Office of Clinical Pharmacology Review

BLA Number	125559
Link to EDR	\\cdsesub1\evsprod\BLA125559\0359
Submission Dates	5/10/2023
Submission Type	Efficacy supplement (S039)
Brand Name	PRALUENT
Generic Name	Alirocumab
Dosage Form and Strength	Solution; 75 or 150 mg/mL
Route of Administration	Subcutaneous
Proposed Indication	As an adjunct to diet and other LDL-C-lowering therapies for the treatment of pediatric patients aged 8 to 17 years with HeFH to reduce LDL-C.
Applicant	Regeneron Pharmaceuticals, Inc.
OCP Review Team	Tian Zhou, PhD
OCP Final Signatory	Li Li, PhD (Team Leader)

Table of Contents

1. EXECUTIVE SUMMARY

The sponsor submitted a supplemental BLA (sBLA) to BLA 125559 for PRALUENT (alirocumab) to present efficacy, safety, and pharmacokinetic data to support the following indication and dosing regimen in pediatric patients:

Indication:

The proposed indication is as an adjunct to diet and other LDL-C-lowering therapies for the treatment of pediatric patients aged 8 to 17 years with HeFH to reduce LDL-C. The proposed dosing regimen is shown below:

Dosing regimen

- The recommended dosage of PRALUENT for patients with a body weight (BW) less than 50 kg is 150 mg once every 4 weeks (Q4W) administered subcutaneously.
- The recommended dosage of PRALUENT for patients with a BW of 50 kg or more is 300 mg once Q4W administered subcutaneously.
- If the LDL-C response is inadequate, the dosage may be adjusted for patients with a BW less than 50 kg to 75 mg subcutaneously once every 2 weeks (Q2W) or for patients with a BW of 50 kg or more to 150 mg subcutaneously once Q2W.

Alirocumab is a human monoclonal antibody that binds to proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 binds to the LDL receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. LDLR is the primary receptor that clears circulating LDL. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL, thereby lowering LDL-C concentrations. Alirocumab is approved in the United States for the following indications:

- To reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease.
- As adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C.
- As an adjunct to other LDL-C-lowering therapies in adult patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed clinical pharmacology data of BLA 125559 Supplement 39 (Sequence

0359, Supporting Document Number 1444, submitted on 5/10/2023), and found the data acceptable. OCP/DCEP recommends approval of BLA 125559 Sequence 0359 for pediatric patients aged 8 to 17 years with HeFH.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness*	Study DFI14223: This open-label dose-ranging study provides supportive evidence of efficacy and safety. This study evaluated the effect of alirocumab administered Q2W or Q4W on LDL-C levels after 8 weeks of treatment in 4 cohorts of pediatric patients: Cohort 1: BW <50 kg: 30 mg Q2W, BW ≥50 kg: 50 mg Q2W Cohort 2: BW <50 kg: 40 mg Q2W, BW ≥50 kg: 75 mg Q2W Cohort 3: BW <50 kg: 75 mg Q4W, BW ≥50 kg: 150 mg Q4W Cohort 4: BW <50 kg: 150 mg Q4W, BW ≥50 kg: 300 mg Q4W Dose-dependent reduction in LDL-C was observed. Specifically, the mean percent change from baseline in LDL-C for cohorts 1 and 3 were -21.2% and -7.8%, respectively, vs -46.1% and -44.5% for cohorts 2 and 4, respectively. There was no meaningful difference in the safety profile across the cohorts. As the doses in Cohorts 1 and 3 did not result in the expected efficacy for this pediatric population, the higher doses Cohorts 2 and 4 were selected for further evaluation in the Phase 3 study. Study EFC14643: This pivotal, randomized, double-blind, placebo-controlled phase 3 study provides primary evidence of efficacy and safety for alirocumab for the treatment of pediatric patients with HeFH. The open-label treatment period of this study provides long-term efficacy and safety data. • Q2W SC dosing regimen: o BW<50 kg: 40 mg Q2W, with up-titration to 75 mg Q2W as needed o BW ≥50 kg: 75 mg Q2W, with up-titration to 150 mg Q2W as needed • Q4W SC dosing regimen: o BW<50 kg: 150 mg Q4W, with up-titration to 75 mg Q2W as needed o BW ≥50 kg: 300 mg Q4W, with up-titration to 150 mg Q2W as needed In this pivotal Phase 3 trial, comparable steady-state exposure of alirocumab was achieved in pediatric population with BW <50 kg and BW ≥50 kg in all dose cohorts. The marked reduction of free PCSK9 in the serum suggests that alirocumab target saturation was achieved for most pediatric

	participants treated with Q2W and Q4W weight-tiered dose regimens. A trend for further reduction in free PCSK9 was observed for participants who required dose adjustment at week 12, i.e., >20% more participants attained concentrations free PCSK9 concentrations below the limit of quantitation after dose adjustment. In the pediatric Q2W and Q4W cohorts, the LS mean percent change in LDL-C from baseline to Week 24 was -33.6% and -38.2%, respectively. Fewer participants in the Q4W cohort required dose adjustment compared with the Q2W cohort (28.8% vs 44.9%). Due to the lower need for dose-modifications in the Q4W cohort versus Q2W, and a comparable safety profile between the 2 cohorts, the Q4W dose regimens were selected as the proposed doses for pediatric patients with HeFH (see details in the review of Study EFC14643 in Section 4.2 below).
General dosing instructions	• The recommended dosage of PRALUENT for patients with a body weight (BW) less than 50 kg is 150 mg once every 4 weeks (Q4W) administered subcutaneously. • The recommended dosage of PRALUENT for patients with a BW of 50 kg or more is 300 mg once Q4W administered subcutaneously. • If the LDL-C response is inadequate, the dosage may be adjusted for patients with a BW less than 50 kg to 75 mg subcutaneously once every 2 weeks (Q2W) or for patients with a BW of 50 kg or more to 150 mg subcutaneously once Q2W.
Dosing in patient subgroups (intrinsic and extrinsic factors)	As mentioned above, the proposed dosing is based on body weight of pediatric patients. The applicant is not proposing specific dosing recommendations for other pediatric patient subgroups such as age, gender, race.
Bridge between the to-be- marketed and clinical trial formulations/present ations	Commercial formulation of PRALUENT was used in the phase 2 and phase 3 trials in pediatric patients. Comparability between two drug delivery devices: • The Applicant conducted the pivotal Phase 3 study and the Phase 2 dose-finding study in pediatric patients using the pre-filled syringe (PFS) and proposes to use the currently approved pre-filled autoinjector pen (DAI-PFP) in pediatric patients. • Based on the original BLA Clinical Pharmacology review (Reference ID: 3772547, Table 22), both PFS and pre-filled autoinjector pen (DAI-PFP) have been used in the pivotal clinical trials in adults. In addition, PK cross-study comparison shows a similar alirocumab exposure between two drug device presentations (see details in Section 3.3.4 below). Therefore, it appears that a bridging study is not needed to support the use of DAI-PFP in the pediatric patients. We defer to the

	review team on the assessment of the human factor study.

* The applicant also conducted an additional pediatric study (EFC14660) in the alirocumab clinical development program and submitted the data of this study in the current supplement. It was conducted in pediatric patients with homozygous familial hypercholesterolemia (HoFH). Patients with HoFH have higher total cholesterol levels than patients with HeFH. The dosing regimen of this study was 75 mg Q2W and 150 mg Q2W, and modest overall effect on LDL-C was observed. The applicant states that the data from this study will not provide supportive evidence of efficacy for the proposed indication, but will provide supportive evidence of safety for the use of alirocumab in the pediatric population. Therefore, the applicant submitted this study in the current supplement for completeness.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Systemic serum total alirocumab concentrations at steady state in pediatric patients with HeFH are consistent with those observed in adult patients with HeFH (see details from the Phase 3 study DFI14223 below).

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The applicant is proposing the following dosing regimen:

In pediatric patients with HeFH from 8 to 17 years of age, the recommended dose (administered subcutaneously) is based on body weight (BW):

- If BW < 50 kg: 150 mg once every 4 weeks (Q4W).
- If BW ≥ 50 kg: 300 mg Q4W.
- If the LDL-C response is inadequate, the dosage may be adjusted:
  - if BW < 50 kg: adjust to 75 mg Q2W;
  - if BW ≥ 50 kg: adjust to 150 mg Q2W.

Reviewer's assessment is shown below:

Phase 2 dosing-finding study DFI14223

The Phase 2 dosing-finding study DFI14223 evaluated the effect of alirocumab administered Q2W or Q4W dosing regimens on LDL-C levels after 8 weeks of treatment in 4 cohorts of pediatric patients:

Cohort 1: BW <50 kg: 30 mg Q2W, BW ≥50 kg: 50 mg Q2W
Cohort 2: BW <50 kg: 40 mg Q2W, BW ≥50 kg: 75 mg Q2W
Cohort 3: BW <50 kg: 75 mg Q4W, BW ≥50 kg: 150 mg Q4W
Cohort 4: BW <50 kg: 150 mg Q4W, BW ≥50 kg: 300 mg Q4W

Dose-dependent increase in total alirocumab concentration, total PCSK9 and decrease in free PCSK9 were observed. In particular, highest total alirocumab concentrations (C_{trough}), total PCSK9 concentrations and decrease in free PCSK9 were observed in Cohort 4. The LDL-C reduction (mean percent change from baseline) in cohorts 1 and 3 were -21.2% and -7.8%, respectively, vs -46.1% and -44.5% for cohorts 2 and 4, respectively. There was no meaningful difference in the safety profile across the cohorts.

When comparing the results between Cohort 3 and Cohort 2 for the patient group with BW ≥50 kg, the 75 mg Q2W regimen appeared to result in greater alirocumab concentration (C_{trough}), total PCSK9 and decrease in free PCSK9 compared to the 150 mg Q4W, although the total drug amounts received over the 4-weeks period are the same between these two regimens (see Figures 4.1 and 4.4 below in the review of study DFI14223).

