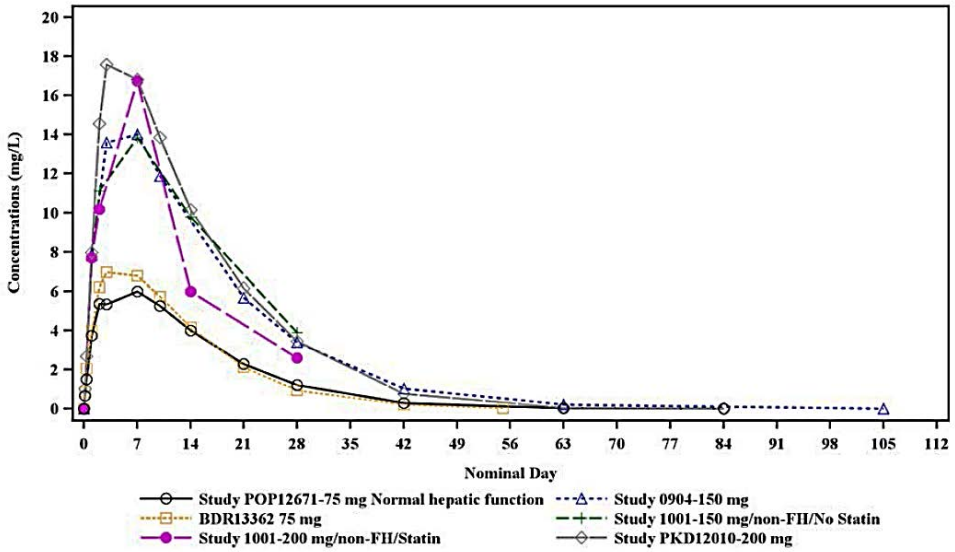
Study CL-0902 [A] and CL-0904) [B]

In addition, alirocumab steady state exposure after 150 mg Q2W SC administration was comparable when administered using the PFP or PFS in patients, indicating that bioavailability was independent of the drug product presentation.

Table 3. Alirocumab steady state exposures at 150 mg by drug product presentation in pivotal studies - Study POH0377

Alirocumab 150 mg			
Drug product presentation	**n**	**Cmax (mg/L) Mean (CV) [Median]**	**AUC_{0-336} (mg.h/L) Mean (CV) [Median]**
Prefilled syringe (PFS)	1437	18.0 (46.6%) [16.5]	5030 (53.6%) [4470]
Prefilled pen (PFP)	203	19.0 (46.7%) [18.3]	5390 (52.4%) [5030]

Figure 2. Mean concentration-time profiles after SC administration of alirocumab in healthy subjects across Phase I studies (POP12671, BDR13362, CL-0904, PKD12010, and CL-1001)



4.2.2.2. Bioavailability

Absolute bioavailability

The absolute bioavailability of alirocumab after SC administration was about 85% as determined in the POP PK analysis (Study POH0377).

Influence of food

No food effect study was conducted as alirocumab is administered SC and food is not anticipated to impact the PK.

Effect of administration location

The PK of alirocumab in healthy subjects after single SC injection of 75 mg into the abdomen, upper arms, or thigh was similar. The site of injection was not reported as a significant covariate impacting the PK profile of alirocumab (Study POH0377).

Dose proportionality

In healthy subjects, following both single-dose IV and SC administrations, alirocumab AUCs increased slightly more than expected from dose proportionality, though the deviation from linearity is modest. Cmax appeared to increase in a dose proportional manner.

In patients, alirocumab exposure increased in a dose proportional or slightly more than expected from dose proportionality with a 2.1 to 2.7 fold increase in alirocumab concentrations for a 2 fold increase in dose from 75 mg to 150 mg Q2W. These findings were consistent with the saturation of the target mediated clearance of alirocumab at both 75 mg and 150 mg Q2W explained by a complete or nearly complete binding of free PCSK9 through the whole dosing interval.

Table 4. Dose proportionality assessment on alirocumab C_{max} and AUC in healthy subjects after single intravenous dose ranging from 0.3 to 12 mg/kg - Study CL-0902

Day	Parameter	Dose ratio	Ratio	
			Estimate	90% CI
Day 1	Cmax	(r) = 2	2.00	(1.95 to 2.05)
		(r) = 40	39.79	(34.61 to 45.76)
		Beta	1.00	(0.96 to 1.04)
	AUC	(r) = 2	2.32	(2.25 to 2.40)
		(r) = 40	88.25	(74.50 to 104.50)
		Beta Estimate	1.21	(1.17 to 1.26)

Note: for C_{max} and AUC, dose proportionality was assessed on Day 1 using the empirical power model (PK parameter = $\alpha \times dose^{\beta}$). Estimates with 90% confidence intervals for β will be obtained, and further used to obtain estimates and 90% confidence intervals for the PK parameter increases associated with an r fold (r = 2 and r = high dose / low dose) increase in dose. C_{max} = 28.87 x $dose^{1.00}$ for Day 1. AUC = 212.49 x $dose^{1.21}$ for Day 1

Table 5. Dose proportionality assessment on alirocumab C_{max} and AUC in healthy subjects after single subcutaneous dose ranging from 50 to 250 mg - Study CL-0904

Parameter	Dose ratio	Ratio	
		Estimate	90% CI
Cmax	(r) = 2	1.96	(1.62 to 2.37)
	(r) = 5	4.77	(3.06 to 7.44)
	Beta	0.97	(0.69 to 1.25)
AUC	(r) = 2	2.23	(1.83 to 2.72)
	(r) = 5	6.42	(4.05 to 10.20)
	Beta Estimate	1.16	(0.87 to 1.44)

Note: for Cmax and AUC, dose proportionality was assessed on Day 1 using the empirical power model (PK parameter = α×doseβ). Estimates with 90% confidence intervals for β will be obtained, and further used to obtain estimates and 90% confidence intervals for the PK parameter increases associated with an r fold (r = 2 and r = high dose / low dose) increase in dose. C_{max} = 0.10 x dose0.97 for Day 1. AUC = 0.74 x dose1.16 for Day 1.

Table 6. Dose proportionality on alirocumab steady state trough concentrations and AUC_{0-336} in patients after 75 mg and 150 mg Q2W

Study	75 mg Q2W		75/150 mg Q2W or 150 mg Q2W[a]		Dose proportionality
C_{trough} (mg/L)					
	n	Mean (SD)	n	Mean (SD)	
EFC11716	30	6.99 (4.42)	10	14.8 (10.2)	2.1
EFC12492	146	4.47 (2.47)	113	12.1 (8.94)	2.7
EFC11569	313	3.95 (2.73)	62	8.38 (10.9)	2.1
AUC_{0-336} (mg.day/L)					
	n	Mean (SD)	n	Mean (SD)	
EFC11716	40	3080 (1450)	15	7660 (3960)	2.5
EFC12492/EFC11569/ LTS11717	514	2150 (908)	1625	5050 (2690)	2.3

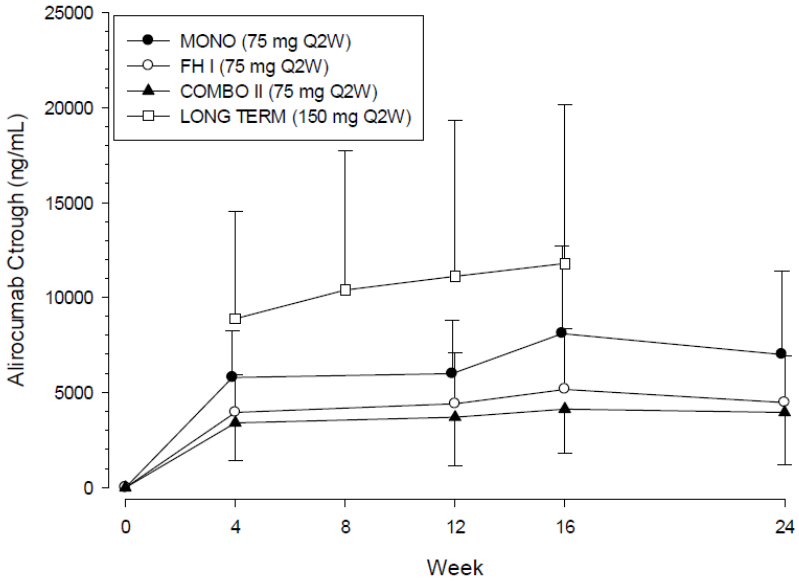
Note: dose proportionality = mean C_{trough} or AUC at 150 mg/ mean C_{trough} or AUC at 75 mg : 75/150 mg Q2W for Studies EFC12492/EFC11569 and 150 mg Q2W for Study LTS11717.

Steady state - Accumulation ratio

None of the studies conducted in healthy subjects were designed to assess either steady state achievement or an accumulation ratio.

In patients after 75 mg and 150 mg Q2W SC administration, graphical assessment of alirocumab trough concentrations indicated that steady state was reached after 2 to 3 doses (2 to 4 weeks) (Studies EFC12492 [FH I], EFC11716 [MONO], EFC11569 [COMBO II]).

Figure 3. Mean (SD) trough concentration of alirocumab after subcutaneous 75 mg or 150 mg Q2W administration in patients (Mono, FHI, COMBO II, and LONG TERM)



Based on post-hoc individual predicted PK parameters from the POP PK analysis, the median accumulation ratio was 1.7 and 1.9 after alirocumab 75 mg and 150 mg Q2W dosing regimens, respectively, with no apparent difference when administered as monotherapy or in combination with other LMTs (Study POH0377). These observed accumulation ratios in patients were close to those predicted in healthy subjects from single dose data suggesting that alirocumab PK is predictable from single dose data and is time-independent.

Table 7. Alirocumab predicted accumulation ratio from single 75 to 150 mg dose studies in healthy subjects

Dose	Study	Predicted accumulation ratio [a]
75 mg	BDR13362	1.4 to 1.6
	POP12671 [b]	1.5
100 mg	TDU12910	1.5
150 mg	TDU12910	1.8

[a] Predicted accumulation ratio= median AUC/ median AUC0-14. [b] From healthy subjects only.

4.2.2.3. Distribution

As typical for monoclonal antibodies (mAbs) alirocumab is distributed in the circulatory system as illustrated by the small volume of distribution (0.04 to 0.05 L/kg) seen in Study CL-0902.

4.2.2.4. Metabolism

Specific metabolism studies were not conducted because alirocumab is a protein. It is generally accepted that antibodies are metabolised by degradation into small peptides and individual amino acids.

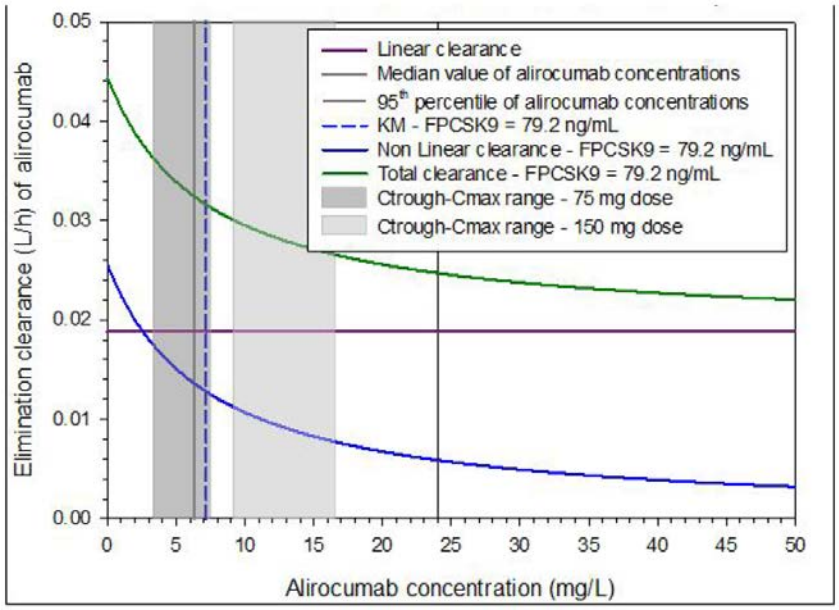
4.2.2.5. Excretion

Clearance of Alirocumab after a single IV administration of doses ranging between 0.3 mg/kg and 12 mg/kg (Study CL-0902) decreased by approximately 2 fold from 0.00620 to 0.00317 L/day/kg. Mean T½z ranged from 4.8 days to 8 days with no meaningful dose effect.

Based on the POP PK analysis, elimination of alirocumab was characterised by saturable target mediated clearance. At lower alirocumab concentrations the target mediated process predominates but linear clearance predominates at higher alirocumab concentrations. However, even at concentrations achieved over the dosing interval at therapeutic doses, the target mediated clearance still contributes to total clearance. In situations where the target concentration varies, the contribution of the target mediated clearance will vary. For example, in patients receiving alirocumab 75 mg Q2W in combination with statins, the linear clearance represented 50% to 60% of the total clearance. This is consistent with the near saturation of free PCSK9 through the dosing interval and with the only slight supra-dose proportionality observed in patients from 75 mg to 150 mg Q2W.

In patients receiving statins co-administered with alirocumab at 75 mg and 150 mg Q2W, alirocumab median steady state apparent half-life over the dosing interval was 12 days. In monotherapy after 75 mg and 150 mg Q2W dosing regimens, the median apparent half-life of alirocumab over the dosing interval was 17 to 20 days. Statin co-administration shortens alirocumab half-life by increasing production of PCSK9 and thus increasing the target mediated clearance of alirocumab.

Figure 4. Dependence of total, linear and nonlinear clearance on alirocumab concentrations in patients co-administered with statins from Phase III studies – POH0377



4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

Alirocumab is eliminated partly through target mediated clearance at lower concentrations. Its elimination could therefore vary, based on a dependence on PCSK9 (target) concentrations, production, and elimination. As PCSK9 is produced, secreted, and largely eliminated by the liver, the effect of mild and moderate hepatic impairment on alirocumab PK was assessed in a Phase I study after a single 75 mg SC dose (Study POP12671).

The results showed that in subjects with mild and moderate hepatic impairment after a single 75 mg dose of alirocumab, alirocumab PK profiles were similar to that observed in healthy

subjects. There was a high degree of consistency in C_{max}, and T_{max} with a non-significant shift toward faster elimination in the hepatic impaired groups. The peak percent LDL-C decrease in the hepatic impairment groups (reaching 33.2% and 35.8% in mild and moderate hepatic impairment groups, respectively), was somewhat less than in healthy subjects (peak decrease reaching 45.4%.).

Even with this slightly attenuated effect of LDL-C in patients with hepatic impairment, the effect observed with alirocumab 75 mg was clinically meaningful, therefore no dose adjustment of alirocumab would be required due to the presence of mild or moderate hepatic impairment, and given the lower systemic concentrations of alirocumab, and slightly less lowering of LDL-C in these patients, there is no trend in these data which would preclude mild to moderate hepatic impairment patients from up-titration to 150 mg Q2W.

No data on patients with severe hepatic impairment was provided and so no recommendations on these patients can be made.

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

Consistent with other mAbs, alirocumab elimination by the renal route is likely to be insignificant due to its large molecular weight which prevents efficient filtration through the glomerulus. Secretion into the bile is also not anticipated to be a significant contributor to the elimination of alirocumab. Therefore it is unlikely that renal impairment would impact the alirocumab PK profile. No dedicated study was conducted to assess the effect of renal function impairment on the PK of alirocumab.

The impact of renal impairment on alirocumab PK was assessed through the POP PK analysis. Renal function (measured by estimated creatinine clearance and estimated glomerular filtration rate) was not identified as a significant covariate impacting alirocumab population parameters (Study POH0377). However, unexpectedly, alirocumab exposure (AUC_{0-336}) at steady state at both 75 and 150 mg Q2W dosing regimen increased by 22% to 35%, and 49% to 50% in patients with mild and moderate renal impairment, respectively, compared to patients with normal renal function. This unexpected difference in exposure is most likely explained by the indirect effect of 2 confounding factors (body weight and age) and is unlikely to reflect a direct effect of renal function on alirocumab PK. This is supported by the lack of renal function as a significant covariate in the POP PK model, when controlling for body weight and age.

4.2.3.3. Pharmacokinetics according to age

Age was identified as a significant covariate in the final POP PK model impacting alirocumab peripheral volume of distribution. However, this effect was minimal and not considered clinically significant, with the peripheral volume of distribution increasing from 2.79 L for a 60 year old patient to 2.86 L for a 65 year old patient and 2.99 L for a 75 year old patient (Study POH0377). No dose adjustments are recommended in elderly patients.

4.2.4. Pharmacokinetic interactions

Since alirocumab is a mAb, it is not anticipated to directly interact with cytochrome P450 enzymes, other drug metabolising enzymes, or drug transporters, thus no typical drug-drug interactions of alirocumab on other drugs via these mechanisms are expected, and therefore no specific PK drug-drug interaction studies have been conducted.

Nevertheless, if present, an unanticipated drug-drug interaction that might lead to high statin concentrations could potentially cause statin mediated toxicity. Therefore, the effect of alirocumab on atorvastatin and rosuvastatin exposures was evaluated as a secondary objective in some clinical studies (Study CL- 1001 and Study CL-1003). The effect of background therapy of LMTs on alirocumab PK was also evaluated in the POP PK analysis of pooled data from studies in healthy subjects and patients including patients receiving maximum tolerated statin doses (Study POH0377).

Statins were identified as a significant covariate affecting alirocumab exposure. When administered in combination with statins, a more pronounced target mediated clearance of alirocumab was observed due to increased levels of PCSK9 induced by statins. This impact of statins translated into a 28% to 29% lower alirocumab exposure at steady state in statin treated patients. When other LMTs, such as ezetimibe or fenofibrate, were co-administered with alirocumab in healthy subjects, a smaller effect on target mediated clearance was observed.

Table 8. Alirocumab steady state exposures by LMT category in patients from Phase III – Study POH0377

Covariate		75 mg Q2W			150 mg Q2W		
		n	Cmax (mg/L)	AUC0-336 (mg.h/L)	n	Cmax (mg/L)	AUC0-336 (mg.h/L)
Lipid modifying therapy	No statin	40	10.8 (41.0)	3080 (47.2)	15	25.5 (47.8)	7660 (51.7) [6330]
	Statin	514	7.93 (35.6)	2150 (42.2)	1625	18.0 (46.5)	5050 (53.2) [4520]
	No ezetimibe	441	8.01 (38.8)	2180 (45.8)	1374	18.2 (47.7)	5130 (54.4) [4550]
	Ezetimibe	113	8.64 (32.5)	2350 (39.4)	266	17.3 (40.4)	4790 (46.8) [4390]

Descriptive statistics are Mean (CV%) [Median]

Overall, in the pivotal efficacy studies, with a Q2W dosing regimen and the opportunity for dose up-titration in patient starting at 75 mg alirocumab, a mean LDL-C reduction from baseline of close to -50% was observed, demonstrating a sufficient effect independently of the background therapy. Therefore no adjustment to the dose is anticipated.

4.3. Evaluator's overall conclusions on pharmacokinetics

There were 3 studies conducted to investigate the bioequivalence of the formulations used in the clinical development program. None of the studies were powered to demonstrate bioequivalence and no explanation for this is provided. The studies showed only that the PK of alirocumab was similar between the 2 alirocumab cell lines, and process lots:

- between 2 different formulations 175 mg/mL and 150 mg/mL drug product forms, both produced using the C1 cell line; (Study PKD12010)
- between investigational medicinal product batches produced using 2 different cell lines (C1 and C2; Study PKD12011) and
- between the administration of the same dose with different injection volumes or number of injections: 1 injection of 2 mL of 150 mg/mL, 1 injection of 1.71 mL of 175 mg/mL or two injections of 1 mL of 150 mg/mL, each produced using the C2 cell line (Study PKD12275).

The PK profile was described by non-linear target mediated clearance and at low concentrations of alirocumab exposure increased in a greater than dose proportional manner. Upon achieving target saturation, exposure continued to increase in a linear and dose proportional manner. The concentration-time profiles of alirocumab following SC administration are characterised by an initial absorption phase followed by a bi-phasic elimination phase consisting of a linear beta elimination, followed by a terminal target mediated elimination phase.

When alirocumab is administered in combination with other LMTs known to increase the production of the target (PCSK9), an enhanced target mediated elimination phase is observed, with a more rapid clearance, compared to alirocumab administered alone. When administered using a Q2W dosing regimen, alone or in combination with other LMTs, steady state concentrations of total alirocumab were achieved within 2 or 3 SC administrations.

The main intrinsic sources of PK variability identified in patients are age, body weight and free PCSK9, but they have a moderate effect (less than 1.6 fold). As expected for a mAb, race, gender, and mild or moderate hepatic or renal impairment did not impact the PK of alirocumab. Because patients with severe hepatic or renal impairment were excluded from the studies, there is no data on alirocumab exposure in such patients. Patients with severe hepatic impairment were not included in the POP12671 study, justified by the observation that most of these patients have decreased lipid levels, and hypercholesterolemia is rarely observed.

The proposed Product Information (PI) is consistent with the data from the PK clinical studies conducted.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

The table below shows the studies relating to each PD topic and the location of each study summary.

Table 9 Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	Primary aim
Primary Pharmacology	Effect on LDL-C	R727-CL-1018i	PD
		PKD12910	PD
Population PD and PK-PD analyses	Healthy subjects and Target population	POH0394	PK/PD

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional PD studies in humans unless otherwise stated.

5.2.1. Mechanism of action

Alirocumab is a fully human monoclonal antibody (mAb) (IgG1 isotype) that targets proprotein convertase subtilisin kexin type 9 (PCSK 9). Alirocumab is a covalent heterotetramer consisting of 2 disulfide linked human heavy chains, each covalently linked through a disulfide bond to a fully human kappa light chain, and is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture. The variable domains of the heavy and light chains combine to form complementarity determining regions for the binding of alirocumab to its target, PCSK9.

Alirocumab binds with high affinity and specificity to PCSK9. PCSK9 is secreted from cells following synthesis and autocatalytic cleavage. PCSK9 binds to the low density lipoprotein receptors (LDLRs) on the surface of hepatocytes. The LDLR is the major pathway through which cholesterol rich low density lipoprotein (LDL) particles are cleared from circulation and hepatic LDL uptake is a major determinant of circulating LDL-C levels. When an internalised LDLR is bound to PCSK9, this promotes the degradation of the LDLR, preventing its recycling to the cell surface. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL particles, thereby lowering LDL-C levels.

5.2.2. Pharmacodynamic effects

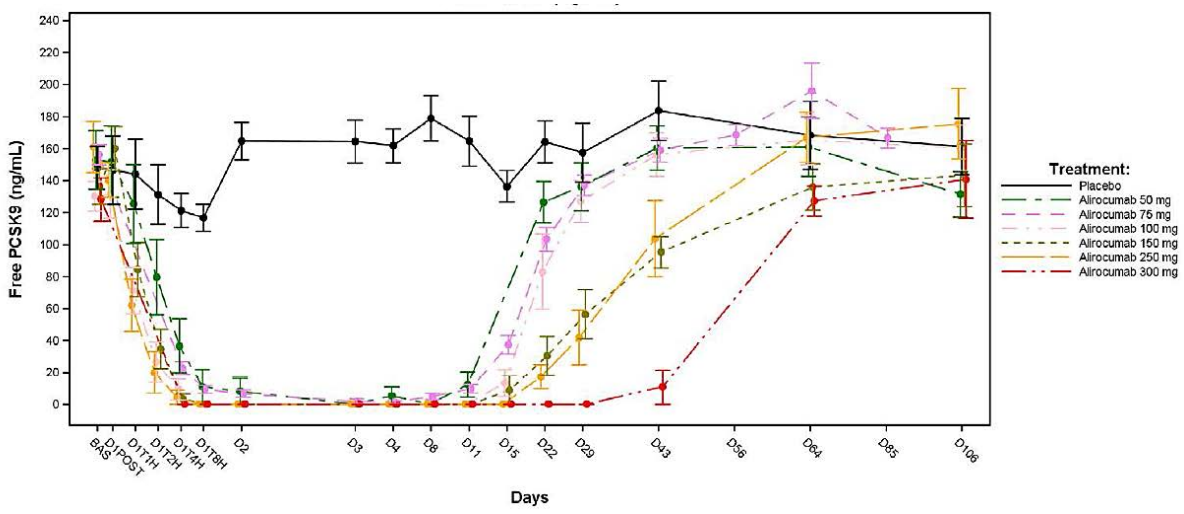
5.2.2.1. Primary pharmacodynamic effects

The extracellular concentration of PCSK9 has an effect on LDL-C concentrations by binding to LDLR and promoting its degradation. LDLR is the primary receptor that clears circulating LDL-C, and this PCSK9 mediated decrease in LDLR results in increased levels of LDL-C. The PD effect of alirocumab in lowering LDL-C is indirect, mediated through the binding of the mAb directed against PCSK9 and inhibition of the negative-regulatory effect of PCSK9 on the LDLR. PCSK9 bound to alirocumab is biologically inert. The PD effect of alirocumab is governed by saturable PCSK9 (target) binding.

Effect on PCSK9 (Target)

After a single SC administration of alirocumab from 50 to 300 mg, free PCSK9 decreased with mean free PCSK9 concentrations initially falling below the LLOQ (that is, 31.2 ng/mL) between Days 2 and 11. When doses of alirocumab were increased sufficiently to suppress free PCSK9 below the LLOQ, further dose escalation of alirocumab resulted in a prolongation of this suppression. Following a single SC dose, detectable concentrations of free PCSK9 were restored between Day 11 and Day 29 in a dose-dependent manner.

Figure 5. Pool Phase I data: Means (± SEM) free PCSK9 concentrations

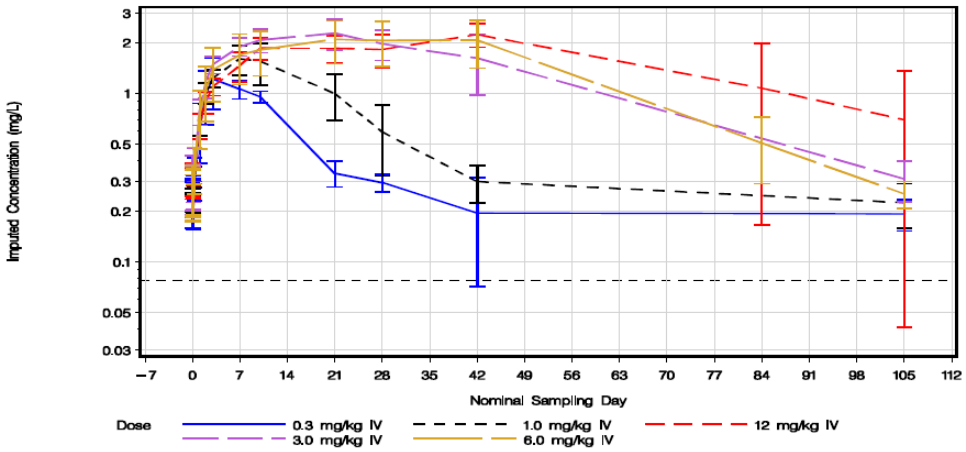


Pool of studies R727-CL-0904, TDU12190, BDR13362, POP12671 (healthy subjects only). Note: Baseline is the value on Day 1 pre-dose assessments and is the average of 3 pre-dose values for the POP12671 study. The end of study visit is Day85 for BDR13362 and POP12671, and Day 106 for R727-CL-0904 and TDU12190.

The decrease in free PCSK9 is accompanied by a corresponding increase in total PCSK9, the vast majority being in the biologically inert bound complex. When alirocumab is in excess and free PCSK9 is depleted (target saturation), then any newly formed PCSK9 is immediately complexed, so that the rate limiting step in the formation of total PCSK9 then becomes the availability of newly formed PCSK9. With the elimination of PCSK9-alirocumab complex being slow relative to formation, the concentration of total PCSK9 plateaus. Thus, measurement of total PCSK9 serves as a direct and useful marker of target saturation.

Once the concentrations of alirocumab were no longer sufficient to complex all newly synthesised free PCSK9, the concentrations of total PCSK9 declined. This decline in total PCSK9 concentrations coincided closely with the return of detectable concentrations of free PCSK9. Once target binding is saturated, further increases in dose no longer results in further increases in total PCSK9 concentrations, but rather a prolongation of the plateau in total PCSK9 concentrations.

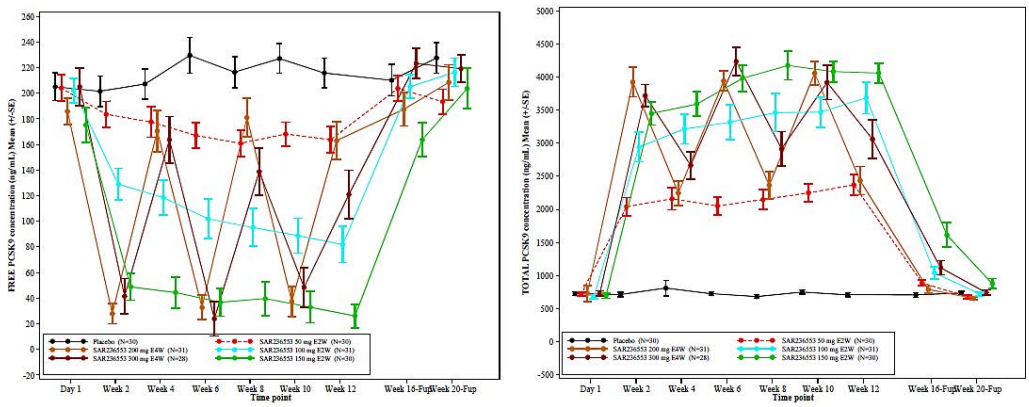
Figure 6. Study R727-CL-0902: Mean (±SD) Log-scaled concentrations of total PCSK9 versus nominal day following a single IV infusion in normal healthy subjects



Notes: 1 SD around the mean is presented. Concentrations below the LLOQ (horizontal black dashed line) are imputed as LLOQ/2 = 0.039 mg/L.

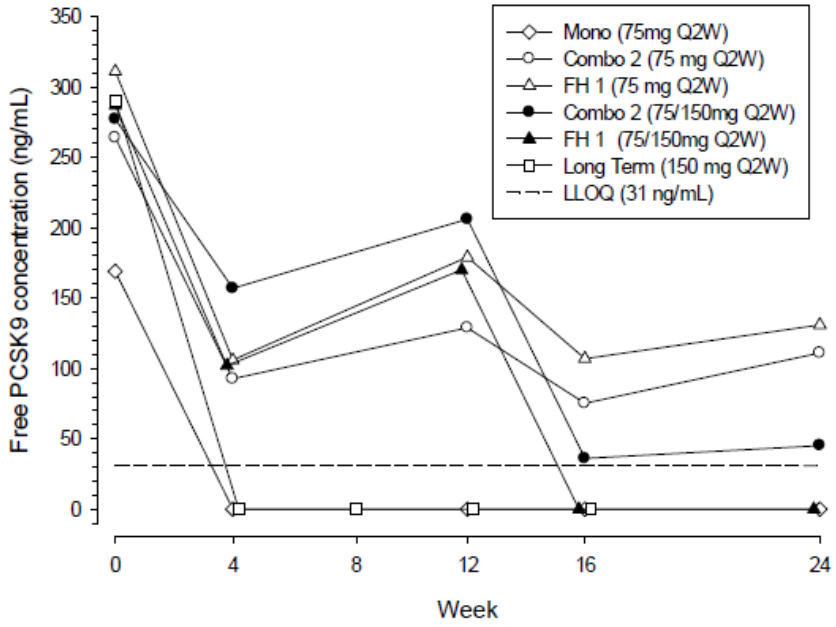
In studies DFI11565, and CL-1003, the regimen and dose of alirocumab were investigated in patients with background statin treatment. Large and significant decreases in free PCSK9 from baseline to 12 weeks were observed in the studies with all doses administered regardless of regimen (Q2W or Q4W). However, the reduction in free PCSK9 concentrations was not fully maintained over the Q4W interval in all these statin treated patients. The largest decrease in free PCSK9 was seen in the 150 mg Q2W group. Dose levels higher than 150 mg did not result in higher total PCSK9 concentrations, indicating that saturation was achieved at 150 mg Q2W.

Figure 7. Study DFI11565: Free (left) and total (right) PCSK9



In the efficacy studies, in patients using either an initial dosing regimen of 75 mg Q2W, or 150 mg Q2W, a significant reduction in free PCSK9 concentrations was observed at the first post-baseline assessment. In patients requiring up-titration to 150 mg Q2W, a further reduction of free PCSK9 was noted after starting the 150 mg Q2W regimen. However, the increase in total PCSK9 was marginal, suggesting that the 75 mg Q2W dose was approaching target saturation. This marginal increase in total PCSK9 resulting from up titration also indicated that there is little opportunity for higher doses to have an even greater reduction of LDL-C.

Figure 8. Median trough free PCSK9 concentrations - Efficacy studies



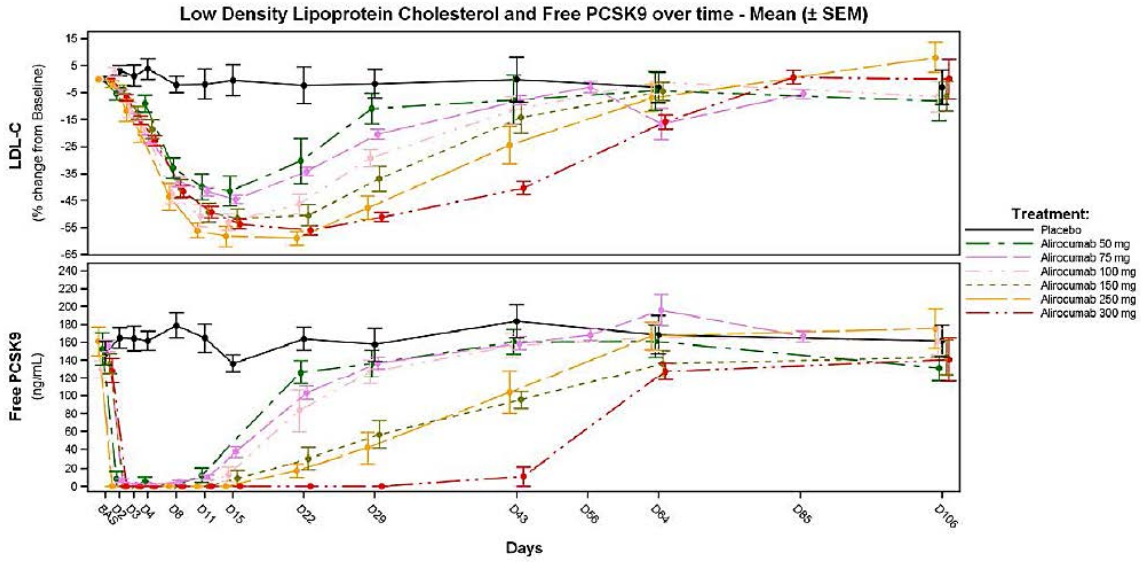
Note: up-titration to 150 mg planned on Week 12.

Effect on LDL-C

In order to assess the alirocumab dose effect relationship on LDL-C reduction, LDL-C data from single-dose Phase I studies conducted in healthy subjects using SC formulation (studies CL-0904, PKD12010, PKD12011, PKD12275, and TDU12190) were pooled and results are presented below. The subjects included in these studies were not receiving concomitant LMT.

Consistent profiles of LDL-C reduction after alirocumab administration were observed across all these single dose studies using SC administration. A similar pattern was observed with the IV administration, for both peak reduction and duration of effect (Study CL-0902). A dose-related decrease in the maximally obtained LDL-C reduction was observed as well as a positive dose-relationship with the duration of LDL-C reduction. For doses ranging from 50 mg to 300 mg, the maximum mean percent reductions in LDL-C ranged from 40% to 56% and occurred between Day 15 and Day 22. At doses above 100 mg only a limited increase in the maximal LDL-C reduction was observed with increasing dose. The main effect of dose increase was on the duration of maximum LDL-C reduction. At the highest dose reductions in LDL-C close to 50% were achieved by Day 11 post-administration and maintained up to Day 29. Consistent with the indirect mechanism of action of alirocumab on LDL-C through depletion of free PCSK9, with concentrations of alirocumab sufficient to maximally bind free PCSK9, any additional increases of alirocumab concentrations were not observed to further reduce LDL-C through this mechanism, but the duration of the LDL-C lowering was extended.

Figure 9. Summary plots of mean (90% CI) percent change from baseline in LDL C (mmol/L) or mean Free PCSK9 - PD population - Pooled data



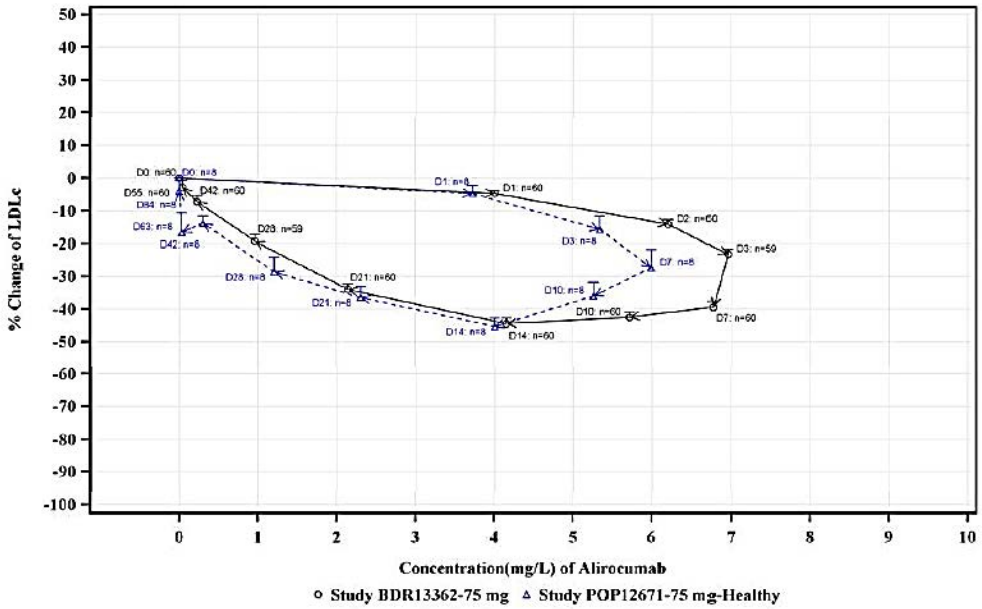
LDL-c graph: Pool of CL-0904, PKD12010, PKD12011, PKD12275, TDU12190, BDR13362, POP12671 (healthy subjects only) studies. PCSK9 graph: Pool of CL-0904, TDU12190, BDR13362, POP12671 (healthy subjects only) studies. BAS = Baseline value on Day 1 pre-dose assessments (for the POP12671 study, this is the average of 3 pre-dose values). The end-of-study visit is D85 for PKD12010, PKD12011, PKD12275, BDR13362 and POP12671, and D106 for R727-CL-0904 and TDU12190.

5.2.3. PK/PD relationship

Alirocumab lowers LDL-C through an indirect mechanism requiring first formation of a complex with PCSK9, with a subsequent increase in hepatocyte cell surface LDLRs and increased clearance of LDL-C from the circulation. These latter physiological effects are expected to result in some temporal delay related to this underlying biology. This temporal delay also occurs in the reverse direction with the restoration of LDL-C upon declining concentrations of alirocumab.

The PK/PD relationship between systemic concentrations of alirocumab and the LDL-C concentrations results in a clockwise hysteresis loop. The formation of this hysteresis loop reflects the temporal delay between alirocumab concentrations and LDL-C lowering, while the clockwise direction of this loop is a reflection of the inhibitory effect of alirocumab on the negative regulation of PCSK9 on LDL-C. Furthermore, the asymptotic or saturating effect of alirocumab on LDL-C is observed by the flat profile in the lower portion of the hysteresis loop and the overall oblong nature of this hysteresis.

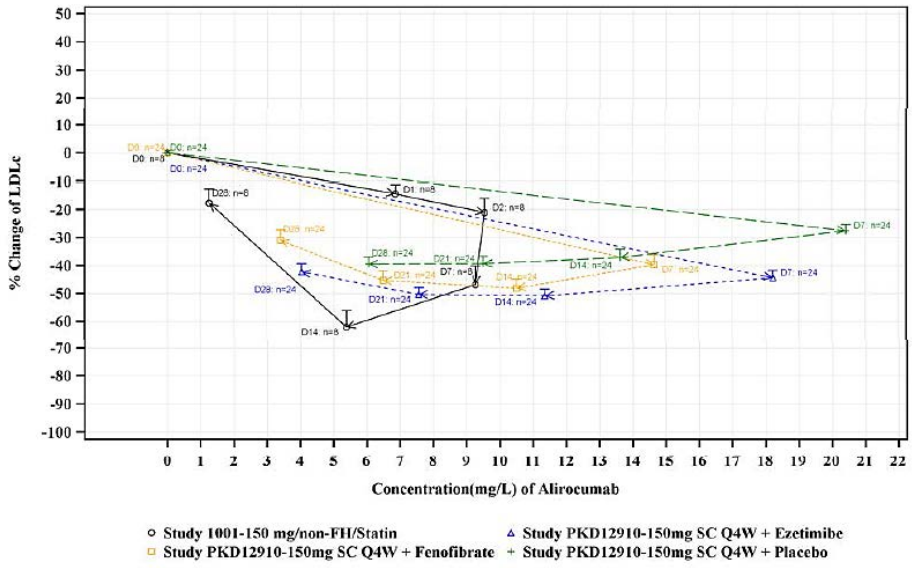
Figure 10. Mean (SE) % change of LDL-C concentrations versus mean concentrations of alirocumab



Effect of LMT on the hysteresis and PK/PD profile of alirocumab on LDL-C

By augmenting PCSK9 production, LMTs may increase the target mediated clearance of alirocumab and reduce alirocumab exposure. Co-administration of alirocumab with either ezetimibe or fenofibrate had a modest impact on this PK/PD relationship. However, concomitant use of statins (that is, atorvastatin) resulted in a horizontal compression of the alirocumab PK/PD hysteresis. This longitudinal compression of the PK/PD relationship may result from the decrease of maximal systemic concentrations of alirocumab from statin-induced increases in PCSK9 production and increased target mediated clearance. The impact of statins on PCSK9 production, and the resulting downstream increase in alirocumab clearance suggested by this modification in the observed hysteresis, is consistent with the POP PK finding that statins, but not ezetimibe or fenofibrate, are an important factor in the clearance of alirocumab.

Figure 11. Mean (+SE) % change of LDL-C concentrations versus mean concentrations of alirocumab



5.3. Evaluator's overall conclusions on pharmacodynamics

The clinical pharmacology data demonstrated that alirocumab decreases LDL-C, through binding and inhibition of PCSK9, which regulates LDLR. When free PCSK9 was completely bound, maximal LDL-C reductions of 55 to 70%, were observed. Higher concentrations of alirocumab did not result in further reduction of LDL-C, but resulted in a prolongation of the maximal binding of free PCSK9 and a corresponding prolongation of LDL-C reduction.

Alirocumab was designed to bind and inhibit PCSK9, a negative regulator of LDLR. This inhibition of PCSK9 by complex formation with alirocumab resulted indirectly in the increase in LDLR and a corresponding decrease in LDL-C. When PCSK9 was maximally bound, higher concentrations of alirocumab did not result in further reduction of LDL-C through this mechanism. However, increasing the dose of alirocumab prolonged the time of maximal binding of free PCSK9 with a corresponding prolongation of LDL-C reduction. With restoration of detectable concentrations of free PCSK9 and with continued increases in PCSK9 concentrations, LDL-C concentrations increase with both parameters returning to pre-treatment concentrations once alirocumab is no longer present.

As a negative regulator of LDL-R, the increase in PCSK9 induced by statins appears to limit their maximal efficacy (reduction in LDL-C). When used in combination with statins, the ability of alirocumab to inhibit PCSK9 suppresses this negative regulatory effect of statins, resulting in a further reduction of circulating LDL-C. However, the increase in PCSK9 concentrations induced by statins and other LMTs also shortened the duration of alirocumab effect through enhanced target mediated clearance. These effects were less pronounced when alirocumab was combined with other LMTs such as ezetimibe and fenofibrate.

