9 November 2023
EMA/576403/2023
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

EVKEEZA

International non-proprietary name: evinacumab

Procedure No. EMEA/H/C/005449/II/0011

Note

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

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List of abbreviations

ADA	Anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ANGPTL3	angiopoietin-like protein 3
Apo A1	apolipoprotein A1
Apo B	apolipoprotein B
APOB	*apolipoprotein B gene*
ASCVD	atherosclerotic cardiovascular disease
AUCtau.ss	area under the concentration-time curve at steady state to end of dosing
BLQ	below lower limit of quantification
CAD	coronary artery disease
CI	confidence interval
cIMT	carotid intima-media thickness
Cmax	peak concentration
COVID-19	coronavirus disease 2019
CSR	clinical study report
CV	cardiovascular
CVD	cardiovascular disease
DBTP	Double-blind Treatment Period
EAS	European Atherosclerosis Society
ECG	electrocardiogram
ESC	European Society of Cardiology
FDA	United States Food and Drug Administration
FH	familial hypercholesterolemia
FHBL2	familial combined hypobetalipidemia-2
GLP	Good Laboratory Practice
HEART	Hyperlipidaemia Education and Atherosclerosis Research Trust
HDL-C	high-density lipoprotein-cholesterol
HeFH	heterozygous familial hypercholesterolemia
HoFH	homozygous familial hypercholesterolemia
ICH	International Council for Harmonisation of Technical Requirements for

Pharmaceuticals for Human Use	
ITT	intent-to-treat
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein-cholesterol
LDLR	low-density lipoprotein receptor (*gene*)
LDLRAP1	LDLR adaptor protein 1 gene
LOF	loss-of-function
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
NAb(s)	neutralizing antibody(ies)
NICE	National Institute for Health and Care Excellence
NPC1L1	Niemann-Pick C1-Like 1 Intracellular Cholesterol Transporter 1
OLTP	Open-label Treatment Period
PASS	post-authorization safety study
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic(s)
PIP	Paediatric Investigation Plan
PL	package leaflet
PT	preferred term
Q4W	every 4 weeks
Q2W	every 2 weeks
QW	every week
SAE	serious adverse event
SC	subcutaneous(ly)
SD	standard deviation
SmPC	summary of product characteristics
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglyceride
TPV	total plaque volume
UK	United Kingdom
US	United States
Vmax	maximum elimination rate

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Ultragenyx Germany GmbH submitted to the European Medicines Agency on 26 May 2023 an application for a variation.

The following variation was requested:

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

Extension of indication to include the treatment of paediatric patients with homozygous familial hypercholesterolaemia (HoFH) aged 5 years and older for EVKEEZA, based on interim results from study R1500-CL-17100, as well as supportive information from an updated interim analysis of study R1500-CL-1719, and an extrapolation analysis (including population PK, population PK/PD, and simulation analyses). R1500-CL-17100 is an ongoing multicentre, three-part, single-arm, open-label study evaluating the efficacy, safety, and tolerability of evinacumab in paediatric patients aged ≥ 5 to 11 years with HoFH. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. In addition, the marketing authorisation holder took the opportunity to introduce minor editorial changes to the PI. Furthermore, the PI is brought in line with the latest QRD template version 10.3.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0087/2023 on the agreement of a paediatric investigation plan (PIP).
At the time of submission of the application, the PIP P/0087/2023 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Alar Irs

Timetable	Actual dates
Submission date	26 May 2023
Start of procedure:	17 June 2023
CHMP Rapporteur Assessment Report	04 August 2023
PRAC Rapporteur Assessment Report	17 August 2023
CHMP Co-Rapporteur Assessment	23 August 2023
PRAC Outcome	31 August 2023
CHMP members comments	04 September 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	08 September 2023
Request for supplementary information (RSI)	14 September 2023
PRAC Rapporteur Assessment Report	29 September 2023
CHMP Rapporteur Assessment Report	27 September 2023
PRAC members comments	n/a
CHMP members comments	02 October 2023
Updated CHMP Rapporteur Assessment Report	05 October 2023
Request for supplementary information (RSI)	12 October 2023
CHMP Rapporteur Assessment Report	25 October 2023
PRAC Rapporteur Assessment Report	25 October 2023
CHMP members comments	n/a
PRAC members comments	30 October 2023
Updated CHMP Rapporteur Assessment Report	31 October 2023
Updated PRAC Rapporteur Assessment Report	n/a
Opinion	09 November 2023

2. Scientific discussion

2.1. Introduction

The marketing authorisation holder, Ultragenyx Germany GmbH, is submitting a type II variation to extend the therapeutic indication for Evkeeza to include paediatric patients aged 5 years or above. Evkeeza received a marketing authorisation (MA) under exceptional circumstances.

2.1.1. Problem statement

Disease or condition

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder of lipid metabolism, a life-threatening condition resulting in severely elevated LDL-C (> 13mmol/L) leading to premature cardiovascular disease (CVD) and, in untreated patients, premature death. The goal of therapy in patients with HoFH is to reduce LDL-C, thereby reducing atherogenesis and subsequently reducing CVD events and mortality. Currently, patients with HoFH tend to be treated with multiple lipid-lowering therapies (LLT) but are not able to achieve guideline-recommended LDL-C targets.

HoFH is most often caused by the presence of loss-of-function variants in the low-density lipoprotein (LDL) receptor, which leads to low or absent hepatic clearance of LDL cholesterol from the circulation. Genetic alterations that cause a virtually complete absence of LDL-receptor expression (null homozygotes) result in higher LDL cholesterol levels than genetic alterations that partially reduce LDL-receptor activity with either two non-null alleles or one null and one non-null allele (non-null homozygotes).

Mutations in low-density lipoprotein receptor (LDLR) are classified into the following subtypes:

1. “Null/null” where little to no LDL binding and uptake activity exists (<15% LDLR activity)
2. Genotypically “negative/negative” where mutations in stop codons, frame shifts, splice site changes, small and large insertions/deletions, and copy number variations (CNVs) result in the loss of function of both LDLR alleles
3. Genotypically "defective" where missense mutations (hypomorphs) result in diminished LDLR activity (>15% LDLR activity).

State the claimed the therapeutic indication

In the current variation, a modified indication is proposed by the Applicant to include the treatment of paediatric patients with homozygous familial hypercholesterolaemia (HoFH) aged 5 -≤11 years for EVKEEZA, based on interim results from study R1500-CL-17100, as well as supportive information from an updated interim analysis of study R1500-CL-1719, and an extrapolation analysis (including population PK, population PK/PD, and simulation analyses).

The claimed indication reads as follows (in bold the proposed extension of the indication):

Therapeutic indications
Evkeeza is indicated as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and ~~adolescent~~paediatric patients aged 5~~1~~2 years and older with homozygous familial hypercholesterolaemia (HoFH).

Epidemiology

HoFH is a rare (~1 in 300,000 in the EU) and life-threatening genetic condition resulting in severely elevated LDL-C (> 13mmol/L) from birth and premature cardiovascular disease (CVD). If left untreated, HoFH patients rarely live past the first or second decade of life. Moreover, even with the currently available lipid-lowering therapies, many patients still do not reach their target LDL-C goal and consequently are still at high risk for a CVD event. In a recent retrospective study in Italian patients

with HoFH, 22% of the patients had a CVD event before age 20, and 16.7% died before age 21, despite starting lipid-lowering treatments early (Stefanutti 2019).

Biologic features

Regardless of the underlying mutations, this disorder is characterised by a markedly elevated plasma LDL-C level from birth, which results in an increased risk of premature atherosclerotic cardiovascular disease. In children as young as 7 years of age, coronary atherosclerosis can be evident even without any clinically apparent coronary artery disease (CAD). For example, one study showed increased carotid intima-media thickness (cIMT) and cIMT progression at a rate approximately double that of unaffected siblings (Kusters, 2014). This accelerated atherosclerosis results in premature atherosclerotic cardiovascular disease (ASCVD) and an increased risk for cardiovascular (CV) events. Moreover, patients with mutations considered null/null or negative/negative have higher LDL-C levels and worse clinical outcomes. These patients develop xanthomas sooner, and untreated patients rarely live past the second decade (Moorjani, 1993) (Kolansky, 2008).

Clinical presentation, diagnosis

Because of the rarity of the condition (approximately 1 in 300,000), there is a paucity of data on CV risk in patients with HoFH; however, one study found significant CV morbidity early in life with evidence of ASCVD well before the age of 20 (Sjouke 2015). If left untreated, HoFH patients rarely live past the first or second decade of life, with one study indicating the mean age of the first event at 12.8 years and an average age of ASCVD death of 17.7 years (Raal 2011). Further, a recent retrospective study in Italian and Chinese patients with HoFH showed that despite starting lipid-lowering treatments early (mean age of 5.6 year, Italian cohort, and 10.7 year, Chinese cohort), 22% (Italian cohort) and 45% (Chinese cohort) of the patients had a CVD event before age 20 and 16.7% (Italian cohort) and 31.8% (Chinese cohort) had died before age 21 (Stefanutti 2019). Additionally, another retrospective analysis showed that on-treatment total cholesterol is a major determinant of survival in patients with HoFH, with higher total cholesterol levels associated with a significantly increased risk of all-cause mortality (11.5 times greater in quartile 4 [>15.1 mmol/L] compared to quartile 1 [<8.1 mmol/L]) (Thompson 2018).

Management

Attempts to lower cholesterol levels often require multiple lipid-lowering drugs and LDL apheresis. Despite these therapies, a majority of patients with this disorder do not reach guideline-recommended LDL cholesterol levels. Patients with HoFH are often treated with multiple lipid-lowering treatments (LLTs) including statins, evolocumab, ezetimibe, and lipid apheresis; however, these treatments are largely ineffective for patients either due to LDLR mutations, problems with tolerability, and/or they are not available for the paediatric population.

Statin therapy is the cornerstone treatment for LDL-C lowering in the paediatric population aged 6 years and older and causes a 50% reduction in patients with heterozygous familial hypercholesterolemia (HeFH), however only a 15-30% reduction in LDL-C in patients with HoFH. The safety and efficacy of ezetimibe in children with HoFH aged less than 18 years have not been established. Further, lomitapide is not approved for use in paediatric patients.

Evolocumab, a PCSK9 inhibitor, is indicated for paediatric HoFH patients aged 10 years and older. Anti-PCSK9 therapy on top of maximally tolerated lipid-lowering therapy resulted in a mean reduction in LDL-C of approximately 30% compared to placebo. Of note, only evolocumab is currently approved for patients with HoFH; use of alirocumab in patients with HoFH is considered off label.

Despite intensive drug therapy, most of the patients with HoFH cannot achieve their treatment LDL-C goal (minimum of 50% reduction in LDL-C according to American heart Association/American College of Cardiology), also since statins and PCSK9 inhibitors are dependent on increasing LDLR activity, but many patients with HoFH are refractory to these treatments due to their mutations. Therefore, apheresis is an important adjunctive treatment for HoFH; a single treatment reduces LDL-C by 55%-70% relative to pre-treatment levels. However, apheresis may be burdensome, and its availability is limited. Also, only a temporal reduction in LDL-C is achieved.

Liver transplantation can be used to treat HoFH, although it is rarely used and considered as a last resort treatment option due to the many disadvantages, including a high risk of post-transplantation surgical complications and mortality, the paucity of donors, and the need for life-long treatment with immunosuppressive therapy.

Due to the limitations of currently available treatments, there exists a high unmet medical need for new therapeutic options that reduce LDL-C and the inevitable risk for premature ASCVD in paediatric patients with HoFH. The unmet medical need is particularly severe for paediatric HoFH patients with null/null or negative/negative mutations where currently available LLTs provide little benefit in lowering LDL-C and for paediatric HoFH patients who lack treatment options.

2.1.2. About the product

Evinacumab is a human monoclonal antibody that specifically binds to and inhibits angiopoietin-like 3 (ANGPTL3), which leads to reductions in LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs). This gives a similar lipid phenotype that is found in humans with ANGPTL3 loss of function (LOF). This phenotype is associated with hypolipidemia and protection against atherosclerotic cardiovascular disease.

Evinacumab reduces LDL-C independent of the presence of LDL receptor (LDLR) by promoting very low-density lipoprotein (VLDL) processing and clearance upstream of LDL formation; however, the exact mechanism of increased VLDL processing and clearance is not exactly known. Evinacumab blockade of ANGPTL3 lowers TGs and HDL-C by rescuing lipoprotein lipase and endothelial lipase activities, respectively.

Evinacumab is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Evkeeza is a 150 mg/ml concentrate for solution for infusion. The recommended dose is 15 mg/kg administered by intravenous infusion (IV) over 60 minutes once monthly (Q4W).

Evinacumab (Evkeeza) obtained full approval under exceptional circumstances as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolaemia (HoFH).

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

Paediatric investigation plan

The application is based on the results of the paediatric development program in line with the approved PIP P/0087/2023 (Table 1) as also indicated by the partial compliance check by the EMA (EMA/145021/2023). EMA decision dated 16 May 2023: Studies R1500-CL-17100 and R1500-CL- 1719 are confirmed to be compliant as set out in the EMA's Decision (P/0087/2023) of 10 March 2023.

The initial marketing authorization of evinacumab for the treatment of HoFH in adult and adolescent patients aged 12 years and older was based on data from R1500-CL-1629, a Phase 3, pivotal double-

blind, placebo-controlled study in adult and adolescent patients (12 to <18 years) with HoFH, with a 24-week double-blind treatment period (DBTP) in a background of other lipid-lowering therapies (e.g. statins, ezetimibe, PCSK9 inhibitor antibodies, lomitapide, and lipoprotein apheresis, and a 24-week Open-label Treatment Period (OLTP) and was further supported by several other studies, including early data from an ongoing long-term, open-label safety and efficacy extension study in patients with HoFH (R1500-CL-1719). Adolescent patients were included in the pivotal phase 3 study (R1500-CL-1629) as well as in the open-label extension study (R1500-CL-1719) due to the high unmet medical need in this patient group.

The current extension of indication application is based on data from Study R1500-CL-17100, an ongoing Phase 1b/3 single-arm, open-label study designed to evaluate the long-term safety and efficacy of evinacumab in paediatric (≥5 to <12 years) patients with HoFH, and a recent interim analysis of the ongoing open-label extension study, R1500-CL-1719, which provides updated long-term safety and efficacy data from adolescent (and adult) patients treated with evinacumab.

Additionally, a robust extrapolation analysis, including population pharmacokinetics (PK), population PK/pharmacodynamics (PD; population PK/PD), and simulations, based on data from multiple clinical studies is provided in support of the proposed indication.

Table 1. Paediatric investigation plan

Area	Description
Quality-related studies	Not applicable.
Non-clinical studies	Study 1 (R1500-TX-18035) Dose range-finding juvenile toxicity study to inform dose selection for Study 2 Study 2 (REGN1-TX-17093) A 17-Week Intravenous Study in Juvenile Rabbits with a 31-week Recovery Period Study 3 (R1500-TX-17094) Intravenous and Subcutaneous Toxicology Study in Juvenile Rats
Clinical studies	Study 4 (R1500-CL-1629) Double-blind, randomised, placebo controlled trial of 24 weeks to evaluate safety and efficacy of Evinacumab as add-on to lipid modifying therapies (LMT) in children from 12 years to less than 18 years of age (and adults) with insufficiently controlled homozygous familial hypercholesterolaemia (HoFH) on stable LMT, followed by a 24 week open label treatment period to evaluate safety and a 24-week follow-up period after the last dose of study drug for those patients who choose not to enter the open-label long term safety study (Study 6) Study 5 (R1500-CL-17100)

	A three-part, single arm, open-label trial to evaluate pharmacokinetics, safety and activity of Evinacumab in children from 5 years to less than 12 years of age with HoFH Study 6 (R1500-CL-1719) Open-label, long term trial to evaluate safety and activity of Evinacumab in children from 12 years to less than 18 years of age (and adults) with HoFH following completion of Study 4 or are evinacumab naïve and directly enrolled into this study
Extrapolation, modelling and simulation studies	Study 7 (R1500-CL-17100-Extrapolation) Extrapolation study to evaluate the use of Evinacumab in the proposed paediatric indication in children from 5 to less than 12 years of age with HoFH
Other studies	Not applicable

2.2. Quality aspects

Evinacumab concentrate for solution for infusion is a clear to slightly opalescent, colorless to pale yellow liquid that is essentially free from visible particles.

Evinacumab drug product (DP) is an aqueous buffered solution nominally containing 150 mg/mL of evinacumab. Other ingredients are: arginine hydrochloride, histidine hydrochloride monohydrate, proline, histidine, polysorbate 80 and water for injections (WFI).

There are two DP presentations: One vial of 2.3 mL of concentrate containing 345 mg of evinacumab. One vial of 8 mL of concentrate containing 1,200 mg of evinacumab.

The MAH wishes to extend the indication for EVKEEZA to include the treatment of paediatric patients with homozygous familial hypercholesterolaemia (HoFH) aged 5 years and older.

Excipients: No direct safety issues are foreseen with regards to the excipients.

Dosing: No dose adjustment is required for paediatric patients aged 5 to 17 years. The recommended dose is 15 mg/kg administered by intravenous infusion over 60 minutes once monthly (every 4 weeks).

According to the Denekamp schaal for bodyweight in children, the body weight for a 5-year-old girl is 19 kg and for a 5 year old boy 19,5 kg. This gives a starting dose of 285 mg every 4 weeks, which is adequately covered by the smaller presentation (345 mg vial).

2.3. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

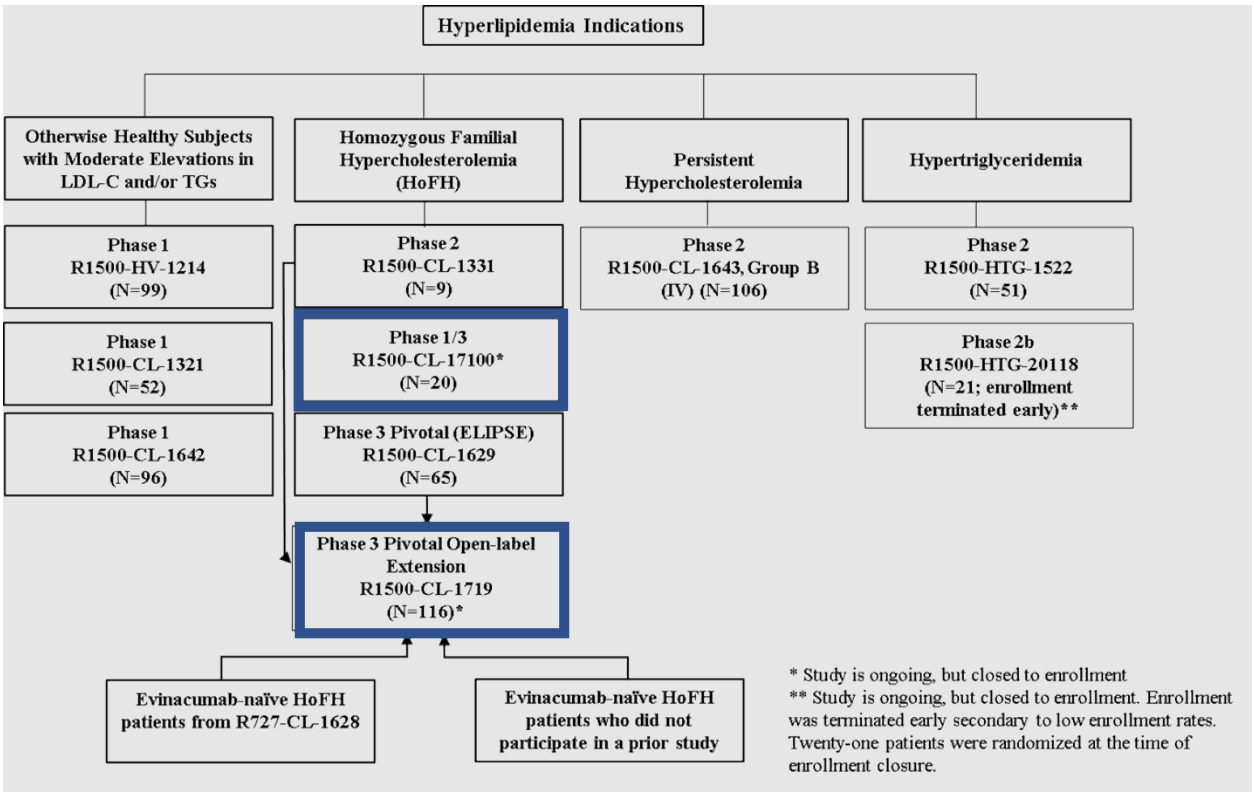
Evinacumab is a monoclonal antibody consisting of linked naturally occurring amino acid, and is therefore exempted from Environmental Risk Assessment (ERA) studies.

2.4. Clinical aspects

2.4.1. Introduction

An overview of the Phase 1, 2, and 3 studies in the evinacumab clinical program is presented in the figure below (*Figure 1*). This figure highlights the clinical studies for the target HoFH paediatric indication.

Figure 1. Clinical studies in the evinacumab program



HoFH, homozygous familial hypercholesterolemia; IV, intravenous; LDL-C, low-density lipoprotein-cholesterol; TGs, triglycerides. N = number of randomized and treated patients (ie, the Safety Analysis Set).

GCP

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

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

- Tabular overview of clinical studies

Protocol Number	Study Title	EU Participating Countries	Non-EU participating countries
R1500-CL-17100	A Three-Part, Single-Arm, Open-Label Study to Evaluate the Efficacy, Safety, And Pharmacokinetics of Evinacumab in Pediatric Patients with Homozygous Familial Hypercholesterolemia	Austria, Netherlands	Australia, Taiwan, United States
R1500-CL-1719	An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of Evinacumab in Patients with Homozygous Familial Hypercholesterolemia	Austria, Czech Republic, France, Greece, Italy, Netherlands	Australia, Canada, Japan, South Africa, Ukraine, United States

2.4.2. Pharmacokinetics

In the current procedure, the marketing authorisation holder, Ultragenyx Germany GmbH, is submitting a type II variation to extend the therapeutic indication for evinacumab to include paediatric patients aged 5 years to <12 years with homozygous familial hypercholesterolemia (HoFH) and is seeking approval under exceptional circumstances. The proposed posology is 15 mg/kg evinacumab administered via a Q4W infusion, which is similar to the posology in HoFH patients >12 years.

A summary of individual studies in the adult clinical pharmacology program, including pharmacokinetic (PK) and pharmacodynamic (PD) modelling and simulation analyses for evinacumab was previously provided in the original marketing authorization application (MAA) for evinacumab (*Figure 1*).

The newly provided clinical pharmacology data primarily focus on interim results from paediatric Study R1500-CL-17100 and supportive updated interim data for adolescents and adults from Study R1500-CL-1719 (*Table 2*, *Figure 1*). Evinacumab PK data in children ≥5 to <12 years of age with HoFH was assessed using two population pharmacokinetic(/pharmacodynamic) analyses. The submitted studies and corresponding data were in line with the approved PIP, EMEA-002298-PIP01-17-M05 (PIP decision number P/0087/2023).

The first population pharmacokinetic analyses (R1500-PK-22070-SR-01V1) focussed on characterising the pharmacokinetics of patients ≥5 years to <12 years enrolled in Study R1500-CL-17100 (Part A and Part B). Additionally, data was included from 6 studies in healthy adult subjects and adult and adolescent patients with HoFH (Study R1500-HV-1214, R1500-CL-1321, R1500-CL-1642, R1500-CL-1331, R1500-CL-1629, R1500-CL-1719). In the second population pharmacokinetic/pharmacodynamic analysis, additional pharmacokinetic data from the ongoing R1500-CL-1719 study in adolescents and adults with HoFH were combined with the data included in first population pharmacokinetic analyses (R1500-PM-23041-SR-01V1). In addition, the relationship between total evinacumab concentration and low-density lipoprotein (LDL) response was also evaluated.