Based on results from the Phase 2 study, higher doses used in Cohorts 2 and 4 (as compared to the lower doses used in Cohorts 1 and 3) were selected for the Phase 3 study. In addition, it also provides supportive evidence that if inadequate response is observed, up-titration from the Q4W regimen to Q2W regimen while maintaining the same drug amount received during the 4-week treatment period may further improve efficacy.

Phase 3 pivotal study EFC14643

The Phase 3 pivotal study EFC14643 provides primary evidence of efficacy and safety for alirocumab for the treatment of pediatric patients with HeFH. The open-label treatment period of this study provides long-term efficacy and safety data.

- Q2W SC dosing regimen:
  - BW<50 kg: 40 mg Q2W, with up-titration to 75 mg Q2W as needed
  - BW ≥50 kg: 75 mg Q2W, with up-titration to 150 mg Q2W as needed

- Q4W SC dosing regimen:
  - BW<50 kg: 150 mg Q4W, with up-titration to 75 mg Q2W as needed
  - BW ≥50 kg: 300 mg Q4W, with up-titration to 150 mg Q2W as needed

In this Phase 3 pivotal trial, steady-state of alirocumab concentration was reached at or before Week 8 for all the dosing regimens. Comparable steady-state drug exposure was achieved in pediatric population with BW <50 kg and BW ≥50 kg after administration of alirocumab 40 mg or 75 mg Q2W, respectively. Similar findings were observed after administration of alirocumab 150 mg and 300 mg Q4W (for corresponding BW <50 kg and ≥50 kg). Concentration-time profiles for free PCSK9 were comparable across BW tiers of <50 kg and ≥50 kg within each dose cohort.

Total PCSK9 concentration was increased after the administration of alirocumab and reached a plateau at or before Week 8. Administration of alirocumab resulted in a decrease in free PCSK9 concentration at or before Week 8 that was maintained up to Week 24. The mean free PCSK9 concentrations were reduced at week 8 and were generally at or below the LLOQ (31 ng/mL) at week 12 which was maintained until week 24. The marked reduction of free PCSK9 in the serum suggests that alirocumab target saturation was achieved for most pediatric participants treated

with Q2W and Q4W weight-tiered dose regimens. A trend for further reduction in free PCSK9 was observed for participants who required dose adjustment at week 12, i.e., 20% more participants attained concentrations free PCSK9 concentrations below the limit of quantitation after dose adjustment. This is consistent with the observation in the adult clinical trials, where dose adjustment from Q4W regimen to a Q2W regimen may provide additional treatment effect if alirocumab concentrations are insufficient to saturate PCSK9, allowing clinicians more flexibility in clinical practice to address the individual needs of their patients.

In the pediatric Q2W and Q4W cohorts, the LS mean percent change in LDL-C from baseline to Week 24 was -33.6% and -38.2%, respectively. Fewer participants in the Q4W cohort required dose adjustment compared with the Q2W cohort (28.8% vs 44.9%, see the review of study EFC14643 in Section 4.2 below). Due to the lower need for dose-modifications in the Q4W cohort versus Q2W, and a comparable safety profile between the 2 cohorts, the Q4W dose regimens were selected as the proposed doses for pediatric patients with HeFH. Also, a once-monthly dose regimen (Q4W) is easier for patients and their caregivers to manage than Q2W dosing and may improve patient convenience and flexibility. Additionally, a numerically greater proportion of alirocumab-treated participants in the Q4W cohort compared to the Q2W cohort consistently achieved guideline-recommended LDL-C targets in the responder analyses for <130 mg/dL (76.3% vs 73.3%), <110 mg/dL (67.2% vs 57.2%), ≥30% reduction (72.5% vs 66.7%), and ≥50% reduction (32.4% vs 21.6%) (see the review of study EFC14643 in Section 4.2 below).

Overall, based on the abovementioned data obtained from the Phase 2 and Phase 3 studies, the reviewer deems that the proposed dosing regimen is acceptable.

2.2.2 Therapeutic individualization

As mentioned above, the proposed dosing is based on body weight of pediatric patients. The applicant is not proposing specific dosing recommendations for other patient subgroups such as age, gender, race.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

On first page of label, in Section Dosage and Administration, add the following:

As an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 8 years and older with HeFH to reduce LDL-C.

In Section 2.2, Recommended Dosage in Pediatric Patients aged 8 years and older with HeFH, add the following:

- The recommended dosage of PRALUENT for patients with a body weight less than 50 kg is 150 mg once every 4 weeks administered subcutaneously.
  - If the LDL-C lowering response is inadequate, the dosage may be adjusted to 75 mg subcutaneously once every 2 weeks *[see Dosage and Administration (2.4)]*.
- The recommended dosage of PRALUENT for patients with a body weight of 50 kg or more is 300 mg once every 4 weeks administered subcutaneously.
  - If the LDL-C lowering response is inadequate, the dosage may be adjusted to 150 mg subcutaneously once every 2 weeks *[see Dosage and Administration (2.4)]*.
- Assess LDL-C when clinically appropriate. The LDL-lowering effect of PRALUENT may be measured as early as 4 weeks after initiation.

In Section 8.4, Pediatric Use, add the following:

The safety and effectiveness of PRALUENT as an adjunct to diet and other LDL-C-lowering therapies for the treatment of HeFH have been established in pediatric patients aged 8 years and older. Use of PRALUENT for this indication is based on data from a 24-week, randomized, placebo-controlled, double-blind trial in pediatric patients with HeFH. In the trial, 101 patients received PRALUENT 150 or 300 mg (based on body weight) subcutaneously every 4 weeks or 40 (40 mg is not an approved dose), 75, or 150 mg (based on body weight and LDL-C response) subcutaneously every 2 weeks and 52 patients received placebo; 26 patients (17%) were 8 to 9 years of age *[see Adverse Reactions (6.1)* and *Clinical Studies (14)]*.

The safety and effectiveness of PRALUENT have not been established in pediatric patients with HeFH who are younger than 8 years of age or in pediatric patients with other types of hyperlipidemia.

In Section 12.3, Pharmacokinetics, add the following:

Pediatric Patients

The pharmacokinetics of alirocumab were evaluated in 140 pediatric patients aged 8 to 17 years with HeFH. The steady-state mean C_{trough} was reached at or before week 8 (first PK sampling during repeated dosing) with recommended dosing regimen *[see Dosage and Administration (2.2)]*.

In Section 12.6, Immunogenicity, add the following:

In pediatric patients aged 8 to 17 years with HeFH (Trial 12), the incidence of ADA for patients treated with PRALUENT was 3.1% (3/98) with a median treatment exposure of 24 weeks in the Q2W cohort and 22.9 weeks in the Q4W cohort. Of the 3 pediatric patients who developed ADA, no one tested positive for NAb.

There was no identified clinically significant effect of ADA on pharmacokinetics, pharmacodynamics, safety, or effectiveness of PRALUENT in pediatric patients over the treatment duration.

Reviewer's note: See the review of individual studies DFI14223 and EFC14643 in Section 4.2 below for details of immunogenicity assessments. The information about ADA and NAb development in clinical studies are summarized in Tables 3 and 4 in Section 4.2 below.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

3.2 General Pharmacology and Pharmacokinetic Characteristics

For the general clinical pharmacology information of alirocumab, see Dr. Sang Chung's review of alirocumab's original BLA 125559 submission at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125559Orig1s000ClinPharmR.pdf.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The clinical pharmacology information of the pivotal Phase 3 study (EFC14643) and the Phase 2 dosing-finding study DFI14223 provide supportive evidence of effectiveness for alirocumab as an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 8 years and older with HeFH to reduce LDL-C. See Section 2.2.1 above Reviewer's assessment of proposed dosing regimen for details.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen of 150 mg Q4W for BW < 50 kg or 300 mg Q4W for BW ≥ 50 kg with up-titration to 75 mg Q2W (BW < 50 kg) or 150 mg Q2W (BW ≥ 50 kg) is appropriate for the proposed indication from a clinical pharmacology perspective. See Section 2.2.1 above Reviewer's assessment of proposed dosing regimen for details.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic and extrinsic factors?

The applicant is not proposing specific dosing recommendations for other pediatric patient subgroups such as age, gender, race.

3.3.4 Is a bridging study needed for the proposed drug delivery device?

The Applicant conducted the pivotal Phase 3 study and the Phase 2 dose-finding study in pediatric patients using the pre-filled syringe (PFS) and proposes to use the currently approved pre-filled autoinjector pen (DAI-PFP) in pediatric patients.

The sponsor states the following to support the comparability between the two drug delivery devices:
"*In addition to the comparable design and performance of the PFS, PFS-S, and DAI-PFP, in vivo PK comparability between the PFS and DAI-PFP in adults and in vivo PK comparability between adults and children when administered alirocumab by PFS supports use of the DAI-PFP in pediatric patients. Pharmacokinetics comparability between the PFS presentation and the DAIPFP was demonstrated in the original BLA supporting the use of DAI-PFP in adults (BLA 125559 [SN0000] Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods). The pharmacokinetics of alirocumab are also comparable across devices between pediatrics and adult patients. Alirocumab trough concentrations were generally comparable between pediatrics and adults at the administered doses.*"

The reviewer checked the original BLA Clinical Pharmacology review (Reference ID: 3772547, Table 22), and found that the presentations including formulations (75 and 150 mg/mL) and device (prefilled syringe and pre-filled pen) have been used in the pivotal clinical trials supporting the original BLA approval in adult patients. Therefore, there is no need for comparability studies between the PFS and approved DAI-PFP. PK cross-study comparison was made to evaluate the comparability between two final presentations in clinical trials as a supplemental data, and it seems PK was comparable (see Table 1 below).