6. Dosage selection for the pivotal studies

The doses and dose regimens of alirocumab tested in two Phase II dose finding studies (DFI11565 and CL-1003): 50, 100, and 150 mg Q2W, and 200 and 300 mg Q4W were selected based on the observation of dose-dependent reductions in LDL-C concentrations seen in the Study CL-1001, as well as the absence of dose-related adverse events (AEs) in Phase I studies. The dose range included doses expected to maintain maximum LDL-C lowering efficacy, based on the observed reduction of free PCSK9 concentrations in the Phase I studies.

The 150 mg Q2W dose demonstrated safety and biological activity in Phase I and Phase II studies. In the 2 dose-finding studies of 12-week treatment duration (DFI11565 and CL-1003) in patients who were also administered statins, statistically significant decreases in the percent change from baseline in LDL-C were observed in all of the alirocumab groups investigated (50 mg, 100 mg, and 150 mg Q2W; 150 mg, 200 mg, and 300 mg Q4W) compared with the placebo group; the largest decrease was seen in the 150 mg Q2W group. The 300 mg alirocumab Q4W dose also showed significant decreases in LDL-C, but the maximum treatment effect was not fully maintained over the 4-week inter-dosing interval in all of the statin-treated patients. The Q2W regimen maintained constant LDL-C lowering throughout the inter-dosing interval in all patients, regardless of the background therapy. Although found to be safe and biologically active throughout the dosing interval, the full LDL-C lowering effect of the 150 mg Q2W dose may be more than is needed to achieve individual target LDL-C in some patients, and therefore a lower initiation dose was considered using a dose-response model. Through this model, the dose of 75 mg Q2W was predicted to provide an approximately 50% decrease in LDL-C from baseline.

7. Clinical efficacy

7.1. Indication 1 Heterozygous Familial Hypercholesterolaemia, not adequately controlled by current lipid modifying therapy

7.1.1. Pivotal efficacy studies

7.1.1.1. Study EFC12492 - (FH I)

A Randomised, Double Blind, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 [Alirocumab] in Patients with Heterozygous Familial Hypercholesterolaemia Not Adequately Controlled With Their Lipid Modifying Therapy.

Comment: The clinical study report (CSR) is based on the results of the first step analysis of efficacy data up to Week 52; and safety, PK and other results up to the common cut-off date of 16 April 2014 (the date of the last patient's Week 52 visit). The study is ongoing and the results of the second-step analysis of Week 78 efficacy endpoints and final safety, PK and other analyses have not been reached and so are not included in this submission.

Study design, objectives, locations and dates

A randomised, double blind, placebo controlled, unbalanced (2:1 alirocumab:placebo), parallel group, multinational, multicentre study conducted at 89 sites in 14 countries (Austria, Canada, Czech Republic, Denmark, France, Israel, Netherlands, Norway, Russia, South Africa, Spain, Sweden, UK and USA from July 2012 to April 2014).

- Primary objective: To demonstrate the reduction of LDL-C by alirocumab as add-on therapy to stable maximally tolerated daily statin therapy, with or without other lipid modifying therapy (LMT) in comparison with placebo after 24 weeks of treatment in patients with heterozygous familial hypercholesterolaemia.
- Secondary objectives: To evaluate:
  - Effect of alirocumab 75 mg in comparison to placebo on LDL-C after 12 weeks of treatment
  - Effect of alirocumab on other lipid parameters – Apo B, non-HDL-C, total-C, Lp(a), HDL-C, TG, and Apo A-1
  - Long term effect of alirocumab in LDL-C
  - Safety and tolerability of alirocumab
  - The development of anti-drug (alirocumab) antibodies (ADAs)
  - The PK of alirocumab.

The study consisted of 3 periods with a total duration of 89 weeks: a screening period of up to 3 weeks, a double blind treatment period of 78 weeks and a follow up period of 8 weeks if patients did not enter a long term extension study. At the end of the 18 months (78 weeks) double blind treatment period patients were able to enter the long term extension study (LTS13463**,** not included in submission) in which all patients received alirocumab.

Inclusion and exclusion criteria

- Inclusion criteria**:** Healthy male and female (non-childbearing potential) patients aged ≥ 18 years with heterozygous familial hypercholesterolaemia (heFH) who were not adequately controlled while on maximally tolerated daily dose of statin with or without other LMT.
- Exclusion criteria: Included: use of fibrates, other than fenofibrate within 6 weeks of enrolment; use of nutraceutical products or over-the-counter therapies including red yeast

rice products that may affect lipids which have not been at a stable dose/amount for at least 4 weeks prior to enrolment; unstable cardiovascular disease or requiring interventions eg PCI or CABG; newly diagnosed or poorly controlled diabetes (HbA1c > 9%).

Study treatments

Patients were randomised to 1 of the 2 arms, alirocumab or placebo for alirocumab, in a 2:1 ratio, during the double-blind treatment period:

- Alirocumab
  - 75 mg alirocumab SC Q2W starting at Week 0 (randomisation) up to Week 12
  - 75 mg (if Week 8 LDL-C < 1.81 mmol/L [70 mg/dL] or 150 mg alirocumab SC Q2W (if Week 8 LDL-C level ≥ 1.81 mmol/L) [70 mg/dL], starting at Week 12, and continuing up to last dose at Week 76 that is, 2 weeks before the end of the double-blind treatment period
- Placebo for alirocumab SC Q2W starting at Week 0 (randomisation), and continuing up to Week 76

All IMP injections were administered SC in the abdomen, thigh, or outer area of the upper arm Q2W using an auto-injector, by the patient or another designated person and it was recommended to rotate within an anatomical area or change the anatomical area based on the patient's preference.

All patients were on a maximally tolerated stable daily dose of statin (atorvastatin, rosuvastatin, or simvastatin) with or without other LMT throughout the duration of the study.

Efficacy variables and outcomes

The primary efficacy outcome was the percent change in calculated LDL-C from baseline to Week 24 in the ITT population using all LDL-C values regardless of adherence to treatment.

The primary endpoint was defined as: 100 x (calculated LDL-C value at week 24 - calculated LDL-C value at baseline)/calculated LDL-C value at baseline.

The key secondary endpoints are listed in the order of hierarchical testing used to handle multiplicity:

- percent change in calculated LDL-C from baseline to Week 24 in the mITT population, using all LDL-C values during the efficacy treatment period (on-treatment)
- percent change in calculated LDL-C from baseline to Week 12 (ITT)
- percent change in calculated LDL-C from baseline to Week 12 (on-treatment)
- percent change in Apo B from baseline to Week 24 (ITT)
- percent change in Apo B from baseline to Week 24 (on-treatment)
- percent change in non-HDL-C from baseline to Week 24 (ITT)
- percent change in non-HDL-C from baseline to Week 24 (on-treatment)
- percent change in Total-C from baseline to Week 24 (ITT)
- percent change in Apo B from baseline to Week 12 (ITT)
- percent change in non-HDL-C from baseline to Week 12 (ITT)
- percent change in Total-C from baseline to Week 12 (ITT)
- percent change in calculated LDL-C from baseline to Week 52 (ITT)

- proportion of very high CV risk patients reaching calculated LDL-C < 70mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C < 100 mg/dL (2.59 mmol/L) at Week 24 (ITT)
- proportion of very high CV risk patients reaching calculated LDL-C < 70mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C < 100 mg/dL (2.59 mmol/L) at Week 24 (on-treatment)
- proportion of patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) at Week 24 (ITT)
- proportion of patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) at Week 24 (on-treatment)
- percent change in Lp(a) from baseline to Week 24 (ITT)
- percent change in HDL-C from baseline to Week 24 (ITT)
- percent change in fasting TGs from baseline to Week 24 (ITT)
- percent change in Apo A-1 from baseline to Week 24 (ITT).
- percent change in Lp(a) from baseline to Week 12 (ITT).
- percent change in HDL-C from baseline to Week 12 (ITT).
- percent change in fasting TGs from baseline to Week 12 (ITT).
- percent change in Apo A-1 from baseline to Week 12 (ITT).

Randomisation and blinding methods

Patients were randomised to receive either alirocumab or placebo during the double-blind study treatment period using a 2:1 ratio, with permuted-block randomisation. Randomisation was stratified according to prior history of MI or ischemic stroke (Yes/No), statin treatment (high intensity statin, as defined by atorvastatin 40 or 80 mg daily or rosuvastatin 20 or 40 mg daily versus simvastatin whatever the daily dose, atorvastatin below 40 mg daily, or rosuvastatin below 20 mg daily), and geographic region. Randomisation was via either the interactive voice response system (IVRS) or the interactive web response system (IWRS).

The study was double blind. To protect the blind, alirocumab and placebo for alirocumab were provided in identically matched auto-injectors and packaged identically with a double-blind label.

Analysis populations

- ITT population - defined as all randomised patients who had an evaluable primary efficacy endpoint ie a baseline calculated LDL-C value and at least 1 calculated LDL-C value on or off-treatment within 1 of the analysis windows up to Week 24.
- mITT population (on treatment) - defined as all randomised patients who took at least 1 dose or part of a dose of the double-blind IMP injection and had an evaluable primary efficacy endpoint during the efficacy treatment period ie a baseline calculated LDL-C value and at least 1 calculated LDL-C value on treatment within 1 of the analysis windows up to Week 24.
- Safety population – defined as all randomised patients who actually received at least 1 dose or part of a dose of the double-blind IMP injection.

Sample size

A total sample size of 45 patients (30 in alirocumab and 15 in placebo) has 95% power to detect a difference in mean percent change in LDL-C of 30% with a 0.05 2-sided significance level and

assuming a common standard deviation of 25% and all these 45 patients having an evaluable primary endpoint.

The sample size was increased to meet regulatory requirements across the program, to assess the safety of alirocumab. In order to have at least 225 patients on alirocumab treated for 12 months in this study, and assuming a dropout rate of 10% over the first 3 month period and a dropout rate of 20% over the remaining 9 month period, the final total sample size was increased and rounded to 471 with a randomisation ratio of 2:1 (alirocumab: 314, placebo: 157).

Statistical methods

The percent change from baseline in calculated LDL-C at Week 24 was analysed in the ITT population using a mixed effect model with repeated measures (MMRM) approach. All post-baseline data available within Week 4 to Week 52 analysis windows were used, regardless of treatment adherence, and missing data were accounted for by the MMRM model. The model included the fixed categorical effects of treatment group (placebo versus alirocumab), randomisation strata (as per IVRS), time point (Week 4, Week 8, Week 12, Week 16, Week 24, Week 36, and Week 52), treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. This model provided baseline adjusted LS means estimates at Week 24 for both treatment groups with their corresponding standard errors (SEs) and 95% confidence intervals (CIs). To compare the alirocumab group to the placebo group, an appropriate contrast statement was used to test the differences of these estimates, at the 2-sided 0.05 level.

Within group LS means and SEs were provided using weights equal to the observed proportion of patients in strata variable levels in the study population (That is, "population weight") rather than equal weights. Population weights were considered more appropriate than equal coefficients due to imbalances between levels of the randomisation stratification factors observed in the study population.

The MMRM model relies on the "missing-at-random" assumption. Because the possibility for a not-missing-at-random missingness mechanism can never be excluded, sensitivity analyses to explore the impact of non-ignorable missingness on the primary efficacy analysis were conducted using 2 approaches, specifically the tipping-point approach and the new pattern mixture model approach using mixed imputation in the randomised population.

A hierarchical procedure pre-specified in the protocol using the specified order of key secondary endpoints was used to control the type 1 error of 5% and handle multiple endpoints.

- Continuous secondary variables anticipated to have a normal distribution (that is lipids other than TGs and Lp(a)) were analysed using the same MMRM model as for the primary endpoint.
- Continuous secondary endpoints anticipated to have a non-normal distribution (ie TGs and Lp(a)) were analysed using multiple imputation approach for handling of missing values followed by robust regression model with endpoint of interest as response variable using M-estimation with treatment group, randomisation strata and corresponding baseline value(s) as effects to compare treatment effects. Combined estimate for mean in both treatment groups, as well as the difference in these estimates, with their corresponding SEs, 95% CI, and p value were provided.
- Binary secondary efficacy endpoints were analysed using multiple imputation approach for handling of missing values followed by stratified logistic regression with treatment group as main effect and corresponding baseline value(s) as covariate, stratified by randomisation factors. Combined estimates of odds ratio versus placebo, 95% CI, and p value were provided. In the data dependent case in which logistic regression was not applicable (For example response rate was zero in 1 treatment arm and thus the maximum likelihood

estimate may not exist), the last observation carried forward (LOCF) approach was used for handling of missing values and an exact conditional logistic regression was performed to compare treatment effects.

Participant flow

Table 10 Study EFC12492: Patient disposition

	Placebo (N=163)	Alirocumab 75 Q2W/Up150 Q2W (N=323)	Total
Randomised	163	323	486
Randomised and treated	163 (100%)	322 (99.7%)	
Randomised but not treated	0	1 (0.3%)	
Completed 18 months of double blind treatment period (Week 78)	2 (1.2%)	7 (2.2%)	9
Did not complete the study treatment period	18 (11.0%)	36 (11.1%)	
Did not complete the first Week 52 study treatment period	15 (9.2%)	34 (10.5%)	
Treatment ongoing	144 (88.3%)	280 (86.7%)	424
Reason for not completing study treatment period			
Discontinued due to Adverse event	8 (4.9%)	12 (3.7%)	
Discontinued due to poor compliance to protocol	4 (2.5%)	8 (2.5%)	
Protocol became inconvenient to participate	2 (1.2%)	4 (1.2%)	
Life events made continuing too difficult	0	2 (0.6%)	
Other reasons	2 (1.2%)	2 (0.6%)	
Other reasons	6 (3.7%)	16 (5.0%)	
Physician decision	1 (0.6%)	0	
Patient moved	0	3 (0.9%)	
Patient withdrew consent	0	1 (0.3%)	
Related to IMP autoinjector administration	0	1 (0.3%)	
Other [a]	5 (3.1%)	11 (3.4%)	
Sudden death	0	2 (0.6%)	
Patient declined	1 (0.6%)	4 (1.2%)	
Failure to meet inclusion/exclusion criteria	0	2 (0.6%)	
sponsor decision	0	1 (0.3%)	
Wanted to start family	0	1 (0.3%)	
Failure to meet end of treatment assessment window	1 (0.6%)	1 (0.3%)	
Failure to receive Week 76 injection	2 (1.2%)	0	
Site not available	1 (0.6%)	0	
Patient's decision for treatment discontinuation [b]	12 (7.4%)	26 (8.0%)	

Note: Percentages are calculated using the number of patients randomized as denominator. Only the main reason for stopping treatment was entered in CRF. [a] Includes patients who completed the 18 months DB treatment period (at least 76 weeks of exposure and visit W78 performed) but did not meet the definition of "completer per CRF". [b] Additional information as regards study treatment discontinuation. Source: Study EFC12942 CSR Table 7 amended with data from text for total (Section 9.1

Table 11 Study EFC12492: Analysis populations

	Placebo	Alirocumab 75 Q2W/Up150 Q2W	All
Randomised population	163 (100%)	323 (100%)	486 (100%)
Efficacy populations			
Intent-to-Treat (ITT)	163 (100%)	322 (99.7%)	485 (99.8%)
Modified Intent-to-Treat (mITT)	163 (100%)	321 (99.4%)	484 (99.6%)
Quality-of-life population	162 (99.4%)	314 (97.2%)	476 (97.9%)
PK population	161	318	479
Anti-alirocumab antibody population	157	307	464
Safety population	163	322	485

Note: The safety, PK and anti-alirocumab antibody population patients are tabulated according to treatment actually received (as treated). For the other populations, patients are tabulated according to their randomised treatmentSource: Study EFC12492 CSR Table 10

Major protocol violations/deviations

GCP non-compliance was identified at 2 sites – 1 in Russia and 1 in USA. These sites were terminated, the patients discontinued from the study and the relevant health authorities notified. A total of 15 patients were affected at the 2 sites (14 in Russia and 1 in USA), 12 alirocumab patients and 3 placebo patients. These patients were excluded from the efficacy analysis and sensitivity analysis demonstrated that inclusion or exclusion of the patients did not affect the results.

Overall, major protocol deviations that could potentially impact efficacy analyses were reported for 58 patients (18.0%) in the alirocumab group and 22 patients (13.5%) in the placebo group observed across both treatment groups, with no apparent distribution pattern. The sponsor concluded that they were unlikely to have any impact on the overall outcome of the study. The most common deviation was failure to have an LDL-C assessment within the Week 24 analysis window (from days 155 to 182). These missing values were accounted for by the MMRM model in the primary analysis of the primary efficacy endpoint and by sensitivity analyses to the handling of missing data.

Baseline data

Demographic characteristics at baseline were similar between both treatment groups. Overall, the numbers of female (212; 43.6%) and male (274; 56.4%) patients randomised in the study were well balanced between the treatment groups. Patients were mostly White (91.4%) with a mean age of 51.9 years (range: 20 to 87 years). The percentage of patients aged 65 years or older was 16.7%, 1.9% of patients were 75 years of age or older. The mean BMI was 29.3 kg/m^2 and the percentage of patients with BMI ≥ 30 kg/m^2 was 35.9% in the alirocumab group and 44.2% in the placebo group.

The medical history data was balanced between the treatment groups. Overall, 51.2% of patients had a history of CHD or CHD risk equivalent (other CVD or significant risk factors) that would categorise their CV risk as “very high”.

Results for the primary efficacy outcome

A statistically significant decrease in calculated LDL-C from baseline to Week 24 (ITT analysis) was observed in the alirocumab group (LS mean [SE] versus baseline: -48.8% [1.6]), compared to the placebo group (LS mean [SE] versus baseline: +9.1% [2.2]), with an LS mean difference for alirocumab versus placebo of -57.9% ([95% CI: -63.3 to -52.6]; p< 0.0001).

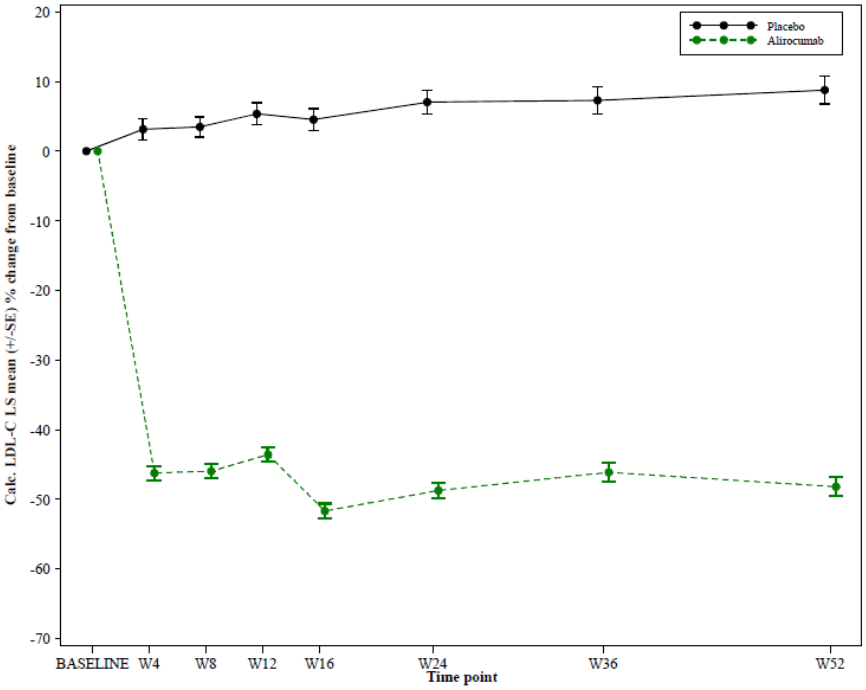
The primary endpoint was also analysed by an ANCOVA model using measured LDL-C instead of calculated LDL-C in patients from the ITT population with an assessment available at baseline and during the Week 24 analysis window. A decrease in measured LDL-C from baseline to Week 24 (ITT analysis) was observed in the alirocumab group (LS mean [SE] versus baseline: -50.1% [1.7]), compared to the placebo group (LS mean [SE] versus baseline: +12.6% [2.4]), with an LS mean difference for alirocumab versus placebo of -62.7% ([95% CI: -68.5 to -56.9]; p< 0.0001).

Table 12 Study EFC12492: Percent change from baseline in calculated LDL-C at Week 24: MMRM - ITT analysis

Calculated LDL Cholesterol	Placebo (N=163)	Alirocumab 75 Q2W/Up150 Q2W (N=322)
Baseline (mmol/L)		
Number	163	322
Mean (SD)	3.739 (1.213)	3.748 (1.326)
Median	3.574	3.497
Min : Max	1.71 : 9.17	1.01 : 9.95
Baseline (mg/dL)		
Number	163	322
Mean (SD)	144.4 (46.8)	144.7 (51.2)
Median	138.0	135.0
Min : Max	66 : 354	39 : 384
Week 24 percent change from baseline (%)		
LS Mean (SE)	9.1 (2.2)	-48.8 (1.6)
LS mean difference (SE) vs placebo		-57.9 (2.7)
95% CI		(-63.3 to -52.6)
p-value vs placebo		< 0.0001*

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomisation strata as per IVRS, time point, treatment-by-time point and strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline calculated LDL-C value-by-time point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model. The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level. Source: Study EFC12492 CSR Table 21

Figure 12. Study EFC12492: Calculated LDL-C LS mean (+/- SE) percent change from baseline: Time profile – ITT analysis



Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C-by-time point interaction. Source: Study EFC12492 CSR Figure 2

Sensitivity analyses to a range of variables: the use of calculated versus measured LDL-C measurements, randomisation strata and handling of missing data were comparable to those of the primary analysis. Results of the sensitivity analysis performed for the primary efficacy endpoint excluding patient data from 2 sites where research activities for the study were terminated due to a serious breach of compliance with GCP, were consistent with those of the primary analysis.

Results for other efficacy outcomes

A hierarchical procedure was used to test the key secondary endpoints while controlling for multiplicity. For some key secondary endpoints, both the ITT analysis and the on-treatment analysis were pre-specified as part of the hierarchical testing procedure.

Since statistical significance was reached for the primary efficacy endpoint, the hierarchical testing was applied to the key secondary endpoints. All key secondary endpoints are statistically significant according to the hierarchical procedure.

Table 13 Study EFC12492: Secondary efficacy outcomes - Hierarchical testing strategy applied

Endpoint	Analysis	Results		P-value
		LS mean difference versus placebo	combined estimate for odds-ratio versus placebo	
Calculated LDL-C Percent change from baseline to Week 24	On-treatment	-58.1%		< 0.0001
Calculated LDL-C Percent change from baseline to Week 12	ITT	-49.2%		< 0.0001
Calculated LDL-C Percent change from baseline to Week 12	On-treatment	-49.5%		< 0.0001
Apo-B Percent change from baseline to Week 24	ITT	-45.8%		< 0.0001
Apo-B Percent change from baseline to Week 24	On-treatment	-45.9%		< 0.0001
Non-HDL-C Percent change from baseline to Week 24	ITT	-52.4%		< 0.0001
Non-HDL-C Percent change from baseline to Week 24	On-treatment	-52.6%		< 0.0001
Total-C Percent change from baseline to Week 24	ITT	-38.7%		< 0.0001
Apo-B Percent change from baseline to Week 12	ITT	-37.5%		< 0.0001
Non-HDL-C Percent change from baseline to	ITT	-43.7%		< 0.0001

Endpoint	Analysis	Results		P-value
		LS mean difference versus placebo	combined estimate for odds-ratio versus placebo	
Week 12				
Total-C Percent change from baseline to Week 12	ITT	-32.5%		< 0.0001
Calculated LDL-C Percent change from baseline to Week 52	ITT	-56.2%		< 0.0001
Proportion of very high CV risk patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C < 100 mg/dL (2.59 mmol/L) at Week 24	ITT		156	< 0.0001
Proportion of very high CV risk patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C < 100 mg/dL (2.59 mmol/L) at Week 24	On-treatment		156.6	< 0.0001
Proportion of patients reaching calculated LDL-C< 70 mg/dL (1.81 mmol/L) at Week 24	ITT		244.9	< 0.0001
Proportion of patients reaching calculated LDL-C< 70 mg/dL (1.81 mmol/L) at Week 24	On-treatment		240	< 0.0001
Lp(a) Percent change from baseline to Week 24	ITT		-17.7%	< 0.0001
HDL-C Percent change from baseline to Week 24	ITT	8%		< 0.0001
Fasting TGs Percent change from baseline to Week 24	ITT		-16%	< 0.0001

Endpoint	Analysis	Results		P-value
		LS mean difference versus placebo	combined estimate for odds-ratio versus placebo	
Apolipoprotein A1 Percent change from baseline to Week 24	ITT	4.7%		0.0002
Lp(a) Percent change from baseline to Week 12	ITT		-17.3%	< 0.0001
HDL-C Percent change from baseline to Week 12	ITT	4.3%		0.0031
Fasting TGs Percent change from baseline to Week 12	ITT		-9.7%	0.0003
Apolipoprotein A1 Percent change from baseline to Week 12	ITT	2.8%		0.0187

Source: Study EFC12492 CSR Table 23 (amended format)

Compared with placebo, alirocumab significantly reduced Apo B, non-HDL C, and Total C following the same trend as was observed for LDL-C at Week 12 and Week 24. A significant decrease from baseline in fasting TGs and Lp (a), and increases in HDL C and Apo A-1 were observed at Week 12 and 24 in the alirocumab group. Results obtained at Week 52 were consistent with the results obtained at Week 24.

Subgroup analysis

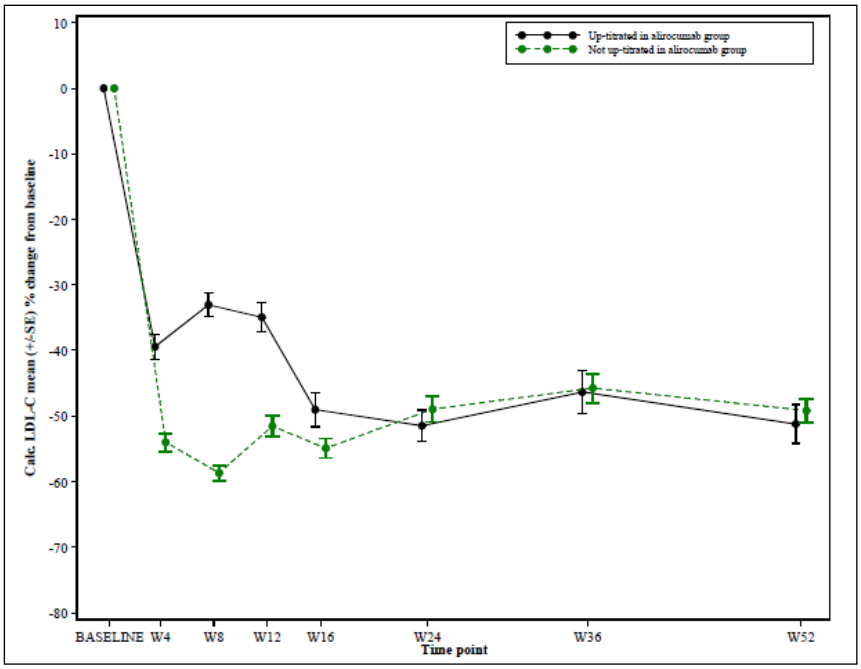
Subgroup analyses of the primary efficacy endpoint showed consistent reduction of calculated LDL-C from baseline with alirocumab versus placebo across a range of demographic and baseline characteristics including age, ethnicity, BMI, region, prior history of MI or ischaemic stroke, diabetes, baseline total and free PCSK9 levels, baseline calculated LDL-C, HDL-C, fasting TGs, Lp(a), intensity of background statin, and statins with versus without other additional LMTs at randomisation. Analyses by race were not performed because almost all patients (91.4%) were White, with too few patients in other race categories to perform the subgroup analysis for this characteristic.

No qualitative interactions were identified. A quantitative interaction (that is, p-value< 0.10) was detected for gender, however, a clinically meaningful reduction in LDL-C was observed, regardless of gender.

Up-titration

One hundred and thirty five patients (135/311) in the alirocumab group who had at least 1 injection after Week 12, had dose up-titrated to 150 mg and 176 patients remained at 75 mg. In patients without dose up titration, the mean (SD) percent change from baseline was -51.5% (21.5%) at Week 12, and was maintained at Week 16 (-54.9% [20.6%]) and Week 24 (-48.9% [26.1%]). In patients with dose up-titration, the mean (SD) percent change from baseline at Week 12 was -34.9% (25.9%). At Week 24, further reduction was observed (-51.5% [27.1]).

Figure 13. Study EFC12492: Study Calculated LDL-C mean (+/- SE) percent change from baseline according to up-titration status: Time profile - ITT analysis - ITT population - Patients in alirocumab group with at least 1 injection post - Week 12



Note: up-titrated patients according to IVRS Week 12 transaction with at least one injection of alirocumab 150 mg afterwards

7.1.1.2. Study R727-CL-1112 - (FH II)

A Randomised, Double Blind, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolaemia Not Adequately Controlled with Their Lipid Modifying Therapy.

Comment: The clinical study report (CSR) is based on the results of the first-step analysis of efficacy data up to the last time point reached by all randomised patients up to the common cut-off date of 13 May 2014 (the date of the last patient's Week 52 visit). The study is ongoing and the results of the second-step analysis of Week 78 efficacy endpoints and final safety, PK and other analyses have not been reached and so were not included in this submission.

Study design, objectives, locations and dates

A randomised, double blind, placebo controlled, parallel group, multinational study conducted at 26 sites in the Czech Republic, Netherlands, Norway and the UK from November 2012 until the cut off for the analysis in May 2014.

The study consisted of a screening period of up to 2 weeks, a double blind treatment period of 78 weeks and a follow up period of 8 weeks. At the end of the double blind treatment period all patients completing are able to enter a long term extension study (Study LTS13463**,** not included in submission).

- Primary objective: To demonstrate the reduction of LDL-C by alirocumab as add-on therapy to stable, maximally tolerated daily statin therapy with or without other LMT in comparison with placebo after 24 weeks of treatment in patients with heFH.
- Secondary objectives:
  - To evaluate the effect of alirocumab 75 mg in comparison with placebo on LDL-C after 12 weeks of treatment and on other lipid parameters, eg, Apo B, non-HDL-C, Total-C, Lp(a), HDL-C, TG levels, and Apo A-1 levels
  - To evaluate the long-term effect of alirocumab on LDL-C
  - To evaluate the safety, tolerability and immunogenicity of alirocumab

Inclusion and exclusion criteria

Same as for previous study (EFC12492).

Study treatments

Same as for previous study (EFC12492).

Efficacy variables and outcomes

Same as for previous study (EFC12492).

Randomisation and blinding methods

Same as for previous study (EFC12492).

Analysis populations

Same as for previous study (EFC12492).

Table 14. Study R727-CL-1112: analysis populations

	Placebo (N=82)	Alirocumab 75 Q2W/Up150 Q2W (N=167)	All (N=249)
Randomised population	82 (100%)	167 (100%)	249 (100%)
Efficacy population:			
Intent-to-Treat (ITT)	81 (98.8%)	166 (99.4%)	247 (99.2%)
Modified Intent-to-Treat (mITT)	81 (98.8%)	166 (99.4%)	247 (99.2%)
Quality-of-life population	80 (97.6%)	164 (98.2%)	244 (98.0%)
Anti-alirocumab antibody population	77 (93.9%)	163 (97.6%)	240 (96.4%)
Safety population	81 (98.8%)	167 (100%)	248 (99.6%)

Note: The safety and anti-alirocumab antibody populations were tabulated according to the treatment actually received (as treated). For the other populations, patients were tabulated according to their randomized treatment.

Sample size

A total sample size of 45 patients (30 in the alirocumab group and 15 in the placebo group) was calculated to have 95% power to detect a difference in mean percent change in LDL-C of 30% with a 2-sided significance level of 0.05, assuming a common standard deviation (SD) of 25% and that all 45 patients had an evaluable primary endpoint.

The sample size was increased to 126 patients in the alirocumab group, with the intent to evaluate safety in a larger population. To have at least 126 patients on alirocumab treatment for 12 months in this study, assuming a drop out rate of 10% over the first 3 month period and a drop out rate of 20% over the remaining 9 month period, the total sample size was increased and rounded to 250 with a randomisation ratio of 2:1 (alirocumab:167, placebo:83).

Statistical methods

Same as for previous study (EFC12492).

A mixed effect model with repeated measures (MMRM) approach was used to evaluate the primary efficacy endpoint. The model contained the fixed categorical effects of treatment groups, randomisation strata, time points (Weeks 4, 8, 12, 16, 24, 36 and 52), strata by time point interaction, and treatment by time point interaction as well as the continuous fixed covariates of corresponding baseline vales and baseline value by time point interaction. A hierarchical procedure was planned to test the key secondary endpoints while controlling for multiplicity.

Participant flow

Table 15. Study R727-CL-1112: patient disposition

	Placebo (N=82)	Alirocumab 75 Q2W/ Up150 Q2W (N=167)
Randomised	82	167
Randomised but not treated	1 (1.2%)	0
Reason for not treated		
Subject withdrew consent	1 (1.2%)	0
Randomised and treated	81 (98.8%)	167 (100%)
Completed 18 months of double-blind treatment period (at least 76 weeks of exposure and visit Week 78 performed)	0	0
Completed the study treatment period	0	0
Did not complete the study treatment period	3 (3.7%)	11 (6.6%)
Did not complete 52 weeks of treatment	2 (2.4%)	11 (6.6%)
Treatment ongoing	78 (95.1%)	156 (93.4%)
Reason for not completing study treatment period		
Discontinued due to adverse event	1 (1.2%)	5 (3.0%)
Discontinued due to poor compliance to protocol	1 (1.2%)	2 (1.2%)
Protocol became inconvenient to participate in	0	0
Life events made continuing too difficult	0	2 (1.2%)
Poor compliance to protocol - other reasons	1 (1.2%)	0
Other reasons	1 (1.2%)	4 (2.4%)
Physician decision	0	0
Study terminated by sponsor	0	0
Subject moved	0	0
Subject withdrew consent	0	0
Related to IMP administration	0	1 (0.6%)

	Placebo (N=82)	Alirocumab 75 Q2W/ Up150 Q2W (N=167)
Injection too frequent	0	1 (0.6%)
Other reason – other	1 (1.2%)	3 (1.8%)
Patient's decision for treatment discontinuation	3 (3.7%)	11 (6.6%)
Inclusion into LTS13463 open-label extension study	0	0

Note: Percentages were calculated using the number of patients randomized as denominator. Only the main reason for stopping treatment was entered in the e-CRF. For detailed reasons related to IMP autoinjector administration several reasons may be provided.

Major protocol violations/deviations

Major protocol deviations that could potentially impact efficacy analyses were reported for 33 patients (19.8%) in the alirocumab group and 14 patients (17.1%) in the placebo group. Of these patients, 1 patient (0.6%) in the alirocumab group and 1 patient (1.2%) in the placebo group did not have an LDL-C value within any of the analysis windows up to Week 24 and were excluded from the ITT and mITT populations.

Baseline data

Demographic characteristics at baseline were generally similar between both treatment groups, with the exception of BMI. The proportion of patients with BMI ≥ 30 kg/m^2 was notably higher in the placebo group (82.9%) compared with the alirocumab group (64.7%). There were 118 (47.4%) female and 131 (52.6%) male; the majority were White (98.0%); mean age was 53.2 years (range 22 to 85 years); 79.5% were < 65 years and 20.5% were ≥ 65 years; 8.6% had a history of CHD or CHD risk equivalent that would categorise their CV risk as "very high"; all patients had received statins as background LMT, with 88.0% receiving atorvastatin 40 - 80 mg, rosuvastatin 20 to 40 mg or simvastatin 80 mg daily and 69.9% of patients receiving other LMT. The mean calculated LDL-C was 3.480 ± 1.0065 mmol/L. The baseline values of lipid parameters were similar between the treatment groups in the randomised population.

Results for the primary efficacy outcome

A statistically significant decrease in calculated LDL-C from baseline to Week 24 (ITT analysis) was observed in the alirocumab group (LS mean [SE] versus baseline, -48.7% [1.9%]) compared with the placebo group (LS mean [SE] versus baseline, +2.8% [2.8%]), and the LS mean difference in percent change from baseline for alirocumab versus placebo was -51.4% (95% CI, -58.1% to -44.8%; p < 0.0001).

Table 16 Study R727-CL-1112: Percent change in calculated LDL-C from Baseline to Week 24 (ITT Analysis): MMRM Analysis - ITT population

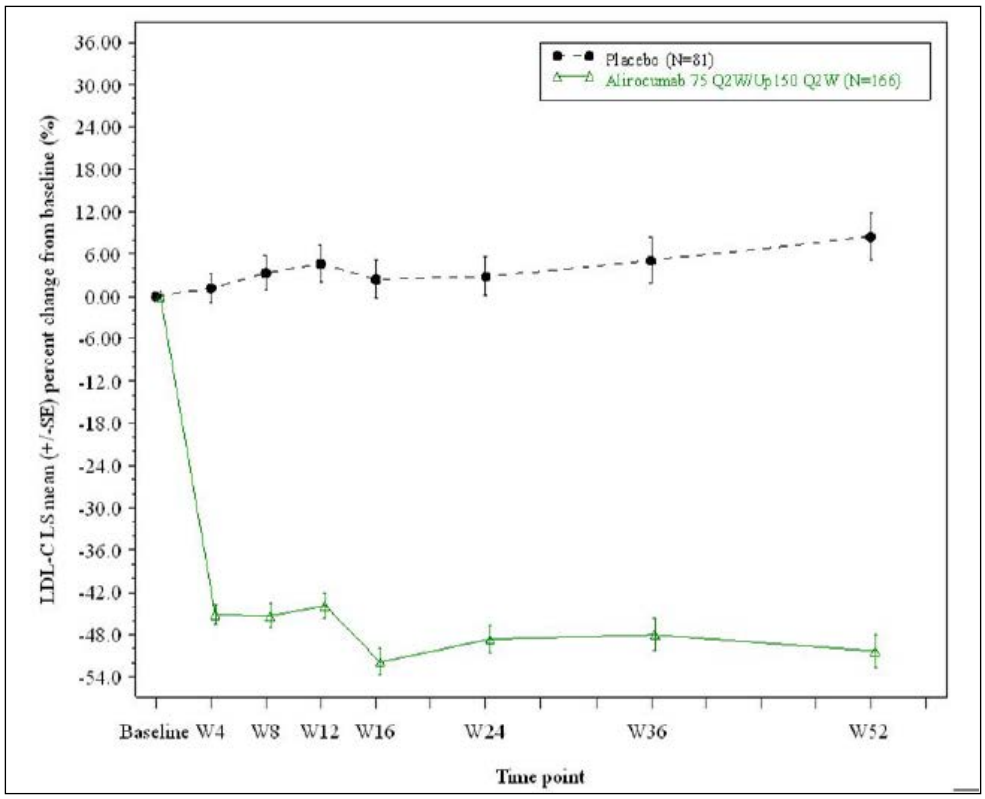
Calculated LDL Cholesterol	Placebo (N=81)	Alirocumab 75 Q2W/ Up150 Q2W (N=166)
Baseline (mmol/L)		
Number	81	166
Mean (SD)	3.470 (1.078)	3.486 (1.069)
Median	3.263	3.289
Min:Max	1.92:7.64	1.50:7.85
Week 24 percent change from baseline (%)		
LS mean (SE)	2.8 (2.8)	-48.7 (1.9)

Calculated LDL Cholesterol	Placebo (N=81)	Alirocumab 75 Q2W/ Up150 Q2W (N=166)
LS mean difference (SE) vs Placebo		-51.4 (3.4)
95% CI		(-58.1 to -44.8)
p-value vs Placebo		< 0.0001

Note: LS means, SE and p-value taken from MMRM analysis. The model included the fixed categorical effects of treatment group, randomisation strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value by time-point interaction. MMRM and baseline description were run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

An LDL-C reduction in the alirocumab group was observed from the first post dose measurement at Week 4 and was maintained at all time points up to Week 52.

Figure 14. Study R727-CL-1112: Calculated LDL-C LS Mean (+/- SE) percent change from Baseline (ITT Analysis): time profile - ITT population



Results for other efficacy outcomes

A hierarchical procedure was planned to test the key secondary endpoints while controlling for multiplicity.

Because statistical significance was reached for the primary efficacy endpoint, the hierarchical testing was applied to the key secondary endpoints. Statistical significance was not reached for the percent change in Apo A-1 from baseline to Week 12. This was the last key secondary endpoint in the hierarchical testing process. Consequently, inferential conclusions could be made for all key secondary endpoints.

Table 17. Study R727-CL-1112: secondary outcomes - hierarchical testing strategy applied

Key Secondary Endpoint	Analysis	P-Value (Alirocumab Versus
The percent change in calculated LDL-C from baseline to Week 24 in the on-treatment analysis, using all LDL-C values during the efficacy treatment period	On-treatment	< 0.0001
The percent change in calculated LDL-C from baseline to Week 12	ITT	< 0.0001
The percent change in calculated LDL-C from baseline to Week 12	On-	< 0.0001
The percent change in Apo B from baseline to Week 24	ITT	< 0.0001
The percent change in Apo B from baseline to Week 24	On-	< 0.0001
The percent change in non-HDL-C from baseline to Week 24	ITT	< 0.0001
The percent change in non-HDL-C from baseline to Week 24	On-	< 0.0001
The percent change in Total-C from baseline to Week 24	ITT	< 0.0001
The percent change in Apo B from baseline to Week 12	ITT	< 0.0001
The percent change in non-HDL-C from baseline to Week 12	ITT	< 0.0001
The percent change in Total-C from baseline to Week 12	ITT	< 0.0001
The percent change in calculated LDL-C from baseline to Week 52	ITT	< 0.0001
The proportion of very high CV risk patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C < 100 mg/dL (2.59 mmol/L) at Week 24	ITT	< 0.0001
The proportion of very high CV risk patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C < 100 mg/dL (2.59 mmol/L) at Week 24	On-treatment	< 0.0001
The proportion of patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) at Week 24	ITT	< 0.0001
The proportion of patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) at Week 24	On-treatment	< 0.0001
The percent change in Lp(a) from baseline to Week 24	ITT	< 0.0001
The percent change in HDL-C from baseline to Week 24	ITT	0.0009
The percent change in fasting TGs from baseline to Week 24	ITT	0.0012
The percent change in Apo A-1 from baseline to Week 24	ITT	0.0062
The percent change in Lp(a) from baseline to Week 12	ITT	< 0.0001
The percent change in HDL-C from baseline to Week 12	ITT	0.0147
The percent change in fasting TGs from baseline to Week 12	ITT	0.0240
The percent change in Apo A-1 from baseline to Week 12	**ITT**	**0.1475**

Subgroup analysis

Reductions in LDL-C from baseline to Week 24 consistent with the overall treatment effect of alirocumab versus placebo were observed across a range of demographic and baseline characteristics, including gender, age group, BMI, non-moderate CKD, diabetes, baseline calculated LCL-C, baseline HDL-C, baseline fasting TGs, baseline Lp(a), intensity of statin treatment and LMT other than statin.