Specific objectives of the paediatric clinical pharmacology program were to select an appropriate dosing regimen for patients with HoFH aged ≥5 to <12 years and to characterise the total evinacumab serum PK, the total ANGPTL3 serum concentrations, as a measure of target engagement, and the immunogenicity potential of evinacumab in these patients.

Table 2 Reports of Human Pharmacokinetic (PK) Studies.

Study	Study population/analysis sets	PK-related objective	Study design and duration	Dose, route of administration, number of patients
R1500-CL-1719 Study ongoing	Patients with HoFH ≥12 years of age on background lipid-lowering therapy	Provide additional PK and LDL-C data in adolescent patients to refine the existing popPK/PD model.	Phase 3 open-label safety and efficacy study including patients from study R1500-CL-1331 and study R1500-CL-1629, and evinacumab naïve patients. Sparse sampling for PK	15 mg/kg IV Q4W Evinacumab N=116
R1500-CL-17100 Study ongoing	Patients with HoFH 5 to <12 years of age on background lipid-lowering therapy	Assess the PK of evinacumab in paediatric patients with HoFH.	Phase 1b/3, 3-part (Parts A, B, and C), open-label safety, efficacy, and PK study; Part C extension study available to patients who complete Parts A or B Dense sampling for PK in Part A; sparse sampling for PK in Parts B and C	Part A: Single administration of 15 mg/kg IV Part B: 15 mg/kg IV Q4W x 6 doses Part C: 15 mg/kg IV Q4W x 12 doses Evinacumab N = 20 (6 from Part A and 14 from Part B)

Methodology

Bioanalysis

Total evinacumab concentration in serum

There were no changes to the analytical methods for determining total evinacumab concentrations in human serum since the initial marketing authorization application. Briefly, a validated enzyme-linked immunosorbent assay (ELISA) was used to measure the concentrations of total evinacumab in human serum (both free evinacumab, and evinacumab bound to 1 or 2 molecules of ANGPTL3), validation report REGN1500-AV-13001. The LLOQ of the assay is 78 ng/mL in neat human serum. Total evinacumab concentration is stable in human serum for at least 24 months at -20°C and at least 24 months at -80°C.

In study R1500-CL-1719, a total of 55 of the 57 plates met the run acceptance criteria. The two failed runs indicated that the percent of analyte recovery did not meet the assay specification for the QC samples. No incurred sample reanalysis of samples was performed in this study.

In study R1500-CL-17100, a total of 10 of the 12 plates met the run acceptance criteria. The two failed runs indicated that the percent of analyte recovery did not meet the assay specification for the QC samples. Incurred sample reanalysis of samples (n = 32) was performed in this study with a total passing rate of 100%.

Total ANGPTL3 concentration in serum

There were no changes to the analytical methods for determining total AngPTL3 concentrations in human serum since the initial marketing authorization application. In short, total AngPTL3 concentrations in human serum were measured using a qualified ELISA (qualification study REGN1500-MX-15060; long-term stability study REGN1500-MX-15070). The LLOQ of the assay is 19.5 ng/mL in neat human serum. Total AngPTL3 is stable in human serum for at least 12 months at -20°C and at least 24 months at -80 °C.

In study R1500-CL-1719, a total of 51 of the 79 plates met the run acceptance criteria. All but one of the failed runs indicated that the percent of analyte recovery did not meet the assay specification for the QC samples. In addition, one run failed due to the percent of analyte recovery for non-zero standard did not meet the assay specification. No incurred sample reanalysis of samples was performed.

In study R1500-CL-17100, a total of 8 of the 9 plates met the run acceptance criteria. One of the failed runs indicated that the percent of analyte recovery did not meet the assay specification for the QC samples and the analyte recovery for non-zero standards did not meet the assay specification. No incurred sample reanalysis of samples was performed.

Immunogenicity

There were no changes to the analytical methods for determining total evinacumab concentrations in human serum since the initial marketing authorization application. In short, a validated, titer-based, bridging immunoassay (validation report: R1500-AV-18078) was used to detect anti-drug antibodies (ADA) in human serum samples. The bridging assay procedure uses biotinylated evinacumab (Bio-REGN1500) and ruthenium-labeled evinacumab (Ru-REGN1500) as the bridge components. The ADA method uses a floating cut point to determine positive responses in serum samples and involves a 3-tiered approach: an initial screen to identify samples that are potentially positive for ADA, a confirmation step to determine whether positive responses in the screening assay can be inhibited by the presence of excess drug, and a titer procedure to assess the level of ADA in confirmed positive samples. The sensitivity of the assay in neat serum is 1.8 ng/mL of the monoclonal antibody positive control (REGN2092). The drug tolerance limit (DTL) in neat serum is 1366 µg/mL of evinacumab with 250 ng/mL of REGN2092.

In study R1500-CL-1719, all 33 plates run in the ADA assay met the run acceptance criteria. The cut points in the ADA assay were determined using baseline (treatment-naïve) samples from patients with elevated levels of triglycerides (150-500 mg/dL) and low-density lipoprotein (LDL) (≥100 mg/dL). Based on the screening cut point factor (CF) from this population, the observed screening positivity rate for baseline serum samples from participants in this study was 10%. In this study, a total of 2 patients (1 Adolescent patient each in the New Evinacumab and Continue Evinacumab groups) had a transient, treatment emergent ADA response with titer of 50. A total of 4 patients (1 Adolescent and 1 Adult patient in the New Evinacumab group, and 1 Adolescent and 1 Adult patient in the Continue Evinacumab group) tested positive for Neutralising antibodies (NAbs). In 3 of the 4 patients, Nabs were detected post-baseline; in the remaining patient, baseline data was not available.

In study R1500-CL-17100, a total of 4 of the 4 plates met the run acceptance criteria. The cut points in the ADA assay were determined using baseline (treatment-naïve) samples from patients with elevated levels of triglycerides (150-500 mg/dL) and low-density lipoprotein (LDL) (≥100 mg/dL). Based on the screening cut point factor (CF) from this population, the observed screening positivity rate for baseline (treatment-naïve) serum samples from this study was 20.0%. In this study, 1 patient in Part B developed treatment emergent ADAs of low titer. Two other patients tested positive for pre-existing ADAs. In the patient with treatment emergent ADAs, results of Nab testing were negative.

Population pharmacokinetic (and pharmacodynamic) model (R1500-PK-22070-SR-01V1)

Objectives

Evinacumab pharmacokinetic data in paediatrics from 5 to 11 years of age with HoFH from Study R1500-CL-17100 (n=20) was analysed using the previously developed population pharmacokinetic model (R1500-PK-19139-SR-01V1), which was already assessed and described in the initial marketing application for evinacumab. The primary objectives of the current population pharmacokinetic analysis were to:

- Assess the adequacy of the existing evinacumab adult population pharmacokinetic model in describing evinacumab pharmacokinetics in paediatric patients (age 5 to 11 years) with homozygous familial hypercholesterolemia (HoFH) from Part A and Part B of Study R1500-CL-17100.
- Generate individual steady-state exposure metrics based on empirical Bayesian estimates for paediatric HoFH patients and compare exposure predictions between paediatric and adult HoFH patients.

Data

The dataset for Study R1500-CL-17100 in paediatric patients (age 5 to 11 years) with homozygous familial hypercholesterolemia (HoFH) described pharmacokinetic sample concentrations, dates and times, dose amounts with associated dates and times, and patient demographics and covariates. This study evaluated single dose 15 mg/kg IV (Part A) and 15 mg/kg Q4W (Part B). The data from R1500-CL-17100 was appended to the original Master Dataset, which included 6 evinacumab studies in healthy adults and adults and adolescents with HoFH (Studies R1500-HV-1214, R1500-CL-1321, R1500-CL-1331, R1500-CL-1629, R1500-CL-1642, and R1500-CL-1719). However, subsequent to the original population PK model development for evinacumab (Report R1500-PK-19139-SR-01V1), it was noted that 488 quantifiable pharmacokinetic samples (i.e., concentrations > 0.078 mg/L) from Study R1500-CL-1642 had been mislabelled as below the lower limit of quantification (BLQ) in the original dataset. These concentrations were corrected by removing the BLQ flag in the original dataset, which will be termed the corrected dataset.

Methods

The population pharmacokinetic analyses were performed using NONMEM version 7.4.1 (ICON Development Solutions, Ellicott City, Maryland) using the Monte-Carlo importance sampling assisted by mode a posteriori (IMPMAP) method. As the previous population pharmacokinetic model, submitted during initial marketing application, was only fitted without the mis-labelled data, this previous model was re-fitted to a dataset including the mis-labelled data (without paediatric data from Study R1500-CL-17100).

Final model

As the model submitted during the initial marketing analysis formed the basis of the modelling analyses in the current procedure, the model will be briefly described below. In short, a two-compartment model disposition model with IV infusion into the central compartment or first-order SC absorption with dual linear and saturable (Michaelis-Menten) elimination was developed with evinacumab concentration data from healthy adults and adolescents and adults with HoFH. Baseline weight, AngPTL3, and disease state were covariates on Volume of distribution and clearance (weight), and Vmax (AngPTL3, disease state). Inter-individual variability was included on the absorption parameters (lagtime and absorption rate constant) and on clearance and volume of distribution of the central compartment.

Model comparison

A comparison of parameter estimates from the existing model (Run 165) and re-estimation of model parameters with the additional 488 quantifiable samples is provided in *Table 3*. The re-estimation of Run 165 with the updated dataset was largely consistent with the original population pharmacokinetic model (Report R1500-PK-19139-SR-01V1); only Km, intercompartmental rate constants (K23, K32) and extent to which the disease state affects nonlinear elimination had > 20% percent change, and linear clearance and central volume changed by < 5% from the original model.

Table 3 Parameter Estimates from Existing Model (Run 165) for Evinacumab in Adults and Adolescents Comparing Previous and Updated Datasets

Parameter (units)	Existing Model (6 studies) - Run 165 with Updated Dataset [a]			Existing Model (6 studies) - Run 165 with Previous Dataset [b]	Percent Difference
	Population Estimate	Percent RSE	95% CI	Population Estimate	
PK Parameter					
Clearance (L/day for 74.1 kg subject)	0.0962	3.80	(0.0890, 0.103)	0.101	-4.75
Central Volume (L for 74.1 kg subject)	2.69	1.98	(2.58, 2.79)	2.59	3.86
KA (1/day)	0.178	5.92	(0.158, 0.199)	0.179	-0.56
F for SC dose	0.743	2.32	(0.709, 0.777)	0.748	-0.67
K23 (1/day)	0.0927	6.96	(0.0800, 0.105)	0.135	-31.3
K32 (1/day)	0.106	6.49	(0.0922, 0.119)	0.150	-29.3
Vmax (mg/day)	3.12	2.29	(2.98, 3.26)	3.18	-1.89
Km (mg/L)	1.54	5.01	(1.39, 1.69)	1.01	52.5
Absorption lag time (days)	0.147	12.2	(0.112, 0.182)	0.142	3.52
Covariates					
V~Baseline Weight (centered on 74.1 kg)	0.914	8.16	(0.768, 1.06)	0.87	5.06
Linear Clearance ~ Baseline Weight (centered on 74.1 kg)	0.75 (fixed)	-	-	0.75 (fixed)	0
Vmax ~Baseline AngPTL3 (centered on AngBL of 0.0941 mg/L)	0.422	8.53	(0.352, 0.493)	0.461	-8.46
Vmax ~Disease state (reference: healthy volunteers)	-0.278	10.6	(-0.336, -0.220)	-0.352	-21.0
Inter-Individual Variability (%CV)					
CL	44.8		(34.4, 53.9)	36.0	
ρ(CL,V)	0.0139			0.190	
V	25.1		(17.7, 30.9)	21.7	
Ka	57.4		(50.0, 64.4)	74.6	
Alag	128		(99.0, 159)	116	
Residual error					
Additive (mg/L)	0.349	5.59	(0.311, 0.387)	0.339	
Proportional (CV)	0.192	1.96	(0.185, 0.200)	0.192	

PK = Pharmacokinetic; RSE = Relative standard error, CV = Coefficient of variation; KA = Absorption rate constant for SC administration; F = Bioavailability for SC administration; K23/K32 = Intercompartment rate constants; Km = Concentration achieving half of the maximum elimination rate; V = Volume; CL = Clearance; Alag = Lag time in SC absorption

[a] Includes an additional 488 quantifiable PK samples from Study R1500-CL-1642 which had been mislabeled as BLQ in the existing model (Report R1500-PK-19139-SR-01V1).

[b] Reference: Population Pharmacokinetic Modeling Report R1500-PK-19139-SR-01V1

Population pharmacokinetic/pharmacodynamic model pooled analysis (R1500-PM-23041-SR-01V1)

Objectives

The objectives of this analysis were to:

- Assess the adequacy of the existing population pharmacokinetic (PK) model of evinacumab in describing evinacumab PK in paediatric patients with HoFH ≥5 years of age enrolled in Studies R1500-CL-17100 and R1500-CL-1719

- Refine the existing population PK model using the pooled data from Study R1500-CL-17100 in paediatric (5 to <12 years old) patients and the adolescent and adult Studies R1500-HV-1214, R1500-CL-1321, R1500-CL-1642, R1500-CL-1331, R1500-CL-1629, and R1500-CL-1719.
- Refine the existing pharmacokinetic/pharmacodynamic (PK/PD) model of evinacumab effect on low- density lipoprotein cholesterol (LDL-C) using the pooled data from Study R1500-CL-17100 in paediatric (5 to <12 years old) patients and the adolescent and adult Studies R1500-CL-1331, R1500-CL-1629, and R1500-CL-1719
- Predict the evinacumab PK and associated LDL-C reduction in a large virtual population of paediatric (5 to <12 years old), adolescent (12 to <18 years old) and adult (≥18 years old) patients with HoFH using model-based simulations and compare these predicted metrics across age and body weight categories

Data

The creation of the master dataset and the derived analysis dataset, data exploration, model diagnostics, and presentations in graphical and tabular outputs was performed using R version 4.2.1 (R Core Team, 2022).

For the purpose of the population pharmacokinetic analysis, the master dataset including all data from all 7 studies (studies R1500-HV-1214, R1500-CL-1321, R1500-CL-1331, R1500-CL-1629, R1500-CL-1642, R1500-CL-1719, and R1500-CL-17100) was subset by excluding LDL-C concentration records, total alirocumab concentration records, total PCSK9 concentration records, total ANGPTL3 concentration records (baseline ANGPTL3 concentrations were kept as a covariate), apheresis records (for most models), data collected from Part C of the ongoing Study R1500-CL-17100, and evinacumab concentration records collected prior to the 1st active dose. Evinacumab concentration records collected after dose records for which the amount was imputed were excluded from the PK analysis.

For the purpose of the PK/PD analysis, the master dataset was subset by excluding total evinacumab concentration records, total alirocumab concentration records, total PCSK9 concentration records, total ANGPTL3 concentration records (baseline ANGPTL3 concentrations were kept as a covariate), apheresis records (in some models only), data collected from Part C of the ongoing Study R1500-CL-17100, LDL-C concentration records collected after dose records for which the amount was imputed, and LDL-C records associated with an absolute value of the conditional weighted residual (CWRES)>5.

For PK and LDL-C observations with unknown or missing sampling information, the information on sample label or in pre-defined protocol was used. If a dose amount was missing, the administered dose was calculated. A likelihood-based approach (M3) was used to handle data below the lower limit of quantification, consistent with the previous population pharmacokinetic model. The dataset for final population pharmacokinetic modelling included a total of 322 unique participants with at least one quantifiable sample and 5698 post-dose records, including 5085 quantifiable samples and 613 samples that were BLQ. A total of 10.8% of the post-dose samples were BLQ. The dataset for the final PK/PD modelling included a total of 3316 LDL-C measurements and 139 unique participants with at least one LDL-C measurement. None of the LDL-C measurements were BLQ.

Methods

Population modelling was performed by nonlinear mixed-effects analyses using NONMEM version 7.5.0, accessed through the front-end application (Perl-speaks-NONMEM version 4.6.0). Model-based simulations were conducted using the mrgsolve R package version 1.0.6.

Evinacumab PK in healthy adults and paediatric (≥ 5 years of age) and adult patients with HoFH was previously described by a 2-compartment model with first-order absorption after SC dosing and with dual linear and saturable (Michaelis-Menten) elimination (R1500-PK-22070-SR-01V1). Baseline body weight, ANGPTL3 concentration, and disease status were identified as significant predictors of variability in evinacumab PK: clearance and volume of distribution of the central compartment were both predicted to increase with increasing body weight according to power relationships. Vmax was predicted to be 25.1% lower in patients with HoFH compared to healthy participants and increased with increasing baseline ANGPTL3 concentrations according to relatively shallow power relationship (R1500-PK-22070-SR-01V1) (R1500-PK-19141-SR-01V1). This existing population model was evaluated on its ability to adequately capture the evinacumab concentration data newly introduced in the current PK dataset using visual predictive checks (VPCs). The existing PK model was then re-estimated and refined using the current PK analysis dataset.

The effect of evinacumab on LDL-C reduction in adolescent (≥ 12 years of age) and adult patients with HoFH was previously described by an indirect response model in which evinacumab concentrations inhibit the production of LDL-C according to a saturable (Michaelis-Menten) relationship (R1500-PK-19141-SR-01V1). LDL-C concentrations were calculated using the Friedewald formula (Friedewald *et al.*, 1972) or, if triglyceride values exceeded 400 mg/dL or if calculated LDL-C values were below 25 mg/dL, LDL-C was measured via the beta quantification method. A sequential approach was applied for the development of the population PK/PD model of evinacumab effect on LDL-C reduction, by which the PD parameters of the model were estimated while the structure and individual parameter of the PK model were fixed to the Bayesian estimates obtained from the final PK model. To allow the evaluation of the existing PK/PD model in paediatric patients, the covariate effects (race as additive on logit scale and linear effect of bodyweight on logit scale) on Imax were first re-parameterized on the logit scale to ensure that Imax remains between 0 and 1. If the re-estimated model was deemed adequate, the effects of age on Imax and IC50 were to be assessed in a limited covariate analysis.

Model development

The evaluation of the existing population pharmacokinetic model by VPC was not provided. However, successful convergence could not be achieved when re-estimating the model parameters using FOCEI. Similarly, re-estimation of the model using IMPMAP resulted in highly correlated estimates of the first-order rates of distribution from the central to peripheral compartments (K23) and from the peripheral to central compartments (K32). This issue was resolved by changing the model parameterisation and estimating a distribution clearance (Q) and volume of peripheral compartment (VP). Additional refinements included the use of time-varying body weight to drive allometric scaling of disposition parameters and the allometric scaling of Q and VP, in anticipation of model extrapolation to younger populations in subsequent analysis. The effects of age on CL, VC, and Vmax were evaluated separately. In all cases, the 90% CI associated with the estimates included 0, suggesting that age had no effect on the tested parameters within the age range available in the data. Covariate effects included in the existing population PK model were retained.

Convergence of the re-parameterized PK/PD model could not be achieved. Therefore, the PK/PD model was refined. Baseline LDL-C concentrations were estimated rather than fixed to observed values. Given that lipid apheresis is a key intervention to reduce LDL-C concentrations in patients with HoFH, its effect was also estimated as an additional time-varying elimination process. The statistical significance of the covariate effects retained from the existing PK/PD model was re-assessed in a limited backward elimination process. Both effects of observed baseline LDL-C concentration and racial classification on Imax did not reach the pre-defined level of statistical significance (α = 0.001, or a change of 10.83-point difference in objective function for 1 degree of freedom) and were removed from the model.

Furthermore, the effects of age on baseline LDL, Imax, IC50 and Kin were evaluated. Age was found to be a significant covariate on baseline LDL.

Final models

The final population PK model for evinacumab SC and IV administration in healthy participants and patients with HoFH was a 2-compartment model with first-order absorption after SC dosing and with dual linear and saturable (Michaelis-Menten) elimination. The disposition parameters CL, VC, Q, and VP were allometrically scaled on time-varying body weight, while Vmax was dependent on baseline ANGPTL3 concentrations and differed in patients with HoFH compared to healthy participants. The parameter estimates for the final population PK model, along with the bootstrap median and 95% CI, are provided in *Table 4*. Parameters were well estimated with RSE ≤ 23% for all structural parameters, except the allometric exponent on Q (%RSE = 34.2%), and %RSE ≤ 28.1% for IIV parameters. The magnitude of IIV was modest for CL (27.4% CV) and VC (37.5% CV) and large for the first-order rate of absorption (ka, 86% CV) and absorption lag time (ALAG1, 175% CV) after SC dosing. Shrinkage in IIV was small for CL (16.4%), VC (10.6%), ka (3.07%), ALAG1 (13.5%). VPC plots for the final population pharmacokinetic model for studies R1500-CL-17100 and R1500-CL-1719 are shown in *Figure 2*. p(v)cVPC plot for the final population pharmacokinetic model in paediatrics aged 5 to 12 years old are shown in Figure 3.