Table 1. Alirocumab steady state exposures at 150 mg by drug presentation after 150 mg Q2W repeated administration to patients from phase 3 studies – Study POH0377 (Mean (CV%) [Median])

Drug presentation	Alirocumab 150 mg		
	N	Cmax (mg/L)	AUC0-366 (mg/L*h)
Prefilled syringe	1437	18.0 (46.6%) [16.5]	5030 (53.6%) [4470]
Prefilled pen	203	19.0 (46.7%) [18.3]	5390 (52.4%) [5030]

(Source: Table 22 in abovementioned Clinical Pharmacology review)

Therefore, it appears that no bridging study is needed to support the use of DAI-PFP in pediatric patients.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance for the Phase 2 and Phase 3 studies

The applicant used validated assays for the quantitation of total alirocumab, total PCSK9, free PCSK9, anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) in serum in the Phase 2 dosing-finding study and Phase 3 pivotal study. These validated assays are documented in the following standard operating procedures (SOPs):

BMP-PCL2914 Quantitative Measurement of Total REGN727 in Human Serum

BMP-PCL2903 Quantitative Measurement of Free PCSK9 in Human Serum

BMP-PCL2935 Quantitative Measurement of Total PCSK9 in Human Serum

BMP-PCL2988 Detection of Anti-REGN727 Antibodies in Human Serum

BMP-PCL3022 Detection of Neutralizing Anti-REGN727 Antibodies in Human Serum

The same bioanalytical methods had been used in clinical studies in adults and were deemed acceptable under the original BLA review (e.g., Phase 3 study R727-CL-1216 for adult population supporting the initial approval of the BLA) (see Module 5.3.5.1. Sequence 0172. Bioanalytical Report of Study R727-CL-1216).

4.2 Clinical PK and/or PD Assessments

Study DFI14223

Study DFI14223 was an open-label, sequential, repeated dose-finding study to evaluate the efficacy and safety of alirocumab in children and adolescent patients with HeFH, aged 8 to 17 years, followed by an extension phase. The primary objective, study design, dosing regimen (N=5-6 for each cohort), duration of treatment and study population are listed in Table 2 below.

Table 2. Summary of Study DFI14223

Study Identifier, Location of Study Report, Study Status, Type of Report	Primary Objective	Study Design, Type of Control, Duration of Treatment	Test Product(s), Dosage Regimen, Route of Administration	Number of Participants	Healthy Subjects or Diagnosis of Patients
DFI14223 Phase 2 Module 5.3.4.2 Completed Final CSR	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 on optimal stable daily dose of statin therapy ± other LMTs	Open-label, dose-finding, sequential group, multi-national, multi-center study OLDFI Period: 8 weeks (cohorts 1, 2 and 3); 12 weeks (cohort 4) OLE Period: treatment with alirocumab continued until at least 10 weeks before the patient's entry into the pediatric heFH Phase 3 study (EFC14643)	SC Alirocumab Injection: • Cohort 1: 30 mg Q2W SC if BW <50 kg and 50 mg Q2W SC if BW ≥50 kg. • Cohort 2: 40 mg Q2W SC if BW <50 kg and 75 mg Q2W SC if BW ≥50 kg. • Cohort 3: 75 mg Q4W SC if BW <50 kg and 150 mg Q4W SC if BW ≥50 kg. • Cohort 4: 150 mg Q4W SC if BW <50 kg and 300 mg Q4W SC if BW ≥50 kg.	OLDFI: 42 OLE: 41	Patients 8 to 17 years of age with HeFH

BW: Body weight; HeFH: Heterozygous familial hypercholesterolemia; LDL-C: Low density lipoprotein-Cholesterol; LMT: Lipid modifying therapies; OLDFI: Open-label dose finding; OLE: Open-label extension; Q2W: Every 2 weeks; Q4W: Every 4 weeks; SC: Subcutaneous

Source: Module 5.2. Tabular Listing of all Clinical Studies – Pediatric HeFH. Figure 1.

The applicant's rationale for dose and dose regimen selection was initially based on the assumption of a similar exposure-response in the pediatric population as that observed in the adult clinical trials. From this perspective, using allometric scaling from the adult population pharmacokinetic model (BLA 125559 [SN0000] Module 2.7.2), the applicant simulated a number of weight-tiered dose regimens across the body weight range of the intended pediatric population.

From these simulations, the applicant predicted that the 4 dose cohorts across 2 BW tiers (ie, BW <50 kg and ≥50 kg) included in the phase 2 dose-finding study (DFI14223) would have comparable exposure across the 4 dose cohorts as well as to that observed in the adult population.

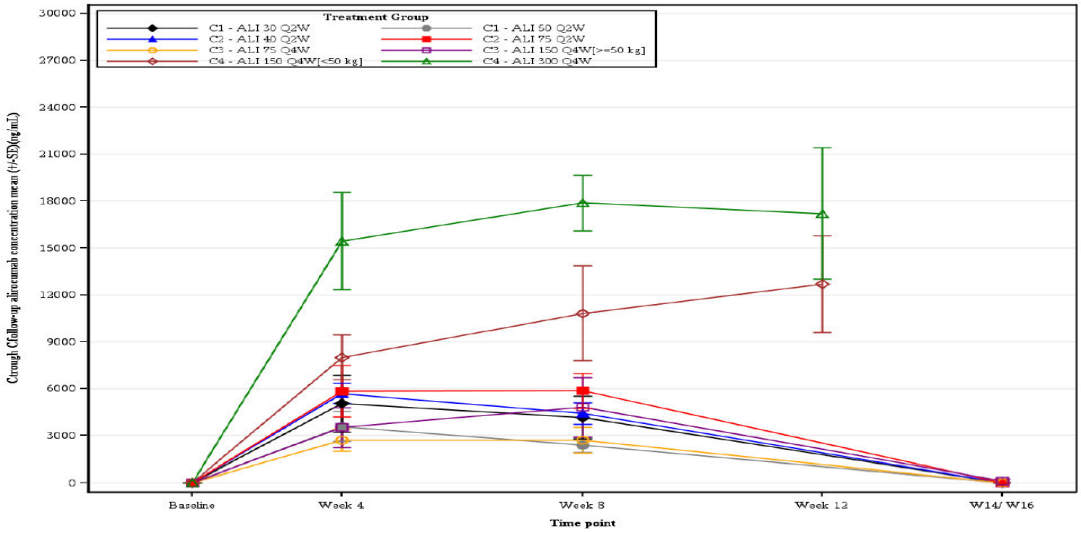
Samples for the evaluation of alirocumab, total and free PCSK9 concentrations, and immunogenicity were collected at the time points specified in the protocol.

Serum total alirocumab concentrations:

Pharmacokinetic samples were collected from all patients at baseline in the PK population (42 patients) and from almost all patients at Week 4 and Week 8. For Cohort 4, samples were also collected at Week 10 and 12 (n=7 and n=10, respectively)

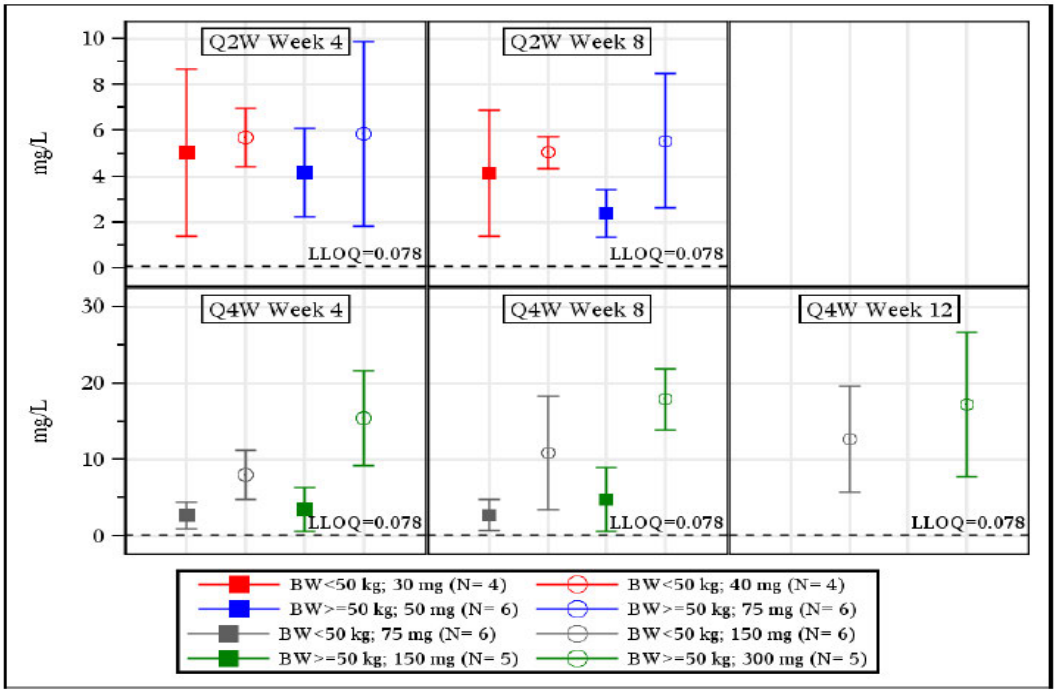
Mean concentrations of total alirocumab increased with dose for both Q2W and Q4W dosing regimens, as shown in Figure 4.1. The highest mean alirocumab C_{trough} were observed in Cohort 4, at 150 mg Q4W in patients with BW <50 kg and 300 mg Q4W in patients with BW ≥50 kg (Figure 4.1). Mean alirocumab concentrations achieved steady state by week 4 (Figure 4.2).

Figure 4.1 - C_{trough} and C_{follow}-up alirocumab concentrations mean (+/-SE) (ng/mL) over time



Source: Module 5.3.4.2. Clinical Study Report- DFI14223. Figure 8.