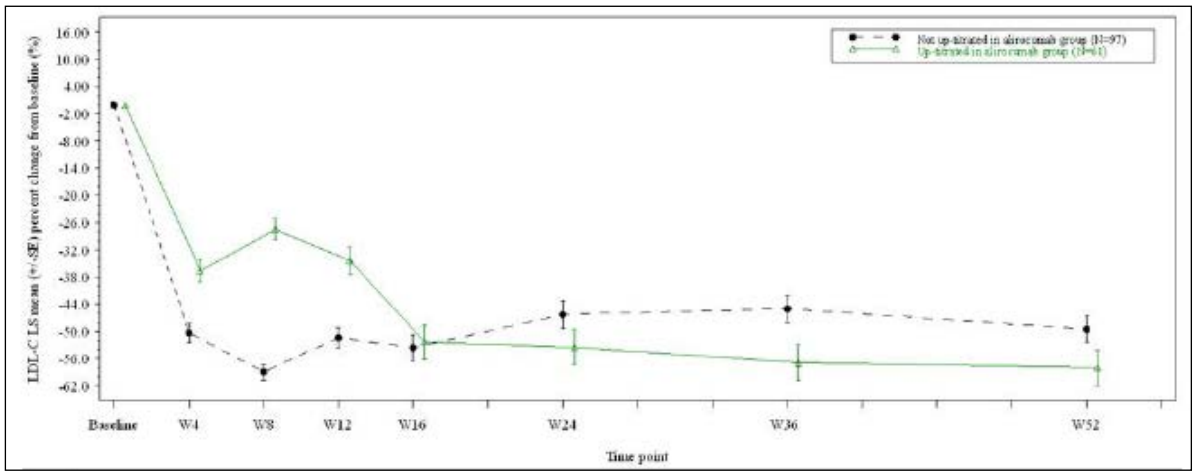
Up titration

Among 158 patients in the alirocumab group who had at least 1 injection after Week 12, 61 patients (38.6%) had their dose up-titrated to alirocumab 150 mg Q2W, and 97 patients (61.4%) remained at alirocumab 75 mg Q2W.

In patients whose dose was not up-titrated, the mean (SD) percent change from baseline was -49.3% (17.7%) at Week 12 and was maintained at Week 24 (-46.1% [26.9%]). In patients

whose dose was up-titrated, the mean (SD) percent change from baseline at Week 12 was -37.4% (25.5%). A further reduction was observed at Week 24 (-54.1% [28.4%]).

Figure 15. Study R727-CL-1112: calculated LDL-C LS mean (+/- SE) percent change from Baseline according to up-titration status: time profile – patients in the alirocumab group – ITT population



Note: Up-titrated patients according to IVRS Week 12 transaction with at least one injection of alirocumab 150 mg afterwards.

7.1.1.3. Study EFC12732 (High FH)

A Randomised, Double Blind, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 in Patients with Heterozygous Familial Hypercholesterolaemia and LDL-C Higher or Equal to 160 Mg/Dl with Their Lipid Modifying Therapy.

Comment: The CSR is based on the results of the first-step analysis of efficacy data up to Week 52; and safety and other results up to the common cut-off date of 19 May 2014 (the date of the last patient's Week 52 visit). The study is ongoing and the results of the second-step analysis of Week 78 efficacy endpoints and final safety, and other analyses have not been included in this submission.

Study design, objectives, locations and dates

A randomised, double blind, parallel group, placebo controlled, unbalanced, multinational study conducted at 33 sites in 5 countries (Canada, Netherlands, Russian Federation, South Africa and USA) from June 2012 until cut-off date for analysis at May 2014.

Objectives

Same as previous studies (EFC12492 and R727-CL-1112).

The study had same design as the previous studies, that is, it consisted as 3 periods – up to 3 week screening period, a double blind treatment period of 78 weeks and a follow up period of 8 weeks. At the end of the double blind period patients would be offered enrolment in an open label extension study (LTS13463) in which all patients will receive alirocumab treatment.

Inclusion and exclusion criteria

Same as for previous studies (EFC12492 and R727-CL-1112) but the exclusion criteria were set at LDL-C < 160 mg/dL (< 4.14 mmol/L) at the screening visit (Week -3) while the 2 previous studies it was set at LDL-C < 70 mg/dL (< 1.81 mmol/L) at the screening visit (Week -3).

Study treatments

Patients were randomised to 1 of the 2 arms, alirocumab or placebo, in a 2:1 ratio, during the double-blind treatment period. Patients were administered 150 mg alirocumab or placebo SC Q2W, starting at Week 0 (randomisation) and continuing up to the last injection (Week 76), 2 weeks before the end of the double blind treatment period.

All IMP injections were administered SC in the abdomen, thigh, or outer area of the upper arm Q2W, with rotation within an anatomical area or change the anatomical area based on the patient's preference. Alirocumab (or placebo), provided in an auto-injector (AI), was administered by self injection or by another designated person (such as a spouse, relative, etcetera).

Statin and other LMT (if applicable) were to be stable (including dose) for at least 4 weeks and/or fenofibrate for at least 6 weeks, as applicable, prior to the screening visit (Week -2), from screening to randomisation and during the first 24 weeks of the double-blind treatment period barring exceptional circumstances. From Week 24 onwards, background LMT could be modified only under certain conditions including the TGs alert and the LDL-C rescue alert.

Efficacy variables and outcomes

The efficacy variables were the same as for the previous studies.

Randomisation and blinding methods

Same as for previous studies.

Analysis populations

Same as for previous studies.

Table 18. Study EFC12732: Analysis populations

	Placebo	Alirocumab 75 Q2W/ Up150 Q2W	All
Randomised population	163 (100%)	323 (100%)	486 (100%)
Efficacy populations			
Intent-to-Treat (ITT)	163 (100%)	322 (99.7%)	485 (99.8%)
Modified Intent-to-Treat (mITT)	163 (100%)	321 (99.4%)	484 (99.6%)
Safety population	163	322	485

Note: The safety, PK and anti-alirocumab antibody population patients are tabulated according to treatment actually received (as treated). For the other populations, patients are tabulated according to their randomized treatment.

Sample size

A total sample size of 45 patients (30 in alirocumab and 15 in placebo) has 95% power to detect a difference in mean percent change in LDL-C of 30% with a 0.05 two-sided significance level and assuming a common standard deviation of 25% and all these 45 patients having an evaluable primary endpoint.

The sample size was increased to assess the safety of alirocumab. In order to have at least 50 patients on alirocumab treated for 12 months in this study, and assuming a dropout rate of 10% over the first 3 month period and a dropout rate of 20% over the remaining 3- to 12 month period, the final total sample size was increased and rounded to 105 with a randomisation ratio of 2:1 (alirocumab 70: placebo 35).

Statistical methods

Same as for previous studies.

Participant flow

Table 19. Study EFC12732: patient disposition - randomised population

	Placebo (N=35) N (%)	Alirocumab 75 Q2W/ Up150 Q2W (N=72) N (%)
Randomised but not treated	0	0
Randomised and treated	35 (100)	72 (99.7)
Complete 18 months of double-blind treatment period (at least 76 weeks of exposure and visit W78 performed)	5 (14.3)	6 (8.3)
Complete the study treatment period (as per CRF)	4 (11.4)	6 (8.3)
Did not complete the study treatment period (as per CRF)	6 (17.1)	15 (20.8)
Did not complete the first Week 52 study treatment period	6 (17.1)	15 (20.8)
Treatment ongoing	25 (71.4)	51 (70.8)
Reason for not completing study treatment period (as per CRF)	6 (17.1)	15 (20.8)
Discontinued due to AE	1 (2.9)	3 (4.2)
Discontinued due to Poor compliance to protocol	1 (2.9)	4 (5.6)
Life events made continuing too difficult	0	2 (2.8)
Other reasons	1 (2.9)	2 (2.8)
Other reasons	4 (11.4)	8 (11.1)
Patient moved	0	2 (2.8)
Other [a]	4 (11.4)	6 (8.3)
Patient declined	1	1
sponsor decision	2	4
Job change	0	1
Site unavailable	1	0
Patient's decision for treatment discontinuation	4 (11.4)	11 (15.3)
Inclusion into Study LTS13463 open-label extension study	4 (11.4)	6 (8.3)

Note: Percentages are calculated using the number of patients randomized as denominator. Only the main reason for stopping treatment was entered in CRF. [a] Includes patients who completed the 18 months DB treatment period (at least 76 weeks of exposure and visit W78 performed) but did not meet the definition of "completer per CRF".

Major protocol violations/deviations

During the course of the study, 2 sites (1 in Russia and 1 in the USA) were investigated for Good Clinical Practice (GCP) non-compliance based on findings during routine monitoring visits. Both sites were terminated and the relevant Health Authorities and Independent Ethics Committees were notified. The patients from these sites were included in some of the efficacy data but sensitivity analysis with the data excluded did not affect the final results.

Comment: It is noted that the excluded sites were the same investigators who were involved in Study EFC12492. Review of the full investigator lists shows that the 2 studies had 29 investigators in common and the studies also overlapped in time.

Major protocol deviations that could potentially impact efficacy analyses were reported for 10 patients (13.9%) in the alirocumab group and 2 patients (5.7%) in the placebo group. The deviations were sporadic with respect to the timing of their occurrence and were observed across all the treatment groups, with no apparent distribution pattern. Consequently, they were unlikely to have any impact on the overall outcome of the study.

Baseline data

The number of female patients was higher in the alirocumab group compared to the placebo group (51.4% of patients versus 37.1%, respectively); patients were mostly White (87.9%) with a mean age of 50.6 years (range: 18 to 80 years); the percentage of patients aged 65 years or more was 13.1%; mean BMI was 28.86 kg/m^2 and the percentage of patients with BMI ≥ 30 kg/m^2 was similar between the treatment groups. 57.0% of patients had a history of CHD or CHD risk equivalent (other CVD or significant risk factors) that would categorise their CV risk as "very high"; Most of the patients (53 of 61 patients) had a history of CHD, with a similar proportion of patients having a history of MI (approximately 23%), but some imbalances otherwise, notably for the history of coronary revascularisation procedures (40% of patients in the placebo group and 15.3% in the alirocumab group). The other heFH patients (43.0%) were categorised as having high CV risk.

Results for the primary efficacy outcome

A statistically significant decrease in percent change in LDL-C from baseline to Week 24 (ITT analysis) was observed in the alirocumab group (LS mean [SE] versus baseline: -45.7% [3.5]) compared to the placebo group (LS mean [SE] versus baseline: -6.6% [4.9]), with an LS mean difference for alirocumab versus placebo of -39.1% ([95% CI: -51.1 to -27.1], p < 0.0001).

Table 20. Study EFC12732: Percent change from baseline in calculated LDL-C at Week 24: MMRM - ITT analysis – ITT population

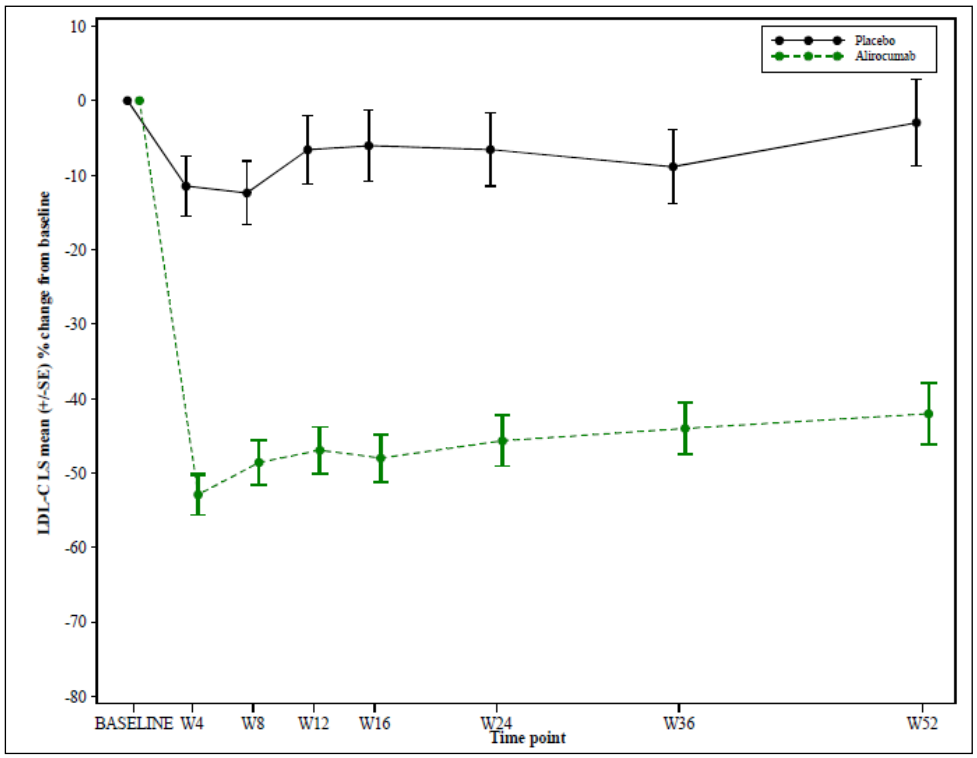
Calculated LDL Cholesterol	Placebo (N=35)	Alirocumab 150 Q2W (N=71)
Baseline (mmol/L)		
Number	35	71
Mean (SD)	5.205 (1.125)	5.083 (1.499)
Median	5.206	4.662
Min : Max	3.55: 7.23	2.31: 10.41
Baseline (mg/dL)		
Number	35	71
Mean (SD)	201.0 (43.4)	196.3 (57.9)
Median	201.0	180.0
Min : Max	137: 279	89: 402
Week 24 percent change from baseline (%)		
LS Mean (SE)	-6.6 (4.9)	-45.7 (3.5)
LS mean difference (SE) versus placebo		-39.1 (6.0)
95% CI		(-51.1 to -27.1)
p-value versus placebo		< 0.0001*

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomisation strata as per IVRS, time point, treatment-by-time point and strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline calculated LDL-C value-by-time point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model. The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level.

A calculated LDL-C reduction compared with baseline in the alirocumab group was observed from the first post-dose measurement at Week 4 and was maintained at all time points up to Week 52. In the alirocumab group, the calculated LDL-C reduction observed at Week 24 (LS mean versus baseline) was -45.7% and -42.1% at Week 52.

Sensitivity analysis showed similar consistent results whatever methodology was used to handle missing data. Sensitivity analysis also showed similar results when the analysis excluded the patients from the 2 sites identified for GCP non-compliance.

Figure 16. Study EFC 12732: LDL-C LS mean (+/- SE) percent change from baseline: Time profile - ITT analysis – ITT population



Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C-by-time point interaction.

Results for other efficacy outcomes

A hierarchical procedure was used to test the key secondary endpoints while controlling for multiplicity. For some key secondary endpoints, analyses using both the ITT analysis and the on-treatment analysis were pre-specified as part of the hierarchical testing procedure.

Since statistical significance was reached for the primary efficacy endpoint, the hierarchical testing was applied to the key secondary endpoints. All key secondary endpoints are statistically significant according to the hierarchical testing procedure through the Lp (a) endpoint at Week 24 (ITT estimand). Statistical significance was not reached for the percent change from baseline in HDL-C at Week 24 (ITT analysis). Consequently, subsequent key secondary endpoints were not tested: fasting TGs at Week 24 (ITT), Apo A-1 at Week 24 (ITT), Lp(a) at Week 12 (ITT), HDL-C at Week 12 (ITT), fasting TGs at Week12 (ITT), Apo A-1 at Week 12 (ITT), calculated LDL-C< 70 mg/dL (1.81 mmol/L) at Week 24 (ITT), and calculated LDL-C< 70 mg/dL (1.81 mmol/L) at Week 24 (on-treatment). P-values are presented for these endpoints for descriptive purpose only.

Table 11. Study EFC 12732: secondary outcomes - hierarchical testing strategy applied

Endpoint	Analysis	Results	P-value
Calculated LDL-C % change from baseline to Week 24	On-treatment	LS mean difference versus placebo of -38.9%	< 0.0001

Endpoint	Analysis	Results	P-value
Calculated LDL-C % change from baseline to Week 12	ITT	LS mean difference versus placebo of -40.3%	< 0.0001
Calculated LDL-C % change from baseline to Week 12	On-treatment	LS mean difference versus placebo of -40.3%	< 0.0001
Apo-B %change from baseline to Week 24	ITT	LS mean difference versus placebo of -30.3%	< 0.0001
Apo-B % change from baseline to Week 24	On-treatment	LS mean difference versus placebo of -30.2%	< 0.0001
Non-HDL-C % change from baseline to Week 24	ITT	LS mean difference versus placebo of -35.8%	< 0.0001
Non-HDL-C % change from baseline to Week 24	On-treatment	LS mean difference versus placebo of -35.5%	< 0.0001
Total-C % change from baseline to Week 24	ITT	LS mean difference versus placebo of -28.4%	< 0.0001
Apo-B % change from baseline to Week 12	ITT	LS mean difference versus placebo of -30.2%	< 0.0001
Non-HDL-C % change from baseline to Week 12	ITT	LS mean difference versus placebo of -34.5%	< 0.0001
Total-C %change from baseline to Week 12	ITT	LS mean difference versus placebo of -27.8%	< 0.0001
Calculated LDL-C % change from baseline to Week 52	ITT	LS mean difference versus placebo of -39.1%	< 0.0001
Proportion of very high CV risk patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C < 100 mg/dL (2.59 mmol/L) at Week 24	ITT	combined estimate for odds- ratio versus placebo of 11.7	0.0016
Proportion of very high CV risk patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C < 100 mg/dL (2.59 mmol/L) at Week 24	On-treatment	combined estimate for odds- ratio versus placebo of 11.9	0.0014
Lp(a) % change from baseline to Week 24	ITT	combined estimate for adjusted mean difference versus placebo of -14.8%	0.0164
HDL-C % change from baseline to Week 24	ITT	LS mean difference versus placebo of 3.7%	0.2745
Fasting TGs % change from baseline to Week 24	ITT	combined estimate for adjusted mean difference versus placebo of -8.7%	0.1386
Apolipoprotein A1 % change from baseline to Week 24	ITT	LS mean difference versus placebo of 3.6%	0.1715
Lp(a) % change from baseline to Week 12	ITT	combined estimate for adjusted mean difference versus placebo of -21.7%	0.0005
HDL-C % change from baseline to Week 12	ITT	LS mean difference versus placebo of -0.1%	0.9727
Fasting TGs % change from baseline to Week 12	ITT	combined estimate for adjusted mean difference versus placebo of -5.1%	0.4195
Apolipoprotein A1 % change from baseline to Week 12	ITT	LS mean difference versus placebo of 3.6%	0.1845
Proportion of patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) at Week 24	ITT	combined estimate for odds- ratio versus placebo of 16.1	0.0082
Proportion of patients reaching calculated LDL-C < 70 mg/dL (1.81	On-treatment	combined estimate for odds- ratio versus placebo of 16.3	0.0080

Endpoint	Analysis	Results	P-value
mmol/L) at Week 24			

Subgroup analysis

Subgroup analyses of the primary efficacy endpoint (ITT analysis) showed consistent reduction of LDL-C from baseline with alirocumab versus placebo across a range of demographic and baseline characteristics: gender, BMI, region, statin treatment (intensity of background statin), prior history of MI or ischemic stroke, baseline calculated LDL-C, baseline HDL-C, baseline fasting TGs, and baseline Lp (a).

7.2. Indication 2 – Patients with high cardiovascular risk and hypercholesterolaemia not adequately controlled by statins and other LMT.

7.2.1. Pivotal efficacy studies

7.2.1.1. Study EFC11568 - (Combo I)

A Randomised, Double Blind, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 in High Cardiovascular Risk Patients with Hypercholesterolaemia Not Adequately Controlled with Their Lipid Modifying Therapy.

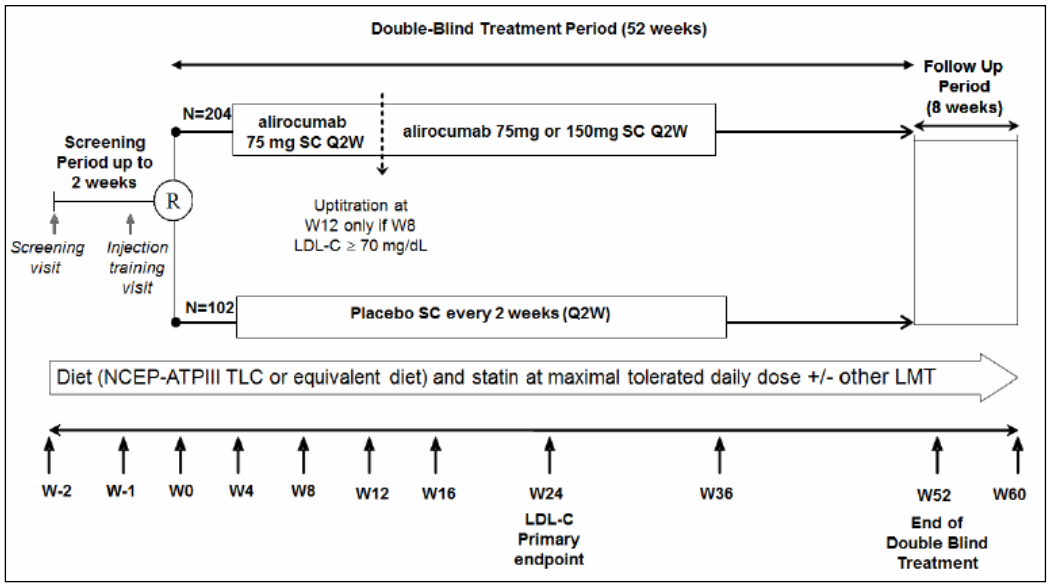
Study design, objectives, locations and dates

A randomised, double blind, placebo controlled, parallel group, unbalanced (2:1 alirocumab: placebo) study conducted at 80 centres in the USA from July 2012 to April 2014.

- Primary objective: to demonstrate the reduction of LDL-C by alirocumab as add-on therapy to stable maximally tolerated daily statin therapy with or without other LMT in comparison with placebo after 24 weeks of treatment in high cardiovascular risk patients with hypercholesterolaemia.
- Secondary objectives: to evaluate:
  - effect of alirocumab 75 mg in comparison with placebo in LDL-C after 12 weeks of therapy
  - effect of alirocumab on other lipid parameters (Apo B, non-HDL-C, Total-C, Lp(a), HDL-C, TGs and Apo A-1)
  - the long term effect of alirocumab on LDL-C
  - the safety and tolerability of alirocumab
  - the development of anti-drug antibodies

The study consisted of 3 periods with a total duration of 62 weeks for each patient: a screening period of up to 2 weeks, a double blind treatment period of 52 weeks and a follow up period of 8 weeks.

Figure 17 Study EFC11568: Study design



Inclusion and exclusion criteria

- Inclusion criteria: Male or female (non-childbearing potential) patients (> 18 years) with hypercholesterolemia and established CHD or CHD risk equivalents who were not adequately controlled with a maximally tolerated daily dose of statin with or without other LMT, both at stable doses for at least 4 weeks prior to the screening visit.
- Exclusion criteria: Known history of homozygous or heterozygous familial hypercholesterolemia; not on a stable dose of LMT (including statin) for at least 4 weeks and/or fenofibrate for at least 6 weeks, as applicable; prior to the screening visit or currently taking a statin other than simvastatin, atorvastatin, or rosuvastatin; recent (within 3 months) MI, unstable angina leading to hospitalisation, PCI, CABG, uncontrolled cardiac arrhythmia, stroke, transient ischemic attack, carotid revascularisation, endovascular procedure or surgical intervention for peripheral vascular disease; newly diagnosed (within 3 months) or poorly controlled diabetes (HbA1c > 8.5%).

Study treatments

Patients were randomised to 1 of the 2 arms, alirocumab or placebo for alirocumab, in a 2:1 ratio, during the double-blind treatment period:

- Alirocumab
  - 75 mg alirocumab SC Q2W starting at Week 0 (randomisation) up to Week 12
  - 75 mg or 150 mg alirocumab SC Q2W (based on their Week 8 LDL-C level), starting at Week 12, and continuing up to Week 50, that is, 2 weeks before the end of the double-blind treatment period
- Placebo for alirocumab SC Q2W, starting at Week 0 (randomisation), and continuing up to Week 50

The up titration was that at the Week 12 visit, patients randomised to alirocumab continued on alirocumab 75 mg every 2 weeks if the Week 8 LDL-C was < 1.81 mmol/L (< 70 mg/dL). Patients with Week 8 LDL-C ≥ 1.81 mmol/L, were up titrated to alirocumab 150 mg.

All IMP injections were administered SC in the abdomen, thigh, or outer area of the upper arm Q2W, with recommendation to rotate within an anatomical area or change the anatomical area based on the patient's preference. Alirocumab (or placebo for alirocumab), provided in an auto-

injector (AI), was to be administered by self injection or by another designated person (such as a spouse, relative, etcetera).

Efficacy variables and outcomes

The primary efficacy outcome was the percent change in LDL-C from baseline to Week 24.

Other efficacy outcomes included as listed for Study ECF12492.

ADAs were assessed at baseline (before the first IMP injection), at Week 12, Week 24, Week 52/or early termination, and during follow-up (Week 60). ADA samples were analysed using a validated, non-quantitative, titre-based bridging immunoassay. The sensitivity of the assay was approximately 5.6 ng/mL based on the monoclonal antibody positive control. The drug tolerance limit at 500 ng/mL of monoclonal antibody positive control was 191 µg/mL.

Randomisation and blinding methods

Patients were randomised to receive either alirocumab or placebo during the double-blind study treatment period using a 2:1 ratio, with permuted-block randomisation. Randomisation was stratified according to prior history of MI or ischemic stroke (Yes/No), statin treatment (high intensity statin, as defined by atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily, versus simvastatin whatever the daily dose, atorvastatin below 40 mg daily, or rosuvastatin below 20 mg daily).

The study was double blinded with alirocumab and placebo for alirocumab provided in identically matched auto-injectors (AI) and packaged identically with a double-blind label.

Analysis populations

- ITT population (311 patients) was defined as all randomised patients who had an evaluable primary efficacy endpoint. The primary efficacy endpoint was evaluable when the following 2 conditions were met:
  - Availability of baseline calculated LDL-C value
  - Availability of at least 1 calculated LDL-C value on or off-treatment within 1 of the analysis windows up to Week 24.
- The modified ITT (mITT) population (309 patients) was defined as all randomised patients who took at least 1 dose or part of a dose of the double-blind IMP injection and had an evaluable primary efficacy endpoint during the efficacy treatment period. The primary efficacy endpoint was evaluable when the following 2 conditions were met:
  - Availability of baseline calculated LDL-C value
  - Availability of at least 1 calculated LDL-C value on-treatment, that is, during the efficacy treatment period and within 1 of the analysis windows up to Week 24.

  The efficacy treatment period was defined as the time period from the first double-blind IMP injection up to the day of last injection +21 days.
- The safety population (314 patients) was defined as the randomised patients who actually received at least 1 dose or part of a dose of the double-blind IMP injection. Patients were analysed according to the treatment actually received.

Sample size

A total sample size of 45 patients (30 in alirocumab and 15 in placebo) has 95% power to detect a difference in mean percent change in LDL-C of 30% with a 0.05 2 sided significance level and assuming a common standard deviation (SD) of 25% and all these 45 patients having an evaluable primary endpoint.

The sample size was increased to assess the safety of alirocumab. In order to have at least 147 patients on alirocumab treated for 12 months in this study, and assuming a dropout rate of 10%

over the first 3 month period and a dropout rate of 20% over the remaining 9 month period, the final total sample size was increased and rounded to 306 with a randomisation ratio of 2:1 (alirocumab: 204, placebo: 102).

Statistical methods

Same as for previous studies.

Participant flow

Table 22. Study EFC1568: participant flow

	Placebo (N=107)	Alirocumab 75 Q2W/Up150 Q2W (N=209)
Randomised but not treated	0	2 (1.0%)
Randomised and treated	107 (100%)	207 (99.0%)
Complete 12 months of double-blind treatment period (at least 50 weeks of exposure and visit W52 performed)	80 (74.8%)	167 (79.9%)
Complete the study treatment period (as per CRF)	75 (70.1%)	156 (74.6%)
Did not complete the study treatment period (as per CRF)	32 (29.9%)	51 (24.4%)
Reason for not completing study treatment period (as per CRF)		
Discontinued due to Adverse event	8 (7.5%)	13 (6.2%)
Discontinued due to Poor compliance to protocol	9 (8.4%)	10 (4.8%)
Protocol became inconvenient to participate	2 (1.9%)	0
Life events made continuing too difficult	5 (4.7%)	9 (4.3%)
Other reasons	2 (1.9%)	1 (0.5%)
Other reasons	15 (14.0%)	28 (13.4%)
Physician decision	1 (0.9%)	2 (1.0%)
Patient moved	1 (0.9%)	2 (1.0%)
Related to IMP autoinjector administration	2 (1.9%)	1 (0.5%)
Other [a]	11 (10.3%)	23 (11.0%)
sponsor termination of site	2	2
Randomisation error	0	1
Patient moved	0	2
Death	1	2
Patient did not want to take IMP	4	2
Patient did not meet eCRF criteria for completion	4	12
Patient's decision for treatment discontinuation [b]	21 (19.6%)	27 (12.9%)

Note: Percentages are calculated using the number of patients randomized as denominator. Only the main reason for stopping treatment was entered in CRF.[a] Includes patients who completed the 12 months DB treatment period (at least 50 weeks of exposure and visit W52 performed) but did not meet the definition of "completer per CRF".

Major protocol violations/deviations

During the course of the study 1 site was terminated due to serious non-compliance with the clinical protocol and violations of GCP. A total of 5 patients were randomised at this site and the patients were discontinued from the study.

Major protocol deviations that could potentially impact efficacy analyses were reported for 37 patients (17.7%) in the alirocumab group and 18 patients (16.8%) in the placebo group. 4

patients (1.9%) in the alirocumab group and 1 patient (0.9%) in the placebo group had major protocol deviations (no LDL-C value within any of the analysis window up to Week 24) that led to exclusion from the ITT population. The other protocol deviations did not result in exclusion from the ITT population.

Baseline data

Demographic characteristics at baseline were similar between both treatment groups with the exception that the number of female patients was slightly higher in the alirocumab group compared to the placebo group (37.3% of patients versus 28.0%, respectively). Patients were mostly White (81.6%) with a mean age of 63.0 years (range: 39 to 87 years). The percentage of patients > 65 years was 41.5%, 10.1% were ≥ 75 years of age. Overall, the mean BMI was 32.42 kg/m^2 and the percentage of patients with BMI ≥ 30 kg/m^2 was similar between the treatment groups (61.5% in the alirocumab group and 56.1% in the placebo group).

Overall, the majority of patients (78.2%) in both treatment groups had a history of CHD with history of coronary revascularisation procedures (61.1%) being the most common CHD event or procedure, and 41.1% of patients with a history of MI. The majority of patients (96.2%) had CV risk factors; 88.6% had hypertension and 43.0% had type 2 diabetes and at baseline, 41.8% were former smokers and 19.0% were current smokers.

Results for the primary efficacy outcome

The primary efficacy endpoint was the percent change in calculated LDL-C from baseline to Week 24 in the ITT population, using all LDL-C values regardless of adherence to treatment.

A statistically significant decrease in calculated LDL-C from baseline to Week 24 was observed in the alirocumab group (LS mean [SE] versus baseline: -48.2% [1.9]), compared to the placebo group (LS Mean [SE] versus baseline: -2.3% [2.7]), with an LS mean difference for alirocumab versus placebo of -45.9% ([95% CI: -52.5 to -39.3]; p < 0.0001).

The primary endpoint was also analysed by an ANCOVA model using the measured LDL-C instead of the calculated LDL-C, in patients from the ITT population with an assessment available at baseline and during the Week 24 analysis window and the results from this sensitivity analysis were consistent with the primary analysis.

Table 23. Study EFC 11568: percent change from baseline in calculated LDL-C at Week 24: MMRM – ITT population

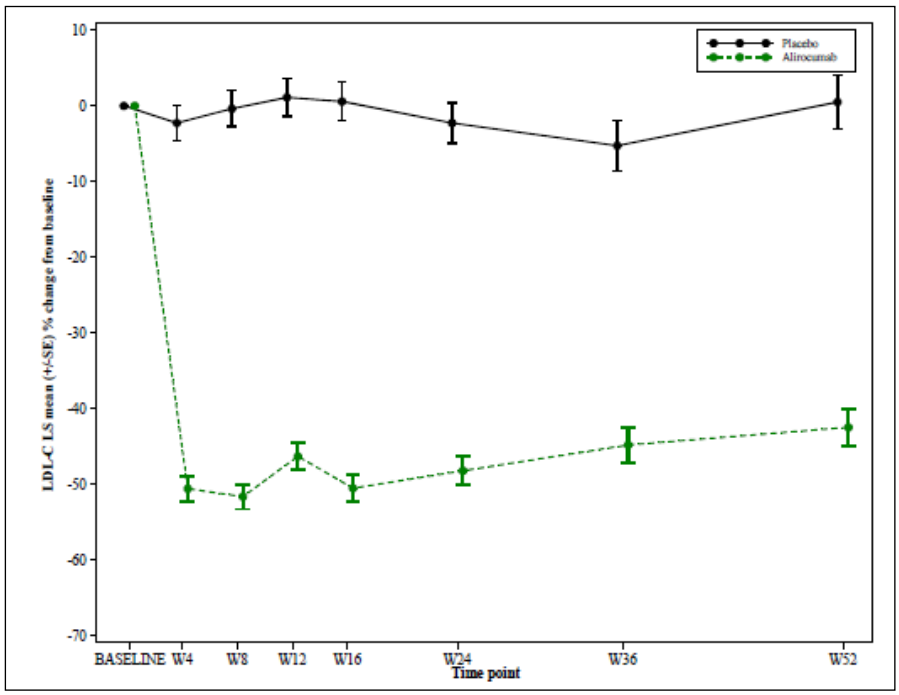
Calculated LDL Cholesterol	Placebo(N=106)	Alirocumab 75 Q2W/Up150 Q2W(N=205)
Baseline (mmol/L)		
Number	106	205
Mean (SD)	2.709 (0.836)	2.597 (0.770)
Median	2.499	2.538
Min : Max	1.58 : 6.29	0.85 : 6.22
Baseline (mg/dL)		
Number	106	205
Mean (SD)	104.6 (32.3)	100.3 (29.7)
Median	96.5	98.0

Calculated LDL Cholesterol	Placebo(N=106)	Alirocumab 75 Q2W/Up150 Q2W(N=205)
Min : Max	61 : 243	33 : 240
Week 24 percent change from baseline (%)		
LS Mean (SE)	-2.3 (2.7)	-48.2 (1.9)
LS mean difference (SE) versus placebo		-45.9 (3.3)
95% CI		(-52.5 to -39.3)
p-value versus placebo		< 0.0001*

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point and strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline calculated LDL-C value-by-time point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model. The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level.

In the alirocumab group, an LDL-C reduction compared with baseline was observed from the first post-dose measurement at Week 4 and maintained at all time points.

Figure 18. Study EFC 11568: LDL-C LS mean (+/-SE) percent change from baseline: time profile – ITT population



Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C-by-time point interaction.

Results for other efficacy outcomes

A hierarchical procedure was used to test the key secondary endpoints while controlling for multiplicity. For some key secondary endpoints, analyses using both the ITT analysis and the on-treatment analysis were pre-specified as part of the hierarchical testing procedure. For these key secondary endpoints, the on-treatment analysis is considered part of the hypothesis-testing procedure.

Since statistical significance was reached for the primary efficacy endpoint, the hierarchical testing was applied to the key secondary endpoints. All key secondary endpoints are statistically significant according to the hierarchical testing procedure down through the HDL-C endpoint at Week 24 (ITT analysis) included. Statistical significance was not reached for the change from baseline in fasting TGs at Week 24 (ITT analysis). Consequently subsequent key secondary endpoints were not tested: Apo A-1 at Week 24, as well as Lp (a), HDL-C, fasting TGs, and Apo A-1 at Week 12. P-values are presented for these endpoints for descriptive purposes.

Table 24. Study EFC 11568: Secondary efficacy outcomes: Hierarchical testing strategy applied

Endpoint	Analysis	Results	P-value
Calculated LDL-C - Percent change from baseline to Week 24	On-treatment	LS mean difference versus placebo of -49.9%	< 0.0001
Calculated LDL-C - Percent change from baseline to Week 12	ITT	LS mean difference versus placebo of -47.4%	< 0.0001
Calculated LDL-C - Percent change from baseline to Week 12	On-treatment	LS mean difference versus placebo of -49.3%	< 0.0001
Apo-B - Percent change from baseline to Week 24	ITT	LS mean difference versus placebo of -35.8%	< 0.0001
Apo-B - Percent change from baseline to Week 24	On-treatment	LS mean difference versus placebo of -37.5%	< 0.0001
Non-HDL-C - Percent change from baseline to Week 24	ITT	LS mean difference versus placebo of -37.5%	< 0.0001
Non-HDL-C - Percent change from baseline to Week 24	On-treatment	LS mean difference versus placebo of -40.4%	< 0.0001
Total-C - Percent change from baseline to Week 24	ITT	LS mean difference versus placebo of -25%	< 0.0001
Apo-B - Percent change from baseline to Week 12	ITT	LS mean difference versus placebo of -38.2%	< 0.0001
Non-HDL-C - Percent change from baseline to Week 12	ITT	LS mean difference versus placebo of -40.1%	< 0.0001
Total-C - Percent change from baseline to Week 12	ITT	LS mean difference versus placebo of -26.4%	< 0.0001
Calculated LDL-C - Percent change from baseline to Week52	ITT	LS mean difference versus placebo of -43%	< 0.0001

Endpoint	Analysis	Results	P-value
Proportion of patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) at Week 24	ITT	combined estimate for odds- ratio versus placebo of 38.5	< 0.0001
Proportion of patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) at Week 24	On-treatment	combined estimate for odds- ratio versus placebo of 50	< 0.0001
Lp(a) - Percent change from baseline to Week 24	ITT	combined estimate for adjusted mean difference versus placebo of -14.6%	< 0.0001
HDL-C - Percent change from baseline to Week 24	ITT	LS mean difference versus placebo of 7.3%	0.0001
Fasting TGs - Percent change from baseline to Week 24	ITT	combined estimate for adjusted mean difference versus placebo of -0.6%	0.8699
Apolipoprotein A1 - Percent change from baseline to Week 24	ITT	LS mean difference versus placebo of 5.8%	0.0002
Lp(a) - Percent change from baseline to Week 12	ITT	combined estimate for adjusted mean difference versus placebo of -19.7%	< 0.0001
HDL-C - Percent change from baseline to Week 12	ITT	LS mean difference versus placebo of 9.2%	< 0.0001
Fasting TGs - Percent change from baseline to Week 12	ITT	combined estimate for adjusted mean difference versus placebo of -14.3%	< 0.0001
Apolipoprotein A1 - Percent change from baseline to Week 12	ITT	LS mean difference versus placebo of 5.6%	0.0006

Subgroup analyses

Subgroup analyses of the primary efficacy endpoint (ITT analysis) showed consistent reduction of LDL-C from baseline with alirocumab versus placebo across a range of demographic and baseline characteristics including race, gender, age, BMI, baseline calculated LDL-C, HDL-C, fasting TGs, Lp (a), intensity of statin treatment and CKD.

7.2.1.2. Study EFC11569 – (Combo II)

A Randomised, Double Blind, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 Versus Ezetimibe in High Cardiovascular Risk Patients with Hypercholesterolaemia Not Adequately Controlled with Their Statin Therapy.

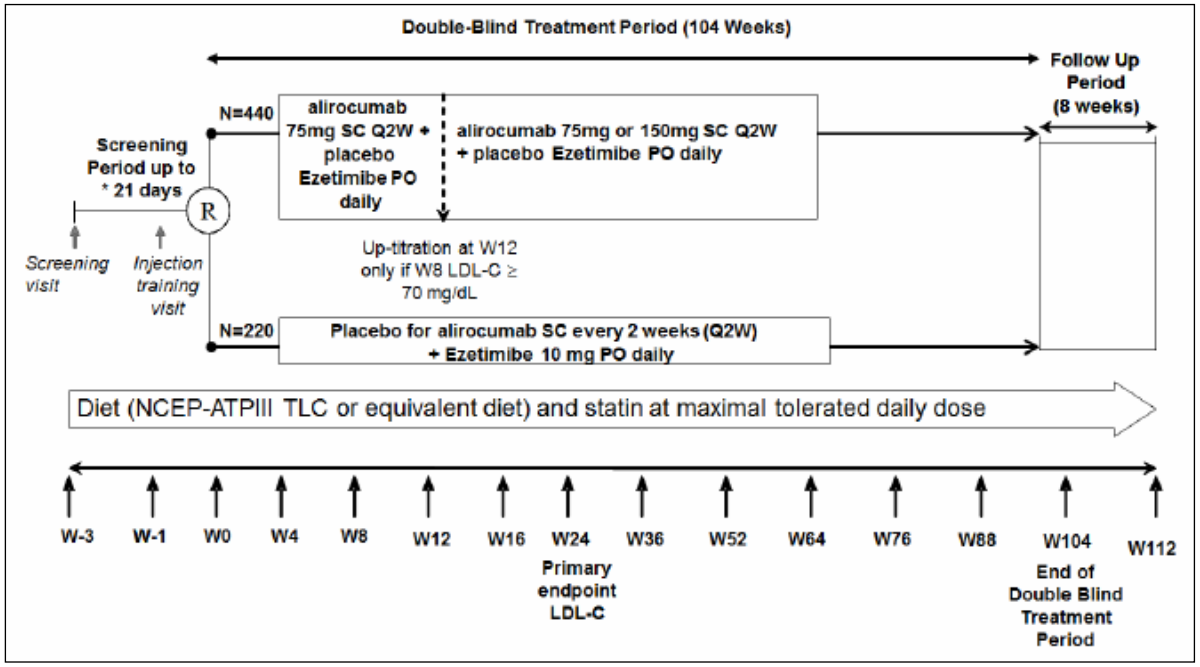
Comment: The CSR is based on the results of the first-step analysis of efficacy data up to Week 52; and safety and other results up to the common cut-off date of 30 May 2014 (the date of the last patient's Week 52 visit). The study is ongoing: the results of the second-step analysis of Week 104 efficacy endpoints and final safety, and other analyses is stated to be presented in a separate study report at a later time.

Study design, objectives, locations and dates

A randomised, double blind, parallel group, double dummy ezetimibe controlled, unbalanced (2:1 alirocumab:ezetimibe) multinational study conducted in 126 centres in 10 countries (Canada, Denmark, France, Hungary, Israel, Russia, South Africa, South Korea, USA and Ukraine) from August 2012 to May 2014 (cut-off date for first step analysis).

- Primary objective: to demonstrate the reduction of LDL-C by alirocumab as add-on therapy to stable maximally tolerated daily statin in comparison with ezetimibe 10 mg daily after 24 weeks of treatment in patients with high cardiovascular risk
- Secondary objectives: same as for Study EFC 11568.

Figure 19. Study EFC 15569: Study design



Inclusion and exclusion criteria

The target population was patients with high CV risk not at goal with their maximally tolerated statin therapy at stable dose for at least 4 weeks prior to the screening visit.

The inclusion and exclusion criteria were the same as for Study EFC 11568. See Section 18.6 for definitions of high CV risk and maximally tolerated statin therapy.

Study treatments

Patients were randomised to 1 of the 2 arms, alirocumab or ezetimibe, in a 2:1 ratio, during the double-blind treatment period:

- Alirocumab (+ placebo for ezetimibe)
  - 75 mg alirocumab SC Q2W starting at Week 0 (randomisation) up to Week 12
  - 75 mg or 150 mg alirocumab SC Q2W (based on their Week 8 LDL-C level), starting at Week 12, and continuing up to Week 102, that is, 2 weeks before the end of the double-blind treatment period
- Ezetimibe (+placebo for alirocumab)
  - Ezetimibe 10 mg capsules once daily at approximately the same time of the day, with or without food from Week 0 to Week 104

The up titration of alirocumab was based on the same criteria as for Study EFC 11568.

All IMP injections were administered SC in the abdomen, thigh, or outer area of the upper arm Q2W, and it was recommended to rotate within an anatomical area or change the anatomical area based on the patient's preference.

Efficacy variables and outcomes

The primary efficacy outcome was the percent change in LDL-C from baseline to Week 24 in the ITT population using all LDL-C values regardless of adherence to treatment (ITT population).

The secondary outcomes were the same as for the previous studies.

Randomisation and blinding methods

Patients were randomised to receive alirocumab or ezetimibe during the double-blind, double-dummy study treatment period using a 2:1 ratio (alirocumab: ezetimibe), with permuted-block randomisation. Randomisation was stratified according to prior history of MI or ischaemic stroke (Yes/No), statin treatment (high intensity statin, as defined by atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily; versus simvastatin whatever the daily dose, atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily) and geographic region. The treatment kit numbers were allocated using the centralised treatment allocation system. For patients in the alirocumab treatment arm, the treatment kit allocated at Week 12 was based on their Week 8 LDL-C level following the up-titration rules (75 mg or 150 mg alirocumab based on the direct transfer of data from the central laboratory).