Table 4 Parameter Estimates and Bootstrap Confidence Interval for the Final Evinacumab Population Pharmacokinetic Model

Parameter (unit)	Estimate	%RSE	Bootstrap median (95% CI)
CL: Elimination clearance (L/day)	0.0993	4.49	0.0988 (0.0933, 0.104)
CL ~ Power effect of weight	0.776	12.6	0.817 (0.675, 0.97)
VC: Central volume (L)	2.78	2.81	2.92 (2.74, 3.13)
VC ~ Power effect of weight	0.668	10.4	0.704 (0.575, 0.872)
Q: Distribution clearance (L/day)	0.2	10.8	0.123 (0.0877, 0.166)
Q ~ Power effect of weight	1.08	34.2	1.41 (0.847, 2.02)
VP: Peripheral volume (L)	2.07	4.92	1.9 (1.66, 2.14)
VP ~ Power effect of weight	0.986	11.1	1.1 (0.849, 1.34)
VMAX: Maximum saturable elimination rate (mg/day/L)	3.03	6.97	2.78 (2.48, 3.09)
VMAX ~ Power of baseline ANGPTL3	0.395	23	0.348 (0.176, 0.534)
VMAX ~ Proportional effect of HoFH	0.75	10.3	0.777 (0.661, 0.898)
KM: Half-inhibitory concentration (mg/L)	2.61	18.7	2.74 (2.23, 3.44)
KA: First-order absorption rate (1/day)	0.188	8.03	0.196 (0.16, 0.234)
ALAG1: Absorption lag time (day)	0.136	15	0.126 (0.0937, 0.161)
F1: Bioavailability after SC dosing	0.709	4.79	0.705 (0.641, 0.775)
IIV in CL (%CV)	27.4	20.3	28.2 (24.3, 33)
IIV in VC (%CV)	37.5	27.9	41.2 (31.9, 53)
IIV in KA (%CV)	86	22.5	103 (73, 163)
IIV in ALAG1 (%CV)	175	23.3	142 (96.1, 246)
cov(IIV in CL, IIV in VC)	0.032	28.1	0.0446 (0.0206, 0.0725)
Constant CV residual variability component	0.0667	7.41	0.0714 (0.0631, 0.0816)
Additive residual variability component	0.0806	39.7	0.0115 (0.00469, 0.0214)

ANGPTL3 = Angiopoietin-like protein 3; CI = Confidence interval; cov = Covariance; CV = Coefficient of variation; HoFH = Homozygous familial hypercholesterolemia; IIV = Interindividual variability; RSE = Relative standard error; SC = Subcutaneous
Shrinkage: IIV in CL (16.4%), IIV in VC (10.6%), IIV in KA (3.07%), IIV in ALAG1 (13.5%)

Typical values of model parameters can be calculated as:

$$CL = 0.0993 \times \left(\frac{weight}{72}\right)^{0.776} \qquad Q = 0.2 \times \left(\frac{weight}{72}\right)^{1.08}$$

$$V_C = 2.78 \times \left(\frac{weight}{72}\right)^{0.668} \qquad V_P = 2.07 \times \left(\frac{weight}{72}\right)^{0.986}$$

$$V_{max} = 3.03 \times \left(\frac{ANGPTL3}{0.0908}\right)^{0.395} \times 0.75^{HoFH}$$

where $weight$ is the time-varying body weight (kg), $ANGPTL3$ is the baseline ANGPTL3 concentration (mg/L), and $HoFH$ is 0 for healthy participants and 1 for patients with homozygous familial hypercholesterolemia

Figure 2 Visual Predictive Check for the Final Evinacumab Population Pharmacokinetic Model

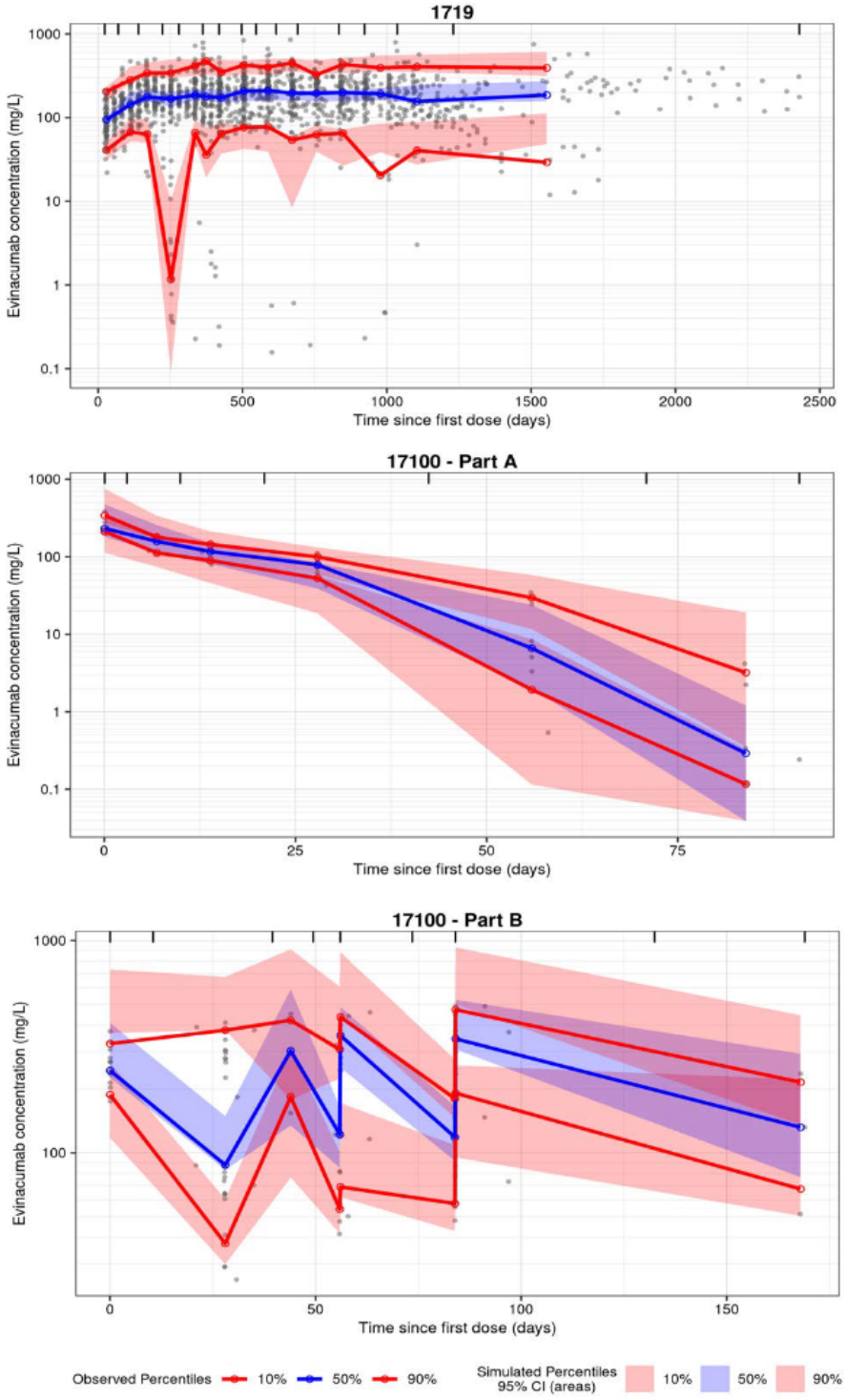
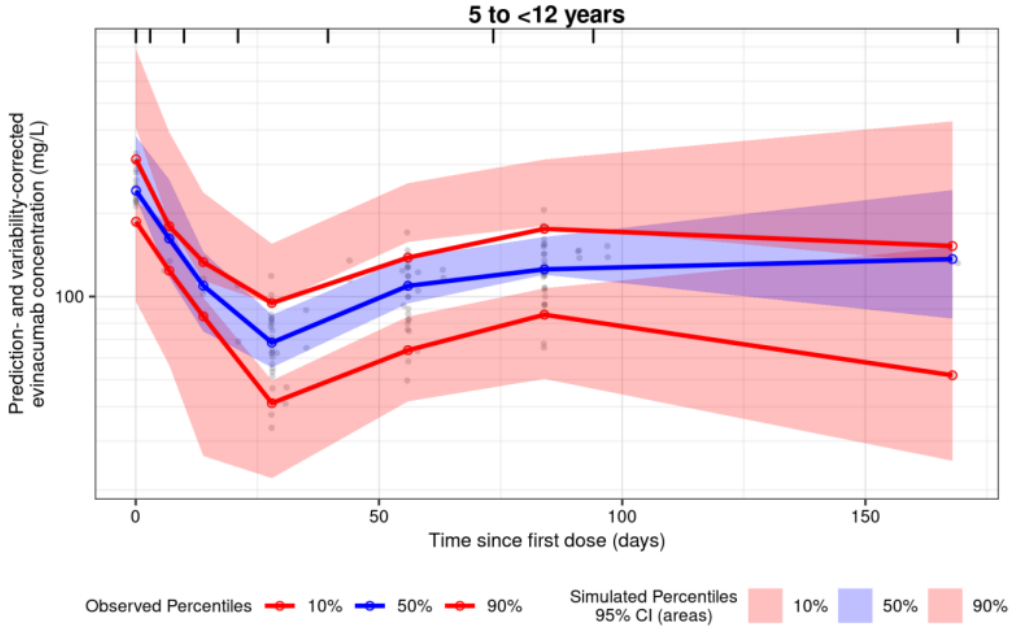
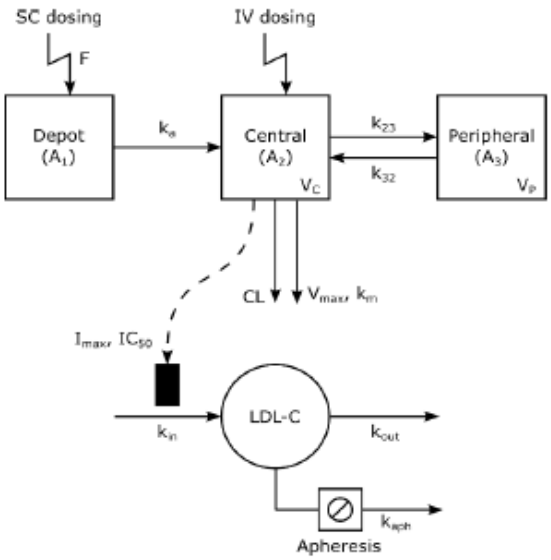


Figure 3 Predicted and Variability Corrected Visual Predictive Check for the Final Evinacumab Paediatric Population Aged 5 to 12 Years Old.



The final population PK/PD model for evinacumab effects on LDL-C concentrations in patients with HoFH was an indirect response model in which evinacumab concentrations inhibits the production of LDL-C according to a saturable (Michaelis-Menten) relationship, and which included a second elimination pathway driven by apheresis treatment. The overall PK/PD model structure is displayed in *Figure 4*4.

Figure 4 Final PK/PD model structure.



A_1, Amount of evinacumab in the deport compartment; A_2, Amount of evinacumab in the central compartment; A_3, Amount of evinacumab in the peripheral compartment; CL, linear elimination clearance; I_{max}, Maximal inhibitory effect; IC_{50}, Evinacumab concentration to reach 50% of I_{max}; IV, Intravenous; k_{23}, k_{32}, Inter-compartmental rate constants; k_a, First-order absorption rate constant after subcutaneous injection; k_{aph}, elimination rate via apheresis; k_{in}, LDL-C production rate; k_m, Concentration achieving half of the maximum elimination rate; k_{out}, LDL-C elimination rate; LDL-C, Concentration of low-density lipoprotein cholesterol; SC, Subcutaneous; V_C, Volume of central compartment; V_P, Volume of peripheral compartment; V_{max}, Maximum target-mediated rate of elimination

The PK/PD model included two covariates (i.e. increasing age was associated with a decrease in baseline LDL-C concentration and increasing body weight was associated with decrease in the maximum inhibitory effect of evinacumab). The parameter estimates for the final population PK/PD model are provided in

Table 5 and VPC plots for the final popPK/PD model for studies R1500-CL-17100 and R1500-CL-1719 are shown in *Figure 5*5.

Parameters were well estimated with %RSE ≤ 36.1% for all structural parameters and %RSE ≤ 37.3% for IIV parameters. The magnitude of IIV was moderate for LDLC0 (53.7% CV) and Imax (30% CV for a 72-kg individual) and kin (54.5% CV). Shrinkage in IIV was for baseline LDL 4.4%, for Imax 16.7%, and for kin 44.2%.

Table 5 Parameter estimates and bootstrap confidence interval (CI) for the final evinacumab population pharmacokinetic/pharmacodynamic model

Parameter (unit)	Estimate	%RSE	Bootstrap median (95% CI)
LDLC0: Baseline LDL-C concentration (mg/dL)	214	9.74	214 (193, 240)
LDLC0 ~ Power effect of age (unitless)	-0.32	36.1	-0.321 (-0.445, -0.204)
KIN: LDL-C production rate (mg/dL/day)	34.7	16.9	35.3 (29, 42.9)
IMAX: Maximum inhibition (unitless)	0.574	5.95	0.577 (0.515, 0.643)
IMAX ~ Linear effect of weight (logit scale)	-0.0186	32.2	-0.0181 (-0.0316, -0.00795)
IC50: Half-inhibitory concentration (mg/L)	32.7	23.9	32.7 (20.2, 53)
KAPH: Rate of elimination via apheresis (1/day)	8.36	18	8.66 (5.85, 12)
IIV in LDLC0 (%CV)	53.7	12.6	53.6 (46.8, 61.1)
IIV in IMAX (%CV)	30	24.5	30.3 (20.3, 44.3)
IIV in KIN (%CV)	54.5	37.3	53.4 (32.9, 94.5)
Constant CV residual variability component	0.0631	22	0.0581 (0.0368, 0.0822)
Additive residual variability component	60.3	103	78.2 (4.43, 203)

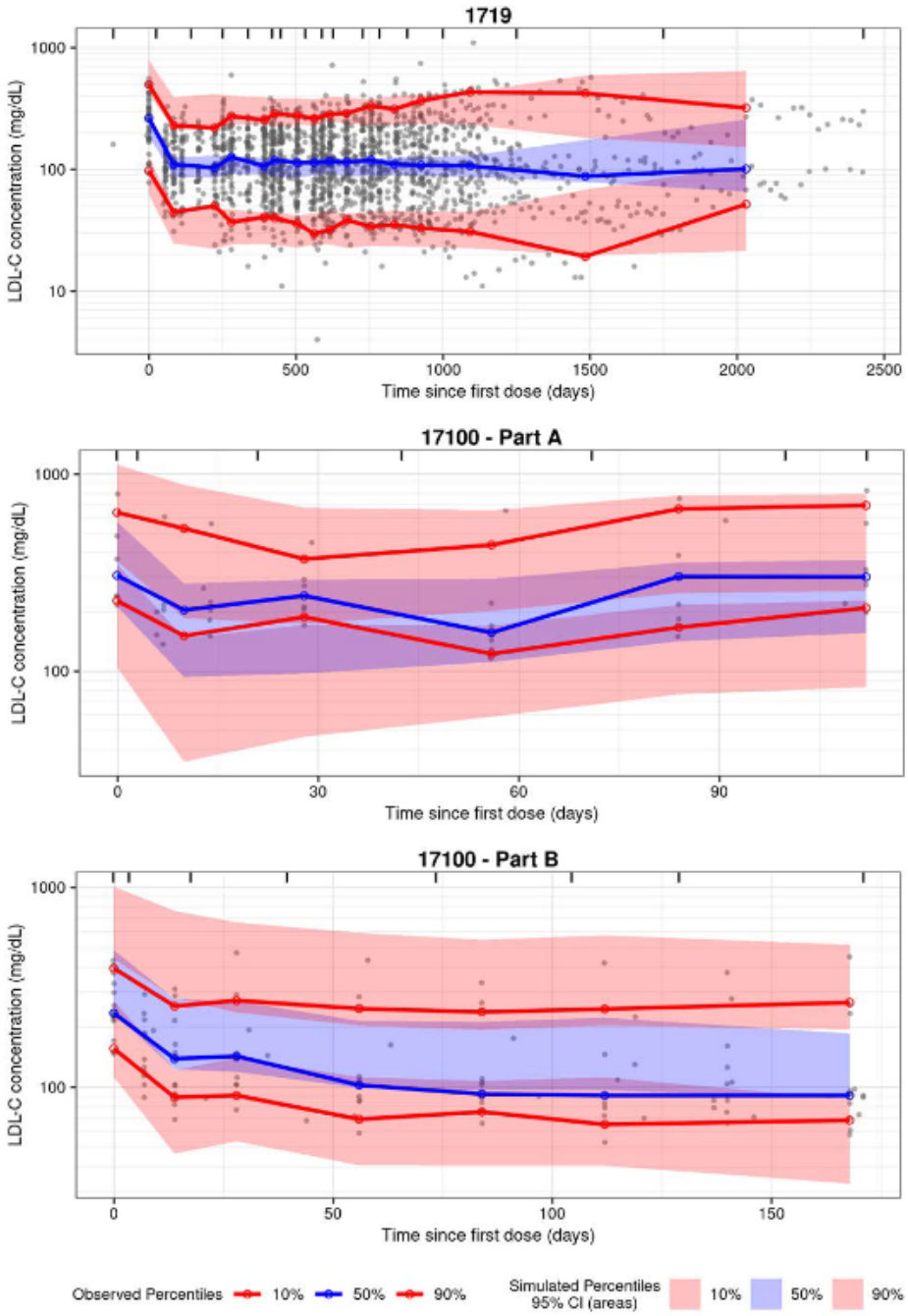
CI = Confidence interval; CV = Coefficient of variation; IIV = Interindividual variability; LDL-C = Low-density lipoprotein cholesterol; RSE = Relative standard error
Shrinkage: IIV in LDLC0 (4.37%), IIV in IMAX (16.7%), IIV in KIN (44.2%)

Typical values of model parameters can be calculated as:

$$LDLC0 = 214 \times \left(\frac{age}{43}\right)^{-0.32} \qquad I_{max} = \frac{1}{1 + e^{-log\left(\frac{0.574}{1-0.574}\right)+0.0186\times(weight-72)}}$$

where age is the baseline age (years) and $weight$ is the time-varying body weight (kg).

Figure 5 Visual Predictive Check for the final evinacumab population pharmacokinetic/pharmacodynamic model



Model application

Model parameter estimates from the final PK and PK/PD models were used to predict evinacumab concentrations and the percentage of reduction in LDL-C from baseline (%ΔLDL-C) in patients with HoFH receiving 10 consecutive 15 mg/kg evinacumab infusions every 4 weeks (Q4W).

Deterministic simulations using the population parameter estimates were conducted in prototypical individuals, to explore the magnitude of statistically significant covariate effects on evinacumab exposures at steady-state and on %ΔLDL-C at Week 24 relative to a typical patient, and to explore the effect of age on exposures and %ΔLDL-C following evinacumab and/or apheresis treatment.

Evinacumab exposures after 10 consecutive evinacumab infusions and %ΔLDL-C at Week 24 were also predicted and summarized by age and body weight groups, using the individual post-hoc EBEs obtained in the patients included in the analysis dataset (15 mg/kg Q4W), or using model-based estimates (15 and 20 mg/kg Q4W) in a population of 1000 virtual paediatric, 1000 virtual adolescent and 1000 virtual adult patients with HoFH generated by random sampling. Simulations were performed under the assumption that apheresis treatments were received at frequencies and in proportions of the simulation population that were representative of those observed in the analysis population.

Pharmacokinetics in adult population

After updating the population PK model by correcting the mis-labelled data from study R1500-CL-1642 and adding additional data (i.e. studies R1500-CL-17100 and R1500-CL-1719), model parameters were re-estimated. This resulted in some changes in the SmPC section 5.2 (absorption, distribution and elimination sections), which also concern the description of the pharmacokinetics in adults. These differences are summarised below and briefly discussed.

Absorption

The mean predicted C_{min}, C_{max}, AUC_{tau} at steady state (after 10 doses of 15 mg/kg Q4W) in adult patients with HoFH are 230 (±81.3) mg/L, 681 (± 185.0) mg/L and 10100 (± 2720) mg.day/L, respectively.

The accumulation ratio based on the predicted mean C_{min} at week 40 in adult patients with HoFH was estimated in the population pharmacokinetic analysis at approximately 2.6 (± 0.4).

Distribution

Based on the updated population pharmacokinetic model, the volume of distribution was found to be 4.9 L in a typical individual weighing 72 kg (the central volume of distribution was 2.8 L and peripheral volume of distribution was 2.1 L).

Elimination

PopPK analysis for patients with HoFH showed that after repeated doses of 15 mg/kg IV Q4W, the median time for evinacumab to decrease below the lower limit of quantitation was approximately 20 weeks overall across the age groups.

Pharmacokinetics in paediatric population

Evinacumab exposure and its corresponding effect on LDL-C were characterised in paediatric patients with HoFH (age 5 to 11 years) in the phase 1b/3 study R1500-CL-17100 following a single 15 mg/kg IV infusion (Part A) and during multiple 15 mg/kg Q4W IV infusions (Part B), and were subsequently compared to adolescent and adult data using population PK and PK/PD modelling. The study is still ongoing (Part C), which consists of a 48-week treatment period and 24-week follow-up period of evinacumab 15 mg/kg IV Q4W in patients who previously completed parts A and B.

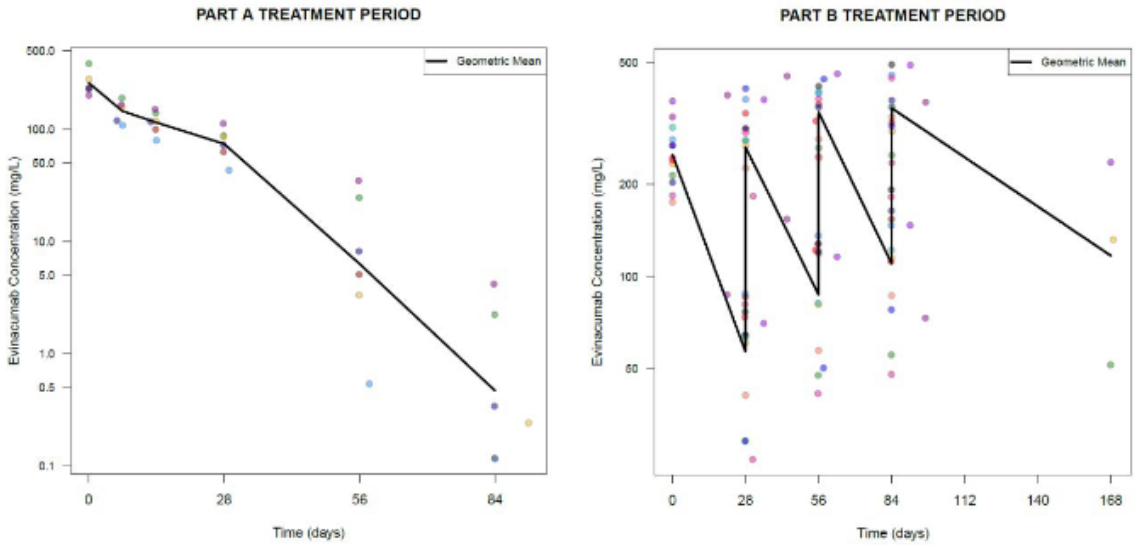
In total, 20 paediatric patients aged 5 to 11 years, mean age of 9 (± 1.8), bodyweight of 38 (± 13.1) kg and AngPTL3 of 0.075 (± 0.031) mg/L. A comparison with adolescent and adult patients, based on the data included in the second population pharmacokinetic model (R1500-PM-23041-SR-01V1), is provided in Table 6.

Table 6 Summary of demographics, stratified by age group

Variable	Group or Statistic	5 - <12 years (n = 20)	12 - <18 years (n = 14)	>=18 years (n = 288)	Overall (n = 322)
Individual status, N (%)	Healthy	0 (0%)	0 (0%)	183 (63.5%)	183 (56.8%)
	HoFH	20 (100%)	14 (100%)	105 (36.5%)	139 (43.2%)
Age (years)	Mean (SD)	9 (1.84)	14.4 (1.82)	43.3 (11.9)	40 (15)
	Median	9	15	43	42
	Min, Max	5, 11	12, 17	18, 75	5, 75
Sex, N (%)	Male	8 (40%)	9 (64.3%)	156 (54.2%)	173 (53.7%)
	Female	12 (60%)	5 (35.7%)	132 (45.8%)	149 (46.3%)
Racial classification, N (%)	White	14 (70%)	7 (50%)	214 (74.3%)	235 (73%)
	Black or African American	1 (5%)	1 (7.14%)	11 (3.82%)	13 (4.04%)
	Asian	2 (10%)	3 (21.4%)	47 (16.3%)	52 (16.1%)
	American Indian or Alaska Native	1 (5%)	0 (0%)	1 (0.347%)	2 (0.621%)
	Other	0 (0%)	1 (7.14%)	8 (2.78%)	9 (2.8%)
	Unknown	2 (10%)	2 (14.3%)	7 (2.43%)	11 (3.42%)
Baseline body weight (kg)	Mean (SD)	37.9 (13.1)	58.3 (13.5)	77 (17.9)	73.7 (20.1)
	Median	35.3	57.2	74.4	72
	Min, Max	19.7, 69.1	45, 94.3	42.4, 152	19.7, 152
Baseline body mass index (kg/m2)	Mean (SD)	18.8 (4.19)	20.4 (3.08)	27 (4.8)	26.2 (5.24)
	Median	17.5	20.2	26.4	25.6
	Min, Max	14.3, 29.6	16.3, 28.9	17.6, 46.4	14.3, 46.4
Estimated glomerular filtration rate (mL/min)	Mean (SD)	140 (26.9)	112 (29.8)	105 (15.6)	107 (19.2)
	Median	138	102	107	108
	Min, Max	102, 211	67.8, 171	52.7, 139	52.7, 211
Baseline total ANGPTL3 (mg/L)	Mean (SD)	0.0751 (0.0311)	0.0614 (0.0188)	0.094 (0.0323)	0.0914 (0.0327)
	Median	0.0683	0.0606	0.0937	0.0908
	Min, Max	0.033, 0.144	0.0299, 0.102	0.0204, 0.287	0.0204, 0.287
Baseline LDL cholesterol (mg/dL)	Mean (SD)	302 (149)	300 (100)	179 (120)	192 (127)
	Median	240	304	146	152
	Min, Max	147, 793	140, 428	10, 907	10, 907
Baseline LDL cholesterol (mmol/L)	Mean (SD)	7.81 (3.86)	7.77 (2.6)	4.63 (3.11)	4.96 (3.28)
	Median	6.21	7.85	3.78	3.93
	Min, Max	3.8, 20.5	3.62, 11.1	0.259, 23.5	0.259, 23.5
Baseline triglyceride (mg/dL)	Mean (SD)	91.8 (49.5)	87.1 (48.5)	194 (348)	183 (331)
	Median	72	65.5	128	118
	Min, Max	32, 220	44, 225	27, 3620	27, 3620

Evinacumab concentration-time profiles for patients in Study R1500-CL-17100 Part A and Part B are illustrated in *Figure 6*. The NCA-based AUC_{last} was 4576 (± 1568) mg.day/L and observed C_{max} was 238 (± 90.8) mg/L in part A. Pharmacokinetic parameters in part B were determined using the population pharmacokinetic models.