Figure 4.2. Mean (SD) Alirocumab C_{trough}, in Pediatric Patients with HeFH by Treatment (Study DFI14223)



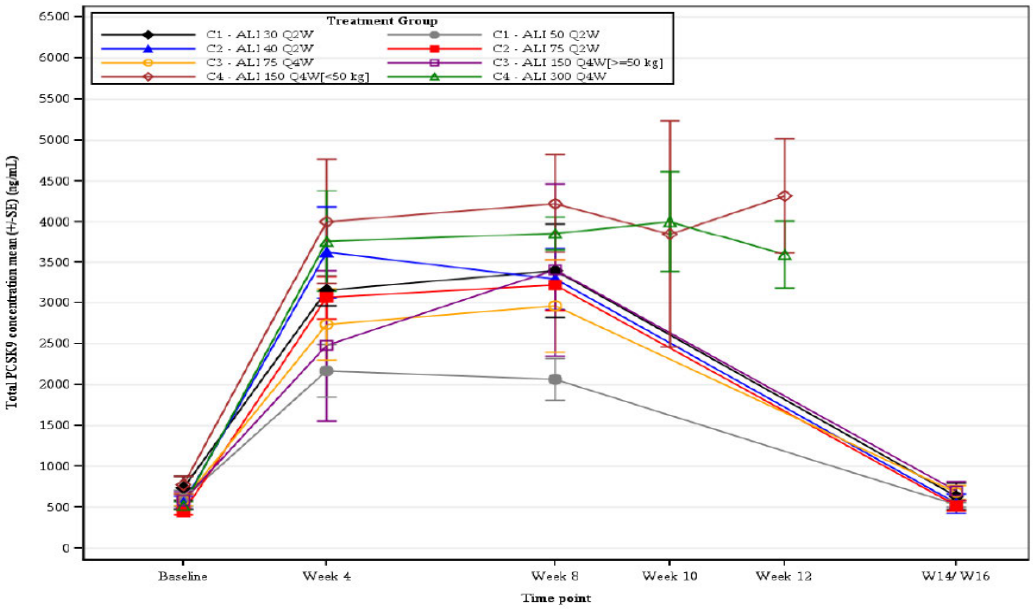
BW, body weight; C_{trough}, trough serum concentration; HeFH, heterozygous familial hypercholesterolemia; LLOQ, lower limit of quantification; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation.
Source: Module 5.3.4.2 DFI14223 CSR Tables 70 to 72.

Source: Module 2.7.2. Summary of Clinical Pharmacology Studies. Figure 3 (graphed using data from Module 5.3.4.2 DFI14223 CSR Tables 70 to 72).

Total PCSK9 concentrations:

As shown in Figure 4.3 below, a dose-dependent increase in total PCSK9 concentration from baseline to Week 48 has been observed with the administration of alirocumab. The highest increase in total PCSK9 was observed in Cohort 4, at 150 mg Q4W in patients with BW <50 kg and 300 mg Q4W in patients with BW ≥50 kg. In the post-treatment follow-up period for Cohorts 1 to 3, total PCSK9 concentrations returned approximately to baseline levels at the end of this period.

Figure 4.3 - Total PCSK9 concentration mean (+/-SE) (ng/mL) over time

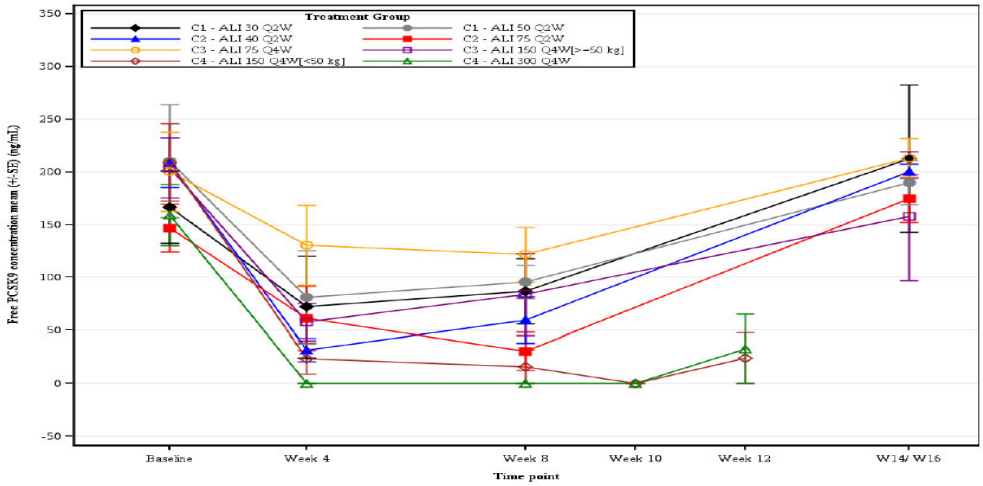


Source: Module 5.3.4.2. Clinical Study Report- DFI14223. Figure 9.

Free PCSK9 concentration

As shown in Figure 4.4 below, consistent with the total PCSK9 observations, administration of alirocumab resulted in a decrease in free PCSK9 concentration from Week 4. This decrease is dose-dependent, the more 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. Free PCSK9 concentrations returned approximately to baseline levels at the end of the post-treatment follow-up period for Cohorts 1 to 3 (Figure 4.4).

Figure 4.4 - Free PCSK9 concentration mean (+/-SE) (ng/mL) over time

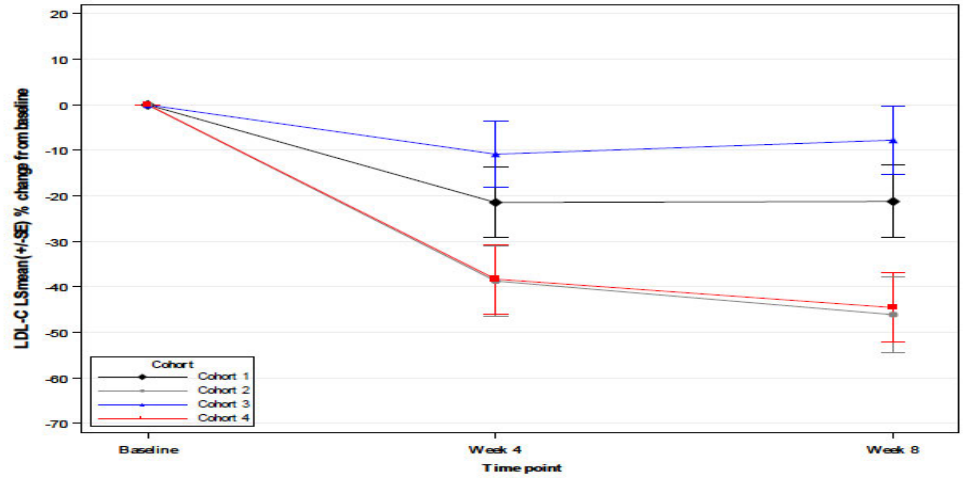


Source: Module 5.3.4.2. Clinical Study Report- DFI14223. Figure 10.

PK/PD relationship:

Consistent with the dose dependent decrease of free PCSK9 concentrations observed at the first post-baseline assessment, a dose dependent LDL-C reduction from baseline was achieved from Week 4. The greatest decrease in free PCSK9 from baseline, with level below or close to the limit of quantification, was observed in Cohort 4, for both BW groups, while the greatest reductions in LDL-C from baseline was observed in Cohorts 2 and 4. The LS mean percent change in LDL-C at week 8 for the lower dose cohorts 1 and 3 were -21.2% and -7.8%, respectively, vs -46.1% and -44.5% for the higher dose cohorts 2 and 4, respectively (Figure 4.5).

Figure 4.5 - Calculated LDL-C: LS mean (+/-SE) percent change from baseline: Time profile (without adjustment on baseline) - On-treatment analysis - OLDFI period



Source: Module 5.3.4.2. Clinical Study Report- DFI14223. Figure 6.

Immunogenicity evaluation:
Out of 42 alirocumab-treated participants, 4 participants developed anti-drug antibodies (ADAs) and also tested positive for neutralizing antibodies (NAbs). 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. No effect of the low level of immunogenicity on the pharmacokinetic profile was observed in this study. In addition, no safety concern related to positive anti-drug antibodies (ADAs) was raised.

The two tables below (Tables 3 and 4) summarize ADA Status, ADA Category and Maximum Titer Category of Participants in Pediatric Studies DFI14223, EFC14643, and EFC14660 by Treatment Group:

Table 3. Summary of ADA information in three clinical studies (DFI14223, EFC14643, and EFC14660)

ADA Status	DFI14223 Alirocumab n (%)	EFC14643 Placebo n (%)	EFC14643 Q2W Dose Regimen n (%)	EFC14643 Q4W Dose Regimen n (%)	EFC14643 Q2W and Q4W Dose Regimen n (%)	EFC14660 n (%)
Total ADA Patients	42 (100%)	51 (100%)	48 (100%)	50 (100%)	98 (100%)	18 (100%)
Negative	37 (88.1%)	50 (98.0%)	44 (91.7%)	46 (92.0%)	90 (91.8%)	18 (100%)
Pre-existing	1 (2.4%)	0	1 (2.1%)	4 (8.0%)	5 (5.1%)	0
Treatment Boosted Response	0	0	0	0	0	0
Treatment Emergent Response	4 (9.5%)	1 (2.0%)	3 (6.3%)	0	3 (3.1%)	0
Persistent	1 (2.4%)	0	0	0	0	0
Transient	3 (7.1%)	1 (2.0%)	3 (6.3%)	0	3 (3.1%)	0
Indeterminate	0	0	0	0	0	0
Maximum Titer						
Low (<1,000)	4 (9.5%)	1 (2.0%)	3 (6.3%)	0	3 (3.1%)	0
Moderate (1,000 to 10,000)	0	0	0	0	0	0
High (>10,000)	0	0	0	0	0	0
Time to onset of treatment-emergent ADA response (week)						
N	4	1	3	0	3	0
Mean (SD)	11.7 (4.11)	67.3 (0)	16.4 (6.58)	. (---)	16.4 (6.58)	. (---)
Median	11.3	67.3	13.1	--	13.1	--
Q1 : Q3	8.21 : 15.2	67.3 : 67.3	12.1 : 24.0		12.1 : 24.0	
Min : Max	8.14 : 16.1	67.3 : 67.3	12.1 : 24.0		12.1 : 24.0	

ADA, anti-drug antibody; Max, maximum; Min, minimum; n, number of participants for descriptive statistics; Q, quartile; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation.
Note: Patients enrolled in the phase 2 study (DFI14223) were eligible to participate in the phase 3 study (EFC14643) after study completion.

