European Medicines Agency
SCIENCE MEDICINES HEALTH

12 October 2023
EMA/529151/2023
Committee for Medicinal Products for Human Use (CHMP)

CHMP Extension of indication variation assessment report

Invented name: **Praluent**

International non-proprietary name: alirocumab

Procedure No. EMEA/H/C/003882/II/0078

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA: anti-drug antibody
AE: adverse event
AESI: adverse event of special interest
ANCOVA: analysis of covariance
Apo A-1:   apolipoprotein A-1
Apo B: apolipoprotein B
BW: body weight
CI: confidence interval
cIMT: carotid intima-media thickness test
COVID-19:   coronavirus disease 2019
CPK-MB: creatine phosphokinase MB
CSR: clinical study report
CVD: cardiovascular disease
DB: double-blind
DBP: diastolic blood pressure
DHEAS: dehydroepiandrosterone sulfate
EMA: European Medicine Agency
FH: familial hypercholesterolemia
FMD: flow mediated dilatation
FSH: follicle stimulating hormone
HDL-C: high density lipoprotein cholesterol
heFH: heterozygous familial hypercholesterolemia
hoFH: homozygous familial hypercholesterolemia
hs-CRP: high sensitivity C-reactive protein
IMP: investigational medicinal product
ITT: intent-to-treat
LDL-C: low-density lipoprotein cholesterol
LDL-R: low-density lipoprotein receptor
LDLRAP1:   LDL receptor adaptor protein 1
LH: luteinazing hormone
LLN: lower limit of normal
LLOQ: lower limit of quantification
LLT: lipid-lowering therapy
LMT: lipid modifying therapy
Lp(a):   lipoprotein (a)
mAB: monoclonal antibody
MMRM: mixed-effect model with repeated measures
mRNA: messenger ribonucleic acid
non-HDL-C: non-high density lipoprotein cholesterol
OL: open-label
PCSK9:   proprotein convertase subtilisin kexin type 9
PD: pharmacodynamic
PK: pharmacokinetic
PT: preferred term

Q2W:	every 2 weeks
Q4W:	every 4 weeks
SAE:	serious adverse event
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SD:	standard deviation
SE:	standard error
STAP1:	signal transducing adaptor family member 1
TG:	triglyceride
Total-C:	total-cholesterol
ULN:	upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Winthrop Industrie submitted to the European Medicines Agency on 2 February 2023 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of paediatric patients 8 years of age and older with heterozygous familial hypercholesterolemia (HeFH) as an adjunct to diet, alone or in combination with other LDL-C lowering therapies, based on final results from study EFC14643 listed as a category 3 study in the RMP; this is a randomized, double-blind, placebo-controlled study followed by an open-label treatment period to evaluate the efficacy and safety of alirocumab in children and adolescents with heterozygous familial hypercholesterolemia. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.0 of the RMP is also submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0550/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0550/2021 was completed. The PDCO issued an opinion on compliance for the PIP P/0550/2021.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Vrijlandt   Co-Rapporteur: Alar Irs

Timetable	Actual dates
Submission date	2 February 2023
Start of procedure	25 March 2023
CHMP Rapporteur Assessment Report	17 May 2023
PRAC Rapporteur Assessment Report	25 May 2023
PRAC members comments	31 May 2023
CHMP Co-Rapporteur Assessment	1 June 2023
PRAC Outcome	8 June 2023
CHMP members comments	12 June 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 June 2023
Request for supplementary information (RSI)	22 June 2023
CHMP Rapporteur Assessment Report	20 September 2023
CHMP members comments	2 October 2023
Updated CHMP Rapporteur Assessment Report	5 October 2023
CHMP Opinion	12 October 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Familial hypercholesterolemia (FH), which includes heterozygous and homozygous forms, is an inherited disorder of lipid metabolism, characterized by severely elevated levels of LDL-C leading to premature atherosclerosis and CVD.

State the claimed therapeutic indication

In the current variation, a modified indication is proposed by the Applicant to include one new paediatric indication in paediatric patients 8 years of age and older with heterozygous familial hypercholesterolemia (HeFH) as an adjunct to diet, alone or in combination with other LDL-C lowering therapies, based on final results from study EFC14643 listed as a category 3 study in the RMP.

The claimed indication that is now under assessment reads as follows (in **bold** the proposed extensions of the indication):

Primary hypercholesterolaemia and mixed dyslipidaemia

Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, **and in paediatric patients 8 years of age and older with heterozygous familial hypercholesterolaemia (HeFH)** 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 are statin-intolerant, or for whom a statin is contraindicated.

Established atherosclerotic cardiovascular disease

Praluent is indicated in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,

- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1.

Epidemiology

The disorder has a high prevalence in Caucasian populations, where an estimated 1 in 250 individuals are affected.

Biologic features, Aetiology and pathogenesis

Defects in at least 3 different genes that code for proteins involved in hepatic clearance of LDL-C can cause FH. These include mutations in the gene coding for the LDL-R that removes LDL-C from the circulation, and less commonly, in the gene for Apo B, which is the major protein of the LDL-C particle. In rare cases, the gene coding for PCSK9, an enzyme involved in degrading the LDL-R (gain of function mutation), is mutated. Additionally, rare mutations in LDLRAP1, a protein which interacts with the LDL-R or STAP1 gene have been noted. In all cases, these mutations result in an accumulation of LDL-C in the plasma from birth, and subsequent development of tendon xanthomas, xanthelasmas, atheromata, and CVD. Although genetic testing is useful in the diagnosis of HeFH, it is not without limitations. There are patients who have clinical FH but no known genetic basis for HeFH. Five to 30% of cases of phenotypic FH may arise from mutations in unidentified genes or have a polygenic cause. Accordingly, this program allowed for patients to be included with either a clinical diagnosis or a genetic diagnosis of HeFH.

Clinical presentation, diagnosis and stage/prognosis

Familial hypercholesterolemia is well recognized for developing cardiovascular consequences beginning in childhood. Even though cardiovascular events are rare in childhood, children with HeFH already have functional and morphological changes of the vessel wall as illustrated by an impaired FMD of the brachial artery and an increased cIMT, with a progression rate for cIMT of approximately double to that observed in unaffected siblings. Both are surrogate markers for atherosclerotic vascular disease and, thus, indicate that the atherosclerotic process has already been initiated early in childhood. Indeed, there is now strong evidence that lesions of atherosclerosis found in adults begin in childhood and are progressive throughout the life span. These findings suggest that to be effective at preventing CHD, prevention, by lowering LDLC, must begin decades prior to the onset of symptoms.

Because of the high risk of progression to premature clinical CVD associated with these findings, paediatric guidelines recommend LDL-C lowering intervention and specific lipid targets for children and adolescents with HeFH. An LDL-C level of <130 mg/dL (3.37 mmol/L) is considered acceptable and <110 mg/dL (2.84 mmol/L) ideal for children with HeFH, or the achievement of ≥50% reduction in LDL-C.

Management

Available lipid lowering therapies for children with HeFH include:

- **Statins** (oral tablets): Statins has been approved for the treatment of paediatric patients 6 to 17 years of age with HeFH. According to the 2019 ESC/EAS guideline for the management of dyslipidaemias, statin treatment (in combination with a heart-healthy diet) should be considered at >8 years of age. Statin treatment should be started with low doses and the dose should be increased to reach therapeutic goals. The therapeutic goal in children >10 years of age is an LDL-C <3.5 mmol/L (<135 mg/dL) and at younger ages a >50% reduction of LDL-C.

- **PCSK9 inhibitors** (injectable monoclonal antibody or siRNA): Evolocumab, another PCSK9 inhibitor monoclonal antibody (mAb), has been approved for the treatment of paediatric patients 10 to 17 years of age with HeFH.

- **Ezetimibe** (oral tablets): Ezetimibe is not indicated for the paediatric HeFH population. According to the labeling of Ezetrol (ezetimibe), the safety and efficacy of ezetimibe in children aged 6 to 17 years has not been established; available data are described in the SmPC, however, no recommendation on a posology can be made.

- **Apheresis** is a non-pharmacological treatment option; a single treatment reduces LDL-C by 55%-70% relative to pre-treatment levels. However, apheresis may be burdensome and limited available. Also, only temporal reduction in LDL-C is achieved.

Some patients, especially those with high LDL-C, are unable to achieve recommended LDL-C levels. Not surprisingly, many patients with FH cannot achieve recommended goals despite using maximum doses of statin (in combination with ezetimibe), further emphasizing the need for additional treatment options.

2.1.2. About the product

Alirocumab (also referred to as Praluent, SAR236553 and REGN727) is a fully human monoclonal antibody that binds with high affinity to proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 binds to low-density lipoprotein receptor (LDL-R) and promotes the internalization and removal of LDL-R on hepatocytes. The increased degradation of LDL-Rs leads to a reduced LDL-C removal and, therefore, higher LDL-C circulating levels. By blocking PCSK9 from binding to LDLR, alirocumab increases the number of LDL-R available for removing LDL-C from circulation. Hence, alirocumab is an effective treatment for lowering LDL-C and reducing the risk for CVD.

Alirocumab was approved in the EU on 23 September 2015. In the initial submission, alirocumab had demonstrated a substantial and consistent reduction in LDL-C (a surrogate biomarker for cardiovascular risk reduction) and other lipid parameters as add-on to statins, with or without other lipid modifying therapies (LMTs), in patients with primary HeFH and non-FH, including patients with mixed dyslipidaemia and diabetic patients, either as monotherapy or as add-on to their existing non-statin LMT, including patients with statin intolerance.

Based on these observations, alirocumab was indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in combination with the maximum tolerated dose of a statin with or without other LLTs or, alone or in combination with other LLTs in patients who are statin-intolerant, or for whom a statin is contraindicated. At the time of the initial MA, a statement was included in Section 4.1 of the EU SmPC that the effect of alirocumab on cardiovascular morbidity and mortality has not yet been determined, as the outcome study, ODYSSEY OUTCOMES (EFC11570), was ongoing. In 2018, the MAH submitted the results of ODYSSEY OUTCOMES study to extend the indication with the reduction in risk of cardiovascular events in adults with established cardiovascular disease (CVD) (EMEA/H/C/003882/II/0042).

The **current approved** indication reads as follow:

Primary hypercholesterolaemia and mixed dyslipidaemia

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 are statin-intolerant, or for whom a statin is contraindicated.

Established atherosclerotic cardiovascular disease

Praluent is indicated in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,

- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Paediatric investigation plan

The current Paediatric Investigational Plan was approved on 31 December 2021 (Decision P/0550/2021).The Sponsor committed to complete the PIP by September 2023. The paediatric development plan in HeFH includes 2 clinical studies in children and adolescents 8 to 17 years of age with HeFH (**Table 1**): a Phase 2 dose-escalating study (DFI14223) and a Phase 3 efficacy and safety study (EFC14643) that is the subject of the present submission.

A Phase 3 clinical efficacy and safety study in children and adolescents 8 to 17 years of age with hoFH (EFC14660) has also been conducted and is referred to in this submission to complement safety analysis.

The completed paediatric development program is in line with the approved EU PIP (PIP decision number P/0550/2021) as also indicated by the completed **full compliance check**.

Of note, both DFI14223 and EFC14660 studies are part of the EU-PIP and have already been submitted in EU. EFC14643 study is also part of the EU-PIP.

Table 1. Clinical studies for alirocumab

Paediatric PK Studies

Age group	Type of Study	Comments	Deferral Request Planned for the Study (Y/N)
0 – 8 years	Waiver accepted	The most recent paediatric guidelines recommend the start of drug therapy as young as 8 years of age in children and adolescents with heFH	
8 - ≤18 years	Phase 2 dose-escalating PK/PD	Study DFI14223: to evaluate efficacy, safety, and pharmacokinetics in order to support appropriate dose selection for the Phase 3 studies	Y

Clinical Effectiveness and Safety Studies

Age group	Type of Study	Comments	Deferral Request Planned for the Study (Y/N)
0 – 8 years	Waiver accepted	The most recent paediatric guidelines recommend the start of drug therapy as young as 8 years of age in children and adolescents with heFH	
8 - ≤18 years	Efficacy and safety in heFH patients (R, DB, PC)	Study EFC14643: 6-month DB efficacy study to evaluate effect of alirocumab on LDL-C levels versus PBO followed by 18-month OLE	Y
8 - ≤18 years	Efficacy and safety in hoFH patients (OL)	Study EFC14660: 12-month open label efficacy and safety of alirocumab	Y

PK = pharmacokinetics; PD = pharmacodynamics; R = randomized; DB = double blind; PC = placebo-controlled; OL = open label; OLE = open label extension; PBO = placebo; heFH = heterozygous familial hypercholesterolemia; hoFH = homozygous familial hypercholesterolemia

2.1.4. General comments on compliance with GCP

The studies used as a basis for clinical data presented in this dossier were conducted in compliance with Good Clinical Practice (GCP), as required by the ICH E6 Guideline for Good Clinical Practice. The studies also meet with the requirements of the Declaration of Helsinki, standard operating procedures for clinical investigations and documentation of the Sponsor, applicable national laws and regulations and the ethical principles of the Directive 2001/20/EC.

2.2. Quality aspects

Praluent for paediatric use

The drug product is a solution for injection consisting of L-histidine and L-histidine monohydrochloride and monohydrate, sucrose, polysorbate 20 and water for injection.

The presentation used for administration in paediatric patients 8 years of age and older is the Praluent 75 mg, 150 mg or 300 mg pre-filled pen. The Praluent pre-filled pens that will be used for the paediatric population are identical to the ones that are used for the adult population. With regards to the excipients, no safety issues are foreseen for the paediatric population. The administered volume will be 1mL or 2mL per injection site , once every 2 or 4 weeks.

With regards to needle length, the same Pre-filled pen as used for the adult population will be used for the paediatric population. It is stated by the applicant that due to the differences in the skin and subcutaneous tissue thickness between paediatric patients (8- <12 years of age) and adolescents/adults, the risk of intramuscular injection is higher for paediatric patients. To mitigate this risk, the applicant added an instruction to the Instructions for Use (IFU) for a skin pinch at the injection site to increase the subcutaneous tissue area prior to and during the injection of paediatric patients. This information is particularly emphasized for children under 12 years of age.

A NBOp is only required if there is a change to the design or intended purpose of the device (part), or if a new device is introduced. That is not the case with this extension of the indication to include paediatric patients. The same pre-filled pen will be used and the inclusion of the paediatric population does not constitute a change to the intended purpose of the device, as it will still be used for subcutaneous injection. It is agreed with the applicant that there is no need for a NBOp for this application.

Supplemental Human Factors Evaluation Summary for Extension of Intended User Population for Alirocumab Pre-filled Pen for Adolescent (12-17 years of age) and Paediatric Patients (8 to <12 years of age)

The applicant has conducted a human factors (HF) engineering program for the extension of the Praluent (alirocumab) pre-filled pen (PFP) for treatment of heterozygous familial hypercholesterolemia (HeFH) in adolescent patients (12 to17 years of age) and paediatric patients (8 to <12 years of age). This section contains a summary of the supplemental human factors validation study (sHFVS) conducted to support the indication extension and a summary of the HF engineering program with all activities including details of the sHFVS.

The Praluent (alirocumab) PFP was originally developed using the design control process for the treatment of HeFH in adult patients administered either by the patient, healthcare professional (HCP) or lay caregiver. The user interface for the 75mg and 150mg Praluent (alirocumab) PFP was validated in a summative human factors study.

The intent is to extend the intended users for the alirocumab PFP to include adolescent patients (12-17 years of age) and paediatric patients (8 -< 12 years of age).

Adolescent patients (12-17 years of age), if deemed capable by the HCP, are expected to self-administer the product under adult supervision and for paediatric patients (8-<12 years of age) the injection should be administered by an HCP or lay caregiver. Due to the differences in the skin and subcutaneous tissue thickness between paediatric patients (8- <12 years of age) and adolescents/adults, the risk of intramuscular injection is higher for paediatric patients. To mitigate this risk, the applicant added an instruction for a skin pinch (pinch a fold of skin at the injection site to increase the subcutaneous tissue area) prior to and during the injection of paediatric patients 8 to <12 years of age to the Instructions for

Use (IFU). The purpose of the supplemental HF Validation study was to validate that the Praluent (alirocumab) PFP user interface including the IFU (including skin pinch instructions) supports safe and effective use in the extended user populations, self-injection adolescent patients and lay caregivers of paediatric patients. The 150 mg Praluent (alirocumab) PFP was used for the supplemental HF Validation Study (sHFVS). As both the 75 mg and 150 mg Praluent (alirocumab) doses are in a 1mL PFP and the tasks of use are the same for both, the 150 mg dose was used in the sHFVS.

Study Design

The sHFVS was conducted involving certain number of participants who were representative of the intended users (adolescent HeFH patients (12-17 years of age) accompanied by a caregiver, injection experienced lay care givers of HeFH paediatric patients ((8-11 years of age) and injection naïve lay caregivers of HeFH paediatric patients. Prior to the study, the critical tasks were identified based on comprehensive task and risk analyses. Definitions of success or failure in the user performance of each critical task were established prior to the study based on the task analysis and the risk analysis.

During study execution, participants completed the following scenarios in test environment representative of a home environment:

• Scenario 1a: Injection Task - IFU Use Optional. Participants were given a Praluent (alirocumab) product carton containing 2 PFPs and IFU and asked to perform injection into an injection pad as they would at home while moderator observed. Participants/participant pairs were allowed to use the IFU if they chose to do so, but the moderator did not mention the IFU or direct the participant(s) to use it during the injection tasks. If moderator observed incorrect use, the participant/participant pair moved to Scenario 1b and asked to complete another injection using another Praluent (alirocrumab) PFP. If moderator observe correct use, participants moved to Scenario 2.

• Scenario 1b: Injection Task- IFU Use Optional. Participants were asked to perform injection into an injection pad as they would at home while moderator observed using the remaining Praluent (alirocumab) PFP in the carton from Scenario 1a. Participants/participant pairs were allowed to use the IFU if they chose to do so, but the moderator did not mention the IFU or direct the participant(s) to use it during the injection tasks.

• Scenario 2: Injection Task IFU Mandatory. Participants were given a Praluent (alirocumab) product carton containing 2 PFPs and IFU and asked to perform injection into an injection pad following the IFU step-by-step.

• Scenario 3: Knowledge task questions (KTQs). Moderator asked participant questions related to safety and critical information contained in the IFU. Participants were instructed to use the IFU to answer questions.

Observation and interview data were collected, focusing on incorrect use (including task failures) and use difficulties. After performing all the use tasks in the study, each participant was interviewed to obtain his or her subjective perspective on any incorrect use or other problems that occurred. The occurrences of all incorrect use and other use problems on critical tasks were analyzed to identify the root causes and determine the need to implement additional risk controls.

Study Results

The data generated from the sHFVS demonstrate that the Praluent (alirocumab) PFP user interface including the IFU can be used safely and effectively by adolescents (12-17 years of age) under adult supervision and by lay caregivers to administer Praluent (alirocumab) to paediatric patients 8 to <12 years in the home environment.

<u>Conclusion</u>

The study results were consistent with those of the previous alirocumab PFP human factors validation study for adult patient populations. Thus, the Sponsor concludes that the sHFVS data did not identify any patterns of use errors or task failures that would result in harm or incorrect dose administration, and the results of the sHFVS demonstrate that the Praluent (alirocumab) PFP 75 mg and 150 mg user interface, including the revised IFU, supports safe and effective use of the Praluent (alirocumab) PFP by the intended users, for the intended use, in the intended use environment.

The applicant concluded from the results of the Human Factors Evaluation study that Praluent, with the revised Instructions for use can be used safely and effective by the paediatric population. This conclusion was initially not entirely supported. For paediatric patients 8-11 years of age, the injection should be administered by an HCP or lay caregiver. The skin should be pinched in order to increase the subcutaneous tissue area and to mitigate the risk of intramuscular injection. For this purpose, in the Instructions for use a sentence is added stating that "Pinching of the skin before and during the injection is required in children less than 12 years of age." During the HF study, the most common use error observed was lay caregivers not pinching the skin at the injection site prior to and during the injection. In 7 out of 15 cases the lay caregiver participants did not pinch the skin at the injection site despite being asked to follow the IFU. Considering the number of times that pinching was not correctly performed the Applicant was requested to amend the Instructions for use to emphasize further the importance of "pinching the skin". In response to this request, the MAH has adapted the Instructions for Use by highlighting the requirement of pinching the skin in children less than 12 years. This adaptation emphasizes the requirement of pinching the skin and was considered acceptable by CHMP.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.4. Clinical aspects

2.4.1. Introduction

- Tabular overview of clinical studies

The Paediatric Investigational Plan was approved on 31 December 2021 (Decision P/0550/2021). The Sponsor committed to complete the PIP by September 2023.

The paediatric development plan includes 3 clinical studies in children and adolescents 8 to 17 years of age (**Table 1**):

- a Phase 2 dose-escalating study (DFI14223 – "An 8-Week Open-Label, Sequential, Repeated Dose- Finding Study to Evaluate the Efficacy and Safety of Alirocumab in Children and Adolescents with Heterozygous Familial Hypercholesterolemia (HeFH) followed by an Extension Phase"). The corresponding final study report was submitted to EMA through a Type II variation (EMEA/H/C/003882/II/0053) on 21 October 2019 and approved through CHMP opinion dated March 2020, without any Product Information update.

- a Phase 3 clinical efficacy and safety study (EFC14660 - "An Open-Label Study to Evaluate the Efficacy and Safety of Alirocumab in Children and Adolescents with Homozygous Familial Hypercholesterolemia (HoFH)"). The corresponding final study report was submitted to EMA

through a Type II variation (EMEA/H/C/003882/II/0059) in August 2020 and approved through CHMP opinion dated 12 November 2020, with Product Information update.

- a Phase 3 clinical efficacy and safety study (EFC14643 - "A randomized, double-blind, placebo controlled study followed by an open label treatment period to evaluate the efficacy and safety of alirocumab in children and adolescents with heterozygous familial hypercholesterolemia (heFH) ") that is the subject of the present Type II variation.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

Alirocumab is a fully human monoclonal antibody that targets proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 is involved in regulating the levels of the low-density lipoprotein receptor (LDL-R) protein. Once PCSK9 is secreted into plasma it directly binds to the LDL-R and promotes its degradation. The increased degradation of LDLRs leads to a reduced low-density lipoprotein cholesterol (LDL-C) removal and, therefore higher LDL-C circulating levels. Therefore, blocking PCSK9 binding to the LDL-R can potentially benefit patients with hypercholesterolemia by decreasing their plasma LDL-C levels.

The currently approved adults posology is:

The usual starting dose for alirocumab is 75 mg administered subcutaneously once every 2 weeks. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg once every 2 weeks, or 300 mg once every 4 weeks (monthly), administered subcutaneously.

The dose of alirocumab can be individualised based on patient characteristics such as baseline LDL-C level, goal of therapy, and response. Lipid levels can be assessed 4 to 8 weeks after treatment initiation or titration, and dose adjusted accordingly (up-titration or down-titration). If additional LDL-C reduction is needed in patients treated with 75 mg once every 2 weeks or 300 mg once every 4 weeks (monthly), the dosage may be adjusted to the maximum dosage of 150 mg once every 2 weeks.

The proposed posology in paediatric patients is:

Table 2: HeFH in paediatric patients 8 years of age and older

Body weight of patients	Recommended dose	Recommended dose if additional LDL-C reduction is needed*
Less than 50 kg	150 mg once every 4 weeks	75 mg once every 2 weeks
50 kg or more	300 mg once every 4 weeks	150 mg once every 2 weeks

* Lipid levels can be assessed 8 weeks after treatment initiation or titration and dose adjusted accordingly.

2.4.2.1. Methods – Study EFC14643

Study EFC14643 included 153 paediatric participants (8 to 17 years of age) with heFH who were randomized to receive alirocumab or placebo intervention. Among participants in the alirocumab groups, 49 participants from the Q2W cohort (25 with body weight (BW) <50 kg and 24 with BW ≥50 kg receiving

40 and 75 mg, respectively) and 48 participants from the Q4W cohort (19 with BW <50 kg and 29 with BW ≥50 kg receiving 150 and 300 mg, respectively) had at least one PK sample collected and assessed during the double blinded treatment period.

Furthermore, participants could have their dose regimen up-titrated or adjusted to 75 mg/150 mg Q2W at Week 12 in the Q2W or the Q4W cohort, respectively. In the Q2W cohort 11 participants were up titrated from 40 mg to 75 mg and 11 participants from 75 to 150 mg. In the Q4W cohort the dose of 5 participants was adjusted from 150 mg Q4W to 75 mg Q2W and 10 participants from 300 mg Q4W to 150 mg Q2W.

- Alirocumab concentration and PCSK9 concentrations

Total serum alirocumab concentrations, as well as total and free PCSK9 concentrations were measured from the same PK sample. Blood samples for were collected at baseline (week 0), week 8, week 12 and week 24. PK samples were analysed for the determination of total alirocumab concentrations (ie, free alirocumab and alirocumab present in PCSK9: alirocumab complexes) using an already validated ELISA (REGN727-AV-11051-SA-01V3). An ISR assessment for the total alirocumab assay was performed with samples from the Phase 2 study (DFI14223) in the paediatric patient population. The assay met the ISR acceptance criteria with a passing rate of 100%, indicating that the assay generated robust data in this population. The PK samples were also analysed for total and free PCSK9 levels using 2 already validated ELISAs, REGN727-AV-11081-VA-01V1 and REGN727-AV-11084-VA-01V2, respectively.

- Sampling for antidrug-antibodies (ADA)

Serum samples for ADA determination were collected at baseline (week 0), week 12, week 24, week 68 and week 104. The ADA samples were analysed using an already validated, titer-based, bridging immunoassay (REGN727-AV-10014-VA-01V3). It involves an initial screen, a confirmation assay based on drug specificity, and a measurement of the titer of anti-alirocumab antibodies in the sample. Samples that were positive in the ADA assay were assessed for neutralizing antibodies using an already validated, competitive ligand binding assay (REGN727-AV-11083-VA-01V2).

- Analytical and statistical methods

The PK of alirocumab in paediatric participants with heFH was assessed using descriptive statistics on C_{trough} collected in the Phase 2 (DFI14223) and Phase 3 (EFC14643) studies.

Each of the bioanalytical methods used to analyse samples from clinical studies DFI14223 and EFC14643 were described in the original marketing application for the adult hypercholesterolemia patient population.

PK and ADA samples from clinical studies DFI14223 and EFC14643 were analysed by the Regeneron Clinical Bioanalysis Group. PK samples were analysed for the determination of total alirocumab concentrations (ie, free alirocumab and alirocumab bound to PCSK9: alirocumab complexes) using an already validated ELISA. The LLOQ for the alirocumab assay is 0.078 µg/mL [REGN727-AV-11051-SA-01V3].

The PK samples were also analysed for total (free PCSK9 + bound PCKS9 to alirocumab) and free PCSK9 levels using two validated ELISAs. The LLOQ is 0.156 µg/mL for the total PCSK9 assay [REGN727-AV-11081-VA-01V1] and 0.0312 µg/mL for the free PCSK9 assay [REGN727-AV-11084-VA-01V2].

An ISR assessment for the total alirocumab assay was performed with samples from the Phase 2 study (DFI14223) in the paediatric patient population. The assay met the ISR acceptance criteria with a passing rate of 100%, indicating that the assay generated robust data in this population.

The ADA samples were analysed using a validated, titer-based, bridging immunoassay. It involves an initial screen, a confirmation assay based on drug specificity, and a measurement of the titer of anti-alirocumab antibodies in the sample. The sensitivity of the assay is approximately 5.6 ng/mL of the monoclonal antibody positive control. The drug tolerance limit is 191 µg/mL of alirocumab at 500 ng/mL of monoclonal antibody positive control (Bioanalytical validation report [REGN727-AV-10014-VA-01V3]).

Samples that were positive in the ADA assay were assessed for neutralizing antibodies using a validated, competitive ligand binding assay (Bioanalytical Validation Report [REGN727-AV-11083-VA-01V2]). The sensitivity of the assay based on a monoclonal antibody positive control was 470 ng/mL. The drug tolerance limit at 500 ng/mL of monoclonal antibody positive control was 547 ng/mL of alirocumab in neat serum.

2.4.2.2. Methods - Population PK analysis in paediatric patients with heFH (POH0925)

- Studies and data included in the model

The PK of alirocumab was also evaluated in a Pop PK analysis in paediatric patients with heFH (POH0925) using pooled data from 2 clinical studies (DFI14223 and EFC14643). For both studies, sparse sampling was used and most of PK points were trough samples. The dataset was composed of 377 PK observations from 140 paediatric patients with heFH.

- Objectives of modelling

The main objective of the Pop PK model was to evaluate the pop PK parameters in children and to use it to predict alirocumab exposures in children with heFH given different dose regimens. For each patient, C_{max}, T_{max}, AUC_{0-336} (for Q2W regimen) or AUC_{0-672} (for Q4W regimen) were estimated after one administration, and at steady state before and after up-titration.

- Model development

Most of sparse PK samples collected in the study being trough concentrations, it was not possible to achieve successful modelling based on the paediatric data alone. Consequently, although a standalone model was planned to be tested, a modelling strategy was implemented that used a previously developed adult population pharmacokinetic model of alirocumab to describe the paediatric data.

The adult reference model was a population PK Michaelis-Menten TMDD model.

This analysis was performed with 2799 subjects and 13717 alirocumab concentrations in adult participants using data from Phase 1, Phase 2, and Phase 3 studies covering different adult populations with primary hypercholesterolemia, including patients with heFH, or with dyslipidemia (described in the original submission). In this pooled dataset, alirocumab was administered as a single dose by IV or SC routes, and after repeated SC administration Q2W or Q4W, alone or in combination with various lipid modifying therapies. The final model used was a 2-compartment model with linear absorption and an additional nonlinear, saturable elimination pathway using Michaelis-Menten kinetics. Age, BW, statin, and free PCSK9 were found to significantly influence alirocumab pharmacokinetics.

The adult Pop PK model (POH0377, described in the original submission) was updated by including allometric scaling (POH0472, see Figure 1). The dataset included the original population PK alirocumab dataset (POH0377) and was expanded with the Phase 3 CHOICE 1 and CHOICE 2 studies, where Q4W dosing regimen were tested, encompassing about 3502 adults and 17 979 PK observations in total.

Figure 1 POH0472 PK model
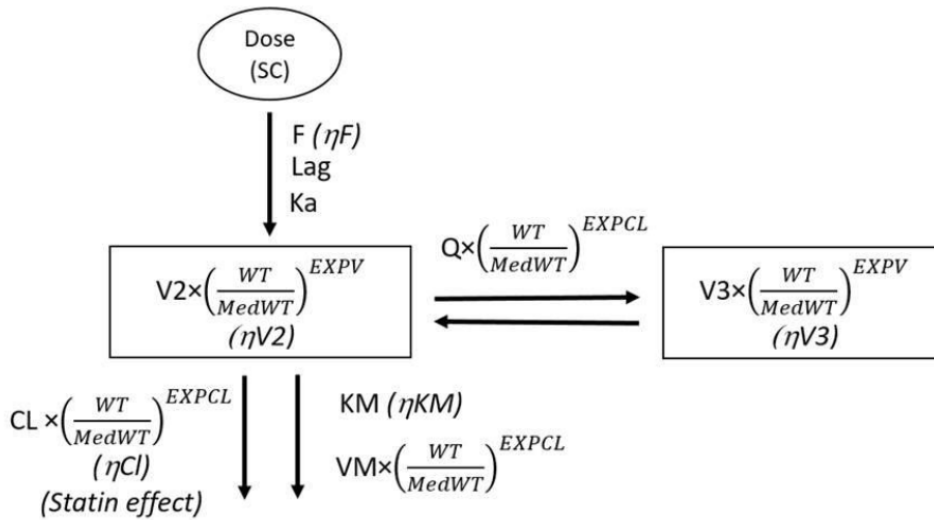
The paediatric data was described using a population pharmacokinetic analysis (POH0925) with Bayesian priors that were based on the adult model (POH0472) priors (using $PRIOR routine in NONMEM). Before doing so, the original POH0472 model was fitted again after removing STATIN covariate influence on CL, because more than 95 % of paediatric patients were co-medicated with statins.

- Covariates

No further covariate search was conducted and the paediatric model was considered to be the final model. The final model parameters are provided in Table 3.

Table 3 Final population PK model parameters

Parameter	Estimate	% RSE	[95%CI]
Typical value for CLL (θ1, L/h) [P]	0.00982	6.25%	[0.00859 ; 0.011]
Typical value for V2 (θ2, L) [P]	2.93	6.11%	[2.57 ; 3.29]
Typical value for KA (θ3, h⁻¹) [P]	0.00844	3.43%	[0.00786 ; 0.00901]
Typical value for V3 (θ4, L) [P]	1.99	5.43%	[1.78 ; 2.21]
Typical value for Q (θ5, L/h) [P]	0.0188	7.32%	[0.0161 ; 0.0216]
Typical value for VM (θ6, mg/h) [P]	0.148	10.80%	[0.116 ; 0.18]
Typical value for KM (θ7,mg/L) [P]	8.61	10%	[6.89 ; 10.3]
Typical value for F (θ8, unitless) [P]	0.669	4.35%	[0.61 ; 0.727]
Typical value for LAG (θ9, h) [P]	0.661	3.59%	[0.613 ; 0.708]
Typical value for EXPCL (θ10, unitless)	0.888	9.80%	[0.714 ; 1.06]
Typical value for EXPV (θ11, unitless)	0.881	20.80%	[0.515 ; 1.25]
Inter-individual variability			
Parameter	Estimate (CV%)	% RSE	[95%CI] (Shrinkage %)
ω^2 CL	0.169 (42.9 %)	7.77%	[0.143 ; 0.195] (42.9 %)
ω^2 V2	0.38 (67.9 %)	6.70%	[0.33 ; 0.429] (69.1 %)
ω^2 V3	0.0694 (26.8 %)	24.20%	[0.0365 ; 0.102] (77.1 %)
Omega Block (KM: V3)	-0.104	26.70%	[-0.158 ; -0.0494]
ω^2 KM	0.262 (54.8 %)	22.40%	[0.147 ; 0.377] (72.3 %)
ω^2 F1	0.36 (65.8 %)	13%	[0.268 ; 0.452] (63.7 %)
Residual variability			
Multiplicative error (θ12)	0.285	9.31%	[0.232 ; 0.339]
Additive error (θ13)	0.816	34%	[0.261 ; 1.37]

%RSE: Percentage of Relative Standard Error (100% * SE / Estimate). 95%CI: 95% confidence interval
θ and ω are the PopPK parameters (θ) and the variance of their associated inter-individual variability (ω²)
For omega block correlation is reported
Parameters with prior are labelled with P

PRED and IPRED values were plotted versus OBS using linear and logarithmic scale (**Figure 2** and **Figure 3**) to evaluate the global quality of the model fitting.

Figure 2 Goodness of fit plot for PRED and IPRED versus observations _Linear scale

Legend: Dash red line: identity line – Blue line: regression line with its confidence interval (grey area)
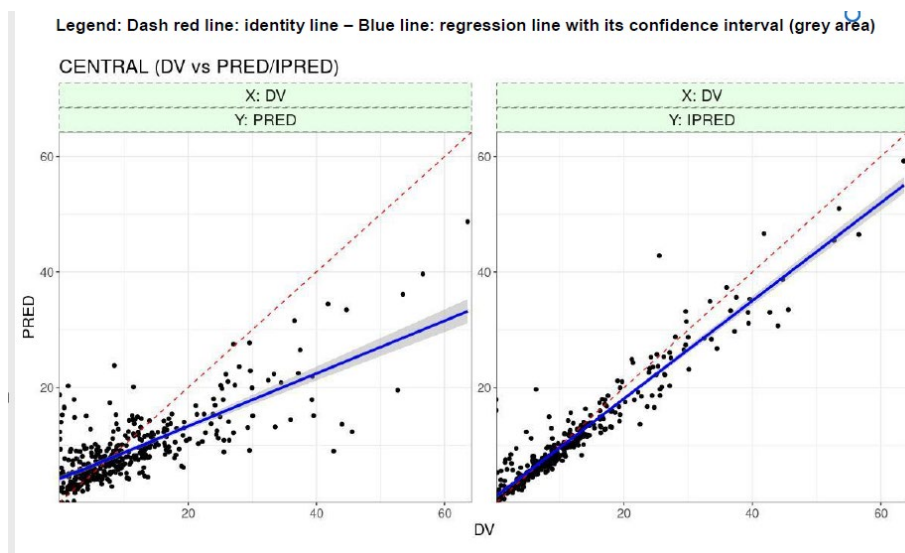
Figure 3 Goodness of fit plot for PRED and IPRED versus observations _Log scale

Legend: Dash red line: identity line – Blue line: regression line with its confidence interval (grey area)
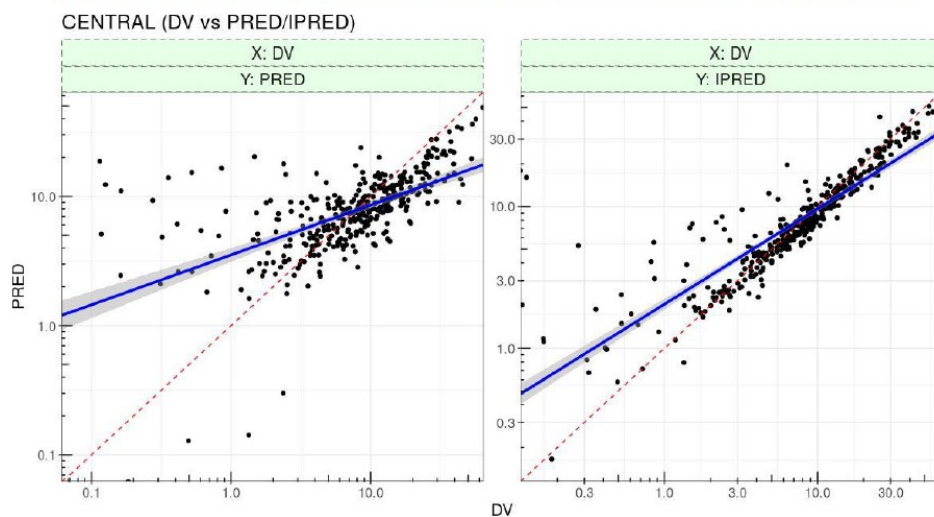
A VPC was used to evaluate the predictive performance of the final model. Results are presented according to the time from first dose in linear and logarithmic scales **Figure 4**.

Figure 4 Visual predictive check results – time after last dose over 20 h

Legend - Black dots: observations; —— and - - -: Median and 90% percentile interval of observations; Blue areas: 90% Prediction interval; Top: linear scale; Bottom: semi-log scale
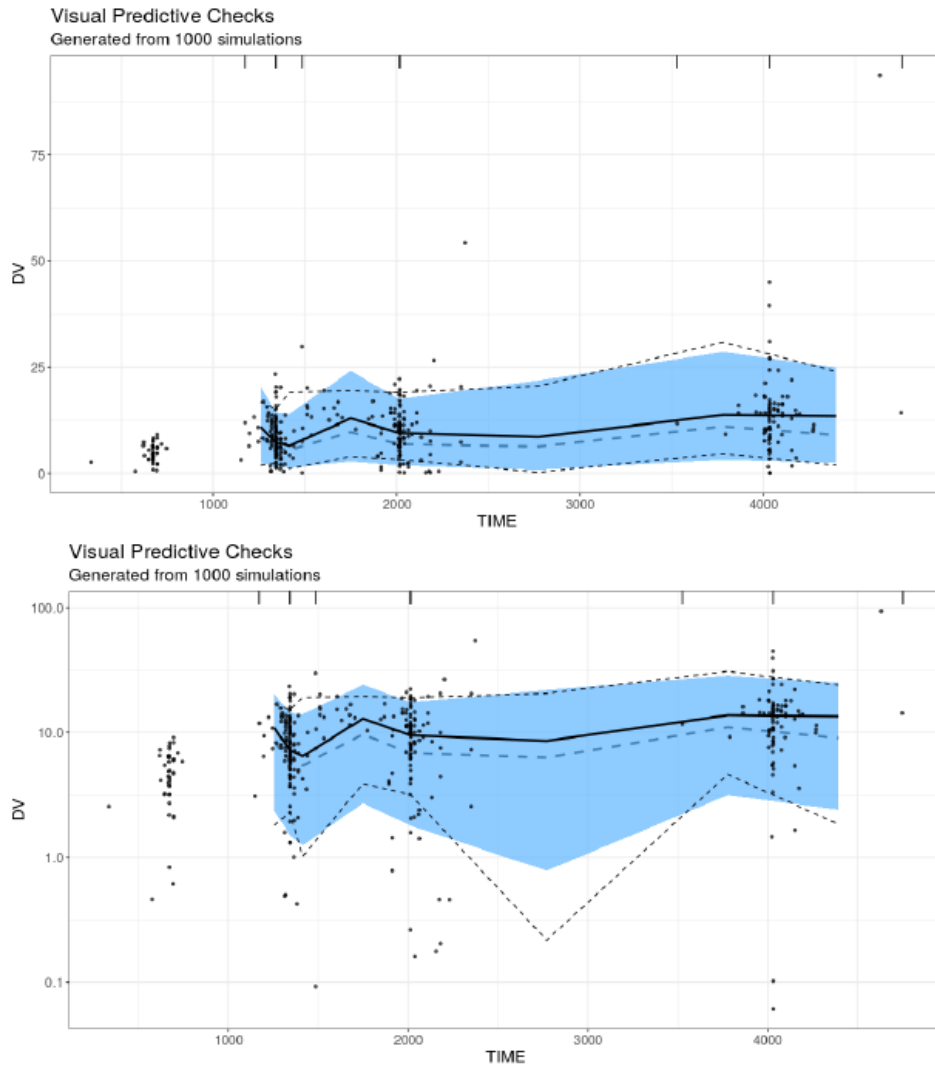
2.4.2.3. Results– Study EFC14643

Pharmacokinetics of total alirocumab

Following administration of alirocumab 40 mg or 75 mg Q2W, and 150 mg or 300 mg Q4W, the mean C_{trough} for total alirocumab are given below in Figure 5, Table 4 and Table 5..