Figure 6 Geometric mean observed evinacumab concentration time profiles for patients in study R1500-CL-17100 receiving 15 mg/kg IV as a single dose (Part A) or 15 mg/kg IV Q4W (Part B)



The influence of covariates weight and age on the pharmacokinetics of evinacumab was evaluated using population pharmacokinetic model (R1500-PM-23041-SR-01V1). Post-hoc estimates of C_{min}, C_{max}, and $AUC_{0\text{-}tau}$ at first dose and at steady-state were presented for patients with HoFH in *Table 7*. Evinacumab exposures after 15 mg/kg IV infusions were predicted to be lower in younger patients and patients with a lower body weight. The mean predicted values of AUC at steady state (after 10 doses) were 7020, 8650, and 10100 mg.day/L in patients between 5 and <12 years of age, between 12 to <18 years of age, and above 18 years of age, respectively.

Table 7 Summary of post-hoc Bayesian estimates of evinacumab exposure metrics at the first dose and steady-state in patients with homozygous familial hypercholesterolemia after 15 mg/kg infusions every 4 weeks, stratified by age and weight group

Exposure	Category	n	Mean (SD)		Median (5th, 95th)	
			First dose	Last dose	First dose	Last dose
C_{min} (mg/L)	5 - <12 years	20	58 (17.6)	160 (57.6)	60.1 (28.1, 81.5)	167 (66.9, 218)
	12 - <18 years	14	74.1 (25.2)	198 (75.5)	79.8 (38.4, 105)	189 (100, 299)
	>=18 years	105	88.1 (23.1)	230 (81.3)	87.5 (51.7, 127)	222 (119, 362)
	<35 kg	9	48.6 (15.8)	136 (51.1)	51.9 (27.3, 67.8)	141 (66.3, 192)
	35 - <50 kg	20	64 (16)	166 (57.6)	63 (40.9, 89.2)	152 (88.8, 269)
	50 - <65 kg	35	77.1 (19.6)	197 (59.6)	78.4 (45.6, 104)	207 (105, 284)
	65 - <80 kg	40	88.5 (20.7)	236 (78.1)	90.2 (58.6, 118)	223 (128, 353)
	>= 80 kg	35	99.7 (23.6)	264 (86.7)	103 (72.7, 132)	264 (158, 394)
C_{max} (mg/L)	5 - <12 years	20	257 (51.9)	419 (99.4)	251 (186, 342)	415 (282, 589)
	12 - <18 years	14	365 (155)	566 (206)	394 (166, 582)	626 (296, 851)
	>=18 years	105	453 (137)	681 (185)	449 (270, 732)	660 (416, 1030)
	<35 kg	9	222 (28.2)	362 (75)	229 (176, 251)	377 (257, 449)
	35 - <50 kg	20	320 (124)	488 (147)	292 (200, 536)	473 (316, 690)
	50 - <65 kg	35	394 (125)	590 (164)	376 (227, 564)	573 (367, 886)
	65 - <80 kg	40	450 (144)	683 (172)	443 (281, 782)	665 (462, 1010)
	>= 80 kg	35	504 (122)	765 (183)	481 (342, 692)	783 (506, 1050)
AUC_{tau} (mg x day/L)	5 - <12 years	20	3390 (637)	7020 (1930)	3340 (2440, 4370)	7310 (3990, 9410)
	12 - <18 years	14	4210 (1220)	8650 (2770)	4730 (2440, 5640)	8680 (4960, 12300)
	>=18 years	105	4940 (959)	10100 (2720)	4930 (3360, 6370)	9890 (6230, 14400)
	<35 kg	9	2980 (481)	6110 (1670)	3190 (2290, 3500)	6360 (3790, 7980)
	35 - <50 kg	20	3800 (780)	7510 (1890)	3760 (2870, 4910)	7370 (4980, 10600)
	50 - <65 kg	35	4460 (930)	8820 (2160)	4480 (3020, 6100)	8990 (5370, 11800)
	65 - <80 kg	40	4930 (892)	10200 (2490)	4940 (3560, 6320)	10000 (6760, 14100)
	>= 80 kg	35	5410 (914)	11300 (2890)	5560 (4170, 6750)	11600 (7500, 15400)

* C_{min} corresponds to concentration after 2 8 days, i.e. C_{tau}

Immunogenicity

In the ongoing phase 3 study R1500-CL-17100, 1 patient in Part B developed treatment emergent ADAs of low titer. Two other patients tested positive for pre-existing ADAs. In the patient with treatment emergent ADAs, results of NAb testing were negative. There was no apparent effect of ADA on the pharmacokinetics of evinacumab or the LDL-C response profile in this patient.

2.4.3. Pharmacodynamics

Mechanism of action

Evinacumab is a recombinant human monoclonal antibody, which specifically binds to and inhibits angiopoietin-like protein (ANGPTL3). ANGPTL3 is an angiopoietin-like protein that is expressed primarily in the liver and plays an important role in the regulation of lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL).

In genetic studies in humans, individuals with loss-of-function (LOF) mutations in *ANGPTL3* had lower levels of LDL-C, high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG) and reduced risk of coronary artery disease (CAD) compared to individuals without these mutations.

Evinacumab reduces LDL-C independent of the presence of LDL receptor (LDLR) by promoting very low-density lipoprotein (VLDL) processing and clearance upstream of LDL formation. Evinacumab blockade of ANGPTL3 lowers TG and HDL-C by rescuing LPL and EL activities, respectively.

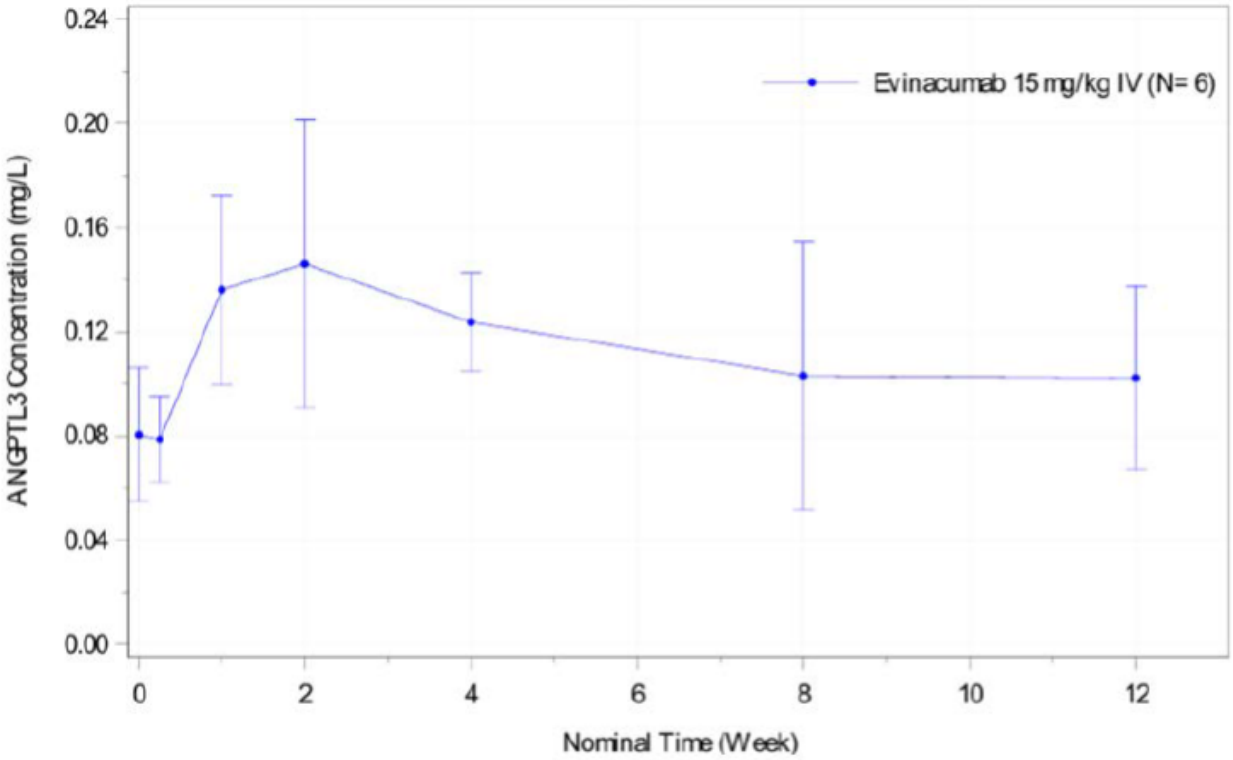
Primary and secondary pharmacology

Total ANGPTL3

When evinacumab is administered and is in excess of free ANGPTL3, the newly formed free target is rapidly complexed and ANGPTL3 primarily circulates in the complex form. With the slower elimination of the ANGPTL3-evinacumab complex relative to the formation of ANGPTL3 evinacumab complex, the concentrations of total ANGPTL3 increase from baseline.

In the phase1b/3 study R1500-CL-17100, following single dose administration of evinacumab 15 mg/kg IV in the 6 patients in Part A (5 who received apheresis), concentration-time profiles of total ANGPTL3 demonstrated the formation of a slowly eliminated complex between evinacumab and its target, ANGPTL3 (*Figure 7*). The concentration of ANGPTL3 increased in the 2 weeks following evinacumab administration and declined slowly back to baseline thereafter.

Figure 7. Mean (±SD) Concentrations of ANGPTL3 in Serum by Nominal Time in Paediatric Patients with HoFH Administered a Single Dose of Evinacumab 15 mg/kg IV in Part A (Study R1500-CL-17100)



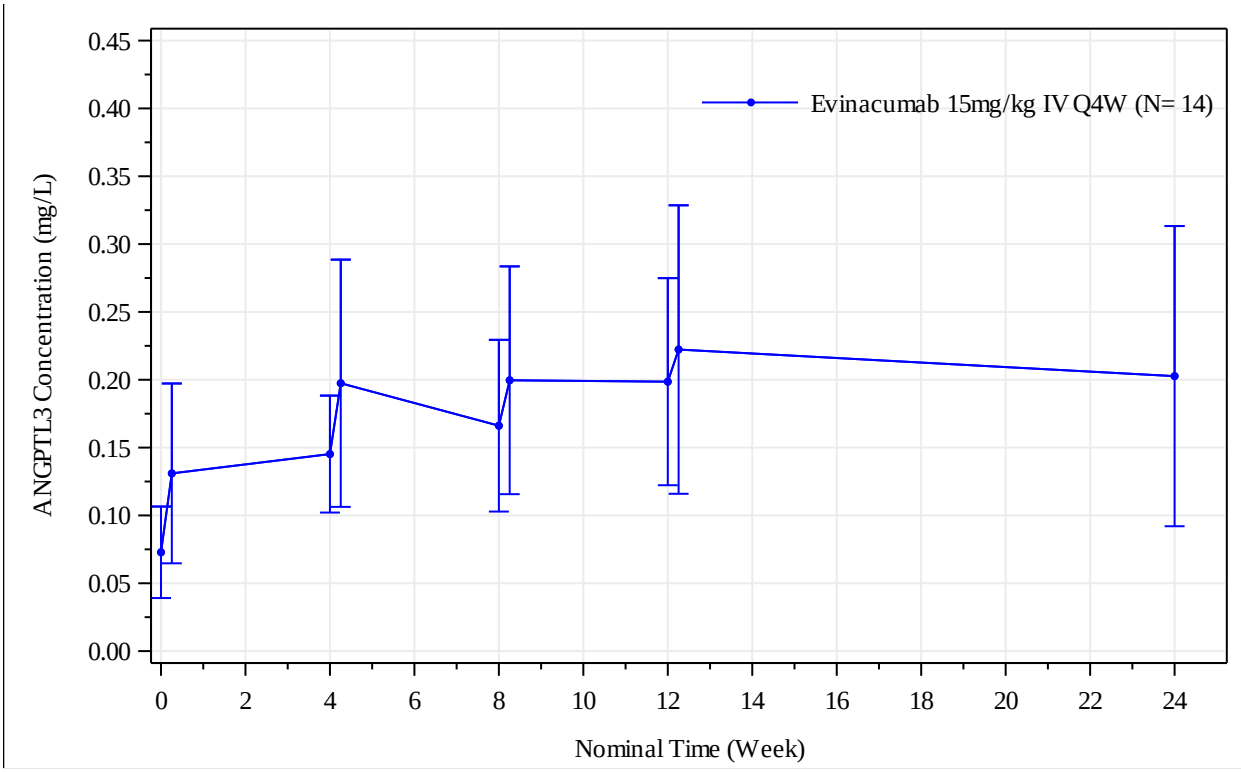
Actual Treatment for Period 01	W0 PRE	W0 EOI	W1	W2	W4	W8	W12
Evinacumab 15 mg/kg IV	6	5	5	6	6	6	6

N = Number of patients; EOI = End of infusion, Pre = Predose
Note: Concentrations below the lower limit of quantification (LLOQ; 0.0195 mg/L) are set to 0. Pre and EOI concentrations are jittered to separate the trough and peak concentrations.

Following multiple-dose administration of evinacumab 15 mg/kg IV in the 14 patients in Part B (7 who received apheresis), the concentration-time profiles of ANGPTL3 showed that mean ANGPTL3 concentrations tended to increase over time with notable increases between pre- and post-dose time points on each evinacumab administration until approximately week 12, commensurate with the accumulation and the time to achieve steady-state of evinacumab (*Figure 8*).

The ANGPTL3 concentrations during evinacumab treatment tended to be lower among the 7 patients in Part B who underwent apheresis compared with patients who did not undergo apheresis (*Figure 9*).

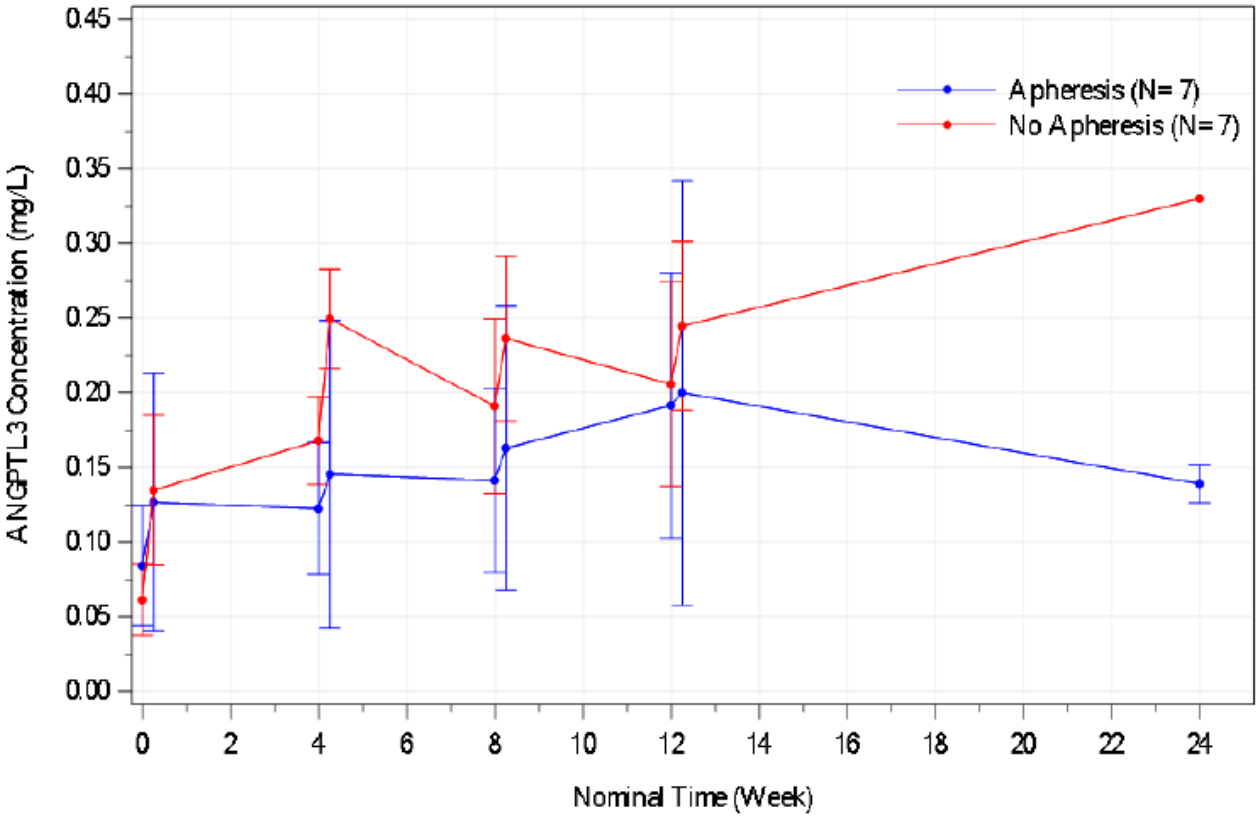
Figure 8. Mean (±SD) Concentrations of ANGPTL3 in Serum by Nominal Time in Paediatric Patients with HoFH Administered Evinacumab 15 mg/kg IV Q4W in Part B (Study R1500-CL-17100)



Actual Treatment for Period 01	W0 PRE	W0 EOI	W4 PRE	W4 EOI	W8 PRE	W8 EOI	W12 PRE	W12 EOI	W24
Evinacumab 15mg/kg IV Q4W	14	13	14	14	14	14	14	14	3

ANGPTL3, Angiopoietin-like protein 3; EOI, End of infusion; HoFH, homozygous familial hypercholesterolemia; IV, intravenously; N, Number of patients; Pre, Predose; Q4W, Every 4 weeks.
Note: Concentrations below the lower limit of quantification (LLOQ; 0.0195 mg/L) are set to 0. Pre and EOI concentrations are jittered to separate the trough and peak concentrations.

Figure 9. Mean (±SD) Total Concentrations of ANGPTL3 by Nominal Time and Apheresis Status in Paediatric Patients with HoFH Administered Evinacumab 15 mg/kg Q4W IV in Part B (Study R1500-CL-17100)



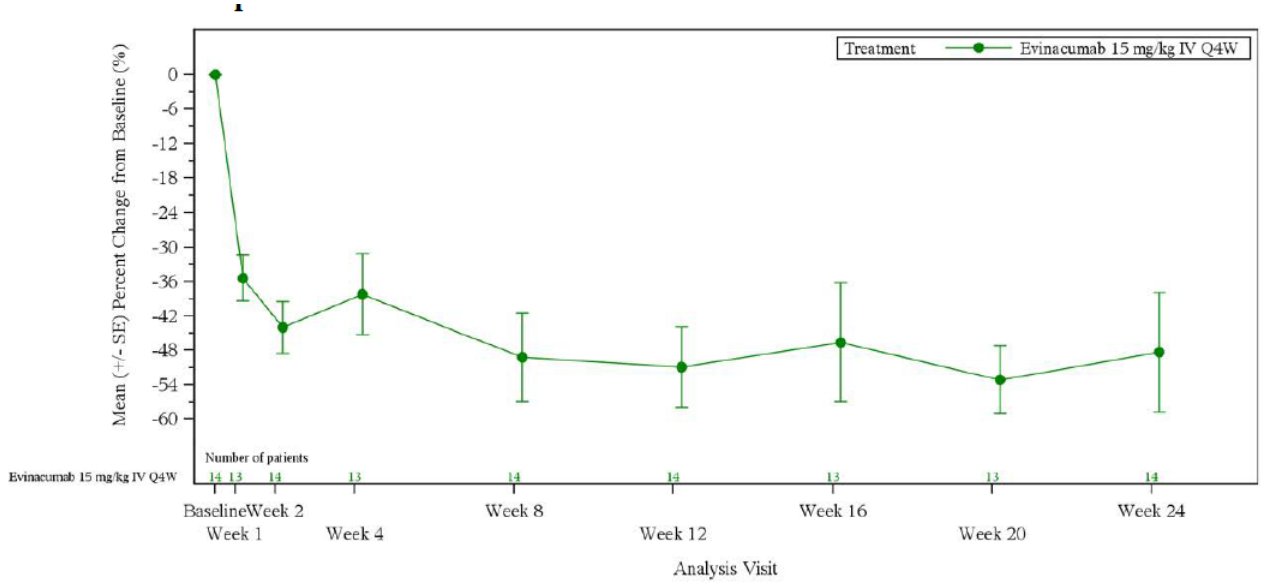
Apheresis Status	W0 PRE	W0 EOI	W4 PRE	W4 EOI	W8 PRE	W8 EOI	W12 PRE	W12 EOI	W24
Apheresis	7	6	7	7	7	7	7	7	2
No Apheresis	7	7	7	7	7	7	7	7	1

N = Number of patients; EOI = End of infusion, Pre = Predose
Note: Concentrations below the lower limit of quantification (LLOQ; 0.0195 mg/L) are set to 0. Pre and EOI concentrations are jittered to separate the trough and peak concentrations.

LDL-C

In study R1500-CL-17100, LDL-C concentrations decreased after a single 15 mg/kg IV administration of evinacumab in Part A, and 15 mg/kg Q4W evinacumab administration in Part B showed treatment-related decrease in LDL-C concentrations. For Part A, LDL-C decreased following the single dose IV administration and returned to baseline levels by Week 12 as the evinacumab concentrations approached below the limit of quantification (BLQ). For Part B, LDL-C decreases were near-maximal by week 4 and means did not change markedly throughout the rest of the treatment period even though mean evinacumab concentrations continued to increase until achievement of steady-state (ie, up to weeks 8 to 12) (*Figure 10*).

Figure 10. Calculated LDL-C Combined Estimate of Mean (±SE) Percent Change from Baseline Over Time (ITT estimand) in Part B: Raw Data Description – ITT Population



Immunogenicity

One patient demonstrated a treatment-emergent ADA response which was low-titer and observed during Q4W dosing in Part B. The LDL-C response profiles of the ADA-positive patients lay within the distribution of the LDL-C response profiles of ADA-negative patients, suggesting that the positive ADA results did not affect the LDL-C responses for this patient. Similar trends were apparent in corresponding plots for change from baseline in ApoB, non-HDL-C, and Lp(a).

2.4.4. PK/PD modelling

The relationship between evinacumab pharmacokinetics and pharmacodynamics (LDL-C lowering) was evaluated in the population pharmacokinetic/pharmacodynamic analysis.