Source: Module 2.7.2. Summary of Clinical Pharmacology Studies. Table 4 (made by applicant using data from Module 5.3.4.2 DFI14223 CSR Tables 76 and 77; Module 5.3.5.1 EFC14643 CSR Appendix 16.2.5 Dosing and Drug Concentration Data, Listings 16.2.5.4.2.1 and 16.2.5.4.2.3.1; Module 5.3.5.2 EFC14660 CSR Appendix 16.2.5 Compliance and Drug Concentration Data, Listing 16.2.5.4).

Table 4. Summary of NAb information in three clinical studies (DFI14223, EFC14643, and EFC14660)

NAb Status	DFI14223 Alirocumab n (%)	EFC14643 Placebo n (%)	EFC14643 Q2W Dose Regimen n (%)	EFC14643 Q4W Dose Regimen n (%)	EFC14643 Q2W and Q4W Dose Regimen n (%)	EFC14660 n (%)
Total ADA Patients	42 (100%)	51 (100%)	48 (100%)	50 (100%)	98 (100%)	18 (100%)
NAb Status						
NAb Negative	38 (90.5%)	51 (100%)	48 (100%)	50 (100%)	98 (100%)	18 (100%)
NAb Positive	4 (9.5%)	0	0	0	0	0

ADA, anti-drug antibody; n, number of participants for descriptive statistics; NAb, neutralizing antibody; Q2W, every 2 weeks; Q4W, every 4 weeks.
Note: Patients enrolled in the phase 2 study (DFI14223) were eligible to participate in the phase 3 study (EFC14643) after study completion.
Source: Module 5.3.4.2 DFI14223 CSR Tables 76 and 77; Module 5.3.5.1 EFC14643 CSR Appendix 16.2.5 Dosing and Drug Concentration Data, Listings 16.2.5.4.2.1 and 16.2.5.4.2.3.1; Module 5.3.5.2 EFC14660 CSR Appendix 16.2.5 Compliance and Drug Concentration Data, Listing 16.2.5.4.

Source: Module 2.7.2. Summary of Clinical Pharmacology Studies. Table 5 (made by applicant using data from Module 5.3.4.2 DFI14223 CSR Tables 76 and 77; Module 5.3.5.1 EFC14643 CSR Appendix 16.2.5 Dosing and Drug Concentration Data, Listings 16.2.5.4.2.1 and 16.2.5.4.2.3.1; Module 5.3.5.2 EFC14660 CSR Appendix 16.2.5 Compliance and Drug Concentration Data, Listing 16.2.5.4)

Conclusions:

All patients were treated with alirocumab and completed the OLDFI treatment period. All patients except one were included in the OLE period.

Mean concentrations of total alirocumab increased with dose for both Q2W and Q4W dosing regimens. Alirocumab Ctrough were comparable across BW tiers within each cohort. Dose-dependent increase in total PCSK9 and decrease in free PCSK9 and LDL-C were observed.

Overall, the results showed a positive benefit/risk profile with alirocumab in this pediatric population. The highest effect on LDL-C reduction was observed in Cohort 2 (40 mg Q2W for BW <50 kg and 75 mg Q2W for BW ≥50 kg) and in Cohort 4 (150 mg Q4W for BW <50 kg and 300 mg Q4W for BW ≥50 kg).

The larger observed reductions in free PCSK9 concentrations and LDL-C for the higher dose cohorts 2 and 4, compared to cohorts 1 and 3, respectively, indicated that these higher dose regimens merited further investigation in a randomized phase 3 study.

Study EFC14643

Study EFC14643 was a randomized, 24-week double-blind, placebo-controlled, parallel group, multi-national, multi-center study followed by an OLTP of 80 weeks (total study duration: 104 weeks) to assess the efficacy and safety of alirocumab on top of stable lipid modifying therapy (LMT) background treatment(s) in children and adolescents with HeFH.

The primary objective, study design, dosing regimen (N=5-6 for each cohort) and study population are listed in Table 5 below.

Table 5. Summary of Study EFC14643

Study Identifier, Location of Study Report, Study Status, Type of Report	Primary Objective	Study Design, Type of Control, Duration of Treatment	Test Product(s), Dosage Regimen, Route of Administration	Number of Participants	Healthy Subjects or Diagnosis of Patients
EFC14643 Phase 3 Module 5.3.5.1 Completed Final CSR	To evaluate the efficacy of alirocumab administered Q2W and Q4W versus placebo on LDL-C levels in patients with HeFH 8 to 17 years of age on optimal stable daily dose of statin therapy ± other LMTs	Phase 3, randomized, double-blind, placebo-controlled, parallel group, multi-national, multi-center study followed by an open-label treatment period DBTP: 24 weeks OLTP: 80 weeks	DBTP (24 weeks): Q2W SC dosing regimen (alirocumab [N=49], placebo [N=25]): • BW<50 kg: 40 mg Q2W, with up-titration to 75 mg Q2W as needed • BW ≥50 kg: 75 mg Q2W, with up-titration to 150 mg Q2W as needed Q4W SC dosing regimen (alirocumab [N=52], placebo [N=27]): • BW<50 kg: 150 mg Q4W, with up-titration to 75 mg Q2W as needed • BW ≥50 kg: 300 mg Q4W, with up-titration to 150 mg Q2W as needed OLTP (80 weeks): Continued dosing regimen of alirocumab, adjustment possible (N=145)	DBTP: 153 OLTP: 145	Patients 8 to 17 years of age with HeFH

BW: Body weight; DBTP: Double-blind treatment period; HeFH: Heterozygous familial hypercholesterolemia; LDL-C: Low density lipoprotein-Cholesterol; LMT: Lipid modifying therapies; OLTP: Open-label treatment period; Q2W: Every 2 weeks; Q4W: Every 4 weeks; SC: Subcutaneous

Source: Module 5.2. Tabular Listing of all Clinical Studies – Pediatric HeFH. Figure 2.

The applicant's rationale for dose selection is based on the results from Phase 2 dose-finding study DFI14223. Given the favorable results observed for cohort 2 (40 mg/75 mg Q2W) and cohort 4 (150 mg/300 mg Q4W), these dose regimens were selected as the 2 weight-tiered doses, with an optional dose up-titration, in the pediatric phase 3 study EFC14643.

In the DBTP of this study, participants in low and high BW categories (<50 kg and ≥50 kg, respectively) were randomized to 1 of 2 dose cohorts, designated as Q2W and Q4W. In the Q2W dose cohort (N=49), participants with BW <50 kg initially received 40 mg Q2W and participants with BW ≥50 kg initially received 75 mg Q2W. In the Q4W dose cohort (N=52), participants with BW <50 kg initially received 150 mg Q4W and participants with BW ≥50 kg initially received 300 mg Q4W. Alirocumab was provided in PFSs with finger grip, replaced by PFSs with safety system once available.

At week 12, participants who achieved the LDL-C target (week 8 LDL-C was <110 mg/dL) continued treatment at the same dose. Participants who did not achieve their specific LDL-C target

had their dose adjusted at week 12 from 40 mg Q2W to 75 mg Q2W (BW <50 kg) and from 75 mg Q2W to 150 mg Q2W (BW ≥50 kg), or had their dosing interval reduced from 150 mg Q4W to 75 mg Q2W (BW <50 kg) and from 300 mg Q4W to 150 mg Q2W (BW ≥50 kg).

A total of 153 participants were randomized to receive alirocumab or placebo intervention. Of these, 74 participants were enrolled in the Q2W dosing regimen cohort (49 received alirocumab and 25 received placebo) and 79 participants were enrolled in the Q4W dosing regimen cohort (52 received alirocumab and 27 received placebo). A total of 29 participants (39.2%) in the Q2W cohort and 3 participants (3.8%) in the Q4W cohort previously participated in DFI14223 (Phase 2) study. A total of 145 participants entered the OL period.

No PK evaluation was performed during the OL treatment period. The PK results were obtained from DB treatment period.

Serum total alirocumab concentrations

Among participants in the alirocumab groups, a total of 49 participants (25 with BW <50 kg and 24 with BW ≥50 kg) from the Q2W cohort and 48 participants (19 with BW <50 kg and 29 with BW ≥50 kg) from the Q4W cohort had at least one PK sample collected and assessed during the DB treatment period.

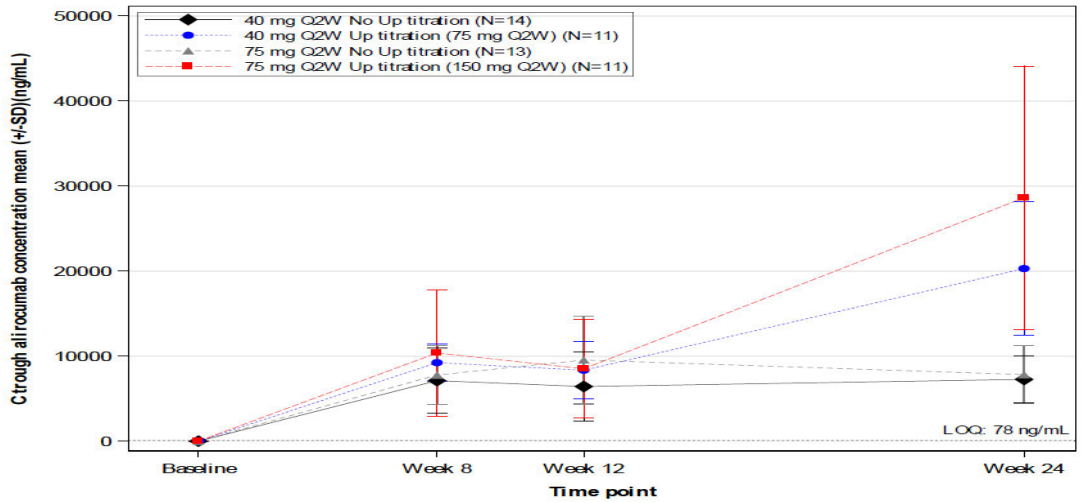
The steady state in mean alirocumab Ctrough appears to be reached at or before Week 8 in participants receiving 40 mg or 75 mg Q2W, and 150 mg or 300 mg Q4W.