Figure 5 Pivotal efficacy study EFC14643 C_{trough} alirocumab concentrations Mean (±SD) (ng/mL) over time according to up-titration/dose adjustment and BW - Q2W cohort (left) and Q4W cohort (right) - PK population
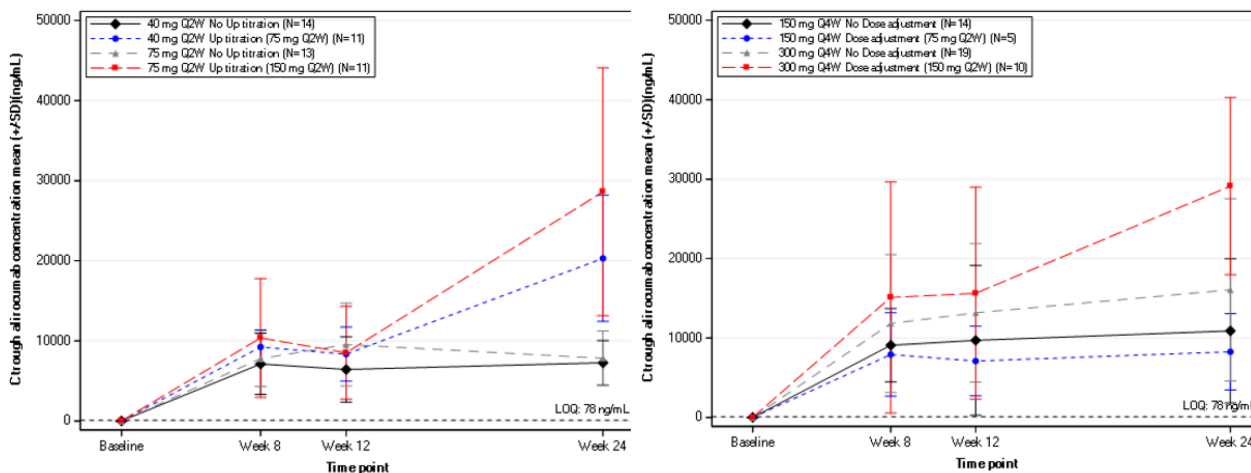
Table 4. C_{trough}, alirocumab concentrations (ng/mL) over time according to up-titration/dose adjustment status as per IVRS and by dose of alirocumab - Double-blind period - Patients in the Q2W cohort - PK population - Patients with at least one injection post-IVRS transaction at Week 12

Alirocumab concentrations Time-point	Alirocumab 40 mg Q2W/up75 mg Q2W		Alirocumab 75 mg Q2W/up 150 mg Q2W	
	Not up-titrated/dose-adjusted (N=14)	Up-titrated/dose-adjusted (N=11)	Not up-titrated/dose-adjusted (N=13)	Up-titrated/dose-adjusted (N=11)
Baseline concentrations (ng/mL)				
Number	14	11	12	11
Mean (SD)	0.0 (0.0)	8.2 (27.1)	0.0 (0.0)	12.5 (41.6)
Median	0.0	0.0	0.0	0.0
Min ; Max	0 ; 0	0 ; 90	0 ; 0	0 ; 138
C_{trough} concentrations (ng/mL)				
Week 8				
Number	14	8	11	8
Mean (SD)	7117.1 (3819.3)	9232.5 (2160.4)	7781.8 (3474.4)	10372.5 (7406.2)
Median	5885.0	9420.0	8050.0	10600.0
Min ; Max	2100 ; 13700	5260 ; 12800	2650 ; 13500	0 ; 19300
Week 12				
Number	13	10	13	9
Mean (SD)	6426.2 (4069.7)	8344.0 (3371.6)	9542.9 (5173.3)	8520.0 (5801.8)
Median	4450.0	8065.0	8660.0	8950.0
Min ; Max	1570 ; 14000	3210 ; 13700	118 ; 17900	0 ; 14800
Week 24				
Number	10	9	9	8
Mean (SD)	7267.0 (2778.3)	20300.0 (7879.9)	7829.7 (3407.2)	28625.0 (15482.9)
Median	6750.0	16600.0	8690.0	30700.0
Min ; Max	2660 ; 12800	12200 ; 30100	817 ; 12200	0 ; 52700

Table 5 C$_{trough}$, alirocumab concentrations (ng/mL) over time according to up-titration/dose adjustment status as per IVRS and by dose of alirocumab - Double-blind period - Patients in the Q4W cohort - PK population - Patients with at least one injection post-IVRS transaction at Week 12

Alirocumab concentrations Time-point	Alirocumab 150 mg Q4W/up 75 mg Q2W		Alirocumab 300 mg Q4W/up 150 mg Q2W	
	Not up-titrated/dose-adjusted (N=14)	Up-titrated/dose-adjusted (N=5)	Not up-titrated/dose-adjusted (N=19)	Up-titrated/dose-adjusted (N=10)
Baseline concentrations (ng/mL)				
Number	14	5	19	10
Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Median	0.0	0.0	0.0	0.0
Min ; Max	0 ; 0	0 ; 0	0 ; 0	0 ; 0
C$_{trough}$ concentrations (ng/mL)				
Week 8				
Number	12	3	17	8
Mean (SD)	9087.6 (4609.7)	7916.7 (5255.8)	11823.1 (8695.5)	15116.6 (14555.7)
Median	8630.0	9070.0	9570.0	12325.0
Min ; Max	411 ; 17000	2180 ; 12500	852 ; 25600	163 ; 44000
Week 12				
Number	12	4	18	8
Mean (SD)	9696.8 (9432.9)	7097.5 (4388.8)	13171.3 (8713.4)	15627.1 (13353.6)
Median	7930.0	6730.0	13350.0	12900.0
Min ; Max	321 ; 36000	2130 ; 12800	524 ; 29300	357 ; 39600
Week 24				
Number	12	5	15	7
Mean (SD)	10895.5 (9075.6)	8263.0 (4800.3)	16070.0 (11471.5)	29130.0 (11156.8)
Median	10550.0	8850.0	11600.0	29700.0
Min ; Max	126 ; 29600	115 ; 12100	4100 ; 45600	8510 ; 39400

2.4.2.4. Results - Pop PK simulations of PK-parameters in paediatric patients and adults

Simulated exposure parameters AUC and C$_{max}$ in paediatric patients and adults are shown in Table 6.

Table 6 Mean (SD) alirocumab exposure in paediatric (POH0925) and adults (POH0377/BAY0041) population after the last administration (steady state)

Pediatric population (POH0925)					Adult Population (POH0377/BAY0041*)			
Dose	BW	N	C$_{max}$ (mg/L)	AUC$_{0-336}$ /AUC$_{0-672}$ (mg.h/L)	Dose	N	C$_{max}$ (mg/L)	AUC$_{0-336}$ /AUC$_{0-672}$ (mg.h/L)
40 mg Q2W	BW <50 kg	19	11.1 (3.47)	3060 (1090)	75 mg Q2W	514	7.93 (2.82)	2150 (907)
75 mg Q2W	BW ≥50 kg	19	12.4 (4.49)	3480 (1390)				
75 mg Q2W up-titration	BW <50 kg	10	26.7 (5.85)	7980 (1870)	150 mg Q2W	1625	18.0 (8.37)	5050 (2687)
150 mg Q2W up-titration	BW ≥50 kg	10	34.8 (15.0)	10300 (4660)				
150 mg Q4W	BW <50 kg	19	33.4 (9.16)	14900 (5640)	300 mg Q4W*	251	26.6 (10.6)	11200 (5660)
300 mg Q4W	BW ≥50 kg	22	40.7 (11.0)	18800 (6840)				

Simulated AUC and C_{max} in paediatric patients and adults plotted against the bodyweight are shown in **Figure 6** and **Figure 7**.

Figure 6 Individual alirocumab Cmax and AUC0-336 as a function of BW in paediatric (POH0925) and adult (POH0377) patients after Q2W administration
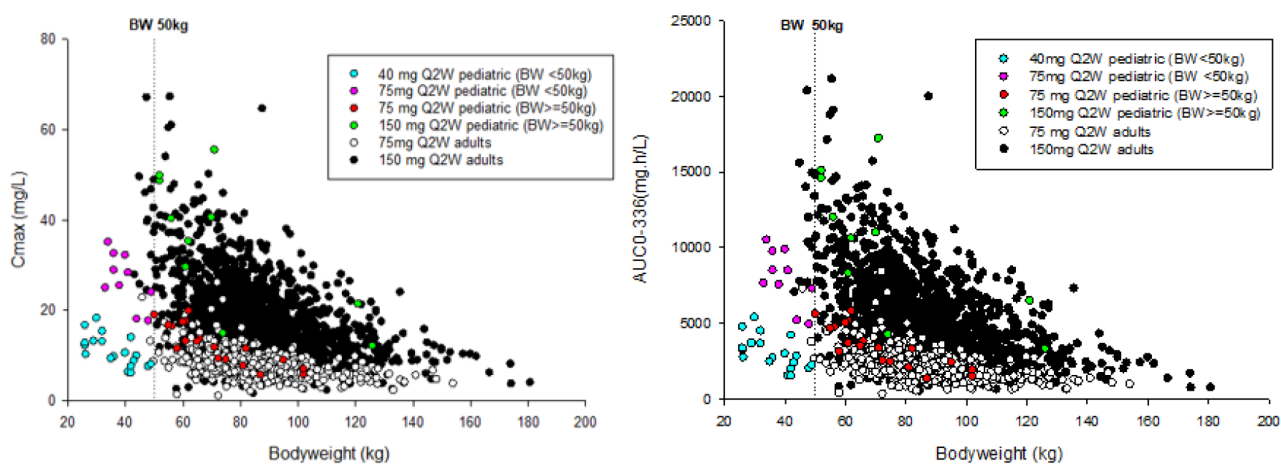
Figure 7 Individual alirocumab Cmax and AUC0-672 as a function of BW in paediatric (POH0925) and adult (BAY0041) patients after Q4W administration
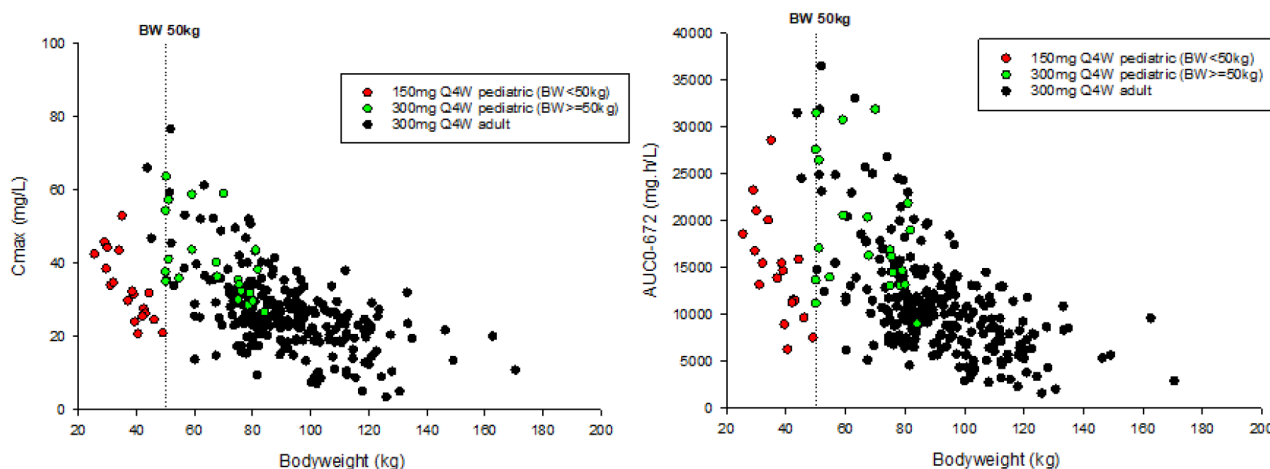
2.4.2.5. Results – Immunogenicity

In the DB treatment period, one (2.1%) participant in the alirocumab group in Q2W cohort and 4 (8.0%) participants in the alirocumab group in the Q4W cohort had positive ADA status at baseline, before the first investigational medicinal product (IMP) administration.

Treatment-emergent positive ADA responses were observed in 3 (6.3%) participants in the alirocumab group of the Q2W cohort. No participants had treatment-emergent ADA response with a titer above 240. No participants had ADA response with neutralizing status. No participants had a treatment emergent positive ADA response classified as persistent.

No treatment-emergent positive ADA responses were observed in participants in the alirocumab group of the Q4W cohort. Among the 4 participants with positive ADA status at baseline in this cohort (ie, Q4W), 1 participant had a positive ADA response at baseline but the ADA titer decreased over time from 120 at the baseline to 60 at Week 24. All other ADA positive samples exhibited a low ADA response with no titer exceeding 240. No participants had ADA response with neutralizing status.

None of the placebo patients had positive ADA status at any time.

In the OL treatment period, none of the participants in the Q2W cohort reported treatment-emergent ADA positive response.

In the Q4W cohort, 1 participant from the "Placebo in DB treatment period" group developed treatment-emergent ADA response classified as transient (detected only at Week 68). None of the participants in the Q4W cohort reported treatment-emergent ADA response that were classified as persistent.

No participants had ADA response with neutralizing status.

2.4.3. Pharmacodynamics

Mechanism of action

Alirocumab is a fully human monoclonal IgG1 antibody that binds to PCSK9. 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 the circulation and hepatic LDL uptake is a major determinant of circulating LDL-C levels. When an internalized 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.

Primary and secondary pharmacology

Total PCSK9

In the Phase 3 study (EFC14643), for all dose cohorts, the total PCSK9 concentration was increased after the administration of alirocumab and reached a plateau at or before Week 8 suggesting that at these dose regimens in these paediatric patients, target saturation was achieved. Up-titration/dose adjustment appeared to have a limited effect on total PCSK9 levels in the study participants who underwent a change in dosing at Week 12 (**Figure 8**).

Figure 8. Pivotal efficacy study EFC14643 Total PCSK9 concentrations Mean (±SD) (ng/mL) over time according to Up-titration/dose adjustment - Q2W (left) and Q4W cohort (right) - PK population
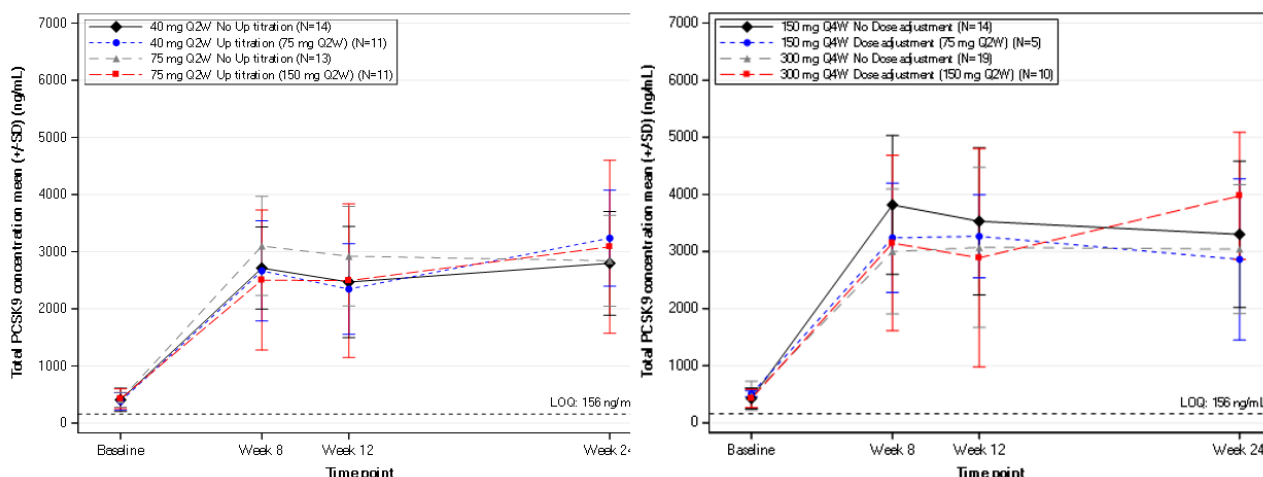
Free PCSK9

In the Phase 3 study (EFC14643), consistent with the total PCSK9 observations, administration of alirocumab resulted in a decrease in free PCSK9 concentrations at or before Week 8 (**Figure 9**). For all cohorts, this decrease was maintained up to the last sample collection on Week 24.

Up-titration/dose adjustment appeared to have a limited effect on free PCSK9 levels in study participants who underwent a change in dosing at Week 12.

Figure 9. Pivotal efficacy study EFC14643 Free PCSK9 concentrations Mean (±SD) (ng/mL) over time according to up-titration/dose adjustment – Q2W (left) and Q4W cohort (right)- PK population
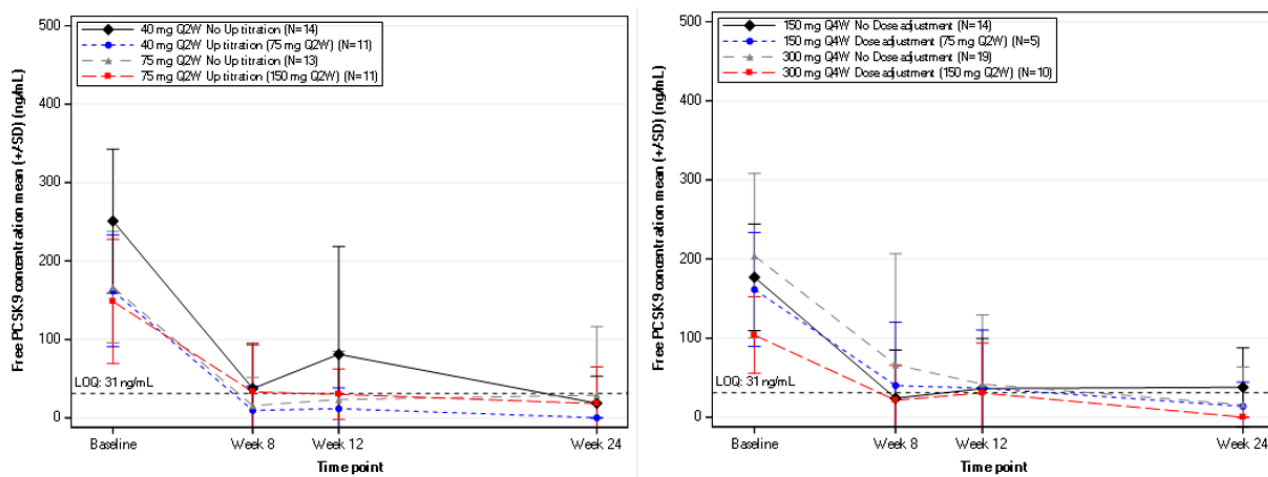
2.4.4. PK/PD modelling

Although no specific PK/PD analysis was done in the present paediatric population, a PK/PD model was developed at the time of the initial submission in the adult population.

In the adult population, alirocumab lowers LDL-C through an indirect mechanism requiring first a complex formation 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.

2.4.5. Discussion on clinical pharmacology

Pharmacokinetics (PK)

Evaluation of Pop PK model (POH0925) for simulation of paediatric exposure parameters

The PK of alirocumab was evaluated in a Pop PK analysis in paediatric patients with HeFH (POH0925) using pooled data from 2 clinical studies (DFI14223 and EFC14643). Because most of the sparse PK samples were trough samples, a modelling strategy was implemented in order to inform paediatric data with PK structural model parameters from a qualified and updated model for alirocumab established in adults (POH0472).

Instead of merging the paediatric observations with the adults Pop PK model, which would marginalize the paediatric dataset, Bayesian priors were used in the model development to develop a stand-alone model for the paediatric population. As a requirement for this approach, it was necessary to modify the reference model and remove the covariate statin co-medication with V2, which is not ideal as this biases

the parameter estimates of the adult model and will increase interindividual variability estimates of the adult model. However, the impact of removing this covariate is estimated to be low as interindividual estimates of the paediatric population will have enough flexibility in the model to describe the paediatric data. Any trends with age and bodyweight will be visible in the ETA versus covariate plots. It should be noted that a direct comparison between adult and paediatric simulations has not been performed with a single model.

The VPC plots of the final model showed that most of the observations are captured by the model as the data falls within the 90% prediction interval, indicating reasonable model performance. Furthermore, the GOF plots of IPRED versus observations showed that the model is suitable for estimating individual pharmacokinetic parameters, but population predictions are biased.

In summary, Pop PK model POH0925 is suitable for the purpose of simulating individual exposure parameters of the paediatric population. However, comparing paediatric vs. adults should be interpreted carefully as different models are used for simulating data for both populations.

<u>Steady state after multiple dosing</u>

The descriptive statistics show that steady state for total alirocumab concentrations have been approximately reached at week 8. The further increase in pre-dose concentrations after week 12 results from up-titration.

<u>Starting doses 40 mg (<50 kg) and 75 mg (≥50 kg) Q2W</u>

From study EFC14643, it can be observed that the initial Q2W doses for paediatric patients of 40 mg (<50 kg) and 75 mg (≥50 kg) resulted in higher alirocumab total C_{trough} concentrations as the C_{trough} observed in adults receiving the initial dose of 75 mg Q2W from MONO, FHI and COMBO studies (6426 – 7267 ng/mL (40 mg) and 7782 – 9543 ng/mL (75 mg) vs. 3950-6990 ng/mL in adults).

Furthermore, Pop PK simulations for the starting doses of 40 mg Q2W (<50 kg) and 75 mg Q2W (≥50 kg) demonstrate that the C_{max} and AUC are 1.4- to 1.6-fold higher compared to the starting dose of 75 mg Q2W in adults. Considering the simulated C_{max}/AUC vs. bodyweight scatter-plots, it seems that the higher exposure is probably due to the weight-effect and the differences in weight between the paediatric and adult populations. It can however not be excluded that there are differences in the pharmacokinetics, other than the difference introduced by a difference in bodyweight, as a direct comparison (i.e. one model describing both paediatric and adult data) has not been conducted. Graphical exploration shows that any differences, other than by bodyweight, are very pronounced.

<u>Starting doses 150 mg (<50 kg) and 300 mg (≥50 kg) Q4W</u>

From the Phase 3 paediatric HeFH study (EFC14643) it can be observed that the initial Q4W doses for paediatric patients of 150 mg (<50 kg) and 300 mg (≥50 kg) resulted in C_{trough} concentrations of 8630 – 10896 ng/mL and 11823 – 16070 ng/mL, respectively. These were higher compared to the trough concentrations for adults receiving the 75 mg Q2W starting dose (3950-6990 ng/mL in adults, MONO, FHI and COMBO studies) and also slightly higher compared to adults receiving the 300 mg Q4W higher dose (8620 ng/mL, Choice I study).

Simulated data show 1.3- to 1.5-fold higher C_{max} and 1.3- to 1.7-fold higher AUC of these starting doses compared to the higher regimen of 300 mg Q4W in adults. Again, these slightly higher exposure parameters in the paediatric population might be due to the weight effect, as the simulated exposure parameters in the scatter plots follow the same trend as in adults. However, as mentioned above, it is still unclear if maturation factors may contribute to this effect, as a direct comparison has not been conducted. These effects are, however, not expected to be very pronounced.

<u>Doses 75 mg (<50 kg) and 150 mg (≥50 kg) Q2W</u>

The Q2W doses for paediatric patients of 75 mg (<50 kg) and 150 mg (≥50 kg) intended for the up-titration of the therapy resulted in higher C_{trough} concentrations as the C_{trough} observed in adults receiving the higher dose of 150 mg Q2W from the Choice I study (6730 – 20300 ng/mL and 8520 – 29130 ng/mL vs. 5650 - 6010 ng/mL in adults).

Simulated data show 1.6- to 2.0-fold higher AUC and 1.5- to 1.9-fold higher C_{max} of these Q2W doses compared to the higher regimen of 150 mg Q2W in adults. The higher exposure parameters in the paediatric population is probably due to the weight effect, as the simulated exposure parameters in the scatter plots follow the same trend as in adults. The comparison of the simulated data should be interpreted carefully (see above).

In summary, comparing the observed C_{trough} in adults receiving a starting dose of 75 mg Q2W with the paediatric population receiving 40/75 mg Q2W, the paediatric population showed a higher exposure. The difference in exposure was even higher when compared to the starting dose of 150/300 mg Q4W in paediatric patients. Moreover, the Q4W starting dose in the paediatric population showed higher exposure compared to adults receiving the 300 mg Q4W dose, which is the higher/up-titrated dose in the adult regimen. This was even noticeable when comparing 75/150 mg Q2W dose in the paediatric population versus the 150 mg Q2W dose in adults. Observed alirocumab steady state C_{trough} versus bodyweight plots showed overlap of the C_{trough} values between the paediatric and adults population at equivalent doses for the Q2W as well as the Q4W regimens. C_{trough} versus age plots were only provided for the paediatric population, because this data was collected only for the paediatric and adolescents population with HeFH. Visually no effect of age on the C_{trough} can be observed in the paediatric and adolescent population in the range of 8-18 years. Also, in the PopPK-model for adults, age was considered as a significant covariate on peripheral volume of distribution. However, age did not result in differences in alirocumab exposure of a clinically relevant magnitude as the exposures were within the exposure ranges observed across the clinical development program. Furthermore, no significant effect of bodyweight and age on the PopPK-model parameters (CL, V2, V3, Km and F1) can be observed from the ETA distribution versus bodyweight and age plots. In conclusion, the higher mean exposure of alirocumab in the paediatrics population can be explained by the relatively lower bodyweight compared to the adults population. No additional effect of age can be observed on the exposure of alirocumab applying the proposed weight-based dosing.

Furthermore, the paediatric Q2W starting doses resulted in a plateau in total PCSK9-levels and nearly undetectable free PSCK9-levels, which did not change with higher alirocumab doses (see pharmacodynamics (PD) section). This may indicate an excess in alirocumab and that full inhibition of PCSK9 was already reached with the Q2W starting dose in paediatric patients. Establishing a minimum alirocumab C_{trough} value which yields sufficient LDL-C reduction is not possible for the paediatric patient population, because only an indirect link exists between alirocumab concentrations and LDL-C results. Alirocumab lowers LDL-C through an indirect mechanism requiring first a complex formation with PCSK9, with a subsequent increase in hepatocyte cell-surface LDLRs and increased clearance of LDL-C from the circulation. This is confirmed by alirocumab C_{trough} versus LDL-C change from baseline plots in the paediatric population, wherein no obvious trends are observed due to the interindividual variation for the relationship. Lastly, also for the adults population, no minimal C_{trough} and PCSK9 inhibition was defined for sufficient LDL-C reduction was defined. In conclusion, it is not possible to define a minimal C_{trough} to establish sufficient LDL-C reduction for alirocumab with the current data. In order to get more insight for the minimal doses needed for the paediatric population, simulations were submitted of C_{trough} versus bodyweight for the Q2W (5-100 mg in steps of 5 mg) and Q4W (10-300 mg in steps of 10 mg) regimens with the PopPK-model. As it is not possible to define a minimum C_{trough} to establish sufficient LDL-C reduction due to the indirect mechanism of alirocumab, the Km-value of 8610 ng/mL from the PopPK-

model was used as a reference line in the requested plots, which is acceptable. The simulations showed that paediatric patients weighing 25-50 kg need a dose of 40-70 mg Q2W or 110-210 mg Q4W for C_{trough} above the Km-value. Patients weighing 50-80 kg need a dose of 70-100 mg Q2W or 210-300 mg Q4W. The simulations may support the need for up-titrated doses (see also Clinical part of AR), as fixed doses of 150 mg Q4W for patients <50 kg and 300 mg Q4W ≥50 kg, may be not sufficient to establish C_{trough} levels above the Km-value for patients in the higher end of the bodyweight categories. Nevertheless, as discussed earlier, there is no direct link between C_{trough} levels of alirocumab and LDL-C reduction. Using the threshold value of 8610 ng/mL (Km-value in the PopPK-model), because it is not possible to define a minimum C_{trough} to establish sufficient LDL-C reduction, has also limited implications.Therefore, the simulations should be interpreted with caution.

Immunogenicity

A low level of immunogenicity was observed in the paediatric population in the Phase 3 study (EFC14643). No participants in the Q2W or Q4W cohorts reported persistent positive ADA response or neutralising ADA in either cohort in the DB and OL treatment periods (ie, a positive ADA response detected in at least 2 consecutive post-baseline samples separated by at least a 12-week period). It was noted that ADA responses were observed more frequently in the Q4W dose regimen, however these were not neutralising.

Pharmacodynamics

In the Phase 3 study EFC14643, total PCSK9 concentration was increased after both Q2W or Q4W dose regimens and reached a plateau at or before Week 8, indicating target saturation. Consistent with the total PCSK9 finding, administration of alirocumab resulted in a decrease in free PCSK9 concentration at or before Week 8, and the subsequent decrease in LDL-C (see clinical efficacy section), which was maintained up to the last sample collection on Week 24.

According to **Figure 8** and **Figure 9**, dose up-titration at Week 12 seems to have a limited effect on both total and free PCSK9 levels and LDL-C levels (see efficacy section). Nevertheless, the absolute data at the different time points showed that subjects who received up-titration had stronger PCSK9 inhibition than prior up-titration. For the Q4W regimen (currently proposed starting regimen in the SmPC) in the dose-adjusted paediatric subjects, the mean (SD) free PCSK9 level was 123.0 (61.5) ng/mL at baseline and 32.5 (63.3) ng/mL at Week 12, which was further reduced to 4.9 (18.3) ng/mL at Week 24 upon up-titration. In the subgroup of subjects who were not dose adjusted, free PCSK9 levels remained stable between Week 12 and Week 24 (mean (SD) free PCSK9 of 39.5 (77.2) ng/mL at Week 12 versus 24.3 (48.8) ng/mL at Week 24)(see clinical efficacy section).

2.4.6. Conclusions on clinical pharmacology

From a pharmacokinetic point of view, the proposed alirocumab doses for the paediatric population are sufficiently bridged to the alirocumab doses used in the adult population.

Similar to the adult population, the proof of concept of alirocumab in inhibition of PCSK9, as measured by an increase in total PCSK9, a decrease in free PCSK9, and the subsequent decrease in LDL-C has sufficiently been demonstrated in the paediatric population.

2.5. Clinical efficacy

2.5.1. Dose response study

Phase 2 dose finding study (DFI14223)

Study DFI14223 - An 8-Week Open-Label, Sequential, Repeated Dose-Finding Study to Evaluate the Efficacy and Safety of Alirocumab in Children and Adolescents with heFH Followed by an Extension Phase

Methods

The open-label dose escalating Phase 2 study (DFI14223) was designed to evaluate the effect of alirocumab administered Q2W or Q4W on LDL-C levels after 8 weeks of treatment in participants with HeFH aged 8 to 17 years, with LDL-C ≥ 3.37 mmol/L (130 mg/dL) on optimal stable daily dose of statin therapy ± other LMTs or a stable dose of non-statin LMTs in case of intolerance to statins, for at least 4 weeks prior to the screening period. Diagnosis of HeFH was performed through genotyping or clinical criteria based on Simon Broome criteria for possible or definite FH.

There was a sequential enrollment into 4 separate and independent cohorts, Cohorts 1 to 4. The choice of the doses in this study was based on simulations performed on the final adult population PK model including Phase 3 data. The model included BW as a covariate (on clearance/volume) and allowed to perform simulations with different BWs (POH0472). Based on these simulations, fixed dose regimen were defined according to BW categories < 50 kg and ≥ 50 kg. The duration of the open-label dose finding (OLDFI) treatment period was 8 weeks for the first 3 cohorts, and 12 weeks for Cohort 4. Each independent cohort below included approximately 10 patients with no less than 4 patients in each BW category:

- Cohort 1 received 30 mg Q2W for BW <50 kg (n=4) and 50 mg Q2W for BW ≥50 kg (n=6).

- Cohort 2 received 40 mg Q2W for BW <50 kg (n=4) and 75 mg Q2W for BW ≥50 kg (n=6).

- Cohort 3 received 75 mg Q4W for BW <50 kg (n=6) and 150 mg Q4W for BW ≥50 kg (n=5).

- Cohort 4 received 150 mg Q4W for BW <50 kg (n=6) and 300 mg Q4W for BW ≥50 kg (n=5).

To note: Given inconclusive efficacy results for the Q4W dosing regimen, an additional cohort (Cohort 4) had been including evaluating the Q4W dosing regimen at higher doses of 150 mg for BW <50kg and 300 mg for BW ≥50 kg to see if an effect on LDL-C closer to the therapeutic target of approximately 50% could be achieved.

At the end of the post-treatment follow-up period for Cohorts 1 to 3 and at the end of the 12-week open-label dose-finding treatment period for Cohort 4, patients who successfully completed the OLDFI period (providing they had not experienced adverse events [AEs] leading to permanent discontinuation during the OLDFI treatment period and had no significant protocol deviations, in the Investigator's judgment) were offered entry into an optional open-label extension (OLE) period.

Pre-dose PK samples for evaluation of alirocumab, total and free PCSK9 concentration were collected at baseline, Weeks 4 and 8 during the on-treatment period in all cohorts, and at Week 14/16 in Cohorts 1, 2, and 3 during the follow up period. In Cohort 4, additional pre-dose PK samples were collected at Weeks 10 and 12 on-treatment. This cohort did not include a follow-up period.

Results

All patients were treated with alirocumab and completed the OLDFI treatment period. All patients but one from Cohort 1 were included in the OLE period (patient did not want to enter the OLE period)(Table 7). Two patients enrolled in Cohort 4 were not treated in the OLE period: one patient discontinued treatment due to TEAE (neutropenia) reported at the end of the OLDFI period and one patient was erroneously registered and not treated in the OLE phase (patient did not want to enter the OLE period).

In the OLE period, 3 patients (all in Cohort 1) did not complete the OLE study treatment period: one patient discontinued the treatment due to AE (fatigue) and 2 patients discontinued due to other reason (patient's decisions).

Table 7. Patient disposition - by cohort, all doses combined - Included population in OLE period

	Cohort 1 (N=9)	Cohort 2 (N=10)	Cohort 3 (N=11)	Cohort 4 (N=11)	All (N=41)
Included and not treated in OLE period	0	0	0	2 (18.2)	2 (4.9)
Treated in OLE period	9 (100)	10 (100)	11 (100)	9 (81.8)	39 (95.1)
Complete the OLE study treatment period	6 (66.7)	10 (100)	11 (100)	9 (81.8)	36 (87.8)
Treatment ongoing in the OLE treatment period	0	0	0	0	0
Did not complete the OLE study treatment period	3 (33.3)	0	0	0	3 (7.3)
Reason for OLE treatment discontinuation					
Adverse event	1 (11.1)	0	0	0	1 (2.4)
Death	0	0	0	0	0
Poor compliance to protocol	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0
Site terminated by sponsor	0	0	0	0	0
Other reasons	2 (22.2)	0	0	0	2 (4.9)
Subject moved	0	0	0	0	0
Life events made continuing too difficult	0	0	0	0	0
Related to IMP administration	0	0	0	0	0
Other	2 (22.2)	0	0	0	2 (4.9)
Patient's decision for OLE treatment discontinuation	3 (33.3)	0	0	0	3 (7.3)
Status at last study contact	9 (100)	10 (100)	11 (100)	11 (100)	41 (100)
Alive	9 (100)	10 (100)	11 (100)	11 (100)	41 (100)

In Cohort 1 evaluating the lower Q2W doses showed an overall LS mean [SE] percent change from baseline to Week 8 of -21.2% [7.9](Table 8). The response was not consistent across the doses by the BW category with a reduction in calculated LDLC of -41.1% (12.6) with the 30 mg Q2W dose for BW <50 kg and of -7.9% (10.3) with the 50 mg Q2W dose for BW ≥50 kg.

In Cohort 2 evaluating the Q2W dosing regimen, LS mean [SE] percent change from baseline to week 8 showed a reduction of -46.1% [8.3]; with a reduction observed in both BW categories (LS mean [SE] of -40.6% [13.2] with 40 mg Q2W for BW <50 kg, and -49.8% [10.6] with 75 mg Q2W for BW ≥50 kg).

In Cohort 3 evaluating the Q4W dosing regimen, overall, the LS mean [SE] percent change from baseline to Week 8 in calculated LDL-C was moderate (-7.8% [7.6]). The response was also not consistent across the 2 doses by the BW category with a reduction of -17.5% (10.3) with the 75 mg Q4W dose for BW <50 kg and an increase in calculated LDL-C of 4.0% (11.2) with the 150 mg Q4W for BW ≥50 kg.

In Cohort 4, which was implemented subsequent to the other cohorts to further evaluate the Q4W dosing regimen, a clinically meaningful reduction in calculated LDL-C was observed (LS mean [SE] percent change from baseline to Week 8 of -44.5% [7.6]). Reductions were observed in both BW categories with a higher effect observed with 300 mg Q4W: 31.9% [10.3] with the 150 mg Q4W dose for BW <50 kg, and 59.8% [11.2] with the 300 mg Q4W dose for BW ≥50 kg. Alirocumab was well tolerated at all doses assessed in the 4 cohorts. Consistent results to those observed at Week 8 for the calculated LDL-C were

noted at Week 12. The LS mean (SE) percent change from baseline to Week 12 in calculated LDL-C showed a clinically meaningful reduction of -38.6% [5.1]. Similar to what was observed for the primary endpoint analysis, a greater effect was observed in the higher BW group with the 300 mg Q4W dose: LS mean (SE) percent change from baseline to Week 12 of -29.7% (6.9) with the 150 mg Q4W dose for BW <50 kg and of -49.2% (7.5) with the 300 mg Q4W dose for BW ≥50 kg.

The high doses used in Cohort 2 (40/75 mg Q2W) and Cohort 4 (150/300 mg Q4W) were selected for further investigation in the efficacy and safety Phase 3 study in paediatric patients with HeFH (Study EFC14643).

Table 8. Percent change from baseline in calculated LDL-C over time during the OLDFI efficacy treatment period: MMRM (without adjustment on baseline) – On-treatment analysis – by cohort, all doses combined- mITT population

Calculated LDL-Cholesterol	Cohort 1 (N=10)	Cohort 2 (N=10)	Cohort 3 (N=11)	Cohort 4 (N=11)
Baseline (mmol/L)				
Number	10	10	11	11
Mean (SD)	4.671 (1.079)	4.144 (0.985)	4.475 (1.154)	4.891 (1.022)
Median	4.534	3.925	4.160	4.470
Min ; Max	2.20 ; 5.88	3.05 ; 6.27	3.29 ; 6.41	3.70 ; 6.69
Baseline (mg/dL)				
Number	10	10	11	11
Mean (SD)	180.3 (41.7)	160.0 (38.0)	172.8 (44.5)	188.9 (39.5)
Median	175.1	151.5	160.6	172.6
Min ; Max	85 ; 227	118 ; 242	127 ; 247	143 ; 258
Week 4 percent change from baseline (%)				
LS Mean (SE)	-21.4 (7.7)	-38.7 (7.7)	-10.8 (7.4)	-38.3 (7.6)
95% CI	(-37.2 to -5.7)	(-54.4 to -23.0)	(-25.8 to 4.1)	(-53.7 to -22.8)
Week 8 percent change from baseline (%)				
LS Mean (SE)	-21.2 (7.9)	-46.1 (8.3)	-7.8 (7.6)	-44.5 (7.6)
95% CI	(-37.4 to -5.1)	(-62.8 to -29.4)	(-23.2 to 7.7)	(-60.0 to -29.1)

The efficacy treatment period ends at last OLDFI injection date +21 days (for Cohorts 1 & 2) or +35 days (for Cohorts 3 & 4)
Note: Least-squares (LS) means, standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis.
The model includes the fixed categorical effects of Alirocumab dose group, time point and dose-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.

Comparison and analyses of results across studies

The Phase 2 study DFI14223 evaluated fixed dosages of alirocumab according to BW categories at Week 8 (Week 12 in Cohort 4) in an open-label fashion, whereas the Phase 3 study EFC14643 evaluated dosing regimens including automatic (via IVRS) up-titration/dose-adjustment at Week 12 in a double-blind, placebo-controlled fashion. Analysis of results across studies has been made on results obtained at Week 8 and Week 12, before any dose-adjustment (Table 9).

Table 9. Comparison and analyses of results across studies

	Study DFI14223 (Phase 2 dose-finding)				Study EFC14643			
LDL-C reduction	Cohort 2 40 mg Q2W (BM < 50kg)	Cohort 2 75 mg Q2W (BW ≥50 kg)	Cohort 4 150 mg Q4W (BM < 50kg)	Cohort 4 150 mg Q4W (BW ≥50 kg)	40 mg Q2W (BM < 50kg)	75 mg Q2W (BW ≥ 50 kg)	150 mg Q4W (BM < 50kg)	300 mg Q4W (BW ≥ 50 kg)
Week 8 % change LS mean (SE)	-40.6 (13.2)	-49.8 (10.6)	-31.9 (10.3)	-59.8 (11.2)				
Week 12 % change LS mean SE			-29.7 6.9)	-49.2 (7.5)	-34.9 (4.3)	-34.3 (4.6)	-45.9 (5.2)	-35.4 (4.1)

Analysis of clinical information relevant to dosing recommendations

In the Phase 3 study, there was no evidence of any differential effect on LDL-C of alirocumab versus placebo between the Q4W and Q2W regimens, overall or by BW category (interaction p-value 0.5814) (Table 10)

Table 10. Percent change from baseline in LDL-C at Week 24: MMRM - Comparison of the two alirocumab dosing regimens - Subgroup analysis according to Body weight as per IVRS - ITT analysis - ITT population (Study EFC14643)

Subgroup factor Percent change from baseline in LDL-C at Week 24 (%)	Placebo Q2W (N=25)	Alirocumab Q2W (N=49)	Placebo Q4W (N=27)	Alirocumab Q4W (N=52)	Q2W vs Q4W	Interaction p-value
Body weight strata as per IVRS						0.5814
< 50 kg						
Number	13	25	9	19		
LS mean (SE)	12.5 (5.9)	-35.9 (4.8)	-6.7 (7.1)	-41.2 (6.5)		
LS mean difference (SE) versus placebo within dose regimen		-48.5 (7.6)		-34.5 (9.5)		
97.5% CI		(-66.0 to -30.9)		(-56.4 to -12.6)		
LS mean difference (SE) between dose regimen[a]					-14.0 (12.2)	
97.5% CI					(-41.7 to 13.7)	
≥ 50 kg						
Number	12	24	17	31		
LS mean (SE)	5.6 (6.4)	-32.5 (5.0)	-2.6 (5.0)	-35.5 (5.0)		
LS mean difference (SE) versus placebo within dose regimen		-38.0 (7.8)		-32.9 (7.0)		
97.5% CI		(-56.0 to -20.0)		(-49.0 to -16.9)		

Subgroup factor Percent change from baseline in LDL-C at Week 24 (%)	Placebo Q2W (N=25)	Alirocuma b Q2W (N=49)	Placebo Q4W (N=27)	Alirocuma b Q4W (N=52)	Q2W vs Q4W	Interaction p-value
LS mean difference (SE) between dose regimen[a]					-5.1 (10.4)	
97.5% CI					(-28.9 to 18.6)	

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The p-value is not adjusted for multiplicity and provided for descriptive purpose only.

The model includes the fixed categorical effects of treatment group (Placebo Q2W, alirocumab Q2W, Placebo Q4W and alirocumab Q4W), randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, treatment group-by-BW strata as per IVRS, and treatment group-by-BW strata as per IVRS-by-time point, as well as the continuous fixed covariates of baseline 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.

[a] LS mean difference of LS mean differences versus placebo measured in each dosing regimen (Q2W versus Q4W).