Observed baseline LDL-C concentration was higher in paediatric patients compared to adolescent, and adult patients (*Table 6*). In the final PK/PD model, age was identified as a statistically significant descriptor on baseline LDL (LDL0 parameter) resulting in a higher baseline LDL-C concentration in patients with a lower age.

Despite these lower exposures, the predicted magnitude of LDL-C reduction was maintained and appeared even larger in paediatrics and adolescents compared to adults. Simulation based upon post-hoc Bayesian estimates predicted median values of the percent change (reduction) from baseline in LDL-C at Week 24 of 67.9%, 59.6%, and 56% in patients ≥5 to <12 years of age, ≥12 to <18 years of age, and ≥18 years of age, respectively (*Figure 11* and Table PK8).

Figure 11 Median and 80% Prediction Interval of Post-hoc Model-Based Predictions of Percent Change from LDL-C Baseline in Patients with Homozygous Familial Hypercholesterolemia After 15 mg/kg Infusions Every 4 Weeks, Stratified by Age Group

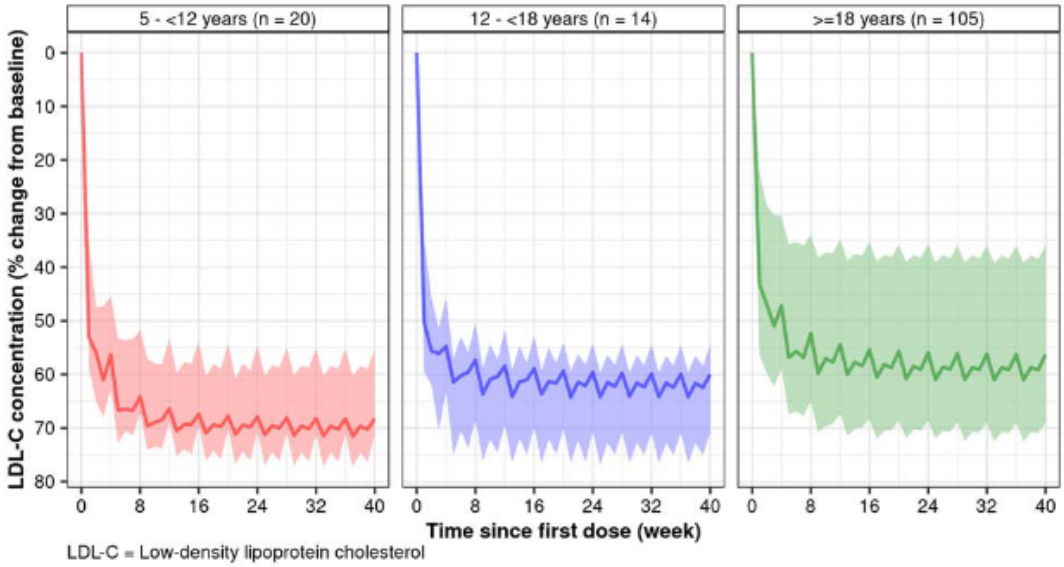


Table PK8. Post-hoc Bayesian Estimates of Percent Change (Reduction) from LDL-C Baseline at Week 24 in Patients with Homozygous Familial Hypercholesterolemia

Variable	Category	Mean (SD)	Median	Min, Max	n
Age	5 - <12 years	64.2 (8.26)	67.9	38.3, 73.9	20
	12 - <18 years	61.7 (7.25)	59.6	50.8, 76.4	14
	>=18 years	53.7 (13.2)	56	16.7, 86.5	105
Weight	<35 kg	65.5 (10.6)	69.4	38.3, 72.3	9
	35 - <50 kg	61.2 (7.33)	61	46.2, 76.4	20
	50 - <65 kg	58 (10.6)	57.2	34.2, 86.5	35
	65 - <80 kg	57 (11.8)	58.1	16.7, 79.2	40
	>= 80 kg	47.6 (14.6)	48	19.8, 68.9	35
Overall		56 (12.7)	58	16.7, 86.5	139

Max, Maximum; Min, Minimum; LDL-C, Low-density lipoprotein cholesterol; n, Number of patients; SD, Standard deviation

2.4.5. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of evinacumab in paediatric patients have been appropriately evaluated using population pharmacokinetic models. The first population pharmacokinetic analysis was not deemed fit for purpose as it was discovered during the analysis that 488 quantifiable pharmacokinetic samples (i.e., concentrations > 0.078 mg/L) from Study R1500-CL-1642 had been mislabelled as below the lower limit of quantification (BLQ) in the original dataset that formed the basis of the population pharmacokinetic model submitted at initial marketing application. This update and comparison of pharmacokinetics between paediatrics, adolescents and adults was therefore based on the second population pharmacokinetic analysis (R1500-PM-23041-SR-01V1). Additional p(v)cVPCs of the studies stratified by age group (i.e. aged 5 to 12 years, 12 to 18 years, and >18 years) were provided by the Applicant. These diagnostic plots indicate that the model is appropriate to characterise the

typical evinacumab pharmacokinetic profile over the paediatric age range (5 years and over) and adult patients. Overall, the final model is considered to describe the paediatric data sufficiently well.

The absorption, distribution and elimination sub-sections of section 5.2 of the SmPC were updated based on the submitted second population pharmacokinetic model (R1500-PM-23041-SR-01V1), which is appropriate.

Pharmacodynamics

Evinacumab has a proposed new mechanism of action. It is a human monoclonal antibody against angiopoietin-like protein 3 (ANGPTL3), which play a role in the regulation of lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL). This would lead to a reduction in LDL-C; independent of the presence of an LDL receptor, by promoting very-low-density lipoprotein (VLDL) processing and clearance, thereby reducing the VLDL pool available to generate LDL. Although the mechanism is not completely understood, based on more recent studies, it is hypothesized that especially endothelial lipase (EL) rather than LPL plays a more crucial role in the reduction of LDL-C via VLDL processing. Further, it is not known how evinacumab influences HDL-C function as a consequence of lowering of HDL-C and alteration of the homeostasis of other lipid parameters, especially in the setting of extremely elevated LDL-C levels as presented by the HoFH phenotype. Any potential for liver fat accumulation seems unlikely, as studies suggest no role of evinacumab in the VLDL processing in the liver.

Total ANGPTL3 was used as target engagement marker, whereas LDL-C is the main lipid parameters used to assess the pharmacodynamics of evinacumab.

Effects on ANGPTL3 and LDL-C have been characterized following a single 15 mg/kg IV infusion (Part A) and during multiple 15 mg/kg Q4W IV infusions (Part B) in paediatric patients with HoFH aged 5-≤ 11 years in the phase 1b/3 study R1500-CL-17100. A single dose administration of evinacumab 15 mg/kg IV in the 6 patients with HoFH aged 5-≤ 11 years in Part A (5 who received apheresis) resulted in increases in total ANGPTL3 up to week 2 after which total ANGPTL3 declined slowly back to baseline. Multiple-dose administrations of evinacumab 15 mg/kg IV in the 14 paediatric patients with HoFH aged 5-≤ 11 years in Part B (7 who received apheresis) resulted in an increase in total ANGPTL3 over time with notable increase between pre- and post-dose time points until ~ week 12, i.e. the time to achieve steady state. Further, ANGPTL3 concentrations during evinacumab treatment were lower in patients who underwent apheresis compared with patients who did not undergo apheresis.

Regarding the PD parameter LDL-C, multiple doses of evinacumab 15 mg/kg IV in the 14 paediatric patients with HoFH aged 5-≤ 11 years in Part B in study R1500-CL-17100, resulted in near-maximal LDL-C decreases by Week 4 of ~40% even though mean evinacumab concentrations continued to increase until achievement of steady-state (i.e. up to weeks 12) (see also efficacy section).

Further, a low incidence of anti-drug antibody has been observed (n=1 in study R1500-CL-17100), which was low-titer and did not affect the LDL-C response.

Pharmacokinetics/Pharmacodynamics

The pharmacokinetic and pharmacodynamic (LDL-C reduction) relationship of evinacumab in paediatric patients has been sufficiently evaluated. VPCs of the studies R1500 CL 1719 and R1500 CL 17100 are considered acceptable, even though the final model slightly overestimates the mean observed LDL-

C concentrations and its variability in paediatrics (study R1500 CL 17100 part B). Overall, the final model is considered to describe the paediatric data sufficiently well.

2.4.6. Conclusions on clinical pharmacology

To support the extension of the therapeutic indication for evinacumab to include paediatric patients aged 5 years to <12 years with homozygous familial hypercholesterolemia (HoFH), interim results from paediatric Study R1500-CL-17100 and supportive updated interim data for adolescents and adults from Study R1500-CL-1719 were provided and assessed in an extrapolation analysis (including population pharmacokinetic, population pharmacokinetic/pharmacodynamic, and simulations analyses). The analysis was a partial extrapolation of efficacy, as both pharmacokinetic and pharmacodynamic (LDL-C) samples were obtained in the population aged 5 years and older.

Pharmacokinetics

The results of the population pharmacokinetic analysis demonstrate that the overall plasma exposure in paediatric patients of 5-12 years is approximately 30% lower compared to adult patients, which is most likely explained by the lower bodyweight in the paediatric population. Immunogenicity results in the paediatric population are limited, but indicate no clinical impact.

Pharmacodynamics

Similar to the adult population, the proof of concept of evinacumab in inhibition of ANGPTL3, as measured by an increase in total ANGPTL3, and the subsequent decrease in LDL-C has sufficiently been demonstrated in the paediatric population.

Pharmacokinetics/Pharmacodynamics

The results of the population pharmacokinetic and pharmacokinetic/pharmacodynamic modelling demonstrate that the plasma exposure in paediatric patients is slightly lower compared to adolescent and adult patients. However, it can be concluded that the LDL-C reduction is higher in paediatric patients. The difference can most likely not be explained by differences in target saturation between populations throughout the treatment period, but is more likely explained by differences in disease severity between paediatric, adolescent and adult patients. Therefore, it can be concluded that the 15 mg/kg dose is also suitable for paediatric patients.

2.5. Clinical efficacy

The initial marketing authorization of evinacumab for the treatment of HoFH in adult and adolescent patients aged 12 years and older was based on data from R1500-CL-1629, a pivotal Phase 3, double-blind, placebo-controlled study in adult and adolescent patients (12 to <18 years) with HoFH, with a 24-week double-blind treatment period (DBTP), in a background of other lipid-lowering therapies (e.g. statins, ezetimibe, PCSK9 inhibitor antibodies, lomitapide, and lipoprotein apheresis), and a 24-week Open-label Treatment Period (OLTP). The study was further supported by several other studies, including early data from an ongoing long-term, open-label safety and efficacy extension study in patients with HoFH (R1500-CL-1719). Adolescent patients were included in the pivotal phase 3 study (R1500-CL-1629) as well as in the open-label extension study (R1500-CL-1719) due to the high unmet medical need in this patient group.

The current extension of indication application is based on interim data from Study R1500-CL-17100, an ongoing Phase 1b/3 single-arm, open-label study designed to evaluate the long-term safety and efficacy of evinacumab in paediatric (≥5 to <12 years) patients with HoFH, as well as supportive information from a recent updated interim analysis of the ongoing open-label extension study, R1500-

CL-1719 in adolescent (and adult) patients with HoFH, and an extrapolation analysis (including population PK, population PK/PD, and simulation analyses) (Table 9).

Table 9. Phase 3 Clinical Studies in the Evinacumab Clinical Program

Study / Report Status	Study Population/ Analysis Sets	Efficacy-Related Objective	Study Design and Duration	Treatment: Dose, Route of Administration, Frequency (number of patients treated)
Phase 3 Studies				
R1500-CL-17100 Part A: Completed Part B: Completed Part C: Ongoing, closed to enrollment	Males and females aged ≥5 to <12 years with HoFH, diagnosed by either genetic or clinical criteria, receiving any combination of LMT	Demonstrate a reduction of LDL-C (and other lipid parameters) by evinacumab	3-part single-arm, OL study: Part A: single dose PK/PD Part B: 24-week efficacy and safety Part C: 48-week treatment period; 24-week follow-up period (may forgo if continuing evinacumab by other means)	Evinacumab 15 mg/kg IV single dose (Part A N=6) Evinacumab 15 mg/kg IV Q4W (Part B N=14; all 20 patients continued in Part C)
R1500-CL-1719 Ongoing, closed to enrollment	Male and female adults (≥ 18 years of age) and adolescents (≥ 12 to < 18 years of age) with HoFH. Includes patients from R1500-CL-1331 and R1500-CL-1629 studies and evinacumab-naïve patients	Evaluate the effect of evinacumab on lipid parameters (ie LDL-C, Apo B, non-HDL-C, TC, and TG))	OL study that consists of a run-in period (for patients who may require HoFH genotyping, patients whose background medical LMT has not been stable prior to screening, or those whose apheresis settings and/or schedule have not been stable for at least 8 weeks prior to screening), a Screening Period, an OLTP, and a Follow-up Period	Evinacumab 15 mg/kg IV Q4W for up to approximately 4 years (Total Population N=116; New Evinacumab n=46, Continue Evinacumab n=70; Adolescent Population n=14)[a]

[a] The remaining patient (#20) transitioned to Part C after the Part B data cut-off.
CSR, Clinical Study Report; DBTP, Double-blind Treatment Period; HoFH, homozygous familial hypercholesterolemia; IV, intravenous; OL, open-label; OLE, Open-label Extension; OLTP, Open-label Treatment Period; Q4W, every 4 weeks.

2.5.1. Extrapolation concept

To support use of evinacumab in patients ≥5 to <12 years of age with HoFH, an extrapolation analysis (including population pharmacokinetics [PK], population PK/pharmacodynamics (PD) [population PK/PD], and simulations analyses) has been conducted.

There are several considerations that justify the overall approach to extrapolate data from adults as outlined in outlined in the CHMP "*Reflection paper on the use of extrapolation in the development of medicines for paediatrics" (EMA/189724/2018) and the draft "ICH guideline E11A on paediatric extrapolation" (EMA/CHMP/ICH/205218/2022)*.

Development of a paediatric extrapolation concept requires an understanding of the factors that influence the similarity of disease, the pharmacology of the drug and the response to therapy as well as the safety of use in all the relevant populations.

Disease similarity

HoFH is an ultra-rare and serious genetic condition, which requires early diagnosis and treatment beginning in infancy for the best outcomes. The aetiology of the hypercholesterolemia observed in patients with HoFH is the same for both adult and paediatric patients. Hypercholesterolemia is a consequence of the abnormal lipoprotein metabolism due to mutations in the key genes, mutations in the low-density lipoprotein receptor (*LDLR*) gene and less frequently by mutations in the proprotein convertase subtilisin/kexin type 9 (*PCSK9*), apolipoprotein B (*APOB*), and LDL receptor adaptor protein 1 (*LDLRAP1*) genes, and the markedly diminished hepatic LDL-C clearance from plasma. Additional phenotypic characteristics include premature CVD, aortic valve disease, and tendon xanthomas in the hands and Achilles' tendons.

As the aetiology of HoFH is the same for both adult and paediatric patients, the overarching goal of therapy is also the same, to lower LDL-C, and subsequently the risk of ASCVD:

- The EAS/European Society of Cardiology (ESC 2014) consensus panel on FH recommends initiation of lipid-lowering therapy in patients with HoFH as soon as possible after diagnosis, with the goal of reducing LDL-C levels to <2.5 mmol/L (<100 mg/dL) in adults or <3.5 mmol/L (<135mg/dL) in children or <1.8 mmol/L (70 mg/dL) in adults with clinical ACVD (Cuchel et al., 2014; Wiegman et al., 2015).
- The ESC/EAS Consensus panel recommends that in patients with FH and at very high risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended (Mach et al., 2020).

  In the same guideline, in children, testing for HF is recommended from the age of 5 or earlier if HoFH is suspected. Children with FH should be educated to adopt a proper diet and treated with a statin from 8-10 years of age. Goals for treatment should be LDL-C < 3.5 mmol/L (<135 mg/dL) at > 10 years of age.

Similar drug pharmacology

No specific information on this consideration has been provided by the Applicant.

Similar exposure response

No specific information on this consideration has been provided by the Applicant.

2.5.2. Dose response study(ies)

The collective results from the aforementioned phase 1 studies in healthy participants (R1500-HV-1214, R1500-CL-1321, and R1500-CL-1642) as well as phase 2 (R1500-CL-1331) and phase 3 (R1500-CL-1629 and R1500-CL-1719) studies in adult and adolescent patients with HoFH were used to inform the paediatric clinical pharmacology program for evinacumab. The objectives of the paediatric clinical pharmacology program were to select the appropriate dose regimen for paediatric patients with HoFH (aged ≥5 to <12 years) and to characterize the total evinacumab serum PK, the total ANGPTL3 serum concentrations, as a measure of target engagement, and the immunogenicity potential of evinacumab in these patients. In Part A of Study R1500-CL-17100, paediatric patients with HoFH were administered a single dose of evinacumab 15 mg/kg IV. The PK data from Part A were analyzed and evaluated in concert with the data from adults and adolescents using population PK methods which

confirmed that the 15 mg/kg dose in paediatric patients was comparable to the EMA approved dose in the adult and adolescent populations studied. In Part A, the mean percent LDL C reductions at Week 4 after single-dose evinacumab was approximately -26.0%. Based on these analyses, a dose of 15 mg/kg IV Q4W was selected for Part B of study R1500-CL-17100 wherein patients received multiple doses of evinacumab over 24 weeks. In Part B, the mean percent LDL C reductions at Week 4 after single-dose evinacumab administration was approximately -38.3%, which was consistent with the percent LDL-C reductions at Week 4 previously reported for adults from Study R1500-CL-1331 (approximately -30.1%) and adults and adolescents from the double-blind treatment period (DBTP) of Study R1500-CL-1629 (approximately -39.6%). Multiple dose administration of evinacumab 15 mg/kg IV Q4W over 24 weeks in the paediatric population resulted in lower steady-state evinacumab concentrations relative to those observed in the adult population. Despite these lower exposures, at 24 weeks, the 48.3% LDL-C reduction in the paediatric population was comparable to the 47.1% LDL C reduction observed in the adult and adolescent population in the DBTP of Study R1500 CL-1629, suggesting that the steady-state evinacumab concentrations in paediatric patients were sufficient to achieve maximal target engagement.

Based on the clinically and statistically meaningful reduction in LDL-C comparable to that observed in the adult and adolescent populations with HoFH, together with PK and ANGPTL3 data, the dose regimen of 15 mg/kg IV Q4W was confirmed for this paediatric population.

Multiple model-based simulations were performed to predict and compare evinacumab exposures and LDL-C lowering effects in paediatric, adolescent, and adult patients with HoFH at the clinically relevant dosing regimen of 15 mg/kg IV Q4W. Results based upon typical estimates in prototypical individuals, post-hoc Bayesian estimates in the patients with HoFH included in the PK/PD analysis dataset, or the model predicted variability in a large population of virtual paediatric and adult patients consistently indicated that, although evinacumab exposures were lower in paediatric patients than in adult patients, similar or greater magnitudes of LDL-C reduction from baseline could be achieved in younger patients at the same mg/kg dose. Simulations based upon post-hoc Bayesian estimates predicted median values of percent change (reduction) from baseline in LDL-C at Week 24 of 67.9%, 59.6%, and 56% in patients ≥5 to <12 years of age, ≥12 to <18 years of age, and ≥18 years of age, respectively.

Similarity of treatment response across age groups was also demonstrated using model-based simulations to estimate the percentage of patients predicted to achieve LDL-C concentrations <2.8 mmol/L (or <110 mg/dL) and <3.4 mmol/L (or <130 mg/dL) by Week 24 following 15 mg/kg Q4W infusions. The threshold of <3.4 mmol/L (<130 mg/dL) was achieved by more than half of all virtual patients in all age and weight groups, despite baseline LDL-C concentrations being higher in the 5 to <12 age group (422 mg/dL on average) than in adults (255 mg/dL on average), with the percentage of target attainment ranging from 56.4% in patients ⩾5 to <12 years of age to 67.4% in adult patients.

2.5.3. Main study(ies)

Study R1500-CL-17100- A three-part, single-arm, open-label study to evaluate the efficacy, safety, and pharmacokinetics of evinacumab in paediatric patients with homozygous familial hypercholesterolaemia

R1500-CL-17100 is an ongoing 3-part, phase 1b/3 open-label study evaluating evinacumab in a total of 20 paediatric patients with HoFH aged ≥5 to <12 years. The study includes Part A (PK/PD), Part B (24-week primary efficacy and safety) and Part C (48-week treatment period and 24-week follow-up

period). For Part C, patients who entered a compassionate use program (CUP) or early access program (EAP) may forgo the 24-week follow-up period.

Methods

The study is composed of 3 parts:

- Part A (completed; data cut-off 11 Feb 2011): phase 1b, single arm, single dose (evinacumab 15 mg/kg IV) PK/PD study in patients (completed) aged 5 to 11 years with HoFH (Figure 12).

  Part A consisted of up to 4 periods: run-in (≤ 8 weeks); screening (1-2 weeks); single-dose open-label treatment and 16-week observation post drug administration; and a follow-up period (for patients who do not enter Part C). Upon completion of Part A, patients had the opportunity to continue into Part C.

- Part B (completed; data cut-off 31 Ja 2022): phase 3, single-arm, 24-week, open-label efficacy and safety study of evinacumab 15 mg/kg IV Q4W in patients age 5 to 11 years with HoFH (Figure 13). Patients enrolled into Part B did not include patients from Part A.

  Part B consisted of up to 4 periods: run-in (≤ 8 weeks); screening (1-2 weeks); 24-week open-label treatment; follow-up. (Since all patients entered Part C, the follow-up period of Part B was not applicable). Upon completion of Part B, all patients continued into Part C.

- Part C (ongoing; data cut-off 02 June 2022): ongoing phase 3, 48-week treatment period and 24-week follow-up period of evinacumab 15 mg/kg IV Q4W in patients who previously completed Parts A and B (patients who enter a compassionate use or early access program may forgo the 24 week follow-up period)(Figure 14). The first visit (visit 1) in Part C could occur on the same day as the EOT visit in Part A (visit 11)/Part B (visit 11).

Following completion of Part A, the PK, LDL-C, and safety data were evaluated in order to determine the dose to be used in Parts B and Part C. The dose determined from Part A for use in subsequent parts was 15 mg/kg IV Q4W, the same dose approved for patients aged ≥12 years.