The time profile for mean serum alirocumab Ctrough according to up titration and body weight is provided in the figures below (Figures 4.6 and 4.7).

In Q2W participants, the steady state exposures achieved in pediatric patients with BW <50 kg (40 mg Q2W) and BW ≥50 kg (75 mg Q2W) were comparable (Figure 4.6).

In the Q2W participants who were up-titrated on Week 12, mean alirocumab Ctrough increased with doses from 40 mg Q2W to 75 mg Q2W in participants with BW <50 kg, and from 75 mg Q2W to 150 mg Q2W in participants with BW ≥50 kg (Figure 4.6).

Figure 4.6 - Ctrough alirocumab concentrations (ng/mL) over time according to up-titration status - Double-blind period - Patient in the Q2W cohort

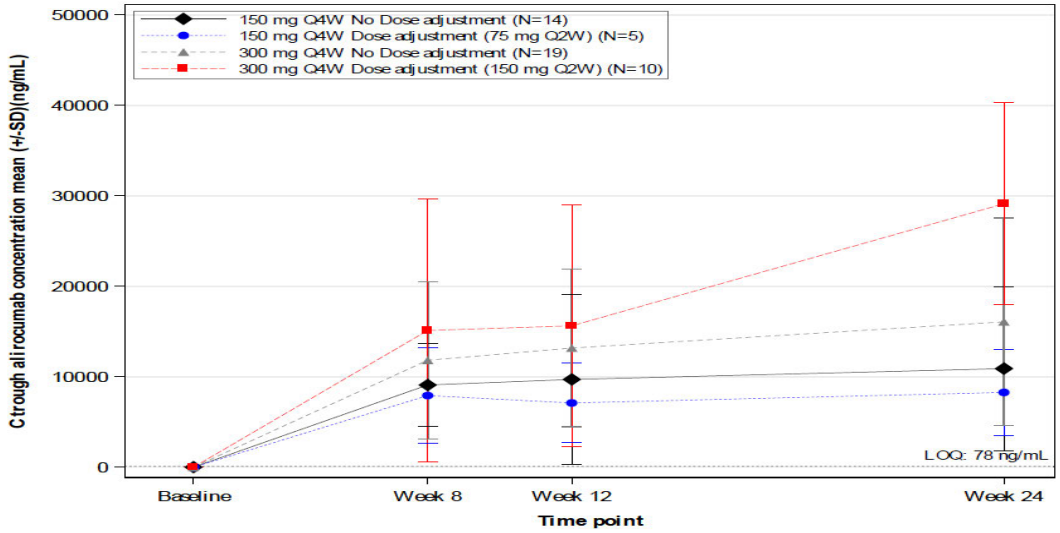


Source: Module 5.3.5.1. Clinical Study Report- EFC14643. Figure 13.

In Q4W participants, the steady state alirocumab exposures achieved in pediatric patients with BW<50 kg (150 mg Q4W) and BW≥50 kg (300 mg Q4W) were comparable (Figure 4.7).

In the alirocumab Q4W cohort, where some participants had dose adjustment to 75 mg Q2W (BW < 50kg) or 150 mg Q2W (BW ≥50 kg) after Week 12, the mean Ctrough increased after the dose adjustment for the group 150 mg Q2W only. For participants starting with 150 mg Q4W and adjusted to 75 mg Q2W, it is difficult to conclude due to the small number of participants in this sub-group (N=5) (Figure 4.7).

Figure 4.7 - Ctrough alirocumab concentrations (ng/mL) over time according to up-titration status - Double-blind period - Patient in the Q4W cohort



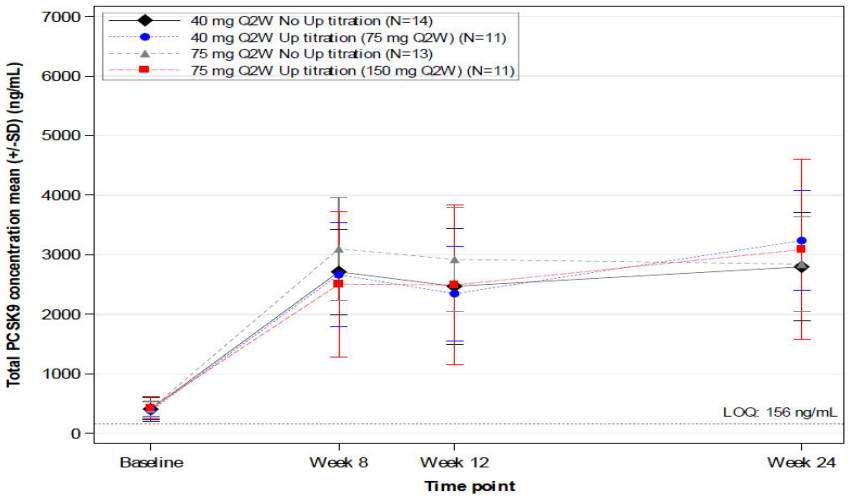
Source: Module 5.3.5.1. Clinical Study Report- EFC14643. Figure 14.

The highest mean alirocumab concentrations (Ctrough) were observed on Week 24 at 150 mg Q2W in up-titrated/dose-adjusted participants with BW ≥50 kg from Q2W and Q4W cohorts (Figures 4.6 and 4.7). Similar alirocumab concentrations (Ctrough) were observed at 150 mg Q2W in both cohorts.

Total PCSK9 concentrations

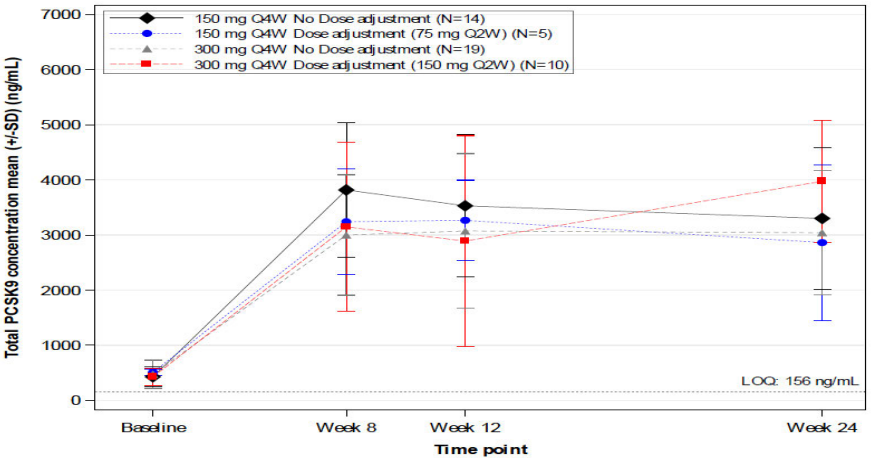
Total PCSK9 concentrations time profiles for alirocumab treatment Q2W and Q4W cohorts according to up-titration and body weight status are shown in Figures 4.8 and 4.9 below.

Figure 4.8 - Total PCSK9 concentrations (ng/mL) over time during treatment period according to up-titration status - Double-blind period - Patient in the Q2W cohort



Source: Module 5.3.5.1. Clinical Study Report- EFC14643. Figure 15.

Figure 4.9 - Total PCSK9 concentrations (ng/mL) over time during treatment period according to up-titration status - Double-blind period - Patient in the Q4W cohort

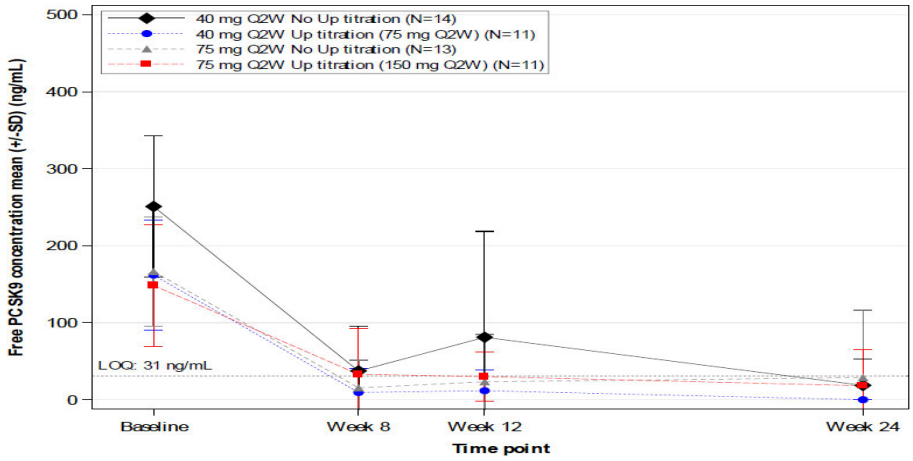


Source: Module 5.3.5.1. Clinical Study Report- EFC14643. Figure 16.

