12 March 2020
EMA/330215/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Praluent

International non-proprietary name: alirocumab

Procedure No. EMEA/H/C/003882/II/0053

Note

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

Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure:	18 November 2019	18 November 2019
☐	CHMP Rapporteur Assessment Report	19 December 2019	18 December 2019
☐	CHMP members comments	07 January 2020	N/A
☐	Updated CHMP Rapporteur Assessment Report	09 January 2020	N/A
☐	Start of written procedure	14 January 2020	14 January 2020
☐	Request for supplementary informatuion	16 January 2020	16 January 2020
☐	Submission of responses	11 February 2020	11 February 2020
☐	Re-start of procedure	12 February 2020	12 February 2020
☐	CHMP Rapporteur Assessment Report	26 February 2020	28 February 2020
☐	CHMP members comments	02 March 2020	N/A
☐	Updated CHMP Rapporteur Assessment Report	05 March 2020	N/A
☐	Start of written procedure	10 March 2020	10 March 2020
☒	Opinion	12 March 2020	12 March 2020

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

Procedure resources	
CHMP Rapporteur:	Hans Hillege

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, sanofi-aventis groupe submitted to the European Medicines Agency on 21 October 2019 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the final report from study DFI14223, listed as a category 3 study in the RMP in order to fulfil MEA 029. The submission serves also to comply with article 46 of the regulation (EC) N° 1901/2006 (as amended). This is an 8-week open label, sequential, repeated dose-finding study to evaluate the efficacy, safety and PK profile of alirocumab in children and adolescents with heterozygous familial hypercholesterolemia followed by an extension phase.

The requested variation proposed no amendments to the Product Information.

2. Overall conclusion and impact on the benefit/risk balance

A phase 2, open-label dose finding study in heterozygous familiar hypercholesteraemia (HeFH) paediatric patients (8 to 17 years of age) on top of statins or in statin intolerance to evaluate appropriate doses to be selected for the phase 3 studies including a study in homozygous familiar hypercholesterolaemia (HoFH) patients and a study in HeFH patients has been conducted and submitted in accordance with article 46 of the regulation (EC) N° 1901/2006 (as amended). No changes to the SmPC are proposed.

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. For the 42 patients included, doses of 30 and 40 mg every 2 weeks (Q2W) were tested for body weight (BW) < 50 kg and 50 and 75 mg for BW > 50 kg, and 75 and 150 mg every 4 weeks (Q4W) for BW < 50 kg and 150 and 300 mg Q4W for BW> 50 kg in four cohorts (2 cohorts with Q2W regimen and 2 cohorts with Q4W regimen).

The mean Ctrough levels (exposure) observed in the pediatric population receiving alirocumab Q2W doses and the lowest dose cohort on Q4W dose were close to adults exposures. However, exposure for the highest Q4W dose in the BW ≥ 50 kg subgroup (300 mg) was substantially higher than observed in adults (17880 ng/mL vs 8620ng/ml). Although the mean Ctrough alirocumab concentration was higher, the exposure range of these patients of cohort 4 was within the exposure range observed for the adult population with the same dose and bodyweight category. The results observed with the cohort 4 300 mg Q4W dose should however be interpreted with caution, as only 5 pediatric patients were treated with this alirocumab dose, compared to 458 adult patients who received the same dosing regimen in study CHOICE I. Nevertheless, the higher exposure of alirocumab observed in the 5 children and adolescents with BW ≥ 50 kg can likely be mainly attributed to the lower body weight of the children as compared to the body weight of the overall adult population in the CHOICE I study.

For the genetically and clinically confirmed HeFH patients with mean baseline LDL-C levels of 4.6 mmol/L, the higher Q2W dose showed greater reductions in LDL-C (-46.1%) as compared to the lower Q2W dose (-21.1%), although slight differences appear in the effect according to body weight (-40.6 [sd13.2] with 40 mg Q2W for BW <50 kg, and -49.8% [standard deviation: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: 75 mg and 150 mg QW4), with respectively -17.5% (10.3) and 4.0% (11.2) 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), although with variability in effect according to BW. Other endpoints supported the primary endpoint across the efficacy effects for the different cohorts including absolute change in LDL-C (-1.296, -1.947, -0.456 and -2.017 mmol/L, respectively cohort 1 to 4), proportion of patients achieving pre-specified LDL-C targets (3.37 mmol/L target: 60%, 89%, 27%, 72%; 2.84 mmol/L target: 0%, 77%, 18%, 72%), LDL-C reduction and end of the open-label extension phase (-23%, -52%, -23% and –48%) as well as PCSK9 level monitoring.

Overall, a more pronounced effect can be observed in the higher Q2W dose and in the higher Q4W dosing in comparison to the respective lower dose groups. Although some variation exists between the body weight categories, with greater efficacy in the BW ≥50 kg groups. Exposure data are in agreement with these LDL-C efficacy observations and may thus likely explain the observed differences, although no exposure response data have been presented.

With regard to safety, the database was very limited to address the safety profile in paediatric patients. Adverse events were generally in line with those observed for adult patients. Serious events were not reported, which is reassuring. It can be reasonably supported that the two events of diabetes mellitus were not considered treatment related, although it is expected that such events of special interest will also be monitored during the phase 3 studies as an effect on glucose and diabetes mellitus has been observed in adults. No other relevant unexpected laboratory abnormalities were observed.

Based on the comparison of the preliminary efficacy data from children in cohort 4 of study DFI14223 (in pediatric patients with BW (≥50 kg)) and the adult subgroup (50 to 80 kg) from CHOICE I study comparable efficacy of LDL-C reduction is achieved with the alirocumab 300 mg Q4W dose (-59% vs -67%). Although a higher exposure is observed, it can reasonably be expected that this will likely not emerge to important safety issues, as no exposure dependent adverse events are known with the use of alirocumab. For instance, no difference in safety profile is kwown between different doses previously examined. Based on this consideration, it is acceptable to have taken this dose further to be evaluated in the ongoing study EFC14643. Further safety data will be generated in study EFC14643 to confirm the safety profile in this paediatric population.

Overall, it is reasonable to have considered the higher Q2W and Q4W doses and taken them forward to the phase 3 studies (already ongoing). The company is expected to present a combined overview of all pharmacokinetic data in the paediatric population, upon completion of all paediatric studies. It is agreed that current data are premature to consider these to be included in the SmPC.

The benefit-risk balance of Praluent remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the final report from study DFI14223, listed as a category 3 study in the RMP in order to

fulfil MEA 029. The submission serves also to comply with article 46 of the regulation (EC) N° 1901/2006 (as amended). This is an 8-week open label, sequential, repeated dose-finding study to evaluate the efficacy, safety and PK profile of alirocumab in children and adolescents with heterozygous familial hypercholesterolemia followed by an extension phase.

☒ is recommended for approval.

Amendments to the marketing authorisation

The variation leads to no amendments to the terms of the Community Marketing Authorisation.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Praluent-H-C-003882-II-53'

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Background on the product

Alirocumab is a fully human monoclonal antibody (mAb) that binds with high affinity to proprotein convertase subtilisin kexin type 9 (PCSK9). Alirocumab increases the number of LDLR available for removing LDL-C from the circulation by blocking PCSK9 from binding to low-density lipoprotein receptor (LDLR). Alirocumab lowers LDL-C and reduces the risk of CVD. Currently, alirocumab has been approved in the EU for the treatment of primary hypercholesterolemia and mixed dyslipidemia in adults. Alirocumab is also approved for the prevention of cardiovascular events in adults with established atherosclerotic cardiovascular disease in the EU.

Background on the disease

Familial hypercholesterolemia (FH) is an inherited disorder of lipid metabolism, characterized by severely elevated levels of low-density lipoprotein cholesterol (LDL-C) that lead to premature atherosclerosis and cardiovascular disease (CVD).

Familial hypercholesterolemia is most clearly documented to have important cardiovascular consequences beginning in childhood. Even though cardiovascular events are rare in childhood, children with heterozygous FH (heFH) already have functional and morphological changes of the vessel wall illustrated by an impaired flow-mediated dilation of the brachial artery and an increased intima media thickness of the carotid artery (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 is initiated early in childhood. Indeed, there is 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 coronary heart disease (CHD), prevention must begin decades prior to the onset of symptoms.

Because of the high risk of progression to premature clinical CVD associated with these findings, pediatric guidelines recommend LDL-C lowering intervention and specific lipid targets for children and adolescents with heFH. An LDL-C level <130 mg/dL (3.4 mmol/L) is considered acceptable and <110 mg/dL (2.85 mmol/L) ideal for children with heFH, or the achievement of ≥50% reduction in LDL-C. Pediatric guidelines recommend LDL-C lowering intervention to start with statins first. However, not all patients can achieve target LDL-C reductions with currently available lipid modifying therapies (LMTs). Therefore, these pediatric patients represent a group with an identified unmet medical need that could be addressed by adding alirocumab to their LMT.

Study rationale

A phase 2, dose-finding study was undertaken to evaluate the safety and the magnitude of LDL-C reduction with alirocumab in the heFH pediatric population and to support appropriate dose selection for the Phase 3 pediatric heFH and homozygous FH (hoFH) program. The current submission includes the results of the DFI14223 Study as per the Applicant's postmarketing commitment (MEA/FSR 029, related to PIP Decision P/0047/2018).

This study is part of the European Paediatric Investigation Plan (PIP Number: EMEA-001169-PIP01-11) of alirocumab in the "treatment of elevated cholesterol". This PIP for alirocumab was issued by the EMA decision on 29 November 2013 and was subsequently modified with the EMA decision on 15 April 2016 (P/0102/2016) to update the key features of the phase 2, dose-ranging study, DFI14223. The current PIP version (EMA-001169-PIP01-11M04) was approved on 19 February 2018 (Decision P/0047/2018).

A waiver for children from birth to less than 8 years was granted on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments. A deferral for one or more measures was granted for the pediatric population from 8 to less than 18 years of age for the treatment of heterozygous and homozygous familial hypercholesterolemia.

The agreed PIP includes 2 additional pediatric phase 3 clinical studies in children older than 8 years with FH:

- An open-label study to evaluate the efficacy and safety of alirocumab in children and adolescents with homozygous FH (Study EFC14660). Completion of this study is expected by no later than June 2021, as indicated in the PIP.
- 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 (Study EFC14643). Completion of this study is expected by no later than September 2023, as indicated in the PIP.

6. Study DFI14223 - methods and study design

General study design

The DFI14223 study was an open-label, dose-finding, sequential group, multinational, multicenter study. Repeated doses of subcutaneous (SC) alirocumab were administered every 2 (Q2W) or 4 weeks (Q4W) in children and adolescents (aged 8-17 years) with heFH having LDL-C ≥130 mg/dL (3.37 mmol/L) despite 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.

Study participant

Key inclusion criteria

- Children and adolescent male and female patients aged 8 to 17 years at the time of signed informed consent (*Russia only: aged ≥12 and ≤17 years at the time of signed informed consent)*
- Diagnosis of heterozygous familial hypercholesterolemia (heFH) through genotyping or clinical criteria*.
- Treated with optimal dose of statin** ± other LMT(s) or non-statin LMT(s) if statin intolerant*** at stable dose for at least 4 weeks.
- Calculated LDL-C greater than or equal to 130 mg/dL (≥3.37 mmol/L) obtained during the screening period after the patient has been on stable LMT (ie, stable optimal dose of statin ± other stable LMTs or stable non-statin LMTs in statin intolerant patients) treatment for at least 4 weeks.
- Body weight greater than or equal to 25 kg.
- Patients aged of 8 to 9 years to be at Tanner stage 1 and patients aged of 10 to 17 years to be at least at Tanner stage 2 in their development.

* Diagnosis of heFH had to be made either by previous genotyping, current 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 consenting to undergo mandatory genotyping during the screening period with results supporting a diagnosis of heFH. The clinical diagnosis had to be based on the Simon Broome criteria for possible or definite FH. Once eligibility was confirmed based on prior genetic testing or Simon Broome criteria, results of elective genetic testing did not impact patient's eligibility.

** 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 AEs on higher doses. For patients not receiving the maximally tolerated dose of statin, statin intensification were to be carefully considered prior to inclusion 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 had not to exceed the maximum labeled dose of statin for pediatric 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.

**** Patients age of 8 to less than 10 years had to have other available interventions to lower calculated LDL-C but these were insufficient.