Based on these study results and given the lower patient burden associated with monthly injections as compared to bi-weekly injections, the Q4W dose regimen will be recommended for children and adolescents 8 to 17 years of age with HeFH, in adjunct to optimal stable daily dose of statin therapy ± other LMTs or a stable dose of non-statin LMTs in case of intolerance to statins.

The recommended starting dose will be:

- 150 mg Q4W for children and adolescents with BW <50 kg.

- 300 mg Q4W for children and adolescents with BW ≥50 kg.

Dose up-titration/adjustment at Week 12 provided no or moderate additional LDL-C reduction in the Q2W cohort and Q4W cohort.

The efficacy and safety of alirocumab in the paediatric patient population with HeFH were first evaluated in the Phase 2 dose-finding DFI14223 study. The choice of doses in this study was based on simulations performed on the final adult population PK model, including Phase 3 data. DF114223 was an open-label dose-escalating Phase 2 study to evaluate appropriate doses to be selected for the Phase 3 studies; A study in HoFH patients and a study in HeFH patients have been conducted and submitted following PIP requirements as outlined in post-approval commitments. Repeated doses of subcutaneous alirocumab were administered in 2 cohorts every 2 weeks (Q2W) and 2 cohorts every 4 weeks (Q4W) in children and adolescents (aged 8-17 years) with HeFH having LDL-C ≥ 3.37 mmol/L despite an optimal stable daily dose of statin therapy ± other LMTs, or a stable dose of non-statin LMTs in case of intolerance to statins, for at least 4 weeks prior to the screening period. HeFH was diagnosed based on genetic testing or following the clinical Broome criteria, which is acceptable. Patients were dosed according to body weight which is acceptable considering that body weight is a significant covariate on the exposure of alirocumab in adults (see also pharmacology section). Doses of 30 and 40 mg Q2W were tested for < 50 kg, 50 and 75 mg Q2W for ≥ 50 kg, 75 and 150 mg Q4W for < 50 kg and 150 and 300 mg Q4W for ≥ 50 kg body weight.

Overall 42 patients were enrolled approximately evenly distributed according to the different doses investigated and according to the body weight subcategories and thus appears acceptable. Furthermore, all patients completed the open-label dose-finding (OLDF) period of 8 weeks and only 3 patients did not enter the open-label phase, which is reassuring.

After 8 weeks of treatment, the higher Q2W dose (cohort 2: 40 mg Q2W for < 50 kg and 75 mg for ≥ 50 kg) showed greater reductions in LDL-C (-46.1%) as compared to the lower Q2W dose (30 and 50 mg,

respectively, -21.1%). Slight differences appear in effect according to body weight (LS mean (SE): -40.6 (13.2) with 40 mg Q2W for BW <50 kg, and -49.8% (10.6)) with 75 mg Q2W for BW ≥50 kg). For the monthly dosing, only a moderate effect was observed for the lower dosing (cohort 3) with -17.5% (10.3) for 75 mg Q4W for BW <50 kg and 4.0% (11.2) for 150 mg Q4W BW ≥50 kg after 8 weeks. Based on these results, subsequent dosing with higher doses (cohort 4) showed greater efficacy (-31.9% [10.3] with 150 mg Q4W for BW <50 kg, and -59.8% [11.2] with 300 mg Q4W for BW ≥50 kg). Overall, a more pronounced effect can be observed in the higher Q2W dose in cohort 2 and the higher QW4 dose in cohort 4 compared to the respective lower dose groups. However, some variation exists between the body weight categories, with greater efficacy in the ≥50 kg groups.

From an efficacy point of view, it is considered appropriate that the doses used in cohort 2 and cohort 4 have been selected for the Phase 3 study EFC 14643.

In the pivotal study EFC14643, alirocumab demonstrated a substantial reduction in the primary endpoint of percent change from baseline to week 24 in LDL-C, with a LS mean difference versus placebo of -43.3% ([97.5% CI: -56.0 to -30.7]; p<0.0001) in the Q2W cohort, and -33.8% ([97.5% CI: -46.4 to -21.2]; p<0.0001) in the Q4W cohort. The higher effect in the Q2W cohort was mainly due to a larger (unexpected) increase in LDL-C in the placebo group. Dose up-titration/adjustment at Week 12 provided no additional LDL-C reduction in both the Q2W cohort and Q4W cohort (see efficacy main study). Overall, the effect size in LDL-C lowering of ~35-40% observed at week 24 in this study in paediatric subjects with HeFH is consistent with the LDL-lowering effect of 39% in adult HeFH patients (HIGH FH study). Furthermore, no differential effect on LDL-C of alirocumab versus placebo was observed between the Q2W and Q4W regimens and the BW categories.

Based on these study results and given the lower patient burden associated with monthly injections as compared to bi-weekly injections, the 150 mg or 300 mg Q4W for BW < 50 and ≥ 50 kg, respectively, dose regimen is currently proposed for children and adolescents 8 to 17 years of age with HeFH in section 4.2 of the SmPC, which can be acceptable. The Q4W starting regimen (150 mg or 300 mg Q4W for < 50 and ≥ 50 kg, respectively) is a 2-fold higher cumulative monthly dose compared to Q2W starting regimen (40 mg or 75 mg Q2W for < 50 and ≥ 50 kg, respectively). Consequently, in the Q4W cohort, higher Ctrough values were observed compared to the Q2W starting regimen. However, considering that no differences in safety profiles between the Q2W and Q4W regimens were observed, the selection of the Q4W regimen is accepted. In this respect, the focus to justify the dose adjustments was primarily on the up-titration regimen combined with the Q4W starting dose regimen. Overall, it can be concluded that paediatric patients with HeFH who do not reach the recommended LDL-C treatment target with the starting Q4W dose of alirocumab may benefit from the proposed up-titration regimen of 75 mg Q2W for BW < 50 kg or 150 mg Q2W for BW ≥50 kg (see below "outcomes and estimation" for results and detailed discussion on the up-titration regimen).

The Ctrough values with both Q2W and Q4W cohorts in the paediatric HeFH population tended to be higher compared with the Q2W and Q4W dose regimens in HeFH adults. However, the higher mean exposure of alirocumab in the paediatrics population can be explained by the relatively lower bodyweight compared to the adult population. No additional effect of age can be observed on the exposure of alirocumab applying the proposed weight-based dosing (see PK section).

2.5.2. Main study

Study EFC14643 is the Phase 3 study to support the proposed indication.

***Study EFC14643 -A randomized, double-blind, placebo-controlled study followed by an open
label treatment period to evaluate the efficacy and safety of alirocumab in children and
adolescents with heterozygous familial hypercholesterolemia***

Methods

Study EFC14643 was a randomized, 24-week double-blind, placebo-controlled, parallel group study to
evaluate the efficacy and safety of alirocumab administered at 40 mg or 75 mg Q2W (for BW <50 kg or ≥
50 kg) and 150 mg or 300 mg Q4W (for BW <50 kg or ≥50 kg) as a starting dose, on top of background
lipid-lowering background therapy in paediatric population 8 to 17 years of age with HeFH. The 24-week
double-blind treatment period was followed by an 80-week open label (OL) treatment period. A flow
mediated dilatation (FMD) exploratory sub-study to assess endothelial function in the brachial artery was
conducted in a sub-set of the study population during the DB treatment period.

Study participants

The main inclusion/exclusion criteria are provided in Table 11 below.

Table 11. Key inclusion/exclusion criteria of study EFC14643

Study EFC14643
Inclusion Criteria
- Male and female children and adolescents aged 8 to 17 years diagnosed with heterozygous familial hypercholesterolemia * inadequately controlled (see threshold mentioned in the exclusion criterion 2)** despite treatment with optimal dose of statin *** with or without other LMTs, or non-statin LMTs if statin intolerant ****, at stable dose(s) for at least 4 weeks *****. * Diagnosis of HeFH must be made either by previous genotyping, current centralized genotyping, or by clinical criteria according to Simon Broome criteria. Previous genotyping referred to documented results that were available from prior genotyping testing supporting a diagnosis of HeFH. Current centralized genotyping referred to patients electing to undergo genotyping during the run-in period with results supporting a diagnosis of HeFH. The clinical diagnosis was to be based on the Simon Broome criteria for possible or definite HeFH. Once eligibility was confirmed based on prior genetic testing or Simon Broome criteria, results of elective genetic testing would not impact patient's eligibility. ** Patients who had previously participated in the DFI14223 study had already met this LDL-C requirement when they screened for the DFI14223 study and thus were not excluded based on LDL-C <130 mg/dL (3.37 mmol/L). *** The optimal dose of statin was defined as the stable daily dose prescribed based on regional practice or local guidelines or was the stable daily dose that was maximally tolerated due to adverse effects on higher doses. For patients not receiving the maximally tolerated dose of statin, statin intensification was to be carefully considered prior to randomization in this study in order to ensure that the addition of a non-statin LDL-C lowering therapy (ie, alirocumab) would be the next appropriate step in the management of the patient's hypercholesterolemia. The highest dose of statin should not exceed the maximum labelled dose of statin for paediatric patients as per the local prescribing information. **** Statin intolerant patient was defined as the inability to tolerate at least 2 statins: one statin at the lowest daily starting dose, 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 (eg, 1 to 3 times weekly) were also considered as not able to tolerate a daily dose. ***** Before enrolling more than 2 siblings, the Investigator would discuss with the Sponsor study team.
Exclusion Criteria
- Children and adolescents aged less than 8 years or more than 17 years at the time of informed consent signature unless different local regulation applies (eg, for Russia only: patients aged less than 12 years or more than 17 years at the time of informed consent signature). Note: Patients aged of 8 to less than 10 years who had not had previous attempts to lower LDL-C by other means were to be excluded
- Patients with LDL-C <130 mg/dL (3.37 mmol/L) (ie, adequately controlled) obtained during the screening period after the patient had been on stable LMTs (ie, stable optimal dose of statin ± other stable LMTs, or stable non-statin LMTs in statin intolerant patients) treatment for at least 4 weeks

Note: Patients who had previously participated in the DFI14223 study had already met this LDL-C requirement when they screened for the DFI14223 study and thus were not excluded based on LDL-C <130 mg/dL (3.37 mmol/L)
- Patients with BW less than 25 kg.
- Patients aged of 8 to 9 years not at Tanner Stage 1 and patients aged of 10 to 17 years not at least at Tanner Stage 2 in their development
- Patients with secondary hyperlipidemia (such as decompensated hypothyroidism, nephrotic syndrome, obstructive liver disease, anorexia nervosa, obesity, and drug treatment [eg, isotretinoids]).
- Patients diagnosed with homozygous familial hypercholesterolemia
- Patients who had received lipid apheresis treatment within 2 months prior to the screening period or had plans to receive it during the study.
- Patients with uncontrolled (ie, HbA1c levels above local guidelines or equivalent) Type 1 or 2 diabetes mellitus.
- Patients with known uncontrolled thyroid disease (ie, thyroid stimulating hormone levels above or below the laboratory's reference range within the past 6 months that were obtained due to clinical indication).
- Patients with uncontrolled (ie, SBP or DBP above local guidelines or equivalent) hypertension.
- Fasting triglycerides >350 mg/dL (3.95 mmol/L) at the screening visit.
- Severe renal impairment (ie, eGFR <30 mL/min/1.73 m2) at the screening visit.
- Alanine aminotransferase or AST >2 x ULN (1 repeat lab was allowed).
- Creatine phosphokinase >3 x ULN (1 repeat lab was allowed).

General inclusion criteria seem appropriate to reflect the patients for which an indication is being sought, i.e. paediatric patients with HeFH. HeFH was diagnosed based on genetic testing or in accordance with the clinical Broome criteria, which is acceptable. The use of optimized background lipid-lowering therapy for ≥ 4 weeks prior to screening was another eligibility criteria. Furthermore, the LDL-C level of ≥ 3.4 mmol/L at screening is in line with the treatment goal for paediatric patients with HeFH recommended in the ESC guidelines for the treatment of dyslipidaemias (2019) and therefore acceptable. Patients who previously participated in the DFI14223 study and already met the LDL-C ≥ 3.37 mmol/L when they were screened for the DFI14223 study were also eligible to enroll in the Phase 3 study. This approach is considered acceptable since all patients completed the open-label dose finding period of the DFI14223 study and none patients discontinued due to adverse events. Consequently no preselection based on tolerability exists has occurred. Moreover, the patients from study DFI14223 went through a wash-out period of at least 10 weeks between the last injection of alirocumab in the DFI14223 study and the screening lipid assessment at entry in the screening period of this Phase 3 study. This approach is considered appropriate.

Exclusion criteria can also generally be accepted. Key is that HoFH patients were not to be included.

Treatments

The study included 4 periods:

- A run-in period (as needed) of up to 4 weeks (+2 days): Participants who consented to participate in the study but had not been on stable LMTs for at least 4 weeks or required statin intensification when initially seen were required to participate in a run-in period until LMT dose(s) had been stable for at least 4 weeks. Participants with suspected HeFH but without confirmation by previous genetic testing and not meeting Simon Broome criteria were also required to participate in the run-in period and to undergo centralized genetic testing during this period.

- A screening period (for all participants) of up to 2 weeks (+5 days): Participants who consented to participate in the study and had met all inclusion criteria and none of the exclusion criteria after screening period assessments were eligible to be enrolled in the study. An intermediate visit for injection training might occur during which the participants if aged 12 years and above (or another designated person such as parent, etc) were to be trained to self-inject/inject with placebo for alirocumab after the eligibility criteria were checked and it was confirmed that the participant was likely to be randomized.

- A DB treatment period of 24 weeks: Participants were to be blinded to the study intervention and randomized to receive subcutaneously either alirocumab or placebo (in 2:1 ratio) in addition to their stable background therapy for one of the following 2 dosing regimen cohorts (Table 12 and Table 13):

  – Q2W dosing regimen cohort: 40 mg Q2W (if BW <50 kg) OR 75 mg Q2W (if BW ≥50 kg)

  – Q4W dosing regimen cohort: 150 mg Q4W (if BW <50 kg) OR 300 mg Q4W (if BW ≥50 kg)

During DB treatment period of this study, participants from each cohort (Q2W or Q4W) randomized to alirocumab were to receive an alirocumab starting dose based on their BW. Participants were to maintain their starting doses until Week 12. Dose up-titration or adjustment occurred in a blinded manner at Week 12, based on their LDL-C level at Week 8 (**Table 12**).

  – Q2W dosing regimen cohort: continued alirocumab 40 mg or 75 mg Q2W if the Week 8 LDL-C <110 mg/dL (2.85 mmol/L) OR up-titrated to alirocumab 75 mg Q2W (for participants on 40 mg) or 150 mg Q2W (for participants on 75 mg) if the Week 8 LDL-C ≥ 110 mg/dL (2.85 mmol/L).

  – Q4W dosing regimen cohort*: continued alirocumab 150 mg or 300 mg Q4W if the Week 8 LDL-C <110 mg/dL (2.85 mmol/L) OR dose-adjusted to alirocumab 75 mg Q2W (for participants on 150 mg Q4W) or 150 mg Q2W (for participants on 300mgQ4W) if the Week 8 LDL-C is ≥110 mg/dL (2.85 mmol/L).

*For Q4W dosing regimen cohort, participants receiving alirocumab were under a " sham Q2W" regimen from Week 12 to Week 24, with alirocumab Q4W alternating with placebo Q4W, when applicable. Participants receiving placebo received a placebo injection every other week (Q2W) from Week 12 to week 24.

- An OL treatment period of 80 weeks: During 80 weeks of OL treatment period, participants were to receive open-label doses of alirocumab. From Week 24 onwards, the Investigator had to manage, adjustment of alirocumab dose on his/her own judgment, taking in to account, e.g., LDL-C level and changes in BW. However, if the Investigator considered that the up-titration/adjustment would potentially negatively impact participants' safety, he/she was allowed to exercise his/her judgement in a manner that safeguarded the safety and well-being of the participant. The following was applied based on changes in BW (Table 13):

  – If participant was on 40 mg Q2W, the dose was adjusted to 75 mg Q2W if BW changed from <50 kg to ≥50 kg.

  – If participant was on 150 mg Q4W, the dose was adjusted to 300 mg Q4W if BW changed from <50 kg to ≥50 kg.

  – For participants whose weight oscillated around 50 kg the dose was to be adjusted only once during the open-label treatment period.

From Week 32, according to the LDL-C measurements and the judgment of the Investigator, participants might have their alirocumab dose regimen adjusted further.

The total duration of the study was up to 110 weeks (+7 days) for each participant. The end of the study was defined as the last patient last visit planned per protocol.

The route of administration is subcutaneous injections in the abdomen, thigh or outer area of upper arm.

Table 12. Summary table of alirocumab dose modification - double-blind period

Treatment regimen	Q2W	Q4W
Starting dose	40 mg, for BW < 50 kg 75 mg, for BW ≥ 50 kg	150 mg, for BW < 50 kg 300 mg, for BW ≥ 50 kg
Up titration dose adjustment at week 12 (If LDL-C ≥110 mg/dL at Week 8)	75 mg, for BW < 50 kg 150 mg, for BW ≥ 50 kg	75 mg/Q2W, for BW < 50 kg 150 mg/Q2W, for BW ≥ 50 kg

BW: body weight; LDL-C: low density lipoprotein cholesterol; Q2W: every 2 weeks; Q4W: every 4 weeks
Table summarized based on 16-1-1-amended-protocol03 [8.1]

Table 13. Summary table of alirocumab dose modification - Open-label period

Treatment regimen	Q2W alirocumab	Q4W alirocumab
Starting dose at Week 24	40 Q2W mg, for BW < 50 kg 75 Q2W mg, for BW ≥ 50 kg	150 mg Q4W, for BW < 50 kg 300 mg Q4W, for BW ≥ 50 kg
After Week 24, dose up-titration according to BW increase	40 mg to 75 mg, for BW increased from <50 kg to ≥ 50 Kg	150 mg Q4W to 300 mg Q4W, for BW increased from <50 kg to ≥ 50 kg
Week 32 and onwards: Dose modification according to LDL-C and based on the Investigator's judgement	Up-titration: 40 mg Q2W to 75 mg Q2W, for BW < 50 kg; 75 mg Q2W to 150 mg Q2W, for BW ≥ 50 kg	Up-titration: 150 mg/Q4W to 75 mg/Q2W, for BW < 50 kg; 300 mg/Q4W to 150 mg/Q2W, for BW ≥ 50 kg
	Down-titration: 75 mg Q2W to 40 mg Q2W, for BW < 50 kg; 150 mg Q2W to 75 mg Q2W, for BW ≥ 50 kg	Down-titration: 75 mg Q2W to 40 mg Q2W, for BW < 50 kg; 150 mg Q2W to 75 mg Q2W, for BW ≥ 50 kg

BW: body weight; LDL-C: low density lipoprotein cholesterol; Q2W: every 2 weeks; Q4W: every 4 weeks
Table summarized based on 16-1-1-amended-protocol03 [8.1]

The study design is presented in **Figure 10** and **Figure 11** below.

Figure 10. Graphical Study Design - Q2W dosing regimen cohort
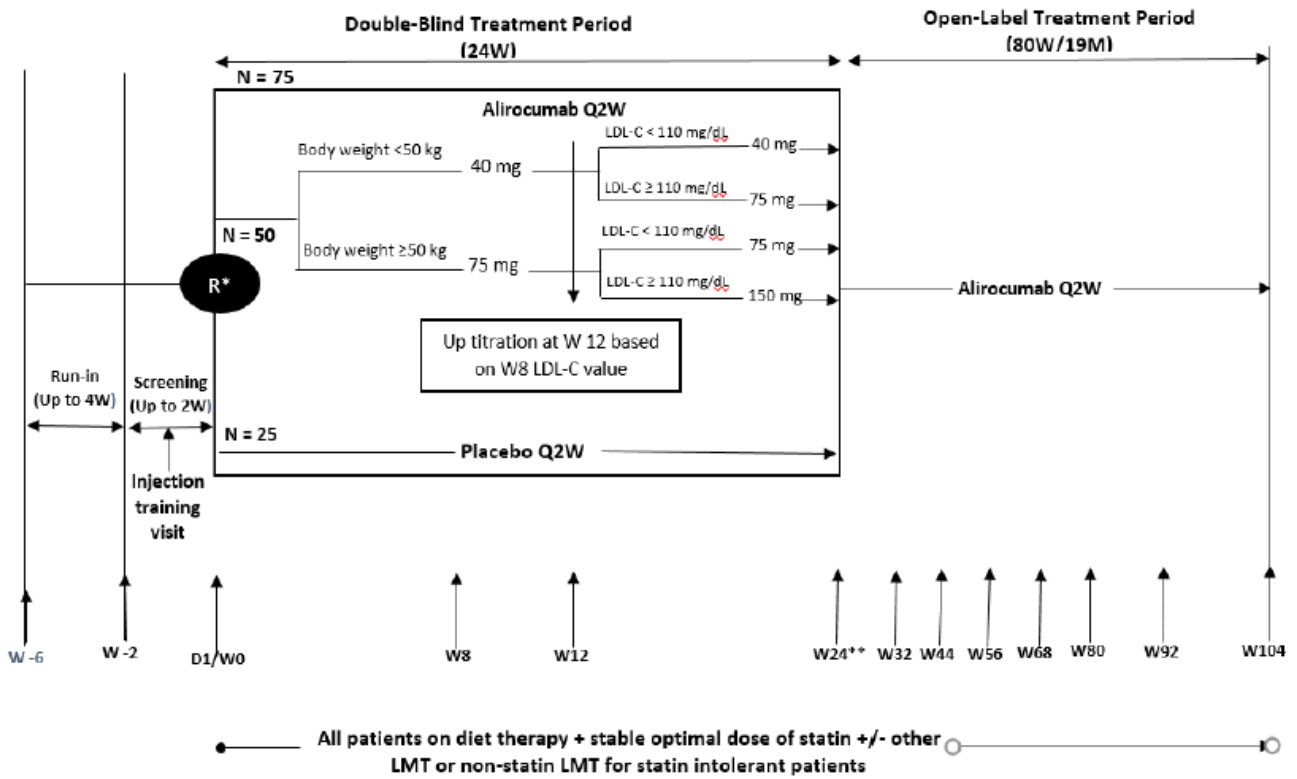
*Randomization will be stratified according to previous participation (yes or no) to the phase 2 DFI14223 study and baseline body weight (<50 or ≥50 kg)

**Primary efficacy endpoint at Week 24

Figure 11. Graphical Study Design - Q4W dosing regimen cohort

Figure 11 - Study Design – Q4W dosing regimen cohort
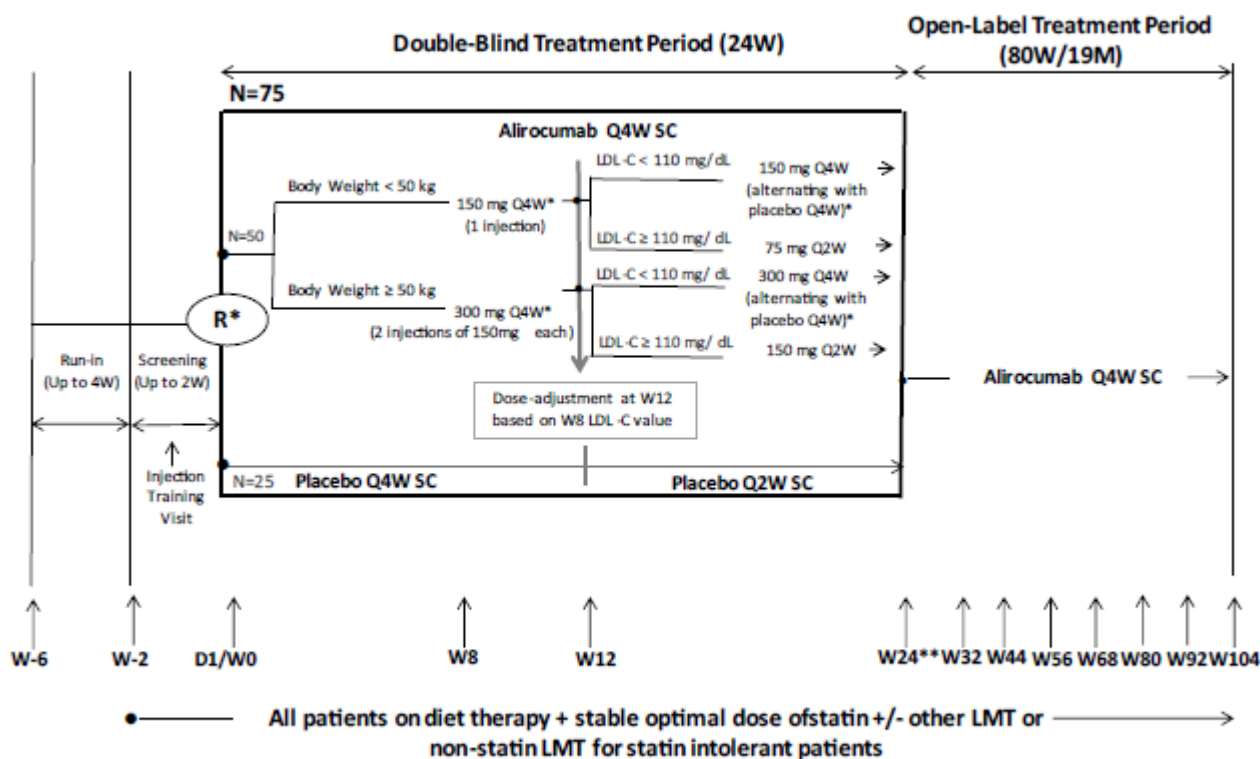
- First 12 weeks: administration Q4W. From W12 to W24, patients continuing alirocumab Q4W (w/o dose-adjustment) will be under a "fake Q2W*" regimen, with alirocumab Q4W alternating with placebo Q4W.
** Primary endpoint at W24.

The multicentre international double-blinded placebo-controlled design of the study is appropriate to achieve the primary objective of the study. The run-in/screening period of 4-6 weeks can be considered sufficient to establish a stable background condition. The 24-week double-blind treatment period is considered appropriate to provide reasonable results on the LDL-C (and other cholesterol parameters) lowering effect of alirocumab. After completing of the double-blind treatment period, subjects were offered to participate in the 80-week open-label treatment period where they will receive open-label alirocumab.

A 2:1 randomization was used in this study, which is considered appropriate.

The study evaluated 40 mg or 75 mg Q2W (for BW <50 kg or ≥50 kg) and 150 mg or 300 mg Q4W (for BW <50 kg or ≥50 kg), as a starting dose, with a subsequent option of up-titration at Week 12 based on Week 8 LDL-C values. Patients were up-titrated to alirocumab 75 mg Q2W (for patients on 40 mg Q2W), 150 mg Q2W (for patients on 75 mg Q2W), 75 mg Q2W (for patients on 150 mg Q4W), or 150 mg Q2W (for patients on 300mgQ4W) if the Week 8 LDL-C is ≥ 2.85 mmol/L (110 mg/dL). The cut-off value of LDL-C ≥ 2.85 mmol/L for up-titration is endorsed as the specific goal in paediatric patients with FH has not yet been determined; LDL-C goals in paediatric patients of <110 mg/dL (2.8 mmol/L), <100 mg/dL (2.6 mmol/L), or <130 mg/dL (3.4 mmol/L) have been proposed.

Objectives/ endpoints

The objectives/endpoints of Study EFC14643 are presented in Table 14.

Table 14. Objectives and endpoints of Study EFC14643

Objectives	Endpoints
Primary	
• To evaluate the efficacy of alirocumab administered every 2 weeks (Q2W) and every 4 weeks (Q4W) versus placebo after 24 weeks of double-blind (DB) treatment on low-density lipoprotein cholesterol (LDL-C) levels in patients with heterozygous familial hypercholesterolemia (heFH) 8 to 17 years of age on optimal stable daily dose of statin therapy ± other lipid modifying therapies (LMTs) or a stable dose of non-statin LMTs in case of intolerance to statins.	• Percent change in LDL-C from baseline to Week 24 in the intent-to-treat (ITT) population, using all LDLC values regardless of adherence to treatment (ITT estimand).
Secondary	
• To evaluate the efficacy of alirocumab versus placebo on LDL-C levels after 12 weeks of DB treatment.	• Percent change in LDL-C from baseline to Week 12 (ITT estimand)
• To evaluate the effects of alirocumab versus placebo on other lipid parameters (eg, Apolipoprotein B [Apo B], non-high density lipoprotein cholesterol [non-HDL-C], Totalcholesterol [Total-C], high-density lipoprotein cholesterol [HDL-C], Lipoprotein [a] [Lp[a]], Triglycerides [TGs], Apolipoprotein A-1[Apo A-1] levels) after 12 and 24 weeks of treatment.	• Percent change in Apo B, non-HDL-C, Total-C, Lp(a), HDL-C, TG, and ApoA1 from baseline to Week 24 (ITT estimand) • Percent change in Apo B, non-HDL-C, Total-C, Lp(a), HDL-C, TG, and ApoA1 from baseline to Week 12 (ITT estimand) • Proportion of patients achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 24 (ITT estimand) • Proportion of patients achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 12 (ITT estimand) • Proportion of patients achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 24 (ITT estimand) • Proportion of patients achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 12 (ITT estimand) • Percent change in LDL-C from baseline to Week 24 in the modified ITT (mITT) population, using all LDL-C values during the treatment period (on treatment estimand).

	• Percent change in LDL-C from baseline to Week 12 in the modified ITT (mITT) population, using all LDL-C values during the treatment period (on treatment estimand).
	• Proportion of patients achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 24 (on treatment estimand)
	• Proportion of patients achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 12 (on treatment estimand)
	• Proportion of patients achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 24 (on treatment estimand)
	• Proportion of patients achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 12 (on treatment estimand)
	• Absolute change in Apo B/Apo A-1 ratio to Week 12 and Week 24 (ITT and on-treatment estimands).
	• Proportion of patients achieving at least 30% reduction, 50% reduction in LDL-C at Week 24 (ITT and on-treatment estimands).
	• Proportion of patients achieving at least 30% reduction, 50% reduction in LDL-C at Week 12 (ITT and on-treatment estimands).
	• Percent change in LDL-C from baseline to Week 104 (ITT and on-treatment estimands).
• To evaluate the safety and tolerability of alirocumab after 24 weeks of treatment in comparison with placebo.	• adverse events (AE), serious AE (SAE), AE of special interest ([AESI] laboratory data, vital signs, body weight, height, Cogstate battery test, and Tanner stage after 24 weeks of treatment.
• To evaluate the efficacy, safety, and tolerability of alirocumab after 80 weeks of open label treatment.	• adverse events (AE), serious AE (SAE), AE of special interest ([AESI] laboratory data, vital signs, body weight, height, Cogstate battery test, and Tanner stage after 80 weeks of open label treatment.
• To evaluate the development of anti-alirocumab antibodies after 24 weeks of treatment during the double-blind (DB) treatment period.	• Anti-alirocumab antibodies assessed after 24 weeks of treatment during the DB treatment period.
Other	
• To evaluate the development of anti-alirocumab antibodies after 80 weeks of open label treatment	• Anti-alirocumab antibodies assessed throughout the study.

• To evaluate the pharmacokinetics (PK) of alirocumab	• Serum alirocumab concentrations assessed throughout the study (until Week 24).

a Primary and key secondary efficacy endpoints were analyzed in the mITT population using the on-treatment estimand.

A FMD sub-study explored the absolute change from baseline to Week 24 in flow mediated dilatation of the brachial artery. The analysis compared alirocumab to placebo, regardless of the dosing regimen cohort.

The primary endpoint of percent change from baseline to week 24 in LDL-C is considered appropriate to establish the LDL-C lowering effect of alirocumab. Secondary endpoints are considered acceptable to provide further insight into and confirmation of the primary objective.

A flow-mediated dilatation (FMD) sub-study explored the absolute change from baseline to Week 24 in flow-mediated dilatation of the brachial artery, which can be endorsed.

Sample size

With a randomization ratio of 2:1 (alirocumab: placebo) for each dosing regimen cohort, a total sample size of 90 patients (30 in each alirocumab dosing regimen group and 15 in each placebo dosing regimen group) will have 92% power to detect a difference in mean percent change in LDL-C of 30% between each alirocumab dosing regimen group and its contemporaneously randomized placebo dosing regimen group, with a 0.025 two-sided significance level per comparison and assuming a common standard deviation (SD) of 25%. Nevertheless, in order to have a sufficient number of paediatric patients for properly assessing the safety and tolerability of alirocumab, sample size was increased to 150 patients in total (50 in each alirocumab dosing regimen group and 25 in each placebo dosing regimen group). The enrollment of 150 patients will allow having a safety assessment over 2 years in approximately 128 patients, assuming a discontinuation rate of 15%.

Randomisation

The randomization followed a 2:1 ratio (2 alirocumab: 1 placebo) and was stratified according to previous participation in the Phase 2 study (DFI14223) and baseline BW value (<50 or $\geq$50 kg).

The randomisation procedure is considered acceptable. Stratification factors are limited to participation in the Phase 2 study and baseline BW value (<50 or ≥50 kg), which is also acceptable.

Blinding (masking)

This study consisted of a double-blind treatment period. During the double-blind treatment period, alirocumab and placebo for alirocumab will be provided in identically matched PFS (with or without safety system, depending on the time in the study) and packaged identically which includes labeling to protect the blind. Each double-blind treatment kit will be labeled with a number. The treatment kit numbers will be obtained by the Investigator at the time of patient randomization and subsequent patient visits scheduled via a centralized treatment allocation system that will be available 24 hours-a-day, 7 days-a-week. In accordance with the double-blind design, study patients, Investigators and study site personnel will remain blinded to study treatment and will not have access to the randomization (treatment codes) except under circumstances.

Statistical methods

The primary analysis population for the efficacy endpoints was the ITT population, defined as all randomized participants analyzed according to the intervention group allocated by randomization (ie, as-randomized intervention group). Statistical analyses for the primary and secondary efficacy endpoints were conducted in the DB treatment period and compared each alirocumab dosing regimen group with its contemporaneously randomized placebo group (i.e., of the same dosing regimen cohort, referred to as "its placebo group" in the result sections):

• alirocumab Q2W versus placebo Q2W

• alirocumab Q4W versus placebo Q4W

Of note, Q2W and Q4W cohorts refer to the dosing regimens initiated at randomization. Efficacy endpoints analyzed with the ITT estimand were analyzed in the ITT population. Efficacy endpoints analyzed with the on-treatment estimand were analyzed in the mITT population. The primary efficacy endpoint defined as percent change in LDL-C from baseline to Week 24 was analyzed in the ITT population using a MMRM approach. All post-baseline data available within Week 8 to Week 24 analysis windows were used and missing data were accounted for by the MMRM model. Sensitivity analyses including the pattern mixture model approach were also performed for the primary efficacy endpoint to explore the impact of non-ignorable missingness.

A separate model was run for each dosing regimen cohort, including the fixed categorical effects of intervention group (alirocumab, placebo), randomization strata, time point (Week 8, Week 12, Week 24), 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. Throughout the MMRM models, each alirocumab dosing regimen group was compared to its contemporaneously randomized placebo dosing regimen group using appropriate contrasts, and the 97.5% CI of the difference was provided.

Continuous secondary endpoints with normal distribution were analyzed within each dosing regimen cohort using the same MMRM models as for the primary endpoint with the corresponding baseline and post-baseline values. In addition, key continuous secondary efficacy endpoints with a normal distribution were also analyzed using the pattern mixture model for missing data as done for the primary efficacy endpoint.

Continuous secondary efficacy endpoints anticipated to have a non-normal distribution (TG and Lp [a]) were analyzed using a multiple imputation approach followed by a robust regression model using M-estimation (using SAS ROBUSTREG procedure) with treatment group, randomization strata as main effects and corresponding baseline value as covariate. For the respect to analyses of the efficacy parameters during the OL period, only descriptive summaries (description of change [% or absolute] over time) were provided in the OL population, which was defined as all randomized participants who received at least one dose or part of dose of the IMP during the OL treatment period.

The summary of other endpoints was presented by intervention group (placebo, alirocumab) within each dosing regimen cohort. A summary by intervention group regardless of the dosing regimen cohorts (pooled across the cohorts) was also displayed, except for pharmacokinetics and anti-alirocumab antibody assessments.

The exploratory endpoint of the FMD sub-study was the absolute change from baseline to Week 24 in flow mediated dilatation of the brachial artery (as determined by the central reading laboratory) regardless of adherence to treatment. The analysis used an ANCOVA model, with unequal variances by treatment group (except if convergence issue).

The extent of study treatment exposure and compliance were assessed and summarized by actual treatment received within the safety population.

The safety analysis was performed on the safety population (defined as the randomized population who did receive at least one dose or partial dose of the investigational product) analyzed according to the treatment actually received. Safety analyses presented each alirocumab dosing regimen group with its contemporaneously randomized placebo dosing regimen group and again each intervention group (placebo, alirocumab) regardless of the dosing regimen cohorts (pooled across the cohorts). Analyses were performed separately for the DB and the OL treatment period.

The database lock of the 24-week DB treatment period and unblinding occurred on 18 May 2021. All CSR results are based on the final analysis done on the final DBL of 31 August 2022.

Results

Participant flow

<u>Double-blind period</u>

A total of 153 participants were randomized to receive alirocumab or placebo intervention at 2:1 ratio. Of these, 74 participants were enrolled in the Q2W dosing regimen cohort (49 participants received alirocumab and 25 participants received placebo) and 79 participants were enrolled in the Q4W dosing regimen cohort (52 received alirocumab and 27 received placebo). Overall, in the randomized population, the rate of premature discontinuation of study intervention was low in both intervention groups (6.9% in the combined alirocumab group and 1.9% in the combined placebo group).

Among the 74 participants in the Q2W cohort, 45 (91.8%) participants in the alirocumab group and 25 (100%) participants in the placebo group completed the DB treatment period. Four (8.2%) participants in the alirocumab group prematurely discontinued before Week 24 due to "Subject moved" (1 [2.0%]), "Life events made continuing too difficult" (1 [2.0%]), and "Other" (2 [4.1%]). None of the treatment discontinuations in the Q2W cohort were due to COVID-19 related issues.

Among the 79 participants in the Q4W cohort, 49 (94.2%) participants in the alirocumab group and 26 (96.3%) participants in the placebo group completed the DB treatment period. Three (5.8%) participants in the alirocumab group and one (3.7%) participant in the placebo did not complete the DB treatment period. The participants who did not complete the 24-week DB treatment in the alirocumab group were due to "AE not related to COVID-19" (2 [3.8%]) and "Other reasons related to COVID-19" (1 [1.9%]), and 1 (3.7%) participant in the placebo group did not complete the 24-week DB treatment due to "Other" reasons not related to COVID-19 and related to IMP administration.

A total of 32 out of 42 (76.2%) participants randomized in the Phase 2 dose ranging study (DFI14223) were randomized in Study EFC14643. A wash-out period of at least 10 weeks was required between the last injection of alirocumab during the open-label extension of the DFI14223 study and the screening lipid assessment at the entry of the screening period for the EFC14643 study.

The figures below illustrate the disposition of participants in the DB treatment period of the study.