Free PCSK9 concentrations

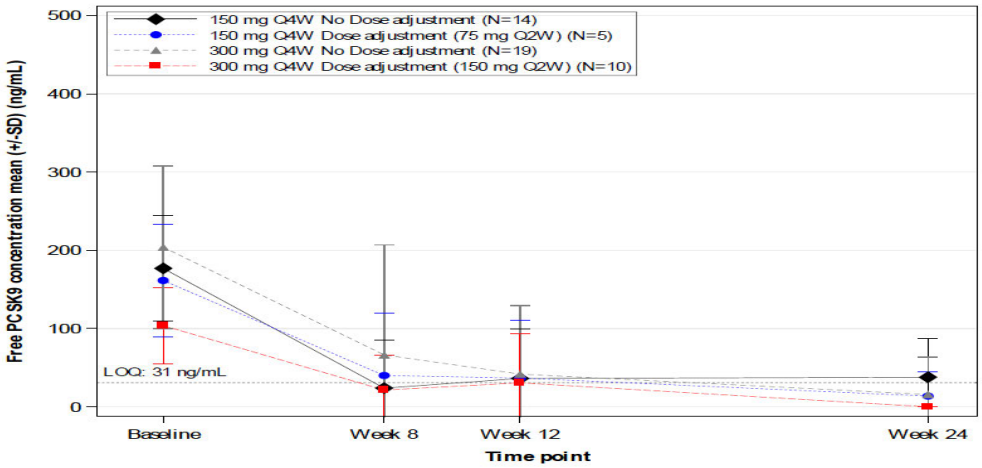
As shown in Figure 4.10 and 4.11 below, consistent with the total PCSK9 observations, administration of alirocumab resulted in a decrease in free PCSK9 concentrations at or before Week 8. For all cohorts, this decrease was maintained up to the last sample collection on Week 24.

Figure 4.10 - Free PCSK9 concentrations (ng/mL) over time during treatment period according to up-titration status - Double-blind period - Patient in the Q2W cohort



Source: Module 5.3.5.1. Clinical Study Report- EFC14643. Figure 17.

Figure 4.11 - Free PCSK9 concentrations (ng/mL) over time during treatment period according to up-titration status - Double-blind period - Patient in the Q4W cohort



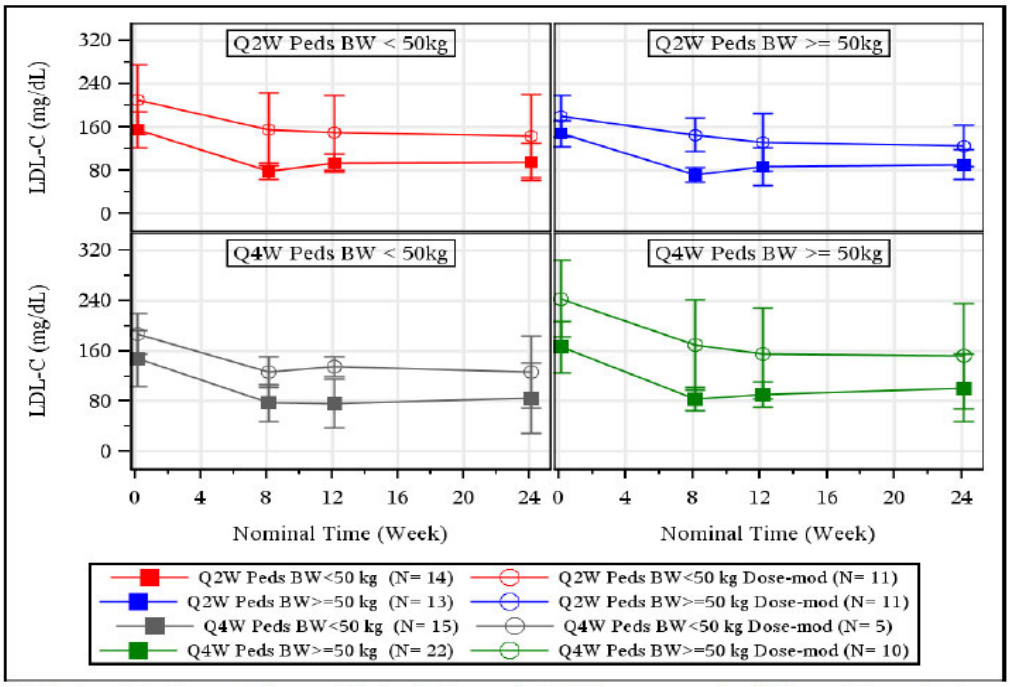
Source: Module 5.3.5.1. Clinical Study Report- EFC14643. Figure 18.

PK/PD relationship:

Decreases in free PCSK9 coincided with reductions in LDL-C in the Q2W and Q4W cohorts (Figure 4.12). As illustrated in Figure 4.12, dose adjustment in participants who had inadequate LDL-C responses at week 12 provided an additional modest LDL-C reduction by week 24 in the Q4W cohort, compared to the Q4W participants who were not dose-adjusted. According to the clinical study report, participants who required a dose adjustment started with higher baseline LDL-C than the participants who were not dose-adjusted.

APPEARS THIS WAY ON ORIGINAL

Figure 4.12 - Mean (SD) LDL-C Relative to Baseline Over Time in Pediatric Patients with HeFH (Study EFC14643)



BW, body weight; Dos-mod, dose modification (adjustment); HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein-cholesterol; N, number of participants in the treatment group within the PK population; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation.

Source: Module 2.7.2. Summary of Clinical Pharmacology Studies. Figure 8 (graphed using data from Module 5.3.5.1 EFC14643 CSR Tables 82 and 83).

As summarized in EFC14643 clinical study report Section 4.6.2 Dose modification, fewer participants in the Q4W cohort required dose adjustment compared with the Q2W cohort (28.8% vs 44.9%), as shown in Tables 6 and 7 below.

Table 6. Number and percentage of participants who required dose adjustment in the Q2W cohort in study EFC14643

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

Source: Study EFC14643. 16.2.5.2.1. Compliance and Drug Concentration Data. Page 10 of 430.

Table 7. Number and percentage of participants who required dose adjustment in the Q4W cohort in study EFC14643

	Placebo (N=27)	Alirocumab (N=52)
Total number of double-blind IMP administrations by patient		
Until week 12		
Number	27	52
Mean (SD)	3.0 (0.3)	2.9 (0.5)
Median	3.0	3.0
Min ; Max	2 ; 4	1 ; 4
From week 12		
Number	26	49
Mean (SD)	5.7 (0.7)	5.6 (1.0)
Median	6.0	6.0
Min ; Max	4 ; 6	3 ; 6
Location of IMP injections		
Thigh	9 (33.3)	17 (32.7)
Abdomen	14 (51.9)	36 (69.2)
Outer area upper arms	19 (70.4)	33 (63.5)
Titration/Dose-adjustment [n (%)]	0	15 (28.8)

Source: Study EFC14643. 16.2.5.2.1. Compliance and Drug Concentration Data. Page 14 of 430.

Additionally, as summarized in EFC14643 clinical study report (see Section 5.1.2.2.1.2 Tables 34-37, and Section 5.1.2.2.2.1), a numerically greater proportion of alirocumab-treated participants in the Q4W cohort compared to the Q2W cohort consistently achieved guideline-recommended LDL-C targets in the responder analyses for <130 mg/dL (76.3% vs 73.3%), <110 mg/dL (67.2% vs 57.2%), ≥30% reduction (72.5% vs 66.7%), and ≥50% reduction (32.4% vs 21.6%).

Immunogenicity evaluation:

The ADA status and Nab status of Phase 3 study EFC14643 are summarized in the Immunogenicity evaluation for study DFI14223 above.

In study EFC14643, 3 out of the 98 alirocumab-treated participants developed ADAs. Of the 3 patients who developed ADA, no one tested positive for NAbs.

Conclusions:

In this Phase 3 pivotal trial, steady state was reached at or before Week 8 for all the dosing regimens. Comparable steady state exposure was achieved in pediatric population with BW <50 kg and BW ≥50 kg after administration of alirocumab 40 mg or 75 mg Q2W, respectively. Similar findings were observed after administration of alirocumab 150 mg and 300 mg Q4W (for corresponding BW <50 kg and ≥50 kg).

Total PCSK9 concentration was increased after the administration of alirocumab and reached a plateau at or before Week 8. Consistent with the increase in total PCSK9 concentration, administration of alirocumab resulted in a decrease in free PCSK9 concentration at or before Week 8 that was maintained up to Week 24.

As discussed above, there was a lower need for dose-modifications in the Q4W cohort versus Q2W, and a comparable safety profile between the 2 cohorts. As observed in the adult clinical trials, dose adjustment to a Q2W regimen may provide additional LDL-C lowering in pediatric patients if alirocumab concentrations are insufficient to saturate PCSK9, allowing clinicians more flexibility in clinical practice to address the individual needs of their patients.

Study EFC14660

The applicant also conducted an additional pediatric study (EFC14660) in the alirocumab clinical development program and submitted the data of this study in the current supplement. It was conducted in pediatric patients with homozygous familial hypercholesterolemia (HoFH). Patients with HoFH have higher total cholesterol levels than patients with HeFH. The dosing regimen of this study was 75 mg Q2W and 150 mg Q2W, and modest overall effect on LDL-C was observed in 18 HoFH patients from 9 to 17 years of age, according to the clinical study report (Module 5.3.5.2. EFC14660 Clinical Study Report). The applicant states that the data from this study will not provide supportive evidence of efficacy for the proposed indication, but will provide supportive evidence of safety for the use of alirocumab in the pediatric population. Therefore, the applicant submitted this study in the current supplement for completeness. A summary of study EFC14660 is provided in Table 8 below.

Table 8. Summary of study EFC14660

Study Identifier, Location of Study Report, Study Status, Type of Report	Primary Objective	Study Design, Type of Control, Duration of Treatment	Test Product(s), Dosage Regimen, Route of Administration	Number of Participants	Healthy Subjects or Diagnosis of Patients
EFC14660 Phase 3 Module 5.3.5.2 Completed Final CSR	To evaluate the efficacy of alirocumab administered Q2W on LDL-C levels at Week 12 of treatment in children with HoFH 8 to 17 years of age on top of background treatments	Phase 3, multi-national, multi-center, uncontrolled, open-label, 48-week treatment study	SC Alirocumab Injection: • BW<50 kg: 75 mg Q2W (N=9) • BW ≥50 kg: 150 mg Q2W (N=9)	N=18	Patients 8 to 17 years of age with HoFH

BW: Body weight; HoFH: Homozygous familial hypercholesterolemia; LDL-C: Low density lipoprotein-Cholesterol; Q2W: Every 2 weeks; SC: Subcutaneous

Source: Module 5.2. Tabular Listing of all Clinical Studies – Pediatric HeFH. Figure 3.