Key exclusion criteria

- Criteria not in agreement with the inclusion criteria: age of less than 8 or greater than 17 years at the time of signed informed consent, calculated LDL-C <130 mg/dL (3.37 mmol/L) during the screening period, after patient has been on stable LMT for at least 4 weeks, patient without a diagnosis of heFH by genotyping or clinical criteria, patients aged of 8 to <10 years in whom other available interventions to lower LDL-C have been sufficient, patients not on a stable dose of LMT (including statin, as applicable) for at least 4 weeks prior to the screening visit and from screening visit to Day 1, daily dose of statin that is above the maximum recommended dose for pediatric patients as per the local prescribing label, body weight <25 kg, patients not previously instructed on a cholesterol-lowering diet prior to the screening visit, patients aged of 8 to 9 years not being at Tanner Stage 1 and patients aged of 10 to 17 years not being at least at Tanner Stage 2 in their development.
- Use of nutraceutical products or over the counter therapies that may affect lipids which have not been at a stable dose for at least 4 weeks prior to the screening visit.
- Patients with a diagnosis of homozygous familial hypercholesterolemia.
- Patient who has received lipid apheresis treatment within 2 months prior to the screening period, or had plans to receive it during the study.
- Known history of type 1 or type 2 diabetes mellitus.
- Known history of thyroid disease.
- Known history of 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).
- Conditions/situations or laboratory findings such as: ALT or AST >2 x ULN (1 repeat lab was allowed), CPK >3 x ULN (1 repeat lab was allowed), any clinically significant abnormality identified at the time of screening that in the judgment of the Investigator or any sub-Investigator would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases.
- Patients considered by the Investigator or any sub-Investigator as inappropriate for this study for any reason, eg: unable to meet specific protocol requirements, unable to administer or tolerate long-term injections
- Treatment with any investigational medicinal product (IMP) within 8 weeks or 5 half-lives prior to the screening period, whichever was longer.
- All contraindications to the background statins or other LMTs (as applicable) warning/precaution of use (when appropriate) as displayed in the respective National Product Labeling.
- Hypersensitivity to alirocumab or to any of the ingredients of alirocumab injections.

For the extension phase the following relevant exclusion criteria were applicable:

- Significant protocol deviation in the main phase based on the Investigator judgment, such as non-compliance by the patient.
- Patient who experienced an adverse event leading to permanent discontinuation from the main open-label dose finding treatment period.
- Patients having any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for entry into the extension phase, or could interfere with the patient participating in or completing the study.

Treatments

Cohorts

There was a sequential enrolment into the 4 separate and independent cohorts, Cohorts 1 to 4.

Based on the results from this dose-finding study (DFI14223), 2 doses/dosing regimen per body weight category were selected to be further evaluated in phase 3 pediatric studies. The rationale for the selection of these doses is as follows.

Since the BW was identified as a significant covariate on alirocumab PK (through clearance), two BW categories (BW <50 kg and BW ≥50 kg) were determined with a fixed dosage in each BW category.

To define the pediatric doses to be tested in the DFI14223, simulations were performed based on the final adult population PK model including Phase 3 data in adults. The model included BW as a covariate (on clearance) and allowed to perform simulations with different BW categories. The targeted lower dose to be tested in pediatric patients was simulated to achieve drug exposure that corresponded to the lowest dose evaluated in adult patients, ie, 50 mg Q2W. This 50 mg Q2W dose in adult Phase 2 resulted in approximately 40% LDL-C reduction. The higher dose was simulated to correspond to the lower adult therapeutic dose of 75 mg Q2W. Simulations were also conducted to achieve approximately 45-50% LDL-C reduction when alirocumab is administered monthly.

Based on these simulations, a fixed dosage was defined per BW categories, with staggered doses of 30 mg Q2W and 40 mg Q2W or 75mg Q4W for children with a BW below 50 kg, and doses of 50 mg Q2W and 75 mg Q2W or 150 mg Q4W for children with a BW ≥50 kg. Given the inconclusive results observed for the Q4W dosing regimen evaluated in Cohort 3 (see efficacy results), an additional cohort (Cohort 4) was subsequently included to evaluate the Q4W dosing regimen at higher doses of 150 mg for BW <50 kg and 300 mg for BW ≥50 kg. The intent was to determine if an effect on LDL-C closer to the therapeutic target of approximately 50% LDL-C reduction could be achieved with a Q4W dosing regimen.

The treatment duration of this open-label, dose-finding 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 and 50 mg Q2W for BW ≥50 kg.
- Cohort 2 received 40 mg Q2W for BW <50 kg and 75 mg Q2W for BW ≥50 kg.
- Cohort 3 received 75 mg Q4W for BW <50 kg and 150 mg Q4W for BW ≥50 kg.
- Cohort 4 received 150 mg Q4W for BW<50 kg and 300 mg Q4W for BW ≥50 kg.

The study included 4 periods as described below.

Screening period

The aim of the screening period, including a run-in period if needed, was to establish eligibility and consisted of a period up to 6 weeks (+1 week). Patients already on stable LMT(s) (ie, stable optimal dose of statin ± other stable LMTs or stable dose of non-statin LMTs in statin-intolerant patients for at least 4 weeks prior to screening LDLC) and with heFH diagnosis confirmed by previous genetic testing or based on Simon Broome criteria could be enrolled within 2 weeks providing they met all other eligibility criteria. Patients not already on stable LMT(s) for at least 4 weeks, as defined above, had to enter a "run-in" period as required to meet this eligibility criterion.

Main treatment period

The main treatment period consisted of an open-label dose finding treatment period of 8 weeks for Cohorts 1 to 3, and 12 weeks for Cohort 4. In each of the 4 independent cohorts (Cohorts 1 to 4), alirocumab was administered via SC injections in a Q2W or Q4W dose regimen. There was a sequential enrollment into the 4 separate and independent cohorts.

Post-treatment follow-up period

Cohorts 1 to 3 had a follow-up period (off treatment) before entering in the extension period.

The follow-up period consisted of 6 weeks for Cohort 3 or 8 weeks for Cohorts 1 and 2 after the end of the open label dose finding (OLDFI) treatment period visit. For these 3 cohorts, the final follow-up visit corresponded to 10 weeks after the last alirocumab injection administered during the open-label dose finding treatment period (in Cohorts 1 and 2, the last injection was at Week 6 and in Cohort 3, it was at Week 4).

Open-label extension (OLE) period: (for patients who successfully completed the OLDFI period).

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 as follows:

- The initial dose of alirocumab that was administered Q2W or Q4W during the OLE period, was to be a continuation of the same doses/dose regimen administered during the OLDFI treatment period of the main phase. However, after completion of the first 3 cohorts, the doses/dosing regimen evaluated in Cohort 2 were selected for the planned Phase 3 study in heFH pediatric patients. Subsequently, these doses/dosing regimens were applied to the OLE period of this study and patients in Cohorts 1 to 3 were switched to the phase 3 doses if they were not already on the selected doses. For Cohort 4 that further evaluated the Q4W dosing regimen, patients remained on their initial regimen due to the delay in initiating this cohort and consequently the limited duration of their participation in the OLE period with regard to the planned study end date.
- All patients from all cohorts that participated in the DFI14223 study had the opportunity to enrol in the pediatric Phase 3 study to be conducted in the heFH pediatric population provided that they met the eligibility criteria. The alirocumab administrations during the OLE period continued until at least 10 weeks (corresponding to the wash out period) before the patient's entry into the Phase 3 pediatric heFH study.

Objectives

Primary objective

The primary objective of the study was to evaluate the effect of alirocumab administered Q2W or Q4W on LDL-C levels after 8 weeks of treatment in heFH patients aged of 8 to 17 years, with LDL-C ≥130 mg/dL (3.37 mmol/L) 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.

Secondary objectives

The secondary objectives of the study were to evaluate the safety and tolerability, the pharmacokinetics profile, the effects of alirocumab on other lipid parameters levels (ie, Total-C, calculated LDL-C, measured LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs), non-high density lipoprotein (non-HDL-C), apolipoprotein B (Apo B), apolipoprotein A-1 (Apo A-1), ratio Apo B/Apo A-1, lipoprotein (a) (Lp[a]) and the development of anti-alirocumab antibodies.

Outcomes/endpoints

Primary efficacy endpoint

The primary efficacy endpoint was the percent change in calculated LDL-C from baseline to Week 8 in the modified intent-to-treat (mITT) population, using all calculated LDL-C values during the OLDFI efficacy treatment period (on-treatment estimand). It was defined as: 100x (calculated LDL-C value at Week 8 minus calculated LDL-C value at baseline)/calculated LDL-C value at baseline.

Additionally, for Cohort 4 only, the percent change from baseline in calculated LDL-C at Week 12 was analyzed.

Secondary efficacy endpoints

The secondary endpoints were:

- The absolute change in calculated LDL-C from baseline to Week 8 (on-treatment estimand);
- The percent change in LDL-C from baseline to Week 12 only for Cohort 4 (on-treatment estimand);
- The percent change in Apo B, non-HDL-C, Total-C, Lp(a), TG, HDL-C, Apo A-1 from baseline to Week 8 (on-treatment estimand);
- The proportion of patients achieving a calculated LDL-C <130 mg/dL (3.37 mmol/L) at Week 8 (on-treatment estimand);

- The proportion of patients achieving a calculated LDL-C level <110 mg/dL (2.84 mmol/L) at Week 8 (on-treatment estimand);
- The absolute change in Apo B, non-HDL-C, Total-C, Lp(a), TG, HDL-C, Apo A-1 and Apo B/Apo A-1 ratio from baseline to Week 8 (on-treatment estimand).

Sample size

The primary efficacy analysis population for OLDFI period and for the OLDFI/OLE combined period was the mITT population, consisting of all included patients who received at least one dose or partial dose of IMP injection and had an evaluable primary endpoint during the OLDFI efficacy treatment period. The primary endpoint was considered as evaluable when both following conditions are met:

- Availability of baseline calculated LDL-C value.
- Availability of at least one calculated LDL-C value during the OLDFI efficacy treatment period and within one of the analysis windows up to Week 8 analysis window.

The OLDFI efficacy treatment period was defined as the period from the first IMP injection to last OLDFI IMP injection + 21 days (for Cohorts 1 and 2) or +35 days (for Cohorts 3 and 4). For patients entering in the OLE, the OLDFI efficacy treatment period was truncated at the day before the first OLE IMP injection in the extension period.

Randomisation

Patients in the mITT population were analyzed according to the alirocumab dose group allocated by Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS)

Blinding (masking)

Not applicable, this study was an open-label design.

Statistical methods

The percent change from baseline in calculated LDL-C at Week 8 was analyzed in the mITT population using a mixed-effect model with repeated measures (MMRM) approach to handle missing data. All post-baseline data available during the OLDFI efficacy treatment period (Week 4 and Week 8) and within analysis windows were used and the missing data were not imputed. The model included the fixed categorical effects of alirocumab doses/dose regimen, time point (Week 4, Week 8), dose-by-time point interaction.

This model provided least-squares means estimates at Week 8 for each alirocumab dose, with their corresponding standard errors (SEs) and 95% confidence intervals (CIs). In addition, least square (LS) mean with 95% CIs was provided for each cohort using appropriate contrasts.

Additionally, for Cohort 4 only, the percent change from baseline in calculated LDL-C at Week 12 was analyzed using the same model. The analyses are presented without adjustment to the baseline.

Continuous secondary efficacy variables anticipated to have a normal distribution (ie, lipids other than TG and Lp[a]) were analyzed in the mITT population using the same MMRM model as for the primary endpoint with fixed categorical effects of alirocumab doses/dose regimen, planned post-baseline time point up to Week 8, dose-by-time point interaction. The analyses are presented without adjustment to the baseline.

Continuous secondary efficacy variables anticipated to have a non-normal distribution (ie, TG and Lp[a]) were analyzed in the mITT population using multiple imputation approach for handling of missing values.

The percent change from baseline at time point of interest was derived from observed and imputed lipid values at this time point. Multiple imputation was followed by robust regression model.

Binary secondary efficacy endpoints were analyzed using multiple imputation approach for handling of missing values as described for non-normally distributed endpoints but without logtransformation.

For the OLDFI treatment period, central laboratory values, percent change from baseline, and/or when appropriate absolute change from baseline, for calculated LDL-C, Total-C, HDL-C, fasting TG, and non-HDL-C at each time point (including Week 10 and Week 12 time points for Cohort 4), for Lp(a), Apo-B, Apo-A1 and ratio Apo-B/Apo-A1 (absolute change from baseline) at Week 8 time points were summarized in the mITT population using:

- For lipids other than TG and Lp(a): LS mean and SE for each alirocumab dose group, obtained from the same MMRM models as used for endpoints above and including planned time points and with raw values, changes from baseline, or percent change from baseline as response variable in the model as appropriate.
- For TG and Lp(a): mean and SE for each alirocumab dose group obtained from multiple imputation approach followed by the robust regression models as used for endpoints above and including planned time points and with raw values or percent changes from baseline as response variable in the model as appropriate.

In addition, quantitative descriptive summaries by time point (value at visit and % change from baseline) were presented for all lipids using observed (ie, non-missing) data. The time profile in % change from baseline of each parameter (except ratio ApoB/Apo A-1 where absolute change was used) was plotted according to alirocumab dose received by using LS mean and SE except for TGs and Lp(a). For these 2 parameters, the combined estimate for mean and SE was used.

For OLDFI /OLE combined period, only quantitative descriptive summaries by time point during the OLDFI/OLE combined efficacy treatment period was presented for all lipids using observed data in the mITT population. Lipid results pre- versus post-switch to the selected Phase 3 Q2W doses were analyzed separately for Cohorts 1 to 3.

The PK analysis in the OLDFI period was performed on all included and treated patients (safety population) with at least one evaluable PK sample post first OLDFI IMP injection and up to the end of OLDFI period or first OLE IMP injection for patients proceeding into OLE period.