Figure 12. Disposition of participants - Double-blind period - Participants in the Q2W cohort

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                    ┌─────────────────┐    ┌────────────────────────────────────────┐
                    │  99 Screened    │    │ 25 (25.3%) screen failure              │
                    └────────┬────────┘    │ Not meeting inclusion criteria: I01 (4)│
                             │  ──────────▶│ Meeting exclusion criteria:            │
                             │             │ E02 (12), E04 (3), E12 (1), E19 (1), and│
                    ┌────────▼────────────┐│ E20 (5)                                │
                    │ 74 randomized and   │└────────────────────────────────────────┘
                    │     treated         │
                    └────────┬────────────┘
              ┌──────────────┴───────────────────────┐
     ┌────────▼─────────────────┐        ┌────────────▼─────────────┐
     │ 49 allocated to alirocumab│        │ 25 allocated to placebo  │
     │ 49 received alirocumab    │        │ 25 received placebo      │
     └────────┬──────────────────┘        └────────────┬─────────────┘
              │   ┌──────────────────────────────────┐ │
              │   │ 4 (8.2%) prematurely discontinued│ │
              │   │ DB treatment                     │ │
              │──▶│   4 due to other reasons         │ │
              │   │   1 related to participant moving│ │
              │   │   1 related to life events made  │ │
              │   │   continuing too difficult       │ │
              │   │   2 due to Otherª                │ │
              │   └──────────────────────────────────┘ │
     ┌────────▼─────────────────┐        ┌────────────▼─────────────┐
     │ 45 (91.8%) completed DB   │        │ 25 (100%) completed DB   │
     │   treatment period        │        │   treatment period       │
     └───────────────────────────┘        └──────────────────────────┘
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Figure 13. Disposition of participants - Double-blind period - Participants in the Q4W cohort