The IMPs were packaged in accordance with 2 randomised lists (1 for capsules and 1 for injections) of treatment kit numbers generated centrally by the sponsor. The study was double blind and double dummy - alirocumab and placebo for alirocumab were provided in identically matched AIs and packaged identically. All ezetimibe double-blind treatment kit boxes, either ezetimibe 10 mg or placebo for ezetimibe, had the same appearance and feel and were labelled with a double-blind label.

Analysis populations

The definitions were the same as for Study EFC 11568.

Table 25. Study EFC 11569: Analysis populations

	Ezetimibe 10 mg	Alirocumab 75 Q2W/ Up150 Q2W	All
Randomised population	241 (100%)	479 (100%)	720 (100%)
Efficacy populations			
Intent-to-Treat (ITT)	240 (99.6%)	467 (97.5%)	707 (98.2%)
Modified Intent-to-Treat (mITT)	235 (97.5%)	464 (96.9%)	699 (97.1%)

Sample size

A total sample size of 96 patients (64 in alirocumab and 32 in ezetimibe) has 95% power to detect a difference in mean percent change in LDL-C of 20% with a 0.05 two-sided significance level and assuming a common SD of 25% and all these 96 patients having an evaluable primary endpoint.

The sample size was increased to assess the safety of alirocumab. In order to have at least 316 patients on alirocumab treated for 12 months in this study, and assuming a dropout rate of 10% over the first 3 month period and a dropout rate of 20% over the remaining 9 month period, the

final total sample size was increased and rounded to 660 with a randomisation ratio of 2:1 (alirocumab: 440, ezetimibe: 220).

Statistical methods

Same as for Study EFX 11569.

Participant flow

Table 26. Study EFC 11569: patient disposition

	Ezetimibe 10mg (N=241)	Alirocumab 75 Q2W/Up150 Q2W (N=479)
Randomised but not treated	0	0
Randomised and treated	241 (100%)	479 (100%)
Complete 24 months of double-blind treatment period (at least 102 weeks of exposure and visit W104 performed)	0	0
Complete the study treatment period (as per CRF)	0	0
Did not complete the study treatment period (as per CRF)	35(14.5%)	73 (15.2%)
- Did not complete the first Week 52 study treatment period	33 (13.7%)	71 (14.8%)
Treatment ongoing	206 (85.5%)	406 (84.8%)
Reason for not completing study treatment period (as per CRF)		
Discontinued due to Adverse event	13 (5.4%)	36 (7.5%)
Discontinued due to Poor compliance to protocol	7 (2.9%)	13 (2.7%)
Protocol became inconvenient to participate	2 (0.8%)	3 (0.6%)
Life events made continuing too difficult	3 (1.2%)	7 (1.5%)
Other reasons	2 (0.8%)	3 (0.6%)
Other reasons	15 (6.2%)	24 (5.0%)
Physician decision	2 (0.8%)	1 (0.2%)
Patient moved	2 (0.8%)	6 (1.3%)
Patient withdrew consent	1 (0.4%)	0
Related to IMP autoinjector administration	2 (0.8%)	2 (0.4%)
Other a	8 (3.3%)	15 (3.1%)
Did not meet inclusion/exclusion criteria	1	2

	Ezetimibe 10mg (N=241)	Alirocumab 75 Q2W/Up150 Q2W (N=479)
Subject withdrew for personal reasons	4	10
Sudden death	3	2
Lost to follow up	0	1
Patient's decision for treatment discontinuation	22 (9.1%)	56 (11.7%)

Note: Percentages are calculated using the number of patients randomised as denominator. Only the main reason for stopping treatment was entered in CRF. [a] Includes patients who completed the 24 months DB treatment period (at least 102 weeks of exposure and visit W104 performed) but did not meet the definition of "completer per CRF". Source: Study EFC 11569 CSR Table 7

Major protocol violations/deviations

Major protocol deviations that could potentially impact the efficacy analyses were reported for similar percentages of patients in the alirocumab (71 patients, 14.8%) and ezetimibe (32 patients, 13.3%) groups. In total, 13 patients had major protocol deviations (no LDL-C value within any of the analysis window up to Week 24) that led to exclusion from the ITT population (12 patients [2.5%] from the alirocumab group and 1 patient [0.4%] from the ezetimibe group).

Baseline data

Demographic characteristics were generally similar between treatment groups. Overall, patients were mostly male (73.6%), white (84.7%) with a mean age of 61.6 years (range: 9 to 88 years). The majority (56.9%) of patients were ≥ 45 to< 65 years of age.

Tabulated baseline data is provided in Section 18.5.

Results for the primary efficacy outcome

The primary efficacy endpoint was the percent change in calculated LDL-C from baseline to Week 24 in the ITT population, using all LDL-C values regardless of adherence to treatment.

There was rapid decrease in calculated LDL-C from baseline to Week 4 in both the alirocumab and ezetimibe groups. The decrease in calculated LDL-C was statistically significant at Week 24 (ITT analysis) for the alirocumab group (LS mean [SE] versus baseline -50.6% [1.4]) compared with the ezetimibe group (LS mean [SE] versus baseline -20.7% [1.9]) (LS mean difference for alirocumab versus ezetimibe of -29.8% [95% CI: -34.4 to -25.3], p< 0.0001).

Table 27. Study EFC11569: Percent change from baseline in calculated LDL-C at Week 24: MMRM - ITT population

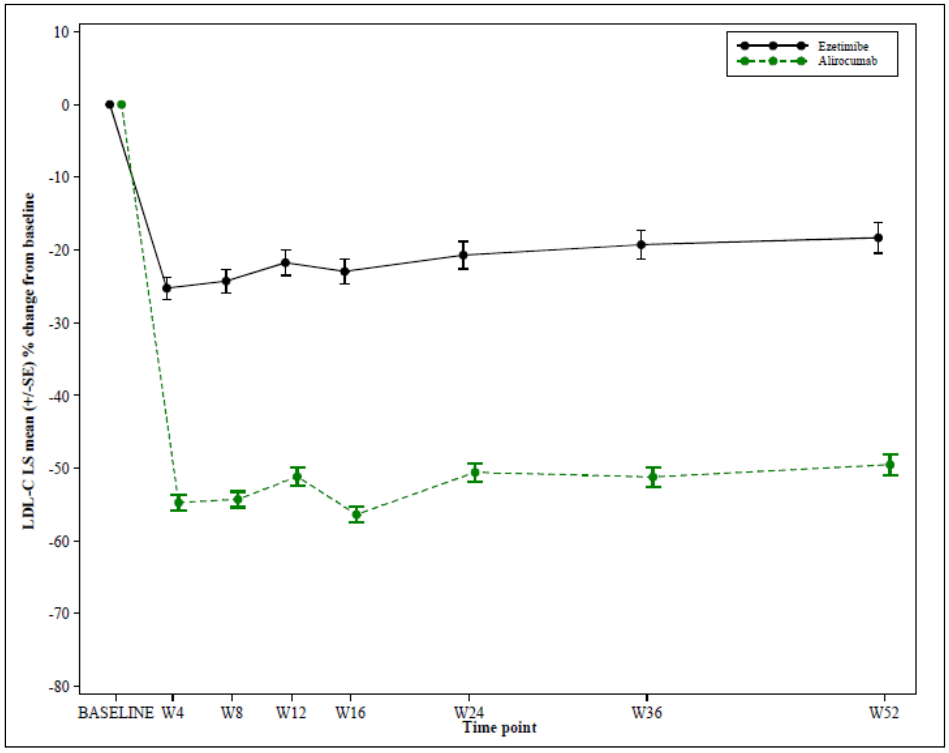
Calculated LDL Cholesterol	Ezetimibe 10 (N=240)	Alirocumab 75 Q2W/Up150 Q2W (N=467)
Baseline (mmol/L)		
Number	240	467
Mean (SD)	2.706 (0.884)	2.805 (0.946)
Median	2.538	2.590
Min : Max	0.98 : 6.29	0.57 : 7.85
Baseline (mg/dL)		

Calculated LDL Cholesterol	Ezetimibe 10 (N=240)	Alirocumab 75 Q2W/Up150 Q2W (N=467)
Number	240	467
Mean (SD)	104.5 (34.1)	108.3 (36.5)
Median	98.0	100.0
Min : Max	38 : 243	22 : 303
Week 24 percent change from baseline (%)		
LS Mean (SE)	-20.7 (1.9)	-50.6 (1.4)
LS mean difference (SE) versus ezetimibe		-29.8 (2.3)
95% CI		(-34.4 to -25.3)
p-value versus ezetimibe		< 0.0001*

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomisation strata as per IVRS, time point, treatment-by-time point and strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline calculated LDL-C value-by-time point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model. The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level. Source: Study EFC11569 CSR Table 24

In the alirocumab group, an LDL-C reduction compared with baseline was observed from the first post-dose measurement at Week4 and maintained at all time points.

Figure 20. Study EFC11569: LDL-C LS mean (+/- SE) percent change from baseline: Time profile - ITT population



Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C-by-time point interaction.

The results of the sensitivity analyses were comparable to those of the primary analysis.

Results for other efficacy outcomes

The same hierarchical procedure was used to test the key secondary endpoints while controlling for multiplicity as in the previous studies. Since statistical significance was reached for the primary efficacy endpoint, the hierarchical testing was applied to the key secondary endpoints. All key secondary endpoints are statistically significant according to the hierarchical testing procedure down through the HDL-C endpoint at Week 24 (ITT analysis) included. Statistical significance was not reached for the percent change from baseline fasting TGs at Week 24 (ITT analysis). Consequently, subsequent key secondary endpoints were not tested: percent change from baseline to Week 24 in Apo A-1 and percent change from baseline to Week 12 in Lp (a), HDL-C, fasting TGs and Apo A-1. P-values presented for these endpoints are for descriptive purposes only.

Table 28. Study EFC11569: secondary efficacy outcomes: hierarchical testing strategy applied

Endpoint	Analysis	Results	P-value
Calculated LDL-C - Percent change from baseline to Week 24	On-treatment	LS mean difference versus ezetimibe of -30.6%	< 0.0001
Calculated LDL-C - Percent change from baseline to Week 12	ITT	LS mean difference versus ezetimibe of -29.4%	< 0.0001
Calculated LDL-C - Percent change from baseline to Week12	On-treatment	LS mean difference versus ezetimibe of -29.7%	< 0.0001
Apo-B - Percent change from baseline to Week 24	ITT	LS mean difference versus ezetimibe of -22.4%	< 0.0001
Apo-B - Percent change from baseline to Week 24	On-treatment	LS mean difference versus ezetimibe of -23%	< 0.0001
Non-HDL-C - Percent change from baseline to Week 24	ITT	LS mean difference versus ezetimibe of -22.9%	< 0.0001
Non-HDL-C - Percent change from baseline to Week 24	On-treatment	LS mean difference versus ezetimibe of -23.5%	< 0.0001
Total-C - Percent change from baseline to Week 24	ITT	LS mean difference versus ezetimibe of -14.7%	< 0.0001
Apo-B - Percent change from baseline to Week 12	ITT	LS mean difference versus ezetimibe of -22.5%	< 0.0001
Non-HDL-C - Percent change from baseline to Week 12	ITT	LS mean difference versus ezetimibe of	< 0.0001

Endpoint	Analysis	Results	P-value
		-22%	
Total-C - Percent change from baseline to Week 12	ITT	LS mean difference versus ezetimibe of -14.3%	< 0.0001
Calculated LDL-C - Percent change from baseline to Week 52	ITT	LS mean difference versus ezetimibe of -31.2%	< 0.0001
Proportion of patients reaching calculated LDL-C< 70 mg/dL (1.81 mmol/L) at Week 24	ITT	combined estimate for odds- ratio versus ezetimibe of 5.4	< 0.0001
Proportion of patients reaching calculated LDL-C< 70 mg/dL (1.81 mmol/L) at Week 24	On-treatment	combined estimate for odds- ratio versus ezetimibe of 5.9	< 0.0001
Lp(a) - Percent change from baseline to Week 24	ITT	combined estimate for adjusted mean difference versus ezetimibe of -21.7%	< 0.0001
HDL-C - Percent change from baseline to Week 24	ITT	LS mean difference versus ezetimibe of 8.1%	< 0.0001
Fasting TGs - Percent change from baseline to Week 24	ITT	combined estimate for adjusted mean difference versus ezetimibe of -0.3%	0.9117
Apolipoprotein A1 - Percent change from baseline to Week 24	ITT	LS mean difference versus ezetimibe of 6.3%	< 0.0001
Lp(a) - Percent change from baseline to Week 12	ITT	combined estimate for adjusted mean difference versus ezetimibe of -23.1%	< 0.0001
HDL-C - Percent change from baseline to Week 12	ITT	LS mean difference versus ezetimibe of 5.8%	< 0.0001
Fasting TGs - Percent change from baseline to Week 12	ITT	combined estimate for adjusted mean difference versus ezetimibe of 1.8%	0.3912

Endpoint	Analysis	Results	P-value
Apolipoprotein A1 - Percent change from baseline to Week 12	ITT	LS mean difference versus ezetimibe of 4.4%	< 0.0001

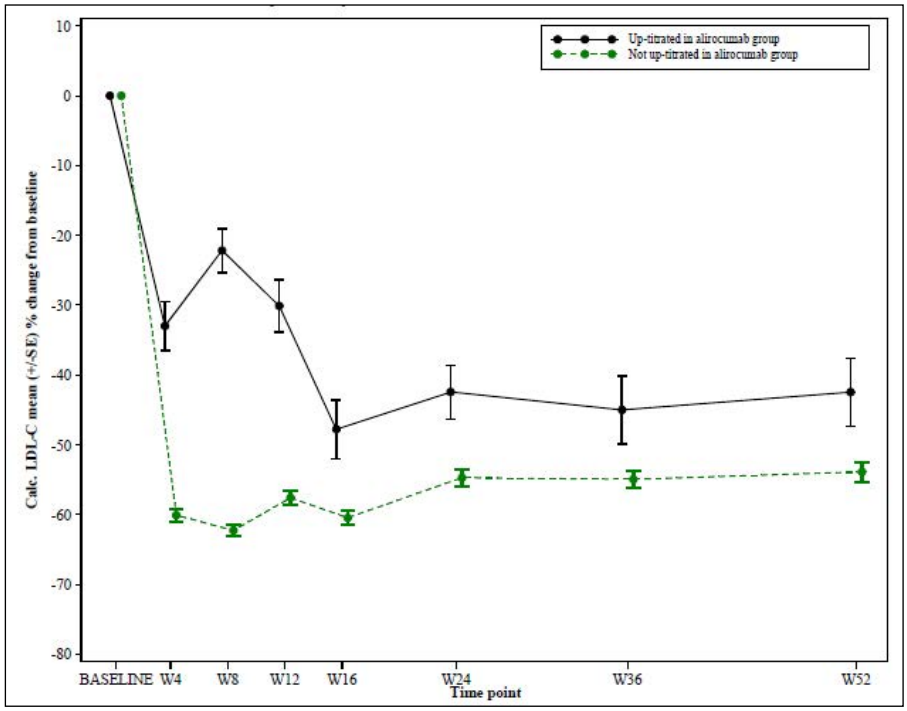
Subgroup analyses

Subgroup analyses of the primary efficacy endpoint (ITT analysis) showed consistent reduction of LDL-C from baseline with alirocumab versus ezetimibe across a range of demographic and baseline characteristics including gender, age, BMI, region, prior history of MI or stroke, baseline PCSK9 levels and baseline LDL-C, Lp (a).

Up titration

Eighty two patients (82/446) in the alirocumab group had the dose up-titrated after Week 12 and 364 patients remained at 75 mg. In patients without dose up-titration, the mean (SD) percent change from baseline in calculated LDL-C was -57.6% (19.9%) at Week 12 and was maintained at Week 24 (-54.7% [24.3%]). In patients with dose up-titration, the mean (SD) percent change from baseline in calculated LDL-C was -30.1% (33.5%) at Week 12. At Week 24, further reduction was observed (-42.5% [33.7%]).

Figure 21. Study EFC11569: Calculated LDL-C mean (+/-SE) percent change from baseline according to up-titration status: time profile



7.2.1.3. Study LTS11717 (Long Term)

Long Term Safety and Tolerability of REGN727 in High Cardiovascular Risk Patients with Hypercholesterolaemia Not Adequately Controlled with Their Lipid Modifying Therapy: A Randomised, Double Blind, Placebo Controlled Study.

Comment: The primary objective of this study was safety. Efficacy was a secondary objective.

Efficacy variables and outcomes

Same as for previous studies.

Primary efficacy outcome was percent change in calculated LDL-C from baseline to Week 24 in the ITT population using all LDL-C values regardless of adherence to treatment (ITT population).

Major protocol violations/deviations

Violations related to GCP non-compliance resulted in closure of 1 site in the USA. The noncompliance issues were: the Investigator failed to maintain adequate records of the investigation, including failure to ensure compliance with regard to the maintenance of medical records to confirm patient eligibility, inadequate documentation of informed consent, lack of maintenance of drug inventory logs, and lack of oversight by the Investigator. Only 1 patient was randomised at this site and subsequently withdrew consent.

Major protocol deviations that could potentially impact efficacy analyses were reported for 237 patients (15.3%) in the alirocumab group and 123 patients (15.6%) in the placebo group. 23 patients (1.5%) in the alirocumab group and 8 patients (1.0%) in the placebo group had major protocol deviations (no LDL-C value within any of the analysis windows up to Week 24) that led to exclusion from the ITT population.

Results for primary efficacy outcome

The primary efficacy outcome was the percent change from baseline in LDL-C at 24 weeks. A statistically significant decrease in calculated LDL-C from baseline to Week 24 (ITT analysis) was observed in the alirocumab group (LS mean [SE] versus baseline: -61.0% [0.7]) compared with the placebo group (LS mean [SE] versus baseline: + 0.8% [1.0]), with an LS mean difference for alirocumab versus placebo of -61.9% ([95% CI: -64.3 to -59.4]; p < 0.0001).

Table 29. Study LTS11717: Percent change from baseline in calculated LDL-C at Week 24: MMRM – ITT population

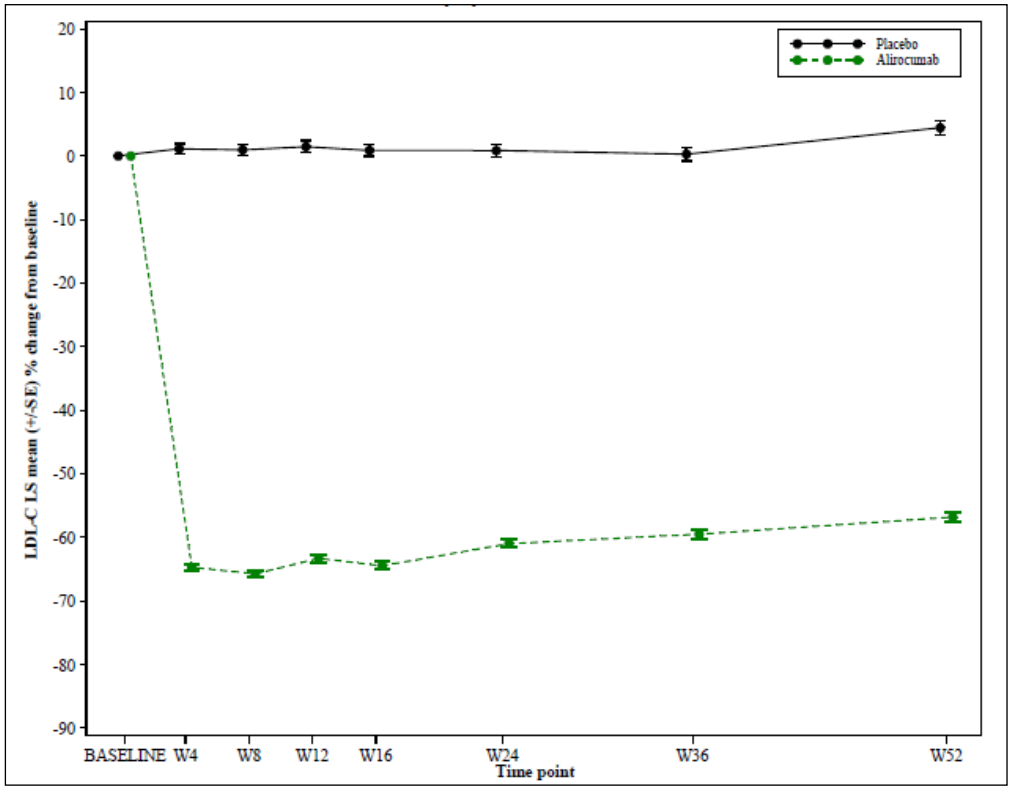
	Placebo (N=780)	Alirocumab 150 Q2W (N=1530)
Calculated LDL Cholesterol		
Baseline (mmol/L)		
Number	780	1530
Mean (SD)	3.159 (1.077)	3.180 (1.106)
Median	2.920	2.974
Min : Max	0.49 : 10.47	1.01 : 10.99
Baseline (mg/dL)		
Number	780	1530
Mean (SD)	122.0 (41.6)	122.8 (42.7)
Median	112.7	114.8
Min : Max	19 : 404	
Week 24 percent change from baseline (%)		39 : 424
LS Mean (SE)	0.8 (1.0)	-61.0 (0.7)
LS mean difference (SE) versus placebo		-61.9 (1.3)
95% CI		(-64.3 to -59.4)
p-value versus placebo		< 0.0001*

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomisation strata as per IVRS, time point, treatment-by-time point and strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline calculated LDL-C value-by-time point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model. The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level.

An LDL-C reduction compared with baseline in the alirocumab group was observed from the first post-dose measurement at Week 4 and was maintained at all time points up to Week 52.

Results from the sensitivity analyses were similar to those of the primary analysis in the ITT population.

Figure 22. Study LTS11717: LDL-C LS mean (+/- SE) percent change from baseline: time profile - ITT population



Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C-by-time point interaction. Source: Study LTS11717 CSR Figure 2

Results of secondary outcomes

Since statistical significance was reached for the primary efficacy endpoint, hierarchical testing was applied to the key secondary endpoints. All key secondary endpoints are statistically significant according to the hierarchical procedure.

Table 30. Study LTS11717: Secondary efficacy outcomes: Hierarchical testing strategy applied

Endpoint	Analysis	Results	P-value
Calculated LDL-C - Percent change from baseline to Week 24	On-treatment	LS mean difference versus placebo of -63.5%	< 0.0001
Calculated LDL-C - Percent change from baseline to Week 12	ITT	LS mean difference versus placebo of -64.8%	< 0.0001
Calculated LDL-C - Percent change from baseline to Week 12	On-treatment	LS mean difference versus placebo of -65.5%	< 0.0001
Measured LDL-C (by ultracentrifugation) - Percent change from baseline to Week 24	ITT	LS mean difference versus placebo of -61.3%	< 0.0001
Apo-B - Percent change from baseline to Week 24	ITT	LS mean difference versus placebo of -54%	< 0.0001
Apo-B - Percent change from baseline to Week 24	On-treatment	LS mean difference versus placebo of -55.5%	< 0.0001
Non-HDL-C - Percent change from baseline to Week 24	ITT	LS mean difference versus placebo of -52.3%	< 0.0001
Non-HDL-C - Percent change from baseline to Week 24	On-treatment	LS mean difference versus placebo of -53.7%	< 0.0001
Total-C - Percent change from baseline to Week 24	ITT	LS mean difference versus placebo of -37.5%	< 0.0001
Apo-B - Percent change from baseline to Week 12	ITT	LS mean difference versus placebo of -56%	< 0.0001
Non-HDL-C - Percent change from baseline to Week 12	ITT	LS mean difference versus placebo of -54.6%	< 0.0001
Total-C - Percent change from baseline to Week 12	ITT	LS mean difference versus placebo of -39%	< 0.0001
Proportion of very high CV risk patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24	ITT	combined estimate for odds- ratio versus placebo of 71.5	< 0.0001
Proportion of very high CV risk patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C< 100 mg/dL (2.59 mmol/L) at Week 24	On-treatment	combined estimate for odds- ratio versus placebo of 93.4	< 0.0001
Proportion of patients reaching calculated LDL-C< 70 mg/dL (1.81 mmol/L) at Week 24	ITT	combined estimate for odds- ratio versus placebo of 74.6	< 0.0001
Proportion of patients reaching calculated LDL-C< 70 mg/dL (1.81 mmol/L) at Week 24	On-treatment	combined estimate for odds- ratio versus placebo of 97.3	< 0.0001

Endpoint	Analysis	Results	P-value
Lp(a) - Percent change from baseline to Week 24	ITT	combined estimate for adjusted mean difference versus placebo of -25.6%	< 0.0001
HDL-C - Percent change from baseline to Week 24	ITT	LS mean difference versus placebo of 4.6%	< 0.0001
Fasting TGs - Percent change from baseline to Week 24	ITT	combined estimate for adjusted mean difference versus placebo of -17.3%	< 0.0001
Apolipoprotein A1 - Percent change from baseline to Week 24	ITT	LS mean difference versus placebo of 2.9%	< 0.0001
Lp(a) - Percent change from baseline to Week 12	ITT	combined estimate for adjusted mean difference versus placebo of -25.1%	< 0.0001
HDL-C - Percent change from baseline to Week 12	ITT	LS mean difference versus placebo of 5.6%	< 0.0001
Fasting TGs - Percent change from baseline to Week 12	ITT	combined estimate for adjusted mean difference versus placebo of -17.9%	< 0.0001
Apolipoprotein A1 - Percent change from baseline to Week 12	ITT	LS mean difference versus placebo of 4%	< 0.0001

Consistent results were observed at Week 12 and Week 52 for both the ITT analysis and the on treatment analysis.

Subgroup analysis

Subgroup analyses of the primary efficacy endpoint showed consistent reductions in LDL-C from baseline with alirocumab versus placebo across a range of demographic and baseline characteristics including age, BMI, heFH, prior history of MI or ischemic stroke, fasting TGs, Lp (a), intensity of background statin treatment, use of additional background LMT at randomisation, and use of ezetimibe at randomisation, atorvastatin at randomisation, rosuvastatin at randomisation, and simvastatin at randomisation.

7.3. Indication 3 – Monotherapy in patients with hypercholesterolaemia and moderate cardiovascular risk.

7.3.1. Pivotal study

7.3.1.1. Study EFC11716 – (Mono)

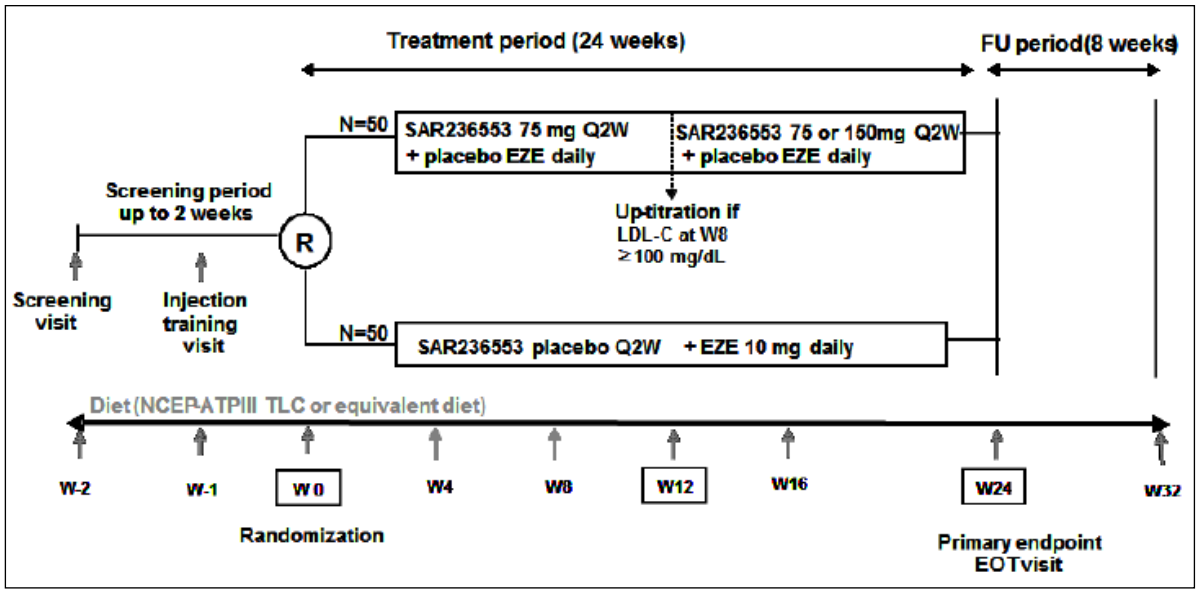
A Randomised, Double Blind, Active Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 Over 24 Weeks in Patients with Hypercholesterolaemia.

Study design, objectives, locations and dates

A randomised, double blind, parallel group, double dummy, active (ezetimibe) controlled, balanced (1:1, alirocumab: ezetimibe) multinational study conducted in 8 centres in the USA, Belgium, Finland and the Netherlands from July 2012 to July 2013.

- Primary objective: to demonstrate the reduction of LDL-C by alirocumab Q2W as monotherapy in comparison with ezetimibe 10 mg daily after 24 weeks of treatment in patients with primary hypercholesterolaemia at moderate CV risk
- Secondary objectives: same as previous studies.

Figure 23. Study EFC11716: Study design



FU – follow-up, N – number of patients randomized, R – randomization, Q2W – every 2 weeks, W – Week, EZE – ezetimibe, EOT – end of treatment.

Inclusion and exclusion criteria

- Inclusion: male and female (non-childbearing potential) patients aged ≥ 18 years with LDL between 2.59 and 4.91 mmol/L (100 – 190 mg/dL) and moderate CV risk, as defined by a 10 year risk of fatal CV disease ≥ 1% and < 5% based on the Systemic Coronary Risk Estimation (SCORE) (Task Force et al, 2011).
- Exclusion**:** History of established CHD or CHD risk equivalents; TIAs or ischaemic stroke or significant carotid artery disease; patients with diabetes mellitus (DM) associated with a risk SCORE ≥ 5% or with any additional risk factor.

Study treatments

Patients were randomised to one of the 2 arms, alirocumab or ezetimibe, during the double-blind treatment period:

- Alirocumab (+placebo for ezetimibe).
  - 75 mg alirocumab SC Q2W starting at Week 0 (randomisation)
  - 75 mg or 150 mg alirocumab (based on their Week 8 LDL-C level) SC, Q2W, starting at Week 12, and continuing up to Week 22, that is, 2 weeks before the end of the double-blind treatment period

    An up-titration of the alirocumab dose was planned for patients with LDL-C levels ≥ 100 mg/dL (2.59 mmol/L) at Week 8
- Ezetimibe(+placebo for alirocumab).
  - 10 mg ezetimibe capsules once-daily at approximately the same time of the day, with or without food from Week 0 to Week 24.

All injections using an auto-injector, were administered SC in the abdomen, thigh, or outer area of the upper arm Q2W, and it was recommended to rotate within an anatomical area or to change the anatomical area based on the patient's preference.

Efficacy variables and outcomes

The primary efficacy outcome was the percent change in calculated LDL-C from baseline to Week 24.

The secondary efficacy outcomes were the same as for the previous studies.

Randomisation and blinding methods

Patients were randomised via either the interactive voice response system (IVRS) or the interactive web response system (IWRS) using a ratio 1:1, with permuted-block randomisation. Randomisation was stratified based on the patient's reported diabetes mellitus status (Yes versus No).

The study was double blind and double dummy; alirocumab and placebo for alirocumab were provided in identically matched AIs packaged identically, with identical labels. All ezetimibe double-blind treatment kit boxes, either ezetimibe 10 mg or placebo for ezetimibe had the same appearance and feel and were labelled with a double-blind label.

Analysis populations

Same as for previous studies.

Sample size

The sample size calculations were based on the primary efficacy variable of LDL-C percent change from baseline to Week 24, with the following assumptions:

- A common standard deviation (SD) of 25%, which was assumed based on results from previous Phase II trial (DFI11565) in a population treated with statin as background therapy
- A 20% mean difference between alirocumab and ezetimibe in percent change from baseline
- A t-test at a 2-sided 5% significance level with 95% power
- Expected exclusion rate from modified intent-to-treat (mITT) population = 5% as per protocol in which the planned primary analysis was initially to be performed with the mITT population.

Based on the above assumptions, 45 patients per arm were needed for this study. The final total sample size was rounded to 100 with a randomization ratio 1:1 (alirocumab: 50, ezetimibe: 50).

Forty five patients per arm resulted in the powers indicated in table below for various SDs:

Table 31. Power calculations for Study EFC11716

Standard deviation			
Percent change difference	20%	25%	30%
20%	> 99%	96%	87%

Statistical methods

Same as for previous studies.

Participant flow

Table 32. Study EFC11716: patient disposition

	Ezetimibe 10 (N=51)	Alirocumab 75 Q2W/Up150 Q2W (N=52)
Randomised and not treated	0	0
Randomised and treated	51 (100%)	52 (100%)
Complete the study treatment period	44 (86.3%)	44 (84.6%)
Did not complete the study treatment period	7 (13.7%)	8 (15.4%)
Reason for treatment discontinuation		
Adverse event	4 (7.8%)	5 (9.6%)
Poor compliance to protocol	1 (2.0%)	0
Life events made continuing too difficult [a]	1 (2.0%)	0
Other reasons	2 (3.9%)	3 (5.8%)
Patient moved [a]	0	1 (1.9%)
Patient withdrew consent [a]	0	1 (1.9%)
Not dosed due to site error	1 (2.0%)	1 (1.9%)
Week 24 performed too late	1 (2.0%)	0
Patient's decision for treatment discontinuation	6 (11.8%)	6 (11.5%)
Status at last study contact		
Alive	51 (100%)	52 (100%)
Dead	0	0

Note: Percentages are calculated using the number of patients randomised as denominator. Only the main reason for stopping treatment was entered in e-CRF. [a] For each main reason, detailed reasons are collected in e-CRF.

Major protocol violations/deviations

Major protocol deviations that could potentially impact efficacy analyses were reported for 15 patients (28.8%) in the alirocumab group and 9 patients (17.6%) in the ezetimibe group. 3 patients (5.8%) in the alirocumab group and 5 patients (9.8%) in the ezetimibe group did not have an LDL-C assessment for the Week 24 analysis window (from days 155 to 182). None of these patients were excluded from the ITT population and their missing data were accounted for by the MMRM model.

A serious error occurred in the up titration system at Week 12. In the automated process for up-titration, an error in the specifications form led to a threshold of 70 mg/dL being applied instead of the threshold of 100 mg/dL planned in the protocol for triggering the up-titration. A total of 14 patients in the alirocumab group were automatically up-titrated in a blinded manner at Week 12 from 75 mg Q2W to 150 mg Q2W, including 13 patients up-titrated based on an LDL-C value between 70 and 100 mg/dL (1.81 and 2.59 mmol/L). Due to the double-blind design of the protocol, neither the sponsor, nor the site, nor the patient, were aware of the error that led to an up-titration to the higher dose of 150 mg alirocumab Q2W until database lock had occurred.

Therefore, instead of assessing the efficacy and safety of alirocumab 75 mg Q2W with up-titration to 150 mg Q2W, based on a LDL-C value of ≥ 100 mg/dL (2.59 mmol/L), the study assesses the efficacy and safety of alirocumab 75 mg Q2W with up-titration to 150 mg Q2W based on a LDL-C value of ≥ 70 mg/dL (1.81 mmol/L). A sensitivity analysis was performed excluding all on-treatment data collected after the Week 12 up-titration for these 13 patients with LDL-C value ≥ 70 and < 100 mg/dL (1.81 and 2.59 mmol/L).

Baseline data

Demographic characteristics were generally similar between treatment groups. Overall, the number of female (48; 46.6%) and male (55; 53.4%) patients randomised in the study was well balanced between the treatment groups. Patients were mostly White (90.3%) with a mean age of 60.2 years (range: 45 to 72 years). The percentage of patients aged 65 years or more was 18.4%, and there was no patient with age ≥ 75 years. There were more patients with BMI ≥ 30 kg/m^2 in the alirocumab group. Of 38 patients (36.9%) in the study with a BMI ≥ 30 kg/m^2, 23 patients were from the alirocumab group.

Results for the primary efficacy outcome

The primary efficacy outcome was the percent change in calculated LDL-C from baseline to Week 24. At Week 24, the percent change from baseline in LDL-C in the ITT population was greater in the alirocumab group (LS Mean [SE] percent change from baseline: -47.2% [3.0]), compared to the ezetimibe group (LS Mean [SE] percent change from baseline: -15.6% [3.1]); and the LS mean difference of percent change from baseline for alirocumab versus ezetimibe of -31.6% ([95% CI: -40.2 to -23.0]; p < 0.0001) was statistically significant.

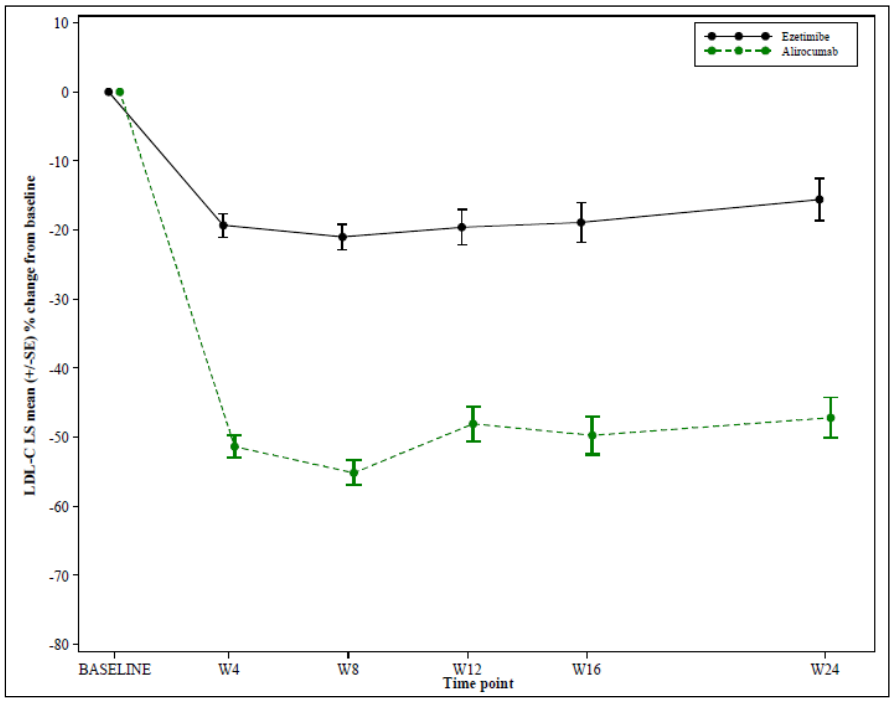
Table 33. Study EFC11716: percent change from baseline in LDL-C at Week 24: MMRM analysis - ITT population

LDL Cholesterol	Ezetimibe 10 (N=51)	Alirocumab 75 Q2W/Up150 Q2W (N=52)
Baseline (mmol/L)		
Number	51	52
Mean (SD)	3.583 (0.636)	3.654 (0.702)
Median	3.652	3.652
Min : Max	1.89 : 4.82	1.99 : 5.36
Baseline (mg/dL)		
Number	51	52
Mean (SD)	138.3 (24.5)	141.1 (27.1)
Median	141.0	141.0
Min : Max	73 : 186	77 : 207
Week 24 percent change from baseline (%)		
LS mean (SE)	-15.6 (3.1)	-47.2 (3.0)
LS mean difference (SE) versus ezetimibe		-31.6 (4.3)
95% CI		(-40.2 to -23.0)
p-value versus ezetimibe		< 0.0001*

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, time point, treatment-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model. The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level.

A larger LDL-C reduction in the alirocumab group as compared to the ezetimibe group was observed from the first post-dose measurement at Week 4 and was maintained at all time points up to Week 24.

Figure 24. Study EFC11716: LDL-C LS mean (±SE) percent change from baseline: time profile - ITT population



Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, time point, treatment-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C-by-time point interaction.

An additional efficacy analysis was performed excluding all on-treatment data collected after the Week 12 up-titration for the 13 patients who were up-titrated based on an LDL-C value between 70 and 100 mg/dL. Results of this sensitivity analysis were comparable to those of the primary analysis. The primary endpoint was also analysed using the mITT population and LDL-C collected during the efficacy treatment period ("on-treatment" analysis). The results from the sensitivity analysis were consistent with the primary analysis in the ITT Population.

Results for other efficacy outcomes

Since statistical significance was reached for the primary efficacy endpoint, the hierarchical testing of the secondary efficacy outcomes was conducted as in the previous studies.

Statistical significance was not reached for Lp (a) at Week 24. Consequently subsequent key secondary endpoints were not tested: HDL-C, fasting TGs, and Apo A-1 at Week 24 and Week 12 as well as Lp (a) at Week 12.

Table 34. Study EFC11716: Secondary efficacy outcomes - Hierarchical testing strategy applied

Key Secondary Endpoint	p-value comparison [a] (alirocumab versus ezetimibe)
Percent change in calculated LDL-C from baseline to Week 12	p < 0.0001, statistically significant
Percent change in Apo B from baseline to Week 24	p < 0.0001, statistically significant
Percent change in non-HDL-C from baseline to Week 24	p < 0.0001, statistically significant
Percent change in Total-C from baseline to Week 24	p < 0.0001, statistically significant
Percent change in Apo B from baseline to Week 12	p < 0.0001, statistically significant
Percent change in non-HDL-C from baseline to Week 12	p < 0.0001, statistically significant
Percent change in Total-C from baseline to Week 12	p < 0.0001, statistically significant
Proportion of patients reaching LDL-C< 100 mg/dL (2.59 mmol/L) at Week 24	p < 0.0001, statistically significant
Proportion of patients reaching LDL-C< 70 mg/dL (1.81 mmol/L) at Week 24	p = 0.0001, statistically significant
Percent change in Lp (a) from baseline to Week 24	**not significant**
Percent change in HDL-C from baseline to Week 24	NAP
Percent change in HDL-C from baseline to Week 12	NAP
Percent change in Lp (a) from baseline to Week 12	NAP
Percent change in fasting TG from baseline to Week 24. Measurements with missing fasting status were excluded from the analysis.	NAP
Percent change in fasting TG from baseline to Week 12. Measurements with missing fasting status were excluded from the analysis	NAP
Percent change in Apo A-1 from baseline to Week 24	NAP
Percent change in Apo A-1 from baseline to Week 12	NAP

NAP: not applicable due to not significant result at the preceding endpoint. a: p value comparison for ITT population.

Subgroup analyses

Subgroup analyses of primary efficacy endpoint suggested no significant treatment-subgroup interactions in the ITT population for various factors including, age, BMI, region, baseline LDL-C, Lp(a), HDL-C and baseline PCSK9 levels, indicating a consistent reduction of LDL-C from baseline with alirocumab versus ezetimibe across a range of demographic and baseline characteristics.

LDL-C analysis according to up-titration status

Additional analyses according to the up-titration status were performed in patients in the alirocumab group based on the up-titration status at Week 12. A total of 14 patients were up-titrated to 150 mg/dL alirocumab Q2W at Week 12, and 32 patients continued 75 mg/dL alirocumab Q2W. The LDL-C mean percent change from baseline up to Week 12 was greater in patients who were not up-titrated. From Week 16 up to Week 24, both groups reached a similar decrease in percent change from baseline.

The mean baseline values for LDL-C, non-HDL-C, Apo B, Total-C, HDL-C, and Apo A-1 were higher in the patients up-titrated to 150 mg alirocumab Q2W compared with patients who continued with 75 mg alirocumab Q2W.

7.4. Other efficacy studies

Three additional studies were submitted which included patients with mixed hyperlipidaemia or variations of therapy which the sponsor considered pivotal.