The anti-alirocumab antibody (ADA) analyses in the OLDFI period and in the OLDFI/OLE combined period were performed on all included and treated patients (safety population) with a blood sample on Week 0 (baseline) and at least one evaluable blood sample for antibodies post first IMP injection and up to the end of OLDFI period for patients not entering into OLE period, for up to end of OLE for patients proceeding into OLE period.

Serum samples were collected for total alirocumab concentration pre-dose (inclusion visit) and then at several visits until the end of the follow-up period (for Cohorts 1-3) / end of OLDFI period (Cohort 4). Total alirocumab concentrations (ie, free alirocumab and alirocumab present in PCSK9: alirocumab complexes) were assayed with a validated enzyme-linked immunosorbent assay (ELISA). Total and free PCSK9 levels were measured using validated ELISA.

Serum samples for ADA determination were drawn periodically throughout the study. ADA samples were analyzed using a validated, non-quantitative, titer-based bridging immunoassay.Samples that were positive in the ADA assay were assessed for neutralizing anti-alirocumab antibodies using a validated, non-quantitative, competitive ligand binding assay.

Concentrations of total alirocumab in serum (Ctrough and Cfollow-up) were summarized on the PK population using descriptive statistics.

6.1. Discussion on study design

A phase 2, open-label dose finding study in HefH paediatric patients (8 to 17 years of age) to evaluate appropriate doses to be selected for the phase 3 studies including a study in HoFH patients and a study in HeFH patients has been conducted and submitted in accordance with PIP requirements as outlined in post-approval commitments. Repeated doses of subcutaneous alirocumab were administered in 2 cohorts every 2 (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 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 in accordance with the clinical Broome criteria which is acceptable. HoFH patients were not to be included. Other exclusion criteria can also be considered reasonable.

The screening period (4-6 weeks) can be considered sufficient to establish stable background conditions. A main treatment period of 8 weeks (or 12 weeks for cohort 4) to evaluate the LDL-C effect as primary endpoint can be considered limited but may be acceptable for a dose finding study and is in agreement with the PIP. There was an optional open label extension phase (36 to 40 weeks) or patients were able to enter the phase 3 study and were treated with the doses selected from this study. This is an acceptable approach. Secondary endpoints included evaluation of other parameters of the lipid profile, proportion of patients achieving LDL-C targets appear valuable to be evaluated for dose finding and are therefore acceptable. Specific attention has been given to PK/exposure related evaluation, which is important as supportive information and possibility for extrapolation and modelling to further support the to be applied doses in phase 3.

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 and 50 and 75 mg for > 50 kg, and 75 and 150 mg Q4W for < 50 kg and 150 and 300 mg Q4W for > 50 kg body weight.

Sample size was limited and no formal power calculation was performed. A mixed effect model to handle for missing data is supported especially to efficiently use the available data, provided missing data are not at random and limited (which appears to be the case, see efficacy result section 7), and therefore acceptable.

7. Clinical Pharmacology aspects

7.1. Methods – analysis of data submitted

Blood sampling

- Alirocumab concentration and PCSK9 concentrations

The PK analysis in the OLDFI period was performed on all included and treated patients (safety population) with at least one evaluable PK sample post first OLDFI IMP injection and up to the end of OLDFI period or first OLE IMP injection for patients proceeding into OLE period.

Serum samples were collected for total alirocumab concentration pre-dose (inclusion visit) and then at several visits until the end of the follow-up period (for Cohorts 1-3) / end of OLDFI period (Cohort 4). Total alirocumab concentrations (ie, free alirocumab and alirocumab present in PCSK9: alirocumab

complexes) were assayed with the validated enzyme-linked immunosorbent assay (ELISA) REGN727-AV-11051.

Total and free PCSK9 levels were measured using validated ELISA (REGN727-AV-11081 and REGN727-AV-11084, respectively).

- Sampling for antidrug-antibodies (ADA)

Serum samples for ADA determination were drawn periodically throughout the study. ADA samples were analyzed using a validated, non-quantitative, titer-based bridging immunoassay. Samples that were positive in the ADA assay were assessed for neutralizing anti-alirocumab antibodies using a validated, non-quantitative, competitive ligand binding assay. The anti-alirocumab antibody (ADA) analyses in the OLDFI period and in the OLDFI/OLE combined period were performed on all included and treated patients (safety population) with a blood sample on Week 0 (baseline) and at least one evaluable blood sample for antibodies post first IMP injection and up to the end of OLDFI period for patients not entering into OLE period, for up to end of OLE for patients proceeding into OLE period.

- Analytical and statistical methods

Concentrations of total alirocumab in serum (Ctrough and Cfollow-up) were summarized on the PK population using descriptive statistics. The analytical and statistical methods used in Study DFI14223 were identical to the methods used in the initial marketing authorisation of Praluent, and therefore not further discussed.

7.2. Results

Pharmacokinetics alirocumab

Mean concentrations of total alirocumab increased with dose for both Q2W and Q4W dosing regimens.

The highest mean alirocumab C_{trough} were observed in Cohort 4, at 150 mg Q4W in children with BW <50 kg and 300 mg Q4W in children with BW ≥50 kg.

Table 1 - C_{trough} concentrations (ng/mL) at Week 8 by cohort - EFC14223

	Patients with body weight <50 kg - PK population			
	Cohort 1 ALI 30 Q2W (N=4)	**Cohort 2 ALI 40 Q2W (N=4)**	**Cohort 3 ALI 75 Q4W (N=6)**	**Cohort 4 ALI 150 Q4W (N=6)**
Number	4	3	6	6
Mean (SD)	4142.5 (2736.4)	5053.3 (690.8)	2713.2 (2036.2)	10830.0 (7411.9)
Median	3095.0	4950.0	2515.0	8485.0
Min ; Max	2270 ; 8110	4420 ; 5790	419 ; 6290	4590 ; 24000
	Patients with body weight ≥50 kg - PK population			
	Cohort 1 ALI 50 Q2W (N=6)	**Cohort 2 ALI 75 Q2W (N=6)**	**Cohort 3 ALI 150 Q4W (N=5)**	**Cohort 4 ALI 300 Q4W (N=5)**
Number	5	5	5	5
Mean (SD)	2390.0 (1034.8)	5544.0 (2922.5)	4802.2 (4215.8)	17880.0 (3958.2)
Median	2080.0	5390.0	3690.0	17500.0
Min ; Max	1450 ; 4100	2460 ; 10300	721 ; 10500	13400 ; 24200

Effect on PCSK9 concentrations

Time profile for total PCSK9 concentrations and free PCSK9 in each dose group is shown in the figures below. The administration of alirocumab resulted in a decrease in free PCSK9 concentration from Week 4. The most pronounced decrease being observed in Cohort 4, at 150 mg Q4W in patients with BW <50 kg and 300 mg Q4W in patients with BW ≥50 kg, with level below or close to the limit of quantification. Free PCSK9 concentrations returned approximately to baseline levels at the end of the post-treatment follow-up period for Cohorts 1 to 3.

Figure 1 Total PCSK9 concentration mean (+/-SE) (ng/mL) over time - PK population

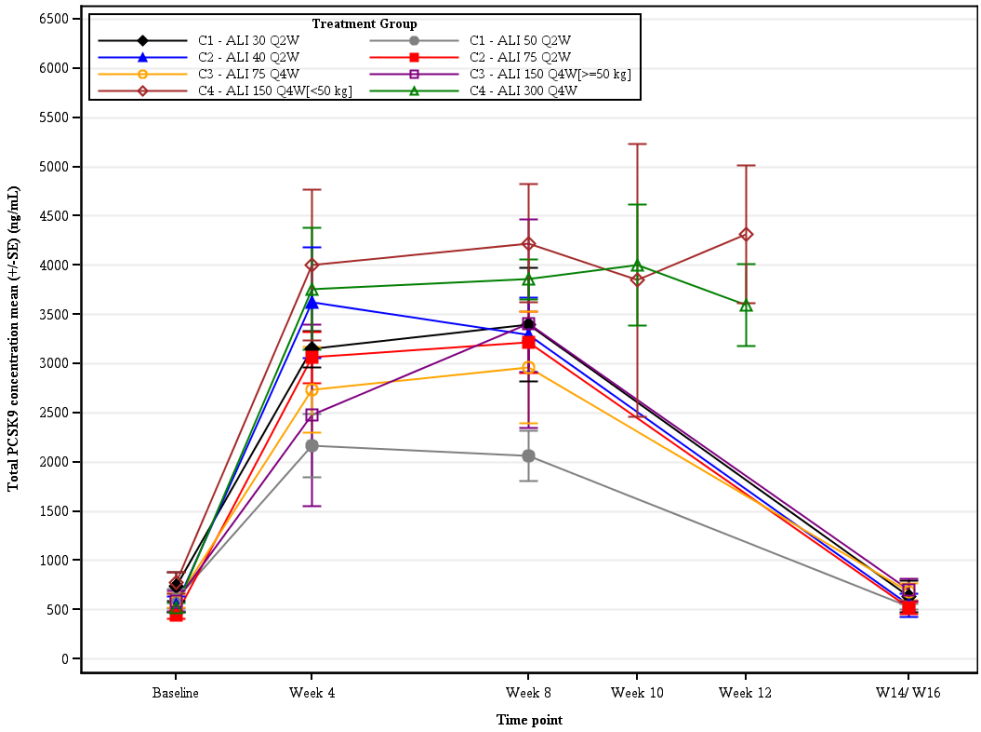
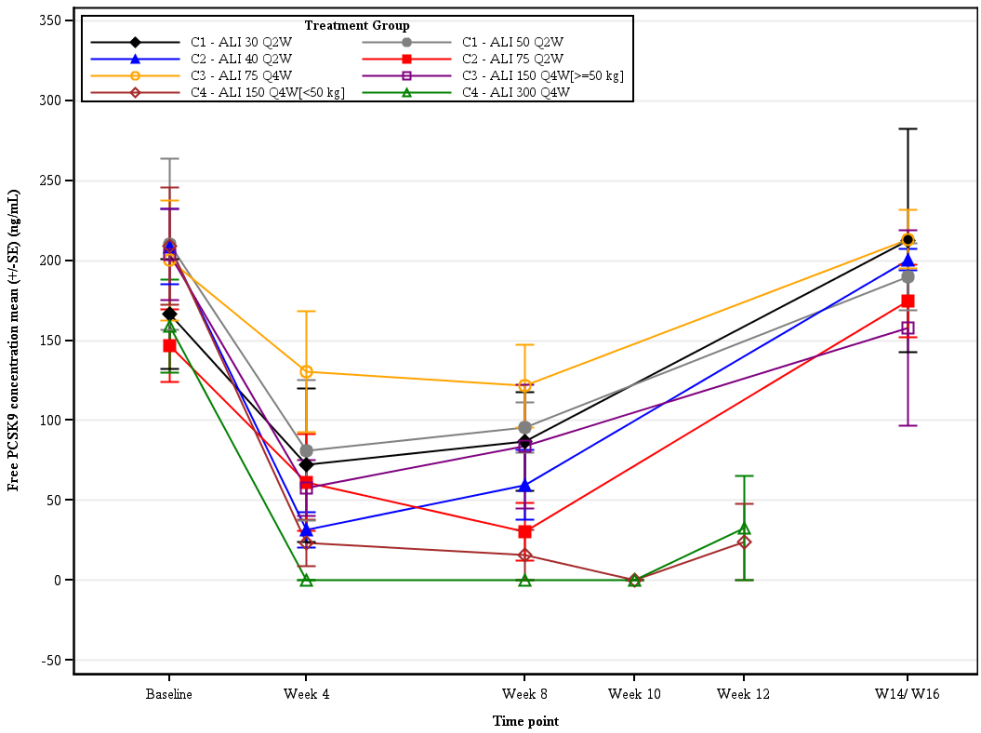


Figure 2 Free PCSK9 concentration mean (+/-SE) (ng/mL) over time - PK population



ADA status

One patient, in Cohort 4, had a positive ADA status at baseline, before the first IMP administration. Four patients out of total 42 patients developed treatment-emergent positive ADA response at least once during the study (OLDFI/OLE combined period up to the switch): 1 patient in Cohort 1, 1 in Cohort 2, and 2 in Cohort 3. Among these 4 treatment-emergent ADA responses, none were classified as persistent. Two were classified as transient responses (1 each in Cohort 1 and Cohort 3), and 2 were classified as indeterminate responses (1 each in Cohort 2 and Cohort 3). The median time to the onset of treatment-emergent ADA response ranged from 8 to 16 weeks. All ADA titers measured in these 4 positive patients were low and did not appear to impact PK. The 4 patients developed neutralizing ADA at one occasion. Only 1 patient in Cohort 1 reported 2 neutralizing ADA post baseline.

7.3. Discussion on clinical pharmacology

In adults, body weight was identified as the most significant covariate in the final population PK model impacting alirocumab pharmacokinetics. Therefore dose selection based on bodyweight is supported.