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                    ┌─────────────────┐    ┌────────────────────────────────────────┐
                    │ 104 Screened    │    │ 25 (24.0%) screen failure              │
                    └────────┬────────┘    │ Not meeting inclusion criteria: I01 (2)│
                             │  ──────────▶│ Meeting exclusion criteria:            │
                             │             │ E02 (14), E04 (2), E20 (3), and E21 (4)│
                    ┌────────▼────────────┐└────────────────────────────────────────┘
                    │ 79 randomized and   │
                    │     treated         │
                    └────────┬────────────┘
              ┌──────────────┴───────────────────────┐
     ┌────────▼─────────────────┐        ┌────────────▼─────────────┐
     │ 52 allocated to alirocumab│        │ 27 allocated to placebo  │
     │ 52 received alirocumab    │        │ 27 received placebo      │
     └────────┬──────────────────┘        └────────────┬─────────────┘
              │ ┌────────────────────────────┐         │ ┌─────────────────────────┐
              │ │ 3 (5.8%) prematurely       │         │ │ 1 (3.7%) prematurely    │
              │ │ discontinued DB treatment  │         │ │ discontinued DB treatment│
              │▶│   2 due to AE              │         │▶│   1 due to other reasons │
              │ │   1 due to other reasons   │         │ └─────────────────────────┘
              │ │   (related to COVID-19     │         │
              │ │   disruption)              │         │
              │ └────────────────────────────┘         │
     ┌────────▼─────────────────┐        ┌────────────▼─────────────┐
     │ 49 (94.2%) completed DB   │        │ 26 (96.3%) completed DB  │
     │   treatment period        │        │   treatment period       │
     └───────────────────────────┘        └──────────────────────────┘
```

Open-label period

Overall, 145 participants entered in open-label treatment period, 71 (95.9%) participants in the Q2W cohort (46 [93.9%] in alirocumab group and 25 [100%] in the placebo group) and 74 (93.7%) participants in the Q4W cohort (49 [94.2%] and 25 [92.6%]) entered the OL treatment Period (**Figure 14**).

Two participants entered the OL period whereas they had not completed all the dosing in the DB period. Specifically, one participant missed the IMP doses at Week 20 and Week 22, and the other participant missed Week 18, Week 20, and Week 22 IMP dose administration.

Among the 71 participants in the Q2W cohort, 65 (91.5%) completed OL treatment period. Six (8.5%) participants did not complete the OL treatment period due to "Adverse event" (1 [1.4%]), "Lack of efficacy" (1 [1.4%]), "Subject moved" (1 [1.4%]),"Life events made continuing too difficult" (1 [1.4%]), "Subject received OL treatment until Week 102 included but the subject didn't complete the visit 14/Week 104 because of family issues" (1 [1.4%]), and "Withdrawn from the study" (1 [1.4%]). Among the 74 participants in the Q4W cohort, 73 (98.6%) completed the OL treatment period. One (1.4%) participant did not complete OL period due to "Subject moved" (1 [1.4%]).

Figure 14. Disposition of participants - Open-label period

A total of 153 patients were randomized of which 74 patients in the Q2W dosing regimen cohort (49 and 25 in the alirocumab and placebo group, respectively) and 79 patients in the Q4W dosing regimen cohort (52 and 27 in the alirocumab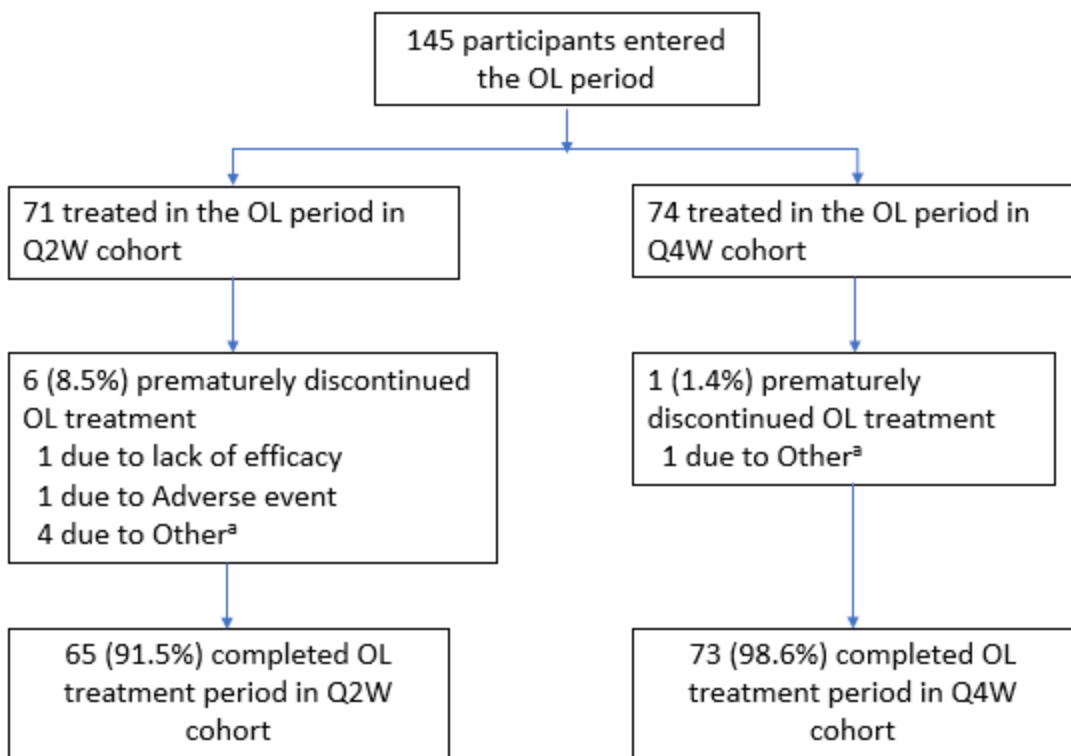 and placebo group, respectively). A high proportion of subjects completed the DB treatment period (91.8% vs 100% for the alirocumab and placebo group in the Q2W cohort and 94.2% vs 96.3% in the Q4W cohort). Four patients in the alirocumab group in the Q2W cohort and 3 patients in the alirocumab group in the Q4W cohort discontinued the DB treatment period of which "other" (n=2) and "due to AE" (n=2) were the most common.

Overall, 145 participants entered the open-label treatment period (71 in the Q2W cohort and 74 in the Q4W cohort). A high proportion of subjects completed the OL treatment period (91.5% (65/71) patients in the Q2W cohort and 98.6% (73/74) patients in the Q4W cohort). The most common reason for discontinuing the OL period was "other" (n=5).

Compliance

Double-blind treatment period

The overall compliance for DB injections was defined for each participant as 100 – (%days with under-planned dosing + %days with above-planned dosing).

Overall, the treatment compliance rate was high among intervention groups in both cohorts. In the Q2W cohort, all participants in both alirocumab and placebo group had ≥80% compliance for IMP injections (i.e., participants took ≥80% of their injections and at the scheduled times). In the Q4W cohort, 44 (84.6%) participants in the alirocumab group and 23 (85.2%) participants in the placebo group had ≥80% compliance for IMP injections.

The overall compliance for double-blind injections was relatively high since all participants in both the alirocumab and placebo group in the Q2W cohort had ≥80% compliance for IMP injections (i.e., participants took ≥80% of their injections and at the scheduled times). In contrast, in the Q4W cohort, 44 (84.6%) participants in the alirocumab group and 23 (85.2%) participants in the placebo group had ≥80% compliance for IMP injections. As such, a small difference in compliance could be observed between the Q2W and Q4W cohorts, however, it is difficult to draw firm conclusions since the number of subjects in each group was relatively small.

Protocol deviations

Criteria were predefined for minor, major, and critical protocol deviations by Sponsor standard procedures before the study start.

Double-blind treatment period

During the DB treatment period, no critical protocol deviations were reported, and major protocol deviations were reported in 51 participants overall. These deviations were sporadic with respect to the timing of their occurrence and were observed across intervention groups, with no apparent distribution pattern.

In the Q2W cohort, 18 participants reported major protocol deviations (15 [30.6%] in the alirocumab group and 3 [12.0%] participants in the placebo group) (Table 15). The most frequently reported major protocol deviations were in the categories "Informed consent procedures" (4 [8.2%] and no participants), "Assessments/Procedures" (4 [8.2%] and 2 [8.0%] respectively), and "source data records" (2 [4.1%] and 2 [8.0%] respectively). No participants in the Q2W cohort were excluded from population without trial impact (disruption) due to COVID-19 during the DB treatment period.

In the Q4W cohort, 33 participants reported major protocol deviations (20 [38.5%] participants in the alirocumab group and 13 [48.1%] participants in the placebo group)(Table 16). The most frequently reported major protocol deviations were in the categories "IMP management" (12 [23.1%] and 5 [18.5%] respectively) and "Assessments/Procedures" (8 [15.4%] and 6 [22.2%] respectively). Among them, 12 participants (6 [11.5%] and 6 [22.2%]) had major protocol deviations without trial impact (disruption) due to COVID-19, with the most frequently reported deviation in the category of "Assessment/Procedures" (5 [9.6%] and 5 [18.5%]) ([16.2.2.10.1]). These 12 participants with major protocol deviations were excluded from the "population without trial impact/disruption due to COVID-19".

Regarding the major protocol deviations in IMP management, in the Q2W dose regimen, 1/25 (4.0%) in placebo group versus 3/49 (6.1%) in the alirocumab group had at least 1 deviation in the "IMP management" category. In 3 patients, 2 in the alirocumab group and one in the placebo group, the IMP management deviation was "IMP not stored /handled as per protocol", however the dose was injected. In the third patient in the alirocumab group, IMP was administered but not as per protocol. In the Q4W dose

regimen, 5/27 (18.5%) in placebo group versus 12/52 (23.1%) in the alirocumab group had at least one major deviation in the "IMP management" category. Most of the protocol deviations in this category were linked to "Compliance below 80%":

- In the placebo group, 3 patients did not switch to a Q2W regimen following the Week 12 visit and continued injecting every 4 weeks, leading to report major protocol deviation linked to IMP management due to low compliance. The 2 remaining patients, both with a bodyweight ≥50 kg, received one injection instead of two in a row up to Week 12.
- In the alirocumab group, 8 patients did not switch to a Q2W regimen following the Week 12 visit and continued injecting every 4 weeks, leading to report major protocol deviation linked to IMP management due to low compliance. Among the 4 other patients, 1 patient forgot to inject at Week 14; 1 patient with a bodyweight ≥50 kg received one injection instead of two in a row up to Week 12; 1 patient missed the second injections on Day 1 and Week 4, and 1 patient missed the Day 1 injection.

Through a post-hoc descriptive analysis excluding patients with a least one major protocol deviations linked to IMP management, it has been verified that excluding these patients had no or little impact on the LDL-C changes from baseline, compared to the ITT analysis:

- In the Q2W cohort, the mean (SD) in the percent change (%) in LDL-C from baseline were 9.4 (21.6) and -34.1 (23.1) in the placebo and alirocumab groups, respectively in the ITT analysis (raw data), compared to 8.8 (21.8) and -35.9 (22.3) in the analysis excluding patients with major protocol deviations linked to IMP management.

- In the Q4W cohort the mean (SD) percent change (%) in LDL-C from baseline was of -5.2 (23.4) and -38.2 (25.7) in the placebo and alirocumab groups, respectively, in the ITT analysis (raw data), compared to -4.6 (25.4) and -39.3 (24.7) in the analysis excluding patients with major protocol deviations linked to IMP management.

Open-label treatment period
During the OL treatment period, no critical protocol deviations were reported, and major protocol deviation were reported in 25 (35.2%) participants in the Q2W cohort and 15 (20.3%) participants in the Q4W cohort. These deviations were sporadic with respect to the timing of their occurrence.

Table 15. Critical or major protocol deviations - Double-blind period - Patients in the Q2W cohort –
Randomized population

Deviation category Deviation term n (%)	Placebo (N=25)	Alirocumab (N=49)
Any critical or major protocol deviations	3 (12.0)	15 (30.6)
Informed consent procedures	0	4 (8.2)
Informed consent/Assent form obtained with a misconduct in consent process or documentation	0	3 (6.1)
Informed consent/Assent form not obtained for an amendment requiring a re-consent	0	1 (2.0)
Inclusion/Exclusion criteria	1 (4.0)	1 (2.0)
Patients not at stable dose(s) of statins +/- other LMTs for at least 4 weeks during the screening period.	1 (4.0)	0
Patients who use systemic corticosteroids.	0	1 (2.0)
Randomization procedure	0	1 (2.0)
Wrong randomization stratum	0	1 (2.0)
IMP Management	1 (4.0)	3 (6.1)
IMP not stored /handled as per protocol	1 (4.0)	2 (4.1)
IMP administered but not as per protocol	0	1 (2.0)
Concomitant Medications/ Therapy	2 (8.0)	2 (4.1)
Protocol-specified co-administered therapy/medication/ vaccine not administered as per protocol	1 (4.0)	1 (2.0)
Protocol prohibited therapy/medication/vaccine administered	0	1 (2.0)
Protocol-specified co-administered therapy/vaccine/medication not administered	1 (4.0)	0
Assessments/Procedures	2 (8.0)	4 (8.2)
Sequence of study procedures as specified in the protocol is not followed	2 (8.0)	2 (4.1)
Study physical visit, phone call or safety contact not performed	0	1 (2.0)
Study procedure performed by unqualified / unauthorized personnel	0	1 (2.0)

Deviation category Deviation term n (%)	Placebo (N=25)	Alirocumab (N=49)
Clinical Safety	0	1 (2.0)

Failure to report
    AE/AESI/SAE/Pregnancy/Overdose to sponsor
    within the protocol-specified time window
	0	1 (2.0)

Regulatory	0	1 (2.0)
Failure to comply with local regulatory requirements	0	1 (2.0)
Source data records	2 (8.0)	2 (4.1)
Lost, nonexistent, missing or incomplete source data	2 (8.0)	2 (4.1)

IMP: Investigational Medicinal Product

n (%) = number and percentage of patients with at least one critical or major automatic/quantitative or manual/qualitative deviation

Note: Percentages are calculated using the number of patients randomized as denominator

A patient can be counted in several deviation categories

Automatic deviations are identified based on pre-configured rules from the data available in the clinical database

Manual deviations are detected based on monitoring activities at site level, and may also be detected during audits or inspections
PGM=PRODOPS/SAR236553/EFC14643/CSR/REPORT/PGM/dev_critmaj_r_t.sas OUT=REPORT/OUTPUT/dev_critmaj_db_q2_r_t_i.rtf
(14SEP2022 12:26)

Table 16. Critical or major protocol deviations - Double-blind period - Patients in the Q4W cohort - Randomized population

Deviation category Deviation term n (%)	Placebo (N=27)	Alirocumab (N=52)
Any critical or major protocol deviations	13 (48.1)	20 (38.5)
Informed consent procedures	1 (3.7)	2 (3.8)

Informed consent/Assent form obtained with a
      misconduct in consent process or
      documentation
	0	2 (3.8)

Informed consent/Assent form not obtained for an amendment requiring a re-consent	1 (3.7)	0
Randomization procedure	4 (14.8)	0
IMP kit number actually dispensed to the subject is different from the IMP kit number allocated	2 (7.4)	0
Subject randomized in IVRS prior to confirmation of eligibility.	1 (3.7)	0
Wrong randomization stratum	1 (3.7)	0
IMP Management	5 (18.5)	12 (23.1)
IMP administered but not as per protocol	5 (18.5)	12 (23.1)
IMP accountability not done	0	1 (1.9)
Assessments/Procedures	6 (22.2)	8 (15.4)
Planned sample (Blood samples, urine samples, PK and ADA) not performed	4 (14.8)	3 (5.8)
Planned sample (Blood samples) not performed within the protocol-specified time window	2 (7.4)	2 (3.8)
Study physical visit, phone call or safety contact not performed	0	2 (3.8)

Planned sample (Blood samples, urine samples,
      PK and ADA) not performed within the
      protocol-specified time window
	0	1 (1.9)

Deviation category Deviation term n (%)	Placebo (N=27)	Alirocumab (N=52)
Clinical Safety	0	1 (1.9)
Failure to report AE/AESI/SAE/Pregnancy/Overdose to sponsor within the protocol-specified time window	0	1 (1.9)

IMP: Investigational Medicinal Product

n (%) = number and percentage of patients with at least one critical or major automatic/quantitative or manual/qualitative deviation

Note: Percentages are calculated using the number of patients randomized as denominator

A patient can be counted in several deviation categories

Automatic deviations are identified based on pre-configured rules from the data available in the clinical database

Manual deviations are detected based on monitoring activities at site level, and may also be detected during audits or inspections

PGM=PRODOPS/SAR236553/EFC14643/CSR/REPORT/PGM/dev_critmaj_r_t.sas OUT=REPORT/OUTPUT/dev_critmaj_db_q4_r_t_i.rtf (14SEP2022 12:26)

The percentages of major protocol deviations were relatively high (30.6% vs 12.0% in the Q2W cohort and 38.5% vs 48.1% in the Q4W cohort for alirocumab and placebo, respectively). The most frequently reported major protocol deviations were in the category "IMP management" (n=3 vs 1 in the Q2W cohort and n=12 vs 5 in the Q4W cohort for alirocumab and placebo, respectively). The Applicant has sufficiently substantiated that the major deviations in IMP management had no impact on efficacy or safety. Additionally, the Applicant had conducted a post-hoc descriptive analysis excluding patients with at least one major protocol deviation linked to IMP management, indicating that these deviations had no or little impact on the LDL-C changes from baseline.

Recruitment

The study was conducted at 43 centers in 24 countries/regions worldwide. Overall, 14 European countries participated in the study: Austria, Bulgaria, Czech Republic, Denmark, Finland, France, Hungary, Italy, the Netherlands, Norway, Poland, Slovenia, Spain, and Sweden. In these countries, a total of 83 patients were randomized and exposed in the study: 45 patients (14 in the placebo group and 32 in the alirocumab group) in the Q2W cohort, and 38 patients (16 in the placebo group and 22 in the alirocumab group) in the Q4W cohortThe first patient was enrolled on 31 May 2018 and the last patient completed their last visit on 5 August 2022.

This study was a multicentre study (n=43). Considering that almost half of the subjects were from Europe (83 out of 153 (54%), the population is sufficiently representative for Europe.

Conduct of the study

The original protocol (dated 21 December 2017) was modified per 1 global nonsubstantial amendment (amended protocol 01 dated 13 September 2018) and 2 global substantial amendments (amended protocol 02 dated 02 January 2019 and amended protocol 03 dated 06 January 2021).

To limit the impact of the COVID-19 pandemic to the study conduct, alternative methods for safety assessments were implemented.

The main reasons for this protocol amendment are the following:

- To enable changes in statistical analyses to reflect the sequential enrolment in the 2 cohorts of patients defined by the dosing regimen, since enrolment in the every 4 weeks (Q4W) cohort started when enrolment in the every 2 weeks (Q2W) cohort was completed,

- To include the possibility to perform remote monitoring in the context of regional or national emergency such as the current COVID-19 pandemic, and

- To clarify the flexibility that the Interactive Response Technology (IRT) system allows during the open-label extension period with regard to the dose adjustment of alirocumab.

No amendments were made that would compromise the endpoints or outcomes of the study. The amendments are considered valuable and are, therefore, acceptable. The enrolment of subjects in the Q4W cohort started when enrolment in the Q2W was completed. During the Phase 2 study it was decided to add an extra 4th cohort with a higher dose since the effect size of the other Q4W dose cohort was considered too low. However, due to the expected time required to conduct the Cohort 4 in the Phase 2 study, and not to delay the Phase 3 study start, the Phase 3 study was initiated with the Q2W cohort only.

Baseline data

Demographic characteristics at baseline were generally similar across the Q2W and Q4W cohorts except for gender and previous participation to the DFI14223 study. More female participants were included in the Q4W cohort (49 [62.0%]) than in the Q2W cohort (38 [51.4%]). More participants had participated in the DFI14223 study in the Q2W cohort than in the Q4W cohort due to the sequential enrollment order (i.e., earlier enrollment for Q2W). Among the 32 participants from the DFI14223 study, 29 (39.2%) were enrolled in the Q2W cohort and 3 (3.8%) in the Q4W cohort. These participants were exposed to alirocumab in the DFI14223 study and went through a wash-out period of at least 10 weeks between the last injection of alirocumab in the DFI14223 study and the screening lipid assessment at entry in the screening period of this Phase 3 study.

The mean (SD) age of the randomized population was 12.9 (2.8) years (range: 8 to 17 years) with most of the participants (98 out of 153 [64.1%]) ≥12 years old at baseline. A total of 66 (43.1%) male and 87 (56.9%) female participants were included in the study, most of them were White (125 [81.7%]). The mean (SD) body weight and BMI of the randomized population were 53.1 (19.1) kg and 21.3 (5.0) kg/m2, respectively.

In the Q2W cohort, demographics and participant characteristics at baseline were balanced between intervention groups except for gender (Table 17): more female participants were in the alirocumab group than in the placebo group (30 [61.2%] versus 8 [32.0%] respectively). The mean (SD) age was 12.8 (2.6) years. Majority of the participants were ≥12 years of age; 30 (61.2%) and 19 (76.0%) participants in the alirocumab and placebo group, respectively. Mean (SD) body weight at baseline was 52.7 (20.1) kg (53.9 [22.2] kg and 50.4 [15.1] kg for alirocumab and placebo group, respectively); and roughly half the participants in each group (25 [51.0%] and 13 [52.0%] respectively) had a BW <50 kg. The mean (SD) BMI was 21.0 (5.3) kg/m2; 12 (16.2%) participants were overweight (BMI percentile ≥85 to <95) and 15 (20.3%) were obese (BMI percentile ≥95).

In the Q4W cohort, demographics and participant characteristics at baseline were balanced between intervention groups (Table 18). The mean (SD) age was 13.0 (3.0) years. Majority of the participants were ≥12 years of age: 32 (61.5%) and 17 (63.0%) participants in the alirocumab and placebo group, respectively. More than half of the participants were female: 34 (65.4%) and 15 (55.6%) female participants were included in the alirocumab and placebo group, respectively. Mean (SD) body weight at baseline was 53.4 (18.3) kg (54.7 [20.2] kg and 50.9 [14.0] kg for the alirocumab and placebo group, respectively). More participants in the Q4W cohort were Hispanic or Latino compared to the Q2W cohort (24 [30.4%] compared to 4 [5.4%] participants, respectively). More participants had a BW ≥ 50 kg, but the distribution is similar in both groups (32 [61.5%] participants in the alirocumab group and 17

[63.0%] participants in the placebo group). The mean (SD) BMI was 21.6 (4.7) kg/m2; 22 (27.8%) participants were overweight (BMI percentile ≥85 to <95) and 15 (19.0%) were obese (BMI percentile ≥ 95).

Baseline values for the primary efficacy parameter (LDL-C) were similar across cohorts and intervention groups in the randomized population. In the Q2W cohort, the mean (SD) LDL-C at baseline was 169.69 (46.74) mg/dL and 175.29 (50.23) mg/dL (for the alirocumab and placebo group, respectively. In the Q4W cohort, the mean (SD) LDL-C at baseline was 176.79 (53.93) mg/dL and 176.57 (49.01) mg/dL , respectively.

All enrolled participants had the diagnosis of HeFH confirmed either by clinical Simon Broome criteria or by genotyping. Sixty-two (83.8%) participants in the Q2W cohort and 76 (96.2%) participants in the Q4W cohort had the diagnosis of HeFH confirmed by genotyping. Other participants had the diagnosis of HeFH made on clinical Simon Broome criteria. The median time from diagnosis of HeFH to study entry was 4.13 years (range: 0 to 13.7 years) for participants in the Q2W cohort and 2.11 years (range: 0 to 13.1 years) for participants in the Q4W cohort.

At baseline, 98.6% and 91.1% of participants in the Q2W and Q4W cohorts, respectively, received any statin (Table 19 and Table 20). A majority of the participants were treated with maximal doses of statin (ie, the maximum tolerated dose of statin due to adverse event at higher dose) at baseline (71 [95.9%] in the Q2W cohort and 71 [89.9%] in the Q4W cohort). Other participants (3 [4.1%] in the Q2W cohort and 8 [10.1%] in the Q4W cohort) were reported statin intolerant as defined by protocol. Among them, 2 participants in the Q2W cohort and 2 in the Q4W cohort were treated with statin but did not tolerate daily doses.

The medical history profiles were balanced between cohorts and intervention groups. Most of the participants had cardiovascular history and cardiovascular risk factors (73 [98.6%] participants in the Q2W cohort and 77 [97.5%] participants in the Q4W cohort). Overall, 42 (27.5%) participants in DB period had a medical history of allergies, and the most frequent allergies were allergic rhinitis (21 [13.7%]), pollen allergies (18 [11.8%]), and asthma (9 [5.9%]).

Table 17. Demographics and patient characteristics at baseline - Double-blind period - Patients in the Q2W cohort – Randomized population

	Placebo (N=25)	Alirocumab (N=49)	All (N=74)
Age (years)			
Number	25	49	74
Mean (SD)	13.2 (2.4)	12.5 (2.7)	12.8 (2.6)
Median	14.0	12.0	13.0
Min ; Max	8 ; 17	8 ; 17	8 ; 17
Age group (years) [n(%)]			
Number	25	49	74
<10	2 (8.0)	9 (18.4)	11 (14.9)
≥10 to <12	4 (16.0)	10 (20.4)	14 (18.9)
≥12	19 (76.0)	30 (61.2)	49 (66.2)

Age group (years) [n(%)]			
Number	25	49	74
<12	6 (24.0)	19 (38.8)	25 (33.8)
≥12	19 (76.0)	30 (61.2)	49 (66.2)

Sex [n(%)]			
Number	25	49	74
Female	8 (32.0)	30 (61.2)	38 (51.4)
Male	17 (68.0)	19 (38.8)	36 (48.6)

Race [n(%)]			
Number	25	49	74
White	23 (92.0)	42 (85.7)	65 (87.8)
Black or African American	0	1 (2.0)	1 (1.4)
Black or African American/White	1 (4.0)	3 (6.1)	4 (5.4)
Asian	1 (4.0)	1 (2.0)	2 (2.7)
Native Hawaiian or other Pacific Islander	0	1 (2.0)	1 (1.4)
Native Hawaiian or other Pacific Islander/White	0	1 (2.0)	1 (1.4)
American Indian or Alaska Native	0	0	0
Not Reported	0	0	0

Ethnicity [n(%)]			
Number	25	49	74
Hispanic or Latino	2 (8.0)	2 (4.1)	4 (5.4)
Not Hispanic or Latino	23 (92.0)	46 (93.9)	69 (93.2)
Not reported	0	1 (2.0)	1 (1.4)
Unknown	0	0	0

Height (cm)			
Number	25	49	74
Mean (SD)	156.6 (14.0)	156.2 (16.5)	156.3 (15.6)
Median	158.0	158.0	158.0
Min ; Max	125 ; 181	125 ; 191	125 ; 191

Weight (kg)			
Number	25	49	74
Mean (SD)	50.4 (15.1)	53.9 (22.2)	52.7 (20.1)
Median	49.0	49.0	49.0
Min ; Max	25 ; 93	26 ; 126	25 ; 126

Weight [n(%)]			
Number	25	49	74
< 50 kg	13 (52.0)	25 (51.0)	38 (51.4)
≥ 50 kg	12 (48.0)	24 (49.0)	36 (48.6)

BMI (kg/m^2)			
Number	25	49	74
Mean (SD)	20.3 (4.2)	21.3 (5.7)	21.0 (5.3)
Median	19.2	20.1	19.5

	Placebo (N=25)	Alirocumab (N=49)	All (N=74)
Min ; Max	15 ; 32	15 ; 45	15 ; 45
BMI percentiles (kg/m^2) [n(%)]			
Number	25	49	74
<P5: Underweight	3 (12.0)	3 (6.1)	6 (8.1)
≥P5 to <P85: Healthy weight	15 (60.0)	26 (53.1)	41 (55.4)
≥P85 to <P95: Overweight	2 (8.0)	10 (20.4)	12 (16.2)
≥P95: Obesity	5 (20.0)	10 (20.4)	15 (20.3)
Previous participation to the DFI14223 study [n(%)][a]			
Number	25	49	74
Yes	10 (40.0)	19 (38.8)	29 (39.2)
No	15 (60.0)	30 (61.2)	45 (60.8)

BMI: Body mass index

a Previous participation to the DFI14223 phase 2 study as per eCRF data.

PGM=PRODOPS/SAR236553/EFC14643/CSR/REPORT/PGM/dem_demo_r_t.sas
OUT=REPORT/OUTPUT/dem_demo_r_q2_t_db_i.rtf (15SEP2022 8:56)

Table 18. Demographics and patient characteristics at baseline - Double-blind period - Patients in the Q4W cohort – Randomized population

	Placebo (N=27)	Alirocumab (N=52)	All (N=79)
Age (years)			
Number	27	52	79
Mean (SD)	12.8 (3.0)	13.1 (3.0)	13.0 (3.0)
Median	13.0	13.5	13.0
Min ; Max	8 ; 17	8 ; 17	8 ; 17
Age group (years) [n(%)]			
Number	27	52	79
<10	7 (25.9)	8 (15.4)	15 (19.0)
≥10 to <12	3 (11.1)	12 (23.1)	15 (19.0)
≥12	17 (63.0)	32 (61.5)	49 (62.0)
Age group (years) [n(%)]			
Number	27	52	79
<12	10 (37.0)	20 (38.5)	30 (38.0)
≥12	17 (63.0)	32 (61.5)	49 (62.0)
Sex [n(%)]			
Number	27	52	79
Female	15 (55.6)	34 (65.4)	49 (62.0)
Male	12 (44.4)	18 (34.6)	30 (38.0)
Race [n(%)]			
Number	27	52	79
White	22 (81.5)	38 (73.1)	60 (75.9)
Black or African American	1 (3.7)	1 (1.9)	2 (2.5)

	Placebo (N=27)	Alirocumab (N=52)	All (N=79)
Black or African American/White	0	0	0
Asian	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Native Hawaiian or other Pacific Islander/White	0	0	0
American Indian or Alaska Native	4 (14.8)	12 (23.1)	16 (20.3)
Not Reported	0	1 (1.9)	1 (1.3)
Ethnicity [n(%)]			
Number	27	52	79
Hispanic or Latino	6 (22.2)	18 (34.6)	24 (30.4)
Not Hispanic or Latino	21 (77.8)	34 (65.4)	55 (69.6)
Not reported	0	0	0
Unknown	0	0	0
Height (cm)			
Number	27	52	79
Mean (SD)	154.2 (13.0)	155.6 (16.5)	155.1 (15.3)
Median	158.5	155.5	156.0
Min ; Max	132 ; 179	126 ; 187	126 ; 187
Weight (kg)			
Number	27	52	79
Mean (SD)	50.9 (14.0)	54.7 (20.2)	53.4 (18.3)
Median	52.0	51.5	51.9
Min ; Max	25 ; 76	26 ; 133	25 ; 133
Weight [n(%)]			
Number	27	52	79
< 50 kg	10 (37.0)	20 (38.5)	30 (38.0)
≥ 50 kg	17 (63.0)	32 (61.5)	49 (62.0)
BMI (kg/m^2)			
Number	27	52	79
Mean (SD)	21.0 (4.0)	22.0 (5.1)	21.6 (4.7)
Median	20.1	21.6	20.9
Min ; Max	14 ; 29	14 ; 45	14 ; 45
BMI percentiles (kg/m^2) [n(%)]			
Number	27	52	79
<P5: Underweight	0	1 (1.9)	1 (1.3)
≥P5 to <P85: Healthy weight	16 (59.3)	25 (48.1)	41 (51.9)
≥P85 to <P95: Overweight	5 (18.5)	17 (32.7)	22 (27.8)
≥P95: Obesity	6 (22.2)	9 (17.3)	15 (19.0)
Previous participation to the DFI14223 study [n(%)][a]			
Number	27	52	79
Yes	1 (3.7)	2 (3.8)	3 (3.8)
No	26 (96.3)	50 (96.2)	76 (96.2)

BMI: Body mass index

a   Previous participation to the DFI14223 phase 2 study as per eCRF data.

PGM=PRODOPS/SAR236553/EFC14643/CSR/REPORT/PGM/dem_demo_r_t.sas OUT=REPORT/OUTPUT/dem_demo_r_q4_t_db_i.rtf
(15SEP2022 8:56)

Table 19. Background LMT at baseline - Double-blind period - Patients in the Q2W cohort – Randomized population

	Placebo (N=25)	Alirocumab (N=49)	All (N=74)
Any Statin	24 (96.0)	49 (100)	73 (98.6)
Atorvastatin daily dose (mg)			
<10	2 (8.0)	2 (4.1)	4 (5.4)
10	6 (24.0)	22 (44.9)	28 (37.8)
20	8 (32.0)	6 (12.2)	14 (18.9)
40	0	0	0
80	0	0	0
Other	0	1 (2.0)	1 (1.4)
Rosuvastatin daily dose (mg)			
<5	0	1 (2.0)	1 (1.4)
5	0	3 (6.1)	3 (4.1)
10	1 (4.0)	6 (12.2)	7 (9.5)
20	2 (8.0)	0	2 (2.7)
40	0	0	0
Other	1 (4.0)	0	1 (1.4)
Simvastatin daily dose (mg)			
<10	0	0	0
10	1 (4.0)	1 (2.0)	2 (2.7)
20	0	0	0
40	0	0	0
>40	0	0	0
Other	0	0	0
Pravastatin daily dose (mg)			
<10	0	0	0
10	2 (8.0)	1 (2.0)	3 (4.1)
20	1 (4.0)	3 (6.1)	4 (5.4)
40	0	1 (2.0)	1 (1.4)
>40	0	0	0
Other	0	1 (2.0)	1 (1.4)
Pitavastatin daily dose (mg)			
0.14	0	1 (2.0)	1 (1.4)
Any LMT other than statin [a]	4 (16.0)	5 (10.2)	9 (12.2)
Any LMT other than nutraceuticals	3 (12.0)	2 (4.1)	5 (6.8)
Ezetimibe	3 (12.0)	2 (4.1)	5 (6.8)
Fenofibrate	0	0	0
Nutraceuticals	1 (4.0)	3 (6.1)	4 (5.4)
Omega 3 fatty acids (<1000mg/day)	0	1 (2.0)	1 (1.4)
Phytosterols	1 (4.0)	2 (4.1)	3 (4.1)
Psyllium/plantago	0	0	0
Policosanol	0	0	0
Other nutraceuticals	0	0	0

a   in combination with statins or not.
Note: LMT are those the patient used at the randomization.
PGM=PRODOPS/SAR236553/EFC14643/CSR/REPORT/PGM/dem_lmt_r_t.sas
OUT=REPORT/OUTPUT/dem_lmt_r_db_q2_t_i.rtf (15SEP2022 9:15)

Table 20. Background LMT at baseline - Double-blind period - Patients in the Q4W cohort – Randomized population

	Placebo (N=27)	Alirocumab (N=52)	All (N=79)
Any Statin	24 (88.9)	48 (92.3)	72 (91.1)
Atorvastatin daily dose (mg)			
<10	3 (11.1)	3 (5.8)	6 (7.6)
10	5 (18.5)	6 (11.5)	11 (13.9)
20	5 (18.5)	8 (15.4)	13 (16.5)
40	4 (14.8)	13 (25.0)	17 (21.5)
80	0	0	0
Other	0	1 (1.9)	1 (1.3)
Rosuvastatin daily dose (mg)			
<5	0	0	0
5	2 (7.4)	2 (3.8)	4 (5.1)
10	1 (3.7)	4 (7.7)	5 (6.3)
20	1 (3.7)	1 (1.9)	2 (2.5)
40	0	2 (3.8)	2 (2.5)
Other	1 (3.7)	2 (3.8)	3 (3.8)
Simvastatin daily dose (mg)			
<10	0	0	0
10	0	1 (1.9)	1 (1.3)
20	0	0	0
40	1 (3.7)	0	1 (1.3)
>40	0	0	0
Other	0	1 (1.9)	1 (1.3)
Pravastatin daily dose (mg)			
<10	0	0	0
10	0	1 (1.9)	1 (1.3)
20	1 (3.7)	3 (5.8)	4 (5.1)
40	0	0	0
>40	0	0	0
Other	0	0	0
Any LMT other than statin [a]	4 (14.8)	15 (28.8)	19 (24.1)
Any LMT other than nutraceuticals	4 (14.8)	12 (23.1)	16 (20.3)
Ezetimibe	4 (14.8)	12 (23.1)	16 (20.3)
Fenofibrate	0	0	0
Nutraceuticals	1 (3.7)	3 (5.8)	4 (5.1)
Omega 3 fatty acids (<1000mg/day)	0	2 (3.8)	2 (2.5)
Phytosterols	0	0	0
Psyllium/plantago	0	0	0
Policosanol	0	0	0
Other nutraceuticals	1 (3.7)	1 (1.9)	2 (2.5)

a in combination with statins or not.
Note: LMT are those the patient used at the randomization.
PGM=PRODOPS/SAR236553/EFC14643/CSR/REPORT/PGM/dem_lmt_r_t.sas
OUT=REPORT/OUTPUT/dem_lmt_r_db_q4_t_i.rtf (15SEP2022 9:16)

In general, baseline data, including age group, BW and LDL-C are well distributed across the two cohorts and treatment groups, which is reassuring for interpreting the data. However, in the Q2W cohort, there were more female patients in the alirocumab group compared with the placebo group (61.2% vs 32.0%, respectively). Furthermore, more patients participated in the Phase 2 dose-finding study in the Q2W cohort than in the Q4W cohort since enrolment in the Q4W cohort started when enrolment in the Q2W cohort was completed. These disbalances would likely not have a clinically relevant impact on the outcome.

Overall, the study population can be considered representative of a paediatric HeFH population. HeFH diagnosis was sufficiently established as the diagnosis was for a large part of the population by genetic testing (83.8% and 96.2% in the Q2W and Q4W cohort, respectively). The mean (SD) age of the randomized population was 12.9 (2.8) years, with most of the patients (64.1% (n= 98/153)) ≥12-17 years of age at baseline, whereas 19.0% (n=29/153) of the patients were ≥10 to < 12 years of age and 16.3% (n=25/153) of the patients were < 10 years of age, which is considered appropriate for the sought indication, i.e. patients aged 8-17 years of age. Moreover, the elevated mean LDL-C baseline value of 4.5 mmol/L reasonably corresponds to an LDL-C level generally observed within a HeFH population.

The majority of the patients have received any statin therapy (98.6% and 91.1% of participants in the Q2W and Q4W cohorts), which is conform the inclusion criterion "Patients must receive the optimal dose of statin defined as the stable daily dose prescribed based on regional practice or local guidelines or was the stable daily dose that was maximally tolerated due to adverse effects on higher doses". Further, 12.2% and 24.1% of patients in the Q2W and Q4W cohorts received any LMTs other than statins, respectively. Other patients (4.1% (n=3) in the Q2W cohort and 10.1% (n=8) in the Q4W cohort) were reported statin intolerant as defined by the protocol. As such, paediatric patients who are statin intolerant were underrepresented. However, given the experience of alirocumab therapy in statin-intolerant adults, this issue is not pursued.

Numbers analysed

The randomized population consisted of 153 participants (Table 21 and Table 22).

During the DB treatment period, all randomized participants were included in the ITT, mITT, and safety population. Accordingly, the ITT, mITT, and safety populations are identical.

The FMD sub-study population included 28 participants (11 in the Q2W cohort and 17 in the Q4W cohort).

The OL population included 145 participants (71 in the Q2W cohort and 74 in the Q4W cohort).

Table 21. Analysis populations - Double-blind period - Patients in the Q2W cohort - Randomized population

	Placebo (N=25)	Alirocumab (N=49)	All (N=74)
Randomized population	25 (100%)	49 (100%)	74 (100%)
Efficacy populations	25 (100%)	49 (100%)	74 (100%)
ITT population	25 (100%)	49 (100%)	74 (100%)
mITT population	25 (100%)	49 (100%)	74 (100%)
Exploratory efficacy population	3	8	11
FMD sub-study population	3	8	11
Safety population	25	49	74
PK population	25	49	74
Anti-alirocumab antibody population	25	48	73
Population without trial impact (disruption) due to COVID-19 during DB period	25	49	74
OLE population	25	46	71
Population without trial impact (disruption) due to COVID-19 during OLE period	23	46	69

Note: The safety and PK population patients are tabulated according to treatment actually received (as treated)
For the other populations, patients are tabulated according to their randomized treatment
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OUT=REPORT/OUTPUT/dis_populations_r_q2_t_db_i.rtf (15SEP2022 8:30)

Table 22. Analysis populations - Double-blind period - Patients in the Q4W cohort - Randomized population

	Placebo (N=27)	Alirocumab (N=52)	All (N=79)
Randomized population	27 (100%)	52 (100%)	79 (100%)
Efficacy populations	27 (100%)	52 (100%)	79 (100%)
ITT population	27 (100%)	52 (100%)	79 (100%)
mITT population	27 (100%)	52 (100%)	79 (100%)

Exploratory efficacy population	5	12	17
FMD sub-study population	5	12	17
Safety population	27	52	79
PK population	26	50	76
Anti-alirocumab antibody population	26	50	76
Population without trial impact (disruption) due to COVID-19 during DB period	21	46	67
OLE population	25	49	74
Population without trial impact (disruption) due to COVID-19 during OLE period	24	49	73

Note: The safety and PK population patients are tabulated according to treatment actually received (as treated)

For the other populations, patients are tabulated according to their randomized treatment

PGM=PRODOPS/SAR236553/EFC14643/CSR/REPORT/PGM/dis_populations_a_t_type.sas

OUT=REPORT/OUTPUT/dis_populations_r_q4_t_db_i.rtf (15SEP2022 8:30)

Outcomes and estimation

Primary endpoint

Double-blind treatment period

The study met its primary objective: a statistically significant difference in favor of alirocumab compared to placebo was observed for the primary efficacy endpoint (percent change in LDL-C from baseline to Week 24 in the ITT population) in both dosing regimen cohorts.

- In the Q2W cohort, the LS mean (SE) percent change in LDL-C from baseline to Week 24 was -33.6% (3.4) in the alirocumab group compared to +9.7% (4.3) in the placebo group, with an LS mean difference versus placebo of -43.3% ([97.5% CI: -56.0 to -30.7]; p<0.0001) (ITT estimand), resulting in an LS mean (SE) LDL-C at Week 24 of 2.929 (0.147) mmol/L in the alirocumab group versus 4.820 (0.213) mmol/L in the placebo group (**Table 23**). Reductions were observed in both BW categories with a higher effect observed with 40 mg Q2W: -48.5% [7.6] with the 40 mg Q2W dose for BW <50 kg, and -38.0% [7.8] with the 75 mg Q2W dose for BW ≥50 kg (Table 10).

- In the Q4W cohort, the LS mean (SE) percent change in LDL-C from baseline to Week 24 was -38.2% (4.0) in the alirocumab group compared to -4.4% (3.7) in the placebo group, with an LS mean difference versus placebo of -33.8% ([97.5% CI: -46.4 to -21.2]; p<0.0001) (ITT estimand), resulting in an LS mean (SE) LDL-C at Week 24 of 2.847 (0.200) mmol/L in the alirocumab group versus 4.177 (0.180) mmol/L in the placebo group (Table 24). The response was consistent across the 2 doses by the BW category with a reduction of -34.5% (9.5) with the 150 mg Q4W dose for BW <50 kg and -32.9% (7.0) with the 300 mg Q4W for BW ≥50 kg (Table 10).

Sensitivity analyses assessing the robustness of the primary efficacy analysis with regard to handling of missing data (i.e., Pattern Mixture Model and Multiple Imputations [under MAR assumption]), randomization stratum mistakes, impact of COVID-19, and excluding participants who previously participated in the Phase 2 DFI14223 study showed results consistent with the primary analysis.

In the alirocumab groups in both Q2W and Q4W dosing regimen cohorts, a rapid decrease in LDL-C from baseline was observed from Week 8 onwards (ie., the first LDL-C post-baseline assessment time point) (**Figure 15** and **Figure 16**). In the alirocumab Q2W and Q4W groups, the percent changes in LDL-C (LS mean [SE] versus baseline) were - 35.4% (3.6) and - 42.0% (2.8) at Week 8, - 34.8% (3.0) and - 39.2% (3.3) at Week 12, and - 33.6% (3.4) and - 38.2% (4.0) at Week 24, respectively.

A sustained reduction in LDL-C was observed at each of the subsequent timepoints, demonstrating maintenance of efficacy over time to Week 24.

Table 23. Percent change from baseline in LDL-C at Week 24: MMRM - ITT analysis - Patients in the Q2W cohort - ITT population

LDL Cholesterol	Placebo (N=25)	Alirocumab (N=49)
Baseline (mmol/L)		
Number	25	49
Mean (SD)	4.540 (1.301)	4.395 (1.211)
Median	4.400	4.000
Min : Max	2.63 ; 7.50	2.69 ; 8.61
Baseline (mg/dL)		
Number	25	49
Mean (SD)	175.3 (50.2)	169.7 (46.7)
Median	169.9	154.4
Min : Max	102 ; 290	104 ; 332
Week 24 percent change from baseline (%)		
LS mean (SE)	9.7 (4.3)	-33.6 (3.4)
LS mean difference (SE) vs Placebo		-43.3 (5.5)
97.5% CI		(-56.0 to -30.7)
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, 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 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 type-I error rate at the 0.025 level within a dosing regimen cohort.

Table 24. Percent change from baseline in LDL-C at Week 24: MMRM - ITT analysis - Patients in the Q4W cohort - ITT population

LDL Cholesterol	Placebo (N=27)	Alirocumab (N=52)
Baseline (mmol/L)		
Number	26	50
Mean (SD)	4.610 (1.280)	4.553 (1.419)
Median	4.440	4.255
Min : Max	2.04 ; 6.65	2.25 ; 8.45
Baseline (mg/dL)		
Number	26	50
Mean (SD)	178.0 (49.4)	175.8 (54.8)
Median	171.4	164.3
Min : Max	79 ; 257	87 ; 326

LDL Cholesterol	Placebo (N=27)	Alirocumab (N=52)
Week 24 percent change from baseline (%)		
LS mean (SE)	-4.4 (3.7)	-38.2 (4.0)
LS mean difference (SE) vs Placebo		-33.8 (5.5)
97.5% CI		(-46.4 to -21.2)
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, BW randomization strata as per IVRS, time point, treatment-by-time point interaction, BW strata-by-time point interaction, as well as the continuous fixed covariates of baseline 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.
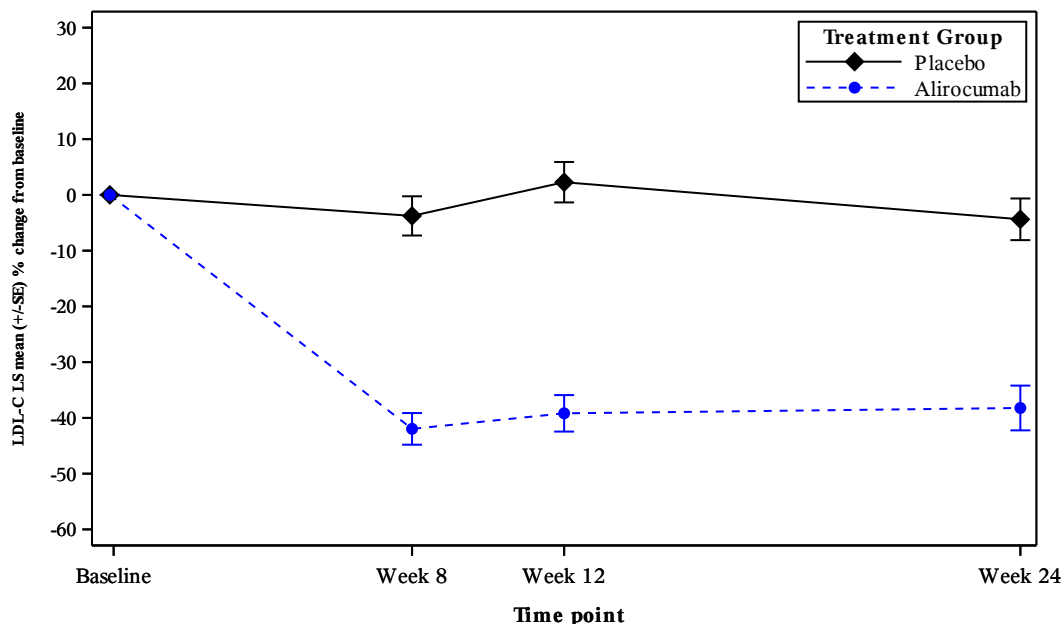
The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the type-I error rate at the 0.025 level within a dosing regimen cohort.

Figure 15. LDL-C LS mean (+/-SE) percent change from baseline: Time profile - ITT analysis - Patients in the Q2W cohort - 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, time point (Week 8, Week 12, Week 24), 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 LDL-C value-by-time point interaction.

Figure 16. LDL-C LS mean (+/-SE) percent change from baseline: Time profile - ITT analysis - Patients in the Q4W cohort - 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, time point (Week 8, Week 12, Week 24), 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 LDL-C value-by-time point interaction.

The between-group (alirocumab versus placebo) LS mean difference estimates in LDL-C percent change from baseline to Week 24 were consistent across all subgroup categories in both Q2W and Q4W cohorts (**Figure 17** and **Figure 18**).

Figure 17. Percent change from baseline in LDL-C at Week 24: Subgroup analyses - Forest plot - ITT analysis - Patients in the Q2W cohort - ITT population
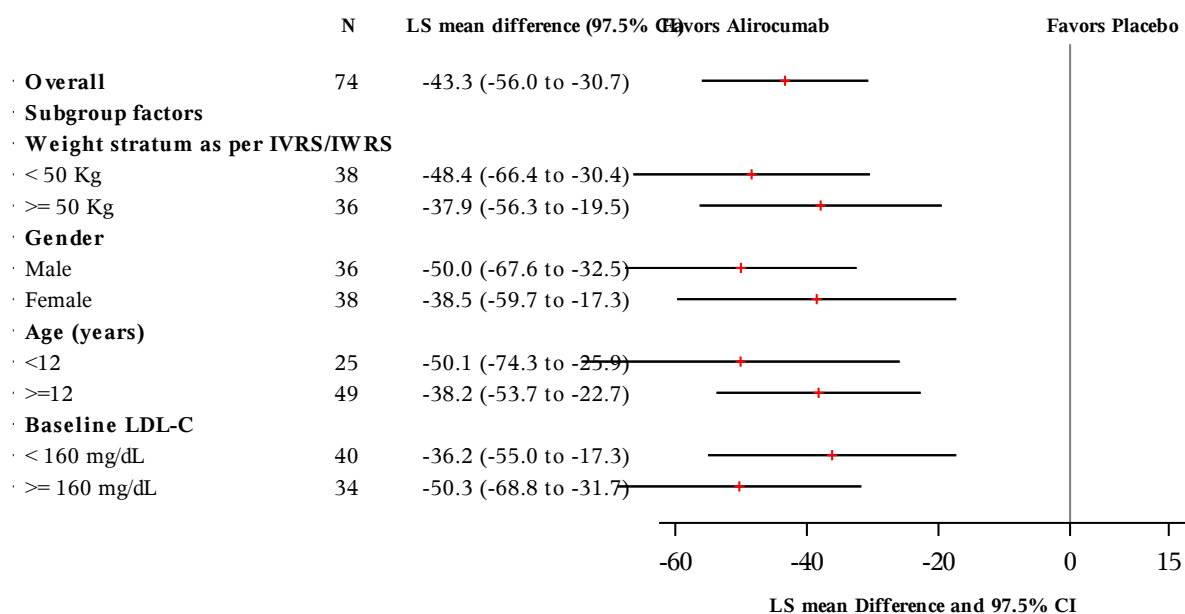
	N	LS mean difference (97.5% CI)	Favors Alirocumab	Favors Placebo
Overall	74	-43.3 (-56.0 to -30.7)		
Subgroup factors				
Weight stratum as per IVRS/IWRS				
< 50 Kg	38	-48.4 (-66.4 to -30.4)		
>= 50 Kg	36	-37.9 (-56.3 to -19.5)		
Gender				
Male	36	-50.0 (-67.6 to -32.5)		
Female	38	-38.5 (-59.7 to -17.3)		
Age (years)				
<12	25	-50.1 (-74.3 to -25.9)		
>=12	49	-38.2 (-53.7 to -22.7)		
Baseline LDL-C				
< 160 mg/dL	40	-36.2 (-55.0 to -17.3)		
>= 160 mg/dL	34	-50.3 (-68.8 to -31.7)		

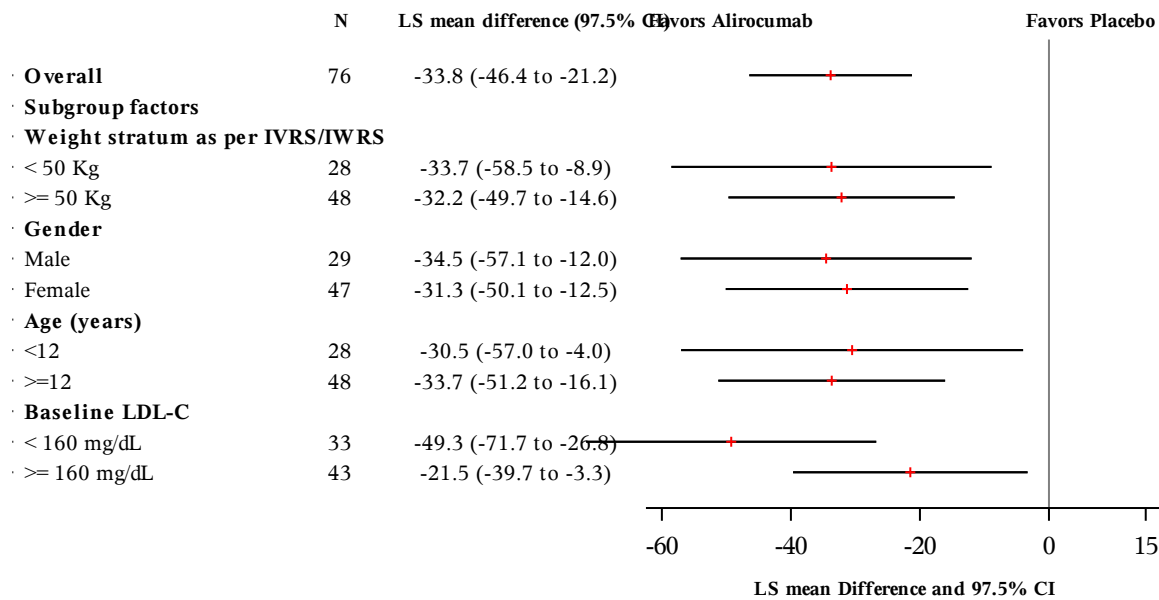LS mean Difference and 97.5% CI

Figure 18. Percent change from baseline in LDL-C at Week 24: Subgroup analyses - Forest plot - ITT analysis - Patients in the Q4W cohort - ITT population

	N	LS mean difference (97.5% CI)	Favors Alirocumab	Favors Placebo
Overall	76	-33.8 (-46.4 to -21.2)		
Subgroup factors				
Weight stratum as per IVRS/IWRS				
< 50 Kg	28	-33.7 (-58.5 to -8.9)		
>= 50 Kg	48	-32.2 (-49.7 to -14.6)		
Gender				
Male	29	-34.5 (-57.1 to -12.0)		
Female	47	-31.3 (-50.1 to -12.5)		
Age (years)				
<12	28	-30.5 (-57.0 to -4.0)		
>=12	48	-33.7 (-51.2 to -16.1)		
Baseline LDL-C				
< 160 mg/dL	33	-49.3 (-71.7 to -26.8)		
>= 160 mg/dL	43	-21.5 (-39.7 to -3.3)		

LS mean Difference and 97.5% CI

(x-axis: -60, -40, -20, 0, 15)

Open-label period

In the Q2W cohort, the LS mean (SE) percent reduction of LDL-C from baseline to Week 104 was - 25.8% (4.9) in the "Alirocumab in the DB period" group and - 22.8% (5.1) in the "Placebo in the DB period" group. In the Q2W cohort, the LS means (SD) percent change of LDL-C from baseline to Week 104 was - 26.3% (28.0) (**Figure 19**).

In the Q4W cohort, the LS mean (SE) percent reduction of LDL-C from baseline to Week 104 was - 23.4 (4.7) in the "Alirocumab in the DB period" group and - 27.6% (7.6) in the "Placebo in the DB period" group. Particularly, the LS means (SD) percent change of LDL-C from baseline to Week 104 was - 23.9% (33.5) in the Q4W cohort (**Figure 20**).

While relatively large reductions of LDL-C were observed in the OL treatment period in both the Q2W and Q4W cohorts, the percent reductions of LDL-C from baseline during the OL treatment period were somewhat lower as compared to the DB treatment period. This observation appeared to be related to a less strict application of the rules regarding dose up titration/adjustment during the OL treatment period, as revealed by the post-hoc analyses.

However, the percent reductions of LDL-C from baseline at Week 104 were associated with meaningful proportion of participants achieving the target of LDL-C below 130 mg/dL or reduction from baseline above 50%, these results are consistent with the therapeutic goals defined for the paediatric population with HeFH in current international guidelines for the management of dyslipidemia.

Figure 19. LDL-C mean (+/-SE) percent change from baseline: Time profile - Combined period - On-treatment analysis - Patients in the Q2W cohort - Open-label extension population
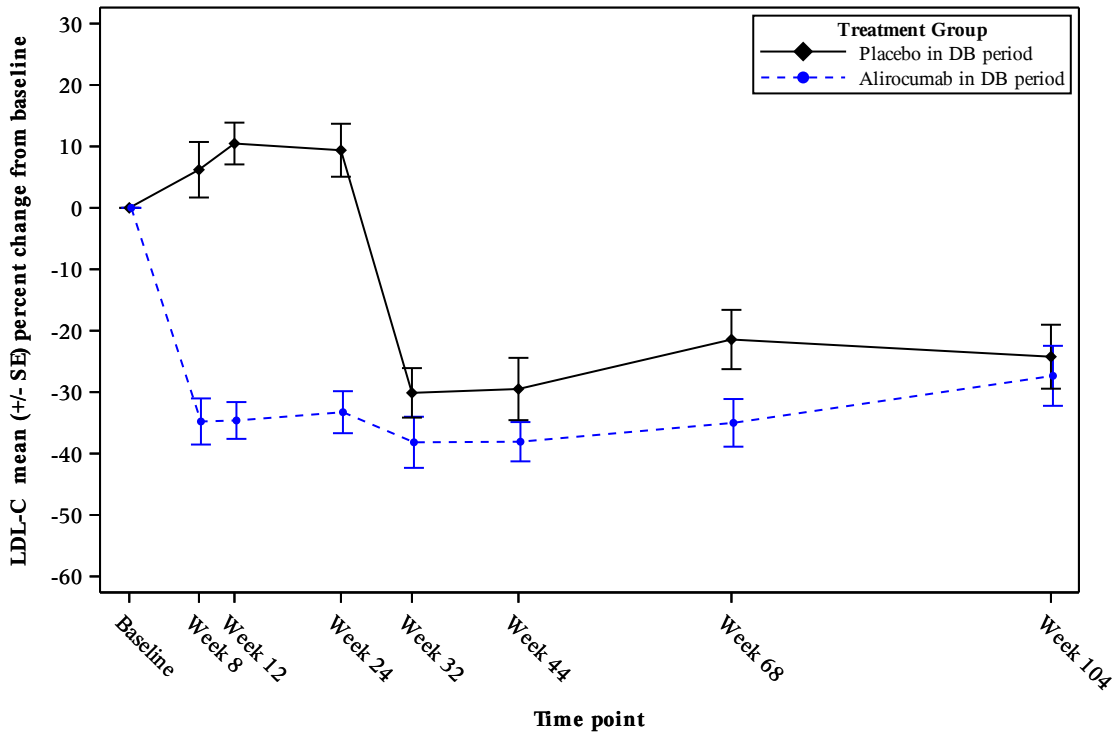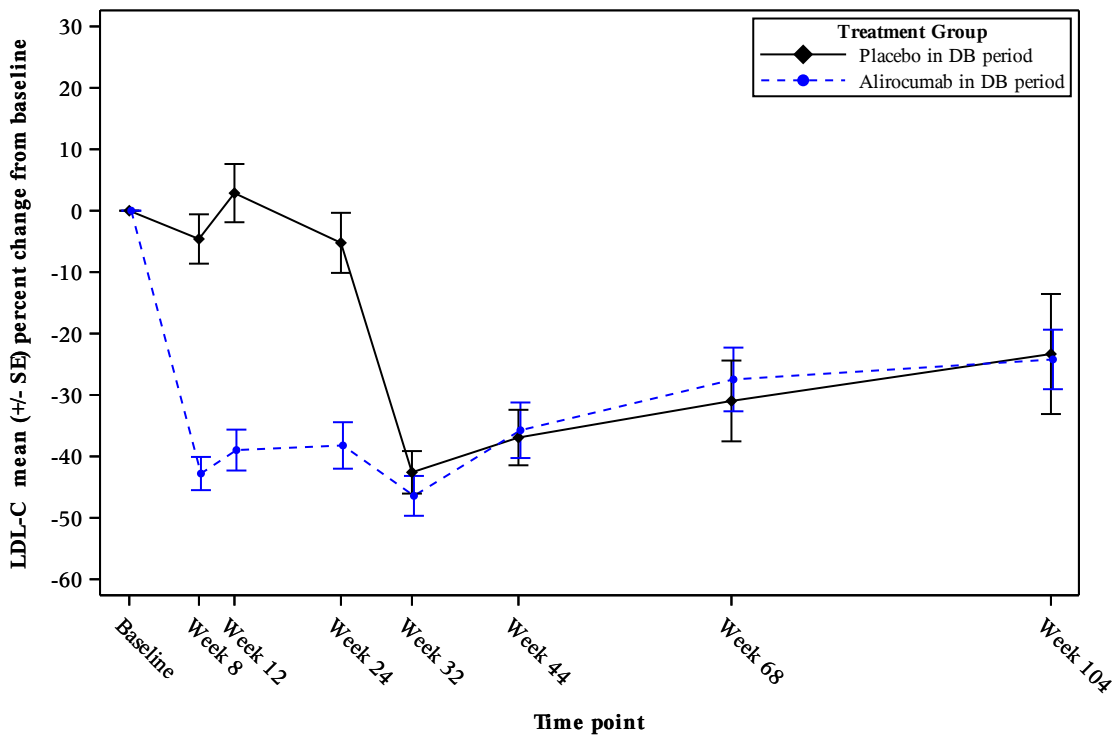

Figure 20. LDL-C mean (+/-SE) percent change from baseline: Time profile - Combined period - On-treatment analysis - Patients in the Q4W cohort - Open-label extension population

<u>Dose modifications</u>

Double-blind treatment period
Among the 74 participants who were in Q2W cohort and received at least 1 injection after Week 12, 22 out of 49 (44.9%) participants in the alirocumab group (11 with BW <50 kg and 11 with BW ≥50 kg) had received automatic dose up-titration in a blinded manner.
Among the 79 participants who were in Q4W cohort and received at least 1 injection after Week 12, 15 out of 52 (28.8%) participants in the alirocumab group (5 with BW <50 kg and 10 with BW ≥50 kg) had received automatic dose adjustment in a blinded manner.

Dose up-titration/adjustment at Week 12 provided an additional moderate LDL-C reduction in the Q4W cohort, and minimal effect in the Q2W cohort in participants who underwent a change in dosing at Week 12 (**Table 25**, **Table 26**, **Figure 21**, and **Figure 22**).

Since the Q4W starting regimen is currently proposed for children and adolescents 8 to 17 years of age with HeFH in section 4.2 of the SmPC, the focus to justify the dose adjustments was primarily on the up-titration regimen combined with the Q4W starting dose regimen. At Week 24, following dose adjustment, an additional decrease in the percent change from baseline in LDL-C was measured in the Q4W cohort (mean percent change from baseline in LDL-C of -34.2% at Week 24 versus -26.8% at Week 12). Dose adjustment allowed also more participants to achieve the recommended target of LDL-C <3.37 mmol/L (9 [64.3%] participants), LDL-C <2.84 mmol/L (5 [35.7%)] participants) and >50 % reduction in LDL-C from baseline (5 [35.7%)] participants) at Week 24 (Table 1). Importantly, the safety profile of alirocumab remained unchanged after dose adjustment. In participants who were not dose adjusted at Week 12, the change from baseline in LDL-C and the proportions of participants reaching the recommended LDL-C targets were either stable or decreased between Week 12 and Week 24. The mean (SD) change from baseline was -1.688 (1.081) mmol/L at Week 24 versus -1.794 (0.907) mmol/L at Week 12 (Table 2). The number (%) of participants achieving LDL-C <3.37 mmol/L was 27 (84.4%) participants) versus 29 (93.5%) participants at Week 12, achieving LDL-C <2.84 mmol/L, 10 (31.3%) participants at Week 24 versus 25 (80.6%) at Week 12, and achieving >50 % reduction in LDL-C from baseline, 10 (31.3%) participants at Week 24 versus 13 (41.9%) at Week 12 (**Table 27**).

Table 25. LDL-C values over time according to up-titration/dose-adjustment status- Q2W cohort

	Without up-titration/dose-adjustment (N=27)			With up-titration/dose-adjustment (N=22)		
	Value	Change from baseline	Percent change from baseline	Value	Change from baseline	Percent change from baseline
LDL-C (mmol/L)						
Baseline						
Number	27			22		
Mean (SD)	3.909 (0.745)			4.991 (1.410)		
Median	3.840			4.855		
Q1 ; Q3	3.450 ; 4.020			3.930 ; 5.640		
Min ; Max	2.69 ; 6.11			2.90 ; 8.61		
Week 8						
Number	27	27	27	22	22	22
Mean (SD)	1.958 (0.375)	-1.951 (0.757)	-48.6 (13.0)	3.891 (1.334)	-1.100 (1.287)	-18.8 (26.3)
Median	1.920	-2.000	-52.0	3.435	-0.930	-23.7
Q1 ; Q3	1.790 ; 2.100	-2.330 ; -1.460	-55.5 ; -42.0	3.040 ; 4.040	-2.360 ; -0.140	-40.9 ; -4.2
Min ; Max	1.04 ; 2.77	-3.83 ; -0.28	-70 ; -9	2.91 ; 8.86	-2.90 ; 1.71	-49 ; 50

Week 12						