7.4.1. Pivotal studies

7.4.1.1. Study R727-CL-1110 – (Options I)

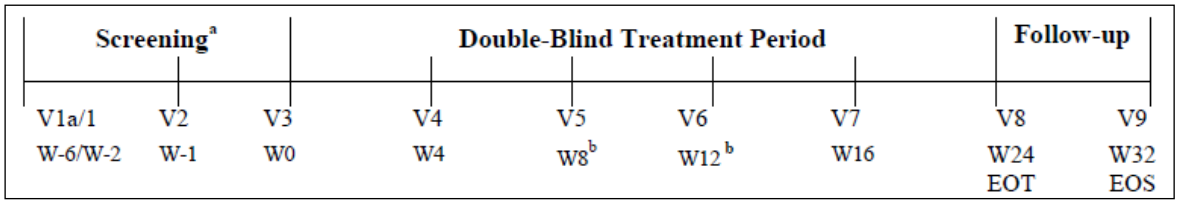
A Randomised, Double Blind Study of the Efficacy and Safety of Alirocumab Added to Atorvastatin Versus Ezetimibe Added on to Atorvastatin Versus Atorvastatin Dose Increase Versus Switch to Rosuvastatin in Patients who are Not Controlled on Atorvastatin.

Study design, objectives, locations and dates

A randomised, double blind, active comparator, parallel group, multinational study conducted at 85 sites in 9 countries (Australia, Canada, France, Germany, Italy, Mexico, Spain, UK and USA) from October 2012 to May 2014.

- Primary objective: to evaluate the reduction of LDL-C by alirocumab as add-on therapy to atorvastatin in comparison with ezetimibe as add-on therapy to atorvastatin, in comparison with doubling the atorvastatin dose, or in comparison with a therapy switch from atorvastatin to rosuvastatin, after 24 weeks of treatment in patients with hypercholesterolemia at high CV risk.
- Secondary objectives:
  - To evaluate the reduction of LDL-C by alirocumab 75 mg as add-on therapy to atorvastatin in comparison with ezetimibe as add-on therapy to atorvastatin, in comparison with doubling of the atorvastatin dose, or in comparison with a switch from atorvastatin to rosuvastatin after 12 weeks of treatment
  - To evaluate the effect of alirocumab on other lipid parameters, eg, Apo B, non-HDL-C, Total-C, Lp(a), HDL-C, TGs, and Apo A-1 To evaluate the safety and tolerability of alirocumab
  - To evaluate the development of anti-alirocumab antibodies

Figure 25. Study R727-CL-1110: study design



Note: The scale is not linear. V=Visit; W=Week; EOT=end of treatment; EOS=end of study. [a] There were 2 or 3 screening visits during the screening period. [b] The dose of alirocumab was up-titrated (using a blinded process) from 75 mg to 150 mg at the Week 12.

Inclusion and exclusion criteria

- Inclusion: Male or female (non-childbearing potential) patients, aged ≥ 18 years with hypercholesterolemia (LDL-C < 70 mg/dL (1.81 mmol/L) at the screening visit (Week -2) in patients with history of documented CHD or non-CHD CVD or LDL-C < 100 mg/dL (2.59 mmol/L) at the screening visit (Week -2) in patients without history of documented CHD or non-CHD CVD but with other risk factors; and established CHD or non-CHD CVD as well as patients who were at high risk for CVD due to other risk factors and who were not adequately controlled with a 20 mg or 40 mg daily dose of atorvastatin, with or without other LMT (except ezetimibe).
- Exclusion: Homozygous FH (clinically or from previous genotyping); currently taking a statin that is not atorvastatin taken daily at 20 mg or 40 mg; currently taking ezetimibe or had received ezetimibe within 4 weeks of screening Visit 1 (Week -2); not on a stable dose of allowable LMT (excluding ezetimibe) for at least 4 weeks and/or fenofibrate for at least 6 weeks prior to the screening visit.

Study treatments

At the discretion of the investigator, patients had an open label 4 week atorvastatin (20 mg or 40 mg) run-in period between the pre-screening period and Visit 1, if they meet the following: had not been on a stable dose of atorvastatin for 4 weeks, were being switched from another statin to atorvastatin, or were not on a statin but should have been according to local guidance.

At entry into the double-blind treatment period, eligible patients were taking either 20 mg or 40 mg atorvastatin daily (QD) and were randomised to 1 of 7 treatment arms to the following groups, according to their baseline atorvastatin dose:

1. Patients on atorvastatin 20 mg baseline regimen.
    a. Alirocumab + atorvastatin 20 mg + placebo for ezetimibe.
    b. Atorvastatin 40 mg + placebos for alirocumab and ezetimibe.
    c. Atorvastatin 20 mg + ezetimibe 10 mg + placebo for alirocumab.
2. Patients on atorvastatin 40 mg baseline regimen.
    a. Alirocumab + atorvastatin 40 mg + placebo for ezetimibe.
    b. Atorvastatin 80 mg + placebos for alirocumab and ezetimibe.
    c. Rosuvastatin 40 mg + placebos for alirocumab and ezetimibe.
    d. Atorvastatin 40 mg + ezetimibe 10 mg + placebo for alirocumab.

Injectable study drug was administered SC Q2W at approximately the same time of day (based upon patient preference). The orally administered study treatments were either atorvastatin or rosuvastatin (1 capsule) and either ezetimibe or placebo for ezetimibe (1 capsule). The patient then continued taking 2 capsules of study drug per day through Week 24 (day 169).

At the Week 12 visit, based on the patient's LDL-C at Week 8 and baseline CV risk, patients in the alirocumab + atorvastatin groups either continued receiving 75 mg Q2W or had the alirocumab dose up-titrated to 150 mg Q2W, in a blinded manner, as follows:

- Patients with heFH, non-FH with a history of documented CHD, non-CHD CVD, or diabetes mellitus with target organ damage were treated as follows:
    – Patients continued alirocumab 75 mg Q2W if the Week 8 LDL-C was < 70 mg/dL (1.81 mmol/L).
    – Patients had their doses up-titrated to alirocumab 150 mg Q2W if the Week 8 LDL-C was ≥ 70 mg/dL (1.81 mmol/L).
- Patients with heFH or non-FH, without CHD or non-CHD CVD, but with a calculated 10-year fatal CVD risk SCORE ≥ 5%, or with moderate CKD, or with diabetes mellitus but no target organ damage were treated as follows:
    – Patients continued alirocumab 75 mg Q2W if the Week 8 LDL-C was< 100 mg/dL (2.59 mmol/L).
    – Patients had their doses up-titrated to alirocumab 150 mg Q2W if the Week 8 LDL-C was ≥ 100 mg/dL (2.59 mmol/L).

Efficacy variables and outcomes

The primary efficacy outcome was the percent change in calculated LDL-C from baseline to Week 24 in the intent-to-treat (ITT) population.

The secondary efficacy outcomes were the same as in previous studies.

Randomisation and blinding methods

For either atorvastatin baseline regimen (20 mg and 40 mg), randomisation was stratified according to the patient's history of MI or ischaemic stroke (Yes/No). Randomisation was done in equal proportions to 1 of 3 treatment groups (atorvastatin 20 mg baseline regimen) or 1 of 4 treatment groups (atorvastatin 40 mg baseline regimen), implementing a permuted-block design to ensure even distribution of the treatment assignments.

Sterile alirocumab (75 mg and 150 mg) and placebo for alirocumab were provided in 1 mL volume in identically matched pre-filled syringes assembled in disposable AI (pre-filled pens). Ezetimibe 10 mg was supplied as an over-encapsulated tablet (contained within a capsule) to match the placebo for ezetimibe, ensuring the double blind. Similarly, atorvastatin 20 mg, 40 mg, and 80 mg, and rosuvastatin 40 mg were supplied as matching over-encapsulated tablets (capsules). The over-encapsulated tablets were indistinguishable from each other.

Analysis populations

Same as for previous studies.

Sample size

Five pairwise comparisons of alirocumab benefit to multiple control groups were hypothesised for the primary efficacy analysis of this study. Using the Bonferroni adjustment for the sample size calculation of the multiple treatment group comparisons, a total of 350 patients was planned for the analysis of the primary measure at Week 24. Specifically, a sample size of 50 patients per group would have 90% power to detect a difference in means of at least 20% in any 1 pairwise comparison (that is, alirocumab mean = 50% and control mean = 30%), assuming that the common SD was 25% using an independent group t-test. The alpha level for each of the 5 pairwise comparisons was adjusted to a 2 sided alpha level of 0.01, thereby maintaining an overall study alpha level of 0.05.

Statistical methods

Same as for previous studies.

Participant flow

859 patients were screened for this study, of whom 504 patients (58.7%) were screen failures based on inclusion and exclusion criteria.

Table 35. Study R727-CL-1110: patient disposition – atorvastatin 20 mg baseline regimen – randomised population

	Atorvastatin 40 mg (N=57)	Ezetimibe 10 mg + Atorvastatin 20 mg (N=55)	Alirocumab 75/150+ Atorvastatin 20 mg (N=57)
Randomised but not treated	0	0	0
Randomised and treated	57 (100%)	55 (100%)	57 (100%)
Completed 24 weeks of double-blind treatment period (at least 22 weeks of exposure and Week 24 visit performed)	47 (82.5%)	41 (74.5%)	48 (84.2%)
Completed the study treatment period (as per e-CRF)	44 (77.2%)	40 (72.7%)	46 (80.7%)
Did not complete the study treatment period (as per e-CRF)	13 (22.8%)	15 (27.3%)	11 (19.3%)
Reason for not completing treatment period (as per e-CRF)			
Adverse event	4 (7.0%)	3 (5.5%)	5 (8.8%)
Poor compliance to protocol	2 (3.5%)	4 (7.3%)	0

	Atorvastatin 40 mg (N=57)	Ezetimibe 10 mg + Atorvastatin 20 mg (N=55)	Alirocumab 75/150+ Atorvastatin 20 mg (N=57)
Protocol became inconvenient to participate	1 (1.8%)	1 (1.8%)	0
Life events made continuing too difficult	0	2 (3.6%)	0
Other reasons	1 (1.8%)	1 (1.8%)	0
Other reasons	7 (12.3%)	8 (14.5%)	6 (10.5%)
Physician decision	0	0	0
Study terminated by sponsor	0	0	0
Subject moved	0	0	1 (1.8%)
Subject withdrew consent	0	0	0
Related to study drug administration	0	0	0
Other [a]	7 (12.3%)	8 (14.5%)	5 (8.8%)
Patient's decision for treatment discontinuation [b]	7 (12.3%)	9 (16.4%)	7 (12.3%)

Note: Percentages are calculated using the number of patients randomized as denominator. Only the main reason for stopping treatment was entered in e-CRF. For detailed reasons related to study drug autoinjector administration, several reasons may be provided. [a] Includes patients who completed the 24-week double-blind treatment period (at least 22 weeks of exposure and Week 24 visit performed) but did not meet the definition of "treatment completer" per the e-CRF. [b] Additional information provided regarding reason for treatment discontinuation.

Table 36. Study R727-CL-1110: patient disposition – atorvastatin 40 mg baseline regimen – randomised population

	Atorvastatin 80 mg (N=47)	Rosuvastatin 40 mg (N=45)	Ezetimibe 10 mg + Atorvastatin 40 mg (N=47)	Alirocumab 75/150 + Atorvastatin 40 mg (N=47)
Randomised but not treated	0	0	1 (2.1%)	0
Reason for not treated				
Other reasons	0	0	1 (2.1%)	0
Related to IMP administration	0	0	1 (2.1%)	0
Patient's decision for not being treated	0	0	1 (2.1%)	0
Randomised and treated	47 (100%)	45 (100%)	46 (97.9%)	47 (100%)
Completed 24 weeks of double-blind treatment period (at least 22 weeks of exposure and visit W24 performed)	42 (89.4%)	43 (95.6%)	42 (89.4%)	42 (89.4%)

	Atorvastatin 80 mg (N=47)	Rosuvastatin 40 mg (N=45)	Ezetimibe 10 mg + Atorvastatin 40 mg (N=47)	Alirocumab 75/150 + Atorvastatin 40 mg (N=47)
Completed the study treatment period (as per e-CRF)	39 (83.0%)	39 (86.7%)	40 (85.1%)	38 (80.9%)
Did not complete the study treatment period (as per e-C RF)	8 (17.0%)	6 (13.3%)	6 (12.8%)	9 (19.1%)
Reason for treatment period discontinuation (as per e-CRF)				
Adverse event	3 (6.4%)	1 (2.2%)	1 (2.1%)	2 (4.3%)
Poor compliance to protocol	0	0	0	1 (2.1%)
Protocol became inconvenient to participate	0	0	0	0
Life events made continuing too difficult	0	0	0	0
Poor compliance to protocol – Other reasons	0	0	0	1 (2.1%)
Other reasons	5 (10.6%)	5 (11.1%)	5 (10.6%)	6 (12.8%)
Physician decision	0	0	1 (2.1%)	1 (2.1%)
Study terminated by sponsor	0	0	0	0
Subject moved	0	0	0	1 (2.1%)
Subject withdrew consent	0	0	0	0
Related to study drug administration	0	0	0	0
Other reason – Other [a]	5 (10.6%)	5 (11.1%)	4 (8.5%)	4 (8.5%)
Patient's decision for treatment discontinuation [b]	4(8.5%)	1(2.2%)	3(6.4%)	5 (10.6%)

Note: Percentages are calculated using the number of patients randomised as denominator. Only the main reason for stopping treatment was entered in e-CRF. For detailed reasons related to study drug autoinjector

administration, several reasons may be provided. [a] Includes patients who completed the 24-week double-blind treatment period (at least 22 weeks of exposure and Week 24 visit performed) but did not meet the definition of "treatment completer" per the e-CRF. [b] Additional information provided regarding reason for treatment discontinuation.

Table 37. Study R727-CL-1110: patient disposition – pooled dose regimens – randomised population

	Pooled Statin Intensification (N=149)	Pooled Ezetimibe (N=102)	Pooled Alirocumab 75/150 (N=104)
Randomised but not treated	0	1 (1.0%)	0
Reason for not treated			
Other reasons	0	1 (1.0%)	0
Related to IMP administration	0	1 (1.0%)	0
Patient's decision for not being treated	0	1 (1.0%)	0
Randomised and treated	149 (100%)	101 (99.0%)	104 (100%)
Completed 24 weeks of double-blind treatment period (at least 22 weeks of exposure and visit W24 performed)	132 (88.6%)	83 (81.4%)	90 (86.5%)
Completed the study treatment period (as per e-CRF)	122 (81.9%)	80 (78.4%)	84 (80.8%)
Did not complete the study treatment period (as per –eCRF)	27 (18.1%)	21 (20.6%)	20 (19.2%)
Reason for treatment period discontinuation (as per e-CRF)			
Adverse event	8 (5.4%)	4 (3.9%)	7 (6.7%)
Poor compliance to protocol	2 (1.3%)	4 (3.9%)	1 (1.0%)
Protocol became inconvenient to participate	1 (0.7%)	1 (1.0%)	0
Life events made continuing too difficult	0	2 (2.0%)	0
Other reasons	1 (0.7%)	1 (1.0%)	1 (1.0%)
Other reasons	17 (11.4%)	13 (12.7%)	12 (11.5%)
Physician decision	0	1 (1.0%)	1 (1.0%)
Study terminated by sponsor	0	0	0
Subject moved	0	0	2 (1.9%)
Subject withdrew consent	0	0	0
Related to study drug administration	0	0	0
Other a	17 (11.4%)	12 (11.8%)	9 (8.7%)
Patient'sdecisionfortreatment discontinuation [b]	12(8.1%)	12(11.8%)	12(11.5%)

Note: Percentages are calculated using the number of patients randomized as denominator. Only the main reason for stopping treatment was entered in e-CRF. For detailed reasons related to study drug autoinjector administration, several reasons may be provided. [a] Includes patients who completed the 24-week double-blind treatment period (at least 22 weeks of exposure and Week 24 visit performed) but did not meet the definition of "treatment completer" per the e-CRF. [b] Additional information provided regarding reason for treatment discontinuation.

Major protocol violations/deviations

Overall 64 patients (18.0%) had major protocol deviations that could potentially impact efficacy analyses in the study. Major deviations resulted in exclusion of 10 patients (2.8%) from the ITT analysis and of 15 patients (4.2%) from the on-treatment analysis at similar proportions across the pooled treatment groups. The main reason for exclusion was no LDL-C value within 1 of the

analysis windows at Week 24 (Visit day ±5 days). Missing data were accounted for by the MMRM model in the sensitivity analysis.

Baseline data

Demographic characteristics at baseline were generally similar across the pooled treatment groups with no notable differences among the groups. The mean (SD) age of patients overall was 62.9 (10.2) years, and ranged from 30 to 85 years. Most patients were male (65.1% [231 of 355]) and 34.9% (124 of 355) were female; most of the study population overall was White (306 patients [86.2%]) or Black (38 patients [10.7%]) and not of Hispanic or Latino descent (288 patients [81.1%]). The mean (SD) BMI of the patients overall was 31.0 (6.4) kg/m^2, and the mean (SD) weight was 89.6 (22.2) kg.

Results for the primary efficacy outcome

- Atorvastatin 20 mg baseline regimen

  A significantly greater decrease in calculated LS mean LDL-C from baseline to Week 24 (ITT analysis) was observed in the alirocumab + atorvastatin 20 mg group (-44.1%) compared with the atorvastatin 40 mg (-5.0%) and atorvastatin 20 mg + ezetimibe 10 mg (-20.5%) groups. Differences for the alirocumab + atorvastatin 20 mg group versus atorvastatin 40 mg (LS mean difference of -39.1%; 99% CI [-55.9 to -22.2]; p < 0.0001) and atorvastatin 20 mg + ezetimibe 10 mg (LS mean difference of -23.6%; 99% CI [-40.7 to -6.5]; p = 0.0004) were statistically significant.

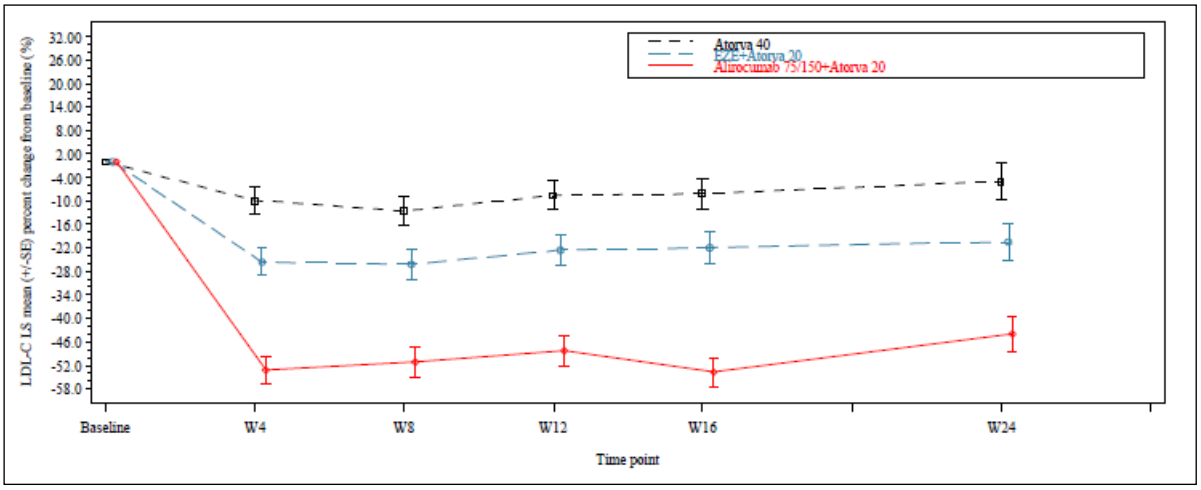
Table 38. Study R727-CL-1110: percent change from baseline in calculated LDL-C at Week 24 (ITT Analysis): MMRM analysis – atorvastatin 20 mg baseline regimen

Calculated LDL Cholesterol	Atorvastatin 40 mg (N=53)	Ezetimibe 10 mg + Atorvastatin 20 mg (N=53)	Alirocumab 75/150+ Atorvastatin 20 mg (N=55)
Baseline (mmol/L)			
Number	53	53	55
Mean (SD)	2.603 (0.800)	2.627 (0.760)	2.679 (0.904)
Median	2.435	2.383	2.486
Min : Max	0.96 : 4.90	1.61 : 5.80	1.48 : 6.16
Baseline (mg/dL)			
Number	53	53	55
Mean (SD)	100.5 (30.9)	101.4 (29.3)	103.4 (34.9)
Median	94.0	92.0	96.0
Min : Max	37 : 189	62 : 224	57 : 238
Week 24 percent change from baseline (%)			
LS Mean (SE)	-5.0 (4.6)	-20.5 (4.7)	-44.1 (4.5)
LS mean difference (SE) (Alirocumab versus Comparator)	-39.1 (6.4)	-23.6 (6.6)	
99% CI	(-55.9 to -22.2)	(-40.7 to -6.5)	
p-value(Alirocumabversus Comparator)	< 0.0001*	0.0004*	

CI = confidence interval; ITT = intent to treat; LDL = low density lipoprotein; LS = least squares; MMRM = mixed effect model for repeated measures; SD = standard deviation; SE = standard error. * P-values with an asterisk were formally tested based on the predefined hierarchical sequence and achieved statistical significance at the 0.01 level. Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value by

time-point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

Figure 26. Study R727-CL-1110: calculated LDL-C LS mean (+/-SE) percent change from baseline: time profile – atorvastatin 20 mg baseline regimen– ITT population



Atorva = atorvastatin; EZE = ezetimibe; ITT = intent-to-treat; LDL = low density lipoprotein; LS = least squares; SE = standard error.

- Atorvastatin 40 mg baseline regimen.

  LS mean reductions from baseline in LDL-C at Week 24 were significantly greater in the alirocumab + atorvastatin 40 mg group (-54.0%) compared with the atorvastatin 80 mg (-4.8%; LS mean difference for alirocumab add-on versus atorvastatin 80 mg of -49.2%; 99% CI [- 65.0 to -33.5]; p< 0.0001), rosuvastatin 40 mg (-21.4%; LS mean difference of -32.6%; 99% CI [-48.4 to -16.9]; p< 0.0001), and atorvastatin 40 mg + ezetimibe 10 mg (-22.6%; LS mean difference of -31.4%; 99% CI [-47.4 to -15.4]; p< 0.0001) groups.

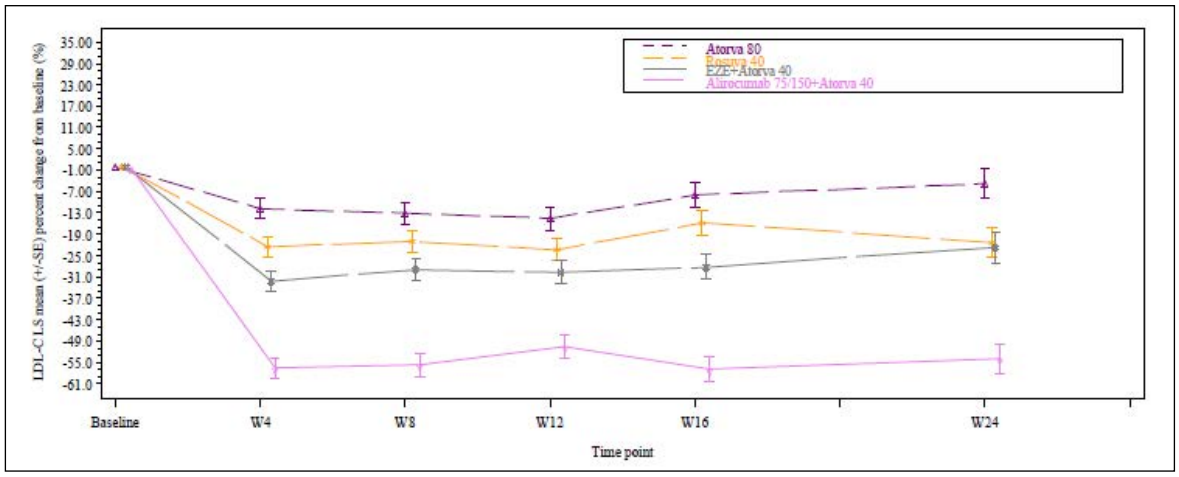
Table 39 Study R727-CL-1110: percent change from baseline in calculated LDL-C at Week 24: MMRM analysis – atorvastatin 40 mg baseline regimen (ITT population)

Calculated LDL Cholesterol	Atorvastatin 80 mg (N=47)	Rosuvastatin 40 mg (N=45)	Ezetimibe 10 mg + Atorvastatin 40 mg (N=46)	Alirocumab 75/150+ Atorvastatin 40 mg (N=46)
Baseline (mmol/L)				
Number	47	45	46	46
Mean (SD)	2.813 (0.970)	2.844 (1.011)	2.569 (0.763)	3.036 (0.968)
Median	2.590	2.564	2.435	2.810
Min : Max	1.48 : 5.72	1.53 : 6.55	1.50 : 4.95	1.74 : 5.72
Baseline (mg/dL)				
Number	47	45	46	46
Mean (SD)	108.6 (37.5)	109.8 (39.0)	99.2 (29.4)	117.2 (37.4)
Median	100.0	99.0	94.0	108.5
Min : Max	57 : 221	59 : 253	58 : 191	67 : 221
Week 24 percent change from baseline (%)				
LS Mean (SE)	-4.8 (4.2)	-21.4 (4.2)	-22.6 (4.3)	-54.0 (4.3)
LS mean difference (SE) (Alirocumab	-49.2 (6.1)	-32.6 (6.0)	-31.4 (6.1)	

Calculated LDL Cholesterol	Atorvastatin 80 mg (N=47)	Rosuvastatin 40 mg (N=45)	Ezetimibe 10 mg + Atorvastatin 40 mg (N=46)	Alirocumab 75/150+ Atorvastatin 40 mg (N=46)
versus Comparator)				
99% CI	(-65.0 to -33.5)	(-48.4 to -16.9)	(-47.4 to -15.4)	
p-value (Alirocumab versus Comparator)	< 0.0001*	< 0.0001*	< 0.0001*	

CI = confidence interval; ITT = intent-to-treat; LDL = low density lipoprotein; LS = least squares; MMRM = mixed effect model for repeated measures; SD = standard deviation; SE = standard error. * P-values with an asterisk were formally tested based on the predefined hierarchical sequence and achieved statistical significance at the 0.01 level. Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomisation strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value by time-point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

Figure 27. Study R727-CL-1110: calculated LDL-C LS mean (+/-SE) percent change from baseline: time profile – atorvastatin 40 mg baseline regimen - ITT population



Atorva = atorvastatin; EZE = ezetimibe; ITT = intent-to-treat; LDL = low density lipoprotein; LS = least squares; Rosuva = rosuvastatin; SE = standard error.

The primary endpoint was also analysed by ANCOVA using an observed case analysis for measured LDL-C instead of calculated LDL-C in patients from the ITT analysis with an assessment available at baseline and during the Week 24 analysis window. The results from this sensitivity analysis were consistent with those of the primary analysis, showing significantly greater reductions in measured LDL-C in the alirocumab + atorvastatin 20 mg group (-44.7%) compared with the atorvastatin 40 mg (8.1%; nominal p< 0.0001) and atorvastatin 20 mg + ezetimibe 10 mg (-10.3%; nominal p < 0.0001) groups. Similar results were seen in the atorvastatin 40 mg baseline regimen, least squares mean reductions from baseline in LDL-C at Week 24 were significantly greater in the alirocumab + atorvastatin 40 mg group (-48.0%) compared with the atorvastatin 80 mg (2.8%; p < 0.0001), rosuvastatin 40 mg (-14.3%; nominal p < 0.0001), and atorvastatin 40 mg + ezetimibe 10 mg (-16.1%; nominal p < 0.0001) groups.

Results for other efficacy outcomes

The 5 pairwise comparisons achieved statistical significance on more than half of the key secondary endpoints, with each pairwise comparison ceasing hypothesis testing at various key secondary endpoints in the second half of the list. Key secondary endpoints that were formally tested and achieved statistical significance at the 0.01 level are denoted with an asterisk.

The first key secondary endpoint in the hierarchical sequence not to reach statistical significance within each treatment group pairwise comparison was as follows:

- Alirocumab + atorvastatin 20 mg versus atorvastatin 40 mg: The percent change in Lp(a) from baseline to Week 24 (ITT)
- Alirocumab + atorvastatin 20 mg versus atorvastatin 20 mg + ezetimibe 10 mg: The proportion of very high CV risk patients reaching calculated LDL C < 70mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C < 100 mg/dL (2.59 mmol/L) at Week 24 (ITT)
- Alirocumab + atorvastatin 40 mg versus atorvastatin 80 mg: The percent change in HDL-C from baseline to Week 24 (ITT)
- Alirocumab + atorvastatin 40 mg versus rosuvastatin 40 mg: The percent change in HDL-C from baseline to Week 24 (ITT)
- Alirocumab + atorvastatin 40 mg versus atorvastatin 40 mg + ezetimibe 10 mg: The percent change in HDL-C from baseline to Week 24 (ITT).

Subsequent hypotheses regarding key secondary efficacy endpoints in the sequential testing within each pairwise comparison were not formally tested; p-values presented in the table below for those key secondary endpoints are for descriptive purposes and are labelled as nominal.

Table 40. Study R727-CL-1110: secondary efficacy outcomes: hierarchical testing strategy applied

Key Secondary Efficacy Endpoint	Analysis	P-Values				
		Atorvastatin 20 mg Baseline		Atorvastatin 40 mg Baseline Regimen		
		Alirocumab + Atorvastatin 20 mg vs Atorvastatin 40 mg	Alirocumab + Atorvastatin 20 mg vs Atorvastatin 20 mg + Ezetimibe 10 mg	Alirocumab + Atorvastatin 40 mg vs Atorvastatin 80 mg	Alirocumab + Atorvastatin 40 mg vs Rosuvastatin 40 mg	Alirocumab + Atorvastatin 40 mg vs Atorvastatin 40 mg + Ezetimibe 10 mg
The percent change in calculated LDL- C from baseline to Week 24 in the mITT population, using all LDL-C values during the efficacy treatment period	On-treatment	p < 0.0001*	p = 0.0002*	p < 0.0001*	p < 0.0001*	p < 0.0001*

Key Secondary Efficacy Endpoint	Analysis	P-Values				
		Atorvastatin 20 mg Baseline		Atorvastatin 40 mg Baseline Regimen		
		Alirocumab + Atorvastatin 20 mg vs Atorvastatin 40 mg	Alirocumab + Atorvastatin 20 mg vs Atorvastatin 20 mg + Ezetimibe 10 mg	Alirocumab + Atorvastatin 40 mg vs Atorvastatin 80 mg	Alirocumab + Atorvastatin 40 mg vs Rosuvastatin 40 mg	Alirocumab + Atorvastatin 40 mg vs Atorvastatin 40 mg + Ezetimibe 10 mg
The percent change in calculated LDL- C from baseline to Week 12	ITT	p < 0.0001*	p < 0.0001*	p < 0.0001*	p < 0.0001*	p < 0.0001*
The percent change in calculated LDL- C from baseline to Week 12	On-treatment	p < 0.0001*	p < 0.0001*	p < 0.0001*	p < 0.0001*	p < 0.0001*
The percent change in Apo B from baseline to Week 24	ITT	p < 0.0001*	p < 0.0001*	p < 0.0001*	p < 0.0001*	p < 0.0001*
The percent change in Apo B from baseline to Week 24	On-treatment	p < 0.0001*	p < 0.0001*	p < 0.0001*	p < 0.0001*	p < 0.0001*
The percent change in non-HDL-C from baseline to Week 24	ITT	p < 0.0001*	p = 0.0002*	p < 0.0001*	p < 0.0001*	p < 0.0001*
The percent change in non-HDL-C from baseline to Week 24	On-treatment	p < 0.0001*	p = 0.0002*	p < 0.0001*	p < 0.0001*	p < 0.0001*
The percent change in Total-C from baseline to Week 24	ITT	p < 0.0001*	p < 0.0001*	p < 0.0001*	p < 0.0001*	p < 0.0001*
The percent change in Apo B from baseline to Week 12	ITT	p < 0.0001*	p < 0.0001*	p < 0.0001*	p < 0.0001*	p < 0.0001*

Key Secondary Efficacy Endpoint	Analysis	P-Values				
		Atorvastatin 20 mg Baseline		Atorvastatin 40 mg Baseline Regimen		
		Alirocumab + Atorvastatin 20 mg vs Atorvastatin 40 mg	Alirocumab + Atorvastatin 20 mg vs Atorvastatin 20 mg + Ezetimibe 10 mg	Alirocumab + Atorvastatin 40 mg vs Atorvastatin 80 mg	Alirocumab + Atorvastatin 40 mg vs Rosuvastatin 40 mg	Alirocumab + Atorvastatin 40 mg vs Atorvastatin 40 mg + Ezetimibe 10 mg
The percent change in non-HDL-C from baseline to Week 12	ITT	p < 0.0001*	p < 0.0001*	p < 0.0001*	p < 0.0001*	p = 0.0001*
The percent change in Total-C from baseline to Week 12	ITT	p < 0.0001*	p < 0.0001*	p < 0.0001*	p < 0.0001*	p = 0.0015*
The proportion of very high CV risk patients reaching calculated LDL-C< 70mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL- C< 100 mg/dL (2.59 mmol/L) at Week 24	ITT	p < 0.0001*	p = 0.0284	p < 0.0001*	p = 0.0025*	p = 0.0011*
The proportion of very high CV risk patients reaching calculated LDL-C <70mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C< 100 mg/dL (2.59 mmol/L) at Week 24	On-treatment	p < 0.0001*	np = 0.0280	p < 0.0001*	p = 0.0015*	p = 0.0008*

Key Secondary Efficacy Endpoint	Analysis	P-Values				
		Atorvastatin 20 mg Baseline		Atorvastatin 40 mg Baseline Regimen		
		Alirocumab + Atorvastatin 20 mg vs Atorvastatin 40 mg	Alirocumab + Atorvastatin 20 mg vs Atorvastatin 20 mg + Ezetimibe 10 mg	Alirocumab + Atorvastatin 40 mg vs Atorvastatin 80 mg	Alirocumab + Atorvastatin 40 mg vs Rosuvastatin 40 mg	Alirocumab + Atorvastatin 40 mg vs Atorvastatin 40 mg + Ezetimibe 10 mg
The proportion of patients reaching calculated LDL-C< 70 mg/dL (1.81 mmol/L) at Week 24	ITT	p < 0.0001*	np = 0.0018	p < 0.0001*	p < 0.0001*	p = 0.0004*
The proportion of patients reaching calculated LDL-C< 70 mg/dL(1.81 mmol/L) at Week 24	On-treatment	p < 0.0001*	np = 0.0054	p < 0.0001*	p < 0.0001*	p = 0.0002*
The percent change in Lp(a) from baseline to	**ITT**	**p = 0.5520**	**np = 0.0294**	**p = 0.0004***	**p < 0.0001***	**p < 0.0001***
The percent change in HDL-C from baseline to Week 24	ITT	np = 0.3152	np = 0.0973	p = 0.4456	p = 0.6086	p = 0.1426
The percent change in TGs from baseline to Week 24	ITT	np = 0.3054	np = 0.1116	np = 0.0403	np = 0.0011	np = 0.3652
The percent change in Apo A-1 from baseline to Week 24	ITT	np = 0.0034	np = 0.0029	np = 0.1986	np = 0.6745	np = 0.0066
The percent change in Lp(a) from baseline to Week 12	ITT	np = 0.0300	np = 0.0010	np < 0.0001	np < 0.0001	np < 0.0001

Key Secondary Efficacy Endpoint	Analysis	P-Values				
		Atorvastatin 20 mg Baseline		Atorvastatin 40 mg Baseline Regimen		
		Alirocumab + Atorvastatin 20 mg vs Atorvastatin 40 mg	Alirocumab + Atorvastatin 20 mg vs Atorvastatin 20 mg + Ezetimibe 10 mg	Alirocumab + Atorvastatin 40 mg vs Atorvastatin 80 mg	Alirocumab + Atorvastatin 40 mg vs Rosuvastatin 40 mg	Alirocumab + Atorvastatin 40 mg vs Atorvastatin 40 mg + Ezetimibe 10 mg
The percent change in HDL-C from baseline to Week 12	ITT	np = 0.0042	np = 0.0220	np = 0.1458	np = 0.3087	np = 0.3083
The percent change in fasting TGs from baseline to Week 12	ITT	np = 0.1946	np = 0.0286	np = 0.1831	np = 0.1429	np = 0.4011
The percent change in Apo A-1 from baseline to Week 12	ITT	np = 0.0036	np = 0.0705	np = 0.0012	np = 0.1189	np = 0.0012

* Key secondary endpoints that were formally tested and were statistically significant at the 0.01 level are denoted with an asterisk (*). Note: Key secondary endpoints after the first failed endpoint within each pairwise comparison in hierarchical sequence were not formally tested; p values presented are for descriptive purposes and are labelled as nominal (np).

Subgroup analysis

Results of the subgroup analyses of the primary efficacy endpoint showed reductions in LDL-C from baseline consistent with the overall treatment effect of alirocumab + atorvastatin 20 mg versus atorvastatin 40 mg and atorvastatin 20 mg + ezetimibe 10 mg across a range of demographic and baseline characteristics, including gender, age group, BMI, prior history of MI or ischemic stroke, non-moderate CKD, diabetes, baseline calculated LDL-C, baseline HDL-C, baseline fasting TGs, baseline Lp(a), and LMTs other than statin at randomisation. No quantitative interactions (that is, p-value< 0.10) were identified for any demographic or baseline characteristic in the atorvastatin 20 mg baseline regimen.

Up titration

13 patients (14.0%) in the alirocumab add-on treatment group at Week 12 had their dose up-titrated to alirocumab 150 mg SC Q2W at Week 12, and, of these, 9 patients (20.9%) were enrolled in the atorvastatin 40 mg baseline regimen. Due to the small numbers analysis of calculated LDL-C over time according to up-titration status was limited. Among patients who did not have their dose up-titrated, reductions observed at Week 12 were maintained at Week 16 and Week 24.

Summary of results

Results of key LDL-C secondary endpoints were also generally consistent with the LDL-C lowering effect of alirocumab demonstrated in the primary efficacy analysis. With the exception of the pairwise comparison of alirocumab 20 mg versus atorvastatin 20 mg + ezetimibe 10 mg, all comparisons for key LDL-C secondary endpoints were statistically significant.

Alirocumab add-on treatment also demonstrated a lowering effect across a number of key secondary lipid endpoints, including Total-C, non-HDL-C, Apo B, and Lp(a). Modest reductions in TGs and increases in HDL-C and Apo A1 were also observed with alirocumab add-on treatment. The lack of statistical significance for these parameters is expected to be a product of the smaller numerical changes as compared to LDL-C (by which the study was powered) and/or the greater variability in these parameters.

Table 41. Study R727-CL-1110: Summary of key secondary lipid endpoints

Percent Change from Baseline to Week 24	Atorvastatin 20 mg Baseline			Atorvastatin 40 mg Baseline Regimen			
	Atorva 40 mg	EZE + Atorva 20 mg	Alirocumab + Atorva 20 mg	Atorva 80 mg	Rosuva 40 mg	EEZE + Atorva 40 mg	Alirocumab 75/150+
Total-C	-4.0%	-11.2%	-27.1%	-4.8%	-11.7%	-15.2%	-
p-value versus alirocumab	< 0.0001*	< 0.0001*		< 0.0001*	< 0.0001*	< 0.0001*	
Non-HDL-C	-6.3%	-15.1%	-36.7%	-6.5%	-17.4%	-21.0%	-
p-value versus alirocumab	p < 0.0001*	p = 0.0002*		p < 0.0001*	p < 0.0001*	p < 0.0001*	
Apo B	-4.4%	-10.1%	-33.7%	-3.5%	-10.9%	-14.3%	-
p-value versus alirocumab	p < 0.0001*	p< 0.0001*		p < 0.0001*	p < 0.0001*	p < 0.0001*	
Lp(a)	-20.2%	-10.6%	-23.6%	-9.7%	-4.9%	+0.2%	-
p-value versus alirocumab	p = 0.5520	np = 0.0294		p = 0.0004*	p < 0.0001*	p < 0.0001*	
HDL-C	+1.9%	-0.1%	+4.8%	+4.7%	+5.7%	+2.0%	+7.7%
p-value versus alirocumab	np = 0.3152	np = 0.0973		p = 0.4456	p = 0.6086	p = 0.1426	
TGs	-6.7%	-3.3%	-12.0%	-7.3%	-0.5%	-13.9%	-
p-value versus alirocumab	np = 0.3054	np = 0.1116		np = 0.0403	np = 0.0011	np = 0.3652	
Apo A-1	+1.2%	+1.0%	+7.6%	+2.2%	+4.7%	-1.8%	+5.8%
p-value versus alirocumab	np = 0.0034	np = 0.0029		np = 0.1986	np = 0.6745	np = 0.0066	

Atorva = atorvastatin; rosuva = rosuvastatin; EZE = ezetimibe. * P-values with an asterisk were formally tested based on the predefined hierarchical sequence and achieved statistical significance at the 0.01 level. Note: Key secondary endpoints after the first failed endpoint within each pairwise comparison in hierarchical sequence were not formally tested; p values presented are for descriptive purposes and are labelled as nominal (np).

7.4.1.2. Study R727-CL-1118 – (Options II)

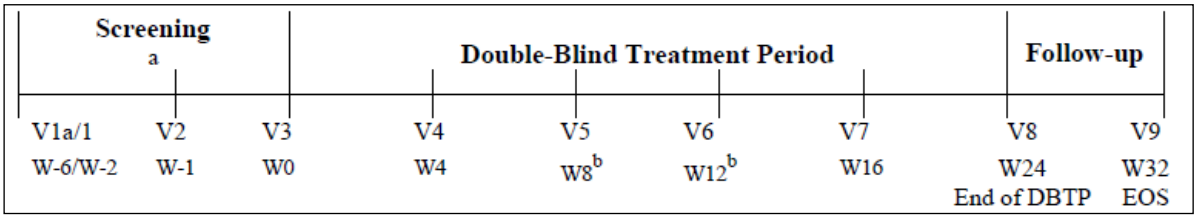
A Randomised, Double Blind, Study of the Efficacy and Safety of REGN727 Added-on to Rosuvastatin Versus Ezetimibe Added-on to Rosuvastatin Versus Rosuvastatin Dose Increase in Patients who are Not Controlled on Rosuvastatin.

Study design, objectives, locations and dates

A randomised, double blind, active comparator, parallel group multinational study conducted at 79 sites in 8 countries (Australia, Canada, Germany, Italy, Mexico, Spain, UK and the USA) from October 2012 to May 2014.

- Primary objective: to evaluate the reduction of LDL-C by alirocumab as add-on therapy to rosuvastatin in comparison with ezetimibe as add-on therapy to rosuvastatin, and in comparison with doubling the rosuvastatin dose, after 24 weeks of treatment in patients with hypercholesterolemia at high CV risk.
- Secondary objectives: To evaluate the reduction of LDL-C by alirocumab 75 mg as add-on therapy to rosuvastatin in comparison with ezetimibe as add-on therapy to rosuvastatin, or in comparison with doubling of the rosuvastatin dose after 12 weeks of treatment and to evaluate the safety and tolerability and development of ADA as in previous studies.

Figure 28. Study R727-CL-1118: study design



Note: The scale is not linear. V=Visit; W=Week; DBTP = double-blind treatment period; EOS=end of study. [a] There were 2 to 3 screening visits during the screening period. [b] The dose of alirocumab was up-titrated (using a blinded process) from 75 mg to 150 mg at the Week 12 visit.

Inclusion and exclusion criteria

- Inclusion: male or female (non-childbearing potential) ≥ 18 years with heFH or non-FH hypercholesterolaemia who had established CHD or non CHD CVD or who were at high risk for CVD due to other risk factors, with LDL-C levels that were not adequately controlled with a 10 mg or 20 mg daily dose of rosuvastatin, with or without other LMT, except ezetimibe.
- Exclusion: LDL-C < 70 mg/dL (< 1.81 mmol/L) at the screening visit (Week -2) in patients with history of documented CHD or non-CHD CVD or LDL-C < 100 mg/dL (< 2.59 mmol/L) at the screening visit (Week -2) in patients without history of documented CHD or non-CHD CVD, but with other risk factors; homologous FH; currently taking a statin that is not rosuvastatin taken daily at 10 mg or 20 mg or currently taking ezetimibe.