The mean C_{trough} levels observed in the pediatric population receiving alirocumab Q2W dose (cohort 1 and 2), are close to the ones observed in adults receiving alirocumab Q2W dose (4142 to 5053 ng/mL (<50 kg) and 2390 to 5544 ng/mL (≥ 50 kg) in this study versus 3950 to 6990 ng/mL in adults receiving the dose of 75 mg Q2W from MONO, FHI and COMBO studies; see EPAR Praluent).The mean C_{trough} levels following the alirocumab Q4W dose (cohort 3), are close to the concentrations observed in adults receiving alirocumab 150 Q4W dose (2515 ng/mL (<50 kg) and 3690 ng/mL (≥ 50 kg) in this study versus mean C_{trough} at week 12 of 3586 - 4663 ng/mL in the alirocumab 150 Q4W/Up 150 Q2W in Choice II study). However, the mean trough concentrations in cohort 4 were higher than observed in adults receiving the dose of 300 mg Q4W (5544 ng/mL (<50 kg (150 mg Q4W)) and 17880 ng/mL (≥ 50 kg (300 mg Q4W)) versus mean C_{trough} at week 12 of 8620ng/ml, in the Choice I study; see variation report EMEA/H/C/003882/II/0009/G). The pharmacokinetic data in cohort 1,2, and 3 were in line with adult data and a higher exposure was observed in cohort 4. However, there appear no clear baseline differences (see table baseline characteristics) that could clearly explain for a higher exposure. As the number of subjects per cohort is low the apparent difference may potentially be attributed to between-subject variability. Therefore, no final conclusions can be made on the pharmacokinetics in children based on this study alone. As the company will further investigate the use of alirocumab in the paediatric population in 2 additional paediatric phase 3 clinical studies in children older than 8 years with FH and although according to the PIP the pharmacokinetics will be assessed in these studies as well, the substantial higher exposure in the highest dose and whether any amendment to these phase 3 studies would be needed should be further discussed (**LOQ**). Further, the company is expected to present a combined overview of all pharmacokinetic data in the paediatric population, upon completion of all paediatric studies. The pharmacokinetic data are too premature to consider these to be included in the SmPC.

The administration of alirocumab resulted in a decrease in free PCSK9 concentration from Week 4.The most pronounced decrease being observed in children treated with the highest dose level. This is line with the concentration-dependent reduction in free PCSK9 which was observed in adults. ADA formation is discussed in the safety section.

8. Clinical Efficacy aspects

8.1. Methods – analysis of data submitted

See section 5 on study design.

8.2. Results

Participant flow

A total of 42 patients were enrolled in the study:

- 10 patients in Cohort 1: 4 patients with BW <50 kg received 30 mg Q2W and 6 patients with BW >50 kg received 50 mg Q2W,
- 10 patients in Cohort 2: 4 patients with BW <50 kg received 40 mg Q2W and 6 patients with BW >50 kg received 75 mg Q2W,
- 11 patients in Cohort 3: 6 patients with BW <50 kg received 75 mg Q4W and 5 patients with BW >50 kg received 150 mg Q4W,
- 11 patients in Cohort 4: 6 patients with BW <50 kg received 150 mg Q4W and 5 patients with BW ≥50 kg received 300 mg Q4W.

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). 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 2 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)

Recruitment

This was a multicenter study conducted in 16 active centers (which screened at least 1 patient) in 10 countries worldwide (Canada, Czech Republic, France, The Netherlands, Norway, Russia, South Africa, Spain, Sweden and United States). Of the 16 centers which screened patients, 14 centers enrolled at least 1 patient.

Conduct of the study

As done for the clinical studies conducted in adults, a conservative approach was applied to qualify the major protocol deviations and more particularly those that could potentially impact efficacy analyses. However, the review of the data does not suggest that these deviations could impact the efficacy results of the study.

Using this conservative approach, major protocol deviations that could potentially impact efficacy analyses were reported in 13 patients overall. The most frequent deviation (reported in 8 patients) was related to the statin therapy. For these cases either statin therapy was temporarily stopped for a few days, or statin dose was changed, or patients were not receiving any statin therapy based on local practice (Spain) and not based on statin intolerance. Details by cohort are provided in the table below.

Table 3 Critical or major protocol deviations potentially impacting efficacy analyses - by cohort, all doses combined - Included population

	Cohort 1 (N=10)	Cohort 2 (N=10)	Cohort 3 (N=11)	Cohort 4 (N=11)
Any critical or major protocol deviations potentially impacting efficacy analyses	3 (30.0)	3 (30.0)	5 (45.5)	2 (18.2)
Concomitant Medications/ Therapy	3 (30.0)	1 (10.0)	4 (36.4)	0
Protocol-specified co-administered dose of statin not administered as per protocol	1 (10.0)	1 (10.0)	4 (36.4)	0
Protocol-specified co-administered STATIN not administered	2 (20.0)	0	2 (18.2)	0
Protocol prohibited oral and injectable corticosteroids, fibrates (except fenofibrates),immunosuppressants administered	0	0	1 (9.1)	0
Protocol-specified co-administered LMTs (excluding statin) not administered as per protocol	1 (10.0)	0	0	0
Assessments/Procedures	0	2 (20.0)	2 (18.2)	2 (18.2)
Planned sample not performed	0	2 (20.0)	2 (18.2)	2 (18.2)
IMP Management	0	0	1 (9.1)	0
IMP administered but not within the protocol-specified time window	0	0	1 (9.1)	0
Inclusion/Exclusion criteria	1 (10.0)	0	0	0
Patients NOT treated with optimal dose of statin	1 (10.0)	0	0	0

In the OLDFI/OLE period, alirocumab was administered as planned in the protocol, ie, the median injection frequency of 14 days in Cohorts 1 and 2 and 28 days in Cohorts 3 and 4. All patients (100.0%) had ≥80% compliance for injections during OLDFI period (ie, patients took ≥80% of their injections and at the scheduled times)

Baseline data

Overall, the median age was 12.0 years (ranged from 8 to 17 years). Six patients (14.3%) were below 10 years. At baseline, 6 patients (2 boys and 4 girls) were prepubescent, 26 patients (16 boys and 10 girls) were pubescent and 10 patients (5 boys and 5 girls) were postpubescent. Overall, mean calculated LDL-C concentration at baseline was 175.8 mg/dL (4.6 mmol/L). At enrollment, all patients except 3 included in Cohort 1, were treated with at least one statin.

Table 4 Summary of demographic and baseline characteristics, by cohort, all doses combined - Safety population

	Cohort 1 (N=10)	Cohort 2 (N=10)	Cohort 3 (N=11)	Cohort 4 (N=11)	All (N=42)
Age (years)					
Number	10	10	11	11	42
Mean (SD)	12.7 (2.8)	13.1 (2.6)	11.6 (2.7)	12.4 (2.3)	12.4 (2.6)
Median	12.0	12.5	12.0	12.0	12.0
Min ; Max	8 ; 17	9 ; 17	8 ; 16	8 ; 17	8 ; 17
Age group (years) [n(%)]					
Number	10	10	11	11	42
<10	1 (10.0)	1 (10.0)	3 (27.3)	1 (9.1)	6 (14.3)
[10-12[	2 (20.0)	1 (10.0)	2 (18.2)	2 (18.2)	7 (16.7)
≥12	7 (70.0)	8 (80.0)	6 (54.5)	8 (72.7)	29 (69.0)
Age group (years) [n(%)]					
Number	10	10	11	11	42
Children (2-11 years)	3 (30.0)	2 (20.0)	5 (45.5)	3 (27.3)	13 (31.0)
Adolescents (12-17 years)	7 (70.0)	8 (80.0)	6 (54.5)	8 (72.7)	29 (69.0)
Weight (kg)					
Number	10	10	11	11	42
Mean (SD)	54.7 (18.3)	60.7 (26.4)	47.9 (17.0)	49.6 (14.1)	53.0 (19.3)
Median	57.4	53.2	48.2	46.0	50.1
Min ; Max	26 ; 87	26 ; 102	26 ; 78	29 ; 78	26 ; 102
Weight in group					
Number	10	10	11	11	42
< 50 kg	4 (40.0)	4 (40.0)	6 (54.5)	6 (54.5)	20 (47.6)

≥ 50 kg	6 (60.0)	6 (60.0)	5 (45.5)	5 (45.5)	22 (52.4)
Sex [n(%)]					
Number	10	10	11	11	42
Female	6 (60.0)	4 (40.0)	6 (54.5)	3 (27.3)	19 (45.2)
Male	4 (40.0)	6 (60.0)	5 (45.5)	8 (72.7)	23 (54.8)
Race [n(%)]					
Number	10	10	11	11	42
Black or African American	0	0	0	2 (18.2)	2 (4.8)
Black or African American/White	0	0	1 (9.1)	0	1 (2.4)
White	10 (100)	10 (100)	10 (90.9)	9 (81.8)	39 (92.9)
Ethnicity [n(%)]					
Number	10	10	11	11	42
Hispanic or Latino	2 (20.0)	0	0	1 (9.1)	3 (7.1)
Not Hispanic or Latino	8 (80.0)	10 (100)	11 (100)	10 (90.9)	39 (92.9)
BMI (kg/m^2)					
Number	10	10	11	11	42
Mean (SD)	20.1 (3.7)	22.0 (6.6)	20.3 (3.3)	20.2 (3.8)	20.6 (4.4)
Median	21.0	20.0	20.3	19.7	20.2
Min ; Max	14 ; 25	15 ; 36	15 ; 25	16 ; 27	14 ; 36
BMI (kg/m^2) [n(%)]					
Number	10	10	11	11	42
<30	10 (100)	8 (80.0)	11 (100)	11 (100)	40 (95.2)
≥30	0	2 (20.0)	0	0	2 (4.8)

Overall, the mean calculated LDL-C concentration at baseline was 175.8 mg/dL (4.6 mmol/L).

Table 5 Lipid efficacy parameters at baseline - Quantitative summary in conventional units - by cohort, all doses combined - Safety population

	Cohort 1 (N=10)	Cohort 2 (N=10)	Cohort 3 (N=11)	Cohort 4 (N=11)	All (N=42)
Calculated LDL-C (mg/dL)					
Number	10	10	11	11	42
Mean (SD)	180.3 (41.7)	160.0 (38.0)	172.8 (44.5)	188.9 (39.5)	175.8 (40.9)
Median	175.1	151.5	160.6	172.6	172.4
Min ; Max	85 ; 227	118 ; 242	127 ; 247	143 ; 258	85 ; 258

At baseline, 6 patients (2 boys and 4 girls) were prepubescent, 26 patients (16 boys and 10 girls) were pubescent and 10 patients (5 boys and 5 girls) were postpubescent. Tanner stage at baseline was well balanced between the cohorts.

Cardiovascular history and cardiovascular risk factors overall were generally similar in all 4 cohorts.

Table 6 Summary of medical history of specific interest - CV history and CV risk factor history -by cohort, all doses combined - Safety population

	Cohort 1 (N=10)	Cohort 2 (N=10)	Cohort 3 (N=11)	Cohort 4 (N=11)	All (N=42)
Cardiovascular History and Cardiovascular Risk Factors	10 (100)	10 (100)	11 (100)	11 (100)	42 (100)
Family history of myocardial infarction[a]	4 (40.0)	1 (10.0)	7 (63.6)	6 (54.5)	18 (42.9)
Family history of raised cholesterols	10 (100)	10 (100)	11 (100)	9 (81.8)	40 (95.2)
Family history of tendon xanthoma (in 1st or 2nd degree relative)	3 (30.0)	1 (10.0)	5 (45.5)	2 (18.2)	11 (26.2)
Familial defective Apo B-100	1 (10.0)	2 (20.0)	0	1 (9.1)	4 (9.5)
DNA-based evidence of an LDL receptor mutation (of the subject)	8 (80.0)	6 (60.0)	7 (63.6)	3 (27.3)	24 (57.1)
Tendon xanthoma (of the subject)	1 (10.0)	0	0	0	1 (2.4)
Subject history of raised Total-C	8 (80.0)	9 (90.0)	11 (100)	9 (81.8)	37 (88.1)
Subject history of raised LDL cholesterol	10 (100)	10 (100)	10 (90.9)	10 (90.9)	40 (95.2)

At enrollment, all patients except 3 included in Cohort 1, were treated with at least one statin. Six patients received another LMT at enrollment (4 in Cohort 1 received ezetimibe and 2 in Cohort 3 received nutraceuticals [phytosterols NOS]). Among the 3 patients not receiving statin at enrollment, 2 from Cohort 1 were only receiving ezetimibe 10 mg/day although statin intolerance was not reported; the absence of use of statin was related to regional practice (Spain). The third patient in Cohort 1 initiated rosuvastatin.