The dosing regimen in the HoFH study (EFC14660) was different from the regimens investigated in the HeFH studies (DFI14223 and EFC14643). In addition, alirocumab pharmacokinetics and pharmacodynamics may differ in the pediatric HoFH compared to the HeFH patient population due to intrinsic differences between the populations such as expression of LDLR, apolipoprotein B, and/or other molecules in this pathway and the effects of statins on the level of expression of these molecules, including PCSK9.

Data from this HoFH study are presented in Module 2.7.3 and Module 2.7.4. However, the immunogenicity results from the HoFH study are included in this module to support the safety data summarized in Module 2.7.4.

Population Pharmacokinetic Analyses of Pooled Data

The applicant performed population pharmacokinetic (PopPK) study (study report number POH0925, Module 5.3.3.5) of pooled data from the Phase 2 dose-finding study (DFI14223) and the Phase 3 pivotal study (EFC14643).

The main objectives of this analysis conducted in HeFH pediatric patients from two phase II/III clinical studies were:

- To develop and qualify a Population PK (PopPK) model for alirocumab in this population;
- To assess the influence of intrinsic and extrinsic factors on alirocumab PK;
- To generate post-hoc estimates for alirocumab, compute individual patients time concentration profiles and derive exposure parameters.

The available data from the abovementioned two studies for PopPK analysis are detailed in Table 9 below:

Table 9. Summary of available data from studies DFI14223 and EFC14643 for PopPK analysis

Study #	N	Alirocumab Route/ Regimen and dose (cohorts)	PK sample	Study Population
DFI 14223 (Open label)	10	Q2W 30 mg for BW<50kg and 50vmg/kg for BW>=50 kg	4 per ID	HeFH pediatric patients (8 to 17 years old), LDL-C ≥130 mg/dL at screening visit, despite treatment with stable lipid modifying therapy (LMT) at optimal doses
	10	Q2W 40 mg for BW<50kg and 75 mg/kg for BW>=50 kg	4 per ID	
	11	Q4W 75 mg for BW<50kg and 150 mg/kg for BW>=50 kg	4 per ID	
	11	Q4W 150 mg for BW<50kg and 300 mg/kg for BW>=50 kg	5 per ID	
EFC 14643 (Double blind over 24 weeks)	~50	**Q2W 40 mg for BW<50kg or 75 mg for BW≥50kg** (dose adjustment possible from Week 12 : Q2W 75 mg for BW<50kg or 150 mg for BW≥50kg)	4 per ID	HeFH pediatric patients (8 to 17 years old), LDL-C ≥130 mg/dL at screening visit, despite treatment with stable LMT at optimal doses
	~50	**Q4W 150 mg for BW<50kg or 300 mg for BW≥50kg** (dose adjustment possible from Week 12 : Q2W 75 mg for BW<50kg or 150 mg for BW≥50kg)		

Source: Module 5.3.3.5. Clinical Study Report – POH0925 (PopPK), Table I.

The data included samples collected up to week 12 in the phase 2 dose-finding study (DFI14223) and up to week 24 for the phase 3 efficacy study (EFC14643), corresponding to the last time point for pharmacokinetic sampling during the treatment period. According to the applicant, the PopPK analysis was performed with the NONMEM computer program (version 7.4.1) running on a LINUX cluster of multi-processor computers. The sparse samples, primarily C_{trough} for 140 participants for a total of 377 pharmacokinetic observations, did not permit the development of a separate pediatric population pharmacokinetic structural model nor allow for a covariate search. Therefore, a model using priors approach was used.

Final population PK model parameters are listed in Table 10 below:

Table 10. Final population PK model parameters

Parameter	Estimate	% RSE	[95%CI]
Typical value for CLL (θ1, L/h)ᵖ	0.00982	6.25%	[0.00859 ; 0.011]
Typical value for V2 (θ2, L) ᵖ	2.93	6.11%	[2.57 ; 3.29]
Typical value for KA (θ3, h^{-1}) ᵖ	0.00844	3.43%	[0.00786 ; 0.00901]
Typical value for V3 (θ4, L) ᵖ	1.99	5.43%	[1.78 ; 2.21]
Typical value for Q (θ5, L/h) ᵖ	0.0188	7.32%	[0.0161 ; 0.0216]
Typical value for VM (θ6, mg/h) ᵖ	0.148	10.80%	[0.116 ; 0.18]
Typical value for KM (θ7,mg/L) ᵖ	8.61	10.0%	[6.89 ; 10.3]
Typical value for F (θ8, unitless) ᵖ	0.669	4.35%	[0.61 ; 0.727]
Typical value for LAG (θ9, h) ᵖ	0.661	3.59%	[0.613 ; 0.708]
Typical value for EXPCL (θ10, unitless)	0.888	9.80%	[0.714 ; 1.06]
Typical value for EXPV (θ11, unitless)	0.881	20.8%	[0.515 ; 1.25]
Inter-individual variability			
Parameter	Estimate (CV%)	% RSE	[95%CI] (Shrinkage %)
ω^2 CL	0.169 (42.9 %)	7.77%	[0.143 ; 0.195] (42.9 %)
ω^2 V2	0.38 (67.9 %)	6.70%	[0.33 ; 0.429] (69.1 %)
ω^2 V3	0.0694 (26.8 %)	24.20%	[0.0365 ; 0.102] (77.1 %)
Omega Block (KM: V3)	-0.104	26.70%	[-0.158 ; -0.0494]
ω^2 KM	0.262 (54.8 %)	22.40%	[0.147 ; 0.377] (72.3 %)
ω^2 F1	0.36 (65.8 %)	13%	[0.268 ; 0.452] (63.7 %)
Residual variability			
Multiplicative error (θ12)	0.285	9.31%	[0.232 ; 0.339]
Additive error (θ13)	0.816	34.0%	[0.261 ; 1.37]

%RSE: Percentage of Relative Standard Error (100% * SE / Estimate). 95%CI: 95% confidence interval

θ and ω are the PopPK parameters (θ) and the variance of their associated inter-individual variability (ω^2)

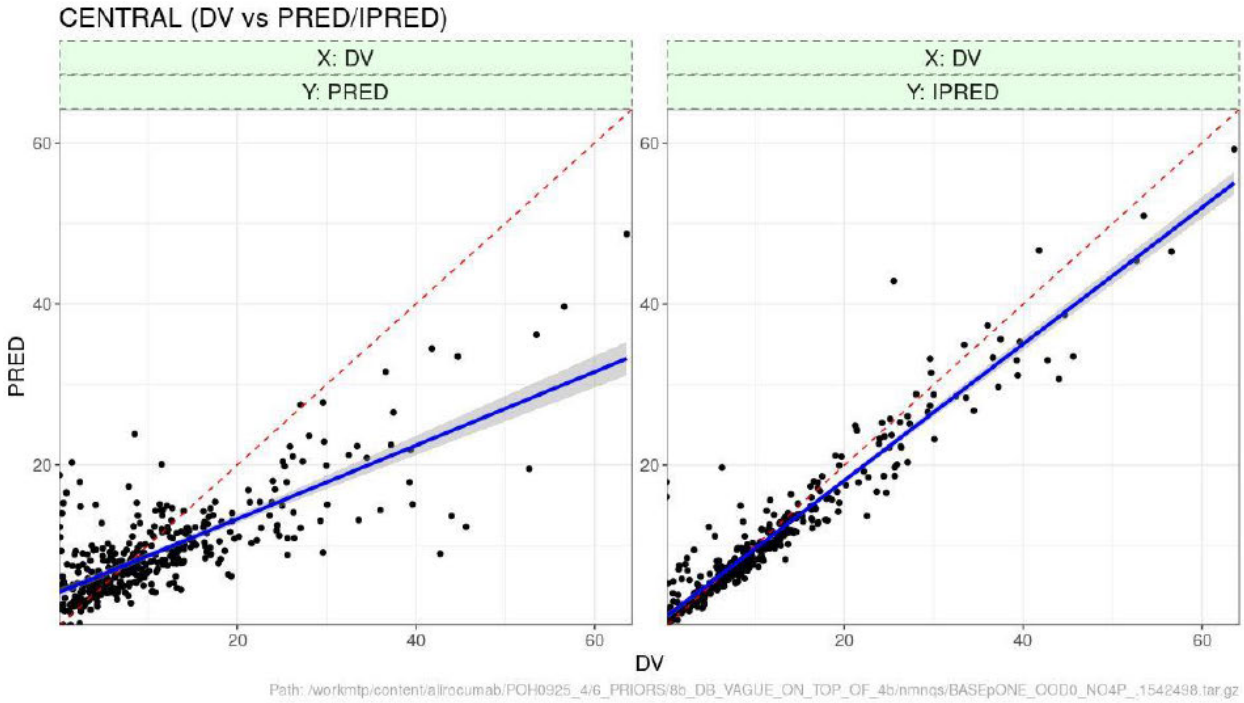
For omega block correlation is reported

Parameters with prior a labelled with p

Source: Module 5.3.3.5. Clinical Study Report – POH0925 (PopPK), Table II.

According to applicant's PopPK report, the final model fulfilled acceptance criteria and was qualified. The inspection of individual patients simulated PK profiles versus observations showed a good performance of the model (Figure 4.13).

Figure 4.13 - Goodness of fits plots for PRED and IPRED versus observations for the final priors-based model



Source: Module 5.3.3.5. Clinical Study Report – POH0925 (PopPK), Figure 1.

As a conclusion of the applicant's PopPK analysis, a PopPK model was developed, and the model described PK concentrations measured in the 2 clinical studies in pediatric patients with HeFH. No covariate search was performed due to limited data from sparse samples available for model development. Therefore, the applicant is not proposing to use PopPK analysis to inform specific dosing recommendations for patient subgroups such as age, gender, race.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TIAN ZHOU
02/14/2024 08:27:30 AM

LI LI
02/14/2024 09:28:46 AM