Study treatments

Patients who entered the study were taking either rosuvastatin 10 mg or rosuvastatin 20 mg. Patients were randomised to 1 of 6 treatment arms according to their rosuvastatin regimen:

1. Rosuvastatin 10 mg baseline regimen:
    a. Alirocumab 75 mg SC Q2W, rosuvastatin 10 mg QD, and placebo for ezetimibe QD.
    b. Placebo for alirocumab SC Q2W, rosuvastatin 20 mg QD, and placebo for ezetimibe QD.
    c. Placebo for alirocumab SC Q2W, rosuvastatin 10 mg QD, and ezetimibe 10 mg QD.
2. Rosuvastatin 20 mg baseline regimen:
    a. Alirocumab 75 mg SC Q2W, rosuvastatin 20 mg QD, and placebo for ezetimibe QD.
    b. Placebo for alirocumab SC Q2W, rosuvastatin 40 mg QD, and placebo for ezetimibe QD.
    c. Placebo for alirocumab SC Q2W, rosuvastatin 20 mg QD, and ezetimibe 10 mg QD.

Injectable study drug was administered SC Q2W at approximately the same time of day (based upon patient preference). The orally administered study drugs were rosuvastatin (1 capsule) and either ezetimibe or placebo for ezetimibe (1 capsule). The patients took 2 capsules of study drug per day through Week 24 (day 169).

The dose of alirocumab was up-titrated (using a blinded process) from 75 mg to 150 mg at the Week 12 visit for patients with heFH or non-FH, and a history of documented CHD or CVD, or other risk factors and who had LDL-C ≥ 70 mg/dL (1.81 mmol/L) at the Week 8 visit. A similar dose up-titration (from 75 mg to 150 mg) took place at the Week 12 visit for patients with heFH or non-FH, but with other risk factors and who had LDL-C ≥ 100 mg/dL (2.59 mmol/L) at the Week 8 visit.

Efficacy variables and outcomes

The primary efficacy outcome was the percent change in calculated LDL-C from baseline to Week 24 in the intent-to-treat (ITT) population.

The secondary efficacy variables were the same as for previous studies.

Randomisation and blinding methods

Patients were randomised, via either an IVRS or the IWRS system. For each rosuvastatin baseline regimen (10 mg and 20 mg), randomisation was stratified according to the patient's history of MI or ischemic stroke (Yes/No). For each rosuvastatin baseline regimen, randomisation was in equal proportions to 1 of 3 treatment arms, implementing a permuted-block design to ensure even distribution of the treatment assignments.

Sterile alirocumab (75 mg and 150 mg) and placebo for alirocumab were provided in 1 mL volumes in identically matched prefilled syringes assembled in disposable AI, also known as prefilled pens. Placebo for alirocumab was prepared in the same formulation as alirocumab, without the addition of protein. Ezetimibe 10 mg and rosuvastatin 10 mg, 20 mg and 40 mg were supplied as over encapsulated tablets (contained within a capsule) to match the placebos for ezetimibe and rosuvastatin, ensuring the double-blind. The over encapsulated tablets were indistinguishable from each other.

Analysis populations

Same as for previous studies.

Sample size

Four pairwise comparisons of alirocumab benefit to multiple control arms were hypothesised for the primary efficacy analysis of this study. Using the Bonferroni adjustment for the sample size calculation of the multiple treatment arm comparisons, a total of 282 patients were planned for the analysis of the primary measure at Week 24. Specifically, a sample size of 47 patients per arm would have 90% power to detect a difference in means of at least 20% in any 1 pairwise comparison (that is, alirocumab mean = 50% and control mean = 30%), assuming that the common SD was 25% using an independent group t-test. The alpha level for each of the 4 pairwise comparisons was adjusted to a 2 sided alpha level of 0.0125, thereby maintaining an overall study alpha level of 0.05. The total sample size was rounded to 300 patients (50 patients per treatment arm).

Statistical methods

Key secondary endpoints were evaluated using the same MMRM model and a hierarchical testing strategy as described in the previous studies within each of the 4 pairwise comparisons was also used to control for multiplicity.

Participant flow

Overall, 672 patients were screened for this study, of whom 367 patients (54.6%) were screen failures based on inclusion and exclusion criteria. Three hundred and five (305) eligible patients

were enrolled based on 1 of 2 rosuvastatin baseline regimens: 145 patients in the rosuvastatin 10 mg baseline regimen and 160 patients in the rosuvastatin 20 mg baseline regimen.

Table 42. Study R727-CL-1118: patient disposition - pooled dose regimens - randomised population

	Double Dose Rosuvastatin (N=101)	Pooled Ezetimibe (N=101)	Pooled Alirocumab 75/150 (N=103)
Randomised but not treated	0	0	0
Patient's decision for not being treated [a]	0	0	0
Randomised and treated	101 (100%)	101 (100%)	103 (100%)
Complete 24 weeks of double-blind treatment period (at least 22 weeks of exposure and visit W24 performed)	90 (89.1%)	84 (83.2%)	87 (84.5%)
Completed the study treatment period (as per CRF)	88 (87.1%)	78 (77.2%)	79 (76.7%)
Did not complete the study treatment period (as per CRF)	13 (12.9%)	23 (22.8%)	24 (23.3%)
Reason for not completing study treatment period (as per CRF)			
adverse event	5 (5.0%)	8 (7.9%)	5 (4.9%)
poor compliance to protocol	1 (1.0%)	2 (2.0%)	4 (3.9%)
Protocol became inconvenient to participate	1 (1.0%)	2 (2.0%)	0
Life events made continuing too difficult	0	0	2 (1.9%)
Other reasons	0	0	2 (1.9%)
Other reasons	7 (6.9%)	13 (12.9%)	15 (14.6%)
Physician decision	1 (1.0%)	0	0
Study terminated by sponsor	0	0	0
Subject moved	0	0	1 (1.0%)
Subject withdrew consent	0	0	0
Related to IMP administration	0	0	0
Other [b]	6 (5.9%)	13 (12.9%)	14 (13.6%)
Patient's decision for treatment discontinuation [a]	6 (5.9%)	13 (12.9%)	14 (13.6%)

Note: Percentages are calculated using the number of patients randomized as denominator. Only the main reason for stopping treatment was entered in e-CRF. For detailed reasons related to IMP auto-injector administration, several reasons may be provided. [a] Additional information as regard study treatment discontinuation. [b] Includes patients who completed the 24 week double-blind treatment period (at least 22 weeks of exposure and Week 24 visit performed) but did not meet the definition of "treatment completer" per the CRF. Other reasons – Other – included patient moved or went overseas (2/305 patients), physician decision (1/305); poor compliance with study capsules (3/305), patient withdrew consent (4/305), death (1/305), lost to follow up (5/305) and sponsor closed site (2/305).

Major protocol violations/deviations

Violations related to GCP noncompliance due to failure to secure compliance at the site resulted in the closure 1 site in the USA. This site contributed 5 patients evaluable for LDL-C at Week 24 all of whom were in the rosuvastatin 20 mg baseline regimen. Of these, 3 patients were randomised to the alirocumab + rosuvastatin 20 mg treatment group, 1 patient was randomised to the rosuvastatin 40 mg treatment group, and 1 patient was randomised the ezetimibe 10 mg + rosuvastatin 20 mg treatment group. A sensitivity analysis with and without these patients was conducted as part of the efficacy analysis.

Overall, 27 patients (26.2%) in the alirocumab add-on group, 13 patients (12.9%) in the double-dose rosuvastatin group, and 22 patients (21.8%) in the ezetimibe add-on group had major protocol deviations that could potentially impact efficacy analyses in the study. Most of the deviations did not result in exclusion of the patient from either the ITT or the mITT populations. The deviations were sporadic with respect to the timing of their occurrence and were observed across all treatment groups with no apparent distribution pattern. Consequently, they were judged by the sponsor to be unlikely to have any impact on the overall outcome of the study.

Baseline data

Demographic characteristics at baseline were generally similar across treatment groups. The mean (SD) age of patients overall was 60.9 (10.4) years, and ages ranged from 27 to 87 years. A higher proportion of patients in the alirocumab add-on group (73 patients [70.9%]) were < 65 years of age compared with the double-dose rosuvastatin (59 patients [58.4%]) and ezetimibe add-on (56 patients [55.4%]) groups. Overall, most patients in the study were male (187 patients [61.3%]), and there was a higher proportion of male patients in the double-dose rosuvastatin group (71 patients [70.3%]) compared with the alirocumab add-on (59 patients [57.3%]) and ezetimibe add-on (57 patients [56.4%]) groups. The majority of patients were white (256 patients [83.9%]) and not Hispanic or Latino (264 patients [86.6%]). The mean (SD) BMI of patients overall was 31.3 (6.6) kg/m^2, and the mean (SD) weight was 89.2 (20.4) kg.

Results for the primary efficacy outcome

- Rosuvastatin 10 mg Baseline Regimen

  At Week 24 in the ITT analysis, reductions from baseline in LS mean LDL-C at Week 24 were significantly greater in the alirocumab + rosuvastatin 10 mg treatment group (-50.6%) compared with the rosuvastatin 20 mg (-16.3%) and ezetimibe 10 mg + rosuvastatin 10 mg (- 14.4%) treatment groups. The LS mean differences in LDL-C at Week 24 were statistically significant when comparing alirocumab + rosuvastatin 10 mg with rosuvastatin 20 mg (difference of -34.2%; 98.75% CI [-49.2 to -19.3]; p< 0.0001) and ezetimibe 10 mg + rosuvastatin 10 mg (difference of -36.1%; 98.75% CI [-51.5 to -20.7]; p < 0.0001). Accordingly, this study met its primary endpoint.

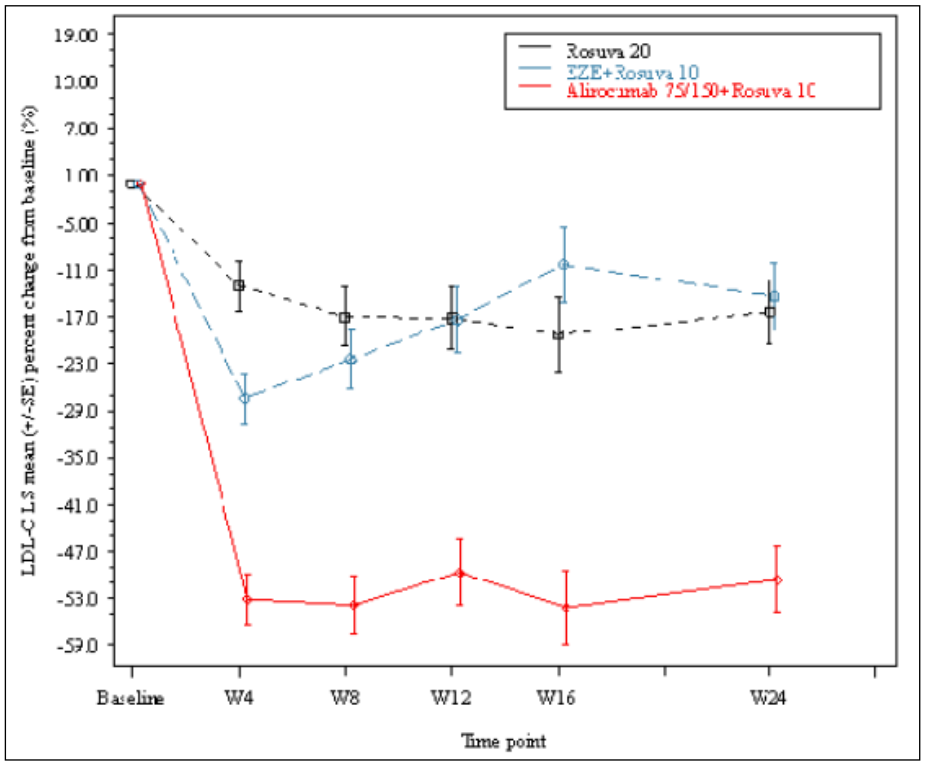
Table 43. Study R727-CL-1118: Percent change from baseline in calculated LDL-C at Week 24: MMRM Analysis - Rosuvastatin 10 mg baseline regimen – ITT population

Calculated LDL Cholesterol	Rosuvastatin 20 mg (N=48)	Ezetimibe 10 mg + Rosuvastatin 10 mg (N=47)	Alirocumab 75/150+ Rosuvastatin 10 mg (N=48)
Baseline (mmol/L)			
Number	48	47	48
Mean (SD)	2.743 (0.933)	2.643 (1.095)	2.791 (0.687)
Median	2.435	2.383	2.668
Min : Max	1.53 : 5.52	1.30 : 7.07	1.74 : 4.84
Baseline (mg/dL)			
Number	48	47	48
Mean (SD)	105.9 (36.0)	102.0 (42.3)	107.8 (26.5)
Median	94.0	92.0	103.0
Min : Max	59 : 213	50 : 273	67 : 187
Week 24 percent change from baseline (%)			
LS Mean (SE)	-16.3 (4.1)	-14.4 (4.4)	-50.6 (4.2)
LS mean difference (SE) (Alirocumab versus Comparator)	-34.2 (5.9)	-36.1 (6.1)	
98.75% CI	(-49.2 to -19.3)	(-51.5 to -20.7)	
p-value (Alirocumab versus Comparator)	< 0.0001*	< 0.0001*	

CI = confidence interval; ITT = intent to treat; LDL = low density lipoprotein; LS = least squares; MMRM = mixed effect model for repeated measures; SD = standard deviation; SE = standard error. * P-values with an asterisk were formally tested based on the predefined hierarchical sequence and achieved statistical significance at the 0.0125 level.Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value by time-point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

The alirocumab + rosuvastatin 10 mg treatment group demonstrated a rapid decrease in calculated LDL-C and greater LS mean LDL-C reductions from baseline over time, from the first post-dose measurement at Week 4 through Week 24, when compared with the rosuvastatin 20 mg and ezetimibe 10 mg+ rosuvastatin 10 mg treatment groups.

Figure 29. Study R727-CL-1118: calculated LDL-C mean (±SE) percent change from baseline: time profile - rosuvastatin 10 mg baseline regimen - ITT population



- Rosuvastatin 20 mg baseline regimen

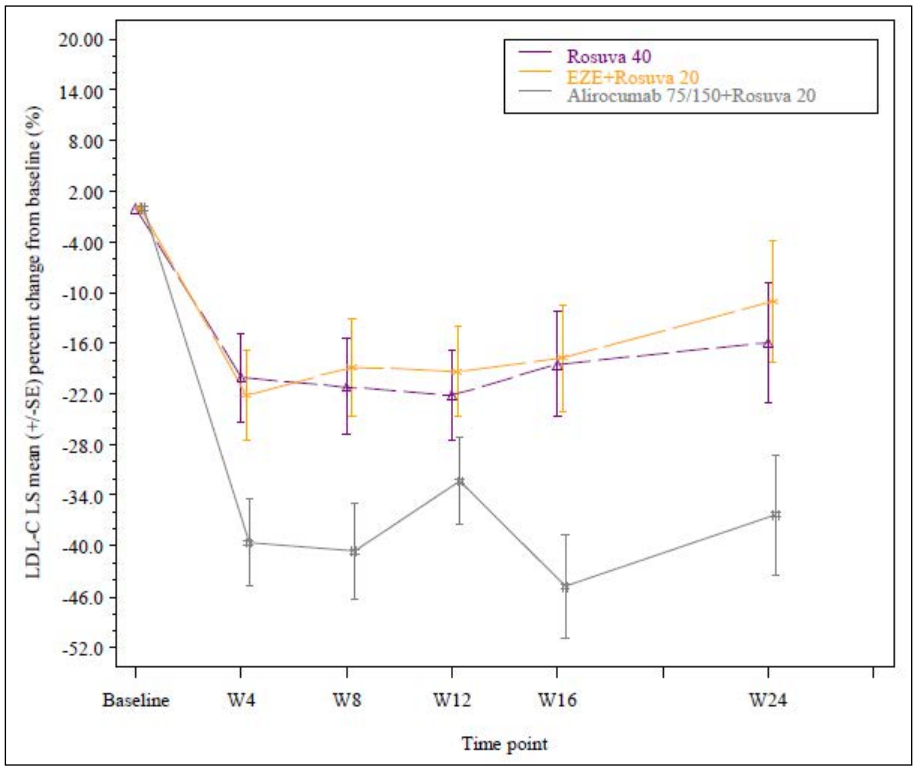
  In the rosuvastatin 20 mg baseline regimen, LS mean reductions from baseline in LDL-C at Week 24 were numerically greater in the alirocumab + rosuvastatin 20 mg treatment group (-36.3%) compared with the rosuvastatin 40 mg (-15.9%) and ezetimibe 10 mg + rosuvastatin 20 mg (- 11.0%) treatment groups. The LS mean differences when comparing alirocumab + rosuvastatin 20 mg with rosuvastatin 40 mg (difference of -20.3%; 98.75% CI [-45.8 to 5.1]; p = 0.0453) and ezetimibe 10 mg + rosuvastatin 20 mg (difference of -25.3%; 98.75% CI [-50.9 to 0.3]; p = 0.0136) did not reach statistical significance at the adjusted alpha level of 0.0125 required due to multiplicity to preserve the overall alpha at 0.05.

Table 44. Study R727-CL-1118: percent change from baseline in calculated LDL-C at Week 24: MMRM analysis - rosuvastatin 20 mg baseline regimen – ITT population

Calculated LDL Cholesterol	Rosuvastatin 40 mg (N=52)	Ezetimibe 10 mg + Rosuvastatin 20 mg (N=50)	Alirocumab 75/150+ Rosuvastatin 20 mg (N=53)
Baseline (mmol/L)			
Number	52	50	53
Mean (SD)	2.946 (1.122)	3.092 (1.257)	3.059 (0.841)
Median	2.707	2.862	2.875
Min : Max	1.17 : 6.16	0.34 : 7.23	1.89 : 4.82
Baseline (mg/dL)			
Number	52	50	53
Mean (SD)	113.7 (36.0)	119.4 (48.5)	118.1 (32.5)
Median	104.5	110.55	110.0
Min : Max	45 : 238	13 : 279	73 : 186
Week 24 percent change from baseline (%)			
LS Mean (SE)	-15.9 (7.1)	-11.0 (7.2)	-36.3 (7.1)
LS mean difference (SE) (Alirocumab versus Comparator)	-20.3 (10.1)	-25.3 (10.1)	
98.75% CI	(-45.8 to 5.1)	(-50.9 to 0.3)	
p-value (Alirocumab versus Comparator)	0.0453 [a]	0.0136 [a]	

CI = confidence interval; ITT = intent to treat; LDL = low density lipoprotein; LS = least squares; MMRM = mixed effect model for repeated measures; SD = standard deviation; SE = standard error. [a] The endpoint was formally tested but did not achieve statistical significance at the 0.0125 level. Subsequent hypotheses regarding key secondary efficacy endpoints in the sequential testing were not formally tested. Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value by time-point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

Figure 30. Study R727-CL-1118: calculated LDL-C mean (±SE) percent change from baseline: time profile - rosuvastatin 20 mg baseline regimen - ITT population



Sensitivity analyses showed similar results. A sensitivity analysis to assess the impact of 1 site with serious GCP non-compliance demonstrated that when the non-compliant site was excluded, a greater difference between the alirocumab + rosuvastatin 20 mg treatment group (-38.6%) and the ezetimibe 10 mg + rosuvastatin 20 mg group (-11.0%, p = 0.0089) was observed in the rosuvastatin 20 mg baseline regimen.

Up titration

Overall, 17 patients (18.5%) had their alirocumab dose up-titrated at Week 12. Patients who did not have their dose up-titrated maintained the reduction in calculated LDL-C observed at Week 12 to Week 24, while patients who had their dose up-titrated at Week 12 showed a further reduction in LDL-C from Week 12 to Week 24.

Results for other efficacy outcomes

Because statistical significance was reached for the primary efficacy endpoint in the rosuvastatin 10 mg baseline regimen, the hierarchical hypothesis testing was applied to the key secondary endpoints.

In the rosuvastatin 10 mg baseline regimen, the comparison between alirocumab + rosuvastatin 10 mg and rosuvastatin 20 mg, and the comparison between alirocumab + rosuvastatin 10 mg and ezetimibe 10 mg + rosuvastatin 10 mg ceased to be significant for the percent change in HDL-C from baseline at Week 24. Subsequent hypotheses regarding key secondary efficacy endpoints in the hierarchy were not tested; p-values presented for those key secondary endpoints are for descriptive purposes.

In the rosuvastatin 20 mg baseline regimen, no hypotheses regarding key secondary endpoints were tested as the primary efficacy endpoint was not met. All p-values presented for secondary endpoints in this regimen are for descriptive purposes.

Table 45. Study R727-CL-1118: secondary efficacy outcomes - hierarchical testing strategy applied

Key Secondary Efficacy Endpoint	Analysis	P-Values			
		Rosuvastatin 10 mg Regimen		Rosuvastatin 20 mg Regimen	
		Alirocumab + Rosuvastatin 10 mg vs Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab + Rosuvastatin 10 mg vs Rosuvastatin 20 mg	Alirocumab + Rosuvastatin 20 mg vs Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab + Rosuvastatin 20 mg vs Rosuvastatin 40 mg
The percent change in calculated LDL- C from baseline to Week 24 in the mITT population, using all LDL-C values during the efficacy	On-treatment	p < 0.0001*	p < 0.0001*	np = 0.0115	np = 0.0131
The percent change in calculated LDL- C from baseline to Week 12	ITT	p < 0.0001*	p <0.001*	np = 0.0861	np = 0.1747
The percent change in calculated LDL- C from baseline to Week 12	On-treatment	p < 0.0001*	p< 0.0001*	np = 0.0718	np = 0.0980
The percent change in Apo B from baseline to Week 24	ITT	p < 0.0001*	p < 0.0001*	np = 0.0057	np = 0.0024
The percent change in Apo B from baseline to Week 24	On-treatment	p < 0.0001*	p < 0.0001*	np = 0.0027	np = 0.0027
The percent change in non-HDL-C from baseline to Week 24	ITT	p < 0.0001*	p < 0.0001*	np = 0.0133	np = 0.0063
The percent change in non-HDL-C from baseline to Week 24	On-treatment	p < 0.0001*	p < 0.0001*	np = 0.0046	np = 0.0008
The percent change in Total-C from baseline to Week 24	ITT	p < 0.0001*	p < 0.0001*	np = 0.1134	np = 0.0193
The percent change in Apo B from baseline to Week 12	ITT	p < 0.0001*	p < 0.0001*	np = 0.0022	np = 0.0013
The percent change in non-HDL-C from baseline to Week 12	ITT	p < 0.0001*	p < 0.0001*	np = 0.0342	np = 0.0226
The percent change in Total-C from baseline to Week 12	ITT	p < 0.0001*	p < 0.0001*	np = 0.1629	np = 0. 1563
The proportion of very high CV risk patients reaching calculated LDL-C< 70mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C< 100 mg/dL (2.59 mmol/L) at Week 24	ITT	p = 0.0007*	p < 0.0001*	np = 0.1177	np = 0.0022
The proportion of very high CV risk patients reaching calculated LDL-C< 70mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C< 100 mg/dL (2.59 mmol/L) at Week 24	On-treatment	p = 0.0010*	p < 0.0001*	np = 0.0928	np = 0.0014
The proportion of patients reaching calculated LDL-C< 70 mg/dL (1.81 mmol/L) at Week 24	ITT	p < 0.0001*	p < 0.0001*	np = 0.0657	np = 0.0006
The proportion of patients reaching calculated LDL-C< 70 mg/dL (1.81 mmol/L) at Week 24	On-treatment	p = 0.0002*	p < 0.0001*	np = 0.0255	np = 0.0002
The percent change in Lp(a) from baseline to Week 24	ITT	p = 0.0001*	p < 0.0001*	np = 0.0131	np = 0.0123

Key Secondary Efficacy Endpoint	Analysis	P-Values			
		Rosuvastatin 10 mg Regimen		Rosuvastatin 20 mg Regimen	
		Alirocumab + Rosuvastatin 10 mg vs Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab + Rosuvastatin 10 mg vs Rosuvastatin 20 mg	Alirocumab + Rosuvastatin 20 mg vs Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab + Rosuvastatin 20 mg vs Rosuvastatin 40 mg
The percent change in HDL-C from baseline to Week 24	ITT	p = 0.1491	p = 0.0311	np = 0.0072	np = 0.0866
The percent change in TGs from baseline to Week 24	ITT	np = 0.6639	np = 0.1454	np = 0.7039	np = 0.8459
The percent change in Apo A-1 from baseline to Week 24	ITT	np = 0.5484	np = 0.6271	np = 0.0063	np = 0.1651
The percent change in Lp(a) from baseline to Week 12	ITT	np = 0.0008	np < 0.0001	np < 0.0001	np = 0.0012
The percent change in HDL-C from baseline to Week 12	ITT	np = 0.0647	np = 0.0840	np = 0.1614	np = 0.0378
The percent change in fasting TGs from baseline to Week 12	ITT	np = 0.3223	np = 0.0001	np = 0.6854	np = 0.1908
The percent change in Apo A-1 from baseline to Week 12	ITT	np = 0.4652	np = 0.9076	np = 0.0041	np = 0.0015

*Key secondary endpoints that were formally tested and were statistically significant at the 0.0125 level are denoted with an asterisk (*). np = nominal p-value, denotes endpoints that were not formally tested based on predefined hierarchical sequence due to previous hypotheses not reaching significance at the level of p < 0.0125.

Subgroup analysis

Subgroup analyses of the primary efficacy endpoint in the rosuvastatin 10 mg baseline regimen showed reductions in LS mean LDL-C from baseline, consistent with the overall treatment effect of the alirocumab + rosuvastatin 10 mg treatment group versus the rosuvastatin 20 mg treatment group and versus the ezetimibe 10 mg + rosuvastatin 10 mg treatment group across a range of demographic characteristics including gender, age, BMI, history of MI or ischemic stroke, presence of moderate CKD, diabetic status, baseline LDL-C, baseline HDL-C, baseline fasting TG, baseline Lp(a), and LMT other than statins at randomisation.

Subgroup analyses of the primary efficacy endpoint showed reductions in LDL-C from baseline consistent with the overall treatment effect of alirocumab + rosuvastatin 20 mg treatment group versus the rosuvastatin 40 mg and versus ezetimibe 10 mg + rosuvastatin 20 mg treatment groups across a range of demographic characteristics. The analyses were conducted with Week 24 LDL-C data, which includes a portion of the patients having been up-titrated from alirocumab 75 mg to 150 mg. It is possible that any apparent differences in LDL-C response could be partially driven by an imbalance in the percentage of patients that were up-titrated from 75 mg Q2W to 150 mg Q2W within each subgroup.

Up-titration

Overall, 17 patients (18.5%) had their alirocumab dose up-titrated at Week 12, of these, 7 patients (15.9%) were enrolled in the rosuvastatin 10 mg baseline regimen and 10 (20.8%) were in the rosuvastatin 20 mg baseline regimen. In patients in the rosuvastatin 10 mg baseline regimen without dose up-titration, the mean percent change from baseline in calculated LDL-C was -56.0% at Week 12 and was maintained at Week 24 (-53.1%). In patients with dose up-titration, the mean percent change from baseline in calculated LDL-C at Week 12 was -38.5%

and a further reduction was observed at Week 24 (-51.9%). In patients in the rosuvastatin 20 mg baseline regimen without dose up-titration, the mean percent change from baseline in calculated LDL-C was -44.7% at Week 12 and was maintained at Week 24 (-45.8%). In patients with dose up-titration, the mean percent change from baseline in calculated LDL-C at Week 12 was -7.7% and a further reduction was observed at Week 24 (-20.8%).

In the pooled dose regimen, in patients without dose up-titration, the mean percent change from baseline in calculated LDL-C was -50.3% at Week 12 and was maintained at Week 24 (-49.3%). In patients with dose up-titration, the mean percent change from baseline in calculated LDL-C at Week 12 was -20.3%, and a further reduction was observed at Week 24 (-34.4%).

Summary of key results

A statistically significant difference in the percent change in calculated LDL-C from baseline to Week 24 using an MMRM model in the ITT analysis was observed for the rosuvastatin 10 mg baseline regimen, but not for the rosuvastatin 20 mg baseline regimen.

The failure of the alirocumab + rosuvastatin 20 mg treatment group to reach statistical significance for the primary analysis when compared with rosuvastatin 40 mg and ezetimibe 10 mg + rosuvastatin 20 mg in the rosuvastatin 20 mg baseline regimen is partly due to larger variability than previously observed in the Phase II studies. Specifically, the sample size chosen for this study would have 90% power to detect a difference in means of at least 20% in any 1 pairwise comparison, assuming that the common SD was 25%. However, the observed SD in the rosuvastatin 20 mg baseline regimen was due to inflated variability and lower than expected differences in means for the alirocumab add-on group. Overall, the Week 24 mean calculated LDL-C percent change from baseline showed less improvement than expected in the alirocumab add-on group and greater improvement than expected in the double-dose rosuvastatin treatment group.

Table 46. Study R727-CL-1118: changes from baseline in key lipid values at Week 24 across all treatment regimens – ITT analysis

Percent Change from Baseline to Week 24	Rosuvastatin 10 mg Baseline Regimen			Rosuvastatin 20 mg Baseline Regimen		
	Rosuvastatin 20 mg	EZE + Rosuvastatin 10 mg	Alirocumab 75/150 + Rosuvastatin 10 mg	Rosuvastatin 40 mg	EZE + Rosuvastatin 20 mg	Alirocumab 75/150 + Rosuvastatin 20 mg
Apo B	-7.3%	-9.7%	-36.5%	-9.8%	-11.2%	-28.3%
p-value versus alirocumab	p < 0.0001*	p < 0.0001*		np = 0.0024	np = 0.0057	
Total-C	-8.3%	-8.7%	-28.9%	-8.5%	-12.4%	-20.6%
p-value versus alirocumab	p < 0.0001*	p < 0.0001*		np = 0.0193	np = 0.1134	
Non-HDL-C	-11.3%	-13.4%	-42.7%	-11.2%	-12.9%	-31.4%
p-value versus alirocumab	p < 0.0001*	p < 0.0001*		np = 0.0063	np = 0.0133	
Lp(a)	-4.0%	-4.3%	-27.9%	-5.2%	-5.8%	-22.7%
p-value versus alirocumab	p < 0.0001*	p = 0.0001*		np = 0.0123	np = 0.0131	

Percent Change from Baseline to Week 24	Rosuvastatin 10 mg Baseline Regimen			Rosuvastatin 20 mg Baseline Regimen		
	Rosuvastatin 20 mg	EZE + Rosuvastatin 10 mg	Alirocumab 75/150 + Rosuvastatin 10 mg	Rosuvastatin 40 mg	EZE + Rosuvastatin 20 mg	Alirocumab 75/150 + Rosuvastatin 20 mg
HDL-C	+1.7%	+4.0%	+9.1%	+1.5%	-1.8%	+7.2%
p-value versus alirocumab	p = 0.0311	p = 0.1491		np = 0.0866	np = 0.0072	
TGs	-1.8%	-8.3%	-11.2%	-9.9%	-11.1%	-8.7%
p-value versus alirocumab	np = 0.1454	np = 0.6639		np = 0.8459	np = 0.7039	
Apo A-1	+5.4%	+5.0%	+6.7%	+2.9%	-0.9%	+6.7%
p-value versus alirocumab	np = 0.6271	np = 0.5484		np = 0.1651	np = 0.0063	

EZE = ezetimibe. * P-values with an asterisk were formally tested based on the predefined hierarchical sequence and achieved statistical significance at the 0.01 level. Note: Key secondary endpoints after the first failed endpoint within each pairwise comparison in hierarchical sequence were not formally tested; p-values presented are for descriptive purposes and are labelled as nominal (np).

7.4.1.3. Study R727-CL-1119 – (alternative)

A Randomised, Double Blind, Double Dummy, Active Controlled Study to Evaluate the Efficacy and Safety of REGN727/SAR236553 in Patients with Primary Hypercholesterolaemia who are Intolerant to Statins.

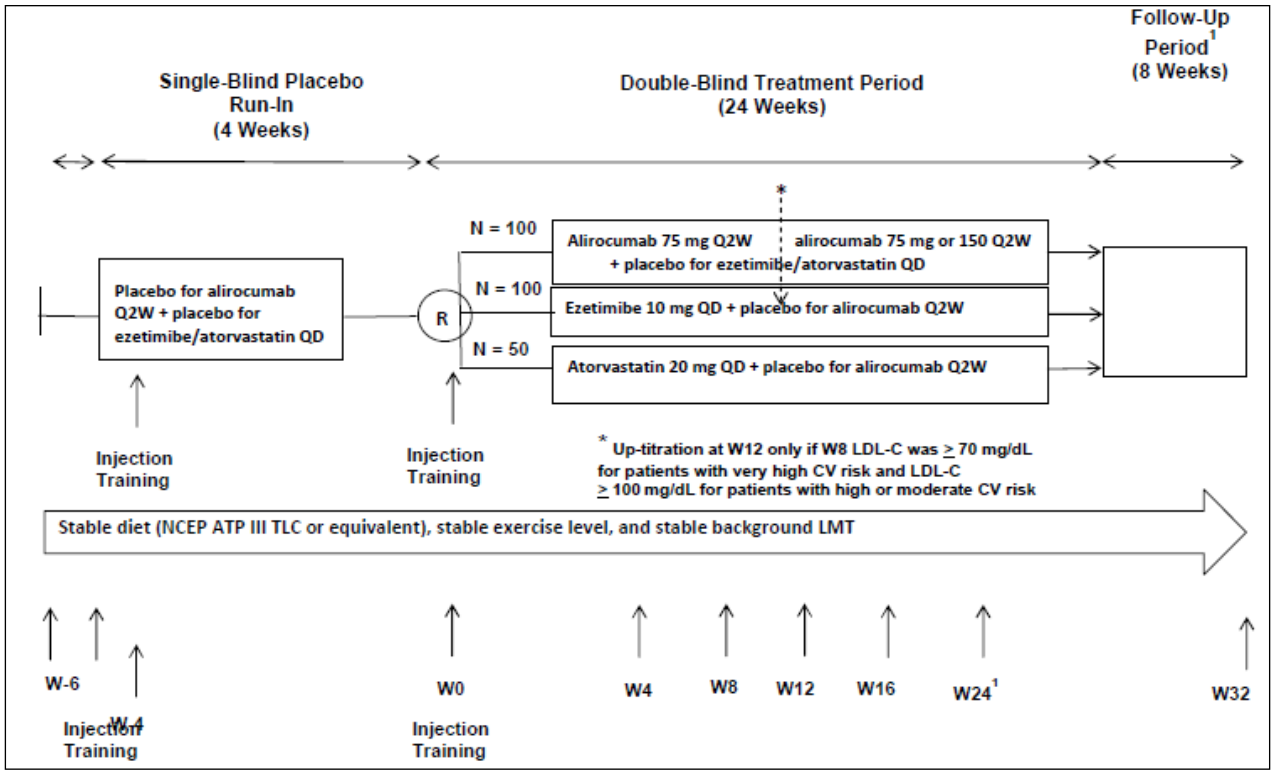
Comment: This CSR is based on the results of the first step analysis of efficacy data up to Week 24 and safety and other results up to the cut-off date of 16 May 2012 (the date of the last patients Week 24 visit). The study is ongoing and the so full results are not yet available.

Study design, objectives, locations and dates

A randomised, double blind, parallel group, double dummy, active controlled, multinational study conducted in 67 sites in 8 countries (Austria, Canada, France, Israel, Italy, Norway, the UK, and the USA) from September 2012 until the cut-off date in May 2014.

- Primary objective: to demonstrate the reduction of LDL-C by alirocumab in comparison with ezetimibe 10 mg PO QD after 24 weeks in patients with primary heFH and non-FH who are intolerant to statins
- Secondary objectives: to evaluate the effect of alirocumab 75 mg in comparison to LDL-C after 12 weeks of treatment; to evaluate the effect of alirocumab on other lipid parameters; to evaluate the safety and tolerability to alirocumab including the characterisation of the incidence rate and treatment withdrawal rate due to skeletal related AEs.

Figure 31. Study R727-CL-1119: Study design



The study design in only shown up to Week 24 which was the timing of the CSR (amended to remove open label treatment period which is ongoing).

Inclusion and exclusion criteria

- **Inclusion:** The study population consisted of patients with hypercholesterolemia (heFH or non-FH) and moderate, high, or very high CV risk who were intolerant to statins.

  The definition of statin intolerance was: the inability to tolerate at least 2 statins: 1 statin at the lowest daily starting dose (defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg), AND another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that began or increased during statin therapy and stopped when statin therapy was discontinued. Patients not receiving a daily regimen of a statin (for example, 1 to 3 times weekly) were also considered not able to tolerate a daily dose and were eligible to enrol in the study if they could not tolerate a cumulative weekly statin dose of 7 times the lowest approved tablet size and the criteria outlined above were also met.

- **Exclusion:** Calculated serum LDL-C < 70 mg/dL (1.81 mmol/L) and very high CV risk at the screening visit (Week -7); Calculated serum LDL-C < 100 mg/dL (2.59 mmol/L) and high or moderate CV risk at the screening visit (Week -7); a 10-year fatal CVD risk SCORE < 1% (ESC/EAS 2011) at the screening visit (Week -7); experience of a skeletal muscle-related AE other than those due to strain or trauma at the time of screening (Week -7), start of single-blind placebo run-in period (Week -4), or baseline (day 1/Week 0).

Study treatments

Patients were randomised to 1 of 3 treatment groups:

- Alirocumab.
  - 75 mg alirocumab SC Q2W starting at Week 0 (randomisation).

  - 75 mg or 150 mg alirocumab (based on the patient's Week 8 LDL-C level and CV risk) SC Q2W starting at Week 12 and continuing up to Week 22, that is, 2 weeks before the end of the double-blind treatment period.
  - 1 placebo capsule for ezetimibe/atorvastatin QD at approximately the same time of the day, with or without food, from Week 0 to Week 24.
- Ezetimibe
  - Placebo for alirocumab SC Q2W starting at Week 0 and continuing up to the last injection (Week 22).
  - 1 ezetimibe 10 mg capsule QD at approximately the same time of day, with or without food, from Week 0 to Week 24.
- Atorvastatin.
  - Placebo for alirocumab SC Q2W starting at Week 0 and continuing up to the last injection (Week 22).
  - 1 atorvastatin 20 mg capsule QD at approximately the same time of day, with or without food, from Week 0 to Week 24.

Efficacy variables and outcomes

The primary efficacy outcome was the percent change in calculated LDL-C from baseline to Week 24 in the intent-to-treat (ITT) population, using all LDL-C values regardless of adherence to treatment.

The secondary efficacy variables are the same as for the previous studies.

Randomisation and blinding methods

Patients were randomised via either IVRS or IWRS to receive alirocumab, ezetimibe, or atorvastatin during the double-blind, double-dummy study treatment period in a ratio of 2:2:1, with permuted-block randomisation. Randomisation was stratified according to history of documented MI or ischaemic stroke (Yes/No).

For the double-blind treatment period, alirocumab and placebo for alirocumab were provided in identically matched AI and were packaged and labelled identically to preserve the blind. The orally administered study drugs were encapsulated and indistinguishable. All ezetimibe, atorvastatin, and ezetimibe/atorvastatin placebo double-blind treatment kit boxes had the same appearance and feel.

Analysis populations

Same as for previous studies.

Sample size

For the analysis of the primary efficacy endpoint, a total sample size of 84 patients (42 patients in the alirocumab treatment group and 42 patients in the ezetimibe treatment group) was calculated to have 95% power to detect a difference in mean percent change from baseline to Week 24 in LDL-C of 20% with a 2-sided significance level and assuming a standard deviation (SD) of 25%. The sample size was increased during the double-blind treatment period to 250 patients, allocating 100 patients in each of the alirocumab and ezetimibe treatment groups, and 50 patients in the atorvastatin treatment group. This sample size assumes that with 100 patients receiving study treatment, each treatment arm would attain a 96% probability of detecting at least 1 withdrawal due to an AE, if the withdrawal event truly occurred in approximately 3.3% of the population (estimate of AE withdrawal rate based on data for ezetimibe).

Statistical methods

Same as for previous studies.

Participant flow

Five hundred and nineteen (519) patients were screened for the study and 361 patients (69.6%) completed the screening period. The commonest reason for not enrolling was not meeting the inclusion/exclusion criteria. Of the 361 patients who completed the screening period, 314 patients (87.0%) completed the single-blind placebo run-in period. 47 patients (13.0%) were run-in failures and were not randomised to a treatment group. Skeletal muscle related AEs other than those due to strain or trauma during the 4 week, single blind, placebo run-in period were the greatest reason for run-in failures (23 patients [48.9%]).

Table 47. Study R727-CL-1119: patient disposition for double blind period - randomised population

	Atorvastatin (N=63)	Ezetimibe (N=125)	Alirocumab 75 Q2W/Up150 Q2W (N=126)	All (N=314)
Randomised but not treated	0	1 (0.8%)	0	1 (0.3%)
Patient's decision for not being treated [a]	0	0	0	0
Reason for not treated				
Visit Window Issue - Instructed By sponsor To Screen Fail	0	1 (0.8%)	0	1 (0.3%)
Randomised and treated	63 (100%)	124 (99.2%)	126 (100%)	313 (99.7%)
Completed 24 weeks of double-blind treatment period (at least 22 weeks of exposure and visit W24 performed)	44 (69.8%)	88 (70.4%)	102 (81.0%)	234 (74.5%)
Complete the study treatment period (as per CRF)	42 (66.7%)	82 (65.6%)	96 (76.2%)	220 (70.1%)
Did not complete the study treatment period (as per CRF)	21 (33.3%)	42 (33.6%)	30 (23.8%)	93 (29.6%)
Patient's decision for treatment discontinuation [a]	15 (23.8%)	33 (26.4%)	26 (20.6%)	74 (23.6%)
Reason for not completing study treatment period (as per CRF)				
Discontinued due to adverse event	16 (25.4%)	31 (24.8%)	23 (18.3%)	70 (22.3%)
Discontinued due to poor compliance to protocol	2 (3.2%)	0	0	2 (0.6%)
Protocol became inconvenient to participate	2 (3.2%)	0	0	2 (0.6%)
Life events made continuing too difficult	0	0	0	0
Poor compliance to protocol - Other reasons	0	0	0	0
Other reasons [b]	3 (4.8%)	11 (8.8%)	7 (5.6%)	21 (6.7%)

Note: Percentages are calculated using the number of patients randomized as denominator. Only the main reason for stopping treatment was entered in e-CRF. For detailed reasons related to IMP auto-injector administration, several reasons may be provided. [a] Additional information as regard study treatment discontinuation. [b] Includes patients who completed the 24-week double-blind treatment period (at least 22 weeks of exposure and Week 24 visit performed) but did not meet the definition of "treatment completer" as per the CRF.

Major protocol violations/deviations

Twenty three (23) patients (18.3%) in the alirocumab treatment group, 11 patients (17.5%) in the atorvastatin treatment group, and 25 patients (20.0%) in the ezetimibe treatment group had a major protocol deviation that potentially impacted efficacy analysis during the study. 1 patient (1.6%) in the atorvastatin treatment group and 3 patients (2.4%) in the ezetimibe treatment group were excluded from the ITT population as a result of a major deviation (no LDL-C value within 1 of the analysis windows up to Week 24 or no baseline LDL-C value), while 3 patients (2.4%) in the alirocumab treatment group, 3 patients (4.8%) in the atorvastatin treatment group, and 7 patients (5.6%) in the ezetimibe treatment group had major deviations resulting in exclusion from the mITT population.