Table 7 Summary of disease characteristics and other relevant baseline data - by cohort, all doses combined - Safety population

	Cohort 1 (N=10)	Cohort 2 (N=10)	Cohort 3 (N=11)	Cohort 4 (N=11)	All (N=42)
Diagnosis of heFH made by Clinical Simon Broome Criteria [n(%)]					
Number	3	9	7	9	28
Definite	2 (66.7)	9 (100)	7 (100)	7 (77.8)	25 (89.3)
Possible	1 (33.3)	0	0	2 (22.2)	3 (10.7)
Diagnosis of heFH made by genotyping at any time prior to or during the study [n(%)][a]					
Number	10	10	11	11	42
Yes	10 (100)	10 (100)	9 (81.8)	9 (81.8)	38 (90.5)
Prior to screening	8 (80.0)	7 (70.0)	6 (66.7)	4 (44.4)	25 (65.8)
At baseline with centralized genotyping	0	2 (20.0)	2 (22.2)	5 (55.6)	9 (23.7)
Post-baseline with centralized genotyping	3 (30.0)	4 (40.0)	2 (22.2)	2 (22.2)	11 (28.9)
No	0	0	2 (18.2)	2 (18.2)	4 (9.5)
Time to diagnosis (years)[b]					
Number	10	10	11	11	42
Mean (SD)	6.5 (3.5)	3.1 (3.8)	3.2 (2.2)	3.7 (2.3)	4.1 (3.2)
Median	5.9	1.8	3.1	3.4	3.5
Min ; Max	2 ; 13	0 ; 13	0 ; 7	1 ; 7	0 ; 13
Statin intolerant (as per protocol definition)					
Number	10	10	11	11	42
Yes	1 (10.0)	0	0	1 (9.1)	2 (4.8)
No	9 (90.0)	10 (100)	11 (100)	10 (90.9)	40 (95.2)
If Yes, reason					
Number	1	0	0	1	2
Patient not receiving a daily regimen of statin / Not tolerating daily dose	1 (100)	0	0	1 (100)	2 (100)
If No, Patient treated with maximal dose of statin he can tolerate due to AE at higher dose					
Number	9	10	11	10	40
Yes	0	1 (10.0)	3 (27.3)	2 (20.0)	6 (15.0)
No	9 (100)	9 (90.0)	8 (72.7)	8 (80.0)	34 (85.0)
If Yes, AE(s) encountered at higher dose					
Number	0	1	3	2	6
Skeletal Muscle Related Events	0	0	2 (66.7)	0	2 (33.3)
Other: Maximal dose for children	0	1 (100)	0	0	1 (16.7)
Other: Symptoms of depression taking rosuvastatin	0	0	1 (33.3)	0	1 (16.7)
If No[a], Statin intensification could not be implemented due to:					
Number	9	9	8	8	34
Regional Practice or Local Guideline	9 (100)	9 (100)	6 (75.0)	6 (75.0)	30 (88.2)
Patient/Parent's Refusal	0	0	2 (25.0)	0	2 (5.9)
Specify: Patient is only 10 years old and not at puberty yet and investigator agreed with mother not to uptitrate statin but would monitor diet	0	0	1 (12.5)	0	1 (2.9)
Other: Increased AST/ALT due to 20 mg dose	0	0	1 (12.5)	2 (25.0)	3 (8.8)
Patients age 8 to <10 years had other interventions to lower calculated LDL-C but these have been insufficient					
Number	1	1	3	1	6
Yes	1 (100)	1 (100)	3 (100)	1 (100)	6 (100)

Numbers analysed

All enrolled patients were included in the different analysis populations.

Table 8 Summary of populations - by cohort, all doses combined

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	All
Included population	10 (100)	10 (100)	11 (100)	11 (100)	42 (100)
mITT population	10 (100)	10 (100)	11 (100)	11 (100)	42 (100)
Anti-alirocumab antibody population	10 (100)	10 (100)	11 (100)	11 (100)	42 (100)
PK population	10	10	11	11	42
Safety population	10	10	11	11	42

Outcomes and estimations

Primary endpoint

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]. 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. 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.

Table 9 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 - Study DFI14223

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.

PGM=PRODOPS/SAR236553/DFI14223/CSR/REPORT/PGM/eff_mmrm_pch_bladj_m_t.sas
OUT=REPORT/OUTPUT/eff_mmrm_pchldl_noadj_m_t_all_i.rtf (21JUN2019 12:30)

Table 10 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, patients with body weight <50 kg - mITT population

Calculated LDL-Cholesterol	Cohort 1 ALI 30 Q2W (N=4)	Cohort 2 ALI 40 Q2W (N=4)	Cohort 3 ALI 75 Q4W (N=6)	Cohort 4 ALI 150 Q4W (N=6)
Baseline (mmol/L)				
Number	4	4	6	6
Mean (SD)	5.169 (0.736)	3.596 (0.630)	4.337 (1.147)	5.100 (1.136)
Median	5.144	3.427	4.110	4.490
Min ; Max	4.51 ; 5.88	3.05 ; 4.48	3.29 ; 5.88	4.21 ; 6.69
Baseline (mg/dL)				
Number	4	4	6	6
Mean (SD)	199.6 (28.4)	138.8 (24.3)	167.4 (44.3)	196.9 (43.8)
Median	198.6	132.3	158.7	173.4
Min ; Max	174 ; 227	118 ; 173	127 ; 227	163 ; 258
Week 4 percent change from baseline (%)				
LS Mean (SE)	-35.6 (12.2)	-30.1 (12.2)	-19.5 (10.0)	-31.6 (10.3)
95% CI	(-60.5 to -10.8)	(-55.0 to -5.3)	(-39.7 to 0.8)	(-52.4 to -10.7)
Week 8 percent change from baseline (%)				
LS Mean (SE)	-41.1 (12.6)	-40.6 (13.2)	-17.5 (10.3)	-31.9 (10.3)
95% CI	(-66.7 to -15.6)	(-67.3 to -13.8)	(-38.4 to 3.3)	(-52.7 to -11.0)

Table 11 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, patients with body weight ≥50 kg - mITT population

Calculated LDL-Cholesterol	Cohort 1 ALI 50 Q2W (N=6)	Cohort 2 ALI 75 Q2W (N=6)	Cohort 3 ALI 150 Q4W (N=5)	Cohort 4 ALI 300 Q4W (N=5)
Baseline (mmol/L)				
Number	6	6	5	5
Mean (SD)	4.339 (1.200)	4.510 (1.052)	4.642 (1.272)	4.641 (0.926)
Median	4.455	4.375	4.160	4.196
Min ; Max	2.20 ; 5.51	3.49 ; 6.27	3.42 ; 6.41	3.70 ; 6.04
Baseline (mg/dL)				
Number	6	6	5	5
Mean (SD)	167.5 (46.3)	174.1 (40.6)	179.2 (49.1)	179.2 (35.7)
Median	172.0	168.9	160.6	162.0
Min ; Max	85 ; 213	135 ; 242	132 ; 247	143 ; 233
Week 4 percent change from baseline (%)				
LS Mean (SE)	-12.0 (10.0)	-44.4 (10.0)	-0.5 (10.9)	-46.3 (11.3)
95% CI	(-32.3 to 8.3)	(-64.7 to -24.1)	(-22.7 to 21.7)	(-69.4 to -23.3)
Week 8 percent change from baseline (%)				
LS Mean (SE)	-7.9 (10.3)	-49.8 (10.6)	4.0 (11.2)	-59.8 (11.2)
95% CI	(-28.8 to 12.9)	(-71.2 to -28.3)	(-18.9 to 26.8)	(-82.6 to -36.9)

Secondary endpoints

- Absolute change in LDL-C

For Cohort 2, the absolute change in calculated LDL-C from baseline to Week 8 was substantial (LS mean [SE]: -75.2 [13.0] mg/dL or 1.947 [0.335] mmol/L). This clinically meaningful reduction was consistently observed in both BW categories with a greater decrease observed for patients with BW ≥50 kg (5.3.5.2 Study DFI14223: LS mean (SE) of -55.5 (20.8) mg/dL or -1.439 (0.539) mmol/L with 40 mg Q2W in patients with BW <50 kg, and -88.3 (16.5) mg/dL or -2.286 (0.429) mmol/L with 75 mg Q2W in patients with BW ≥50 kg.

In Cohort 4, the absolute change in calculated LDL-C from baseline to Week 8 and Week 12 was (LS mean [SE]) -77.9 [11.7] mg/dL or -2.017 [0.304] mmol/L and (LS mean [SE]) -67.8 [8.3] mg/dL or 1.755 [0.216] mmol/L), respectively. A greater reduction was observed in patients in the higher BW group (300 mg Q4W). To Week 8: LS mean (SE) of -55.9 (15.9) mg/dL or -1.447 (0.411) mmol/L with 150 mg Q4W in patients with BW <50 kg, and -104.3 (17.4) mg/dL or -2.700 (0.451) mmol/L with 300 mg Q4W in patients with BW ≥50 kg. To Week 12: LS mean [SE]: -51.9 (11.3) mg/dL or -1.343 (0.293) mmol/L with 150 mg Q4W in patients with BW <50 kg, and -86.8 (12.4) mg/dL or -2.249 (0.321) mmol/L) with 300 mg Q4W in patients with BW ≥50 kg.

Table 12 Absolute change from baseline in calculated LDL-C in mmol/L over time during the OLDFI efficacy treatment period: MMRM (without adjustment on baseline) - On-treatment analysis - by cohort, all doses combined - mITT population - Study DFI14223

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 absolute change from baseline (mmol/L)				
LS Mean (SE)	-1.196 (0.326)	-1.646 (0.326)	-0.605 (0.311)	-1.728 (0.325)
95% CI	(-1.859 to -0.532)	(-2.310 to -0.983)	(-1.237 to 0.028)	(-2.388 to -1.068)
Week 4 absolute change from baseline (mg/dL)				
LS Mean (SE)	-46.2 (12.6)	-63.6 (12.6)	-23.4 (12.0)	-66.7 (12.6)
95% CI	(-71.8 to -20.6)	(-89.2 to -38.0)	(-47.8 to 1.1)	(-92.2 to -41.3)
Week 8 absolute change from baseline (mmol/L)				
LS Mean (SE)	-1.296 (0.319)	-1.947 (0.335)	-0.456 (0.304)	-2.017 (0.304)
95% CI	(-1.944 to -0.648)	(-2.627 to -1.267)	(-1.074 to 0.162)	(-2.635 to -1.399)
Week 8 absolute change from baseline (mg/dL)				
LS Mean (SE)	-50.0 (12.3)	-75.2 (13.0)	-17.6 (11.7)	-77.9 (11.7)
95% CI	(-75.1 to -25.0)	(-101.4 to -48.9)	(-41.5 to 6.3)	(-101.7 to -54.0)

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.

Proportion of patients achieving pre-specified LDL-C targets

At Week 8, 88.8% of patients in Cohort 2 reached a calculated LDL-C <130 mg/dL (3.37 mmol/L) and 76.8% of patients reached a calculated LDL-C <110 mg/dL (2.84 mmol/L).

In Cohort 4, 72.7% of patients who reached a calculated LDL-C <130 mg/dL (3.37 mmol/L) at Week 8 and 72.7% of patients who reached a calculated LDL-C <110 mg/dL (2.84 mmol/L) at Week 8. Similar results were observed in Cohort 4 at Week 12.

Table 13 Proportion of patients reaching calculated LDL-C <130 mg/dL (3.37 mmol/L) over time: Multiple imputation - On-treatment analysis - by cohort, all doses combined - mITT population - Study DFI14223

Calculated LDL-Cholesterol	Cohort 1 (N=10)	Cohort 2 (N=10)	Cohort 3 (N=11)	Cohort 4 (N=11)
Proportion of patients reaching calculated LDL-C < 130 mg/dL (3.37 mmol/L)				
Combined estimate for proportion of patients reaching the level at Week 4 (%)	30.0	90.0	27.3	72.7
Combined estimate for proportion of patients reaching the level at Week 8 (%)	60.0	88.8	27.3	72.7

The efficacy treatment period ends at last OLDFI injection date +21 days (for Cohorts 1 & 2) or +35 days (for Cohorts 3 & 4)

Note: A two-step multiple imputation procedure is used to address missing values in the mITT population (seeds=14223 and 28446 in the two steps respectively; with number of imputations= 1000). In the first step, the monotone missing pattern is induced in the multiply-imputed data. In the second step, the missing data at subsequent visits are imputed using the regression method for continuous variables.
Combined estimate for proportion of patients is obtained by averaging out all the imputed proportions of patients reaching the level of interest.