Figure 12. Study Flow Diagram Part A

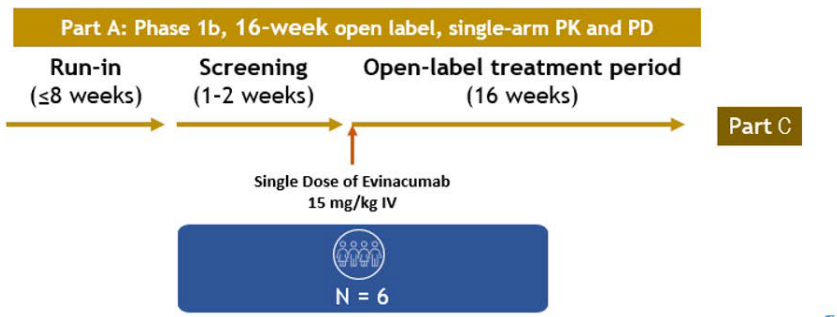


Figure 13. Study Flow Diagram Part B

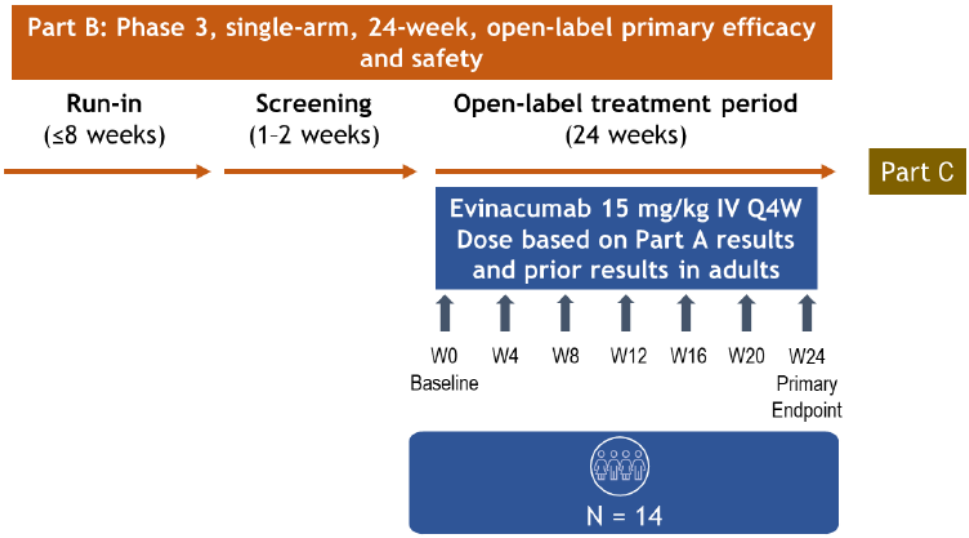
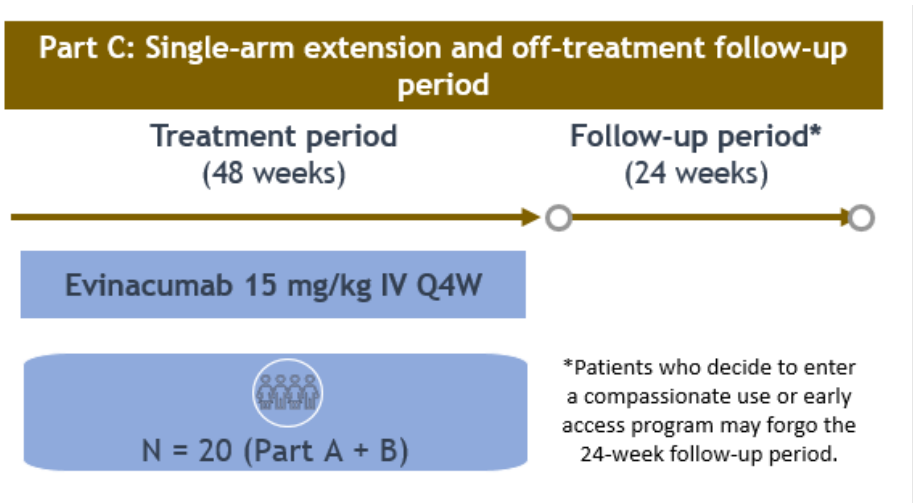


Figure 14. Study Flow Diagram – Extension



Study participants

The main inclusion/exclusion criteria are provided in Table 10 below.

Table 10. Key inclusion/exclusion criteria Study R1500-CL-17100

Study R1500-CL-17100
Inclusion Criteria

- males and females age 5 – 11 years with HoFH diagnosed by either genetic or clinical criteria, receiving any combination of lipid-lowering therapies *Genetic criteria* - Documented functional mutation or mutations in both LDLR alleles Note: Patients who had null receptor mutations on both LDLR alleles, ie, double null, were eligible OR - Documented homozygous mutations in LDLRAP1, or homozygous or compound heterozygous mutations in APOB or PCSK9. Note: Patients who were double heterozygous, i.e. mutations on different genes [LDLR/PCSK9 or LDLR/APOB] were eligible *Clinical criteria* - Untreated TC >500 mg/dL (>13 mmol/L) and triglycerides (TGs) <300 mg/dL (<3.39 mmol/L) AND Both parents with documented TC >250 mg/dL (6.47 mmol/l) OR cutaneous or tendinous xanthoma in the study patient before age 10 years
- LDL-C >130 mg/dL at the screening visit
- Body weight ≥15 kg
- Receiving stable maximally tolerated therapy* at the screening visit *Maximally tolerated therapy could include a daily statin. Note: Patients who were not able to be on a maximum daily statin were required to be on the appropriate dose for the patient or no statin, according to the investigator's judgment. Some examples of acceptable reasons for a patient taking a lower statin dose included, but were not limited to: adverse effects on higher doses, lack of efficacy, regional practices, local prescribing information, concomitant medications. The reason(s) were required to be documented in the case report form (CRF).
Exclusion Criteria
- Background pharmacologic LMT, nutraceuticals or over-the-counter (OTC) therapies known to affect lipids, at a dose/regimen that has not been stable for at least 4 weeks (8 weeks for PCSK9 inhibitors) before the screening visit and patient is unwilling to enter the run-in period
- For patients entering Part A, unable to temporarily discontinue apheresis from the baseline visit through the week 4 visit
- Receiving lipid apheresis, a setting (if applicable) and schedule that has not been stable for approximately 8 weeks before the screening visit or an apheresis schedule that is not anticipated to be stable over the duration of the treatment period (48 weeks). A stable schedule is defined as a weekly (every 7±1 days) or every other week (every 14±2 days) schedule
- Plasmapheresis within 8 weeks of the screening visit, or plans to undergo plasmapheresis during Part A or Part B
- Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins
- Newly diagnosed (within 3 months prior to randomization visit [week 0/day 1]) diabetes mellitus or poorly controlled (hemoglobin A1c [HbA1c] >9%) diabetes
- Chronic use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to randomization Note: topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are not considered as 'systemic' and are allowed
- History of a myocardial infarction (MI), percutaneous coronary intervention (PCI), uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack (TIA), valve replacement surgery, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease within 3 months prior to the screening visit
- Laboratory findings during screening period (not including randomization labs): • Positive urine pregnancy test in females of childbearing potential • Triglycerides >300 mg/dL (>4.52 mmol/L) (1 repeat lab is allowed)

• Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x upper limit of normal (ULN) (1 repeat lab is allowed) • CPK >3 x ULN (1 repeat lab is allowed)

Objectives/endpoints

The objectives/endpoints of Study R1500-CL-17100 are presented in

Table *11*.

Table 11. Objectives and endpoints of Study R1500-CL-17100

Objectives	Endpoints
Primary Objective Part A	Primary Endpoints for Part A
• To assess the PK of evinacumab in paediatric patients with HoFH	• The PK parameters for evinacumab, including maximum concentration (Cmax), area under the plasma concentration-time curve (AUC), and linear half-life (t1/2), following a single administration of evinacumab
Primary Objective Part B	Primary Endpoint for Part B
• To demonstrate a reduction of LDL-C by evinacumab in paediatric (5 to 11 years of age) patients with HoFH	• The percent change in calculated LDL-C from baseline to week 24 (ITT estimand) in Part B. The primary efficacy endpoint is defined as: 100x (calculated LDL-C value at week 24 minus calculated LDL-C value at baseline) divided by calculated LDL-C value at baseline
Secondary Objectives for Part A	Secondary Endpoint for Part A
• To evaluate the safety and tolerability of evinacumab administered IV in paediatric patients with HoFH	• Incidence of TEAEs and other safety variables over time
Secondary Objectives for Part B	Secondary Endpoint for Part B
• To evaluate the effect of evinacumab on other lipid parameters (ie, Apo B, non- HDLC, total cholesterol [TC], lipoprotein a [Lp(a)]) in paediatric patients with HoFH	• The percent change in Apo B from baseline to week 24 (ITT estimand) • The percent change in non-HDL-C from baseline to week 24 (ITT estimand) • The percent change in TC from baseline to week 24 (ITT estimand) • The proportion of patients with ≥50% reduction in calculated LDL-C at week 24 (ITT estimand) • The percent change in calculated LDLC from baseline to week 24 in patients who have

	negative/negative and null/null mutations (ITT estimand) • The percent change in Lp(a) from baseline to week 24 (ITT estimand) • The absolute change in LDL-C at week 24 (ITT estimand)
• To evaluate the safety and tolerability of evinacumab administered IV in paediatric patients with HoFH	• Incidence of TEAEs and other safety ariables over time
• To assess the PK of evinacumab in paediatric patients with HoFH	• Concentrations of total evinacumab over time • PK parameters including $C_{max,ss}$, $AUC_{tau.ss}$, $C_{trough.ss}$
• To assess the immunogenicity of evinacumab in paediatric patients with HoFH over time	• Incidence and titer of treatment emergent anti-drug antibodies (ADA) over time
• To evaluate patient efficacy by mutation status	• The percent change in calculated LDLC from baseline to week 24 (ITT estimand) in Part B by null/null vs. nonnull/ null and negative/negative vs. nonnegative/ negative. The primary efficacy endpoint is defined as: 100x (calculated LDL-C value at week 24 minus calculated LDL-C value at baseline) divided by calculated LDL-C value at baseline
Exploratory Objectives	Exploratory Endpoints
• To evaluate the efficacy of evinacumab in the extension of the study (Part C) in patients with HoFH	• Percent change from baseline in LDL-C, Apo B, Non-HDL-C, Total Cholesterol, and Lp(a) over time
• To explore vascular changes using imaging techniques	• Vascular changes via carotid intima-media thickness at baseline and at 6-month intervals, as clinically indicated (for intra-patient comparison)

Sample size

Not performed.

Randomisation

This was an uncontrolled study.

Blinding (masking)

This was a single arm study.

Statistical methods

In Study R1500-CL-17000, the endpoints were chosen and analyzed to match those for the adult studies.

The derivations and models were performed with conventional units when statistics are not affected from using international and conventional units do not impact the results (e.g. means and least square (LS) means for percent changes from baseline, rates of patients below a threshold). For other statistics (e.g. descriptive statistics at baseline and over time, absolute changes from baseline), derivations were presented in both international and conventional units.

Results

Treatment with evinacumab in the overall Adolescent Population resulted in an absolute mean (SD) and median (Q1:Q3) change from baseline in calculated LDL-C at Week 24 of -4.676 (2.5113) mmol/L (-180.5 [96.88] mg/dL) and -4.615 mmol/L (-6.840:-3.470) (−178.0 mg/dL [-264.0:-134.0]). The respective mean (SD) and median (Q1:Q3) percent change from baseline at Week 24 in the overall Adolescent Population were -55.36% (25.288) and −61.44% (-71.13:-49.96) (n=12) (Table 21). The decreases in mean (SD) and median (Q1:Q3) percent change from baseline in LDL-C were greater in the New Evinacumab group (-60.32% [11.912] and -61.44% [-69.11:-52.91]) (n=10) compared with the Continue Evinacumab group (-30.55% [65.423] and -30.55% [-76.81:15.71]) (n=2) at Week 24, with reductions in LDL-C with evinacumab observed as early as the first post-baseline lipid measurement at Week 8 in the New Evinacumab group.

The reductions from baseline in LDL-C were maintained through at least Week 88 (mean [SD] and median [Q1:Q3] percent change from baseline at Week 88 of −44.95% [39.078] and −57.72% [−62.72:−36.14] for the Total Evinacumab group; n=9), after which time the results were more variable due to the smaller number of patients contributing to data (1 each from the New and Continue Evinacumab groups) (Figure 15).

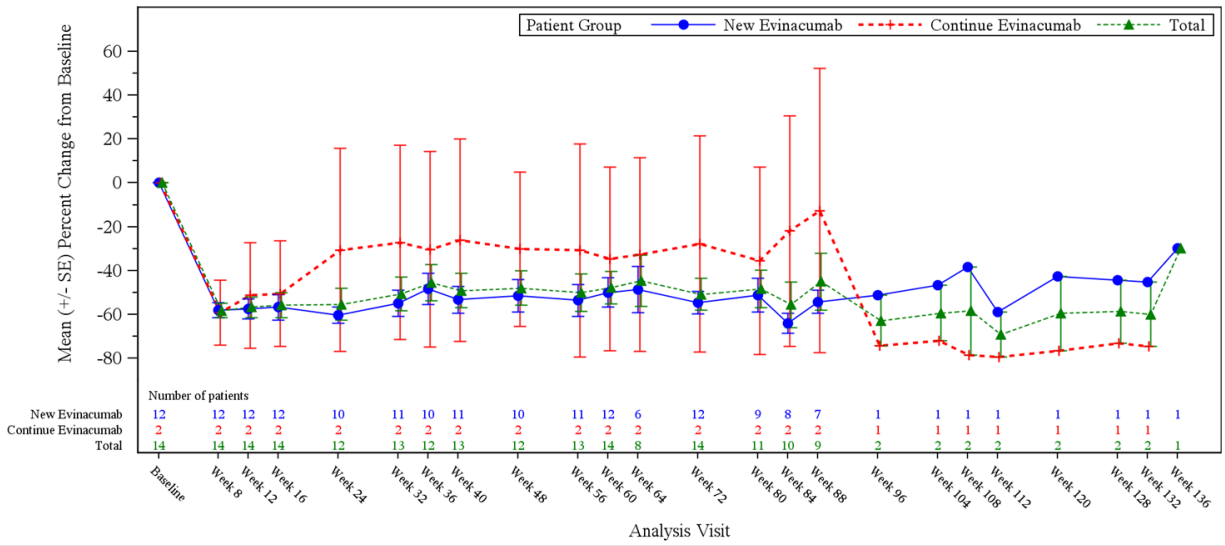
Changes from baseline in LDL-C were in line with results for the Total Population. Treatment with evinacumab in the Total Population resulted in an absolute mean (SD) and median (Q1:Q3) change from baseline in calculated LDL-C at Week 24 of -3.419 (3.2217) mmol/L (-132.0 [124.37] mg/dL) and -2.365 mmol/L (-5.080:-1.300) (-91.5 mg/dL [-196.0:-50.0]). The respective mean (SD) and median (Q1:Q3) percent change from baseline at Week 24 were -43.64% (37.606) and -53.14% (-65.16:-34.99) (n=86). The reductions from baseline in LDL-C were maintained through at least Week 120 (mean [SD] and median [Q1:Q3] percent change from baseline at Week 120 of -30.78% [69.693] and -49.71% [-64.03:-32.96] for the Total Evinacumab group; n=34), after which time the results were more variable.

Within the R1500-CL-1719 Adolescent Population, results of subgroup analysis by sex and race were similar to the Total Population. Regarding mutation status, the mean (SD) percent change in LDL-C from baseline to Week 88 for the 4 patients (Total Evinacumab group) with a null/null mutation was 63.25% (9.789). The mean (SD) percent change in LDL-C from baseline to Week 88 for the 4 patients (Total Evinacumab group) with a negative/negative mutation was 22.21% (52.302).

Table 12. R1500-CL-1719: Calculated LDL-C Over Time in SI Units for Adolescent Population – Safety Analysis Set

	New Evinacumab (N=12)			Continue Evinacumab (N=2)			Total Evinacumab (N=14)		
Calculated LDL-C (mmol/dL)	Value	Change from baseline	Percent change from baseline	Value	Change from baseline	Percent change from baseline	Value	Change from baseline	Percent change from baseline
Baseline									
n	12			2			14		
Mean	7.911			7.010			7.782		
(SD)	(2.4096)			(4.7800)			(2.6034)		
Median	7.860			7.010			7.860		
Q1:Q3	5.815: 10.155			3.630:10.390			4.920:10.390		
Min:Max	4.45 : 11.09			3.63 : 10.39			3.63 : 11.09		
Week 24									
n	10	10	10	2	2	2	12	12	12
Mean	3.177	-4.870	-60.32	3.305	-3.705	-30.55	3.198	-4.676	-55.36
(SD)	(1.2716)	(1.8427)	(11.934)	(1.2657)	(6.0458)	(65.412)	(1.2129)	(2.5113)	(25.294)
Median	3.145	-4.615	-61.42	3.305	-3.705	-30.55	3.145	-4.615	-61.42
Q1:Q3	2.100 : 3.910	-6.290 : -3.470	-69.15 : -52.81	2.410 : 4.200	-7.980: 0.570	-76.80 : 15.70	2.255 : 4.055	-6.840 : -3.470	-71.16 : -49.91
Min:Max	1.32 : 5.34	-8.06 : -2.35	-76.8 : -39.4	2.41 : 4.20	-7.98 : 0.57	-76.8 : 15.7	1.32 : 5.34	-8.06 : 0.57	-76.8 : 15.7
P-value*		<.0001			0.5454			<.0001	
Week 88									
n	7	7	7	2	2	2	9	9	9
Mean	4.103	-5.014	-54.21	3.940	-3.070	-12.61	4.067	-4.582	-44.96
(SD)	(1.2807)	(1.9150)	(13.796)	(2.2345)	(7.0145)	(91.466)	(1.3636)	(3.1042)	(39.050)
Median	3.910	-4.630	-57.71	3.940	-3.070	-12.61	3.910	-4.630	-57.71
Q1:Q3	2.980 : 4.710	-6.580 : -3.370	-62.73 : -36.18	2.360 : 5.520	-8.030: 1.890	-77.29 : 52.07	2.980 : 4.710	-6.580 : -3.370	-62.73 : -36.18
Min:Max	2.80 : 6.45	-7.83 : -2.67	-70.6 : -34.3	2.36 : 5.52	-8.03 : 1.89	-77.3 : 52.1	2.36 : 6.45	-8.03 : 1.89	-77.3 : 52.1

Figure 15. R1500-CL-1719: Calculated LDL-C Mean (+/- SE) Percent Change from Baseline Over Time in the Adolescent Population – Raw Data Description - Safety Analysis Set



LDL-C, low-density lipoprotein cholesterol; SE, standard error.
Note: Baseline in the Continue Evinacumab group refers to baseline from the parent study R1500-CL-1629.

Changes from baseline in additional lipid parameters

Treatment with evinacumab resulted in reduction of multiple lipid parameters associated with CV risk when co-administered with other lipid-lowering therapies as early as the first post-baseline lipid measurement (week 8), with reductions from baseline found for up to at least Week 120 for the Total Population, and Week 88 for the Adolescent Population, after which time results were more variable (Table 13).

For both the Total and Adolescent Populations, the results at later time points were more variable, in part, due to the smaller number of contributing patients. For the Total Population, the variability of results at later time points were also attributed, in part, to patients enrolled from the R1500-CL-1331 study. The baseline lipid parameter results for some patients enrolling from R1500-CL-1331 were confounded by a residual effect of evinacumab treatment from the R1500-CL-1331 study.

Table 13. R1500-CL-1719: Summary of Lipid Parameter (LDL-C, Apo B, non-HDL-C, TC, and Fasting TGs) Results Over Time (SI Units) for both Total and Adolescent Populations

Study Week /Statistic	Population		Population		Population		Population		Population	
	Total	Adolescent	Total	Adolescent	Total	Adolescent	Total	Adolescent	Total	Adolescent
	LDL-C (mmol/L)		Apo B (g/L)		Non-HDL-C (mmol/L)		TC (mmol/L)		Fasting TGs (mmol/L)	
Baseline										
n	115	14	115	14	115	14	115	14	114	14
Mean (SD)	6.8 (4.15)	7.8 (2.60)	1.7 (0.84)	1.9 (0.54)	7.3 (4.20)	8.2 (2.59)	8.4 (4.10)	9.3 (2.43)	1.3 (1.05)	1.0 (0.55)
Week 8										
n	109	14	109	14	109	14	109	14	107	13
Mean (SD) Chg. BL	-3.680 (2.9686)	-4.676 (2.1445)	-0.780 (0.5978)	-0.980 (0.4285)	-3.982 (2.9956)	-4.941 (2.1192)	-4.332 (2.9980)	-5.416 (2.0797)	-0.728 (1.0143)	-0.559 (0.5469)
Mean (SD) % Chg. BL	-46.45 (35.519)	-58.17 (12.159)	-39.74 (25.338)	-50.16 (11.025)	-48.47 (28.365)	-58.59 (11.103)	-47.04 (20.729)	-57.20 (10.626)	-45.99 (26.017)	-51.55 (17.987)
Week 24										
n	86	12	86	12	86	12	86	12	84	12
Mean (SD) Chg. BL	-3.419 (3.2217)	-4.676 (2.5113)	-0.705 (0.6196)	-0.990 (0.4836)	-3.727 (3.2387)	-4.942 (2.3966)	-4.077 (3.2616)	-5.428 (2.3516)	-0.770 (1.0987)	-0.588 (0.5517)
p-value*	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.0005
Mean (SD) % Chg. BL	-43.64 (37.671)	-55.36 (25.294)	-36.98 (27.574)	-49.80 (16.366)	-46.13 (29.161)	-56.99 (18.955)	-44.17 (24.222)	-55.81 (16.523)	-47.04 (24.394)	-53.02 (17.131)
Week 48										
n	95	12	96	12	95	12	95	12	94	12
Mean (SD) Chg. BL	-3.440 (3.4527)	-4.053 (2.7163)	-0.694 (0.6995)	-0.843 (0.5445)	-3.734 (3.5469)	-4.311 (2.6793)	-4.098 (3.5353)	-4.833 (2.6327)	-0.753 (1.0957)	-0.574 (0.5819)
Mean (SD) % Chg. BL	-43.88 (36.055)	-47.92 (27.136)	-35.85 (29.998)	-42.50 (21.185)	-45.16 (33.558)	-49.51 (23.141)	-43.79 (27.824)	-49.88 (19.370)	-43.32 (37.522)	-49.80 (19.945)
Week 72										
n	92	14	93	14	92	14	93	14	92	14
Mean (SD) Chg. BL	−3.498 (3.1578)	-4.289 (2.5324)	-0.739 (0.6151)	-0.877 (0.4663)	-3.814 (3.1792)	-4.536 (2.4619)	-4.162 (3.1883)	-5.051 (2.4326)	-0.777 (1.0341)	-0.539 (0.5623)
Mean (SD) % Chg. BL	-45.16 (31.590)	-50.79 (27.116)	-37.60 (27.292)	-44.63 (18.051)	-46.68 (28.523)	-52.23 (21.648)	-44.58 (25.678)	-52.11 (18.076)	-46.53 (25.775)	-46.26 (22.576)

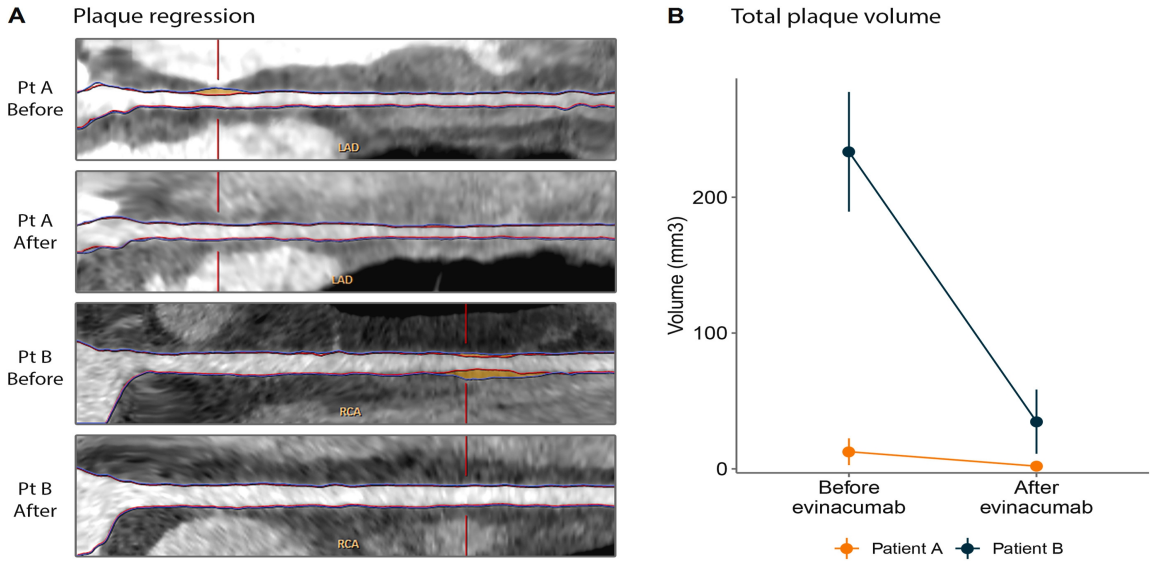
* P-values compared each patient's Week 24 assessment to baseline using t-test for lipids with a normal distribution (provided for descriptive purposes)

Apo B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Mean (SD) Chg. BL, mean (standard deviation) absolute change from baseline; Mean (SD) % Chg. BL, mean (standard deviation) percent change from baseline; SI; Standard International; TC, total cholesterol; TGs, triglycerides

Coronary computed tomography angiography (CCTA)

It has to be noted that during the R1500-CL-1629 pivotal study, two adolescent patients underwent CCTA to assess atherosclerotic soft plaque progression after treatment with evinacumab. The results have been published since the initial authorization of evinacumab (Reeskamp et al., 2021). After 24 weeks of evinacumab treatment (with concomitant statins, ezetimibe, and apheresis), one of the patients showed a 76% reduction in total plaque volume (TPV), from 12.6 ± 8.1 mm3 at baseline to 3.0 ± 1.5 mm^3. Similarly, the other patient showed an 85% reduction in TPV, from 233.5 ± 36.0 mm3 at baseline to 34.8 ± 19.3 mm^3 (Reeskamp et al., 2021)(Figure 16).