Baseline data

In general, demographics did not differ significantly between treatment groups during the double-blind treatment period. There was an even distribution of male and female patients across treatment groups. The mean (SD) age of randomised patients was 63.4 (9.5) years at baseline, with an age range from 31 to 88 years. Patients were predominantly white (93.9%) and not Hispanic or Latino (97.8%); mean (SD) weight and BMI was 83.6 (19.0) kg and 29.1 (5.8) kg/m^2, respectively.

Cardiovascular medical history was generally similar among treatment groups, with the exception of a history of unstable angina which was reported in more patients in the alirocumab treatment group (9.5%) and the ezetimibe treatment group (10.4%) than in the atorvastatin treatment group (3.2%); 54.1% of patients had a history of CHD or CHD risk equivalents (other CVD or significant risk factors) that would categorise their CV risk as "very high," 28.3% of patients were classified as being at "high CV risk," and 13.7% of patients at "moderate CV risk"; 46.5% of all patients had a medical history of CHD, with a history of coronary revascularisation procedures (32.5%) being the most common CHD event or procedure.

Results for the primary efficacy outcome

A significant decrease in LS mean calculated LDL-C from baseline to Week 24 (ITT analysis) was observed during the double-blind treatment period in the alirocumab treatment group (-45.0%) when compared with the ezetimibe treatment group (-14.6%). The difference in LS mean between the treatment groups was -30.4% and was statistically significant (95% CI: -36.6 to -24.2; $p < 0.0001$).

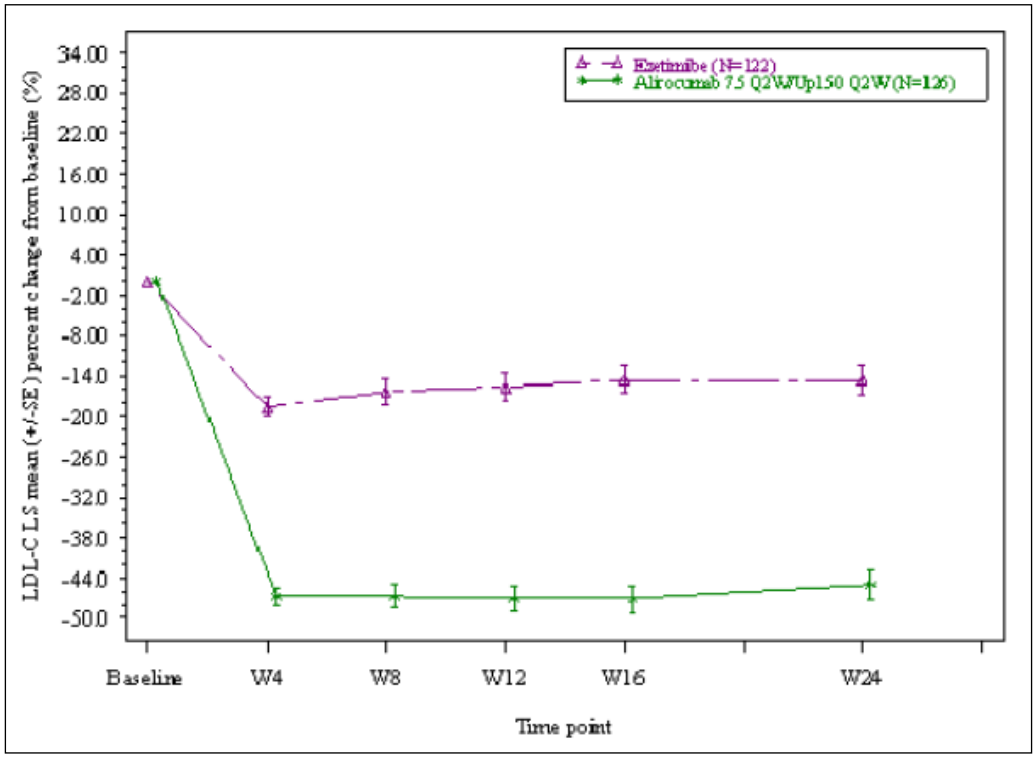
Table 48. Study R727-CL-1119: percent change from baseline in calculated LDL-C to Week 24: MMRM analysis - ITT population

Calculated LDL Cholesterol	Ezetimibe (N=122)	Alirocumab 75 Q2W/Up150 Q2W (N=126)
Baseline (mmol/L)		
Number	122	126
Mean (SD)	5.030 (1.844)	4.951 (1.883)
Median	4.662	4.584
Min : Max	2.10 : 11.06	2.36 : 14.94
Baseline (mg/dL)		
Number	122	126
Mean (SD)	194.2 (71.2)	191.1 (72.7)
Median	180.0	177.0
Min : Max	81 : 427	91 : 577
Week 24 percent change from baseline (%)		
LS Mean (SE)	-14.6 (2.2)	-45.0 (2.2)
LS mean difference (SE) vs Ezetimibe		-30.4 (3.1)
95% CI		(-36.6 to -24.2)
p-value vs Ezetimibe		<.0001*

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomisation strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value by time-point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.*P-values with an asterisk were formally tested and achieved statistical significance at the 0.05 level.

Numerically greater decreases in LS mean calculated LDL-C from baseline were observed for the alirocumab treatment group from the first post-baseline measurement during the double-blind treatment period at Week 4 through Week 24 when compared with the ezetimibe treatment group, as displayed over time.

Figure 32. Study R727-CL-1119: calculated LDL-C LS mean (±SE) percent change from baseline: time profile - ITT population



Sensitivity analyses including the exclusion of the data from GCP non-compliant site demonstrated similar results to the primary analysis.

Results for other efficacy outcomes

Because statistical significance was reached for the primary efficacy endpoint, the hierarchical testing as done in previous studies was conducted.

Statistical significance was not reached for the percent change in HDL-C from baseline to Week 24 (p = 0.6997). Therefore, hypotheses regarding the following subsequent key secondary efficacy endpoints were not formally tested: percent change in TGs from baseline to Week 24, percent change in Apo A-1 from baseline to Week 24, percent change in Lp (a) from baseline to Week 12, percent change in HDL-C from baseline to Week 12, percent change in fasting TGs from baseline to Week 12, and percent change in Apo A-1 from baseline to Week 12. P-values are presented for these endpoints solely for descriptive purposes.

Table 49. Study R727-CL-1119: secondary efficacy outcomes: hierarchical testing strategy applied

Key Secondary Efficacy Endpoint	Analysis	P-Value (Alirocumab Versus Ezetimibe)
The percent change in calculated LDL-C from baseline to Week 24 in the on-treatment analysis, using all LDL-C values during the efficacy treatment period	On-treatment	p < 0.0001*
The percent change in calculated LDL-C from baseline to Week 12	ITT	p < 0.0001*
The percent change in calculated LDL-C from baseline to Week 12	On-treatment	p < 0.0001*
The percent change in Apo B from baseline to Week 24	ITT	p < 0.0001*
The percent change in Apo B from baseline to Week 24	On-treatment	p < 0.0001*
The percent change in non-HDL-C from baseline to Week 24	ITT	p < 0.0001*
The percent change in non-HDL-C from baseline to Week 24	On-treatment	p < 0.0001*
The percent change in Total-C from baseline to Week 24	ITT	p < 0.0001*
The percent change in Apo B from baseline to Week 12	ITT	p < 0.0001*
The percent change in non-HDL-C from baseline to Week 12	ITT	p < 0.0001*
The percent change in Total-C from baseline to Week 12	ITT	p < 0.0001*
The proportion of very high CV risk patients reaching calculated LDL-C< 70mg/dL (1.81 mmol/L) or moderate or high CV risk patients reaching calculated LDL-C< 100 mg/dL (2.59 mmol/L) at Week 24	ITT	p < 0.0001*
The proportion of very high CV risk patients reaching calculated LDL-C< 70mg/dL (1.81 mmol/L) or moderate or high CV risk patients reaching calculated LDL-C< 100 mg/dL (2.59 mmol/L) at Week 24	On-treatment	p < 0.0001*
The proportion of patients reaching calculated LDL-C< 70 mg/dL (1.81 mmol/L) at Week 24	ITT	p < 0.0001*
The proportion of patients reaching calculated LDL-C< 70 mg/dL (1.81 mmol/L) at Week 24	On-treatment	p < 0.0001*
The percent change in Lp(a) from baseline to Week 24	ITT	p < 0.0001*
The percent change in HDL-C from baseline to Week 24	**ITT**	**p = 0.6997**
The percent change in TGs from baseline to Week 24	ITT	p = 0.1426
The percent change in Apo A-1 from baseline to Week 24	ITT	p = 0.2768
The percent change in Lp(a) from baseline to Week 12	ITT	p < 0.0001
The percent change in HDL-C from baseline to Week 12	ITT	p = 0.4148
The percent change in fasting TGs from baseline to Week 12	ITT	p = 0.6855
The percent change in Apo A-1 from baseline to Week 12	ITT	p = 0.2685

The p-value is followed by a '*' if it is statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level.

Subgroup Analyses

Subgroup analysis of the primary efficacy endpoint showed consistent reductions in LDL-C from baseline to Week 24 for the ITT analysis in the alirocumab treatment group versus the ezetimibe treatment group across a range of demographic and baseline characteristics including gender, age, BMI, prior history of MI or ischaemic stroke, moderate chronic kidney disease

status, diabetes, baseline calculated LDL-C, baseline HDL-C, baseline fasting TGs, baseline Lp(a), statin treatment, and LMTs other than statins. A quantitative interaction (that is, p-value < 0.10) was detected for chronic kidney disease status but is likely due to the small numbers in this study with 8 patients in the ezetimibe treatment group and 6 patients in the alirocumab treatment group.

Up-titration

Of the 109 patients in the alirocumab treatment group who had at least 1 injection after Week 12, 54 patients (49.5%) had their dose up-titrated to alirocumab 150 mg at Week 12 during the double-blind treatment period. In patients who did not have their dose up-titrated, the mean percent change from baseline in calculated LDL-C at Week 12 was -57.2% and was maintained at Week 24 (-54.1%). In patients with dose-up-titration, the mean percent change from baseline in calculated LDL-C at Week 12 was -46.3% and a further reduction was observed at Week 24 (-52.6%).

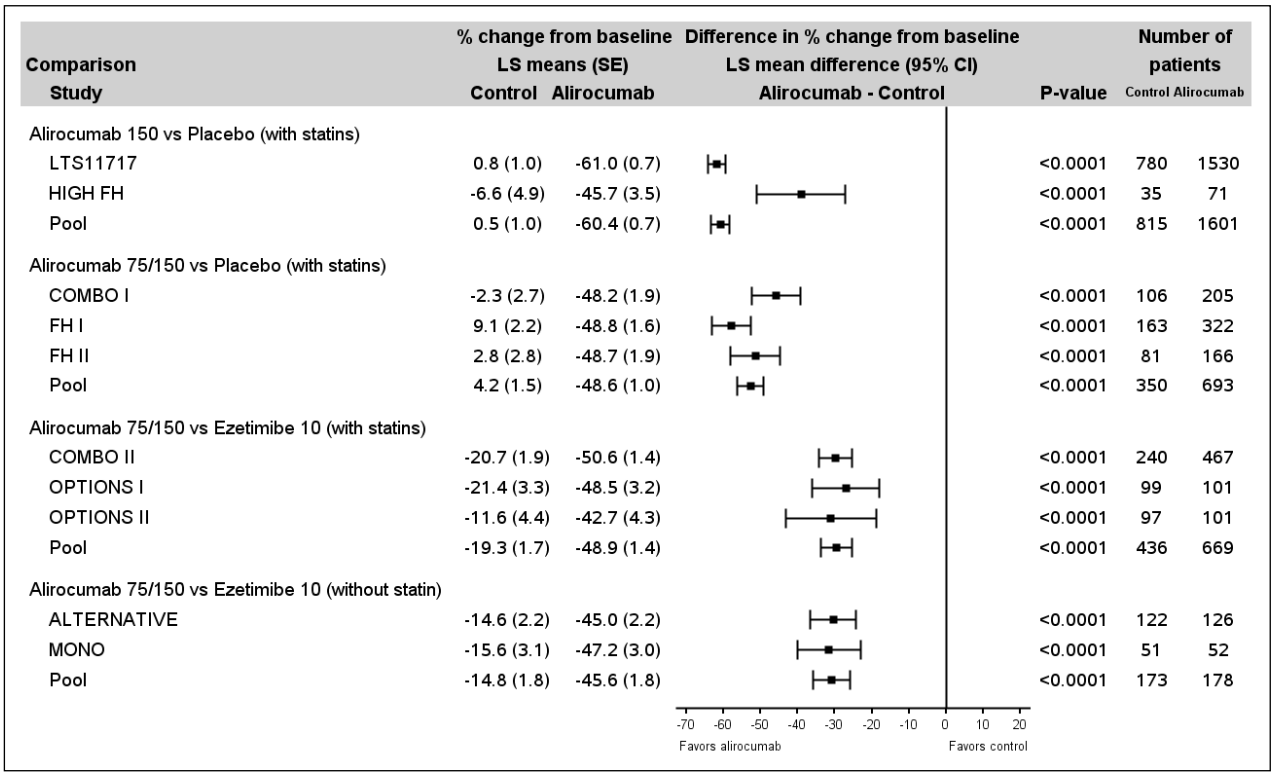
7.4.2. Supportive studies

A summary of the Phase II studies (DFI11566 and DFI12361) which treated patients for 12 weeks were provided but are not discussed in detail here.

7.4.3. Analyses performed across trials (pooled analyses and meta-analyses)

Pooled analysis for the pivotal studies based on the ITT analyses, where all lipid data were taken into account, regardless of adherence to treatment were provided.

Figure 33. Pooled data: percent change from baseline in calculated LDL-C at Week 24: MMRM (ITT analysis) - pivotal studies



7.4.4. Evaluator's conclusions on clinical efficacy

In 8 of 10 Phase III studies described in the CTD, the dose of 75 mg Q2W was used as the initiation dose with up-titration to 150 mg Q2W after 12 weeks of treatment in patients not achieving their individual LDL-C target by Week 8, leading to 1560 patients randomised and treated with this dosing regimen. In the 2 remaining Phase III studies, the 150 mg Q2W dose was used as the initiation dose with 1,622 patient randomised and treated with this dose. This

approach applied in Phase III was aiming to provide data supporting the initiation of treatment with either alirocumab 75 mg or 150 mg Q2W based on the clinical situation.

There were variable percentages of patients in each trial who up-titrated the dose from 75 mg to 150 mg Q2W (from approximately 14% to approximately 44%). The trend is for patients with higher starting LDL-C to be more likely to need up titration but this is not clear and although the sponsor suggests starting at the higher dose based on the "individual patient characteristics and goal of therapy", it is unclear what is intended by "patient characteristics" and it would therefore seem more prudent to start all patients at the lower dose and only increase the dose after 12 weeks if the response (to a target) is less than required. This matches what was done in the majority of trials.

The efficacy studies all had similar design and the same primary endpoint and all demonstrated reduction in the LDL-C, either as add-on to statin or as monotherapy that was superior to placebo and to ezetimibe. The 75 mg dose was associated with a mean reduction in LDL-C of approximately45 to 50% and the 150 mg dose of approximately60% which was sustained for 52 weeks. Long term efficacy of greater than 52 weeks is still awaiting the completion of many of the studies, including the long term safety study.

Consistent reduction in LDL-C was observed with alirocumab across age, BMI, race, baseline LDL-C levels, and patients with diabetes. LDL_C reduction was consistent regardless of which statin was concomitantly used as well as statin dose.

The effect of praluent was not as consistent on the other lipid parameters, especially triglycerides which were reduced in the comparison to placebo studies but not significantly different in the comparison to ezetimibe studies.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

- 10 pivotal Phase III studies - 5 are completed (EFC11568 [COMBO I], EFC11716 [MONO], CL-1110 [OPTIONS I], CL-1118 [OPTIONS II], and the double-blind treatment period of CL-1119 [ALTERNATIVE]). The other 5 studies have completed the prespecified primary assessment period (first step analysis) but are ongoing, in order to obtain additional long-term safety information; the prespecified primary assessment period corresponds to the individual study's cut-off date defined as the last Week 52 visit for EFC11569 (COMBO II), EFC12492 (FH I), CL-1112 (FH II), and EFC12732 (HIGH FH) and as the date when approximately 600 patients had completed the 18-month double-blind treatment period for LTS11717 (LONG TERM).
- Four completed Phase II clinical studies: 3 dose-finding studies (DFI11565, CL-1003, and DFI12361) and 2 exploratory study (DFI11566).

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by recording all adverse events from the time of signed informed consent through the last study visit (the end-of-study visit, or the early termination visit, if the patient withdrew consent). It is noted that how AEs were elicited was not provided in the CSR or Protocol.
- AEs of particular interest, including local injection site reactions, general allergic events, ALT increase, haemolytic anaemia, selected neurologic events (based on SMQs "demyelination", "peripheral neuropathy", and "Guillain-Barré syndrome" excluding the following PTs "acute

respiratory distress syndrome", "asthenia", "respiratory arrest", and "respiratory failure"), neurocognitive events (deliria [including confusion] cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception, mental impairment disorders), ophthalmologic events, muscle-related events, and cardiovascular events were assessed by reviewing those AE identified based on the alirocumab mode of action or "theoretical risks" raised from literature and/or potential risks based on any findings in preclinical studies.

- A Data Monitoring Committee (DMC) monitored the safety of patients enrolled in Phase II/III studies on an ongoing basis. The DMC was set-up at the beginning of the Phase II program and monitored all Phase II and Phase III studies dedicated to the LDL-C lowering indication. The DMC reviewed data at the individual study level as well as safety analyses pooled by placebo-controlled studies and ezetimibe-controlled studies.
- Laboratory tests, including standard haematology and clinical chemistry parameters, were performed at each study visit in each study.
- Additional laboratory parameters were defined in the LONG TERM study and included: vitamin E and other fat soluble vitamins (A, D, and K); cortisol (reflexive ACTH level and /or ACTH stimulation test were to be performed, if cortisol levels were low); and gonadal hormones (analysed in men only)
- Vital signs (heart rate, systolic blood pressure [SBP], and diastolic blood pressure [DBP]) were obtained in sitting position for Phase III studies and supine position for Phase II studies. Body weight was also collected.
- ECGs.
- Anti-drug (alirocumab) antibodies – at baseline and at specified periods during and at end of treatment.

8.1.2. Pivotal studies that assessed safety as a primary outcome

Study LTS11717 was a pivotal study that assessed safety as a primary outcome.

8.1.3. Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data similar to that in the pivotal studies:

- Studies DFI11565.
- Study R727-CL-1032 provided data on patients who received alirocumab in an open label extension study to Study R727-CL-1003.
- Study R727-CL-1003.
- Study DFI11566.
- Study DFI12361.

8.1.4. Other studies evaluable for safety only

Not applicable.

8.1.4.1. Clinical pharmacology studies

There were no safety issues identified in the clinical pharmacology studies.

8.2. Pivotal studies that assessed safety as a primary outcome

8.2.1. Study LTS11717 – (Long term)

Long Term Safety and Tolerability of REGN727/SAR236553 in High Cardiovascular Risk Patients with Hypercholesterolaemia Not Adequately Controlled with Their Lipid Modifying Therapy: A Randomised, Double Blind, Placebo Controlled Study.

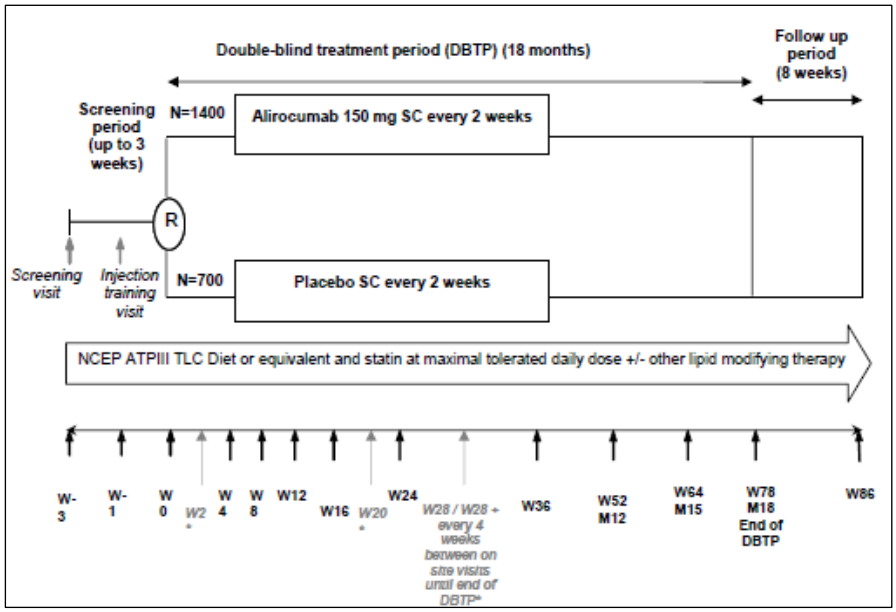
Comment: The CSR is based on the results of the first-step analysis of 52 week efficacy data up to the last time point reached by all randomised patients at the time of analysis; and safety, PK and other results up to the cut-off date of 07 May 2014 (the date when approximately 600 of the patients have completed 78 weeks (18 months) of the double-blind treatment period). The study is ongoing and so the full results are not yet available.

8.2.1.1. Study design, objectives, locations and dates

A randomised, double blind, placebo controlled, parallel group, unbalanced (2:1 alirocumab:placebo), multinational study conducted at 320 centres in 27 countries (Argentina, Belgium, Bulgaria, Canada, Chile, Colombia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Mexico, Netherlands, Norway, Poland, Portugal, Romania, Russia, South Africa, Spain, Sweden, Ukraine, UK and USA).

- Primary objective: to evaluate the long term safety and tolerability of alirocumab in high CV risk patients with hypercholesterolaemia not adequately controlled with their LMTs.
- Secondary objectives: to evaluate the effect of alirocumab on LDL-C levels after 24 weeks of treatment in comparison to placebo; to evaluated the effect on LDL-C at other time points and on other lipid parameters; to evaluate the PK and the development of ADA.

Figure 34. Study LTS11717: study design



*Phone call visits are indicated in italics, and continue every 4 weeks between on-site visits until the end of double-blind treatment period visit.

8.2.1.2. Inclusion and exclusion criteria

Male and female (non-childbearing potential) patients aged ≥ 18 years, at high CV risk not at goal with their LMT, including high intensity or maximally tolerated statin dose and other LMT if previously received at stable dose. Patients were either diagnosed with HeFH with or without established CHD or CHD risk equivalents who were not adequately controlled with a maximally tolerated stable daily dose of statin for at least 4 weeks prior to the screening visit with or

without other LMT or patients with hypercholesterolaemia and established CHD or CHD risk equivalents who were not adequately controlled with maximally tolerated stable daily dose of statin for at least 4 weeks prior to the screening visit with or without other LMT.

8.2.1.3. Study treatments

Patients were randomised to 1 of the 2 arms, alirocumab (150 mg) or placebo during the double-blind treatment period, starting at Week 0 continuing up to the last injection (Week 76) which was at 2 weeks before the end of the double blind treatment period. All IMP injections were self-administered SC in the abdomen, thigh, or outer area of the upper arm Q2W, with rotation within an anatomical area or change the anatomical area based on the patient's preference.

Statin and other LMT (if applicable) were to be stable (including dose) during the first 24 weeks of the double-blind treatment period. From Week 24 onwards, adjustments in background LMT was allowed only under certain conditions including the TG alert and the LDL-C rescue alert.

8.2.1.4. Safety variables and outcomes

The safety variables included:

- Treatment emergent AEs (TEAEs), including SAEs and AEs of special interest:
  - ALT 3 x ULN, allergic events, local injection site reactions, haemolytic anaemia, neurological events, ophthalmologic events, overdose, pregnancy, and CV events
  - Deaths
  - Clinical laboratory data (haematology, standard clinical chemistry, CPK, Vitamin E and other fat soluble vitamins, cortisol with reflexive ACTH and ACTH stimulation and gonadal hormones
  - Vital signs and ECG.

8.2.1.5. Randomisation and blinding methods

Patients were randomised to receive either placebo or alirocumab during the double-blind treatment period using a ratio 1:2. Randomisation was stratified by heFH population (Yes, No), prior history of acute or silent MI or ischemic stroke (Yes, No), statin treatment (atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily, versus simvastatin whatever the daily dose, atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily) and region (North America, Western Europe, Eastern Europe and Rest of World).

The study was double-blind, alirocumab and placebo for alirocumab were provided in identically matched Type 1 glass syringes and packaged identically which included double blind labelling.

8.2.1.6. Analysis populations

The safety population included all randomised patients who actually received at least 1 dose or part of a dose of the double-blind IMP injection. Patients were analysed according to the treatment actually received.

8.2.1.7. Sample size

For safety assessment, a sample size of 2,100 patients (randomisation ratio 2:1, that is, alirocumab: 1,400 and placebo: 700) allows the collection of long-term safety data in a broad database (at least 1,000 patients exposed to alirocumab for a minimum of 12 months, of which approximately 900 patients exposed to alirocumab for 78 weeks).

A sample size of 1,400 patients treated with alirocumab allows detecting AEs with a rate ≥ 0.002 with 95% confidence in the alirocumab group. It was anticipated that between 122 and 142 patients exposed to alirocumab would be evaluated in the ophthalmologic sub-study for at least

12 months considering a sample size of 270 patients and assuming a discontinuation rate of 25% over 12 months. This would allow detection of an ophthalmological event with a true occurrence between 0.021 and 0.024 in the alirocumab group, with 95% confidence.

8.2.1.8. Statistical methods

The safety analysis was descriptive.

8.2.1.9. Participant flow

5,142 patients were screened for the study, of which 2,799 patients (54.4%) were screen failures. The most common reason for screen failure was LDL-C value at screening that was lower than the minimum required for study entry.

Table 50. Study LTS11717: patient disposition - randomised population

	Placebo (N=788) N (%)	Alirocumab 150 Q2W (N=1553) N (%)
Randomised but not treated	0	3 (0.2)
Randomised and treated	788 (100)	1550 (99.8)
Complete 18 months of double-blind treatment period (at least 76 weeks of exposure and visit W78 performed)	202 (25.6)	405 (26.1)
Complete the study treatment period (as per CRF)	176 (22.3)	349 (22.5)
Did not complete the study treatment period (as per CRF)	146 (18.5)	311 (20.0)
- Did not complete the first Week 52 study treatment period	112 (14.2)	220 (14.2)
Treatment ongoing	466 (59.1)	890 (57.3)
Reason for not completing study treatment period (as per CRF)		
Discontinued due to AE	44 (5.6)	98 (6.3)
Discontinued due to poor compliance to protocol	34 (4.3)	54 (3.5)
Protocol became inconvenient to participate	7 (0.9)	11 (0.7)
Life events made continuing too difficult	18 (2.3)	26 (1.7)
Other reasons	9 (1.1)	17 (1.1)
Other reasons	67 (8.5)	159 (10.2)
Physician decision	0	3 (0.2)
Patient moved	4 (0.5)	16 (1.0)
Patient withdrew consent	1 (0.1)	0
Related to IMP administration	4 (0.5)	13 (0.8)
Other [a]	58 (7.4)	127 (8.2)
Patient's decision for treatment discontinuation	94 (11.9)	208 (13.4)
Participation to ophthalmologic sub-study	51 (6.5)	88 (5.7)

Note: Percentages are calculated using the number of patients randomized as denominator. Only the main reason for stopping treatment was entered in CRF. [a] Includes patients who completed the 18 months DB treatment period (at least 76 weeks of exposure and visit W78 performed) but did not meet the definition of "completer per CRF".

There was 1 patient enrolled from the site which was closed due to non-compliance to GCP. This patient withdrew consent after the site was closed. It is not stated if the patient was included in the safety analysis based on the data held to the time of the withdrawal of consent.

8.2.1.10. Baseline data

Demographic characteristics were generally similar between treatment groups. Overall, there were more male patients (1,457; 62.2%) than female patients (884; 37.8%); however, the proportion of male to female patients was well balanced between the treatment groups. Patients were mostly White (92.7%), and the mean age was 60.5 years (range: 18 to 89 years); the percentage of patients 75 years of age or older was 8.1%; the mean BMI was 30.3 kg/m^2 and the percentage of patients with BMI ≥ 30 kg/m^2 was 44.2% in the alirocumab group and 47.4% in the placebo group.

The majority of patients (68.6%) in both treatment groups had a history of CHD, with a history of coronary revascularisation procedures (46.2%) or a history of acute MI (37.2%) being the most frequently reported CHD event or procedure. More non-FH patients had a history of CHD compared with heFH patients (74.5% versus 41.7%). The majority of patients (90.6%) had additional CV risk factors: overall, 75.3% had hypertension (74.2% and 77.3% in the alirocumab and placebo groups, respectively) and 34.6% had type 2 diabetes (34.9% and 33.9% in the alirocumab and placebo groups, respectively). At baseline, 38.9% were former smokers, and 20.7% were current smokers (20.9% and 20.2% in the alirocumab and placebo groups, respectively).

8.2.1.11. Results for the safety outcomes

A total of 1,343 patients in the alirocumab group and 677 patients in the placebo group were exposed to IMP for ≥ 52 weeks. A total of 817 patients were exposed to the IMP injections for ≥ 76 weeks (543 patients [35.1%] in the alirocumab group and 274 patients [34.8%] in the placebo group). Among the 817 patients with ≥ 76 weeks of IMP exposure, 607 patients completed the Week 78 Visit at the time of the first-step analysis cut-off date (405 patients in the alirocumab group and 202 patients in the placebo group).

Adverse Events

Table 51. Study LTS11717: Overview of adverse event profile: treatment emergent adverse events – safety population

	Placebo (N=788) N (%)	Alirocumab 150 Q2W (N=1550) N (%)
Patients with any TEAE	635 (80.6)	1218 (78.6)
Patients with any treatment emergent SAE	139 (17.6)	255 (16.5)
Patients with any TEAE leading to death	8 (1.0)	7 (0.5)
Patients with any TEAE leading to permanent treatment discontinuation	43 (5.5)	96 (6.2)

N (%) = number and percentage of patients with at least one TEAE.

The following 6 TEAEs (PT) were reported more frequently in the alirocumab group compared with the placebo group (with an incidence of ≥ 2.0% and a difference ≥ 0.5% versus placebo), in order of decreasing frequency: injection site reaction (5.7% versus 4.3%), bronchitis (5.2% versus 4.7%), myalgia (4.9% versus 3.0%), muscle spasms (3.7% versus 3.2%), cough (3.2% versus 2.2%), and contusion (2.3% versus 0.8%).

AEs considered related to alirocumab

For 17.0% of patients in the alirocumab group and 14.3% of patients in the placebo group, TEAEs were considered to be related to the IMPs by the Investigator. The most frequently occurring TEAE considered related to the IMP was injection site reaction occurring in 89 patients (5.7%) in the alirocumab group and 34 patients (4.3%) in the placebo group. Other

TEAEs (PT) that were considered related to the IMP and occurred in ≥ 0.5% of patients in either the alirocumab or placebo group, respectively, included the following: headache (0.8% versus 1.4%), diarrhoea (1.0% versus 0.5%), dizziness (0.6% versus 0.6%), nausea (0.6% versus 0.9%), pruritus (0.5% versus 0.1%), arthralgia (0.5% versus 0.5%), myalgia (1.2% versus 0.4%), muscle spasm (0.6% versus 0.5%), fatigue (0.7% versus 0.5%), and decreased blood cortisol (0.4% versus 0.8%).

Table 52. Study LTS11717: number (%) of patients with TEAE(s) that occurred with HLT ≥ 1% patients - safety population

PRIMARY SYSTEM ORGAN CLASS HLT: High Level Term Preferred Term	Placebo (N=788) N (%)	Alirocumab 150 Q2W (N=1550) N (%)
Any class	635 (80.6)	1218 (78.6)
INFECTIONS AND INFESTATIONS	363 (46.1)	705 (45.5)
HLT: Abdominal and gastrointestinal infections	26 (3.3)	46 (3.0)
Gastroenteritis	22 (2.8)	37 (2.4)
HLT: Bacterial infections NEC	10 (1.3)	35 (2.3)
Cellulitis	8 (1.0)	22 (1.4)
HLT: Dental and oral soft tissue infections	22 (2.8)	34 (2.2)
Tooth abscess	10 (1.3)	17 (1.1)
HLT: Infections NEC	19 (2.4)	35 (2.3)
Respiratory tract infection	8 (1.0)	14 (0.9)
HLT: Influenza viral infections	43 (5.5)	84 (5.4)
Influenza	43 (5.5)	84 (5.4)
HLT: Lower respiratory tract and lung infections	75 (9.5)	147 (9.5)
Bronchitis	37 (4.7)	80 (5.2)
Lower respiratory tract infection	23 (2.9)	46 (3.0)
Pneumonia	13 (1.6)	22 (1.4)
HLT: Upper respiratory tract infections	202 (25.6)	363 (23.4)
Nasopharyngitis	100 (12.7)	196 (12.6)
Pharyngitis	7 (0.9)	17 (1.1)
Rhinitis	17 (2.2)	22 (1.4)
Sinusitis	19 (2.4)	40 (2.6)
Upper respiratory tract infection	63 (8.0)	109 (7.0)
HLT: Urinary tract infections	57 (7.2)	97 (6.3)
Cystitis	8 (1.0)	13 (0.8)
Urinary tract infection	49 (6.2)	81 (5.2)
HLT: Viral infections NEC	21 (2.7)	42 (2.7)
Gastroenteritis viral	4 (0.5)	19 (1.2)
METABOLISM AND NUTRITION DISORDERS	66 (8.4)	141 (9.1)
HLT: Diabetes mellitus (incl subtypes)	26 (3.3)	61 (3.9)
Diabetes mellitus	9 (1.1)	23 (1.5)
Type 2 diabetes mellitus	10 (1.3)	27 (1.7)
PSYCHIATRIC DISORDERS	63 (8.0)	91 (5.9)
HLT: Depressive disorders	26 (3.3)	29 (1.9)
Depression	25 (3.2)	28 (1.8)
NERVOUS SYSTEM DISORDERS	140 (17.8)	264 (17.0)
HLT: Headaches NEC	44 (5.6)	75 (4.8)
Headache	44 (5.6)	74 (4.8)
HLT: Neurological signs and symptoms NEC	30 (3.8)	48 (3.1)
Dizziness	29 (3.7)	38 (2.5)
CARDIAC DISORDERS	93 (11.8)	141 (9.1)
HLT: Ischaemic coronary artery disorders	49 (6.2)	73 (4.7)

PRIMARY SYSTEM ORGAN CLASS HLT: High Level Term Preferred Term	Placebo (N=788) N (%)	Alirocumab 150 Q2W (N=1550) N (%)
Acute myocardial infarction	11 (1.4)	6 (0.4)
Angina pectoris	23 (2.9)	32 (2.1)
Angina unstable	9 (1.1)	28 (1.8)
HLT: Supraventricular arrhythmias	25 (3.2)	34 (2.2)
Atrial fibrillation	17 (2.2)	22 (1.4)
VASCULAR DISORDERS	70 (8.9)	122 (7.9)
HLT: Vascular hypertensive disorders NEC	27 (3.4)	54 (3.5)
Hypertension	27 (3.4)	54 (3.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	86 (10.9)	171 (11.0)
HLT: Breathing abnormalities	16 (2.0)	27 (1.7)
Dyspnoea	11 (1.4)	14 (0.9)
HLT: Bronchospasm and obstruction	22 (2.8)	32 (2.1)
Chronic obstructive pulmonary disease	15 (1.9)	19 (1.2)
HLT: Coughing and associated symptoms	19 (2.4)	53 (3.4)
Cough	17 (2.2)	49 (3.2)
HLT: Upper respiratory tract signs and symptoms	7 (0.9)	31 (2.0)
Oropharyngeal pain	2 (0.3)	19 (1.2)
GASTROINTESTINAL DISORDERS	148 (18.8)	288 (18.6)
HLT: Diarrhoea (excl infective)	40 (5.1)	82 (5.3)
Diarrhoea	40 (5.1)	82 (5.3)
HLT: Gastrointestinal and abdominal pains (excl oral and throat)	22 (2.8)	45 (2.9)
Abdominal pain	12 (1.5)	21 (1.4)
Abdominal pain upper	6 (0.8)	21 (1.4)
HLT: Gastrointestinal atonic and hypomotility disorders NEC	26 (3.3)	51 (3.3)
Constipation	14 (1.8)	30 (1.9)
Gastrooesophageal reflux disease	12 (1.5)	21 (1.4)
HLT: Nausea and vomiting symptoms	29 (3.7)	50 (3.2)
Nausea	20 (2.5)	37 (2.4)
Vomiting	12 (1.5)	20 (1.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	225 (28.6)	422 (27.2)
HLT: Joint related signs and symptoms	50 (6.3)	80 (5.2)
Arthralgia	47 (6.0)	70 (4.5)
HLT: Muscle pains	24 (3.0)	77 (5.0)
Myalgia	24 (3.0)	76 (4.9)
HLT: Muscle related signs and symptoms NEC	26 (3.3)	60 (3.9)
Muscle spasms	25 (3.2)	58 (3.7)
HLT: Musculoskeletal and connective tissue pain and discomfort	105 (13.3)	159 (10.3)
Back pain	47 (6.0)	73 (4.7)
Musculoskeletal chest pain	12 (1.5)	7 (0.5)
Musculoskeletal pain	15 (1.9)	36 (2.3)
Neck pain	14 (1.8)	9 (0.6)
Pain in extremity	35 (4.4)	46 (3.0)
HLT: Osteoarthropathies	27 (3.4)	44 (2.8)
Osteoarthritis	24 (3.0)	35 (2.3)
RENAL AND URINARY DISORDERS	47 (6.0)	72 (4.6)
HLT: Renal failure and impairment	17 (2.2)	21 (1.4)
Renal failure acute	8 (1.0)	7 (0.5)

PRIMARY SYSTEM ORGAN CLASS HLT: High Level Term Preferred Term	Placebo (N=788) N (%)	Alirocumab 150 Q2W (N=1550) N (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	134 (17.0)	238 (15.4)
HLT: Asthenic conditions	44 (5.6)	65 (4.2)
Asthenia	10 (1.3)	9 (0.6)
Fatigue	30 (3.8)	47 (3.0)
HLT: General signs and symptoms NEC	22 (2.8)	31 (2.0)
Influenza like illness	14 (1.8)	22 (1.4)
HLT: Injection site reactions	35 (4.4)	91 (5.9)
Injection site reaction	34 (4.3)	89 (5.7)
HLT: Pain and discomfort NEC	27 (3.4)	46 (3.0)
Non-cardiac chest pain	15 (1.9)	28 (1.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	112 (14.2)	207 (13.4)
HLT: Muscle, tendon and ligament injuries	28 (3.6)	31 (2.0)
Ligament sprain	13 (1.6)	8 (0.5)
HLT: Non-site specific injuries NEC	45 (5.7)	82 (5.3)
Fall	32 (4.1)	43 (2.8)
HLT: Skin injuries NEC	16 (2.0)	54 (3.5)
Contusion	6 (0.8)	35 (2.3)
Laceration	5 (0.6)	16 (1.0)

MedDRA 17.0. n (%) = number and percentage of patients with at least one TEAE. Note: Table sorted by SOC internationally agreed order and HLT, PT by alphabetic order. Only HLT with frequency ≥ 2% in at least one treatment group are presented. (Table amended to include only PT ≥ 1%).

AEs of special interest

- Local reactions

  90 (5.8%) in the alirocumab group and 34 (4.3%) in the placebo group had at least 1 local injections site reaction TEAE. The majority of local injection site reactions were mild in severity, of short duration and in most cases represented a single occurrence. 4 (0.3%) patients in the alirocumab group and 4 (0.5%) in the placebo group discontinued treatment due to an injection site reaction.

- Allergic reactions

  TEAEs related to potential allergic reactions were similar in the alirocumab group (140 (9.0%) and the placebo group (71 (9.0%), with a treatment group difference noted only for pruritus (21 [1.4%] in the alirocumab group versus 3 [0.4%] in the placebo group). 5 (0.3%) patients in the alirocumab group and 3 (0.4) in the placebo group reported serious general allergic TEAEs including hypersensitivity drug hypersensitivity, allergic dermatitis, and asthma (2 patients) in the alirocumab group and cytokine release syndrome, asthma and acute respiratory failure in the placebo group. 9 patients in the alirocumab group and no patients in the placebo group discontinued treatment due to a general allergic reaction event.

- Neurologic events

  65 patients (4.2%) in the alirocumab group and 31 patients (3.9%) in the placebo group experienced TEAEs related to neurologic disorders. The most frequently occurring neurologic disorder TEAE was paraesthesia, which occurred with a higher frequency in the alirocumab group (19 patients [1.2%]) compared with the placebo group (5 patients [0.6%]). Neurologic disorders that met the criteria for seriousness were reported for 4 patients (0.3%) in the alirocumab group, including cases of ataxia, demyelination, Miller

Fisher syndrome, and optic neuropathy. No patients in the placebo group experienced an SAE related to neurologic disorders.

Eighteen patients (1.2%) in the alirocumab group and 4 patients (0.5%) in the placebo group experienced TEAEs related to neurocognitive disorders. Neurocognitive disorders that met the criteria for seriousness were reported for 3 patients (0.2%) in the alirocumab group, including confusional state, dementia, and frontotemporal dementia. 1 case of dementia was reported in the placebo group.

- Ophthalmologic sub-study

  Selected sites participated in an ophthalmologic sub-study. Ophthalmologic assessments (including colour vision testing, best corrected visual acuity, slit lamp ophthalmoscopy, intraocular pressure assessment, dilated lens and fundus examination, or optic disc and fundus photographs) were performed periodically throughout the study as per the usual practice of the ophthalmologist/optometrist involved in this sub-study. Abnormalities identified during ophthalmologic assessments were to be reported as AEs.

  Among the 139 patients who participated in the ophthalmological sub-study, 6 patients had an ophthalmological TEAE (4 patients [4.5%] in the alirocumab group and 2 patients [3.9%] in the placebo group). In the alirocumab group the following ophthalmological TEAEs were reported in 1 patient each: age-related macular degeneration, demyelination, detachment of the retinal pigment epithelium, retinal haemorrhage, and retinal tear. In the placebo group, 1 patient each had diabetic neuropathy and macular degeneration.

Deaths and other SAEs

A total of 19 deaths were reported during the on-study period: 15 patients had TEAEs that resulted in death including, 7 patients (0.5%) in the alirocumab group and 8 patients (1.0%) in the placebo group. In addition, 4 patients in the alirocumab group died due to post-treatment AEs. None of the TEAEs leading to death were considered by the Investigator to be related to the IMP.

Of the 7 alirocumab patients: 5 cases were positively adjudicated by the DMC as CV events, 1 was due to traumatic intracranial haemorrhage and 1 due to metastatic lymphoma. All 4 post-treatment AEs leading to death were positively adjudicated by the CEC as CV events. Of the 8 placebo patients: 6 cases were positively adjudicated by the DMC as CV events and the other 2 were due to neoplastic disease (pancreatic cancer and acute myeloid lymphoma).

A post hoc analysis showed a lower incidence of patients with MACE composite endpoint confirmed by adjudication in the alirocumab group (1.4%) compared with the placebo group (3.0%) with a hazard ratio versus placebo of 0.462 (95% CI: 0.259 – 0.824).

Discontinuations due to AEs.

A total of 96 patients (6.2%) in the alirocumab group and 43 patients (5.5%) in the placebo group experienced TEAE leading to treatment discontinuation. No specific clinical pattern was noted among the TEAEs leading to permanent treatment discontinuation.

Adjudicated cardiovascular events

A total of 97 patients had treatment emergent CV events (AEs and procedures) that were confirmed by adjudication, including 62 patients (4.0%) in the alirocumab group and 35 patients (4.4%) in the placebo group as of the cut-off date for this CSR (07 May 2014). The most frequently reported CV event was ischaemia driven coronary revascularisation procedure, reported for 41 patients (2.6%) in the alirocumab group and 20 patients (2.5%) in the placebo group. A lower percentage of patients in the alirocumab group experienced a non-fatal MI compared with the placebo group (0.7% versus 2.2%), and a lower percentage of patients in the alirocumab group experienced CHD death compared with the placebo group (0.2% versus 0.8%).