Table 14 Proportion of patients reaching calculated LDL-C <110 mg/dL (2.84 mmol/L) over time: Multiple imputation - On-treatment analysis - by cohort, all doses combined - mITT population - Study DFI14223

Calculated LDL-Cholesterol	Cohort 1 (N=10)	Cohort 2 (N=10)	Cohort 3 (N=11)	Cohort 4 (N=11)
Proportion of patients reaching calculated LDL-C <110 mg/dL (2.84 mmol/L)				
Combined estimate for proportion of patients reaching the level at Week 4 (%)	20.0	70.0	18.2	54.3
Combined estimate for proportion of patients reaching the level at Week 8 (%)	0.0	76.8	18.2	72.7

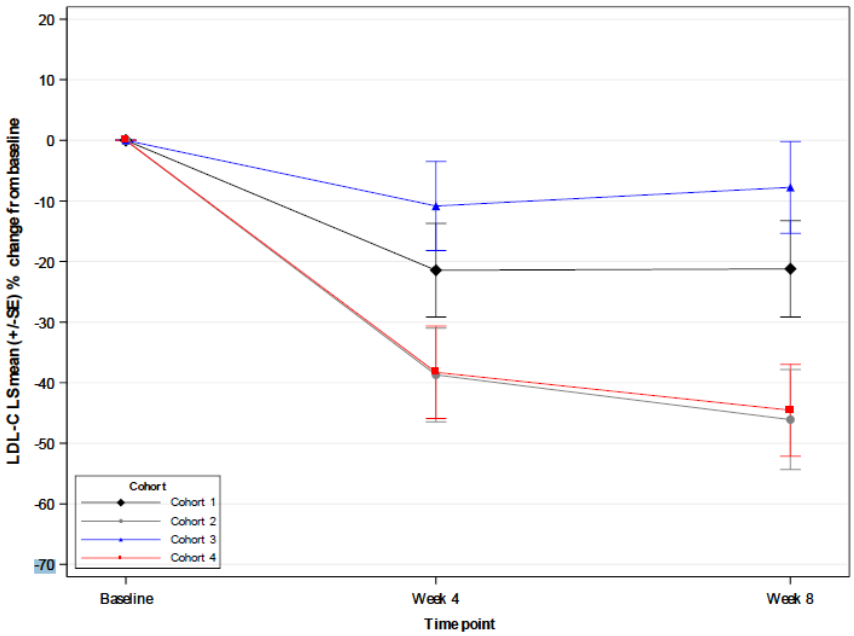
The efficacy treatment period ends at last OLDFI injection date +21 days (for Cohorts 1 & 2) or +35 days (for Cohorts 3 & 4)

Note: A two-step multiple imputation procedure is used to address missing values in the mITT population (seeds=14223 and 28446 in the two steps respectively; with number of imputations= 1000). In the first step, the monotone missing pattern is induced in the multiply-imputed data. In the second step, the missing data at subsequent visits are imputed using the regression method for continuous variables.
Combined estimate for proportion of patients is obtained by averaging out all the imputed proportions of patients reaching the level of interest.

- Calculated LDL-C over time

The calculated LDL-C up to week 8 is displayed in the figure below.

Figure 3 Calculated LDL-C: LS mean (+/-SE) percent change from baseline: Time profile (without adjustment on baseline) - On-treatment analysis - OLDFI period - by cohort, all doses combined - mITT population - Study DFI14223



Open label extension

In the OLE period, the effect in calculated LDL-C was maintained over time in all cohorts up to the switch and after the switch to the Phase 3 Q2W doses for patients in Cohorts 1 to 3. When considering the latest time point before the switch with individual results by cohort, Week 36 for Cohort 4 / Week 38 for Cohort 3/Week 40 for Cohorts 1 and 2, there was a clinically meaningful reduction in calculated LDL-C in all cohorts. As observed in the OLDFI period, there was a greater reduction in Cohort 2 using the Q2W dosing regimen (-52.1% [13.3]) and Cohort 4 using the Q4W dosing regimen (-48.2% [6.1]) as compared with the 2 other cohorts (Cohort 1 Q2W dosing regimen: -23.4% [22.3], Cohort 3 Q4W dosing regimen: -22.9% [18.3]).

Other lipid parameters

In all cohorts, decreases were observed from baseline to Week 8 (on-treatment analysis) for Apo B, non-HDL-C and Total-C with the greatest reductions for Cohort 2 and Cohort 4:

- For Apo B: LS mean [SE]: -38.6% [7.9] for Cohort 2 and LS mean [SE]: -38.2% [6.7] for Cohort 4.
- For non-HDL-C: LS mean [SE]: -42.2% [7.8] for Cohort 2 and LS mean [SE]: -42.0% [7.2] for Cohort 4.
- For Total-C: LS mean [SE]: -32.0% (6.3) for Cohort 2 and LS mean [SE]: -32.1% [5.8] for Cohort 4.

Overall, a decrease in Lp(a) was noted from baseline to Week 8 in all Cohorts with greater reductions for Cohorts 1 and 2. Slight increase in HDL-C and in Apo A-1 was noted without relevant differences between cohorts. For TG as expected, a high variability in the results was observed across the cohorts likely due to the very limited number of patients by cohort; therefore, no conclusion can be drawn for this parameter.

Doses to be selected for the phase 3 studies

According to the MAH, the results identified the doses to evaluate in the pivotal phase 3 studies. The Q2W and Q4W dose regimens assessed in Cohorts 2 and 4 respectively were selected for further evaluation in the phase 3 pediatric heFH study. At these doses, because LDL-C levels remained elevated (LDL-C value ≥110 mg/dL [2.84 mmol/L]) in some patients, an uptitration/dose-adjustment scheme was implemented in the phase 3 pediatric heFH study to optimize LDL-C reduction in patients with LDL-C not at target levels. This dosing scheme is consistent with the dosing recommendations for adults which, in clinical studies, demonstrated that doubling the dose of alirocumab resulted in an additional percent of patients reaching the target LDL-C level for adults (<70 mg/dL or <100 mg/dL depending on the individual patient's CV risk) of about 15%.

8.3. Discussion

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. 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. Also during the open-label phase, the discontinuation rate was low with 1 patients discontinuing due to fatigue and 2 due to patients decision. Several protocol deviations occurred during the study, but it may be questioned whether this has substantially impacted efficacy findings relevant for conclusions to be taken forward to phase 3 studies.

The study population can be considered representative for a paediatric HeFH population. HeFH diagnosis was sufficiently established as the diagnosis was for a large part of the population by genetic testing (90.5%) and based on the clinical Broome criteria (89.3%). Moreover, the elevated mean LDL-C baseline value of 4.6 mmol/L reasonably corresponds to an LDL-C level generally observed within a HeFH population. Except for 3 patients (one reported to be statin intolerant), statins were not used. The age range was generally well represented for each cohort (8-17 years of age). Body weight categories were equally represented, as well as females and males.

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 the effect according to body weight (-40.6 [sd13.2] with 40 mg Q2W for BW <50 kg, and -49.8% [sd10.6] with 75 mg Q2W for BW ≥50 kg).

For the monthly dosing, only a moderate effect was observed for the lower dosing (cohort 3: 75 mg and 150 mg QW4), with respectively -17.5% (10.3) and 4.0% (11.2) 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). Both in cohort 2 and 4 the BW ≥50 kg showed the greatest efficacy.

Effects of other parameters of the lipid profile were consistent with the effects on LDL-C, except for HDL-C and TG, which can be expected based on experience with adult data.

Other endpoints supported the primary endpoint across the efficacy effects for the different cohorts including absolute change in LDL-C (-1.296, -1.947, -0.456 and -2.017 mmol/L, respectively cohort 1 to 4), proportion of patients achieving pre-specified LDL-C targets (3.37 mmol/L target: 60%, 89%, 27%, 72%; 2.84 mmol/L target: 0%, 77%, 18%, 72%), LDL-C reduction and end of the open-label extension phase (-23%, -52%, -23% and –48%).

Overall, a more pronounced effect can be observed in the higher Q2W dose in cohort 2 and in the higher QW4 dosing in cohort 4 in comparison to the respective lower dose groups. Although some variation exists between the body weight categories, with greater efficacy in the ≥50 kg groups. Exposure data are in agreement with these LDL-C efficacy observations and may thus likely explain the observed differences, although no exposure response data have been presented. As mentioned in the pharmacology section, for the higher QW4 dose, great difference in exposure according to body weight exists with exposures exceeding adult exposures for ≥50 kg group. From an efficacy view point, it is reasonable to consider the doses used in cohort 2 and cohort 4 to be taken forward to the phase 3 studies, as has already been done, as these studies have already been initiated. Further PK data are expected from the HeFH phase 3 study as this is included in the protocol as a secondary endpoint (see also pharmacology section).

9. Clinical Safety aspects

9.1. Methods – analysis of data submitted

Introduction

Safety results are presented based on the completed phase 2, dose-finding study DFI14223 in pediatric patients with heFH.

In addition, a general literature search was conducted with for the period of 25 July 2018 through to 24 July 2019, the reporting period of the latest Periodic Benefit Risk Evaluation Report (PBRER) for alirocumab. Seven publications have been identified from the scientific (including nonclinical) and medical literature that included relevant safety findings.

Rapporteur's comment

As the current submission is especially focussed on paediatric data, no specific attention will be given to the literature search.

Safety Population

Safety analyses were descriptive and presented by treatment group. They were performed in the safety population. The safety population considered for safety analyses in the OLDFI period and in OLDFI/OLE combined period comprised patients who actually received at least one dose or part of a dose of the IMP injection. Patients were analyzed according to the dose of alirocumab actually received (ie, as-treated alirocumab dose group).

Immunogenicity Population

The anti-drug antibody (ADA) analyses in the OLDFI period and in the OLDFI/OLE combined period were performed on all included and treated patients (safety population) with a blood sample at Week 0 (baseline) and at least one evaluable blood sample for antibodies post first IMP injection and up to the end of OLDFI period for patients not entering into OLE period, or up to end of OLE for patients proceeding into OLE period.

9.2. Results

Exposure

In the OLDFI period, the median duration of treatment exposure was 8 weeks in Cohorts 1 to 3 and 12 weeks in Cohort 4. In the combined OLDFI/OLE period up to the switch to the Phase 3 Q2W doses, the

median duration of treatment exposure was 70.3 weeks in Cohort 1, 54.3 weeks in Cohort 2, 50.6 weeks in Cohort 3 and 24.0 weeks in Cohort 4.

The difference in the duration of exposure is due to the sequential enrollment of Cohorts 1 to 4 and the common study end date that was applied when Cohort 4 was completed.

Adverse events

Common adverse events

Overall, 21 patients experienced at least one treatment-emergent adverse event (TEAE) in the OLDFI period: 9 in Cohort 1, 2 in Cohort 2, 4 in Cohort 3 and 6 in Cohort 4. After the dose switch, 2 additional patients from Cohort 3 experienced at least one TEAE.

In the combined OLDFI/OLE periods up to the switch to the selected Phase 3 Q2W doses, a total of 29 patients experienced at least one TEAE: 9 patients in Cohort 1, 5 in Cohort 2 (3 additional patients compared to the OLDFI alone), 8 in Cohort 3 (4 additional patients) and 7 in Cohort 4 (1 additional patient). Overall, no effect of the dose or the dose-regimen was observed for any TEAEs.

Two patients experienced a TEAE leading to permanent treatment discontinuation: one patient in Cohort 4 experienced a neutropenia reported at the end of the OLDFI period and another patient from Cohort 1 experienced fatigue during the OLE period after the switch to the selected Phase 3 Q2W doses.

No treatment-emergent SAEs were reported throughout the whole duration of the study, ie, in the OLDFI period, the OLDFI/OLE combined period up to the switch to the Phase 3 Q2W doses, or after the dose switch.

One patient reported a post-treatment serious AE (Type 1 diabetes) in Cohort 4.

Table 15 Overview of adverse event profile: Treatment emergent adverse events - OLDFI period- by cohort, all doses combined - Safety population - Study DFI14223

	Cohort 1 (N=10)	Cohort 2 (N=10)	Cohort 3 (N=11)	Cohort 4 (N=11)
Patients with any TEAE	9 (90.0)	2 (20.0)	4 (36.4)	6 (54.5)
Patients with any treatment emergent SAE	0	0	0	0
Patients with any TEAE leading to death	0	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	0	0	1 (9.1)

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

Table 16 Overview of adverse event profile: Treatment emergent adverse events - OLDFI/OLE combined period, up to the switch to Phase 3 doses- by cohort, all doses combined - Safety population - Study DFI14223

	Cohort 1 (N=10)	Cohort 2 (N=10)	Cohort 3 (N=11)	Cohort 4 (N=11)
Patients with any TEAE	9 (90.0)	5 (50.0)	8 (72.7)	7 (63.6)
Patients with any treatment emergent SAE	0	0	0	0
Patients with any TEAE leading to death	0	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	0	0	1 (9.1)

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

The most commonly reported TEAEs were in the System Organ Class (SOC) Infections and infestations (11 patients in the OLDFI period and 5 additional patients in the OLDFI/OLE combined period up to the

switch to the Phase 3 Q2W doses) and in the SOC Gastrointestinal disorders (7 patients in the OLDFI period and 2 additional patients in the OLDFI/OLE combined period up to the switch).

Overall, the most frequently reported events by Preferred Term during the OLDFI/OLE combined period were nasopharyngitis (5 patients), upper respiratory tract infection (4 patients) and diarrhea (5 patients).

Treatment related adverse events

Few TEAEs were considered related to IMP by the Investigators. In the OLDFI period, 1 patient in Cohort 4 experienced 2 local injection site reactions, and 1 patient in Cohort 2 experienced blood follicle-stimulating hormone (FSH) decrease and blood luteinizing hormone (LH) decrease.

For the latter patient, the laboratory results were from a blood sample taken just before the first dose administration of alirocumab. However, the associated AEs were reported after the dose administration and therefore captured as treatment-emergent. In the OLDFI/OLE combined period up to the dose switch, the patient mentioned above for blood FSH decreased/blood LH decreased experienced LDL-C decreased (one LDL-C value <50 mg/dL). Finally, another local injection site reaction was reported by 1 patient enrolled in Cohort 3 in the OLE period up to the switch.

Adverse events of special interest

No neurological events (requiring additional examinations/procedures and/or referral to a specialist), neurocognitive events, increase in ALT, general allergic events or local injection site reactions (requiring consultation with another physician) meeting the protocol definition of AESI were reported during the study.