Figure 16. Plaque Regression in Adolescents Patients who Participated in Pivotal Study R1500-CL-1629



Stretched multi-planar reconstruction of coronary computed tomography angiography for patient (pt) A (left anterior descending coronary artery; LAD) and B (right coronary artery; RCA) before and after treatment with evinacumab (A and B). Plaques are marked in yellow. (C) Decrease of total plaque volume in both patients.

2.5.4. Discussion on clinical efficacy

Based on the initial MAA in 2021, evinacumab (Evkeeza) was indicated as an *adjunct to diet and other LDL-C lowering therapies for the treatment of adults and adolescent patients aged 12 years and older with HoFH*. A marketing authorization under exceptional circumstances was granted on the basis that the indication is encountered so rarely that the MAH cannot reasonably be expected to provide comprehensive evidence. This extension of indication extends the therapeutic indication for Evkeeza to include *paediatric patients aged 5 years or above,* and is based on interim results from an ongoing Phase 1b/3 single-arm, open-label study R1500-CL-17100 in paediatric (⩾5 to <12 years) patients with HoFH, as well as supportive information from an updated interim analysis of an ongoing open-label study R1500-CL-1719 in adolescent (and adult) patients with HoFH, and an extrapolation analysis (including population PK, population PK/PD, and simulation analyses). The paediatric development program is in line with the approved PIP (PIP decision number P/0087/2023) as also indicated by the partial compliance check by the EMA (EMA/145021/2023). EMA decision dated 16 May 2023: Studies R1500-CL-17100 and R1500-CL- 1719 are confirmed to be compliant as set out in the EMA's Decision (P/0087/2023) of 10 March 2023.

Extrapolation plan

To support use of evinacumab in patients ≥5 to <12 years of age with HoFH, an extrapolation analysis (including population pharmacokinetics [PK], population PK/pharmacodynamics (PD) [population PK/PD], and simulations analyses) has been conducted.

There are several considerations that justify the overall approach to extrapolate efficacy from adults as outlined in outlined in the CHMP "*Reflection paper on the use of extrapolation in the development of medicines for paediatrics" (EMA/189724/2018) and the draft "ICH guideline E11A on paediatric extrapolation" (EMA/CHMP/ICH/205218/2022)*. Development of a paediatric extrapolation concept requires an understanding of the factors that influence the similarity of disease, the pharmacology of the drug and the response to therapy as well as the safety of use in all the relevant populations.

Disease similarity

HoFH is an ultra-rare and serious genetic condition, which requires early diagnosis and treatment beginning in infancy for the best outcomes. The aetiology of the hypercholesterolemia observed in patients with HoFH is the same for both adult and paediatric patients. Hypercholesterolemia is a consequence of the abnormal lipoprotein metabolism due to mutations in the key genes, mutations in the low-density lipoprotein receptor (LDLR) gene and less frequently by mutations in the proprotein convertase subtilisin/kexin type 9 (PCSK9), apolipoprotein B (APOB), and LDL receptor adaptor protein 1 (LDLRAP1) genes, and the markedly diminished hepatic LDL-C clearance from plasma. Additional phenotypic characteristics include premature CVD, aortic valve disease, and tendon xanthomas in the hands and Achilles' tendons.

As the aetiology of HoFH is the same for both adult and paediatric patients, the overarching goal of therapy is also the same, to lower LDL-C, and subsequently the risk of ASCVD:

- The EAS/European Society of Cardiology (ESC) consensus panel on FH recommends initiation of lipid-lowering therapy in patients with HoFH as soon as possible after diagnosis, with the goal of reducing LDL-C levels to <2.5 mmol/L (<100 mg/dL) in adults or <3.5 mmol/L (<135mg/dL) in children (Cuchel et al., 2014; Wiegman et al., 2015).
- The ESC/EAS Consensus panel recommends that in patients with FH and at very high risk, an LDL-C reduction of at least 50% and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered (Mach et al., 2020).

Similar drug pharmacology

The extrapolation study showed that patients achieve steady-state evinacumab concentrations that are sufficient for maximal ANGPTL3 engagement, resulting in comparable LDL-C reductions across paediatric, adolescent, and adult HoFH patients.

In the paediatric population receiving a dosing regimen of 15 mg/kg IV Q4W, PK and PD data consistently described a profile consisting of both linear, non-saturable, and non-linear, target mediated elimination, consistent with that previously reported for adolescents and adults.

At lower concentrations insufficient to saturate the target-mediated pathway, exposure increased in a greater than dose proportional manner. At higher systemic concentrations of evinacumab, sufficient to saturate the target-mediated pathway, the PK of evinacumab trended towards a linear and dose-proportional profile driven by the non-saturable protein catabolism process. Coincident with the observation of systemic concentrations sufficient to achieve linear PK, was evidence of maximal target engagement, as assessed by total ANGPTL3 concentrations, and a maximal PD effect on lipid parameters.

The main source of intrinsic PK variability identified by population PK analysis was body weight. Lower body weights (including in paediatric patients) showed a decrease in exposure. Model-based simulations based upon post-hoc Bayesian estimates predicted that median steady-state exposures were 25% (for Cmin) to 37% (for Cmax) lower in paediatric patients ≥5 to <12 years compared to adult patients ≥18 years after 15 mg/kg IV administrations Q4W. Despite lower exposures in paediatric patients, comparable LDL C reductions were observed and predicted by the population PK/PD model in paediatric, adolescent, and adult populations at week 24, supporting the 15 mg/kg IV dosing regimen across these populations.

Baseline ANGPTL3 and disease status (patients with HoFH versus healthy participants) were descriptors of the variability in the Vmax of the saturable elimination pathway but had marginal influence on evinacumab exposures at clinically relevant doses, due to the pathway saturation. None of the other demographic characteristics (age, race, or gender) had a relevant effect on the PK of evinacumab.

Similar exposure response

In the paediatric Study R1500-CL-17100 including patients aged ≥5 to <12 years with HoFH, the mean percent LDL C reductions at Week 4 after single-dose evinacumab administration in Part A (approximately −26.0%) and Part B (approximately −38.3%) were consistent with the percent LDL-C reductions at Week 4 previously reported for adults from Study R1500-CL-1331 (approximately −30.1%) and adults and adolescents from the DBTP of Study R1500-CL-1629 (approximately −39.6%). Multiple dose administration of evinacumab 15 mg/kg IV Q4W over 24 weeks in the paediatric population resulted in lower steady-state evinacumab concentrations relative to those observed in the adult population. Despite these lower exposures, at 24 weeks, the 48.3% LDL-C reduction in the paediatric population was comparable to the 47.1% LDL C reduction observed in the adult and adolescent population in the Study R1500 CL-1629 DBTP, suggesting that the steady-state evinacumab concentrations in paediatric patients were sufficient to achieve maximal target engagement.

Similarity of treatment response across age groups was also demonstrated using model-based simulations to estimate the percentage of patients predicted to achieve LDL-C concentrations <2.8 mmol/L (or <110 mg/dL) and <3.4 mmol/L (or <130 mg/dL) by Week 24 following 15 mg/kg Q4W infusions. The threshold of <3.4 mmol/L (<130 mg/dL) was achieved by more than half of all virtual patients in all age and weight groups, despite baseline LDL-C concentrations being higher in the 5 to <12 age group (422 mg/dL on average) than in adults (255 mg/dL on average), with the percentage of target attainment ranging from 56.4% in patients ≥5 to <12 years of age to 67.4% in adult patients. Regarding safety, evinacumab displays an acceptable safety profile in paediatric HoFH patients aged 5-≤ 11 consistent to those observed in adult and adolescent HoFH patients.

Discussion

Similarity of disease, the pharmacology of the drug and the response to therapy as well as the safety of use in all the relevant populations has been adequately justified based on the totality of the data. Therefore, extrapolation of data from adults is acceptable.

Design and conduct of clinical studies

Dose selection

The approved dosing regimen in adults and adolescent patients aged 12 years and older is 15 mg/kg IV Q4W. The objectives of the paediatric clinical pharmacology program were to select the appropriate dose regimen for paediatric patients with HoFH (aged ≥5 to <12 years) and to characterize the total

evinacumab serum PK, the total ANGPTL3 serum concentrations, as a measure of target engagement, and the immunogenicity potential of evinacumab in these patients. Based on the PK results of a single dose of evinacumab 15 mg/kg IV in Part A of Study R1500-CL-17100, which were evaluated together with the data from adult and adolescents HoFH patient, a dose of 15 mg/kg IV Q4W was selected for Part B of study R1500-CL-17100. Multiple-dose administrations of evinacumab 15 mg/kg IV over 24 weeks in the 14 paediatric patients with HoFH aged 5-≤ 11 years in Part B resulted in a LDL-C reduction of – 48.3%, which was consistent with the adults and adolescent population in Study R1500-CL-1629 (-47.1%), despite the lower steady-state evinacumab concentrations relative in the paediatric population in study R1500-CL-17100 compared to those observed in the adult population. These findings indicate that the steady-state evinacumab concentrations in paediatric patients were sufficient to achieve maximal target engagement.

Overall, it can be concluded that dose adjustment is not required in paediatric patients aged 5-≤ 12 years and that the 15 mg/kg IV Q4W dose regimen is appropriate for all HoFH patients regardless of age.

Pivotal paediatric study R1500-CL-17100

R1500-CL-17100 is an ongoing 3-part, phase 1b/3 single-arm open-label study evaluating the efficacy, safety and pharmacokinetics of 15 mg/kg IV Q4W evinacumab in a total of 20 paediatric patients with HoFH aged ≥5 to <12 years. General inclusion/exclusion criteria seem appropriate to reflect the patients for which an indication is being sought. It should be noted that the criteria are consistent with those of the pivotal Phase 3 Study R1500-CL-1629 in adolescents and adults submitted and assessed during the initial MAA. The HoFH diagnosis had to be genetically or clinically confirmed by specific criteria, which seems appropriate. Further, the population had to receive stable maximally tolerated therapy including apheresis. Exclusion criteria designed to prevent confounding of efficacy results included background lipid lowering therapy, including apheresis, not stable for a sufficient period prior to screening, as well as the presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins. The design of the study is appropriate to achieve the primary objectives of the study. The study composed of 3 parts: Part A (pharmacokinetics/pharmacodynamics [PK/PD]), Part B (24-week primary efficacy and safety) and Part C (48-week treatment period and 24-week follow-up period). The run-in period of ≤ 8 weeks in Part A and Part B can be considered sufficient to establish a stable background condition. The 24-week treatment period in Part B is considered appropriate to provide reasonable results on the LDL-C (and other cholesterol parameters). After completion of Part A and Part B, patients enrolled in Part C where they were treated for 48-weeks followed by a 24-weeks follow-up period, which is considered sufficient to establish maintenance of effect. The primary endpoint of percent change LDL-C from baseline to week 24 is acceptable and sufficiently long to provide reliable stable data on evaluation of LDL-C reduction for 6 times administration of evinacumab. Within the evinacumab clinical program, LDL-C is used as a surrogate biomarker for cardiovascular risk reduction, which is acceptable, based on the existing unmet need for these patients and knowing that robust evaluation of any potential cardiovascular benefit with evinacumab seems difficult to achieve due to the rarity of the disease. Key secondary endpoints evaluation of other lipid parameters (i.e. Apo-B, non-HDL-C, TC, and Lp(a)) and proportion of patients with ≥50% reduction in LDL-C at week 24 are considered appropriate to provide further insight on and confirmation of the primary objective.

Evkeeza was initially granted a MAA under exceptional circumstances. A non-interventional post-authorisation safety study (PASS) was requested at the time in order to generate further confirmatory data on the cardiovascular implications of treating patients with evinacumab. This was considered important in view of the not completely understood new mechanism of action of evinacumab also in relation to the limited understanding of the implications of the observed potential off target effect of

HDL-C reduction. One objective of the study was to evaluate the atherosclerosis process over time in patients with HoFH who are treated with evinacumab and undergo cardiac imaging. In this context, the exploratory endpoint of “Vascular changes via carotid intima-media thickness at baseline and at 6-month intervals, as clinically indicated (for intra-patient comparison)” is highly endorsed. With respect to statistical analysis, the definition of the analysis population is considered standard and acceptable.

Efficacy data and additional analyses

Pivotal Study R1500-CL-17100

The statistical analysis and handling of missing data were performed adequately.

In the pivotal study R1500-CL-17100, a total of 6 paediatric patients in Part A and a total of 14 paediatric patients in Part B were enrolled, treated, and completed their part of the study. A total of 20 patients (6 patients from Part A, and 14 patients from Part B) were treated in Part C. As of the interim cut-off date of 02 Jun 2022, 6 (30.0%) patients have completed the study and a total of 14 (70.0%) patients were ongoing in the study.

All patients (n=20; 100%) enrolled in this study had important protocol deviations. The most common type of important protocol deviations were “procedural irregularities” which included “PK/drug concentration sample not obtained” (17 (85.0%) patients), “patient not fasting prior to collecting Part B specialty lipid panel” at certain visits (8 (40%) patients), “Part C lipid panel not collected” at certain visits (6 (30.0%) patients), and “patients not fasting prior to collecting Part C lipid panel” at certain visit (6 (30%) patients). The second most common type of protocol deviations was "other", which included 12 patients (60%) whom lipid apheresis was not according to their schedule. Nevertheless, the Applicant has adequately shown that the high number of important protocol deviations are expected not to have a clinically impact on the outcome of the study. The overall compliance to evinacumab therapy was high; Two (33.3%) patients in Part A, 2 (14.3%) patients in Part B and 2 (10%) in Part C had their infusions interrupted but all infusions were resumed within minutes of the interruption, which is reassuring. This study was a multicentre study in 5 countries worldwide (Austria, Australia, the Netherlands, Taiwan, and the United States), and almost half of the subjects were from Europe (n=9; 45%), which is sufficiently representative for Europe. No amendments were made that would compromise the endpoints or outcomes of the study. The amendments are considered valuable and are, therefore, acceptable.

Regarding baseline data, in Part A, the 6 paediatric patients were aged 7 to 11 years. There were 2 (33.3%) male and 4 (66.7%) female patients, all (100%) were White. The mean (SD) baseline LDL-C was 10.1 (5.75) mmol/L. All patients were diagnosed by genotyping and there were no patients with homozygous (LDLRAP1) or double heterozygous (LDL-R and ApoB) mutation. All patients received statin therapy (atorvastatin or rosuvastatin) of which 4 (66.7%) patients receiving high-intensity statins. Additionally, all 6 patients received ezetimibe therapy. Five (83.3%) patients had at least 1 apheresis treatment (4 (66.7%) patients had weekly treatments and 1 (16.7%) patient had bi-weekly treatments). In Part B, the 14 paediatric patients were aged ≥5 to <12 years of which 7 patients aged 5 to 9 years and 7 patients aged 10 or 11 years. There were 6 (42.9%) males and 8 (57.1%) females; 8 patients were White. The mean (SD) baseline LDL-C was at 6.8 (2.35) mmol/L. Thirteen (92.9%) patients were diagnosed by genotyping and 1 (7.1%) patient by clinical diagnosis and there were no patients with homozygous (LDLRAP1) or double heterozygous (LDL-R and ApoB) mutation. At baseline, 12 out of 14 (85.7%) patients used statins (atorvastatin or rosuvastatin) of which 6 (42.9%) were taking high-intensity statins. All 14 patients were taking a non-statin lipid-lowering therapy; 13 (92.9%) patients were taking ezetimibe and 2 (14.3%) patients were taking lomitapide. During Part B, 7 (50.0%) patients had at least 1 apheresis treatment (3 (21.4%]) patients had weekly treatments

and 4 (28.6%) patients had bi-weekly treatments). As Part C enrolled all patients from Part A and Part B, demographic and baseline characteristics for these patients are already described separately above in Part A and Part B. Overall, sufficient HoFH patients aged 5-9 (n=11) vs 10-11 (n=9) have been included and all patients had diagnosis of HoFH and were on maximally stable lipid lowering therapy, including statins, ezetimibe, lomitapide, and lipoprotein apheresis, which is considered appropriate.

In the primary efficacy analysis, treatment with treatment with evinacumab resulted in a substantial reduction in the primary endpoint of mean % change from baseline in LDL-C at week 24 of -48.3% (95% CI 68.8 to 27.8) in paediatric patients ≥5 to <12 years of age in Part B, which corresponds to an absolute mean change in LDL-C of approximately -3.416 mmol/L, which can be regarded as clinically relevant. The reduction in LDL-C with evinacumab were observed as early as Week 1 and sustained over 24 weeks in Part B. The degree of reduction was comparable to that observed in adult and adolescent patients evaluated in the initial MAA. Regarding long-term effect, the mean (SD) % change from baseline in LDL-C at week 48 in Part C was -39.71% (19.9), which was lower than observed in Part B. The Applicant clarified that this smaller long-term effect size was high likely attributed to the small number of patients who contributed to this data (Part C is still ongoing), changes in frequency of apheresis in 6 patients, and an increase in LDL-C of up to 90% in 1 patient who was not compliant with lipid-lowering therapy.

The LDL-C lowering effect appears generally consistent among subgroups, including age, patients receiving apheresis yes or no (-47.9% and -48.8 %, respectively) and the most difficult to treat patients with null/null (-57.2%) and negative/negative (-67.7%) mutations. A smaller effect size was observed in the subgroups of male patients (-31.4%) and age category ≥10-<12 (-30.9%). The Applicant adequately clarified that the difference in these means were driven by 2 male patients aged ≥10 to <12 years who were not able to comply with fasting lipid samples and one who confirmed noncompliance with their lipid-lowering therapy. Moreover, the mean reduction in LDL-C observed in paediatric patients with HoFH aged 5-≤ 11 years treated with evinacumab was consistent to the mean reduction in LDL-C in patients in the R1500-CL-1629 double-blind placebo-controlled study (−47.1% for evinacumab treatment group), as reported in the initial MAA.

The primary endpoint results were further supported by the beneficial effects in secondary cholesterol measurements (e.g. Apo-B, non-HDL-C, Total-C, and Lp(a)). At Week 24, 78.6% of the patients had a ≥50% reduction in LDL-C at Week 24.

Regarding the exploratory endpoint of change in carotid intima-media thickness (cIMT), no beneficial effect was found, which can be attributed to the limited number of patients and the short follow-up of 24 weeks; In 4 (28.6%) patients with matching baseline and 24-week follow-up cIMT measurements, the change from baseline was 0.025 (0.0311) mm.

Supportive Study R1500-CL-1719

Study R1500-CL-1719 is an ongoing OL study designed to evaluate the long-term safety and efficacy of evinacumab in patients with HoFH. The open-label design in considered acceptable, considering the long term (4 year) follow up.

A total of 116 patients (Total Evinacumab) were enrolled and treated (New Evinacumab N=46; Continue Evinacumab N=70) of which 14 adolescent patients with HoFH. At the time of this submission (data cut-off date 25 April 2022 and database lock date of 25 May 2022), 8 adolescent patients (57.1%) completed the study, 5 patients (35.7%) were ongoing in the study, and 1 patient (7.1%) discontinued the study. The reason for study discontinuation was decision by the investigator/Sponsor, due to the availability of evinacumab treatment in an alternative setting.

In the Adolescent Population, treatment with evinacumab resulted in a mean (SD) % change from baseline in LDL-C at week 24 -55.4% (25.29) corresponding to an absolute mean (SD) change from baseline in LDL-C at week 24 of 4.68 (2.5) mmol/L. The mean (SD) % change from baseline in LDL C were greater in the New Evinacumab group (60.32% (11.912)) (n=10) compared with the Continue Evinacumab group (30.55% (65.423)) (n=2) at Week 24 due to one patient which had only a decrease in LDL-C at Week 24 of 15.71% probably due to an increase in the interval of the apheresis sessions.

Nevertheless, the LDL-C reductions in the New Evinacumab and the Continue Evinacumab groups are both considered clinically relevant.

The reductions in LDL-C with evinacumab were seen from the first post-baseline lipid measurement at week 8 and were maintained through at least Week 88 (mean (SD) % change from baseline at Week 88 of −44.95% (39.078) for the Total Evinacumab group; n=9), after which time the results were more variable which may have been due to the small patient numbers (1 each from the New and Continue Evinacumab groups). Efficacy data of the Total population (adolescent and adults) from Study R1500-Cl-1719 showed maintenance of LDL-C reduction, although somewhat smaller compared with week 24, of -30.8% for up to approximately 120 weeks (over 2.5 years). However, this reduction in LDL-C is still considered as clinically relevant. Also in this OL study, the primary endpoint results were further supported by the beneficial effects in secondary cholesterol measurements (e.g. Apo-B, non-HDL-C, Total-C, and fasting TGs).

Atherosclerotic soft plaque progression assessment using coronary computed tomography angiography (CCTA) were available from two adolescent patients. Both adolescents showed a reduction in total plaque volume from 12.6 ± 8.1 mm3 at baseline to 3.0 ± 1.5 mm3 (76%) and from 233.5 ± 36.0 mm3 at baseline to 34.8 ± 19.3 mm3 (85%), however, firm conclusions cannot be made due to the limited number of patients (n=2).

LDL-C lowering results at week 24 in the Adolescent population of the OL study R1500-CL-1719 (-55.4%) were generally consistent with the results observed in paediatric patients with HoFH aged 5-≤ 11 years of age in study R1500-CL-17100 (-48.3%), the Total population of the OL study R1500-CL-1719 (-43.6%) and the adult population in the R1500-CL-1629 double-blind placebo-controlled study (−47.1% for evinacumab treatment group), as reported in the initial MAA. Overall, it can be concluded that treatment with evinacumab resulted in significant and clinically meaningful reductions in LDL-C which were consisted across all Phase 3 studies regardless of age.