Number	27	27	27	20	20	20
Mean (SD)	2.337 (0.704)	-1.572 (0.818)	-39.4 (17.6)	3.632 (1.566)	-1.445 (1.172)	-28.4 (21.8)
Median	2.270	-1.610	-42.0	3.415	-1.360	-28.9
Q1 ; Q3	1.790 ; 2.668	-2.160 ; -0.940	-52.2 ; -30.4	2.690 ; 4.200	-2.470 ; -0.928	-45.8 ; -21.5
Min ; Max	1.09 ; 4.20	-3.60 ; 0.20	-68 ; 5	1.53 ; 7.99	-3.42 ; 0.88	-62 ; 21
Week 24						
Number	24	24	24	21	21	21
Mean (SD)	2.412 (0.785)	-1.536 (0.848)	-38.2 (19.0)	3.462 (1.531)	-1.555 (1.302)	-29.3 (26.7)
Median	2.155	-1.600	-41.8	2.950	-1.640	-36.8
Q1 ; Q3	1.800 ; 3.069	-2.300 ; -0.810	-49.8 ; -25.9	2.480 ; 4.170	-2.240 ; -0.740	-47.5 ; -13.0
Min ; Max	1.23 ; 4.04	-2.77 ; 0.21	-69 ; 5	1.90 ; 8.29	-3.55 ; 1.14	-65 ; 39

Table 26. LDL-C values over time according to up-titration/dose-adjustment status- Q4W cohort

	Without up-titration/dose-adjustment (N=33)			With up-titration/dose-adjustment (N=15)		
	Value	Change from baseline	Percent change from baseline	Value	Change from baseline	Percent change from baseline
LDL-C (mmol/L)						
Baseline						
Number	33			15		
Mean (SD)	3.980 (1.055)			5.753 (1.450)		
Median	3.990			5.510		
Q1 ; Q3	3.280 ; 4.470			4.480 ; 6.810		
Min ; Max	2.25 ; 7.17			3.91 ; 8.45		
Week 8						
Number	33	33	33	13	13	13
Mean (SD)	2.051 (0.576)	-1.929 (1.058)	-46.3 (19.1)	3.852 (1.527)	-2.000 (1.254)	-33.8 (15.0)
Median	2.110	-1.960	-49.4	3.440	-1.810	-35.7
Q1 ; Q3	1.787 ; 2.430	-2.460 ; -1.270	-60.1 ; -35.5	3.060 ; 3.910	-2.920 ; -1.170	-44.9 ; -27.2
Min ; Max	0.39 ; 2.84	-5.15 ; 0.10	-84 ; 4	2.85 ; 8.71	-4.35 ; 0.26	-53 ; 3
Week 12						
Number	31	31	31	14	14	14
Mean (SD)	2.157 (0.779)	-1.794 (0.907)	-44.5 (19.7)	4.022 (1.616)	-1.552 (1.479)	-26.8 (23.7)
Median	2.130	-1.680	-42.3	3.750	-1.470	-29.0
Q1 ; Q3	1.690 ; 2.640	-2.250 ; -1.140	-59.0 ; -34.0	3.140 ; 3.990	-2.720 ; -0.060	-45.6 ; -1.0
Min ; Max	0.57 ; 4.03	-4.23 ; 0.39	-77 ; 17	2.46 ; 8.39	-3.67 ; 1.23	-59 ; 22
Week 24						
Number	31	31	31	14	14	14
Mean (SD)	2.314 (1.155)	-1.688 (1.081)	-42.1 (22.0)	3.700 (1.919)	-2.016 (1.853)	-34.2 (28.3)
Median	2.260	-1.520	-41.3	2.855	-1.881	-43.1
Q1 ; Q3	1.500 ; 2.540	-2.220 ; -0.980	-57.9 ; -34.7	2.710 ; 4.800	-4.080 ; -0.290	-55.3 ; -5.3
Min ; Max	0.75 ; 6.44	-5.09 ; 0.54	-77 ; 19	1.58 ; 8.89	-4.56 ; 0.76	-74 ; 19

Figure 21. LDL-C mean (+/-SE) percent change from baseline according to up-titration/dose-adjustment status - Time Profile - Patients in alirocumab group with at least one- Q2W
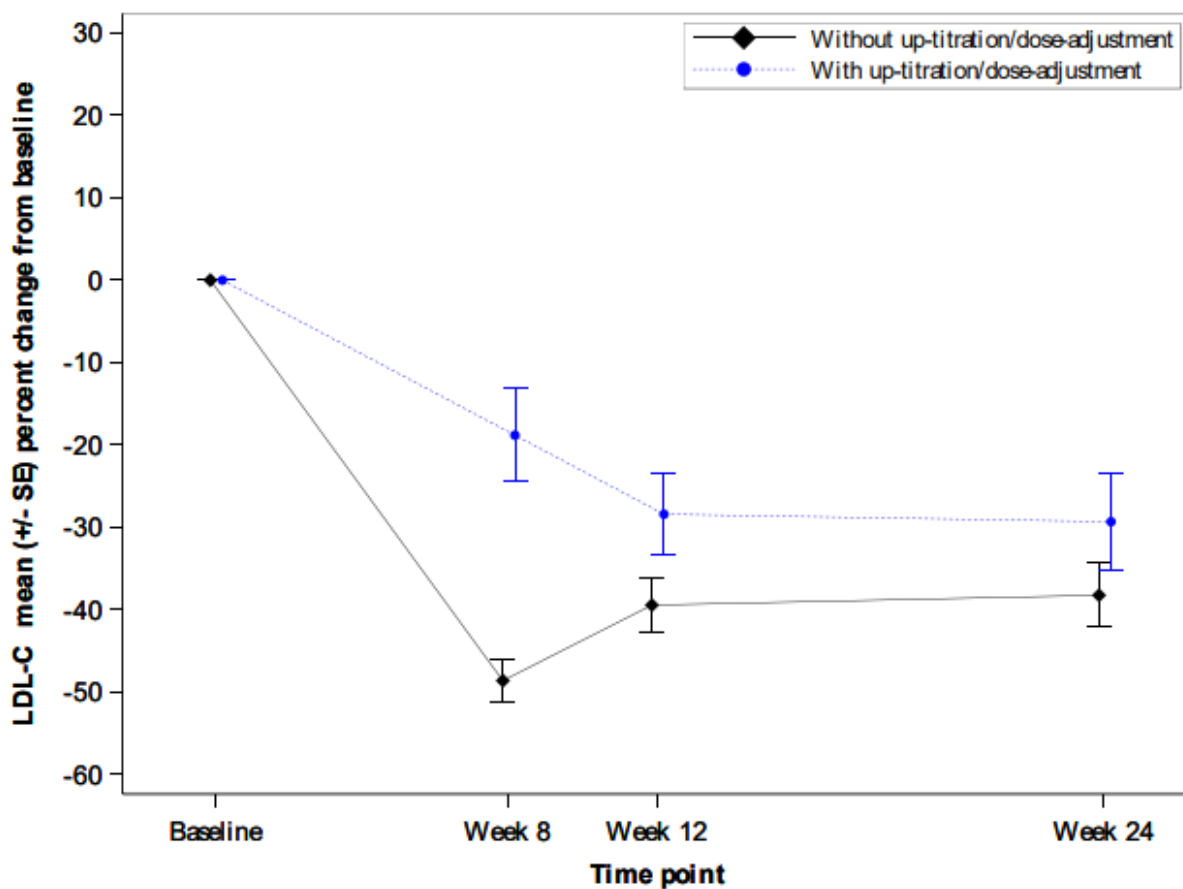
Figure 22. LDL-C mean (+/-SE) percent change from baseline according to up-titration/dose-adjustment status - Time Profile - Patients in alirocumab group with at least one- Q4W
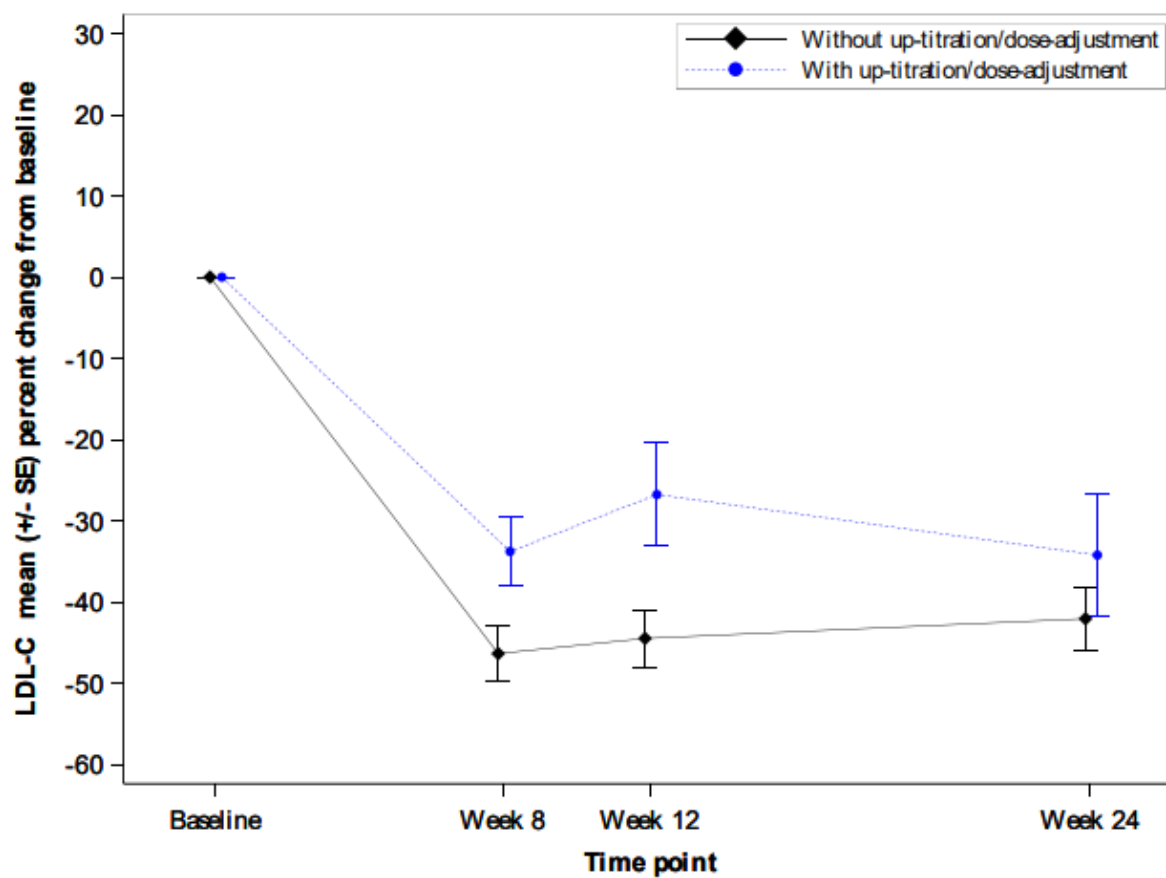
Table 27. Number (%) of patients reaching therapeutic target (LDL-C level < 3.35 mmol/L (<130 mg/dL); < 2.84 mmol/L (<110 mg/dL); or > 50% reduction from baseline at Week 12 and Week 24, according to up-titration/dose adjustment status - ITT analysis – Patients in the Q4W dose regimen cohort

	Not up titrated / (N=33)	Up titrated / (N=15)
Proportion of patients reaching calculated LDL-C <130 mg/dL (3.37 mmol/L)		
Week 12	29/31 (93.5)	5/14 (35.7)
Week 24	27/32 (84.4)	9/14 (64.3)
Proportion of patients reaching calculated LDL-C <110 mg/dL (2.84 mmol/L)		
Week 12	25/31 (80.6)	2/14 (14.3)
Week 24	10/32 (31.3)	5/14 (35.7)
Proportion of patients achieving at least 50% reduction		
Week 12	13/31 (41.9)	2/14 (14.3)
Week 24	10/32 (31.3)	5/14 (35.7)

Open-label treatment period

Among the 71 participants in Q2W cohort, 28 (39.4%) participants had at least 1 up-titration, and 2 (2.8%) participants had down-titration. Majority of the reasons for up-titration were "LDL-C value too high as per Investigator judgment" (21 [61.8%]). Mean (SD) of LDL-C values prior to up-titration was 156.8 (54.9) mg/dL in these 21 participants. The LDL-C value before down-titration was reported in one participant only and was 44.0 mg/dL.

Among the 74 participants in the Q4W cohort, 4 (5.4%) participants had an up-titration, 2 (2.7%) participants had a down-titration, and 9 (12.2%) participants had dose-adjustment. Major reasons included "LDL-C value too low as per Investigator judgment" (5 [29.4%]), "LDL-C value too high as per Investigator judgment" (3 [17.6%]), "Change in body weight" (4 [23.5%]) and "Other" (3 [17.6%]). Mean (SD) LDL-C values prior to the up-titration/dose-adjustment was 212.9 (123.3) mg/dL (value available in 3 participants). Mean (SD) LDL-C values prior to down titration was 36.7 (12.5) mg/dL (value available in 5 participants).

Alirocumab demonstrated a substantial reduction in the primary endpoint of percent change from baseline to week 24 in LDL-C. In the Q2W cohort, alirocumab treatment reduced LDL-C with -33.6% (3.4) compared with +9.7% (4.3) in the placebo group (difference: -43.3% ([97.5% CI: -56.0 to -30.7]; p<0.0001), resulting in a mean LDL-C at Week 24 of 2.929 (0.147) mmol/L in the alirocumab group versus 4.820 (0.213) mmol/L in the placebo group. Reductions were observed in both BW categories with a higher treatment effect compared with placebo observed with 40 mg Q2W: -48.5% (7.6) with the 40 mg Q2W dose for BW <50 kg, and -38.0% (7.8) with the 75 mg Q2W dose for BW ⩾50 kg. This higher effect was mainly due to a larger (unexpected) increase in LDL-C in the placebo group in the 40 mg Q2W cohort compared with the 75 mg Q2W (12.5% (5.9) vs 5.6 (6.4), respectively. In the Q4W cohort, alirocumab treatment reduced LDL-C with -38.2% (4.0) compared with -4.4% (3.7) in the placebo group (difference: -33.8% ([97.5% CI: -46.4 to -21.2]; p<0.0001), resulting in a mean LDL-C at Week 24 of

2.847 (0.200) mmol/L vs. 4.177 (0.180) mmol/L in the alirocumab and placebo group, respectively. The response was consistent across the 2 doses by the BW category with a reduction of -34.5% (9.5) with the 150 mg Q4W dose for BW <50 kg and -32.9% (7.0) with the 300 mg Q4W for BW ⩾50 kg. The LDL-C lowering effect appears generally consistent among several subgroups, including gender, age (< 12, ⩾ 12) and baseline LDL-C in both Q2W and Q4W cohorts. Regarding long-term effect, the percent change of LDL-C from baseline to Week 104 was - 26.3% in the Q2W cohort and -23.9% (33.5) in the Q4W cohort. The effect at week 104 observed during the OL is lower than as compared with the DB treatment period. According to the Applicant, this observation appeared to be related to a less strict application of the rules regarding dose up-titration/adjustment during the OL treatment period, as revealed by the post-hoc analyses, which can be acknowledged. Moreover, it is acknowledged by CHMP that the LDL-C lowering effect in the paediatric HeFH population is still considered clinically relevant. Overall, the effect size in LDL-C lowering of ~35-40% observed at week 24 in this study in paediatric subjects with HeFH is consistent with the LDL-lowering effect of -39% in adult HeFH patients (HIGH FH study). Furthermore, no differential effect on LDL-C of alirocumab was observed between the Q2W and Q4W regimens and the BW categories.

Regarding dose titration, in the Q2W cohort, almost half of the patients in the alirocumab group (22 out of 49 (44.9%); 11 with BW <50 kg and 11 with BW ≥50 kg) received dose up-titration at Week 12. In the Q4W cohort, 15 out of 52 (28.8%) patients were in the alirocumab group (with BW <50 kg and 10 with BW ≥50 kg) at Week 12. The study showed that patients who needed a dose up-titration had a higher mean baseline LDL-C value than patients who did not require a dose up-titration (4.99 vs. 3.91 mmol/L and 5.75 vs 3.99 mmol/L in the Q2W and Q4W cohort respectively). The dose was up-titrated at Week 12 based on LDL-C levels measured at Week 8. Dose up-titration at Week 12 provided an additional moderate LDL-C reduction in the Q4W cohort, and minimal/ no effect in the Q2W cohort in participants who underwent a change in dosing at Week 12. Since the Q4W starting regimen is currently proposed for children and adolescents 8 to 17 years of age with HeFH in section 4.2 of the SmPC, the focus to justify the dose adjustments was primarily on the up-titration regimen combined with the Q4W starting dose regimen. At Week 24, following dose adjustment, an additional decrease in the percent change from baseline LDL-C compared with Week 12 was measured in the Q4W cohort (-34.2% versus -26.8%, respectively), however compared with Week 8 there was no additional decrease (-34.2% at Week 24 versus -33.8% at Week 8). Although this observation can possibly be explained by the differences in sample size at the different time points (n=13 at Week 8 vs n=14 at Week 12 and Week 24), no discussion on this observation has been provided. Instead, the Applicant has highlighted the paediatric patients which had additional benefit with the up-titration step by referring to the secondary endpoints of proportion of patients achieving a LDL-C level lower than 3.37 mmol/L or 2.84 mmol/L, and > 50% reduction in LDL-C at Week 12 (prior to up-titration) vs. Week 24 (after up-titration). The results showed that up-titration allowed more patients to achieve the recommended target of LDL-C <3.37 mmol/L (n=9 (64.3%) vs. n=5 (35.7%) prior up-titration at Week 12), LDL-C <2.84 mmol/L (n=5 (35.7%) vs. n=2 (14.3%) prior up-titration) and >50 % reduction in LDL-C from baseline (n=5 (35.7%) vs. n=2 (14.3%) prior up-titration), whereas in paediatric patients who were not dose adjusted at Week 12, the proportions of subjects reaching the recommended LDL-C targets were decreased between Week 12 and Week 24. Additionally, the results showed that patients who received up-titration had stronger PCSK9 inhibition than prior up-titration. In the dose-adjusted paediatric subjects, mean (SD) free PCSK9 level was 32.5 (63.3) ng/mL at Week 12, compared to 123.0 (61.5) ng/mL at baseline. Following dose up-titration, the mean free PCSK9 level was further reduced to 4.9 (18.3) ng/mL at Week 24. Of note, PCSK9 levels were not entirely consistent with LDL-C effect likely due to statin interference.

Furthermore, the proposed dose titration is in line with the dose up-titration already approved in adult patients, ie. to adjust the dose to the maximum dose of 150 mg Q2W if additional LDL-C reduction is needed. Moreover, contrary to statin therapy, there appear no differences in safety profile of alirocumab

after dose adjustment. Based on above, it can be concluded that paediatric patients with HeFH who do not reach the recommended LDL-C treatment target with the starting dose of alirocumab may benefit from the proposed dose adjustment. Therefore, the proposed up-titration regimen of 75 mg Q2W for BW < 50 kg or 150 mg Q2W for BW ⩾50 kg can be acceptable.

Secondary endpoint

Statistically significant difference in favour of alirocumab compared to the placebo were also observed across the multiplicity-adjusted key secondary endpoints, down through the percent change from baseline in Lp (a) endpoint at Week 24 (ITT estimand) included, according to the hierarchical testing strategy, in both Q2W and Q4W cohorts (Table 28and **Table 29**). For the lower secondary efficacy endpoints, p-values were calculated for descriptive purposes only.

Table 28. Hierarchical strategy applied - Patients in the Q2W cohort - ITT population

Endpoint	Analysis	Results	p-value
Percent change from baseline in LDL-C to Week 12	ITT	LS mean difference vs. placebo of -45.5%	<0.0001*
Percent change from baseline in Apo-B to Week 24	ITT	LS mean difference vs. placebo of -37.8%	<0.0001*
Percent change from baseline in Non-HDL-C to Week 24	ITT	LS mean difference vs. placebo of -40.7%	<0.0001*
Percent change from baseline in Total-C to Week 24	ITT	LS mean difference vs. placebo of -30.8%	<0.0001*
Percent change from baseline in Apo-B to Week 12	ITT	LS mean difference vs. placebo of -38.9%	<0.0001*
Percent change from baseline in Non-HDL-C to Week 12	ITT	LS mean difference vs. placebo of -42.8%	<0.0001*
Percent change from baseline in Total-C to Week 12	ITT	LS mean difference vs. placebo of -32.7%	<0.0001*
Proportion of patients reaching LDL-C <130 mg/dL at Week 24	ITT	Combined estimates for odds ratio vs. placebo of 77.6	0.0001*
Proportion of patients reaching LDL-C <130 mg/dL at Week 12	ITT	Combined estimates for odds ratio vs. placebo of 26.5	<0.0001*
Proportion of patients reaching LDL-C <110 mg/dL at Week 24	ITT	Combined estimates for odds ratio vs. placebo of 52.7	0.0011*
Proportion of patients reaching LDL-C <110 mg/dL at Week 12 - LOCF	ITT	Exact odds ratio vs. placebo of 41.3	<0.0001*
Percent change from baseline in Lp(a) to Week 24	ITT	Combined estimate for adjusted mean difference vs. placebo of -15.2%	0.0237*
Percent change from baseline in Lp(a) to Week 12	ITT	Combined estimate for adjusted mean difference vs. placebo of -5.6%	0.4288
Percent change from baseline in HDL-C to Week 24	ITT	LS mean difference vs. placebo of 6.4%	0.0161
Percent change from baseline in Fasting TG to Week 24	ITT	Combined estimate for adjusted mean difference vs. placebo of 4.3%	0.6836
Percent change from baseline in Apolipoprotein A1 to Week 24	ITT	LS mean difference vs. placebo of 1.1%	0.7133
Percent change from baseline in HDL-C to Week 12	ITT	LS mean difference vs. placebo of 5.6%	0.1387
Percent change from baseline in Fasting TG to Week 12	ITT	Combined estimate for adjusted mean difference vs. placebo of -8.7%	0.3311
Percent change from baseline in Apolipoprotein A1 to Week 12	ITT	LS mean difference vs. placebo of -1.6%	0.5175

The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the type-I error rate at the 0.025 level within a dosing regimen cohort.

Table 29. Hierarchical strategy applied - Patients in the Q4W cohort - ITT population

Endpoint	Analysis	Results	p-value
Percent change from baseline in LDL-C to Week 12	ITT	LS mean difference vs. placebo of -41.5%	<0.0001*
Percent change from baseline in Apo-B to Week 24	ITT	LS mean difference vs. placebo of -30.7%	<0.0001*
Percent change from baseline in Non-HDL-C to Week 24	ITT	LS mean difference vs. placebo of -31.9%	<0.0001*
Percent change from baseline in Total-C to Week 24	ITT	LS mean difference vs. placebo of -23.3%	<0.0001*
Percent change from baseline in Apo-B to Week 12	ITT	LS mean difference vs. placebo of -32.8%	<0.0001*
Percent change from baseline in Non-HDL-C to Week 12	ITT	LS mean difference vs. placebo of -37.5%	<0.0001*
Percent change from baseline in Total-C to Week 12	ITT	LS mean difference vs. placebo of -27.9%	<0.0001*
Proportion of patients reaching LDL-C <130 mg/dL at Week 24	ITT	Combined estimates for odds ratio vs. placebo of 14.9	<0.0001*
Proportion of patients reaching LDL-C <130 mg/dL at Week 12	ITT	Combined estimates for odds ratio vs. placebo of 40.9	<0.0001*
Proportion of patients reaching LDL-C <110 mg/dL at Week 24	ITT	Combined estimates for odds ratio vs. placebo of 43.1	0.0006*
Proportion of patients reaching LDL-C <110 mg/dL at Week 12	ITT	Combined estimates for odds ratio vs. placebo of 104.8	0.0005*
Percent change from baseline in Lp(a) to Week 24	ITT	Combined estimate for adjusted mean difference vs. placebo of -24.9%	0.0043*
Percent change from baseline in Lp(a) to Week 12	ITT	Combined estimate for adjusted mean difference vs. placebo of -13.5%	0.1148
Percent change from baseline in HDL-C to Week 24	ITT	LS mean difference vs. placebo of 4.4%	0.2079
Percent change from baseline in Fasting TG to Week 24	ITT	Combined estimate for adjusted mean difference vs. placebo of -19%	0.0582
Percent change from baseline in Apolipoprotein A1 to Week 24	ITT	LS mean difference vs. placebo of 8.9%	0.0096
Percent change from baseline in HDL-C to Week 12	ITT	LS mean difference vs. placebo of 7.5%	0.0646
Percent change from baseline in Fasting TG to Week 12	ITT	Combined estimate for adjusted mean difference vs. placebo of -8.1%	0.4328
Percent change from baseline in Apolipoprotein A1 to Week 12	ITT	LS mean difference vs. placebo of 5.7%	0.1217

The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the type-I error rate at the 0.025 level within a dosing regimen cohort.

Exploratory endpoint (FMD sub-study)

The exploratory efficacy endpoint of the flow mediated dilatation (FMD) sub-study was the absolute change from baseline to Week 24 in FMD of the brachial artery (as determined by the central reading laboratory) regardless of adherence to treatment (ITT estimand).

As functional and morphological changes of the vessel wall can be illustrated by an impaired FMD of the brachial artery, a positive result is an increase in FMD. Overall, FMD sub-study included 28 participants in the DB period (20 participants from the combined alirocumab group and 8 participants from the combined placebo group), all of them completed the DB treatment period and entered the OL treatment period.

No difference between the alirocumab and the placebo group was observed for the absolute change in percent change in FMD from baseline to Week 24. In ITT analysis, the LS mean (SE) absolute change in %FMD from baseline to Week 24 was - 0.6% (1.6) in the alirocumab combined group compared to - 2.1% (1.7) in the combined placebo group, with an LS mean difference for alirocumab versus placebo of 1.5% ([95% CI: - 3.4 to 6.4]; nominal p=0.5368).

The primary endpoint results were further supported by the beneficial effects in secondary cholesterol measurements (e.g. Apo-B, non-HDL-C, Total-C, Lp(a), HDL-C). At Week 24, 77.6% of patients achieved

an LDL-C level lower than 3.4 mmol/L (130 mg/dL), and 52.7% of patients an LDL-C level lower than 2.84 mmol/L (110 mg/dL) in the alirocumab group.

In the exploratory flow-mediated dilatation (FMD) sub-study, no difference in absolute change from baseline to Week 24 in %FMD was observed (-0.6% vs -2.1% in the alirocumab and placebo group, respectively; p=0.5368).

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30. Summary of Efficacy for study EFC14643

Title: A randomized, double-blind, placebo-controlled study followed by an open label treatment period to evaluate the efficacy and safety of alirocumab in children and adolescents with heterozygous familial hypercholesterolemia				
Study identifier	EFC14643			
Design	A randomized, 24-week double-blind treatment, placebo-controlled, parallel-group, multi-national, multi-center study followed by an open label treatment period of 80 weeks to assess the efficacy and safety of alirocumab 40 mg or 75 mg Q2W (for BW <50 kg or ≥50 kg) and 150 mg or 300 mg Q4W (for BW <50 kg or ≥50 kg), as a starting dose, with a subsequent option of up-titration if specific LDL-C goals are not achieved at Week 12, on top of stable LMT background treatment(s) in children and adolescents 8 to 17 years of age with heFH.			
	Duration of run-in phase:		Up to 4 weeks (+2 days)	
	Duration of screening-in phase:		Up to 2 weeks (+5 days)	
	Duration of DB treatment phase:		24 weeks	
	Duration of OL treatment phase:		80 weeks	
Hypothesis	Superiority			
	Alirocumab	**DB treatment period**:		
			Q2W (n=49)	Q4W (n=52)
		Starting dose:	40 mg, for BW <50 kg	150 mg, for BW <50 kg
			75 mg, for BW ≥50 kg	300 mg, for BW ≥50 kg
		Up-titration/dose modification at Week 12 (if LDL-C ≥110 mg/dL at Week 8):	75 mg, for BW <50 kg	75 mg Q2W, for BW <50 kg*
			150 mg, for BW ≥50 kg	150 mg Q2W, for BW ≥50 kg*
		* Participants whose dose was not up-titrated/modified at Week 12 were under a "sham Q2W" regimen from Week 12 to Week 24, with alirocumab Q4W alternating with placebo Q4W		
		OL treatment period:		
			Q2W (n=71)	Q4W (n=74)
		Starting dose at Week 24:	40 mg, for BW <50 kg	150 mg, for BW <50 kg
			75 mg, for BW ≥50 kg	300 mg, for BW ≥50 kg
		After Week 24, dose up-titration according to BW increase:	40 mg to 75 mg, for BW increase from <50 kg to ≥50 kg	150 mg to 300 mg, for BW increase from <50 kg to ≥50 kg
		Dose modification according to LDL-C from Week 32 onwards:	Up-titration: 40 mg to 75 mg, for BW <50 kg	Up-titration: 150 mg Q4W to 75 mg Q2W, for BW <50 kg
			75 mg to 150 mg, for BW ≥50 kg	300 mg Q4W to 150 mg Q2W, for BW ≥50 kg
			Down-titration: 75 mg to 40 mg, for BW <50 kg	Down-titration: 75 mg Q2W to 40 mg Q2W, for BW <50 kg
			150 mg to 75 mg, for BW ≥50 kg	150 mg Q2W to 75 mg Q2W, for BW ≥50 kg
	Placebo	Alirocumab-matching placebo Q2W or Q4W during the DB treatment period.		

Endpoints and definitions	Primary endpoint	LDL-C	Percent change in LDL-C from baseline to Week 24 in the intent-to-treat (ITT) population, using LDL-C values regardless of adherence to treatment (ITT estimand)
	Key secondary endpoints	LDL-C	Percent change in LDL-C from baseline to Week 12 (ITT estimand) Proportion of patients achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 24 (ITT estimand) Proportion of patients achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 12 (ITT estimand) Proportion of patients achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 24 (ITT estimand) Proportion of patients achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 12 (ITT estimand)
		Apo B	Percent change in Apo B from baseline to Week 24 (ITT estimand) Percent change in Apo B from baseline to Week 12 (ITT estimand)
		Non-HDL-C	Percent change in non-HDL-C from baseline to Week 24 (ITT estimand) Percent change in non-HDL-C from baseline to Week 12 (ITT estimand)
		Total-C	Percent change in Total-C from baseline to Week 24 (ITT estimand) Percent change in Total-C from baseline to Week 12 (ITT estimand)
		Lp (a)	Percent change in Lp(a) from baseline to Week 24 (ITT estimand) Percent change in Lp(a) from baseline to Week 12 (ITT estimand)
		HDL-C	Percent change in HDL-C from baseline to Week 24 (ITT estimand) Percent change in HDL-C from baseline to Week 12 (ITT estimand)
		Fasting TG	Percent change in fasting TG from baseline to Week 24 (ITT estimand) Percent change in fasting TG from baseline to Week 12 (ITT estimand)
		Apo A-1	Percent change in Apo A-1 from baseline to Week 24 (ITT estimand) Percent change in Apo A-1 from baseline to Week 12 (ITT estimand)

Endpoints and definitions (cont'd)	Other secondary efficacy endpoints	LDL-C	All primary and key secondary endpoints in the modified ITT (mITT) population, using LDL-C values during the treatment period (on-treatment estimand) Proportion of patients achieving at least 30% reduction, 50% reduction in LDL-C at Week 24 (ITT and on-treatment estimands) Proportion of patients achieving at least 30% reduction, 50% reduction in LDL-C at Week 12 (ITT and on-treatment estimands) Percent change in LDL-C from baseline to Week 104 (ITT and on-treatment estimands)
		Apo B/Apo A-1 ratio	Absolute change in Apo B/Apo A-1 ratio to Week 12 and Week 24 (ITT and on-treatment estimands)
Database lock	31 August 2022		

Results and Analysis

Only results of the ITT analysis for all primary and secondary efficacy endpoints defined in the DB treatment period are presented in this table. The on-treatment analysis was considered supportive.

Analysis description	**Primary analysis of primary efficacy endpoint: Percent change in LDL-C from baseline to Week 24 (ITT estimand)**				
Analysis population and time point description	ITT population 24 weeks from baseline				
Descriptive statistics and estimate variability	Treatment group	Q2W		Q4W	
		Placebo	Alirocumab	Placebo	Alirocumab
	Number of subject	25	49	27	52
	Percent change in LDL-C from baseline to Week 24 LS mean (SE)	9.7 (4.3)	-33.6 (3.4)	-4.4 (3.7)	-38.2 (4.0)
Effect estimate per comparison	Primary endpoint Percent change in LDL-C from baseline to Week 24	Comparison groups		Alirocumab vs. placebo	
				Q2W	Q4W
		LS mean difference (SE)		-43.3 (5.5)	-33.8 (5.5)
		97.5% CI		-56.0 to -30.7	-46.4 to -21.2
		P-value		<0.0001*	<0.0001*
Notes	The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the type-I error rate at the 0.025 level within a dosing regimen cohort.				
Analysis description	**Primary analysis of key and other secondary efficacy endpoints defined in the DB treatment period (grouped by parameter) (ITT estimand)**				
Analysis population and time point description	ITT population 12 and 24 weeks from baseline				
Descriptive statistics and estimate variability	Treatment group	Q2W		Q4W	
		Placebo	Alirocumab	Placebo	Alirocumab
	Number of subject	25	49	27	52
	Percent change in LDL-C from baseline to Week 12 LS mean (SE) (%)	10.7 (3.6)	-34.8 (3.0)	2.3 (3.6)	-39.2 (3.3)

Descriptive statistics and estimate variability (cont'd)	Proportion of participants achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 24 Combined estimate for proportion of participants reaching the level (%)	8.0	73.3	22.2	76.3
	Proportion of participants achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 12 Combined estimate for proportion of participants reaching the level (%)	16.4	70.6	12.9	72.6
	Proportion of participants achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 24 Combined estimate for proportion of participants reaching the level (%)	4.0	57.2	9.0	67.2
	Proportion of participants achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 12 Combined estimate for proportion of participants reaching the level (%)	0.1	61.7	4.3	57.0
	Proportion of participants achieving at least 30% reduction in LDL-C at Week 24 Combined estimate for proportion of participants reaching the level (%)	4.0	66.7	18.5	72.5
	Proportion of participants achieving at least 30% reduction in LDL-C at Week 12 Combined estimate for proportion of participants reaching the level (%)	0.8	65.8	4.2	70.8
	Proportion of participants achieving at least 50% reduction in LDL-C at Week 24 Combined estimate for proportion of participants reaching the level (%)	0.0	21.6	9.1	32.4
	Proportion of participants achieving at least 50% reduction in LDL-C at Week 12 Combined estimate for proportion of participants reaching the level (%)	0.0	25.2	0.1	31.9
	Percent change in Apo B from baseline to Week 24 LS mean (SE) (%)	10.4 (2.8)	-27.4 (3.2)	-3.6 (3.9)	-34.3 (2.9)
	Percent change in Apo B from baseline to Week 12 LS mean (SE) (%)	8.9 (3.1)	-30.0 (2.5)	1.1 (3.2)	-31.7 (2.9)
	Percent change in non-HDL-C from baseline to Week 24 LS mean (SE) (%)	9.7 (3.9)	-31.0 (3.2)	-3.7 (4.0)	-35.6 (3.5)
	Percent change in non-HDL-C from baseline to Week 12 LS mean (SE) (%)	9.8 (3.8)	-33.0 (2.8)	2.8 (3.5)	-34.7 (2.9)
	Percent change in Total-C from baseline to Week 24 LS mean (SE) (%)	7.4 (3.0)	-23.4 (2.5)	-4.4 (3.3)	-27.7 (2.9)

Descriptive statistics and estimate variability (cont'd)	Percent change in Total-C from baseline to Week 12 LS mean (SE) (%)	7.5 (2.9)	-25.3 (2.2)	0.9 (2.5)	-27.0 (2.3)
	Percent change in Lp(a) from baseline to Week 24 Combined estimate for adjusted mean (SE) (%)	0.5 (5.3)	-14.7 (4.1)	2.5 (7.1)	-22.4 (5.0)
	Percent change in Lp(a) from baseline to Week 12 Combined estimate for adjusted mean (SE) (%)	-7.1 (5.9)	-12.7 (3.9)	-2.5 (6.9)	-16.0 (5.1)
	Percent change in HDL-C from baseline to Week 24 LS mean (SE) (%)	-0.8 (2.1)	5.6 (1.4)	-1.1 (2.7)	3.4 (2.1)
	Percent change in HDL-C from baseline to Week 12 LS mean (SE) (%)	-2.2 (3.2)	3.5 (2.0)	-3.5 (3.2)	4.0 (2.2)
	Percent change in fasting TG from baseline to Week 24 Combined estimate for adjusted mean (SE) (%)	7.7 (8.4)	11.9 (6.3)	12.2 (8.2)	-6.8 (5.5)
	Percent change in fasting TG from baseline to Week 12 Combined estimate for adjusted mean (SE) (%)	6.5 (7.4)	-2.2 (5.0)	7.8 (8.4)	-0.3 (6.0)
	Percent change in Apo A-1 from baseline to Week 24 LS mean (SE) (%)	-0.1 (2.6)	1.0 (1.5)	-4.5 (2.6)	4.4 (2.0)
	Percent change in Apo A-1 from baseline to Week 12 LS mean (SE) (%)	-0.1 (1.8)	-1.7 (1.7)	-0.7 (3.1)	5.0 (1.7)
	Absolute change in Apo B/Apo A-1 ratio to Week 24 LS mean (SE) (%)	0.1 (0.0)	-0.2 (0.0)	0.0 (0.0)	-0.3 (0.0)
	Absolute change in Apo B/Apo A-1 ratio to Week 12 LS mean (SE) (%)	0.1 (0.0)	-0.2 (0.0)	0.0 (0.0)	-0.3 (0.0)

Effect estimate per comparison	Key and other secondary efficacy endpoints (grouped by parameter)	Comparison groups		Alirocumab vs. placebo	
				Q2W	Q4W
	Percent change in LDL-C from baseline to Week 12	LS mean difference (SE)		-45.5 (4.7)	-41.5 (4.9)
		97.5% CI		-56.3 to -34.7	-52.7 to -30.2
		P-value		<0.0001*	<0.0001*
	Proportion of participants achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 24	Combined estimate for odds ratio		77.6	14.9
		97.5% CI		6.3 to 960.0	3.2 to 69.8
		P-value		0.0001*	<0.0001*

Effect estimate per comparison (cont'd)	Proportion of participants achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 12	Combined estimate for odds ratio	26.5	40.9
		97.5% CI	4.0 to 174.8	5.7 to 290.9
		P-value	<0.0001*	<0.0001*
	Proportion of participants achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 24	Combined estimate for odds ratio	52.7	43.1
		97.5% CI	3.5 to 804.3	3.7 to 498.6
		P-value	0.0011*	0.0006*
	Proportion of participants achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 12	Combined estimate for odds ratio	NC	104.8
		97.5% CI	NC	5.2 to 2095.9
		P-value	NC	0.0005*
	Proportion of participants achieving at least 30% reduction in LDL-C at Week 24	Combined estimate for odds ratio	40.1	11.2
		97.5% CI	3.8 to 427.8	2.7 to 46.3
		P-value	0.0005	0.0001
	Proportion of participants achieving at least 30% reduction in LDL-C at Week 12	Combined estimate for odds ratio	NC	54.3
		97.5% CI	NC	5.0 to 589.1
		P-value	NC	0.0002
	Proportion of participants achieving at least 50% reduction in LDL-C at Week 24	Combined estimate for odds ratio	NC	5.3
		97.5% CI	NC	0.8 to 34.1
		P-value	NC	0.0451
	Proportion of participants achieving at least 50% reduction in LDL-C at Week 12	Combined estimate for odds ratio	NC	NC
		97.5% CI	NC	NC
		P-value	NC	NC
	Percent change from baseline in Apo B at Week 24	LS mean difference (SE)	-37.8 (4.2)	-30.7 (4.9)
		97.5% CI	-47.5 to -28.2	-42.0 to -19.4
		P-value	<0.0001*	<0.0001*
	Percent change from baseline in Apo B at Week 12	LS mean difference (SE)	-38.9 (4.0)	-32.8 (4.3)
		97.5% CI	-48.2 to -29.6	-42.8 to -22.7
		P-value	<0.0001*	<0.0001*
	Percent change in non-HDL-C from baseline to Week 24	LS mean difference (SE)	-40.7 (5.0)	-31.9 (5.3)
		97.5% CI	-52.2 to -29.1	-44.1 to -19.7
		P-value	<0.0001*	<0.0001*
	Percent change in non-HDL-C from baseline to Week 12	LS mean difference (SE)	-42.8 (4.7)	-37.5 (4.5)
		97.5% CI	-53.8 to -31.8	-47.9 to -27.0
		P-value	<0.0001*	<0.0001*

Effect estimate per comparison (cont'd)	Percent change in Total-C from baseline to Week 24	LS mean difference (SE)	-30.8 (3.9)	-23.3 (4.4)
		97.5% CI	-39.8 to -21.9	-33.5 to -13.1
		P-value	<0.0001*	<0.0001*
	Percent change in Total-C from baseline to Week 12	LS mean difference (SE)	-32.7 (3.7)	-27.9 (3.4)
		97.5% CI	-41.3 to -24.2	-35.6 to -20.2
		P-value	<0.0001*	<0.0001*
	Percent change in Lp(a) from baseline to Week 24	Combined estimate for adjusted mean difference (SE)	-15.2 (6.7)	-24.9 (8.7)
		97.5% CI	-30.3 to -0.1	-44.4 to -5.4
		P-value	0.0237*	0.0043*
	Percent change in Lp(a) from baseline to Week 12	Combined estimate for adjusted mean difference (SE)	-5.6 (7.1)	-13.5 (8.6)
		97.5% CI	-21.7 to 10.4	-32.7 to 5.7
		P-value	0.4288	0.1148
	Percent change in HDL-C from baseline to Week 24	LS mean difference (SE)	6.4 (2.5)	4.4 (3.5)
		97.5% CI	0.5 to 12.3	-3.6 to 12.5
		P-value	0.0161	0.2079
	Percent change in HDL-C from baseline to Week 24	LS mean difference (SE)	5.6 (3.7)	7.5 (3.9)
		97.5% CI	-3.1 to 14.3	-1.7 to 16.6
		P-value	0.1387	0.0646
	Percent change in fasting TG from baseline to Week 24	Combined estimate for adjusted mean difference (SE)	4.3 (10.4)	-19.0 (10.0)
		97.5% CI	-19.1 to 27.6	-41.5 to 3.5
		P-value	0.6836	0.0582
	Percent change in fasting TG from baseline to Week 12	Combined estimate for adjusted mean difference (SE)	-8.7 (8.9)	-8.1 (10.3)
		97.5% CI	-28.8 to 11.4	-31.3 to 15.1
		P-value	0.3311	0.4328
	Percent change in Apo A-1 from baseline to Week 24	LS mean difference (SE)	1.1 (3.0)	8.9 (3.3)
		97.5% CI	-5.9 to 8.2	1.3 to 16.5
		P-value	0.7133	0.0096*
	Percent change in Apo A-1 from baseline to Week 12	LS mean difference (SE)	-1.6 (2.5)	5.7 (3.6)
		97.5% CI	-7.4 to 4.1	-2.7 to 14.1
		P-value	0.5175	0.1217

Effect estimate per comparison (cont'd)	Absolute change in Apo B/Apo A-1 ratio to Week 24	LS mean difference (SE)	-0.3 (0.1)	-0.3 (0.0)
		97.5% CI	-0.5 to -0.2	-0.4 to -0.2
		P-value	<0.0001	<0.0001
	Absolute change in Apo B/Apo A-1 ratio to Week 12	LS mean difference (SE)	-0.3 (0.0)	-0.3 (0.0)
		97.5% CI	-0.4 to -0.2	-0.4 to -0.2
		P-value	<0.0001	<0.0001
Notes:	The p-value is followed by a "*" if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the type-I error rate at the 0.025 level within a dosing regimen cohort.			

2.5.3. Discussion on clinical efficacy

Based on the initial MA granted in 2015, alirocumab (Praluent) was indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in combination with the maximum tolerated dose of a statin with or without other LLTs or, alone or in combination with other LLTs in patients who are statin-intolerant, or for whom a statin is contraindicated. At the time of the initial MA, a statement was included in Section 4.1 of the EU SmPC that the effect of alirocumab on cardiovascular morbidity and mortality had not yet been determined, as the outcome study, ODYSSEY OUTCOMES (EFC11570), was ongoing. In 2018, the MAH submitted the results of the ODYSSEY OUTCOMES study to extend the indication with the reduction in risk of cardiovascular events in adults with established cardiovascular disease (CVD) (EMEA/H/C/003882/II/0042), which received approval in 2019. This new extension of indication application is based on efficacy and safety data from the Phase 3 study EFC14643 supplemented with efficacy and safety data from the Phase 2 dose-finding study (Study DFI14223) and safety data from the Phase 3 study in paediatric participants with HoFH (Study EFC14660) to include treatment of paediatric HeFH patients 8-≤12 years of age in line with the approved EU PIP) as also indicated by the completed full compliance check (PIP-decision number P/0550/2021) which was concluded positively.

Design and conduct of clinical studies

Dose selection

The approved starting dosing regimen for adult patients is 75 Q2W. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg Q2W, or 300 mg once Q4W. If additional LDL-C reduction is needed in adult patients treated with 75 mg Q2W or 300 mg Q4W, the dosage may be adjusted to the maximum dosage of 150 mg Q2W.

The efficacy and safety of alirocumab in the paediatric patient population with HeFH were first evaluated in the Phase 2 dose-finding DFI14223 study. The choice of the doses in this study was based on simulations performed on the final adult population PK model including Phase 3 data.

DF114223 was an open-label dose-escalating Phase 2 study to evaluate appropriate doses to be selected for the Phase 3 study in paediatric patients with HeFH. Repeated doses of subcutaneous alirocumab were administered in 2 cohorts every 2 weeks (Q2W) and 2 cohorts every 4 weeks (Q4W) in children and adolescents (aged 8-17 years) with HeFH having LDL-C ≥ 3.37 mmol/L despite an optimal stable daily dose of statin therapy ± other LMTs, or a stable dose of non-statin LMTs in case of intolerance to statins. Doses of 30 and 40 mg Q2W were tested for < 50 kg and 50 and 75 mg Q2W for ≥ 50 kg, 75 and 150 mg Q4W for < 50 kg and 150 and 300 mg Q4W for ≥ 50 kg body weight. After 8 weeks of treatment, the higher Q2W dose (cohort 2: 40 mg Q2W for < 50 kg and 75 mg for ≥ 50 kg) showed greater reductions

in LDL-C (-46.1%) as compared to the lower Q2W dose (30 and 50 mg, respectively, -21.1%). Slight differences appear in effect according to body weight (LS mean (SE): -40.6 (13.2) with 40 mg Q2W for BW <50 kg, and -49.8% (10.6)) with 75 mg Q2W for BW ≥50 kg). For the monthly dosing, only a moderate effect was observed for the lower dosing (cohort 3) with -17.5% (10.3) for 75 mg Q4W <50 kg and 4.0% (11.2) for 150 mg Q4W for BW ≥50 kg after 8 weeks. Based on these results, subsequent dosing with higher doses (cohort 4) showed greater efficacy (-31.9% [10.3] with 150 mg Q4W for BW <50 kg, and -59.8% [11.2] with 300 mg Q4W for BW ≥50 kg). Overall, a more pronounced effect was observed in the higher Q2W dose in cohort 2 and the higher QW4 dose in cohort 4 compared to the respective lower dose cohorts groups. However, some variation exists between the body weight categories, with greater efficacy in the ≥50 kg groups. From an efficacy point of view, it is considered appropriate that the doses used in cohort 2 and cohort 4 have been selected for the pivotal Phase 3 study EFC 14643 in paediatric patients with HeFH.

In the pivotal study EFC14643, alirocumab demonstrated a substantial reduction in the primary endpoint of percent change from baseline to week 24 in LDL-C, with an LS mean difference versus placebo of -43.3% ([97.5% CI: -56.0 to -30.7]; p<0.0001) in the Q2W cohort, and -33.8% ([97.5% CI: -46.4 to -21.2]; p<0.0001) in the Q4W cohort. Dose up-titration/adjustment at Week 12 provided no additional LDL-C reduction in both the Q2W cohort and Q4W cohort (see efficacy main study). The higher effect in the Q2W cohort was mainly due to a larger (unexpected) increase in LDL-C in the placebo group. Overall, the effect size in LDL-C lowering of ~35-40% observed at week 24 in this study in paediatric subjects with HeFH is consistent with the LDL-lowering effect of -39.1% in adult HeFH patients (HIGH FH study). Furthermore, no differential effect on LDL-C of alirocumab versus placebo was observed between the Q2W and Q4W regimens and the BW categories. Based on these study results and given the lower patient burden associated with monthly injections as compared to bi-weekly injections, the 150 mg or 300 mg Q4W for BW < 50 and ≥ 50 kg, respectively, dose regimen is currently proposed for children and adolescents 8 to 17 years of age with HeFH in section 4.2 of the SmPC, which can be acceptable. The Q4W starting regimen (150 mg or 300 mg Q4W for < 50 and ≥ 50 kg, respectively) is a 2-fold higher cumulative monthly dose compared to Q2W starting regimen (40 mg or 75 mg Q2W for < 50 and ≥ 50 kg, respectively). Consequently, in the Q4W cohort, higher C_{trough} values were observed compared to the Q2W starting regimen. However, considering that no differences in safety profiles between the Q2W and Q4W regimens were observed, the selection of the Q4W regimen is accepted. In this respect, the focus to justify the dose adjustments was primarily on the up-titration regimen combined with the Q4W starting dose regimen. Overall, it can be concluded that paediatric patients with HeFH who do not reach the recommended LDL-C treatment target with the starting Q4W dose of alirocumab may benefit from the proposed up-titration regimen of 75 mg Q2W for BW < 50 kg or 150 mg Q2W for BW ≥50 kg (see below "outcomes and estimation" for results and detailed discussion on the up-titration regimen).

Considering the potent starting LDL-C lowering strategy and the concerns that lowering cholesterol to very low levels may be disadvantageous, particularly in children, since in addition to its biophysical role in membrane organization, cholesterol is crucial for brain development and serve as a precursor in the biosynthesis of several vitamins, steroids, and sex hormones, the Applicant was requested to elaborate on the lowest acceptable LDL-C level used for the paediatric population in clinical practice. Based on a literature review, the Applicant argued that a lowest acceptable LDL-C levels has not been scientifically validated nor defined by clinical practice guidelines; The 2019 ESC/EAS Guidelines for the management of dyslipidaemias recommend a goal in children >10 years of age of an LDL-C <3.5 mmol/L and at younger ages a >50% reduction of LDL-C but do not indicate a lowest acceptable value for LDL-C levels in the paediatric population. Nevertheless, the Applicant emphasized that the experience in (paediatric) patients treated with PCSK9 inhibitors, including alirocumab, has currently not identified any safety concerns associated with very low LDL-C levels. Additionally, experience of patients with loss of function mutation

for PCSK9 indicates that these patients are healthy despite lifelong very low LDL-C levels. Further, it is acknowledged that in most mammalian cells, cholesterol can be synthesized endogenously and that in some steroidogenic organs, cholesterol is taken up from circulating HDL and not LDL. In this respect, the Applicant was requested to substantiate whether there were patients with very low LDL-C values (< 1.29 mmol/L (<50 mg/dL) or <0.65 mmol/L (< 25 mg/dL)) with the starting regimens 40mg or 75mg Q2W and 150mg or 300mg Q4W for BW < 50 or ≥ 50 kg, respectively, during the study, i.e. without dose up-titration. The Applicant clarified that all events of very low LDL-C values in the double-blind treatment (n=4 (8.2%) in Q2W cohort and n=7 (13.5%) in the Q4W cohort) and in the open-label period (n=5 (7.0%) in the Q2W cohort and n=12 (16.2%) in the Q4W cohort) were reported with the alirocumab starting dose. The percentage of patients with very low LDL-C levels were higher with the Q4W starting regimen compared with the Q2W starting regimen, suggesting that patients treated with the Q4W regimen are more susceptible for achieving very low LDL-C levels. However, a review of baseline characteristics suggests that the occurrence of very low LDL-C levels is associated with LDL-C levels at baseline, since the majority of patients with a very low LDL-C level (9 out of 13) had a LDL-C level at baseline of < 3.5 mmol/L. A justification for this cut-off of baseline LDL-C level < or ≥ 3.5 mmol/L has not been provided, but is highly likely related to the target treatment goal of 3.5 mmol/L for children aged > 10 years as stated in the 2019 ESC/EAS Guidelines for the management of dyslipidaemias (2019). In this context, the Applicant argued that paediatric patients with HeFH with LDL-C levels < 3.5mmol/L will not initiate treatment with alirocumab, minimizing the risk for very low LDL-C levels in these patients, which is acknowledged. Additionally, it is agreed that the LDL-C levels of patients initiating any lipid modifying therapy will be closely monitored. Further, the Applicant argued that the very low LDL-C values may have been overestimated as only calculated LDL-C levels were evaluated in the study, except when TG levels exceeded 4.52 mmol/L), which is acknowledged. Moreover, it is agreed that it is the prescriber's decision to define what the most appropriate target should be for their patient. If a prescriber thinks an LDL-C level is too low, they should exercise their medical judgment to adapt treatment according to the treatment target. Overall, the Applicant has sufficiently addressed the concerns regarding the occurrence of very low LDL-C levels.

Further, the C_{trough} values with both Q2W and Q4W cohorts in the paediatric HeFH population tended to be higher compared with the Q2W and Q4W dose regimens in HeFH adults. However, the higher mean exposure of alirocumab in the paediatrics population can be explained by the relatively lower bodyweight compared to the adult population. No additional effect of age can be observed on the exposure of alirocumab applying the proposed weight-based dosing (see PK section).

Pivotal study EFC14643

Study EFC14643 was a randomized, 24-week double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of alirocumab administered at 40 mg or 75 mg Q2W (for BW <50 kg or ≥ 50 kg) and 150 mg or 300 mg Q4W (for BW <50 kg or ≥50 kg) as a starting dose, on top of background LLT in the paediatric population 8 to 17 years of age with HeFH. The 24-week double-blind (DB) treatment period was followed by an 80-week open-label (OL) treatment period. General inclusion/exclusion criteria seem appropriate to reflect the patients for which an indication is being sought, i.e. paediatric patients with HeFH. Eligible patients to be enrolled were male or female patients, 8- ≤ 17 years of age, diagnosed with HeFH based on genetic testing or in accordance with the clinical Broome criteria, on optimized background lipid-lowering therapy for ≥ 4 weeks prior to screening. Furthermore, the inclusion criterion of the LDL-C level of ≥ 3.4 mmol/L at screening is in line with the treatment goal for paediatric patients with HeFH recommended in the ESC guidelines for the treatment of dyslipidaemias (2019) and, therefore, acceptable. Patients who previously participated in the DFI14223

study and already met the LDL-C ≥ 3.37 mmol/L when they were screened for the DFI14223 study were also eligible to enrol in the Phase 3 study. This approach is considered acceptable since all patients completed the open-label dose-finding period of the DFI14223 study, and no patients discontinued due to adverse events. Consequently, no preselection based on tolerability has occurred. Moreover, the patients from study DFI14223 went through a wash-out period of at least 10 weeks between the last injection of alirocumab in the DFI14223 study and the screening lipid assessment at entry in the screening period of this Phase 3 study, which is considered appropriate. The key exclusion criterion is that HoFH patients were not to be included. The <u>design</u> of the study is appropriate to achieve the primary objective of the study. The run-in/screening period of 4-6 weeks can be considered sufficient to establish a stable background condition. The 24-week double-blind treatment period is considered appropriate to provide reasonable results on the LDL-C (and other cholesterol parameters) lowering effect of alirocumab. After completing of the double-blind treatment period, subjects were offered to participate in the 80-week open-label treatment period where they will receive open-label alirocumab. A 2:1 randomization was used in this study, which is considered appropriate. The study evaluated 40 mg or 75 mg Q2W (for BW <50 kg or ≥50 kg) and 150 mg or 300 mg Q4W (for BW <50 kg or ≥50 kg), as a starting dose, with a subsequent option of up-titration at Week 12 based on Week 8 LDL-C values. Patients were up-titrated to alirocumab 75 mg Q2W for patients with BW < 50 kg or 150 mg Q2W for patients with BW ≥ 50 kg regardless of the dosing cohort if the Week 8 LDL-C is ≥ 2.85 mmol/L (110 mg/dL) is endorsed as the specific goal in paediatric patients with FH has not yet been determined; LDL-C goals in paediatric patients of <110 mg/dL (2.8 mmol/L), <100 mg/dL (2.6 mmol/L), or <130 mg/dL (3.4 mmol/L) have been proposed. The <u>primary endpoint</u> of percent change from baseline to week 24 in LDL-C is considered appropriate to establish the LDL-C lowering effect of alirocumab. <u>Key secondary endpoints</u> evaluation of other lipid parameters (i.e. e.g. Apo-B, non-HDL-C, Total-C, Lp(a), HDL-C, TG, Apo-A1) are considered appropriate to provide further insight on and confirmation of the primary objective. A flow-mediated dilatation (FMD) sub-study explored the absolute change from baseline to Week 24 in flow-mediated dilatation of the brachial artery, which can be endorsed. The <u>sample size</u> calculation, <u>randomization</u> and <u>blinding procedures</u> are acceptable. With respect to <u>statistical analysis</u>, the definition of the analysis population is considered standard and acceptable.

Efficacy data and additional analyses

In the pivotal study EFC14643, a total of 153 patients were randomized, of which 74 patients in the Q2W dosing regimen cohort (49 and 25 in the alirocumab and placebo group, respectively) and 79 patients in the Q4W dosing regimen cohort (52 and 27 in the alirocumab and placebo group, respectively). The percentage of <u>subjects who completed</u> the DB treatment period was high and similar between the alirocumab and placebo group (91.8% vs 100% for the alirocumab and placebo group in the Q2W cohort and 94.2% vs 96.3% in the Q4W cohort). Four patients in the alirocumab group in the Q2W cohort and 3 patients in the alirocumab group in the Q4W cohort discontinued the DB treatment period of which "other" (n=2) and "due to AE" (n=2) were the most common. Further, 145 participants entered the OL treatment period (71 in the Q2W cohort and 74 in the Q4W cohort), of which a high proportion of subjects completed this period (91.5% (65/71) patients in the Q2W cohort and 98.6% (73/74) patients in the Q4W cohort). The most common reason for discontinuing the OL period was "other"(n=5).