- Neurological adverse events

No neurological events (requiring additional examinations/procedures and/or referral to a specialist), or neurocognitive events were reported.

- Injection site reactions

Local injection site reactions (3 events) were reported in 2 patients (1 patient in Cohort 3 and 1 patient in Cohort 4) and were both mild in intensity.

- Hepatic disorders

One patient in Cohort 1 experienced CMV hepatitis after switching to Phase 3 Q2W doses (from 50 mg Q2W to 75 mg Q2W). The event occurred 5 days after the last IMP administration, was of mild intensity and resolved within 39 days. It was not associated with ALT >3 ULN. This patient also experienced fatigue which led to treatment discontinuation.

- Diabetes or diabetic complications

Two patients developed diabetes mellitus:

  - A 17-year old female patient in Cohort 1 was reported to have a treatment-emergent Type 1 diabetes mellitus in the OLE period before the switch to Phase 3 Q2W doses. According to medical history information, this patient had experienced intermittently increased glycaemia for 4 years. An increased fasting glucose value of 7.9 mmol/L (potential clinically significant abnormality (PCSA) value) was only observed after switching to the Phase 3 Q2W doses, at Week 76. The patient was asymptomatic. No changes in weight were observed for this patient during her study participation. The patient was found to be positive for anti-GAD antibodies; however negative for antityrosine phosphatase IA2 and anti-insulin antibodies. The patient did not have any other autoimmune disease. HbA1c value at the time of diagnosis was reported to be increased;

however, the value was not provided. Subsequent available HbA1c values were within the normal range. The event was considered nonserious and not related to study drug by the Investigator. The endocrinologist considered that the mildly increased values of glycemia did not require treatment with insulin. The patient was initiated on metformin.

- An 11-year old male patient in Cohort 4, on levothyroxine treatment for autoimmune thyroiditis was reported to have a post-treatment serious AE (Type 1 diabetes mellitus). During the study participation, the glucose values were normal. The event was reported approximately 3.5 months after the last dose of study drug (glycaemia: 16 mmol/L, HbA1C: 89 mmol/mol (10.3%) and glycosuria 4+). Positive anti-GAD antibodies and highly positive anti-TPO antibodies were reported. Ophthalmological examination was normal. The patient did not experience fluctuations in body weight. The event was assessed as medically significant and led to one week hospitalization. The patient was initiated on human insulin and detemir insulin as corrective treatment. The Investigator considered the event not related to study drug.

- Cataract

No cataracts were reported in the study.

Adverse events from patients with 2 consecutive calculated LDL-C <50 mg/dL (1.30 mmol/L) or <25 mg/dL (0.65 mmol/L)

No patients had 2 consecutive LDL-C values <25 mg/dL.

One patient had 2 consecutive LDL-C value <50 mg/dL in Cohort 2 in the OLE period before the switch to Phase 3 Q2W doses. No TEAEs were reported in this patient after the first of the 2 consecutive LDL-C <50 mg/dL (<1.30 mmol/L) and up to the end of the TEAE period.

Serious adverse events and deaths

Serious adverse events

No treatment-emergent SAEs were reported in the OLDFI/OLE combined period.

Deaths

No deaths were reported in the OLDFI/OLE combined period.

Discontinuations due to adverse events

Two patients experienced TEAEs leading to permanent treatment discontinuation. None of the events were assessed to be related to alirocumab by the Investigators.

- One patient enrolled in Cohort 4 (150 mg Q4W), with mild neutropenia at screening of 1.21 G/L (normal range: 1.65 - 8.15) and 1.16 G/L at Week 8, had an absolute neutrophil count value below 1 G/L (0.78 G/L) at Week 12 following the injection done at Week 8. Although the IMP was discontinued due to this TEAE, the patient entered in the OLE period without taking the IMP. During the OLE period, the patient experienced fluctuating values of neutrophils; which returned to normal (1.73 G/L) 3 months after treatment discontinuation. Neutrophils were again below the lower limit of normal range (LLN) (0.98 G/L) 1 month later while the patient was off-treatment.
- During the OLE period after the switch to the Phase 3 Q2W doses, 1 patient from Cohort 1 experienced fatigue that was associated with the diagnosis of a cytomegalovirus (CMV) hepatitis. Corrective treatment with vitamin B complex and ubidecarenone was initiated. Treatment with alirocumab was discontinued 7 months after the start of the event and the patient recovered around 1 month later.

Laboratory parameters

Blood cell counts

Overall, there were no relevant changes over time for red blood cells, hemoglobin, hematocrit, leukocytes, leukocyte differential counts and platelets during the OLDFI/OLE combined period up to the switch to the Phase 3 Q2W doses in any of the cohorts or after the switch to the Phase 3 Q2W doses.

However, two patients (both in the BW <50 kg category) had abnormal low neutrophils that were reported as non-serious TEAE by the Investigator (neutropenia of mild intensity). One patient, with mild neutropenia at screening of 1.21 G/L (normal range: 1.65 - 8.15) and 1.16 G/L at Week 8, had neutrophil count of 0.78 G/L at Week 12 at the dose of 150 mg Q4W and another had neutrophil count of 1.44 G/L at Week 26 at the dose of 75 mg Q4W. In the former case, the TEAE led to treatment discontinuation. Both events resolved.

Electrolytes

There were no clinically relevant abnormalities in electrolytes observed during the study.

Metabolic function

In the OLDFI/OLE combined period up to the switch to the Phase 3 Q2W doses, 2 patients had PCSA value for fasting glucose and the values returned to normal in the following visits. After the switch to Phase 3 Q2W doses, 1 patient had a PCSA for fasting glucose at Week 76, (7.9 mmol/L), which returned to normal value at Week 100 (5.2 mmol/L). At the end of OLE, fasting glucose was 6.0 mmol/L. This patient was reported with TEAE of type 1 diabetes. One patient had increase in creatine phosphokinase >3 ULN at the end of the OLE period, but the value returned within normal levels 15 days later. No patients had PCSAs for albumin or out-of-normal range value for protein. No laboratory test abnormalities in metabolic parameters were reported as TEAEs that led to treatment discontinuation or met a seriousness criterion.

Renal parameters

During the OLDFI/OLE combined period up to the switch to Phase 3 Q2W doses, PCSAs for renal function were reported in 8 patients: 6 patients had high PCSA value for urea nitrogen (1 in Cohorts 1 and 2 and 4 in Cohort 3), 1 patient had low PCSA value for eGFR in Cohort 1 and 1 patient had high PCSA value for uric acid in Cohort 4. Most patients had PCSA only once and the value returned to normal levels at the following visit. After the switch to Phase 3 Q2W doses, 2 patients had one PCSA value for uric acid. No abnormal values in any of the renal function parameters were reported as TEAEs during the study.

Liver parameters

The incidence of PCSA in liver function parameters was very low during the combined OLDFI/OLE period up to the switch to the Phase 3 Q2W doses (1 patient with abnormally high total bilirubin), as well as during the period after the switch (1 patient with abnormally high alkaline phosphatase). For both patients, abnormal values returned to normal levels at following visits.

There were no clinically relevant abnormalities in liver function parameters observed during the study.

Cortisol and adrenocorticotrophic hormone (ACTH)

Three patients, all in Cohort 3, had abnormal low cortisol value during the OLDFI/OLE combined up to the switch to the Phase 3 Q2W doses and 7 patients when considering the OLDFI/OLE combined period after the switch (Cohorts 1 to 3). For 2 of the 3 patients with abnormally low cortisol, the levels returned to normal values at the subsequent visits and up to the end of the study. The last patient had normal cortisol values at the subsequent 2 visits and then abnormal value at the end of the OLE period. None had abnormal reflexive adrenocorticotrophic hormone (ACTH) value at the stimulation test. They were no clinically relevant abnormalities in cortisol observed during the study.

Gonadal and pituitary hormones assessments

There were no clinically relevant abnormalities in gonadal and pituitary hormones in boys observed during the study. One female patient (16-year-old, pubescent at baseline and at the end of the study) had low LH and FSH on the day of randomization reported as TEAEs. The values returned normal range at the end of the study. No other clinically relevant abnormalities in gonadal and pituitary hormones were observed during the study.

Fat soluble vitamins

With regard to fat soluble vitamins, vitamin D deficiency was reported as a TEAE in 3 patients in the OLDFI/OLE combined period. All of the 3 patients had already low vitamin D values at baseline (35, 50, and 54.4 nmol/L) for which they received vitamin D supplementation. The events were resolved or resolving at the end of the study. A decrease in vitamin E parallel to the decrease in LDL-C levels was observed in all cohorts from baseline to Week 8 and a positive correlation between calculated LDL-C and vitamin E was observed in the OLDFI period. No patient had vitamin E values lower than normal range.

Vital signs

For systolic blood pressure, diastolic blood pressure, heart rate, and weight, the mean changes from baseline were similar in the different cohorts, and none of the changes were clinically significant or reported as TEAEs.

Anti alirocumab antibodies

Four patients developed treatment-emergent positive ADA response during the study (OLDFI/OLE combined period up to the switch): 1 patient in Cohort 1, 1 in Cohort 2, and 2 in Cohort 3. Among these 4 treatment-emergent ADA responses, none were classified as persistent. Two were classified as transient responses (1 each in Cohort 1 and Cohort 3), and 2 were classified as indeterminate responses (1 each in Cohort 2 and Cohort 3).

Four patients had positive neutralizing ADA status post-baseline (OLDFI/OLE combined period up to the switch to Phase 3 Q2W doses). Of those, 3 patients had single episodes of neutralizing ADA, and 1 patient in Cohort 1 had 2 episodes of neutralizing ADA post-baseline.

Among the 4 treatment-emergent ADA positive cases, 2 patients did not present with any adverse events. One patient with a medical history of asthma experienced a non-serious asthma attack 5 months after a transient positive ADA response. The remaining patient had an ADA positive response at several time points between Week 8 and Week 28 with a single titer >240 (480), with ADA negative status at subsequent measures. The patient had recurrent episodes of cold during the period of ADA positivity. She was also diagnosed with diabetes mellitus type 1; however, increased glycaemia had been already in her medical history several years before There were no safety concerns related to positive ADA raised in any of these patients.

9.3. Discussion

The current dose finding study included 42 patients treated for up to a mean of 70 weeks. The number of patients can be considered very limited to evaluate the safety profile in paediatric patients. However, the current study is a dose finding study, and further data are expected from the phase 3 studies, especially the HeFH study as this study aims to include considerably more patients.

Adverse events were reported from 36% to 90% across the different cohorts during the dose finding phase, and 50% to 90% during the open label extension phase. Most adverse events were reported in the SOC Infections and infestations (11 patients in the OLDFI period and 5 additional patients in the OLDFI/OLE combined period with nasopharyngitis (5 patients), upper respiratory tract infection (4 patients) and diarrhea (5 patients) being the most reported adverse events, which appears to be in line with adult findings.

However, only 2 events were considered treatment related (local injection site reactions; blood follicle-stimulating hormone (FSH) decrease and blood luteinizing hormone (LH) decrease). For the latter, this may even be questioned as this was from blood samples taken before study initiation, but reported after initiation. No dose dependent effect was observed, however, data are limited and likely do not allow for such an assessment. Nevertheless, any dose dependent adverse effects have not been observed for adults.

Adverse events of special interest were also examined and were not reported for neurological events, neurocognitive events, ALT increased (hepatic disorders), general allergic event or local injection site reactions, or cataract. No serious adverse events or deaths were reported. However, 2 patients developed diabetes mellitus. The first patient was considered nonserious and not treatment related, however, metformin medication was initiated. The second patient developed type 1 DM which occurred 3.5 months after last dose and was not considered treatment related, which can be considered reasonable.

Discontinuations due to adverse events were limited to 2 patients. These events were not considered to be treatment-related, which can be considered reasonable based on the detailed description of these events.

Laboratory values were generally within the normal range and/or non persistent for blood cell counts, electrolytes, metabolic function, fasting glucose, CK levels, renal parameters, liver parameters, hormone levels. Decrease of vitamin E paralleled the decrease in LDL-C, a known observation also from adult data. However, 2 patients had low neutrophils but these were non-serious, although one patient discontinued treatment. Also, a patient with elevated glucose level and the end of the OLE study was reported with type I diabetes as discussed.

In the paediatric study, about 10% of the subjects had anti-drug antibodies (ADA) detected and all were transient responses. These data are in line with adult data. In the ODYSSEY OUTCOMES study 5.5% of patients treated with alirocumab 75 mg and/or 150 mg every 2 weeks (Q2W) had anti-drug antibodies (ADA) detected, most of these were transient responses. Neutralising antibody (NAb) responses were also limited in this study and observed in 0.5% of patients treated with alirocumab, although data are currently limited. Therefore, based on currently limited data, frequencies appear comparable. ADA formation did not appear to impact clinical results.

Overall, the database was very limited to address the safety profile in paediatric patients. Adverse events were generally in line with those observed for adult patients. Serious events were not reported, which is reassuring. It can be reasonably supported that the two events of diabetes mellitus were not considered treatment related, although it is expected that such events of special interest will also be monitored during the phase 3 studies as an effect on glucose and diabetes mellitus has been observed in adults. No

other relevant unexpected laboratory abnormalities were observed. Overall, the safety profile can be acceptable to continue treatment in the phase 3 studies.