Table 53. Study LTS11717: summary of treatment emergent cardiovascular events (AEs and procedures) according to adjudication - safety population

Category of adjudication	Placebo (N=788) N (%)	Alirocumab 150 Q2W (N=1550) N (%)
Any patients with treatment emergent cardiovascular events confirmed by adjudication	35 (4.4)	62 (4.0)
CHD death (including undetermined cause)	6 (0.8)	3 (0.2)
Non-fatal MI	17 (2.2)	11 (0.7)
Fatal and non-fatal ischemic stroke (including stroke not otherwise specified)	2 (0.3)	8 (0.5)
Unstable angina requiring hospitalization	1 (0.1)	0
Congestive heart failure requiring hospitalization	3 (0.4)	9 (0.)
Ischaemia driven coronary revascularization procedure	20 (2.5)	41 (2.6)

Diabetes

TEAEs of diabetes were reported by 67 patients (4.3%) in the alirocumab group and 31 patients (3.9%) in the placebo group, regardless of the baseline status. Analysis according to the patients' diabetic status at baseline revealed no difference in the incidence of Investigator-reported treatment emergent diabetes between the alirocumab and the placebo groups in non-diabetic patients at baseline. No clinically relevant difference was observed between treatment groups in the changes in fasting glucose and HbA1c, overall and by baseline glucose control category.

Laboratory tests

Overall, none of the clinical laboratory parameters evaluated or the vital signs showed a clinically relevant difference between treatment groups. There were no cases of confirmed haemolytic anaemia. There were no relevant changes in adrenal or gonadal function (in men) during the study. Non-cholesterol adjusted vitamin E levels decreased in the alirocumab group compared with the placebo group which showed little to no change over time.

No safety concerns were identified by ECG.

Immunogenicity.

Seventy five (75) patients in the alirocumab group had a positive ADA status at least once during the study. Twenty-four patients in the alirocumab group (1.6%) and 8 patients in the placebo group (1.1%) had positive ADA status at baseline, with titres ranging from 30 to 480 for the alirocumab group and from 30 to 120 for the placebo group, and none of them developed a treatment emergent positive ADA response during the study.

Among the 75 patients in the alirocumab group with a positive ADA-response during the TEAE period, 63 patients (84.0%) reported at least 1 TEAE. The safety profile in the ADA-positive patients was generally similar to that observed in the ADA-negative patients and similar to the alirocumab group of the safety population as a whole, with the exception of injection site reaction, which occurred with a higher incidence in ADA-positive patients compared with ADA-negative patients: (12.0% versus 5.5%). General allergic TEAEs were not increased in patients who developed a treatment emergent ADA response compared to patients with a negative status. Cases included hypersensitivity (considered an SAE that occurred after the first dose), generalised pruritus, rash and dermatitis in 1 patient each and conjunctivitis in 2 patients. The patient with hypersensitivity was ADA negative at baseline and the time course of events make it likely that the hypersensitivity reaction occurred before the development of ADA. All other cases of allergic TEAEs in ADA positive patients were not considered serious and did not result in treatment discontinuation.

8.3. Patient exposure

Table 54. Number of patients in pivotal studies included in the integrated safety database

Phase	Study	Treatment group		
		Placebo	Alirocumab	Ezetimibe
Phase II				
Placebo-controlled	CL-1003	15	16 [a]	
	DFI11565	31	31 [a]	
	DFI11566	31	61	
	DFI12361	25	50 [b]	
Total		**102**	**158**	
Phase III				
Placebo-controlled	EFC12492 (FH I)	163	322	
	CL-1112 (FH II)	81	167	
	EFC12732 (HIGH FH)	35	72	
	EFC11568 (COMBO I)	107	207	
	LTS11717 (LONG TERM)	788	1550	
Total		**1174**	**2318**	
Ezetimibe-controlled	EFC11569 (COMBO II)		479	241
	CL-1110 (OPTIONS I)		104	101
	CL-1118 (OPTIONS II)		103	101
	CL-1119 (ALTERNATIVE)		126	124
	EFC11716 (MONO)		52	51
Total			**864**	**618**
Grand total		**1276**	**3340**	**618**

[a] Number of patients included in the alirocumab150 mg Q2W group only. [b] Number of patients included in the alirocumab 75 mg and 150 mg Q2W group.

Table 55. Exposure to investigational medicinal product - Pool of placebo-controlled studies and Pool of ezetimibe-controlled studies - (Safety population)

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)
Cumulative injection exposure (patient-years)	1407.6	2758.5	419.4	692.2
Duration of IMP injection exposure (weeks)				
Number	1275	2470	617	861
Mean (SD)	57.60 (22.39)	58.27 (21.86)	35.47 (21.96)	41.94 (23.09)
Median	65.10	65.10	24.00	27.30
Min : Max	2.0 : 84.9	2.0 : 84.0	2.0 : 94.1	2.0 : 93.4
Duration of IMP injection				
Number	1275	2470	617	861
≥ 1 day to < 4 weeks	13 (1.0%)	24 (1.0%)	15 (2.4%)	21 (2.4%)
≥ 4 weeks to < 8 weeks	20 (1.6%)	54 (2.2%)	26 (4.2%)	27 (3.1%)
≥ 8 weeks to < 12 weeks	47 (3.7%)	105 (4.3%)	18 (2.9%)	15 (1.7%)
≥ 12 weeks to < 16 weeks	93 (7.3%)	111 (4.5%)	18 (2.9%)	18 (2.1%)
≥ 16 weeks to < 24 weeks	20 (1.6%)	41 (1.7%)	53 (8.6%)	59 (6.9%)
≥ 24 weeks to < 36 weeks	35 (2.7%)	66 (2.7%)	277	297
≥ 36 weeks to < 52 weeks	37 (2.9%)	70 (2.8%)	1 (0.2%)	15 (1.7%)
≥ 52 weeks to < 64 weeks	277 (21.7%)	576	132	250
≥ 64 weeks to < 76 weeks	444 (34.8%)	848	47 (7.6%)	95 (11.0%)
≥ 76 weeks	289 (22.7%)	575	30 (4.9%)	64 (7.4%)

Placebo-controlled studies: Phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I), Phase II (DFI11565, DFI11566, CL-1003, DFI12361). Ezetimibe-controlled studies: Phase III (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE). The duration of IMP injection exposure in weeks is defined as: (last IMP injection date + 14 days - first IMP injection date)/7, regardless of intermittent discontinuations. Source: Module 2.7.4 Table 6

Table 56. Patient disposition (randomised population) - pool of placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo (N=1277) N (%)	Alirocumab (N=2482) N (%)	Ezetimibe (N=620) N (%)	Alirocumab (N=864) N (%)
Randomised but not treated	1 (<0.1)	6 (0.2)	2 (0.3)	0
Randomised and treated	1276 (>99.9)	2476 (99.8)	618 (99.7)	864 (100)
Did not complete the study treatment period (as per CRF)	214 (16.8)	435 (17.5)	128 (20.6)	155 (17.9)
Treatment ongoing	713 (55.8)	1377 (55.5)	206 (33.2)	406 (47.0)
Reason for not completing the study treatment period (as per CRF)				
Adverse event	66 (5.2)	136 (5.5)	60 (9.7)	76 (8.8)
Poor compliance to protocol	50 (3.9)	79 (3.2)	14 (2.3)	18 (2.1)
Other reasons [a]	97 (7.6)	220 (8.9)	54 (8.7)	61 (7.1)
Missing	1 (<0.1)	0	0	0

Placebo-controlled studies: Phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I), Phase II (DFI11565, DFI11566, CL-1003, DFI12361). Ezetimibe-controlled studies: Phase III (COMBO II, MONO, OPTIONS I,

OPTIONS II, ALTERNATIVE). Note: Percentages are calculated using the number of patients randomized as denominator. Only the main reason for stopping treatment was entered in e-CRF *a* Includes patients who completed the planned treatment duration (i.e. patient exposed to IMP for at least 102 weeks in study COMBO II, at least 76 weeks in studies FH I, FH II, HIGH FH, LTS17117, at least 50 weeks in study COMBO I, or at least 22 weeks in studies OPTIONS I, OPTIONS II, ALTERNATIVE and MONO, with associated visit performed, or completed as per CRF in Phase II studies) but who otherwise did not fulfil the strict CRF criteria for study treatment period completion.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

Table 57. Overview of adverse event profile: treatment emergent adverse events (safety population) - pool of placebo-controlled studies and pool of ezetimibe-controlled studies

n(%)	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo (N=1276) N (%)	Alirocumab (N=2476) N (%)	Ezetimibe (N=618) N (%)	Alirocumab (N=864) N (%)
Patients with any TEAE	975 (76.4)	1876 (75.8)	421 (68.1)	607 (70.3)
Patients with any treatment emergent	182 (14.3)	340 (13.7)	69 (11.2)	113 (13.1)
Patients with any TEAE leading to death	11 (0.9)	13 (0.5)	7 (1.1)	2 (0.2)
Patients with any TEAE leading to permanent treatment discontinuation	65 (5.1)	131 (5.3)	60 (9.7)	76 (8.8)

Placebo-controlled studies: Phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I), Phase II (DFI11565, DFI11566, CL-1003, DFI12361). Ezetimibe-controlled studies: Phase III (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE). n (%) = number and percentage of patients with at least one TEAE.

8.4.1.1. Placebo controlled pool

In the placebo controlled pool, almost all patients took the IMP in addition to concomitant statins. The percentages of patients who experienced at least 1 TEAE, at least 1 treatment emergent SAE, and any TEAE leading to permanent treatment discontinuation were similar between the alirocumab and placebo groups.

TEAEs (PT) reported in a higher proportion of patients in the alirocumab group compared to placebo (incidence ≥ 2.0% in the alirocumab group and difference ≥ 0.5% versus placebo) were as follows: injection site reaction, influenza, myalgia, muscle spasms, contusion, and musculoskeletal pain.

8.4.1.2. Ezetimibe controlled pool

In the ezetimibe controlled pool, approximately 75 to 80% patients took the IMP in addition to concomitant statins. The percentages of patients with at least 1 TEAE, treatment emergent SAE, or TEAE leading to treatment discontinuation were overall similar across alirocumab and ezetimibe groups.

The following TEAEs (PT) were reported in a higher proportion of patients in the alirocumab group compared to the ezetimibe group (incidence ≥ 2.0% in the alirocumab group and difference ≥ 0.5% versus ezetimibe): accidental overdose, headache, influenza, injection site reaction, fatigue, and constipation.

8.4.1.3. Up titration

An analysis of the TEAEs that occurred from the first injection after up-titration (or from the dose administered at the same time point in non-titrated patients) was performed in the placebo controlled and ezetimibe controlled pools, separately. The incidence rates of 'common' events were compared according to the up-titration status of the patients. No relevant

differences were identified in the TEAE profile of alirocumab according to the up-titration status. Specifically, no increase in the incidence of injection site reactions was reported after up-titration to the dose of 150 mg Q2W compared to the incidence in patients who continued treatment at the dose of 75 mg Q2W.

Table 58. Analysis of AEs by dose up-titration

Patient with any:	Alirocumab-treated			
	Placebo pool		Ezetimibe pool	
	Not Uptitrated N=432 N (%)	Uptitrated N=228 N (%)	Not Uptitrated N=606 N (%)	Uptitrated N=180 N (%)
TEAE	286 (66.2)	158 (65.8}	343 (56.6)	96 (53.3)
SAE	41 (9.5)	18 (8.3)	64 (10.6)	15 (8.3)
TEAE leading to death	3 (0.7)	1 (0.4)	1 (0.2)	1 (0.6)
Discontinuation due to TEAE	2.1	3.1	2.5	3.3
Injection site reactions (HLT)	4.9	3.9	1.2	1.1

Not uptitrated = 75 mg every 2 weeks after Week 12. Uptitrated = 150 mg every 2 weeks after Week 12.
Source: Integrated Summary of Safety Appendix 1.4.14.1.1 and 1.4.14.1.2

8.4.2. Treatment-related adverse events (adverse drug reactions)

There were some specific TEAEs (PT) that occurred at a higher incidence in the alirocumab group in 1 analysis and some that occurred at a higher incidence in the control group in another. Differences that were not consistently observed were not considered to represent meaningful signals. There were 3 TEAEs that occurred more frequently in the alirocumab group than in the control group in several analyses and were therefore judged as potentially related to alirocumab therapy.

Table 59. Treatment related AEs

AE (PT)	Alirocumab group N (%)	Placebo group N (%)	Alirocumab group N (%)	Ezetimibe group N (%)
injection site reactions	180 (7.3)	66 (5.2)	26 (3.1)	13 (2.1)
pruritus	28 (1.1)	5 (0.4)	*0.8	*0.5
influenza	141 (5.7)	59 (4.6)	*3.7	*2.3

* Number not provided.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Deaths

In the global pool of Phase II/III studies, on-study deaths were reported in 20 (0.6%) patients in the alirocumab groups and 17 (0.9%) in the control groups. In these patients, mostly at high CV risk, the primary causes of death were CV events.

Table 60. Summary of deaths adjudication results (safety population) - global pool of Phase III studies

Primary cause of death as per adjudication n(%)	Control (N=1792) N (%)	Alirocumab (N=3182) N (%)
Death on-study a	17 (0.9)	20 (0.6)

Primary cause of death as per adjudication n(%)	Control (N=1792) N (%)	Alirocumab (N=3182) N (%)
CHD death	9 (0.5)	12 (0.4)
Any cardiovascular	11 (0.6)	15 (0.5)
Acute myocardial infarction	0	4 (0.1)
Cardiovascular haemorrhage	1 (<0.1)	2 (<0.1)
Cardiovascular procedure	1 (<0.1)	1 (<0.1)
Heart failure or cardiogenic shock	1 (<0.1)	1 (<0.1)
Stroke - haemorrhagic	0	1 (<0.1)
Sudden cardiac death	8 (0.4)	6 (0.2)
Any non-cardiovascular	6 (0.3)	4 (0.1)
Accidental	1 (<0.1)	1 (<0.1)
Pancreatic	1 (<0.1)	1 (<0.1)
Pulmonary	2 (0.1)	2 (<0.1)
Suicide	1 (<0.1)	0
Other non-cardiovascular	1 (<0.1)	0
Non cardiovascular: Infection	1 (<0.1)	0
Non cardiovascular: Malignant	2 (0.1)	2 (<0.1)
New malignancy	1 (<0.1)	1 (<0.1)
Worsening prior malignancy	1 (<0.1)	1 (<0.1)
Not adjudicated	0	1 (<0.1)

Placebo controlled studies: Phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I). Ezetimibe controlled studies: Phase III (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE). Only the primary cause of death is adjudicated. a includes all deaths that occurred after the start of the treatment up to the last protocol planned visit of the patient. Haemorrhage: excluding haemorrhagic strokes and bleeding in the setting of coronary revascularisation. Accidental: for example, physical accidents or drug overdose or trauma. Prescription drug error: for example, prescribed drug overdose, use of inappropriate drug, or drug-drug interaction. Neurological process: neurological process that is not a stroke or haemorrhage.

A meta-analysis performed on the incidences of TEAEs leading to death found an exact odds ratio (OR) versus control, stratified by study, of 0.44 (95% CI: 0.21 to 0.93) compared to controls.

8.4.3.2. Other SAEs

The overall incidence of treatment emergent SAEs was similar in the alirocumab and placebo groups: 340 (13.7%) versus 182 (14.3%), respectively and in the alirocumab and ezetimibe groups: 113 (13.1%) versus 69 (11.2%), respectively. No relevant difference between the treatment groups was observed for any individual SOC.

8.4.4. Discontinuation due to adverse events

8.4.4.1. Placebo controlled pool

The overall incidence of TEAEs leading to treatment discontinuation was similar in the alirocumab (131 [5.3%]) and placebo (65 [5.1%]) groups. No relevant difference between the treatment groups was observed for any individual SOC. In the alirocumab group, the most frequently reported (in at least 3 patients) TEAEs (PTs) that led to treatment discontinuation were injection site reaction and nausea (5 [0.2%] each), myalgia, fatigue, and ALT increased (4 [0.2%] each), and anaemia, vertigo, diarrhoea, and pruritus (3 [0.1%] each). Other TEAEs were isolated cases reported in 1 or 2 patients.

8.4.4.2. Ezetimibe controlled pool

The overall incidence of TEAEs leading to treatment discontinuation was also similar in the alirocumab (76 [8.8%]) and ezetimibe (60 [9.7%]) groups. In the alirocumab group, the most frequently reported (in at least 3 patients) TEAEs (PTs) that led to treatment discontinuation

were myalgia (21 [2.4%]), headache and injection site reaction (3 [0.3%] each). In the ezetimibe group, the most frequently reported (in at least 3 patients) TEAEs (PTs) that led to treatment discontinuation were myalgia (23 [3.7%]), arthralgia (4 [0.6%]), headache and muscular weakness (3 [0.5%] each). The higher rate of discontinuations in this pool was driven by the ALTERNATIVE study, conducted in patients with a documented history of statin intolerance.

8.4.5. Adverse events of special interest

8.4.5.1. Local injection site reactions

The incidence rate of local injection site reactions in the global pool of efficacy studies was higher in the alirocumab group compared to the pooled control group (6.0 versus 4.2 per 100 patient years, respectively; HR [95% CI]: 1.50 [1.15 – 1.95]) The majority of local injection site reactions were mild and transient but were reported as severe in 1 patient (< 0.1%) in the alirocumab group. Local injection site reactions resulted in treatment discontinuation in 8 (0.2%) patients in the alirocumab group and 6 (0.3%) patients in the control group. Local injection site reactions were more frequently reported in alirocumab patients who developed treatment emergent ADA compared with patients who do not develop ADAs (10.2% versus 5.9%).

8.4.5.2. General allergic reactions

There were slightly higher rates of general allergic reactions reported in the alirocumab group versus the control in both the placebo controlled pool and the ezetimibe controlled pool (placebo controlled pool: 7.9 (alirocumab) versus 7.2 (placebo) patients per 100 patient years, HR [95%CI]: 1.10 [8.87 – 1.40]; ezetimibe controlled pool: 8.4 (alirocumab) versus 7.3 (ezetimibe) patients per 100 patient years, HR [95%CI]: 1.31 [0.85 – 2.02]. The difference was mainly due to a higher incidence of pruritus in the alirocumab groups. There were no consistent differences between groups in other TEAEs. The AEs seen in the alirocumab groups included nummular eczema, urticaria, and hypersensitivity vasculitis.

8.4.5.3. Neurological events

Neurological events, focussing on myelin sheath related disorders, were reviewed due to cholesterol being a major component of cellular membranes and myelin. The incidence of AEs related to neurologic events were similar in both the placebo and ezetimibe controlled pools – (placebo controlled pool: 3.5% (alirocumab) versus 3.5% (placebo), HR [95%CI]: 0.98 [0.68 – 1.41]; ezetimibe controlled pool: 3.4% (alirocumab) versus 2.4% (ezetimibe), HR [95%CI]: 1.43 [0.76 – 2.69]. Isolated rare and serious AEs reported in the alirocumab group were: optic neuritis, Miller-Fisher syndrome, demyelination and transverse myelitis.

8.4.5.4. Neurocognitive disorders

Neurocognitive disorders were reviewed due to the recent change in labelling for statins which indicates that memory loss and confusion have been reported with statins and thought to be due to low LDL-C interfering with neurological function. The review of the AE database identified the following AEs of interest: deliria (including confusion), cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders.

In the placebo controlled pool: neurocognitive events were reported in 21 (0.8%) patients in the alirocumab group and 9 (0.7%) in the placebo group (HR [95% CI]: 1.18 [0.54 – 2.58]; in the ezetimibe controlled pool: 8 (0.9%) patients in the alirocumab group and 6 (1.0%) in the ezetimibe group, (HR [95% CI: 0.95 [0.32 – 2.74]). There was no imbalance between the treatment groups for any specific event.

8.4.5.5. Diabetes mellitus

Diabetes related events were reviewed because of the role of PCSK9 and LDLR in glucose homeostasis and a concern that the LDLR up regulation on pancreatic beta cell may adversely impact its function and glycaemic control.

Incidence rates for AEs related to diabetes were similar in the alirocumab group versus the control groups in both the placebo controlled and ezetimibe controlled pools. The incidence rates per 100 patient years were 3.0 versus 2.8 in the alirocumab and placebo groups, respectively, (HR [95% CI]: 1.05 [0.72 - 1.53]) and 2.3 in the alirocumab group and 3.7 in the ezetimibe group, with HR (95% CI): 0.60 (0.31 - 1.19).

8.4.5.6. Hepatic disorders

AEs related to hepatic disorders were similar in the treatment groups. In the placebo controlled pool: incidence rate per 100 patient-years of 2.2 (95% CI: 1.7 - 2.8) in the alirocumab group and 1.6 (95% CI: 1.0 - 2.4) in the placebo group (HR [95% CI]: 1.36 [0.84 - 2.20]; in the ezetimibe controlled pool: the incidence rates were 2.2 (95% CI: 1.3 - 3.6) in the alirocumab group and 3.1 (95% CI: 1.7 - 5.1) in the ezetimibe group (HR [95%CI]: 0.69 [0.34 - 1.43]). The observed incidence rates are consistent with the patient population who are mostly on concomitant statins and many who were obese.

8.5. Laboratory tests

8.5.1. Liver function

In the placebo controlled pool, no relevant changes over time up to Week 52 including last, or worst (lowest or highest) on-treatment value in the placebo-controlled pool and up to Week 24 including last, or worst (lowest or highest) on-treatment value in the ezetimibe-controlled pool were observed for ALT, AST, ALP, GGT, total bilirubin, and LDH.

It is noted that almost all patients in the placebo-controlled pool and the vast majority of patients in the ezetimibe-controlled pool were receiving statin as background therapy (about 80% in the alirocumab group and about 72% in the ezetimibe group). In addition, about half the patients were receiving high doses of statin as background therapy, which are known to cause elevation in transaminases, generally of moderate intensity.

It is noted that there were slightly more patients in the alirocumab group who had ALT increased > 3 ULN compared to placebo; however there was an opposite trend observed for ALT increased > 5 ULN. No case of confirmed Hy's law was identified. In the ezetimibe controlled pool, there were 10 cases of ALT increase > 3 ULN were observed (9 in the alirocumab group and 1 in the ezetimibe group).

8.5.2. Kidney function

There were no relevant changes over time up to Week 52 including last, or worst (lowest or highest) on-treatment value in the placebo-controlled pool and up to Week 24 including last, or worst (lowest or highest) on-treatment value in the ezetimibe-controlled pool for creatinine, BUN, eGFR, or urates.

8.5.3. Other clinical chemistry

No clinically significant differences over time were observed up to Week 52 including last, or worst (lowest or highest) on-treatment value between in either the placebo controlled pool or the ezetimibe controlled pool, with the exception of creatine kinase.

8.5.4. Creatine kinase

During the entire treatment emergent period, the percentages of patients with an increase in CK > 3 x ULN and > 10 x ULN were similar between the 2 treatment groups in both the placebo controlled pool and ezetimibe controlled pool.

In the placebo controlled pool, 3 patients in the alirocumab group reported SAEs and 1 patient in the placebo group reported a non serious TEAE. The 3 SAEs in the alirocumab group, all in Study LTS11717 were: 1 case of rhabdomyolysis, 1 case of myositis leading to treatment discontinuation and 1 case of suicide attempt by intentional overdose with propranolol, rosuvastatin, and ezetimibe. In the placebo group, there was 1 case of CK increased which was reported as a non serious event ("increase CK levels with no muscle symptoms") leading to treatment discontinuation. The other patients with increased CK > 10 ULN did not report associated TEAEs.

8.5.5. Haematology

No clinically significant differences over time were observed in haematological parameters up to Week 52 including last, or worst (lowest or highest) on-treatment value between in either the placebo controlled pool or the ezetimibe controlled pool.

8.5.6. Other laboratory tests

Fat-soluble vitamins, cortisol, and gonadal hormone assessment, were only measured in the LTS11717 study. There were no relevant differences between treatment groups for cortisol levels. No relevant changes were observed in the mean changes from baseline for total testosterone, LH, or SHBG. FSH decreased over time to a greater extent in the alirocumab group compared with the placebo group, with a mean change from baseline in the alirocumab versus placebo groups, respectively, as follows: -0.49 versus -0.04 IU/L at Week 12, -0.48 versus -0.03 IU/L at Week 24, and -0.60 versus -0.16 IU/L at Week 52. There were no relevant changes in vitamin A, D, and K and no apparent correlation was observed with calculated LDL-C and vitamins A, D, and K during the study

8.6. Post-marketing experience

Not applicable as the product is not yet marketed in any country.

8.7. Safety issues with the potential for major regulatory impact

8.7.1. Cardiovascular safety

Suspected CV events and all deaths that occurred from time of randomisation until the follow-up visit were adjudicated by a data monitoring committee in all the pivotal efficacy studies. Analyses of the adjudicated events were performed on the global pool, placebo controlled pool, and ezetimibe controlled pool. The data from the adjudication are presented below with the primary focus on MACE events (CHD death, nonfatal MI, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalisation).

8.7.1.1. MACE Events

The adjudicated MACE events composite endpoint occurred in 52 (1.6%) patients in the alirocumab group and in 33 (1.8%) patients in the control group. The incidence rate (per 100 patient-years) was 1.5 and 1.8 in the alirocumab and control groups, respectively, with HR (95% CI): 0.81 (0.52 to 1.25).

Table 61. Positively adjudicated cardiovascular TEAEs: MACE EVENT - global pool of Phase III studies- safety population

Category of adjudication	Control (N=1792) N (%)	Alirocumab (N=3182) N (%)
Any patients with treatment emergent MACE event		
N (%)	33 (1.8)	52 (1.6%)
95% mid-p CI	1.3 to 2.5	1.2 to 2.1

Category of adjudication	Control (N=1792) N (%)	Alirocumab (N=3182) N (%)
Number of patients with an event per 100 patient year	1.8	1.5
95% CI	1.2 to 2.5	1.1 to 1.9
Hazard ratio versus control (95% CI) b		0.81 (0.52 - 1.25)
CHD death (including undetermined cause)	9 (0.5)	8 (0.3)
Non-fatal MI	23 (1.3)	30 (0.9)
Fatal and non-fatal ischemic stroke (including stroke not otherwise specified)	3 (0.2)	12 (0.4)
Unstable angina requiring hospitalisation	1 (<0.1)	2 (<0.1)

Placebo controlled studies: Phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I). Ezetimibe controlled studies: Phase III (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE). n (%) = number and percentage of patients with at least one event. [a] Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period. [b] calculated using a Cox model stratified on the study.

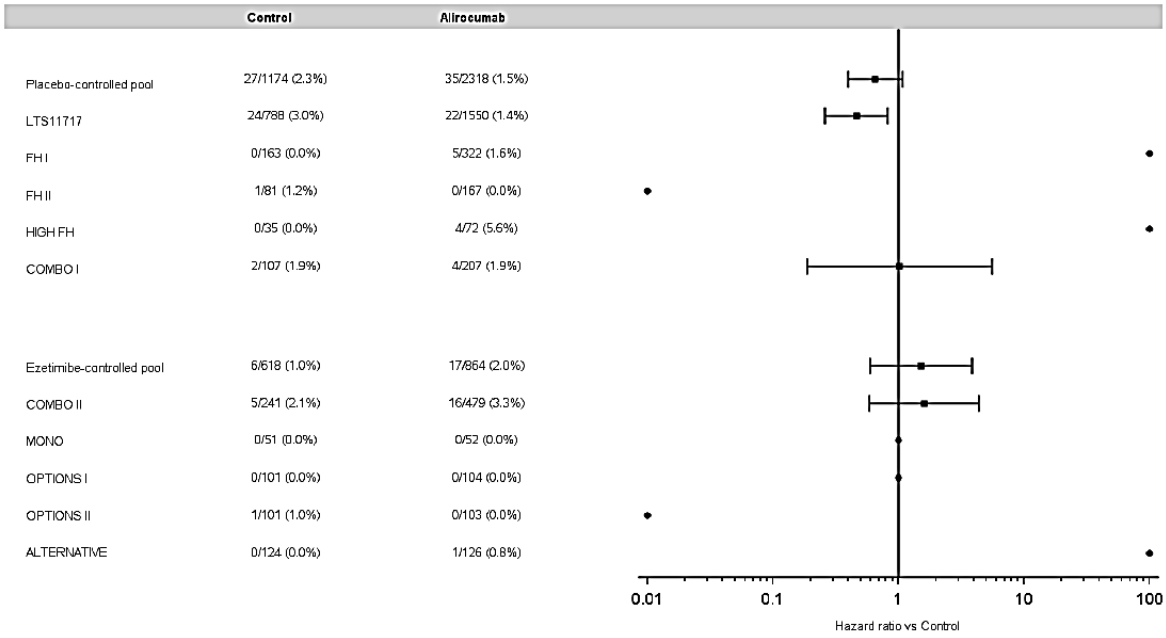
No significant study-by-treatment interaction was identified in the global pool.

Table 62. Positively adjudicated cardiovascular TEAEs: MACE EVENT - summary table according to adjudication (safety population) - pool of Phase III placebo controlled studies and pool of ezetimibe controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
Category of adjudication	Placebo (N=1174) N (%)	Alirocumab (N=2318) N (%)	Ezetimibe (N=618) N (%)	Alirocumab (N=864) N (%)
Any patients with treatment emergent MACE event				
n(%)	27 (2.3)	35 (1.5)	6 (1.0)	17 (2.0)
95% mid-p CI	1.6 to 3.3	1.1 to 2.1	0.4 to 2.0	1.2 to 3.1
Number of patients with an event per 100 patient year [a]	1.9	1.3	1.3	2.3
95% CI	1.3 to 2.8	0.9 to 1.7	0.5 to 2.8	1.4 to 3.7
Hazard ratio versus control (95% CI) [b]		0.65 (0.40 to 1.08)		1.51 (0.59 to 3.85)
CHD death (including undetermined cause)	7 (0.6)	6 (0.3)	2 (0.3)	2 (0.2)
Non-fatal MI	19 (1.6)	17 (0.7)	4 (0.6)	13 (1.5)
Fatal and non-fatal ischemic stroke (including stroke not otherwise specified)	2 (0.2)	11 (0.5)	1 (0.2)	1 (0.1)
Unstable angina requiring hospitalisation	1 (<0.1)	1 (<0.1)	0	1 (0.1)

Placebo-controlled studies: Phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I). Ezetimibe-controlled studies: Phase III (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE). N (%) = number and percentage of patients with at least one event. [a] Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period. [b] calculated using a Cox model stratified on the study.

Figure 35. Positively adjudicated cardiovascular TEAEs: MACE EVENT - Forest plot of hazard ratio versus control by study (safety population) - pool of Phase III placebo controlled studies and pool of ezetimibe controlled studies



Placebo controlled studies: Phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I). Ezetimibe controlled studies: Phase III (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE). Studies with no event in at least one treatment group are conventionally displayed as follows: dot at HR=1 in case of no event in both groups, dot at right extremity in case of 0 event in control arm, dot at left extremity in case of 0 event in alirocumab arm.

The sponsor conclusion on this data is as follows:

"Firm conclusions on the effect of alirocumab on CV morbidity and mortality cannot be drawn from these data. This effect on cardiovascular morbidity and mortality is being further evaluated in the ongoing OUTCOMES study. The primary endpoint of this study is adjudicated MACE events."

8.7.2. Immunogenicity

Serum samples for immunogenicity assessment were collected in all studies. The ADA response was generally assessed at baseline, during the treatment, and after the last alirocumab administration.

In the clinical pharmacology studies, including both healthy subjects and subjects with hypercholesterolaemia, positive low titre responses in the ADA assay were observed in a few subjects at baseline, suggesting a pre-existing reactivity. At the 75 mg dose and 150 mg dose, 22.4% and 16.7% of the subjects were positive in the ADA assay, respectively. Most of the ADA positive samples exhibited a low titre response (≤ 240), except for a few subjects who presented titres up to 1,920. However, titres diminished over time and were not associated with any specific safety findings.

Across all pivotal efficacy studies, pre-existing reactivity was observed in 1.1% of patients from the control group and 1.4% of patients from the alirocumab group. Treatment emergent positive ADA responses were observed in 4.8% of patients in the alirocumab group and in 0.6% of patients in the control group. Most of these treatment emergent ADA responses (63%) in the alirocumab group were classified as transient responses. The median time to the onset of treatment emergent ADA response was 12 weeks (first post-baseline ADA assessment in most studies) in the alirocumab group. The incidence of treatment emergent ADA response was similar according to up-titration status.

Most of the ADA positive samples exhibited low titres (≤240). A few patients (21/3033) had an ADA response with maximum titres above 240 (and up to 3840), but ADA responses in these patients were either negative or exhibiting lower titres at subsequent visits.

ADA status was not identified as a significant covariate impacting alirocumab population parameters (Study POH0377). Patients with an ADA positive status did not exhibit any difference in alirocumab exposure compared to patients that were ADA negative.

A few patients (36/3033, 1.2%) exhibited neutralising antibodies (Nab), all of them in the alirocumab group. Most of these patients had only one positive neutralising sample, indicating most patients only exhibited a transient neutralising response. When looking at the durability of this response, only 10 patients (0.3%) had 2 or more NAb positive samples. This does not suggest a correlation between NAb and LDL-C lowering efficacy or safety.

8.7.3. Musculoskeletal related disorders

Musculoskeletal related events have been associated with the use of statins. Musculoskeletal related events were an AE of special interest for a single study (ALTERNATIVE – R727-CL-1119) that specifically enrolled patients with documented statin intolerance. Patients had to have been intolerant based on musculoskeletal AEs to at least 2 statins, including 1 at the lowest starting dose. A control arm of atorvastatin 20 mg was included in the study and this is likely to have limited enrolment to patients willing to accept the possibility of a statin re-challenge, thus excluding patients with a history of severe reactions. It is noted that despite this criteria about 75% of the patients completed the statin arm of the study and approximately80% had not AEs.

Overall in the ALTERNATIVE study, there were fewer patients with skeletal muscle related TEAEs in the alirocumab group than the atorvastatin (HR 0.61 [0.38 to 0.99]) or ezetimibe (HR 0.70 [0.47 to 1.06]) groups. A lower percentage of patients in the alirocumab group (15.9%) discontinued study treatment due to musculoskeletal adverse events as compared to the atorvastatin group (22.2%). Patients in the alirocumab treatment group had a longer time to first occurrence of a skeletal muscle related TEAE than patients in the atorvastatin and ezetimibe groups.

In the other trials, in the placebo-controlled pool, 15.1% patients in the alirocumab group versus 15.4% patients in the placebo group experienced a skeletal muscle related TEAE. The rate of patients who experienced a skeletal muscle related TEAE leading to permanent treatment discontinuation was 0.4% in the alirocumab group and 0.5% in the placebo group.

8.7.4. Safety profile in patients achieving very low LDL-C

In the global pool, a total of 1,371 (41.0%) patients treated with alirocumab had at least 1 value of LDL- C < 25 mg/dL (< 0.65 mmol/L) and 796 (23.8%) patients had 2 consecutive values of LDL-C < 25 mg/dL (< 0.65 mmol/L) or < 15 mg/dL (< 0.39 mmol/L). These mostly occurred in the studies involving only the 150 mg Q2W dose. The overall rate of patients with at least 1 TEAE, treatment emergent SAE, TEAE leading to death, and TEAE leading to treatment discontinuation was comparable between patients with 2 consecutive values of LDL-C < 25 mg/dL and 2 consecutive values of LDL-C < 15 mg/dL (< 0.39 mmol/L) and the overall alirocumab patient population, as well as the control group. No meaningful differences were observed in neurological or neurocognitive AEs between alirocumab-treated patients and alirocumab-treated patients having reached either 2 consecutive values of LDL-C < 25 mg/dL or 2 consecutive values < 15 mg/dL (< 0.39 mmol/L).

8.8. Other safety issues

8.8.1. Safety in special populations

No relevant safety issues were identified in any special populations.

8.9. Evaluator's overall conclusions on clinical safety

The safety database for alirocumab is based on a large number of patients (3,340 subjects) but because most of the studies have been reported early, after only 24 to 52 weeks on therapy, there is not a large dataset of subjects who have been treated long term. This is especially true when evaluating the cardiovascular safety and the sponsor's requests for a very broad indication including monotherapy.

No specific safety issues were identified in the clinical trials and the only expected AEs are likely to be injection site reactions, pruritus and influenza. General allergic events were more frequently reported in patients treated with alirocumab compared to the pooled control group and the most common AE was pruritus. Rare and sometimes serious allergic reactions (fpr example, hypersensitivity, nummular eczema, urticaria, and hypersensitivity vasculitis) were reported in patients taking alirocumab.

The incidence of the skeletal muscle-related AEs was similar between treatment groups (15.1% of the alirocumab group versus 15.4% of the placebo group). Alirocumab may be an option for patients with documented muscle related statin intolerance who are unwilling to attempt another course of statin therapy.

Treatment-emergent neutralising ADA occurred in 36/3,033 (1.2%) alirocumab treated patients and most events of neutralising ADA were transient and did not appear associated with loss of efficacy.

The data suggest that alirocumab is not associated with hepatic effects or muscle related AEs, which are known safety concerns associated with statins. There was no signal for neurocognitive events or worsening diabetes but the studies are not of long enough duration to conclusively exclude.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of alirocumab in the proposed usage are:

- Consistent lowering of LDL-C in all the studies
- No serious safety issues identified to date but long term data is limited.

9.2. First round assessment of risks

The risks of alirocumab in the proposed usage are:

- No conclusion can be made about cardiovascular benefit as the studies are too short and were not planned to investigate cardiovascular events
- Concern about the long term compliance with an injectable medication intended to be given every 2 weeks for an asymptomatic condition
- AEs of injection site reaction, pruritus and influenza
- Other potential risks of neurocognitive disorders, effects on liver enzymes, glycaemic control and ophthalmic disorders have not been excluded.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of alirocumab, given the proposed usage, is favourable.

Alirocumab has consistently demonstrated that it lowers LDL-C greater than placebo in all the clinical studies and there does not appear to be any serious safety concerns that would preclude approval.

There are however a number of crucial issues to address in considering whether alirocumab can be approved for all the indications requested.

The first issue is the approval of a new product class based solely on the efficacy endpoint of a reduction in LDL-C as the surrogate marker for a reduction in cardiovascular disease. This has generally been the accepted endpoint for cholesterol lowering studies for the lipid lowering agents currently on the market. However the statins and more recently ezetimibe have been found in long term studies after drug approval to lead to a reduction in cardiovascular disease (*Cholesterol Treatment Trialists' Collaboration. Lancet 2010;376:1670-81,* and *Cannon CP, et al. 2015*). This then raises the question as to whether a new class of products can be approved based solely on LDL-C without also demonstrating a reduction in CV events. Should a new product be approved which may be used in place of existing therapy without demonstrating the clinical benefit? This question remains controversial.

The adopted EU guideline states: "*Such studies* [clinical benefit] *are not foreseen for the registration of a new HMG-CoA reductase inhibitor. For other medicinal products acting on LDL-C, at least a detrimental effect on mortality and morbidity should be excluded prior to registration. Until clinical trial data are available, it should be specifically mentioned in the SmPC that beneficial effects on mortality and morbidity have not been evaluated.*

Alirocumab is a new class of product and most of the clinical studies have not yet been completed and the long term study is only reporting the first 52 weeks of therapy (600 patients have only completed 18 months of treatment). Only the long term study is investigating the overall mortality and morbidity. A specific study is planned /underway to address cardiovascular events.

While the studies have demonstrated a consistent LDL-C lowering effect, a detrimental CV effect has not yet been excluded as the number of events to date is too low to make any firm conclusions (see safety section). It is therefore not recommended that the product be approved for monotherapy in place of statins. It is also noted that in the statin intolerant study (R727-CL-119 ALTERNATIVE) where the inclusion criteria required patients to have documented statin intolerance to 2 different statin drugs up to approximately70% of patients were able to tolerate 24 weeks of 20 mg atorvastatain.

There has to be a serious concern about abandoning statins for a new drug which has not established long-term safety and CV benefit. The sponsor's conclusion that the data does not allow for firm conclusions means they have not meet the EU Guideline requirement to exclude a detrimental effect on mortality and morbidity.

Until a cardiovascular benefit or lack of a detrimental effect is proved alirocumab should only be recommended for approval for use in combination with "maximally-tolerated" statin doses.

A further issue, not addressed in the submission, is the question of compliance. Compliance in the "real world" is very difficult to measure in a clinical trial as compliance is always better in the clinical trial setting. Patients completed a dosing diary to document compliance with self injection of study drug and generally the results were very good but it is to be expected that this would be much lower when not in a clinical study, especially given the asymptomatic nature of high cholesterol and the only every second week dosing regimen.

The warning on the lack of a demonstrated cardiovascular benefit should be included in the indication.

It is noted that this recommendation is in line with that the sponsor agreed in the USA.

10. First round recommendation regarding authorisation

Based on the clinical data provided in the submission it is recommended that alirocumab be approved but for an amended indication.

Until the CV benefit of alirocumab is proven and given the obvious benefit of the product in reducing LDL-C, it is recommended that alirocumab is approved only for those patients at highest risk, ie familial hypercholesterolaemia and proven cardiovascular disease on maximal existing statin therapy, and the indication be strictly in line with the conditions of the clinical studies in the submission, that is, that the indication should be:

> *"Alirocumab is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolaemia or documented atherosclerotic cardiovascular disease."*

Approval of the other indications sought for example dyslipidaemia, combination with non statins and other lipid lowering therapy should await the completion of the studies to document no detrimental effect and/or to demonstrate a clinical benefit.

11. Second round evaluation of clinical data submitted in response to questions

No clinical questions were raised. The sponsor has provided a number of documents relevant to the clinical evaluation addressing the issues raised in the first round evaluation, one relating to errors in the first round report and the second detailing response to the review of the proposed Product Information.

11.1. Notification of Errors or Omissions in the Clinical Evaluation Report

The first part of this document detailed a number of minor typographical errors which have been corrected. None of these changes alter the conclusions of the first round report.

The second part of the document is a concern about the First round assessment of benefit and risk. The main concern appears to relate to raising the issue about the controversial question of approving a new class of product without conclusive evidence of a lack of a detrimental effect.

This argument is not accepted. The concern is not about the design of the clinical program but the timing of the submission. Most of the studies have been submitted after the primary efficacy has been reached but prior to completion of the full study. Thus, as acknowledged by the sponsor, the long term safety has not been proven.

It was accepted that the product met the EU Guideline as it was recommended for approval in the first round.

It is unclear why the sponsor should have concerns about the issue of surrogate markers and the lack of definitive conclusions about the cardiovascular safety being in the public domain in an AusPAR. It is noted that these issues have also been raised by both the US FDA and the EU evaluations and their similar concerns and conclusions are now available on the respective websites in the reviews and approved

The comments of the sponsor are noted but do not change the comments or recommendations from the first round.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of alirocumab in the proposed usage are unchanged from those identified in the first round assessment of benefits.

12.2. Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of alirocumab in the proposed usage are unchanged from those identified in in the first round assessment of risks.

12.3. Second round assessment of benefit-risk balance

The benefit-risk balance of alirocumab, given the proposed usage, is favourable.

13. Second round recommendation regarding authorisation

Based on the data submitted in response to the first round evaluation report it is recommended that alirocumab be approved with regard to the comments above. The indication should be:

Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- *in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or.*
- *alone or in combination with other lipid-lowering therapies in patients who have documented atherosclerotic cardiovascular disease and are statin-intolerant, or for whom a statin is contraindicated.*

The effect of Praluent on cardiovascular morbidity and mortality has not yet been determined.

14. References

Cholesterol Treatment Trialists' (CTT) Collaborators, Baigent C et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267-78.

Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-81.

Perk J et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *European Heart Journal*. 2012;33(13):1635-701.

Reiner Z et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *European Heart Journal*. 2011;32(14):1769-818.

Stone NJ 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. *Journal of the American College of Cardiology*. 2014;63(25 Pt B):2889-934.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au