The overall <u>compliance</u> for double-blind injections was relatively high since all participants in both alirocumab and placebo group in the Q2W cohort had ≥80% compliance for IMP injections (ie, participants took ≥80% of their injections and at the scheduled times). In contrast, in the Q4W cohort, 44 (84.6%) participants in the alirocumab group and 23 (85.2%) participants in the placebo group had ≥80% compliance for IMP injections. As such, a small difference in compliance could be observed between the

Q2W cohort and the Q4W cohort however, it is difficult to draw firm conclusions since the number of subjects in each group was relatively small. The percentages of major protocol deviations were relatively high (30.6% vs 12.0% in the Q2W cohort and 38.5% vs 48.1% in the Q4W cohort for alirocumab and placebo, respectively). The most frequently reported major protocol deviations were in the category "IMP management" (n=3 vs 1 in the Q2W cohort and n=12 vs 5 in the Q4W cohort for alirocumab and placebo, respectively). The Applicant has sufficiently substantiated that the major deviations in IMP management had no impact on efficacy or safety. Additionally, the Applicant had conducted a post-hoc descriptive analysis excluding patients with at least one major protocol deviation linked to IMP management, indicating that these deviations had no or little impact on the LDL-C changes from baseline. . This study was a multicentre study (n=43). Considering that almost half of the subjects were from Europe (83 out of 153 (54%), the population is sufficiently representative for Europe. No amendments were made that would compromise the endpoints or outcomes of the study. The amendments are considered valuable and are, therefore, acceptable.

In general, baseline data, including age group, BW and LDL-C are well distributed across the two cohorts and treatment groups, which is reassuring for the interpretation of the data. However, in the Q2W cohort, there were more female patients in the alirocumab group compared with the placebo group (61.2% vs 32.0%, respectively). Furthermore, more patients participated in the Phase 2 dose-finding study in the Q2W cohort than in the Q4W cohort, since enrolment in the Q4W cohort started when enrolment in Q2W cohort was completed. These disbalances would likely not have a clinically relevant impact on the outcome. Overall, the study population can be considered representative of a paediatric HeFH population. HeFH diagnosis was sufficiently established as the diagnosis was for a large part of the population by genetic testing (83.8% and 96.2% in the Q2W and Q4W cohort, respectively). The mean (SD) age of the randomized population was 12.9 (2.8) years, with most of the patients (64.1% (n= 98/153)) ≥12-17 years of age at baseline, whereas 19.0% (n=29/153) of the patients were ≥10 to < 12 years of age and 16.3% (n=25/153) of the patients were < 10 years of age, which is considered appropriate for the sought indication, i.e. patients aged 8-17 years of age. Moreover, the elevated mean LDL-C baseline value of 4.5 mmol/L reasonably corresponds to an LDL-C level generally observed within a HeFH population. The majority of the patients have received any statin therapy (98.6% and 91.1% of participants in the Q2W and Q4W cohorts), which is conform to the inclusion criterion "Patients must receive the optimal dose of statin defined as the stable daily dose prescribed based on regional practice or local guidelines or was the stable daily dose that was maximally tolerated due to adverse effects on higher doses". Further, 12.2% and 24.1% of patients in the Q2W and Q4W cohorts, respectively, received any LMTs other than statins. Other patients (4.1% (n=3) in the Q2W cohort and 10.1% (n=8) in the Q4W cohort) were reported statin intolerant as defined by the protocol. As such, paediatric patients who are statin intolerant were underrepresented. However, given the experience of alirocumab therapy in statin-intolerant adults, this issue is not pursued.

In the primary efficacy analysis, treatment with alirocumab demonstrated a substantial reduction in the primary endpoint of percent change from baseline to week 24 in LDL-C. In the Q2W cohort, alirocumab treatment reduced LDL-C with -33.6% (3.4) compared with +9.7% (4.3) in the placebo group (difference: -43.3% ([97.5% CI: -56.0 to -30.7]; p<0.0001), resulting in a mean LDL-C at Week 24 of 2.929 (0.147) mmol/L in the alirocumab group versus 4.820 (0.213) mmol/L in the placebo group. Reductions were observed in both BW categories with a higher treatment effect compared with placebo observed with 40 mg Q2W: -48.5% (7.6) with the 40 mg Q2W dose for BW <50 kg, and -38.0% (7.8) with the 75 mg Q2W dose for BW ≥50 kg. This higher effect was mainly due to a larger (unexpected) increase in LDL-C in the placebo group in the 40 mg Q2W cohort compared with the 75 mg Q2W (12.5% (5.9) vs 5.6 (6.4), respectively. In the Q4W cohort, alirocumab treatment reduced LDL-C with -38.2% (4.0) compared with -4.4% (3.7) in the placebo group (difference: -33.8% ([97.5% CI: -46.4 to -21.2];

p<0.0001), resulting in a mean LDL-C at Week 24 of 2.847 (0.200) mmol/L vs. 4.177 (0.180) mmol/L in the alirocumab and placebo group, respectively. The response was consistent across the 2 doses by the BW category with a reduction of -34.5% (9.5) with the 150 mg Q4W dose for BW <50 kg and -32.9% (7.0) with the 300 mg Q4W for BW ≥50 kg. The LDL-C lowering effect appears generally consistent among several subgroups, including gender age (<12, ≥ 12 years) and baseline LDL-C in both Q2W and Q4W cohorts. Regarding long-term effect, the percent change of LDL-C from baseline to Week 104 was -26.3% in the Q2W cohort and -23.9% (33.5) in the Q4W cohort. The effect at week 104 observed during the OL is lower than as compared with the DB treatment period. According to the Applicant, this observation appeared to be related to a less strict application of the rules regarding dose-up titration/adjustment during the OL treatment period, as revealed by the post-hoc analyses, which can be acknowledged. Moreover, it is acknowledged by CHMP that the LDL-C lowering effect in the paediatric HeFH population is still considered clinically relevant. Overall, the effect size in LDL-C lowering of ~35-40% observed at week 24 in paediatric subjects with HeFH is consistent with the LDL-lowering effect of -39% in adult HeFH patients (HIGH FH study). Furthermore, no differential effect on LDL-C of alirocumab versus placebo was observed between the Q2W and Q4W regimens and the BW categories.

Regarding dose titration, in the Q2W cohort, almost half of the patients in the alirocumab group (22 out of 49 (44.9%); 11 with BW <50 kg and 11 with BW ≥50 kg) received dose up-titration at Week 12. In the Q4W cohort, 15 out of 52 (28.8%) patients were in the alirocumab group (with BW <50 kg and 10 with BW ≥50 kg) at Week 12. The study showed that patients who needed a dose up-titration had a higher mean baseline LDL-C value than patients who did not require a dose up-titration (4.99 vs. 3.91 mmol/L and 5.75 vs 3.99 mmol/L in the Q2W and Q4W cohort respectively). The dose was up-titrated at Week 12 based on LDL-C levels measured at Week 8. Dose up-titration at Week 12 provided an additional moderate LDL-C reduction in the Q4W cohort, and minimal/no effect in the Q2W cohort in participants who underwent a change in dosing at Week 12. Since the Q4W starting regimen is currently proposed for children and adolescents 8 to 17 years of age with HeFH in section 4.2 of the SmPC, the focus to justify the dose adjustments was primarily on the up-titration regimen combined with the Q4W starting dose regimen. At Week 24, following dose adjustment, an additional decrease in the percent change from baseline LDL-C compared with Week 12 was measured in the Q4W cohort (-34.2% versus -26.8%, respectively), however compared with Week 8 there was no additional decrease (-34.2% at Week 24 versus -33.8% at Week 8). Although this observation can possiblly be explained by the differences in sample size at the different time points (n=13 at Week 8 vs n=14 at Week 12 and Week 24), no discussion on this observation has been provided. Instead, the Applicant has highlighted the paediatric patients which had additional benefit with the up-titration step by referring to the secondary endpoints of proportion of patients achieving a LDL-C level lower than 3.37 mmol/L or 2.84 mmol/L, and > 50% reduction in LDL-C at Week 12 (prior to up-titration) vs. Week 24 (after up-titration). The results showed that up-titration allowed more patients to achieve the recommended target of LDL-C <3.37 mmol/L (n=9 (64.3%) vs. n=5 (35.7%) prior up-titration at Week 12), LDL-C <2.84 mmol/L (n=5 (35.7%) vs. n=2 (14.3%) prior up-titration) and >50 % reduction in LDL-C from baseline (n=5 (35.7%) vs. n=2 (14.3%) prior up-titration), whereas in paediatric patients who were not dose adjusted at Week 12, the proportions of subjects reaching the recommended LDL-C targets were decreased between Week 12 and Week 24. Additionally, the results showed that patients who received up-titration had stronger PCSK9 inhibition than prior up-titration. In the dose-adjusted paediatric subjects, mean (SD) free PCSK9 level was 32.5 (63.3) ng/mL at Week 12, compared to 123.0 (61.5) ng/mL at baseline. Following dose up-titration, the mean free PCSK9 level was further reduced to 4.9 (18.3) ng/mL at Week 24. Of note, PCSK9 levels were not entirely consistent with LDL-C effect likely due to statin interference. Furthemore, the proposed dose titration is in line with the dose up-titration already approved in adult patients, ie. to adjust the dose to the maximum dose of 150 mg Q2W if additional LDL-C reduction is needed. Moreover, contrary to statin therapy, there are no differences in safety profile of alirocumab after dose adjustment.

Based on above, it can be concluded that paediatric patients with HeFH who do not reach the recommended LDL-C treatment target with the starting dose of alirocumab may benefit from the proposed dose adjustment. Therefore, the proposed up-titration regimen of 75 mg Q2W for BW < 50 kg or 150 mg Q2W for BW ≥50 kg can be acceptable.

The primary endpoint results were further supported by beneficial effects in <u>secondary cholesterol measurements</u> (e.g. Apo-B, non-HDL-C, Total-C, Lp(a), HDL-C). At Week 24, 77.6% of patients achieved the treatment goal of LDL-C < 3.4 mmol/L (<130 mg/dL) for paediatric patients with HeFH recommended in the ESC guideline for the management of dyslipidemias (2019) and 52.7% of patients an LDL-C level lower than 2.84 mmol/L (110 mg/dL) in the alirocumab group. In the exploratory flow-mediated dilatation (FMD) sub-study, no difference in absolute change from baseline to Week 24 in %FMD was observed (-0.6% vs -2.1% in the alirocumab and placebo group, respectively; p=0.5368).

2.5.4. Conclusions on the clinical efficacy

In conclusion, alirocumab demonstrated a substantial reduction in LDL-C and other lipid parameters on top of standard of care in HeFH patients aged 8-≤17 years. The open-label treatment period provides data of the maintenance of the effect in the long term; although the effect size appeared lower than observed in the DB treatment period, it is still considered clinically relevant.

2.6. Clinical safety

Introduction

Main safety information on the use of alirocumab in the paediatric population is based on the completed Study EFC14643, supplemented with data from other paediatric studies (Phase 2 dose-finding study DFI14223 and the Phase 3 study EFC14660 in HoFH patients) and data from post-marketing surveillance for approved indications.

In the initial MA dossier, a total of 2856 adult subjects were exposed to alirocumab for ≥ 24 weeks, of which 2408 subjects for ≥ 52 weeks. With the submission of the cardiovascular outcome trial ODYSSEY OUTCOMES, with a total of 18894 patients, the overall exposure data from clinical studies has substantially increased, although exposure in the ODYSSEY was limited to a median of 31 months. So, there was a large safety experience with alirocumab in adult patients, while there was none in the paediatric population. Nevertheless, experience is obtained based on the data of pivotal Phase 3 Study EFC14643 in HeFH patients, the Phase 2 dose-finding study DFI14223, and the Phase 3 study EFC14660 in HoFH patients.

Patient exposure

Double-blind treatment period

The duration of treatment exposure was similar across intervention groups in both cohorts: in the Q2W cohort, the mean (SD) duration of exposure was 23.7 (2.0) weeks for alirocumab group and 24.1 (0.4) weeks for placebo group (Table 31and Table 32). In the Q4W cohort, the mean (SD) duration of exposure was 22.9 (4.5) weeks for alirocumab group and 23.9 (3.3) weeks for placebo group. The exposure to alirocumab was 22.2 patient-years in Q2W cohort and 22.8 patient-years in Q4W cohort.

Table 31. Exposure to investigational medicinal product - Double-blind period - Patients in the Q2W cohort – Safety population

	Placebo (N=25)	Alirocumab (N=49)
Cumulative exposure to treatment (patient years)	11.5	22.2
Duration of IMP exposure (weeks)		
Number	25	49
Mean (SD)	24.1 (0.4)	23.7 (2.0)
Median	24.0	24.0
Min ; Max	23 ; 26	14 ; 26
Duration of IMP exposure by category [n(%)]		
1 day to < 4 weeks	0	0
≥ 4 to < 8 weeks	0	0
≥ 8 to < 12 weeks	0	0
≥ 12 to < 16 weeks	0	1 (2.0)
≥ 16 to < 22 weeks	0	3 (6.1)
≥ 22 weeks	25 (100)	45 (91.8)
Cumulative duration of study treatment by category [n(%)]		
≥ 1 day	25 (100)	49 (100)
≥ 4 weeks	25 (100)	49 (100)
≥ 8 weeks	25 (100)	49 (100)
≥ 12 weeks	25 (100)	49 (100)
≥ 16 weeks	25 (100)	48 (98.0)
≥ 22 weeks	25 (100)	45 (91.8)
Total number of double-blind IMP administrations by patient		
Number	25	49
Mean (SD)	12.0 (0.4)	11.7 (1.0)
Median	12.0	12.0
Min ; Max	11 ; 13	7 ; 13
Location of IMP injections		
Thigh	10 (40.0)	21 (42.9)
Abdomen	10 (40.0)	28 (57.1)
Outer area upper arms	11 (44.0)	29 (59.2)
Titration/Dose-adjustment [n (%)]	0	22 (44.9)

a Including patients with missing duration of study treatment

The duration of IMP exposure corresponds to: (last dose of double-blind IMP injection date - first dose of double-blind IMP injection date + 14 days) / 7, regardless of unplanned intermittent discontinuations.

Table 32. Exposure to investigational medicinal product - Double-blind period - Patients in the Q4W cohort – Safety population

	Placebo (N=27)	Alirocumab (N=52)
Cumulative exposure to treatment (patient years)	12.4	22.8
Duration of IMP exposure (weeks)		
Number	27	52
Mean (SD)	23.9 (3.3)	22.9 (4.5)
Median	24.1	24.0
Min ; Max	8 ; 29	4 ; 26
Duration of IMP exposure by category [n(%)]		
1 day to < 4 weeks	0	0

≥ 4 to < 8 weeks	0	2 (3.8)
≥ 8 to < 12 weeks	1 (3.7)	1 (1.9)
≥ 12 to < 16 weeks	0	0
≥ 16 to < 22 weeks	0	1 (1.9)
≥ 22 weeks	26 (96.3)	48 (92.3)
Cumulative duration of study treatment by category [n(%)]		
≥ 1 day	27 (100)	52 (100)
≥ 4 weeks	27 (100)	52 (100)
≥ 8 weeks	27 (100)	50 (96.2)
≥ 12 weeks	26 (96.3)	49 (94.2)
≥ 16 weeks	26 (96.3)	49 (94.2)
≥ 22 weeks	26 (96.3)	48 (92.3)
Total number of double-blind IMP administrations by patient		
Number	27	52
Mean (SD)	8.5 (1.5)	8.2 (2.0)
Median	9.0	9.0
Min ; Max	2 ; 9	1 ; 10
Total number of double-blind IMP administrations by patient		
Until week 12		
Number	27	52
Mean (SD)	3.0 (0.3)	2.9 (0.5)
Median	3.0	3.0
Min ; Max	2 ; 4	1 ; 4
From week 12		
Number	26	49
Mean (SD)	5.7 (0.7)	5.6 (1.0)
Median	6.0	6.0
Min ; Max	4 ; 6	3 ; 6
Location of IMP injections		
Thigh	9 (33.3)	17 (32.7)
Abdomen	14 (51.9)	36 (69.2)
Outer area upper arms	19 (70.4)	33 (63.5)
Titration/Dose-adjustment [n (%)]	0	15 (28.8)

a   Including patients with missing duration of study treatment

For patients with either a last double-blind IMP injection strictly before the IVRS call at Week 12, or with no IVRS call at Week 12): (last dose of double-blind IMP injection date - first dose of double-blind IMP injection date + 28 days) / 7, regardless of unplanned intermittent discontinuations.

Otherwise: (last dose of double-blind IMP injection date - first dose of double-blind IMP injection date + 14 days) / 7, regardless of unplanned intermittent discontinuations

For patients under Q4W regimen having a BW ≥ 50 kg, 2 SC injections are required per administration, whereas for the other patients only 1 SC injection is required per administration

Open-label treatment period

The duration of treatment exposure was similar in both cohorts: in the Q2W cohort, the mean (SD) duration of exposure was 76.5 (14.8) weeks; in the Q4W cohort, the mean (SD) duration of exposure was 79.7 (6.0) weeks. Cumulative exposure to treatment (patient-years) in the Q2W cohort was 67.8 for

"Alirocumab in DB period" group and 36.4 for "Placebo in DB period" group, which in the Q4W cohort was 75.5 for "Alirocumab in DB period" group and 37.6 for "Placebo in DB period" group.

Most of the participants were exposed to the IMP injections for at least 78 weeks: 64 (90.1%) in the Q2W cohort and 67 (90.5%) in the Q4W cohort. The exposure to alirocumab was 104.1 patient-years in Q2W cohort and 113.1 patient-years in Q4W cohort.

In other paediatric studies, the exposure to alirocumab was of 55.5 patient-years in the DFI14223 study and 16.0 patient-years in the EFC14660.

In the pivotal study EFC14643, a total of 101 paediatric HeFH patients (49 in the Q2W cohort and 52 in the Q4W cohort) received at least 1 dose of alirocumab in the DB period. The mean duration of treatment exposure in the DB treatment period was similar across both treatment groups in both cohorts (23.7 vs. 24.1 weeks in the Q2W cohort and 22.9 vs. 23.9 weeks in the Q4W cohort for alirocumab and placebo, respectively), with a total patient-years exposure of 22.2 in the Q2W cohort and 22.8 in the Q4W cohort. In the OL treatment period, the mean duration of treatment was also similar in both cohorts (76.5 weeks in the Q2W cohort vs 79.7 weeks in the Q4W cohort), with a patient-years exposure to alirocumab of 104.1 in the Q2W cohort and 113.1 in the Q4W cohort, which is considered sufficient.

To note, since approximately similar steady-state exposure was achieved after administration of alirocumab between 40 mg and 75 mg Q2W and 150 mg and 300 mg Q4W (for corresponding BW <50 kg and ≥50 kg), it is acceptable to show safety data according to dosing cohort (Q2W vs Q4W) and not differentiate it further into BW <50 kg and ≥50 kg.

Adverse events

General frequency of adverse events

Double-blind treatment period

During the DB treatment period, in the Q2W cohort, 26 (53.1%) participants in the alirocumab group and 13 (52.0%) participants in the placebo group experienced at least 1 TEAE (Table 33). In the Q4W cohort, 26 (50.0%) participants in the alirocumab group and 16 (59.3%) participants in the placebo group experienced at least 1 TEAE cohort (Table 34). Treatment-emergent SAEs were experienced by 5 participants in the Q2W cohort (4 [8.2%] participants in the alirocumab group and 1 [4.0%] participant in the placebo group) and 3 participants in the Q4W cohort (2 [3.8%] in the alirocumab group and 1 [3.7%] in the placebo group). No participants died during the DB treatment period of the study. No participants in the Q2W cohort and 2 (3.8%) participants in the Q4W cohort (both in the alirocumab group) had TEAEs leading to permanent IMP discontinuation.

The majority of TEAEs were of mild or moderate intensity with no relevant distribution between intervention groups.

Table 33. Overview of adverse event profile: Treatment emergent adverse events - Double-blind period - Patients in the Q2W cohort - Safety population

n (%)	Placebo (N=25)	Alirocumab (N=49)
Patients with any TEAE	13 (52.0)	26 (53.1)
Patients with any severe TEAE	1 (4.0)	1 (2.0)
Patients with any treatment emergent SAE	1 (4.0)	4 (8.2)
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	0
Patients with any treatment-related TEAE	1 (4.0)	4 (8.2)

n (%)	Placebo (N=25)	Alirocumab (N=49)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event

n(%) = number and percentages of patients with at least one TEAE.

Table 34. Overview of adverse event profile: Treatment emergent adverse events - Double-blind

n (%)	Placebo (N=27)	Alirocumab (N=52)
Patients with any TEAE	16 (59.3)	26 (50.0)
Patients with any severe TEAE	1 (3.7)	2 (3.8)
Patients with any treatment emergent SAE	1 (3.7)	2 (3.8)
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	2 (3.8)
Patients with any treatment-related TEAE	0	7 (13.5)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event

n(%) = number and percentages of patients with at least one TEAE.

Open-label treatment period

During the OL treatment period, TEAEs were reported by 40 (56.3%) participants in the Q2W cohort (Table 35) and by 41 (55.4%) in the Q4W cohort (**Table 36**). Four (5.6%) and 5 (6.8%) participants reported treatment-emergent SAEs in the Q2W and Q4W cohorts, respectively. No participants died during the OL period of the study. Treatment-emergent AEs leading to permanent treatment discontinuation were reported by 1 (1.4%) participant in the Q2W cohort (PT: low density lipoprotein decreased) and by no participant in the Q4W cohort.

Table 35. Overview of adverse event profile: Treatment emergent adverse events - Patients in the Q2W cohort - Open-label extension population

n (%)	Placebo in DB period (N=25)	Alirocumab in DB period (N=46)	All (N=71)
Patients with any TEAE	16 (64.0)	24 (52.2)	40 (56.3)
Patients with any severe TEAE	0	0	0
Patients with any treatment emergent SAE	0	4 (8.7)	4 (5.6)
Patients with any TEAE leading to death	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	1 (4.0)	0	1 (1.4)
Patients with any treatment-related TEAE	4 (16.0)	4 (8.7)	8 (11.3)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event

n(%) = number and percentages of patients with at least one TEAE.

Placebo and alirocumab in the header of the column refers to the treatment received during the DB period

Table 36. Overview of adverse event profile: Treatment emergent adverse events - Patients in the Q4W cohort - Open-label extension population

n (%)	Placebo in DB period (N=25)	Alirocumab in DB period (N=49)	All (N=74)
Patients with any TEAE	14 (56.0)	27 (55.1)	41 (55.4)
Patients with any severe TEAE	0	2 (4.1)	2 (2.7)

n (%)	Placebo in DB period (N=25)	Alirocumab in DB period (N=49)	All (N=74)
Patients with any treatment emergent SAE	2 (8.0)	3 (6.1)	5 (6.8)
Patients with any TEAE leading to death	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	0	0
Patients with any treatment-related TEAE	3 (12.0)	4 (8.2)	7 (9.5)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event

n(%) = number and percentages of patients with at least one TEAE.

Placebo and alirocumab in the header of the column refers to the treatment received during the DB period

Other studies

In DFI14223, 31 (74.0%) patients experienced at least one TEAE in the OLDFI/OLE combined period. No treatment-emergent SAEs and no deaths were reported during the study. All TEAEs were mild or moderate. TEAEs considered related to IMP were mainly injection site reactions. Two TEAEs led to permanent treatment discontinuation: one patient with decreased neutrophils already noted at screening, experienced neutropenia which resolved after IMP discontinuation; another patient experienced fatigue, which resolved after IMP discontinuation.

None of these TEAEs were considered related to IMP. No AESIs were reported. No clinically significant changes over time were observed in the safety hematology, serum chemistry, vital signs and other parameters assessed in the study.

In EFC14660, 17 participants out of 18 (94.4%) experienced at least one TEAE. The 3 most frequently reported TEAEs by PT were nasopharyngitis (3 [16.7%]), headache (3 [16.7%]), and aortic valve incompetence (3 [16.7%]). One patient experienced a treatment-emergent SAE (PT: cardiac failure) which led to treatment discontinuation and ultimately to death. The patient died due to decompensated heart failure and severe aortic stenosis. This case was assessed as not related to alirocumab by the Investigator. Treatment related TEAE (injection site reaction) was reported in a single patient.

Common adverse events

Double-blind treatment period

In the Q2W cohort, the 2 most frequently reported TEAEs in either intervention group by PT were: nasopharyngitis (7 [14.3%] participants in the alirocumab group vs. 2 [8.0%] participants in the placebo group) and upper respiratory tract infection (3 [6.1%] vs. 3 [12.0%]). PTs with notably higher frequency in the alirocumab group compared with placebo group (with a difference of ≥5%) were nasopharyngitis (7 [14.3%] in the alirocumab group versus 2 [8.0%] in the placebo group) and Injection site reaction (3 [6.1%] versus none)(**table 37**).

In the Q4W cohort, the 2 most frequently reported TEAE in either intervention group by PT were: upper respiratory tract infection (3 [5.8%] participants in the alirocumab group versus 3 [11.1%] participants in the placebo group) and headache (4 [7.7%] vs. 1 [3.7%]). No PTs with notably higher frequency in the alirocumab group compared with placebo group (with a difference of ≥5%) were reported in the Q4W cohort (**Table 38**).

Table 37. Number (%) of patients with TEAE(s) that occurred with HLT ≥5% in any treatment group by Primary SOC, HLT and PT - Double-blind period - Patients in the Q2W cohort - Safety population

PRIMARY SYSTEM ORGAN CLASS
    HLT: High Level Term
        Preferred Term n(%)
	Placebo
	(N=25)
		Alirocumab
		(N=49)

Any class	13 (52.0)	26 (53.1)
INFECTIONS AND INFESTATIONS	7 (28.0)	17 (34.7)
HLT: Upper respiratory tract infections	6 (24.0)	14 (28.6)
Nasopharyngitis	2 (8.0)	7 (14.3)
Pharyngitis	0	1 (2.0)
Rhinitis	1 (4.0)	1 (2.0)
Sinusitis	0	1 (2.0)
Tonsillitis	1 (4.0)	3 (6.1)
Upper respiratory tract infection	3 (12.0)	3 (6.1)
NERVOUS SYSTEM DISORDERS	4 (16.0)	3 (6.1)
HLT: Headaches NEC	2 (8.0)	3 (6.1)
Headache	2 (8.0)	3 (6.1)
HLT: Migraine headaches	2 (8.0)	0
Migraine	2 (8.0)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	4 (8.2)
HLT: Injection site reactions	0	3 (6.1)
Injection site reaction	0	3 (6.1)

TEAE: Treatment emergent adverse event, SOC: System organ class, HLT: High level term, PT: Preferred term

MedDRA 25.0.

n(%) = number and percentages 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 ≥ 5% in at least one group are presented.

Table 38. Number (%) of patients with TEAE(s) that occurred with HLT ≥5% in any treatment group by Primary SOC, HLT and PT - Double-blind period - Patients in the Q4W cohort - Safety population

PRIMARY SYSTEM ORGAN CLASS
    HLT: High Level Term
        Preferred Term n(%)
	Placebo
	(N=27)
		Alirocumab
		(N=52)

Any class	16 (59.3)	26 (50.0)
INFECTIONS AND INFESTATIONS	8 (29.6)	11 (21.2)
HLT: Upper respiratory tract infections	6 (22.2)	6 (11.5)
Laryngitis	0	1 (1.9)
Nasopharyngitis	2 (7.4)	1 (1.9)
Pharyngitis	1 (3.7)	0
Rhinitis	0	1 (1.9)
Tonsillitis	1 (3.7)	0
Upper respiratory tract infection	3 (11.1)	3 (5.8)
HLT: Viral infections NEC	0	3 (5.8)
Gastroenteritis viral	0	1 (1.9)
Respiratory tract infection viral	0	2 (3.8)
NERVOUS SYSTEM DISORDERS	2 (7.4)	10 (19.2)
HLT: Headaches NEC	1 (3.7)	4 (7.7)
Headache	1 (3.7)	4 (7.7)

PRIMARY SYSTEM ORGAN CLASS
  HLT: High Level Term
    Preferred Term n(%)
	Placebo
	(N=27)
		Alirocumab
		(N=52)

GASTROINTESTINAL DISORDERS	3 (11.1)	3 (5.8)
HLT: Gastrointestinal and abdominal pains (excl oral and throat)	2 (7.4)	1 (1.9)
Abdominal pain	0	1 (1.9)
Abdominal pain upper	2 (7.4)	0

TEAE: Treatment emergent adverse event, SOC: System organ class, HLT: High level term, PT: Preferred term
MedDRA 25.0.

n(%) = number and percentages 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 ≥ 5% in at least one group are presented.

Open-label treatment period

The 2 most frequently reported TEAEs by PT were: headache (6 [8.5%]) and nasopharyngitis (5 [7.0%]) in the Q2W cohort and headache (11 [14.9%]) and COVID-19 (5 [6.8%]) in the Q4W cohort.

Treatment related adverse events (by investigator)

Double-blind treatment period

Overall, TEAEs were considered to be related to the IMP by the Investigator in 4 (8.2%) participants in the alirocumab Q2W group and 7 (13.5%) in the alirocumab Q4W group and 1 (4.0%) participant in the Q2W placebo group. The most frequently related TEAEs were injection site reactions, all reported with alirocumab (in 3 [6.1%] and 2 [3.8%] participants in the Q2W and Q4W cohort, respectively). Other TEAEs considered to be related to IMP by the Investigator were all single occurrence with the exception of syncope, reported in 2 participants in the alirocumab group (Q4W cohort) and headache, reported in 1 participant in the alirocumab group (Q4W cohort) and 1 participant in the placebo group (Q2W cohort).

Open-label treatment period

A total of 15 (10.3%) participants reported TEAEs that were considered to be related to the IMP by the Investigator. Among them 6 participants experienced injections site reactions and 4 had LDL-C decreased reported as AE. Other related events were reported in 1 participant each.

Treatment-emergent adverse events (TEAEs) were frequently reported; however, the percentage of patients with any TEAE in the DB treatment period was approximately similar across both treatment groups in the Q2W cohort (53.1% vs. 52.0% in the alirocumab and placebo group, respectively) or lower in the alirocumab compared with the placebo group in the Q4W cohort (50.0% vs. 59.3%), which is reassuring. In the OL treatment period, the percentage of TEAEs was comparable between subjects who received alirocumab and placebo in the DB period in the Q4W cohort (55.1% vs. 56.0% in the Q4W cohort) or lower in the alirocumab DB group compared with the placebo DB group in the Q2W cohort (52.2% vs. 64.0%). The most frequent AEs with a higher incidence with alirocumab compared with placebo (a difference of ≥ 5%) in the Q2W cohort were nasopharyngitis (14.3% vs. 8.0%) and injection site reaction (6.1% vs. 0%), while there were not AEs with a notably higher frequency in the alirocumab group compared with the placebo group in the Q4W cohort. In the OL treatment period, the 2 most frequently reported AEs were headache (8.5%) and nasopharyngitis (7.0%). The AEs considered treatment-related by the investigator were reported in 4 (8.2%) subjects in the alirocumab Q2W group

and 7 (13.5%) in the alirocumab Q4W group. The most frequently related TEAEs were injection site reactions. The other AEs considered treatment-related concerned single occurrences in the alirocumab group with the exception of syncope (n=2). As indicated below, both events of syncope that occurred were classified as SAE, however, were transient and unique episodes. The Applicant argued that the age and gender of the participants may be predisposing factors as the incidence of syncope was reported to peak between 15 and 19 years of age and to be greater in girls than boys. Further, the study days of the last IMP injection before syncope for these 2 patients were inconsistent (Day 1 and Day 161). Based on above, it is agreed with the Applicant that the causality of alirocumab is unlikely. Moreover, in the initial MA or the ODYSSAY OUTCOME dossier no increased risk for syncope has been observed.

Consistent with the pivotal study EFC14643, the TEAEs in the dose-finding study DFI14223 and the Phase 3 study EFC14660 in HoFH were mild or moderate, with injection site reactions, nasopharyngitis, and headache as the most frequently reported.

Serious adverse event/deaths/other significant events

Serious adverse events

Double-blind treatment period

SAE was experienced by:

- 5 participants in the Q2W cohort (4 [8.2%] participants in the alirocumab group [1 major depression, 1 abdominal hernia, 1 abdominal pain, and 1 sympathetic posterior cervical syndrome] and 1 [4.0%] participant in the placebo group [appendicitis]) and,

- 3 participants in the Q4W cohort (2 [3.8%] in the alirocumab group [2 syncope] and 1 [3.7%] in the placebo group [non-cardiac chest pain])

All treatment-emergent SAEs were reported as resolved or recovered at the end of the DB treatment period. Two of these events were experienced by 2 participants in the alirocumab group in the Q4W cohort (syncope), both events were transient, unique episode and were considered related to the IMP by the Investigator. In one case, the syncope led to study treatment discontinuation due to participant's decision and in the second participant, the treatment with IMP was continued as planned without reoccurrence of the event. The age and gender of the participants may also be predisposing factors as the incidence of syncope was reported to peak between 15 and 19 years of age and to be greater in girls than boys (22). The study days of last IMP injection before syncope for these 2 participants were Day 1 and Day 161, respectively. No diagnostic tests (eg, blood tests) were done. The Sponsor assessed the causality of alirocumab as unlikely.

Open-label treatment period

Treatment-emergent SAEs were reported in:

- 4 (5.6%) participants in the Q2W cohort (PT: pharyngitis streptococcal, pneumonia, hypertension, and calculus urinary) and,

- 5 (6.8%) participants in the Q4W cohort (PT: appendicitis, syncope, angina pectoris, myocarditis, ligament rupture).

All treatment-emergent SAEs were resolved or resolving at the end of the OL treatment period. They were not related to alirocumab injections. Two serious cases of syncope were reported in the Q4W cohort. They were transient, unique episode of moderate or mild intensity. The study days of last IMP injection for these 2 participants were Day 20 and 2 months and 20 days after the last administration of IMP in

blinded phase and unspecified duration after first administration of IMP in OL period. Therapy with IMP was continued as planned without reoccurrence of syncope. Angina pectoris and myocarditis were reported in the same participant, where both events were evaluated as not related to the IMP and no action was taken with the IMP. Both events were assessed by the Investigator as being related to COVID-19 vaccine.

Deaths

No deaths were reported during Study EFC14643.

Adverse events of special interest

Double-blind treatment period

General allergic events

General allergic events were reported in 2 (3.8%) participants in the alirocumab group in Q4W cohort (PT: rash) and in no participants in the alirocumab group Q2W cohort and in the placebo groups.

Local injection site reactions

Local injection site reactions were reported in 3 (6.1%) participants in the alirocumab group in the Q2W cohort and 2 (3.8%) participants in the alirocumab group in the Q4W cohort. No participants reported local injection site reactions in the placebo groups.

Neurologic events

Neurologic event of hypoesthesia was reported in 1 (1.9%) participant from the alirocumab group in Q4W cohort. This participant reported a non-serious hypoaesthesia and did not discontinue study intervention due to this event. No participants reported neurologic event in the alirocumab group in the Q2W cohort and in the placebo groups.

Neurocognitive events

Neurocognitive events of disturbance in attention and memory impairment were reported in 1 (1.9%) participant from the alirocumab group in the Q4W cohort. These events led to treatment discontinuation. No participants reported neurocognitive event in the alirocumab group in the Q2W cohort and in the placebo groups.

LDL-C< 50 mg/dL

In the Q2W cohort, 4 (8.2%) participants in the alirocumab group had 1 LDL-C value <50 mg/dL. The mean time to the first observed low LDL-C value <50 mg/dL was 13.14 (7.57) weeks (range: 8.1 to 24.1 weeks). No participants had more than 1 low LDL-C value and no participants had any LDL-C value <25 mg/dL.

In the Q4W cohort, 7 (13.5%) participants in the alirocumab group had at least 1 LDL-C value <50 mg/dL. The mean time to the first observed LDL-C value <50 mg/dL was 15.84 (7.88) weeks. Among them, 3 (5.8%) participants had 2 consecutive LDL-C values <50 mg/dL including 1 (1.9%) participant who had 2 consecutive LDL-C values <25 mg/dL. One out of 3 (33.3%) participants with 2 consecutive LDL-C <50 mg/dL (1.30 mmol/L) reported TEAEs. This participant experienced pain in extremity and gastroenteritis bacterial after the first of the 2 low LDL-C values and then recovered with corrective treatment. The events were considered not related to the IMP by the Investigator.

Other

There were no cases of hepatic disorders, no cases of diabetes mellitus or diabetic complications, and no cases of cataract

Open-label treatment period

General allergic events

General allergic events were reported in 4 (5.6%) participants in the Q2W cohort (PT: seasonal allergy (n=2), dermitis allergic (n=1), rash (n=1)) and in 3 (4.1%) participants in the Q4W cohort (PT: asthma, rash, seasonal allergy).

Local injection site reactions

Local injection site reactions were reported in 4 (5.6%) participants in the Q2W cohort and in 3 (4.1%) participants in the Q4W cohort.

Neurocognitive events

Neurocognitive event (PT: memory impairment) was reported in 1 (1.4%) participant in Q2W cohort and in 1 (1.4%) participant in the Q4W cohort (PT: attention deficit hyperactivity disorder). Both events were not serious and did not lead to treatment discontinuation.

Hepatic disorder

One (1.4%) participant in the Q2W cohort and 1 (1.4%) participant in the Q4W cohort reported hepatic disorder (PT: alanine aminotransferase increased).

LDL-C< 50 mg/dL

In the Q2W cohort, 5 (7.0%) participants had 1 LDL-C value <50 mg/dL and 2 participants had 2 consecutive LDL-C values <50 mg/dL. The mean time to the observed low LDL-C value was 12.17 (6.91) weeks. One participant had at least 1 LDL-C value <25 mg/dL and no participant had 2 consecutive LDL-C value <25 mg/dL. One participant with 2 consecutive LDL-C <50 mg/dL reported a TEAE (otitis media). The event was considered not related to the IMP by the Investigator.

In the Q4W cohort, 12 (16.2%) participants had one LDL-C value <50 mg/dL (10 [20.4%] in the alirocumab in DB period group and 2 [8.0%] in the placebo in DB period group) and 7 (9.5%) participants had 2 consecutive LDL-C value <50 mg/dL. One participant in alirocumab in DB period group had 2 consecutive LDL-C value <50 mg/dL in both the DB and OL treatment periods as LDL-C value <50 mg/dL was reported at Week 12, Week 24 and Week 32. Two participants had at least 1 LDL-C value <25 mg/dL and no participant had 2 consecutive LDL-C value <25 mg/dL. Three participants with 2 consecutive LDL-C <50 mg/dL experienced TEAEs (COVID-19, low density lipoprotein decreased and nasopharyngitis in the first participant, respiratory tract infection and low density lipoprotein decreased in the second participant, and headache and tremor in the third participant). The events "low density lipoprotein decreased" were considered related to the IMP. The other events were assessed as not related to the IMP by the Investigator.

Other

There were in the Q2W and Q4W no cases of neurologic events, diabetes mellitus or diabetic complication or cataracts.

The percentage of subjects experiencing SAEs was relatively low, however, slightly higher in the alirocumab group compared with the placebo group in the Q2W cohort group (8.2% vs. 4.0%), whereas the percentage of SAEs was comparable in the Q4W cohort group (3.8% vs 3.7%). Overall, no patterns indicative of a safety signal were observed; all SAEs concerned single events except for syncope (n=2) of which the causality to alirocumab was considered unlikely (see above).

No deaths were observed in the pivotal study EFC 14643.

Special attention has been given to certain AEs, including allergic events, local injection site reactions, neurologic events, neurocognitive events, hepatic disorders, diabetes mellitus, and cataract. The incidence in general allergic events was low; Only 2 patients (3.8%) in the Q4W cohort group experienced a rash event. Local injection site reactions occurred with a higher frequency for alirocumab compared with placebo (6.1% vs. 0% in the Q2W cohort and 3.8% vs. 0% in the Q4W cohort, respectively). The frequency in local injection site reactions remained stable throughout the study, with 4 (5.6%) patients in the Q2W cohort and in 3 (4.1%) participants in the Q4W cohort in the OL treatment period. Injection site reaction is already a known ADR from the original dossier. Incidences of neurologic and neurocognitive events were very limited (both n=1 from the alirocumab group of the Q4W cohort in the DB period), making any conclusions difficult. Furthermore, in the DB treatment period, there were no incidences of hepatic disorder, diabetes mellitus or diabetic complications, and cataract.

Regarding very low LDL-C levels, in the DB treatment period, 4 (8.2%) and 7 (13.5%) patients in the alirocumab group of the QW2 and Q4W cohort, respectively, had at least one low LDL-C value of < 1.29 mmol/L (< 50 mg/dL) of which 3 (5.8%) patients had 2 consecutive LDL-C values < 1.29 mmol/L (all Q4W) including 1 (1.9%) participant who had 2 consecutive LDL-C values < 0.65 mmol/L (<25 mg/dL). In the OLE period, 7 (10.0%) and 12 (16.2) in the Q2W and Q4W cohorts had at least one low LDL-C value of < 1.29 mmol/L of which 1 (1.4%) in the Q2W cohort and 7 (9.5%) in the Q4W cohort had 2 consecutive LDL-C values < 1.29 mmol/L. Three patients (1 in Q2W and 2 in Q4W) had one LDL-C value < 0.65 mmol/L. However, there is no evidence of an unexpected safety concern regarding subjects who achieved low LDL-C levels, consistent with the full dataset available for alirocumab.

Laboratory findings

Double-blind treatment period

Immunogenicity

One (2.1%) participant in the alirocumab group in Q2W cohort and 4 (8.0%) participants in the alirocumab group in the Q4W cohort had positive ADA status at baseline, before the first IMP administration. Three participants (6.1%) developed a treatment-emergent positive ADA response, all of them in the alirocumab group of the Q2W cohort. No participants had a treatment-emergent positive ADA response classified as persistent and no titer was above 240.

No participants had ADA response with neutralizing status.

In the OL period, one participant developed a treatment-emergent positive ADA response in the Q4W cohort. The response was classified as transient (detected only at Week 68).

No participants had treatment-emergent ADA response with a titer above 240. No participants had ADA response with neutralizing status.

Hematology

During the DB period, there was no clinically meaningful difference between the alirocumab and the placebo groups for the changes over time in RBCs, platelets, and WBCs in the Q2W and Q4W cohorts:

- In the Q2W cohort, the percentage of postbaseline PCSAs (or abnormalities) was low (ie, <10%) in both intervention groups for RBCs, platelets, and WBCs parameters. For leukocytes, PCSA was reported in 11 (22.4%) participants in the alirocumab group and 7 (28.0%) participants in the placebo group.

- In the Q4W cohort, the most frequently reported PCSAs (>10% of participants in either intervention group) for RBCs, platelets, and WBCs parameters were hematocrit low, leukocytes low, basophils high, and eosinophils high.

No participants had abnormal hematology parameters while on-treatment that were considered as TEAEs.

During the OL period, no clinically meaningful changes over time were reported in RBCs, platelets and WBCs in the Q2W and Q4W cohorts.

- In the Q2W cohort, the percentage of post-baseline PCSAs (or abnormalities) was low (ie, <10%) for all RBCs, platelets and WBCs parameters except for leukocytes low in 23 (32.9%) participants, eosinophils high in 7 (10.0 %) participants, and basophils high in 13 (18.6%) participants.

- In the Q4W cohort, the percentage of post-baseline PCSAs (or abnormalities) was low (ie, <10%) for all RBCs, platelets and WBCs parameters except for leukocytes low in 26 (35.1%) participants, eosinophils high in 10 (13.5%) participants, and basophils high in 12 (16.2%) participants.

Clinical chemistry

In the DB and OL periods, no clinically meaningful changes from baseline were observed for metabolic parameters (glucose, total protein, and creatine phosphokinase), for electrolytes, for renal function parameters, and for liver function in the alirocumab and placebo groups throughout the course of the study.

No participants experienced a PCSA that met the criteria of a potential Hy's law case (ALT >3 x ULN and total bilirubin >2 x ULN).

No participants had abnormal liver function parameters while on-treatment that were considered as TEAEs in DB period. In OL period, one participant in the Q2W cohort and one participant in the Q4W cohort reported hepatic disorder (PT: alanine aminotransferase increased).

Gonadal and pituitary hormones

In the DB and OL periods, no abnormal change over time in the gonadal and pituitary hormones was observed in boys and girls in the Q2W and Q4W cohorts. No boy had testosterone <LLN and LH>ULN and/or FSH >ULN and no girl had estradiol <LLN and LH >ULN and/or FSH >ULN.

Adrenal gland hormones

In the DB and OL periods, no abnormal change over time in DHEAS, cortisol, adrenocorticotropic hormone was observed in any treatment groups. There were 2 girls with DHEAS values >ULN in the alirocumab group in both periods in the Q4W cohort, and 1 boy with DHEAS values >ULN in the OL treatment period

in the Q4W cohort. These abnormal values were not clinically relevant. No participants had both cortisol <LLN and adrenocorticotropic hormone >ULN in either intervention group in the Q2W and Q4W cohorts.

Fat soluble vitamins

In the DB period, there was no clinically meaningful differences between the alirocumab and the placebo groups for changes over time in fat soluble vitamins in the Q2W and Q4W cohorts.

In the OL period, there was no clinically meaningful difference in the Q2W and Q4W cohorts.

A low level of immunogenicity (n=3; all in Q2W cohort) was observed in the paediatric population in the pivotal Phase 3 study EFC14643. The treatment-emergent anti-drug antibody (ADA) responses were classified as very low titer and transient. Further, no participants with neutralizing ADA were reported.

Furthermore, no trends indicative of clinically important treatment-related laboratory abnormalities, including hematology parameters, renal and hepatic function parameters, blood glucose, hsCRP, hormone levels, and vitamins were observed with alirocumab.

Vital signs, physical findings and other observations related to safety

Vital signs and physical findings

For both genders, the mean BW and height in these young participants increased steadily over time which was consistent with the growth velocity expected in this age group and comparable in Q2W and Q4W cohort over the 104 weeks:

- In the Q2W cohort, the mean (SD) height increase from baseline to Week 24 was 1.75 (1.86) cm in the alirocumab group and 1.00 (1.93) cm in the placebo group, for female participants, and was 4.35 (6.08) cm in the alirocumab group and 2.66 (2.29) cm in the placebo group, for male participants. The mean (SD) BW increase from baseline to Week 24 was 1.29 (2.65) kg in the alirocumab group and 2.28 (2.65) kg in the placebo group for female participants and 2.41 (2.03) kg and 1.71 (3.09) kg, respectively for male participants.

- In the Q4W cohort, the mean (SD) height increase from baseline to Week 24 was 1.47 (1.78) cm in the alirocumab group and 1.64 (1.34) cm in the placebo group for female participants and 2.06 (2.61) cm and 1.88 (1.23) cm, respectively for male participants. The mean (SD) BW increase from baseline to Week 24 was 1.48 (3.56) kg in the alirocumab group and 1.78 (3.21) kg in the placebo group for female participants and 1.96 (2.64) kg and 2.62 (2.40) kg, respectively for male participants.

There were no clinically meaningful changes over time in other vital signs (heart rate, SBP, and DBP in sitting position) in both Q2W and Q4W cohorts.

<u>Tanner stages</u>

Double-blind treatment period