10. PRAC advice

N/A

11. Request for supplementary information

11.1. Other concerns

Clinical aspects

PK/Safety

1. A substantial higher exposure for the Q4W 300 mg dose (for patients ≥ 50 kg 8-17 years of age) is observed in comparison to the adult exposure of a similar dose (mean C_{trough} 17880 ng/ml versus 8620ng/ml, respectively). Any possible reasons for this higher exposure should be discussed, and subsequently, whether this should lead to any protocol amendment of the already initiated phase 3 studies in HofH and HeFH paediatric patients.

12. Assessment of the responses to the request for supplementary information

12.1. Other concerns

Clinical aspects

Question 1
A substantial higher exposure for the Q4W 300 mg dose (for patients ≥ 50 kg 8-17 years of age) is observed in comparison to the adult exposure of a similar dose (mean C_{trough} 17880 ng/ml versus 8620ng/ml, respectively). Any possible reasons for this higher exposure should be discussed, and subsequently, whether this should lead to any protocol amendment of the already initiated phase 3 studies in HofH and HeFH paediatric patients.

Summary of the MAH's response
The Marketing Authorisation Holder acknowledges the Rapporteur's observation that a higher exposure of alirocumab was observed in children and adolescents with HeFH treated with the Q4W 300 mg dose, in comparison to the mean exposure observed in adults treated with the same dosing regimen (CHOICE I, R727-CL-1308 study).

Body weight (BW) has been identified as a significant covariate of the exposure to alirocumab in adults and was the only factor used for dose selection in children and adolescents. Compared to adult data, a higher exposure of alirocumab was only observed with the 300 mg Q4W dose regimen in children and adolescents with BW ≥50 kg. At the other doses assessed in children and adolescents with BW≥ 50 kg, i.e., 50 mg Q2W, 75 mg Q2W and 150 mg Q4W, the mean exposure was consistent with that measured at the same dose in adults, which suggests comparable PK behaviors in adults and pediatric patients.

The results observed with the 300 mg Q4W dose should be interpreted with care, as few pediatric patients were treated with this alirocumab dose. Only 5 pediatric patients received 300 Q4W for 12 weeks in study DFI14223, compared to 458 adult patients who received the same dosing regimen in study CHOICE I.

Overall, the mean (SD) BW of the 5 children enrolled in the 300 mg Q4W group was 61.2 (11.9) kg (range: 50 to 78 kg), much lower than the mean BW of the 458 adults who received 300 mg Q4W in the CHOICE I study (mean [SD]: 89.4 [19.9] kg, range: 44 to 171 kg). In order to compare Ctrough values in adult and pediatric populations of similar BW, we compared the mean Ctrough of the 5 children and adolescents who received 300 mg Q4W in study DFI14223 to the mean Ctrough of adult patients with BW between 50 (≥) and 80 kg (<) in the 300 mg Q4W arm of the CHOICE I study.

In the 136 adult patients with PK value available at Week 12 and with a baseline BW between 50 (≥) and 80 kg (<) in the 300 mg Q4W arm of the CHOICE I study, the mean (SD) Ctrough of alirocumab was 13142.1 (9235.0) ng/mL (Table 17). In the 5 children and adolescents who received 300 mg Q4W in study DFI14223, the mean (SD) Ctrough was 17204.0 (9404.2) ng/mL at Week 12 (see previously submitted Study DFI14223 Clinical study report [CSR], Table 72), thus largely overlapping with the Ctrough of adults with BW between 50 (≥) and 80 kg (<) in the 300 mg Q4W arm in study CHOICE I. This overlap is illustrated by the box plots of all Ctrough values collected up to Week 12 at the dose of 300 mg Q4W, in the 5 children and adolescents in the DFI14223 study (Figure 4) and in the 136 adults with BW between 50 (≥) and 80 kg (<) in the CHOICE I study (Figure 5). These PK data confirm the role of BW as a significant covariate of the exposure to alirocumab and point out a large overlap of Ctrough values between adult and pediatric patients of comparable body weights.

From an efficacy view point, the dose of 300 mg Q4W was effective in all 5 pediatric patients of study DFI14223, with mean (LS mean [SE]) LDL-C percent reductions from baseline to Week 8 of -59.2 (11.0) and from baseline to Week 12 of -46.1 (5.3). Importantly, the reduction was not associated with very low LDL-C values (i.e., no patient had 2 consecutive LDL-C value <50 mg/dL). In adult patients with BW between 50 (≥) and 80 kg (<) treated with 300 mg Q4W in the CHOICE 1 study, the mean (LS mean [SE]) LDL-C percent reduction from baseline to Week 12 was -64.1 (1.8) in the modified intent-to-treat (mITT) population (Table 2). These data show that the dose of alirocumab 300 mg Q4W is needed in pediatric patients with BW (≥50 kg) to achieve maximal LDL-C reduction like in adults.

From a safety viewpoint, because alirocumab is a monoclonal antibody (mAb) with a high selectivity towards its target, PCSK9, no "off-target" effects are anticipated. Consistent with the high specificity of alirocumab to inhibit PCSK9, no safety-dose effect or dose exposure was observed in the phase 2/3 clinical studies conducted in adult patients with hypercholesterolemia.

No difference in the safety of the 75 mg or 150 mg Q2W doses was identified in studies pertaining to the initial submission file and subsequently with the 300 mg Q4W dose regimen. Therefore, a higher exposure is unlikely to impact the safety profile in the patients. Treatment-emergent adverse events (TEAEs) reported in the 5 patients enrolled in the 300 mg Q4W group were reviewed in light of the TEAEs reported in the other cohorts of the DFI14223study (see previously submitted Study DFI14223 [CSR, Table 16.2.7.1.2.2.3]) and also in light of the adult data. Review of these TEAEs did not identify any new, unexpected safety findings.

Collectively, these observations show that the 300 mg Q4W dose is the correct dose for further evaluation in children and adolescents with BW ≥ 50 kg for both efficacy and safety. Accordingly, no amendment to the protocol of the ongoing phase 3 study that is using this dosage (EFC14643), is deemed necessary.

The higher exposure of alirocumab observed in the 5 children and adolescents treated with the Q4W 300 mg dose can be attributed to their lower BW as compared to the BW of the overall adult population in the CHOICE I study. Indeed, when we looked at data of adults with BW between 50 (≥) and 80 kg (<), the

exposures at the dose of 300 mg Q4W were within the distribution range of children and adolescents. Within the limits of the small sample, the 300 mg Q4W dose appears to be safe and well-tolerated in children and adolescents with BW >50 kg.

The safety of the 300 mg Q4W dosing regimen will be further characterized in the ongoing EFC14643 study conducted in pediatric patients with HeFH. In this study, safety data are reviewed on a quarterly basis by the Data Monitoring Committee, which at their most recent meeting on December 4th, 2019, recommended to continue the study as planned.

Table 17: Ctrough alirocumab concentrations (ng/mL) over time – Alirocumab 300 mg Q4W – PK population - Patients with baseline BW between 50 and 80 kg - Study R727-CL-1308 (CHOICE I)

Alirocumab concentrations Time-point	SAR236553/REGN727 300 mg (N=144)
Baseline concentrations (ng/mL)	
Baseline	
Number	134
Mean (SD)	0.0 (0.0)
Median	0.0
Min : Max	0 : 0
Ctrough concentrations (ng/mL)	
Week 12	
Number	136
Mean (SD)	13142.1 (9235.0)
Median	1350.0
Min : Max	974 : 52800
Week 20	
Number	124
Mean (SD)	16207.5 (12626.3)
Median	12750.0
Min : Max	1160 : 88500
Week 24	
Number	121
Mean (SD)	14854.6 (11365.4)
Median	11800.0
Min : Max	913 : 71800

Table 18: Percent Change from Baseline in Calculated LDL-C at Week 12 (Alirocumab 300 mg Q4W vs. placebo) : MMRM - On-treatment Analysis - Patients with baseline BW between 50 and 80 kg - Study R727-CL-1308 (CHOICE I)

Calculated LDL Cholesterol	Placebo (N=62)	Alirocumab 300 Q4W/Up 150 Q2W (N=148)
Baseline (mmol/L)		
Number	54	137
Mean (SD)	3263 (1.159)	3.369 (1.017)
Median	3.004	3.212
Min : Max	1.74 : 7.04	1.50 : 6.76
Baseline (mg/dL)		
Number	54	137
Mean (SD)	126.0 (44.7)	130.1 (39.3)
Median	116.0	124.0
Min : Max	67 : 272	58 : 261
Week 12 percent change from baseline (%)		
LS Mean (SE)	3.2 (2.8)	-64.1 (1.8)
LS mean difference (SE) vs placebo		-67.3 (3.3)
		95% CI (-73.9 to -60.7)
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 stratum as per IVRS

related to statin therapy, time point, treatment-by-time point interaction, stratum-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value by time-point interaction.
MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

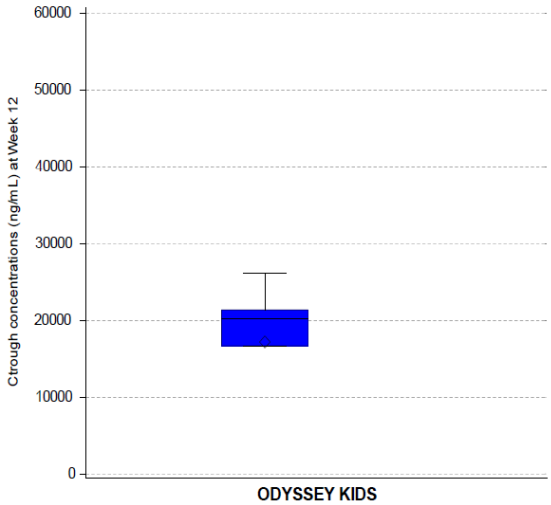


Figure 4: Box plot of Ctrough alirocumab concentrations (ng/mL) to week 12 – Alirocumab 300 mg Q4W - PK population – Patients with baseline BW between 50 and 80 kg - Study DFI14223 (ODYSSEY KIDS)

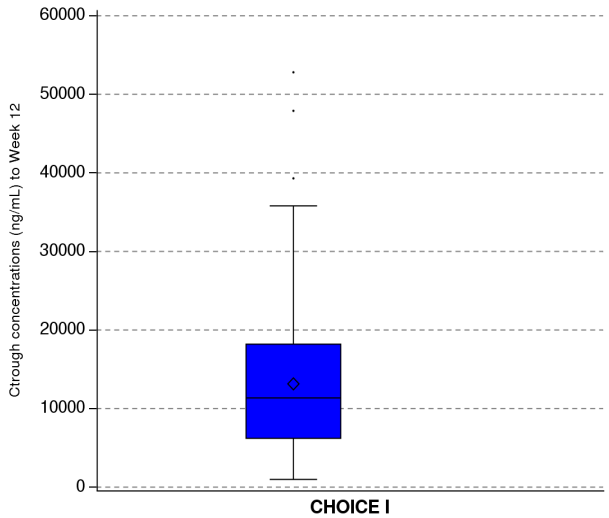


Figure 5: Box plot of Ctrough alirocumab concentrations (ng/mL) to week 12 – Alirocumab 300 mg Q4W - PK population – Patients with baseline BW between 50 and 80 kg – Study R727- CL-1308 (CHOICE I)

Assessment of the MAH's response

The company discussed the possible reasons for the high exposure of alirocumab observed in cohort 4 of Study DFI14223. Cohort 4 contained 5 children and adolescents with body weigght ⩾ 50 kg with the Q4W 300 mg dose. Despite that the results observed with the 300 mg Q4W dose should be interpreted with care, as only 5 pediatric patients were treated with this alirocumab dose, compared to 458 adult patients who received the same dosing regimen in study CHOICE I, it is supported that the higher mean exposure of alirocumab observed in the 5 children and adolescents can likely be mainly attributed to the lower body weight of the children as compared to the body weight of the overall adult population in the CHOICE I study. For example, although the mean Ctrough alirocumab concentration was higher, the exposure range of the 5 pediatric patients treated with alirocumab 300 mg Q4W (Figure 4) was within the exposure range observed for the adult population with BW between 50 and 80mg with the same dose (Figure 5).

Based on the comparison of the efficacy data from children in cohort 4 of study DFI14223 (in pediatric patients with BW (≥50 kg)) and the adult subgroup (50 to 80 kg) from CHOICE I study comparable efficacy of LDL-C reduction is achieved with the alirocumab 300 mg Q4W dose. Although a higher mean exposure is observed it can reasonably be expected that this will likely not emerge to important safety issues, as no exposure dependent adverse events are known with the use of alirocumab. For instance, no difference in safety profile is kwown between different doses previously examined. Based on this consideration, it is acceptable to take this dose further to be evaluated in the ongoing study EFC14643 (as already been done). Further safety data will be generated in study EFC14643 to confirm the safety profile in this paediatric population.

Conclusion

☒ No need to update overall conclusion and impact on benefit-risk balance

13. Attachments

None.