Majority of participants were pubescent at baseline. Specifically, 27 (73.0%) participants from the alirocumab group and 17 (58.6%) participants were at pubescent stage at baseline in safety population of boys, and 29 (45.3%) participants from the alirocumab group and 14 (60.9%) participants from the placebo group were at pubescent stage at baseline in safety population of girls.

As expected, a progression to a more advanced Tanner stage was noted as follows:

- 5 (14.7%) boys in the alirocumab groups (3 in Q2W cohort and 2 in Q4W cohort) and 11 (39.3%) boys in the placebo groups (7 in Q2W cohort and 4 in Q4W cohort) had a change in Tanner stage ≥1 for the development of external genitalia.

- 6 (17.6%) boys in the alirocumab groups (2 in Q2W cohort and 4 in Q4W cohort) and 11 (39.3%) boys in the placebo groups (6 in Q2W cohort and 5 in Q4W cohort) had a change in Tanner stage ≥1 for pubic hair.

- 10 (18.2%) girls in the alirocumab groups (4 in Q2W cohort and 6 in Q4W cohort) and 2 (10.0%) girls in the placebo groups (1 in Q2W cohort and 1 in Q4W cohort) had a change in Tanner stage ≥1 for the breast development.

- 10 (18.2%) girls in the alirocumab groups (5 in Q2W cohort and 5 in Q4W cohort) and 5 (25.0%) girls in the placebo groups (3 in Q2W cohort and 2 in Q4W cohort) had a change in Tanner stage ≥1 for pubic hair.

Open-label treatment period

- 20 (71.4%) boys in the Q2W cohort and 12 (52.2%) boys in the Q4W had a change in Tanner stage ≥1 for the development of external genitalia at Week 104.

- 19 (67.9%) boys in the Q2W cohort and 13 (56.5%) boys in the Q4W cohort had a change in Tanner stage ≥1 for pubic hair at Week 104.

- 16 (59.3%) girls in the Q2W cohort and 19 (47.5%) girls in the Q4W cohort had a change in Tanner stage ≥1 for the breast development at Week 104.

- 19 (70.4%) girls in the Q2W cohort and 19 (47.5%) girls in the Q4W cohort had a change in Tanner stage ≥1 for pubic hair at Week 104.

<u>Cogstate battery test</u>

<u>*Double-blind treatment period*</u>

Overall, there were no clinically meaningful changes over time in Cogstate battery test results in both Q2W and Q4W cohorts. The mean values of each test results (Detection test, Identification test; One Card Learning test; Groton Maze Learning test) at baseline and at Week 24 were similar between intervention groups in both cohorts.

<u>*Open-label treatment period*</u>

Overall, there were no clinically meaningful changes over time in Cogstate battery test results in the Q2W and Q4W cohorts.There were no trends indicative of important vital signs, including systolic blood pressure, diastolic blood pressure, and heart rate abnormalities observed.

Further, assessments of growth and pubertal development (Tanner stage) showed less progression (≥ 1 Tanner stage) in boys in the alirocumab group compared with the placebo group (14.7% vs 39.3% for external genitalia and 17.6% vs 39.3% for pubic hair, respectively) and an approximately comparable progression in girls (18.2% vs 10.0% for the breast development and 18.2% vs 25% for pubic hair. This disbalance in boys is probably due to the higher percentage of pubescent boys at baseline in the alirocumab group vs. the placebo group (73.0% vs 58.6%), whereas this was the other way around for girls (45.3% vs. 60.9%). Nevertheless, the placebo-controlled safety data of 24 weeks exposure to alirocumab is considered too limited to draw firm conclusions on the effect of alirocumab on Tanner staging.

Additionally, assessments of cognitive function (Cogstate battery test) did not reveal a detrimental effect of alirocumab. However, the placebo-controlled safety data of 24 weeks of exposure to alirocumab is also considered too limited to draw firm conclusions on the effect of alirocumab on cognitive function.

Discontinuation due to adverse events

Double-blind treatment period

No participants in the Q2W cohort and 2 (3.8%) participants in the Q4W cohort (both in the alirocumab group) had TEAEs leading to permanent IMP discontinuation. One participant permanently discontinued alirocumab due to 2 neurocognitive AESI (PT: disturbance in attention and memory impairment), and the other one due to syncope, which was also reported as an SAE.

Open-label treatment period

In the Q2W cohort, 1 (1.4%) participant had a TEAE (PT: low density lipoprotein decreased) which led to permanent IMP injection discontinuation. Of note, LDL-C decrease is anticipated with alirocumab. None of the participants in the Q4W cohort discontinued IMP due to a TEAE.

The percentage of patients discontinued due to AEs was relatively low (n=2 (3.8%)), indicating that the drug is well tolerated.

Post marketing experience

In the post-marketing experience, cumulatively from 24 July 2015 to 01 September 2022, a total of 32 Individual Case Safety Reports for paediatric patients were recorded in the Sanofi Global PV database. It represents 0.06% (n=32) of all cases (n= 58 837). Of note, as per the current approved indication, use in paediatric population is off-label use.

Out of the 32 cases, 17 cases reported in the clinical studies EFC14660, DFI14223, and EFC14643 are not included in this analysis.

For the remaining 15 cases:

- In 2 cases, the exposure to alirocumab was improbable due to the patient's age:

  - In 1 case, a 14 day-old-neonate female patient was reported to have experienced increasing anxiety, confusion and cognitive fuzziness, all 14 days after starting treatment with alirocumab. No further information was provided.

  - In 1 case, a 1-month female patient was reported to have experienced leg pain.

- For the rest of cases (n=13), the majority (99%) of reported adverse events were nonserious. When provided, the age of the patient was between 3 months to 17 years (age not specified in 2 cases):

  - In 1 case, a 1-month old female patient was reported to have experienced leg pain. She had expected drug exposure via breast milk, no AE was reported. The patient was assessed for well infant exams up to 6 months of age and then on an as-needed basis. No abnormalities/concerns were noted regarding cognitive/physical development.

Off-label use cases with AEs:

- In 1 case, a 5-year-old female patient experienced skin reaction

- In 1 case, a 6-year-old male patient experienced injection site reaction.

- In 1 case, a 12-year-old male patient experienced gastroenteritis while being treated

- with alirocumab.

- In 1 case, a 15-year-old female patient was diagnosed with moderate Zika virus

  infection while being treated with alirocumab.

Off-label use cases without AEs:

- In 8 other cases, no AEs were reported with the (off-label) use of alirocumab. Among these cases, 3 were paediatric patients treated for HoFH.

No new safety signal was identified in paediatric patients in the post-marketing experience.

2.6.1. Discussion on clinical safety

The safety evaluation is primarily based on the double-blind randomized Study EFC14643 in paediatric patients with HeFH, supplemented with data from other paediatric studies (Phase 2 dose-finding study DFI14223 and the Phase 3 study EFC14660 in HoFH patients) and data from post-marketing surveillance for approved indications.

Patient exposure. In the initial MA dossier, a total of 2856 adult subjects were exposed to alirocumab for $\geq$ 24 weeks of which 2408 subjects for $\geq$ 52 weeks. With the submission of the cardiovascular outcome trial ODYSSEY OUTCOMES, with a total of 18894 patients, the overall exposure data from clinical studies has substantially increased, although exposure in the ODYSSEY was limited to a median of 31 months. So, there was a large safety experience with alirocumab in adult patients; however, there was none in the paediatric population. Nevertheless, experience is obtained based on the data of pivotal Phase 3 Study EFC14643 in HeFH patients, supplemented with the Phase 2 dose-finding study DFI14223 and the Phase 3 study EFC14660 in HoFH patients currently under review.

In the pivotal study EFC14643, a total of 101 paediatric HeFH patients (49 in the Q2W cohort and 52 in the Q4W cohort) received at least 1 dose of alirocumab in the DB treatment period. The mean duration of treatment exposure in this period was similar across both treatment groups in both cohorts (23.7 vs. 24.1 weeks in the Q2W cohort and 22.9 vs. 23.9 weeks in the Q4W cohort for alirocumab and placebo, respectively), with a total patient-years exposure of 22.2 in the Q2W cohort and 22.8 in the Q4W cohort. In the OL treatment period, the mean duration of treatment was also similar in both cohorts (76.5 weeks in the Q2W cohort vs 79.7 weeks in the Q4W cohort), with a patient-years exposure to alirocumab of 104.1 in the Q2W cohort and 113.1 in the Q4W cohort, which is considered sufficient. To note, since

approximately similar steady-state exposure was achieved after administration of alirocumab between 40 mg and 75 mg Q2W and 150 mg and 300 mg Q4W (for corresponding BW <50 kg and ≥50 kg), it is acceptable to show safety data according to dosing cohort (Q2W vs Q4W) and not differentiate it further into BW <50 kg and ≥50 kg.

Adverse events. Treatment-emergent adverse events (TEAEs) were frequently reported; however, the percentage of patients with any TEAE in the DB treatment period was approximately similar across both treatment groups in the Q2W cohort (53.1% vs. 52.0% in the alirocumab and placebo group, respectively) or lower in the alirocumab compared with the placebo group in the Q4W cohort (50.0% vs. 59.3%), which is reassuring. In the OL treatment period, the percentage of TEAEs was comparable between subjects who received alirocumab and placebo in the DB period in the Q4W cohort (55.1% vs. 56.0% in the Q4W cohort) or lower in the alirocumab DB group compared with the placebo DB group in the Q2W cohort (52.2% vs. 64.0%). The most frequent AEs with a higher incidence with alirocumab compared with placebo (a difference of ≥ 5%) in the Q2W cohort were nasopharyngitis (14.3% vs. 8.0%) and injection site reaction (6.1% vs. 0%), while there were not AEs with a notably higher frequency in the alirocumab group compared with the placebo group in the Q4W cohort. In the OL treatment period, the 2 most frequently reported AEs were headache (8.5%) and nasopharyngitis (7.0%). The AEs considered treatment-related by the investigator were reported in 4 (8.2%) subjects in the alirocumab Q2W group and 7 (13.5%) in the alirocumab Q4W group. The most frequently related TEAEs were injection site reactions. The other AEs considered treatment-related concerned single occurrences in the alirocumab group with the exception of syncope (n=2) of which it is agreed with the Applicant that causality of alirocumab is unlikely. Moreover, no increased risk for syncope has been observed in the initial MA or the ODYSSAY OUTCOME dossier. Consistent with the pivotal study EFC14643, the TEAEs in the dose-finding study DFI14223 and the Phase 3 study EFC14660 in HoFH were mild or moderate, with injection site reactions, nasopharyngitis, and headache as the most frequently reported.

AEs of special interest. Special attention has been given to certain AEs, including *allergic events, local injection site reactions, neurologic events, neurocognitive events, hepatic disorders, diabetes mellitus,* and *cataract.* The incidence in *general allergic events* was low; Only 2 patients (3.8%) in the Q4W cohort group experienced a rash event. Local injection site reactions occurred with a higher frequency for alirocumab compared with placebo (6.1% vs. 0% in the Q2W cohort and 3.8% vs. 0% in the Q4W cohort, respectively). The frequency in *local injection site reactions* remained stable throughout the study, with 4 (5.6%) patients in the Q2W cohort and in 3 (4.1%) participants in the Q4W cohort in the OL treatment period. Injection site reaction is already a known ADR from the original dossier. Incidences of *neurologic* and *neurocognitive events* were very limited (both n=1 from the alirocumab group of the Q4W cohort in the DB period), making any conclusions difficult. Furthermore, in the DB treatment period, there were no incidences of *hepatic disorder, diabetes mellitus or diabetic complications*, and *cataract*.

Regarding *very low LDL-C levels*, in the DB treatment period, 4 (8.2%) and 7 (13.5%) patients in the alirocumab group of the QW2 and Q4W cohort, respectively, had at least one low LDL-C value of < 1.29 mmol/L (< 50 mg/dL) of which 3 (5.8%) patients had 2 consecutive LDL-C values < 1.29 mmol/L (all Q4W) including 1 (1.9%) participant who had 2 consecutive LDL-C values < 0.65 mmol/L (<25 mg/dL). In the OLE period, 7 (10.0%) and 12 (16.2) in the Q2W and Q4W cohort had at least one low LDL-C value of < 1.29 mmol/L of which 1 (1.4%) in the Q2W cohort and 7 (9.5%) in the Q4W cohort had 2 consecutive LDL-C values < 1.29 mmol/L. Three patients (1 in Q2W and 2 in Q4W) had one LDL-C value < 0.65 mmol/L. However, there is no evidence of an unexpected safety concern regarding subjects who achieved low LDL-C levels, which is consistent with the full dataset available for alirocumab.

Serious AEs. The percentage of subjects experiencing SAEs was relatively low, however, slightly higher in the alirocumab group compared with the placebo group in the Q2W cohort group (8.2% vs. 4.0%),

whereas the percentage of SAEs were comparable in the Q4W cohort group (3.8% vs 3.7%). Overall, no patterns indicative for a safety signal were observed; all SAEs concerned single events with the exception of syncope (n=2) of which the causality to alirocumab was considered unlikely.

Deaths. No deaths were reported during Study EFC14643.

Laboratory findings. A low level of immunogenicity (n=3; all in Q2W cohort) was observed in the paediatric population in the pivotal Phase 3 study EFC14643. The treatment-emergent anti-drug antibody (ADA) responses were classified as very low titer and transient. Further, no participants with neutralizing ADA were reported.

Furthermore, no trends indicative of clinically important treatment-related laboratory abnormalities, including hematology parameters, renal and hepatic function parameters, blood glucose, hsCRP, hormone levels, and vitamins were observed with alirocumab.

Vital signs. There were no trends indicative of important vital signs, including systolic blood pressure, diastolic blood pressure, and heart rate abnormalities observed.

Further, assessments of growth and pubertal development (Tanner stage) showed less progression (≥ 1 Tanner stage) in boys in the alirocumab group compared with the placebo group (14.7% vs 39.3% for external genitalia and 17.6% vs 39.3% for pubic hair, respectively) and an approximately comparable progression in girls (18.2% vs 10.0% for the breast development and 18.2% vs 25% for pubic hair. This disbalance in boys is probably due to the higher percentage of pubescent boys at baseline in the alirocumab group vs. the placebo group (73.0% vs 58.6%), whereas this was the other way around for girls (45.3% vs. 60.9%). Nevertheless, the placebo-controlled safety data of 24 weeks of exposure to alirocumab is considered too limited to draw firm conclusions on the effect of alirocumab on Tanner staging.

Additionally, assessments of cognitive function (Cogstate battery test) did not reveal a detrimental effect of alirocumab. However, the placebo-controlled safety data of 24 weeks of exposure to alirocumab is also considered too limited to draw firm conclusions on the effect of alirocumab on cognitive function.

Discontinuation due to AEs. The percentage of patients who discontinued due to AEs was relatively low (n=2 (3.8%)), indicating that the drug is well tolerated.

Post marketing experience. It represents 0.06% of all cases (n= 58 837). Out of the 32 cases, 17 cases reported in the clinical studies EFC14660, DFI14223, and EFC14643. From the remaining cases, no new safety signal was identified in paediatric patients in the post-marketing experience.

2.6.2. Conclusions on clinical safety

Alirocumab displays an acceptable safety profile in paediatric HeFH patients aged 8-≤ 17 years compared to those observed in adults HeFH in the initial MA dossier and the ODYSSEY OUTCOMES dossier with very limited patients discontinuing treatment. No new safety signal has been identified. Most of the TEAEs considered treatment-related were injection site reactions, which is a known ADR of alirocumab.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3. Risk management plan

The Applicant provided an updated RMP, version 8.0 with the Data Lock Point (DLP) 31 August 2022. The rationale for the updated RMP was the extension of the indication in paediatric patients of eight years and older with HeFH and to include the results of the clinical trial EFC14643.

The significant changes were the update of the safety specifications including the removal of the missing information 'Use in children and adolescents' and an update of the clinical trial exposure. Further, the pharmacovigilance plan has been updated with actual information regarding the completed study EFC14643 and the pharmacovigilance plan and the rism minimisation measures have been aligned with the new list of safety concerns.

Part I:

Part I was updated with the extension of the indication in paediatric patients of eight years and older, including the dosing scheme for paediatric patients.

Part II – Module SIII: Clinical Trial Exposure

Table39: List of studies described in the clinical trial exposure section SIII.2

| EFC14643 | 24 week double-blind treatment, placebo-controlled period followed by an 80 week open label treatment period to evaluate the efficacy and safety of alirocumab in patients with HeFH 8 to 17 years of age on optimal stable daily dose of statin therapy ± other LMTs or a stable dose of non-statin LMTs in case of intolerance to statins. | Placebo | 101 patients were exposed during DBTP whereas 145 patients were exposed during OLTP. |

Other supportive studies:

Considering the development stage and longstanding postmarketing experience of alirocumab (more than 7 years), the historical exposure data of supportive studies (R727 CL 1308 [CHOICE I]; EFC13786 [CHOICE II]; LTS13463; Pooled Phase 3 OLE studies - OLE including LTS13463 and OLE of CL 1119 [ALTERNATIVE]; MSC14864; LPS14245 (APRISE study); R727 CL 1532; R727 CL 1628) were included till the RMP version 7.0 and have been removed from RMP version 8.0.

Exposure data for EFC14643:

The duration of treatment exposure was similar across intervention groups in both cohorts: in the Q2W cohort, the mean (SD) duration of exposure was 23.7 (2.0) weeks for alirocumab group and 24.1 (0.4) weeks for placebo group; in the Q4W cohort, the mean (SD) duration of exposure was 22.9 (4.5) weeks for alirocumab group and 23.9 (3.3) weeks for placebo group. Of note, the cumulative exposure to treatment (patient-years) in the Q2W cohort was 22.2 for alirocumab group and 11.5 for placebo group, which in the Q4W cohort was 22.8 for alirocumab group and 12.4 for placebo group.

Open-label treatment period for EFC14643:

The duration of treatment exposure was similar in both cohorts: in the Q2W cohort, the mean (SD) duration of exposure was 76.5 (14.8) weeks; in the Q4W cohort, the mean (SD) duration of exposure was 79.7 (6.0) weeks. Cumulative exposure to treatment (patient-years) in the Q2W cohort was 67.8 for "Alirocumab in DB period" group and 36.4 for "Placebo in DB period" group, which in the Q4W cohort was 75.5 for "Alirocumab in DB period" group and 37.6 for "Placebo in DB period" group.

Most of the participants were exposed to the IMP injections for at least 78 weeks: 64 (90.1%) in the Q2W cohort and 67 (90.5%) in the Q4W cohort.

The most frequent sites of alirocumab injection during this study were the outer area of the upper arms and the abdomen.

The module was updated regarding the completed paediatric study EFC14643, including an update of the clinical trial exposure, and the section concerning the historical exposure data of supportive studies was removed.

Clinical Trial exposure of the study EFC14643 in the Q2W cohort was 22.2 patient-years for alirocumab group and 11.5 for placebo group and in the Q4W cohort 22.8 for alirocumab group and 12.4 for placebo group. For OL treatment, the cumulative exposure was in the Q2W cohort 67.8 patient-years for "Alirocumab in DB period" group and 36.4 for "Placebo in DB period" group, while in the Q4W cohort it was 75.5 patient-years for "Alirocumab in DB period" group and 37.6 for "Placebo in DB period" group.

Part II – Module SIV: Populations not studied in clinical trials

Limitations in respect to populations typically under-represented in clinical trials development programmes:

Table40: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	A total of 56 pregnancies were reported in patients treated with alirocumab during the TEAE period in the completed studies. In 3 patients, the pregnancy was normal with a full-term delivery. One other patient also gave birth to a normal baby at term despite of a pregnancy associated with hyperemesis gravidarum, 1 episode of transient blindness probably due to atherosclerotic plaque and threat of premature delivery at 28 amenorrhea weeks. The 5th pregnancy occurred on treatment during a change of contraceptive method (oral contraceptive replaced by intra-uterine device) and was prematurely interrupted due to spontaneous abortion. Two other post-treatment pregnancies were reported in 1 patient in the alirocumab group. The 6th pregnancy was reported in the EFC14643 phase 3 study. It concerns a teenager (≥ 12 years old) with HeFH treated with alirocumab who reported pregnancy during the OLTP in the Q4W cohort. The pregnancy ended due to elective termination (gestation age approximately 5 to 6 weeks). "Use in pregnant and lactating women" is considered as missing information for alirocumab.
Breastfeeding women	There is no experience on the use of alirocumab in nursing/lactating women. "Use in pregnant and lactating women" is considered as missing information for alirocumab.

Type of special population	Exposure
Patients with relevant comorbidities Patients with hepatic impairment	There is no experience in patients with severe hepatic impairment in the clinical development program. "Use in patients with severe hepatic impairment" is considered as missing information for alirocumab.
Children and adolescents	~~Pending~~Following the completion of the ~~pediatric investigational plan, specifically the Phase 3 heFH study EFC14643~~PIP, the alirocumab use in pediatric patients is not considered anymore as missing information. Children and adolescents aged 8 to 17 years are involved in the clinical development of alirocumab through the PIP (the following studies: DFI 14223 ~~and EFC14660 with limited number of patients exposed are completed)~~, EFC14643 and EFC14660 are completed). Overall, alirocumab appeared to be well-tolerated in pediatric patients consistent with the known safety profile of alirocumab in adults. The MAH is submitting a variation to the EMA for an extension of indication of alirocumab in pediatric population 8 to 17 years of age.

One case of exposure pregnant women ($\geqslant$ 12 years old) was added in the section regarding use in special populations. The outcome was an elective abortion, no further information were presented. No safety concern was identified.

Part II – Module SV: Post-Marketing Exposure

Sales figures for the cumulative period were received from MARCO for the period from 01 July 2015 through 31 July 2022. The cumulative exposure to parenteral alirocumab was estimated to be 313 million patient-days corresponding to 857 438 patient-years.

Partner sales (Regeneron):

Based on the sales figures provided by the partner Regeneron from 28 July 2015 through 24 July 2022, the total cumulative exposure to parenteral alirocumab could be estimated to be 154.2 million patient-days corresponding to 422 528 patient-years.

Global cumulative exposure (ie, Sanofi and partner):

The global cumulative exposure to alirocumab could be estimated to be 467.2 million patient days corresponding to 1.3 million patient-years.

Module SV was updated with actual data regarding post-Marketing Exposure.

Cumulatively, post-marketing exposure was 313 million patient-days corresponding to 857 438 patient-years and 154.2 million patient-days corresponding to 422 528 patient-years from partner sales.

Part II - Module SVII: Identified and potential risks

New safety concerns and reclassification with a submission of an updated RMP

In the context of the current variation procedure, the MAH has proposed to review the list of safety concerns, as described in the RMP version 6.0 version 7.0.

Following the completion of the EFC14643 study (conducted in paediatric patients $\geqslant$8 years) and in considering the totality of data now available, the MAH has proposed to remove the missing information

"use in children and adolescents" from the list of safety concerns. Overall, alirocumab appeared to be well tolerated in paediatric patients consistent with the known safety profile of alirocumab in adults.

Table 41: Summary of the Safety Concerns

Important identified risk	Systemic hypersensitivity reactions
Important potential risk	None
Missing information	~~Use in children and adolescents~~
	Use in pregnant and lactating women
	Use in patients with severe hepatic impairment

The missing information 'use in children and adolescents' was removed from the list of safety concerns based on study results obtained in the completed clinical trial in paediatrics. This is accepted. All sections in this module have been updated accordingly.

Part III – pharmacovigilance plan

Additional pharmacovigilance activities:

The following three paediatric studies were part of the pharmacovigilance plan:

• One Phase 2 study DFI14223: an 8 week open-label, sequential, ascending repeated dose-finding study to evaluate the efficacy and safety of alirocumab in children and adolescents with HeFH followed by an extension phase. This study has been completed.

• Two Phase 3 completed studies, the EFC14643 (A randomized, double-blind, placebo-controlled study followed by an open label treatment period to evaluate the efficacy and safety of alirocumab in children and adolescents with HeFH) and the EFC14660 (An open-label study to evaluate the efficacy and safety of alirocumab in children and adolescents with homozygous familial hypercholesterolemia).

Following completion of PIP, the use in children and adolescents is not considered as missing information in the current RMP version 8.0.

The study EFC14643 is now completed at the DLP of the RMP version 8.0 and is thus proposed to be removed from the pharmacovigilance plan. Overall, there are no additional pharmacovigilance activities for this product. The details and status of all these studies are provided under Annex 2.

With the completion of study EFC14643, there are no further additional pharmacovigilance activities planned or ongoing. The summary table of additional pharmacovigilance activities was deleted and the section was updated accordingly to reflect this change.

Part V – Risk minimization measures

Table 42: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Systemic hypersensitivity reactions	Routine risk minimization measures: • Labelled in sections 4.4 and 4.8 of the SmPC. • Labelled in sections 2 and 4 of PL. • Prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
~~Use in children and adolescents~~	~~Routine risk minimization measures:~~ ~~— Labelled in section 4.2 of SmPC~~ ~~— Labelled in section 2 of PL~~ ~~— Prescription only medicine~~ ~~Additional risk minimization measures:~~ ~~None~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:~~ ~~None~~ ~~Additional pharmacovigilance activities:~~ ~~The PIP includes 3 studies:~~

Safety concern	Risk minimization measures	Pharmacovigilance activities
		~~— DFI14223: Pediatric phase 2 dose finding study (status: completed)~~ ~~— EFC14643 and EFC14660: pediatric phase 3 study (only EFC14643 is still ongoing)~~
Use in pregnant and lactating women	Routine risk minimization measures: • Labelled in section 4.6 of SmPC. • Labelled in section 2 of PL. • Prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: As part of routine surveillance, a "specific pregnancy/drug exposure via parent data collection form" is used to document spontaneous or solicited cases of pregnancy exposed to alirocumab. In particular, the following information is collected: parent information, pregnancy information, pregnancy outcome, pre-natal investigations, labor/delivery information, and new-born information. In addition, a neonates/children form, added to the pregnancy form, will also document any developmental defects up to ~~6~~12 months post-birth of children whose mothers are exposed to alirocumab during pregnancy [Annex 4]. Additional pharmacovigilance activities: None
Use in patients with severe hepatic impairment	Routine risk minimization measures: • Labelled in sections 4.2 and 4.4 of SmPC. • Labelled in section 2 of PL. • Prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

The missing information 'Use in children and adolescents' was deleted from section V of the RMP.

Section VI – Summary of the RMP

The Summary of the RMP was updated to reflect the deletion of the missing information 'Use in children and adolescents' and to include the indication extension for use in patients of 8 years and older.

In Annex 2, study EFC14643 was deleted from the list of planned and ongoing studies and transferred into the table of completed studies.

Annex 7 was deleted.

In Annex 8 the changes to the new RMP version 8.0 were displayed.

3.1. Overall conclusion on the RMP

The PRAC considered that the risk management plan version 8.0 is acceptable.

4. Update of the Product Information

As a result of this variation, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC have been updated to include the results on treatment with alirocumab in the paediatric HeFH population. The Package Leaflet (PL) has been updated accordingly.

4.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

"The PIL has been updated with the dosing schedule for the proposed added population, which is largely the same as for the already approved indications for adults, meaning that no new complex information is presented. Additionally, as with the already approved indications, the PIL and IFU are intended to be used by adults. In children less than 12 years of age, Praluent must be given by a caregiver, while in adolescents 12 years and older, Praluent should be given by or under the supervision of an adult. With regards to consultation with target patient groups, the applicant's conclusion is that the updated information in the PIL and IFU regarding the new indication for the treatment of paediatric patients 8 years of age and older with HeFH does not require additional consultation."

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

Familial hypercholesterolemia (FH), which includes heterozygous and homozygous forms, is an inherited disorder of lipid metabolism, characterized by severely elevated levels of LDL-C leading to premature atherosclerosis and cardiovascular disease (CVD).

Heterozygous FH (HeFH) accounts for the large majority of FH overall and is estimated to occur in 1:250 individuals globally. Untreated LDL-C levels in affected individuals are significantly elevated (7.0 ± 0.2 mmol/L]) compared with controls (2.6 ± 0.1 mmol/L). Despite aggressive statin use, there is still a 2-fold excess of coronary heart disease (CHD) related deaths relative to age-matched controls within this population.

The **goal of therapy** in patients with FH is to reduce LDL-C, which reduces atherogenesis and subsequently reduces CVD events and mortality, as demonstrated by the results of the CVOT ODYSSEY OUTCOMES study.

5.1.2. Available therapies and unmet medical need

Available lipid-lowering therapies for children with HeFH include:

- **Statins** (oral tablets): Statins has been approved for the treatment of paediatric patients 6 to 17 years of age with HeFH. According to the 2019 ESC/EAS guideline for the management of dyslipidaemias, statin treatment (in combination with a heart-healthy diet) should be considered at >8 years of age. Statin treatment should be started with low doses, and the dose should be increased to reach therapeutic goals. The therapeutic goal in children >10 years of age is an LDL-C <3.5 mmol/L (<135 mg/dL), and at younger ages a >50% reduction of LDL-C.

- **PCSK9 inhibitors** (injectable monoclonal antibody or siRNA): Evolocumab, another PCSK9 inhibitor mAb , has been approved for the treatment of paediatric patients 10 to 17 years of age with HeFH.

- **Ezetimibe** (oral tablets): Ezetimibe is not indicated for the paediatric HeFH population. According to the labeling of Ezetrol (ezetimibe), the safety and efficacy of ezetimibe in children aged 6 to 17 years has not been established; available data are described in the SmPC, however, no recommendation on a posology can be made.

- **Apheresis** is a non-pharmacological treatment option; a single treatment reduces LDL-C by 55%-70% relative to pre-treatment levels. However, apheresis may be burdensome and limitedly available. Also, only temporal reduction in LDL-C is achieved.

Some patients, especially those with high LDL-C, are unable to achieve recommended LDL-C levels. Many patients with FH cannot achieve recommended goals despite using maximum doses of statin (in combination with ezetimibe), further emphasizing the need for additional treatment options.

5.1.3. Main clinical studies

The completed paediatric development program is in line with the approved EU PIP (PIP decision number P/0550/2021), as also indicated by the completed full compliance check.

The Phase 3 clinical study (Study EFC14643) was designed to evaluate the efficacy and safety of alirocumab administered at 40 mg or 75 mg Q2W (for BW <50 kg or ≥ 50 kg) and 150 mg or 300 mg Q4W (for BW <50 kg or ≥ 50 kg) as a starting dose, on top of an optimal stable daily dose of statin therapy ± other LMTs or stable dose of non-statin LMTs in case of intolerance to statins, in paediatric population 8 to 17 years of age with HeFH. The study was a randomized, 24-week double-blind treatment, placebo-controlled, parallel-group study followed by an 80-week open-label treatment period with the primary endpoint on percent change in LDL-C from baseline to Week 24.

5.2. Favourable effects

Primary endpoint. Alirocumab demonstrated a substantial reduction in LDL-C from baseline to Week 24 compared with placebo in a population of patients (n=153 with 2:1 ratio) aged 8-≤17 years with genetically or clinically confirmed HeFH on optimized background lipid-lowering therapy with a LDL-C baseline level of 4.5 mmol/L; The LS mean (SE) difference versus placebo was -43.3% ([97.5% CI: -56.0 to -30.7]; p<0.0001) in the Q2W cohort, and -33.8% ([97.5% CI: -46.4 to -21.2]; p<0.0001) in the

Q4W cohort. No differential effect of alirocumab versus placebo was observed between the Q2W and Q4W regimens and the BW categories.

Other endpoints. The LDL-C lowering effect was further supported by the beneficial effects in other lipid parameters (e.g. Apo-B, non-HDL-C, Total-C, Lp(a), HDL-C). At Week 24, 77.6% of patients achieved an LDL-C level lower than 3.4 mmol/L (130 mg/dL), and 52.7% of patients an LDL-C level lower than 2.84 mmol/L (110 mg/dL) in the alirocumab group.

Subgroups. The LDL-C lowering effect appears generally consistent among several subgroups, including gender, age (<12, ≥ 12 years) and baseline LDL-C in both Q2W and Q4W cohorts.

5.3. Uncertainties and limitations about favourable effects

Long term. The percent change of LDL-C from baseline to Week 104 was lower than as compared with the DB treatment period (- 26.3% in the Q2W cohort and -23.9% (33.5) in the Q4W cohort.)

Other endpoints. In the exploratory flow-mediated dilatation (FMD) sub-study, no difference in absolute change from baseline to Week 24 in %FMD was observed (-0.6% vs -2.1% in the alirocumab and placebo group, respectively; p=0.5368).

5.4. Unfavourable effects

Exposure. A total of 101 paediatric HeFH patients (49 in the Q2W cohort and 52 in the Q4W cohort) were exposed to alirocumab in the DB treatment period with a mean duration of treatment of 23.7 vs. 24.1 weeks in the Q2W cohort and 22.9 vs. 23.9 weeks in the Q4W cohort for alirocumab and placebo, respectively, and a total patient-years exposure of 22.2 in the Q2W cohort and 22.8 in the Q4W cohort. In the OL treatment period, the mean duration of treatment was similar in both cohorts (76.5 weeks in the Q2W cohort vs 79.7 weeks in the Q4W cohort), with a patient-years exposure to alirocumab of 104.1 in the Q2W cohort and 113.1 in the Q4W cohort, which is considered sufficient.

Adverse events. Treatment-emergent adverse events (TEAEs) were frequently reported, however, the percentage of patients with any TEAE in the DB treatment period was approximately similar across both treatment groups in the Q2W cohort (53.1% vs. 52.0% in the alirocumab and placebo group, respectively) or lower in the alirocumab compared with the placebo group in the Q4W cohort (50.0% vs. 59.3%). The most frequent AEs with a higher incidence with alirocumab compared with placebo (a difference of ≥ 5%) in the Q2W cohort were *nasopharyngitis* (14.3% vs. 8.0%) and *injection site reaction* (6.1% vs. 0%), while there were not AEs with a notably higher frequency in the alirocumab group compared with the placebo group in the Q4W cohort. The most frequent treatment related AEs were *injection site reactions.*

Adverse events of special interest. The incidence in *general allergic events* was low; Only 2 patients (3.8%) in the Q4W cohort group experienced a rash event. Local injection site reactions occurred with a higher frequency for alirocumab than placebo (6.1% vs. 0% in the Q2W cohort and 3.8% vs. 0% in the Q4W cohort, respectively). The frequency in *local injection site reactions* remained stable throughout the study, with 4 (5.6%) patients in the Q2W cohort and in 3 (4.1%) participants in the Q4W cohort in the OL treatment period. Furthermore, in the DB treatment period, there were no incidences of *hepatic disorder, diabetes mellitus or diabetic complications*, and *cataract*.

Regarding *very low LDL-C levels*, in the DB treatment period, 4 (8.2%) and 7 (13.5%) patients in the alirocumab group of the QW2 and Q4W cohort, respectively, had at least one low LDL-C value of < 1.29 mmol/L (< 50 mg/dL) of which 3 (5.8%) patients had 2 consecutive LDL-C values < 1.29 mmol/L (all Q4W) including 1 (1.9%) participant who had 2 consecutive LDL-C values < 0.65 mmol/L (<25 mg/dL).

In the OLE period, 7 (10.0%) and 12 (16.2) in the Q2W and Q4W cohorts had at least one low LDL-C value of < 1.29 mmol/L of which 1 (1.4%) in the Q2W cohort and 7 (9.5%) in the Q4W cohort had 2 consecutive LDL-C values < 1.29 mmol/L. Three patients (1 in Q2W and 2 in Q4W) had one LDL-C value < 0.65 mmol/L. However, there is no evidence of an unexpected safety concern regarding subjects who achieved low LDL-C levels.

Serious AEs. The percentage of subjects experiencing SAEs was relatively low, however, slightly higher in the alirocumab group compared with the placebo group in the Q2W cohort group (8.2% vs. 4.0%), whereas the percentage of SAEs was comparable in the Q4W cohort group (3.8% vs 3.7%). Again, however, no patterns indicative of a safety signal were observed.

Deaths. There were no deaths reported.

Immunogenicity. A low level of immunogenicity (n=3; all in Q2W cohort) was observed in the paediatric population in the pivotal Phase 3 study EFC14643. The treatment-emergent anti-drug antibody (ADA) responses were classified as very low titer and transient. Further, no participants with neutralizing ADA were reported.

Laboratory findings. No trends indicated clinically important treatment-related laboratory abnormalities including hematology parameters, renal and hepatic function parameters, blood glucose, hsCRP, hormone levels, and vitamins were observed with alirocumab.

Vital signs. There were no trends indicative of important vital signs, including systolic blood pressure, diastolic blood pressure, and heart rate abnormalities observed.

Tolerability. The percentage of patients discontinued due to AEs was relatively low (n=2 (3.8%)).

Post marketing experience. It represents 0.06% of all cases (n= 58 837). Of the 32 cases, 17 were reported in the clinical studies EFC14660, DFI14223, and EFC14643. From the remaining cases, no new safety signal was identified in paediatric patients in the post-marketing experience.

5.5. Uncertainties and limitations about unfavourable effects

Adverse events of special interest. An increased risk of *neurocognitive* and *neurological abnormalities* was not observed. However, the data are considered limited, which precludes appropriate assessment.

Very low LDL-C levels. No safety signal with very low LDL-C levels has emerged as yet. However, only limited safety data exist in (paediatric) patients with very low LDL-C.

Vital signs. Assessments of growth and pubertal development (*Tanner stage*) and *cognitive function* did not reveal a detrimental effect. However, the safety data, particularly the placebo-controlled safety data of 24 weeks of exposure to alirocumab, is considered too limited to draw firm conclusions.

5.6. Effects Table

- **Effects Table for alirocumab in the HeFH paediatric population**

Effect	Short description	Unit	Alirocumab (n=101)	Placebo (n=52)	Uncertainties (Unc)/ Strength of evidence (SoE)	Reference
Favourable Effects						
LDL-C	Change from baseline to week 24 Q2W Q4W	%	 -33.6 -38.2	 9.7 -4.4	**SoE**: Difference: Q2W -43.3; p<0.0001, Q4W -33.8; p<0.0001 Clinical relevant change of ~-1.6 mmol/L, No differential effect between the Q2W and Q4W regimens and the BW categories, Effect size in DB period consistent with the adult HeFH population (-39%), Substantial changes observed in other lipid parameters (Apo-B, non-HDL-C, total cholesterol, Lp(a), HDL-C) **Unc**: Effect was lower long-term: -26.3% and -23.9% for Q2W and Q4W at Week 104	EFC14643
Unfavourable Effects						
General allergic reactions	 Q2W Q4W	n (%)	 0 2 (3.8)	 0 0	**SoE**: Frequency consistent with the adult population	EFC14643
Injection site reactions	 Q2W Q4W	n (%)	 3 (6.1) 2 (3.8)	 0 0	**SoE:** Frequency consistent with the adult population	
Anti-alirocumab antibodies	 Q2W Q4W	n (%)	 3 (6.1) 0	 0 0	**SoE**: low titer response (≤ 240 transient, and no neutralizing antibodies)	

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Familial hypercholesterolemia (FH), which includes heterozygous (HeFH) and homozygous (HoFH) forms, is an inherited disorder of lipid metabolism characterized by severely elevated levels of LDL-C leading to premature atherosclerosis and cardiovascular disease (CVD). HeFH accounts for the large majority of FH overall and is estimated to occur in 1:250 individuals globally. Despite aggressive statin use, this population still has a 2-fold excess of coronary heart disease (CHD) related deaths relative to age-matched controls. Therefore, there is an unmet medical need for additional LDL-C lowering therapies. According to the ESC guideline (2019), the goals for treatment of children with FH > 10 years of age should be LDL-C < 3.5 mmol/L and at younger ages ≥ 50% reduction of LDL-C. It must be noted that evolocumab, another PCSK9 inhibitor mAb, has been approved for treating paediatric HeFH patients 10-≤17 years of age.

This extension of indication application is based on efficacy and safety data from the Phase 3 study EFC14643 supplemented with efficacy and safety data from the Phase 2 dose-finding study (Study DFI14223) and safety data from the Phase 3 study in paediatric participants with HoFH (Study EFC14660) to include treatment of paediatric HeFH patients 8-≤17 years of age in line with the approved EU PIP P/0550/2021 as also indicated by the completed full compliance check.

Alirocumab demonstrated a substantial reduction in LDL-C from baseline to Week 24 compared with placebo in a population of patients (n=153 with 2:1 ratio) aged 8-≤17 years with genetically or clinically confirmed HeFH on optimized background lipid-lowering therapy with a LDL-C baseline level of 4.5 mmol/L; The LS mean (SE) difference versus placebo was -43.3% ([97.5% CI: -56.0 to -30.7]; p<0.0001) in the Q2W cohort, and -33.8% ([97.5% CI: -46.4 to -21.2]; p<0.0001) in the Q4W cohort at week 24. No differential effect on LDL-C of alirocumab versus placebo was observed between the Q2W and Q4W regimens and the BW categories. Moreover, at week 24, 77.6% of patients achieved the treatment goal of LDL-C < 3.4 mmol/L (<130 mg/dL) for paediatric HeFH patients recommended in the ESC guideline for the management of dyslipidaemias (2019). The changes in LDL-C are considered to be clinically relevant effects as LDL-C is an important surrogate endpoint with potential benefits in terms of a cardiovascular outcome, as previously confirmed by the results of the ODYSSEY OUTCOME study. The long-term OL period demonstrated maintenance of effect, although the effect size in LDL-C lowering of -26.3% in the Q2W cohort and -23.9% in the Q4W at week 104 was lower compared with the DB period most likely due to reduced compliance, however, the LDL-C lowering effect is still considered clinically relevant. The LDL-C lowering effect was supported by the beneficial effects in other lipid parameters (e.g. Apo-B, non-HDL-C, Total-C, Lp(a), HDL-C).

Regarding safety, alirocumab displays an acceptable safety profile in paediatric HeFH patients aged 8-≤ 17 years compared to those observed in adults HeFH in the initial MA dossier and the ODYSSEY OUTCOMES dossier with very limited patients discontinuing treatment. Additionally, alirocumab did not cause any clinically relevant differences in adverse events of special interest, including allergic events, neurologic events, neurocognitive events, hepatic disorders, diabetes mellitus, and cataract. No new safety signal has been identified. Most of the TEAEs considered treatment related were injections site reactions, which is a known ADR of alirocumab from the initial MA dossier.

Regarding the proposed posology, based on the efficacy and safety results and given the lower patient burden associated with monthly injections as compared to bi-weekly injections, the 150 mg or 300 mg Q4W for BW < 50 and $\geq$ 50 kg, respectively, starting dose regimen is proposed for children and adolescents 8 to 17 years of age with HeFH in section 4.2 of the SmPC, which is acceptable. Regarding the proposed dose up-titration, it can be concluded that paediatric patients with HeFH who do not reach the recommended LDL-C treatment target with the starting dose of alirocumab may benefit from the proposed dose adjustment. Therefore, the proposed up-titration regimen of 75 mg Q2W for BW < 50 kg or 150 mg Q2W for BW $\geq$50 kg is acceptable.

5.7.2. Balance of benefits and risks

Benefits of alirocumab in terms of a substantial reduction in LDL-C are accompanied by limited risks.

5.7.3. Additional considerations on the benefit-risk balance

Not applicable

5.8. Conclusions

The overall B/R of alirocumab for the paediatric HeFH patients aged 8-$\leq$ 10 years is positive

6. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of paediatric patients 8 years of age and older with heterozygous familial hypercholesterolemia (HeFH) as an adjunct to diet, alone or in combination with other LDL-C lowering therapies, based on final results from study EFC14643 listed as a category 3 study in the RMP; this is a randomized, double-blind, placebo-controlled study followed by an open-label treatment period to evaluate the efficacy and safety of alirocumab in children and adolescents with heterozygous familial hypercholesterolemia. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.0 of the RMP was agreed during the procedure.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0550/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.