2.5.5. Conclusions on the clinical efficacy

In conclusion, evinacumab demonstrated a substantial reduction in LDL-C and other lipid parameters in HoFH patients aged 5-≤11 years on top of standard of care, including statins, ezetimibe, lomitapide, and lipoprotein apheresis. The 48-week treatment period in Part C provides data of the maintenance of an effect in the long term; although the effect size appeared somewhat lower than what was observed in the 24-week treatment period in Part B, however, it is still considered clinically relevant. These results in HoFH patients aged 5-≤11 years were consistent to the updated interim analysis of an ongoing open-label study R1500-CL-1719 in adolescent (and adult) patients with HoFH.

2.6. Clinical safety

Introduction

Main safety information on the use of evinacumab in patients with HoFH aged 5 - ≤11 years is based on the pivotal Study R1500-CL-17100, an ongoing Phase 1b/3 single-arm, open-label study designed to evaluate the long-term safety and efficacy of evinacumab in paediatric (≥5 to <12 years) patients with HoFH. In this study, adverse events are reported for Part A separately (single-dose PK/PD) and then as Pooled Parts B+C. Pooled Parts B+C results are reported cumulatively and include data from Part A patients during their participation in Part C and data from Part B patients during their participation in Parts B and C. Part B alone and Part C alone results are not summarized in this report.

Additionally, three updated integrated (pooled) analyses of safety data have been provided (Table 14). Pool 2 was the primary pool for the integrated analysis of safety to support the initial MAA and will not be presented here as no updates are available. Therefore, in this assessment report, the focus is only on updated integrated analysis for Pool 3 (and global exposure of Pool 1).

Pool 3 is an integration of open-label evinacumab 15 mg/kg IV Q4W data in adolescent and adult patients with HoFH (R1500-CL-1629 and R1500-CL-1719) and adults with persistent hypercholesterolemia (R1500-CL-1643) (Table 14). The open-label treatment period (OLTP) of R1500-CL-1629 and R1500 CL-1643, and the OL study R1500-CL-1719, have similar study design elements (eg, assessments, schedule of assessments, and common CRFs), which were pre-planned for the purpose of open-label data integration.

For Pool 3, separate tables, figures and listings were generated for the following analysis populations:

- Adolescent Population: all participants ≥12 but <18 years of age at screening
- Adult Population: all participants ≥18 years of age at screening
- Total Population: all participants enrolled, ie, the Adult Population and the Adolescent Population).

For the analysis of the updated integrated OL safety data from Pool 3, the primary focus is to present an updated summary for the (paediatric) Adolescent Population; then generally summarized for the Total Population for additional context and updated longer-term safety data.

The paediatric study R1500-CL-17100 is not included in Pool 3.

Table 14. Studies Contributing to the Integrated (Pooled) Analysis of Safety Data

Study Number/Status:		Pool 1[a] Global (Updated Exposure)	Pool 2 Placebo-controlled Studies	Pool 3 Uncontrolled Studies (Updated)
Homozygous Familial Hypercholesterolemia				
R1500-CL-1331 (completed)		X		
R1500-CL-1629	DBTP (completed)	X	X	
	OLTP (completed)	X		X
R1500-CL-1719 (ongoing)		X		X
Persistent Hypercholesterolemia				
R1500-CL-1643[b]	DBTP (completed)	X	X	
	OLTP (completed)	X		X

Patient exposure

Study R1500-CL-17100

All 6 (100%) patients in Part A received a single infusion of evinacumab 15 mg/kg. Patients in Part B had a mean (SD) number of infusions of 6.00 (0) over a mean (SD) duration of study drug exposure of 24.17 (0.639) weeks. In the pooled population (Part B +C), patients had a mean (SD) number of infusions of 12.75 (1.482) over a mean (SD) duration of study drug exposure of 51.63 (5.283) weeks (Table 15).

Table 15. R1500-CL-17100: Summary of Study Treatment Exposure for Pooled (Parts B+C) Safety Analysis Set

	Part A Evinacumab 15mg/kg IV Q4W (N=6)	**Part B Evinacumab 15mg/kg IV Q4W (N=14)**	**Total (N=20)**
Total number of study treatment infusions			
N	6	14	20
Mean (SD)	11.67 (0.516)	13.21 (1.528)	12.75 (1.482)
Median	12.00	13.50	12.00
Min : Max	11.0 : 12.0	10.0 : 16.0	10.0 : 16.0
Cumulative duration of study drug exposure (weeks)			
N	6	14	20
Mean (SD)	48.50 (0.797)	52.97 (5.839)	51.63 (5.283)
Median	48.14	53.79	49.50
Min : Max	47.7 : 49.6	42.4 : 63.9	42.4 : 63.9
Cumulative duration of study drug exposure by category [patient, n (%)]			
>=40 weeks to <44 weeks	0	1 (7.1%)	1 (5.0%)
>=44 weeks to <48 weeks	1 (16.7%)	2 (14.3%)	3 (15.0%)
>=48 weeks to <52 weeks	5 (83.3%)	4 (28.6%)	9 (45.0%)
>=52 weeks to <56 weeks	0	0	0
>=56 weeks to <60 weeks	0	5 (35.7%)	5 (25.0%)
>=60 weeks to <64 weeks	0	2 (14.3%)	2 (10.0%)

IV, intravenous; max, maximum; min, minimum; Q4W, every 4 weeks; SD, standard deviation
Cumulative patient duration of study treatment exposure in weeks defined as: Part C treatment exposure for Part A patients, and Part B treatment exposure plus Part C treatment exposure for Part B patients.
Cumulative total number of study treatment infusions by patient defined as: total number of Part C infusions for Part A patients, and total number of Part B infusions plus total number of Part C infusions for Part B patients.

Pool 1

In the updated Pool 1 (global exposure), 223 patients received any IV dose of evinacumab, with a total duration of exposure of 4825.1 months, or 402.1 patient-years. A total of 113 (95.0%) HoFH patients were treated with evinacumab 15 mg/kg IV Q4W for at least 52 weeks, and 28 (23.5%) of these patients were treated for at least 156 weeks. The mean (SD) number of infusions was 23.3 (11.48) over a mean (SD) duration of 94.08 (46.397) weeks.

Pool 3

Adolescent population

The Pool 3 Adolescent Population is comprised of 14 patients who participated in R1500-CL-1629 and/or R1500-CL-1719. In the Pool 3 Adolescent Population (n=14), the mean (SD) number of study drug infusions in the Total Evinacumab group was 24.07 (6.391) with a mean (SD) duration of study drug exposure of 97.22 (25.362) weeks (Table 16).

Table 16. Summary of Study Treatment Exposure – Pool 3 Uncontrolled Studies Adolescent Population (Open label Safety Analysis Set)

	New Evin [1] (N=13)	**Continue Evin [2] (N=1)**	**Total Evin 15 mg/kg (N=14)**
Total number of study treatment infusions			
N	13	1	14
Mean (SD)	22.92 (4.924)	39.00 (.)	24.07 (6.391)
Median	22.00	39.00	22.00
Min : Max	18.0 : 36.0	39.0 : 39.0	18.0 : 39.0
Duration of study drug exposure (weeks)			
N	13	1	14
Mean (SD)	92.63 (19.395)	157.00 (.)	97.22 (25.362)
Median	88.29	157.00	88.29
Min : Max	75.3 : 145.1	157.0 : 157.0	75.3 : 157.0
Duration of study drug exposure by category [patient, n (%)]			
≥24 weeks	13 (100%)	1 (100%)	14 (100%)
≥52 weeks	13 (100%)	1 (100%)	14 (100%)
≥104 weeks	2 (15.4%)	1 (100%)	3 (21.4%)
≥156 weeks	0	1 (100%)	1 (7.1%)

Total population

The Pool 3 Total Population is comprised of 206 patients: 97 patients in the New Evinacumab group and 109 patients in the Continue Evinacumab group. In the updated Pool 3 Total Population (uncontrolled studies, N=206), the mean (SD) number of study drug infusions in the Total Evinacumab group was 20.04 (10.166) with a mean (SD) duration of study drug exposure of 80.97 (41.189) weeks. A total of 103 (50.0%) patients had at least 52 weeks of exposure, and 67 (32.5%) patients had at least 104 weeks of exposure.

Adverse events

General frequency of adverse events

Study R1500-CL-17100

During Part A of the study, a total of 5/6 (83.3%) patients had at least 1 treatment-emergent AE (TEAE) of which all were classified as mild or moderate. There were no patients with serious AEs (SAEs), TEAEs resulting in treatment discontinuation, or death (Table 17).

In the pooled (Parts B+C) population, a total of 19/20 (95.0%) patients had at least 1 TEAE of which the majority were classified mild or moderate. One patient (5.0%) experienced an SAE, and no patients had TEAEs resulting in treatment discontinuation, or death.

Table 17. R1500-CL-17100: Overview of Adverse Event Profile – Pooled Data (Parts B+C) Safety Analysis Set

n (%)	Part A (N=6)	Part B (N=14)	Total (N=20)
Patients with at least one TEAE	5 (83.3%)	13 (92.9%)	19 (95.0%)
Patients with at least one serious TEAE	0	1 (7.1%)	1 (5.0%)
Patients with at least one TEAE resulting in discontinuation of treatment	0	0	0
Patients with any TEAE resulting in death	0	0	0

Pool 3

In the Pool 3 Adolescent Population, 12 (85.7%) patients in the Total Evinacumab group experienced at least 1 TEAE. No patient experienced a TEAE leading to discontinuation of study treatment or death. One (7.1%) patient experienced at least 1 serious TEAE (Table 18).

For the Total Population in updated Pool 3, 166 (80.6%) patients in the Total Evinacumab group experienced at least 1 TEAE. Three patients experienced a TEAE leading to discontinuation of study treatment, and there were 2 deaths (previously reported). Three patients had pregnancies that led to discontinuation of study drug. A total of 34 (16.5%) patients experienced at least 1 serious TEAE. None of serious TEAEs updated for Pool 3 were considered related to study drug.

Table 18. Overview of Treatment-Emergent Adverse Events – Pool 3 Uncontrolled Studies (Open label Safety Analysis Set Adolescent Population)

n (%)	New Evin [1] (N=13)	Continue Evin [2] (N=1)	Total Evin 15 mg/kg (N=14)
Patients with any TEAE	11 (84.6%)	1 (100%)	12 (85.7%)
Patients with at least one serious TEAE	1 (7.7%)	0	1 (7.1%)
Patients with at least one TEAE resulting in discontinuation of treatment	0	0	0
Patients with any TEAE resulting in death	0	0	0

DBTP, double-blind treatment period; OLTP, open-label treatment period; TEAE, treatment-emergent adverse event.
Open-label periods of studies: 1629, 1643, and 1719 (excluding patients who participated in the 1331 parent study).
[1] Patients who were randomized to placebo in 1629/1643 DBTP and then received evinacumab in OLTP, or evin naive patients enrolled in 1719.
[2] Patients who were randomized to evinacumab in 1629/1643 DBTP and also received evinacumab in OLTP.

Common adverse events

Study R1500-CL-17100

Common AEs in Study R1500-CL-17100 were generally similar to those previously reported in the initial MAA and the Adolescent Population and Total Population in updated Pool 3.

In Part A, PTs reported in more than one patient were vitamin D deficiency, cough, oropharyngeal pain, and rhinitis allergic (2 patients each (33.3%)).

In the pooled population (Parts B+C) the most frequently reported PTs were COVID-19 (15/20 [75.0%] patients), and pyrexia (5/20 [25.0%] patients)(Table 19).

Table 19. R1500-CL-17100: Number (%) of Patients with TEAEs that Occurred with PT ≥10% by Primary SOC and PT - Pooled Data (Parts B+ C) Safety Analysis Set

Primary System Organ Class Preferred Term n(%)	Part A Patients Evinacumab 15mg/Kg IV Q4W (N=6)	Part B Patients Evinacumab 15mg/Kg IV Q4W (N=14)	Total (N=20)
Patients with at least one TEAE	6 (100%)	13 (92.9%)	19 (95.0%)
Gastrointestinal disorders	2 (33.3%)	6 (42.9%)	8 (40.0%)
Abdominal pain upper	1 (16.7%)	2 (14.3%)	3 (15.0%)
Diarrhoea	0	3 (21.4%)	3 (15.0%)
Vomiting	1 (16.7%)	2 (14.3%)	3 (15.0%)
Abdominal pain	0	2 (14.3%)	2 (10.0%)
Nausea	0	2 (14.3%)	2 (10.0%)
General disorders and administration site conditions	2 (33.3%)	4 (28.6%)	6 (30.0%)
Pyrexia	2 (33.3%)	3 (21.4%)	5 (25.0%)
Fatigue	1 (16.7%)	2 (14.3%)	3 (15.0%)
Infections and infestations	4 (66.7%)	11 (78.6%)	15 (75.0%)
COVID-19	4 (66.7%)	11 (78.6%)	15 (75.0%)
Nasopharyngitis	0	3 (21.4%)	3 (15.0%)
Rhinitis	2 (33.3%)	1 (7.1%)	3 (15.0%)
Investigations	1 (16.7%)	1 (7.1%)	2 (10.0%)
Body temperature increased	1 (16.7%)	1 (7.1%)	2 (10.0%)
Nervous system disorders	1 (16.7%)	3 (21.4%)	4 (20.0%)
Headache	1 (16.7%)	3 (21.4%)	4 (20.0%)
Respiratory, thoracic and mediastinal disorders	2 (33.3%)	3 (21.4%)	5 (25.0%)
Oropharyngeal pain	1 (16.7%)	3 (21.4%)	4 (20.0%)
Cough	2 (33.3%)	1 (7.1%)	3 (15.0%)
Skin and subcutaneous tissue disorders	1 (16.7%)	1 (7.1%)	2 (10.0%)
Rash	1 (16.7%)	1 (7.1%)	2 (10.0%)

COVID-19, coronavirus-2019; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, Treatment-emergent adverse event.
MedDRA (Version 24.0) coding dictionary applied.
A patient who reported 2 or more TEAEs with the same preferred term is counted only once for that term.
A patient who reported 2 or more TEAEs with different preferred terms within the same system organ class is counted only once in that system organ class.
SOC is sorted alphabetically and PT sorted by decreasing frequency.
Patients enrolled in Part A only contributed Part C data to the pool.
All post-baseline visit data from Part B and Part C were included in the pool.

Pool 3

Adolescent population

The AE profile observed in the Pool 3 Adolescent Population was similar to that observed in the Total Population (Table 20).

Table 20. Number (%) of Patients with TEAEs (by Primary SOC and PT) that Occurred in ≥ 10% of Patients in Any Group – Pool 3 Uncontrolled Studies (Open label Safety Analysis Set Adolescent Population)

Primary System Organ Class Preferred Term	New Evin [1] (N=13)	Continue Evin [2] (N=1)	Total Evin 15 mg/kg (N=14)
Patients with at least one TEAE	11 (84.6%)	1 (100%)	12 (85.7%)
Gastrointestinal disorders	3 (23.1%)	0	3 (21.4%)
Nausea	3 (23.1%)	0	3 (21.4%)
General disorders and administration site conditions	3 (23.1%)	0	3 (21.4%)
Pyrexia	2 (15.4%)	0	2 (14.3%)
Infections and infestations	8 (61.5%)	1 (100%)	9 (64.3%)
Nasopharyngitis	6 (46.2%)	0	6 (42.9%)
Gastroenteritis	2 (15.4%)	1 (100%)	3 (21.4%)
Corona virus infection	2 (15.4%)	0	2 (14.3%)
Rhinitis	2 (15.4%)	0	2 (14.3%)
Investigations	3 (23.1%)	1 (100%)	4 (28.6%)
Blood creatine phosphokinase increased	3 (23.1%)	0	3 (21.4%)
Aortic bruit	0	1 (100%)	1 (7.1%)
Nervous system disorders	2 (15.4%)	0	2 (14.3%)
Headache	2 (15.4%)	0	2 (14.3%)
Respiratory, thoracic and mediastinal disorders	3 (23.1%)	0	3 (21.4%)
Cough	2 (15.4%)	0	2 (14.3%)
Dyspnoea	2 (15.4%)	0	2 (14.3%)

DBTP, double-blind treatment period; MedDRA, Medical Dictionary for Regulatory Activities; OLTP, open-label treatment period; PT, Preferred Term; SOC, System Organ Class; TEAE, treatment-emergent adverse event Open-label periods of studies: 1629, 1643, and 1719 (excluding patients who participated in the 1331 parent study). MedDRA (Version 22.0) coding dictionary applied.
A patient who reported 2 or more TEAEs with the same PT is counted only once for that term.
A patient who reported 2 or more TEAEs with different PTs within the same SOC is counted only once in that SOC.
SOC is sorted alphabetically and PT sorted by decreasing frequency of the Total Evin doses group.
[1] Patients who were randomized to placebo in 1629/1643 DBTP and then received evinacumab in OLTP, or evin naive patients enrolled in 1719.
[2] Patients who were randomized to evinacumab in 1629/1643 DBTP and also received evinacumab in OLTP.

Total population

The AE profile observed in the updated Pool 3 Total Population (uncontrolled studies) was similar to that observed in Pool 2 (placebo-controlled studies) previously reported at the time of initial marketing authorization. The TEAEs of nasopharyngitis, back pain, myalgia, and headache occurred in comparable proportions of patients in the Total Evinacumab group to that observed in the All Evinacumab IV Doses group previously described for Pool 2.

Treatment-emergent AEs that occurred in ≥ 5% of patients in any treatment group in Pool 3 that did not occur in ≥ 5% of patients in any treatment group in Pool 2 (previously reported) were abdominal Pain, blood creatine phosphokinase increased, chest pain, corona virus infection, cough, gastroenteritis, oropharyngeal pain, pyrexia, toothache, upper respiratory tract infection, and urinary tract infection. Of these TEAEs, the majority were mild or moderate in severity and were considered not related to study drug by the Investigator.

Treatment-emergent treatment-related adverse events

Study R1500-CL-17100

In Part A, 1/6 (16.7%) patients experienced a TEAE of infusion site extravasation that was considered related to study treatment.

In the pooled population (Parts B+C), 3 (15.0%) patients experienced TEAEs that were considered by the Investigator to be related to study treatment. One (5.0%) patient experienced Fatigue, 1 (5.0%) patient experienced abdominal pain and nausea, and 1 (5.0%) patient experienced dermatitis contact and rash.

Pool 3

In the Adolescent Population, no patient experienced a TEAE that was considered by the Investigator to be related to study treatment.

In Pool 3, 16 (7.8%) patients in the Total Evinacumab group experienced at least 1 TEAE classified by the Investigator as related to study treatment. All of these occurred in no more than 1 patient with the exception of the events of asthenia (n=2 (1.0%)), muscle spasms (n=2 (1.0%)), and headache (n=2 (1.0%). None of these treatment-related TEAEs resulted in treatment discontinuation.

Adverse drug reactions

Paediatric Population (≥5 to <12 years)

To identify ADRs in patients aged ≥5 to <12 years, safety data from study R1500 CL 17100 were screened. This ADR analysis focused on pooled data from Parts B+C for the following reasons. First, Part A safety data included only single dose exposure in 6 patients; thus, no meaningful interpretation can be made on nonserious events. Second, Parts B+C included multiple doses of evinacumab. Importantly, in Part A, no serious or severe events were observed.

Pooled data from Parts B+C of study R1500-CL-17100 were screened to identify potential new ADRs in the following manner:

1. AESIs were evaluated as these events were of interest with evinacumab as a monoclonal antibody or based on theoretical safety concerns with lipid lowering therapy.
2. SAEs were reviewed to identify any potential serious ADRs.
3. All TEAEs at the PT level occurring in 2 (10%) or more patients were reviewed.
4. Because these safety data are OL, pooled placebo-controlled data in patients >12 years of age were also reviewed for context.

Ad. 1. The general allergic TEAEs, do not suggest any new safety concerns for allergic events and evinacumab. Further, no safety concerns were identified for hepatic disorders (see below for details on adverse events of special interest).

Ad. 2. Only 1 (5.0%) patient experienced an SAE. This was a case of Tonsillitis in one patient, which was considered to be not related to evinacumab by the investigator. No safety concerns were identified from SAEs.

Ad. 3. The following TEAEs at the PT level were reported in ≥ 2 (at least 10.0% of) patients:

- COVID-19: 15 (75.0%) patients
- Pyrexia: 5 (25.0%) patients
- Headache: 4 (20.0%) patients

- Oropharyngeal pain: 4 (20.0%) patients
- Abdominal pain upper: 3 (15.0%) patients
- Cough: 3 (15.0%) patients
- Diarrhoea: 3 (15.0%) patients
- Fatigue: 3 (15.0%) patients
- Nasopharyngitis: 3 (15.0%) patients
- Rhinitis: 3 (15.0%) patients
- Vomiting: 3 (15.0%) patients
- Abdominal pain: 2 (10.0%) patients
- Body temperature increased: 2 (10.0%) patients
- Rash: 2 (10.0%) patients
- Nausea: 2 (10.0%) patients

Of these TEAEs, abdominal pain (and abdominal pain upper), nasopharyngitis, and nausea were previously identified as ADRs in patients aged 12 years or older and do not warrant further analysis.

A review of the other TEAEs occurring in 2 (10.0%) or more patients revealed:

- COVID-19: Evinacumab has not been associated with infections in general, and there is no biologic plausibility that it predisposes to COVID-19 infections. Study R1500 CL-17100 was conducted over a multiple month time period during the COVID-19 pandemic when there was considerable ongoing transmission of SARS CoV-2.
- Pyrexia and Body temperature increased: Given the similarity of these events, they are evaluated together. In total, 6 patients experienced 1 of these events (7 events total) and all events were considered not related to evinacumab by the investigator. None of these events were an infusion reaction. Overall, these events often occurred along with other events suggestive of an infection, without recurrence throughout evinacumab treatment, and are consistent with events typically observed in paediatric patients. These do not appear to be ADRs to evinacumab.
- Headache: 4 (20.0%) patients experienced 6 events of Headache. None of the events were considered by the investigator to be related to evinacumab. Two events occurred in patients who experienced Pyrexia. Two patients experienced Headache in the absence of concurrent events (1 patient on study day 6 and another patient on study day 1 and study day 54). No events of headache were reported as infusion reactions. In the pool of placebo-controlled studies (Pool 2) previously described, Headache was reported in 9.4% of patients treated with evinacumab and 20.4% of placebo-treated patients. Thus, headache is not considered an ADR with evinacumab.
- Oropharyngeal pain: 4 (20.0%) patients experienced 7 events of Oropharyngeal pain. None of the events were considered by the investigator to be related to evinacumab. Two events occurred in a patient who experienced Pyrexia on the same day (described above). One of the other 3 patients experienced repeated episodes of Oropharyngeal pain with repeated events of Cough and Rhinitis. Two patients experienced Oropharyngeal pain in the absence of other concurrent events. In the pool of placebo-controlled studies (Pool 2) previously described in the initial marketing authorization, Oropharyngeal pain was reported in 0.9% of patients treated with evinacumab compared to 0 patients treated with placebo. Overall, these events appear typical of those experienced by paediatric patients and do not suggest an ADR with evinacumab.
- Diarrhoea: 3 (15.0%) patients experienced 3 events of Diarrhoea. None of the events were an infusion reaction or considered by the investigator to be related to evinacumab. All 3 events of Diarrhoea were reported (on study days 28, 130, and 222) in the absence of other concurrent events. In the pool of placebo-controlled studies (Pool 2), Diarrhoea was reported in 2.6% of

patients treated with evinacumab compared to 5.6% of patients treated with placebo as previously described in the initial marketing authorization. Thus, diarrhoea is not considered an ADR with evinacumab.

- Vomiting: 3 (15.0%) patients experienced 4 events of Vomiting. In 1 patient, Vomiting was reported on study day 60 along with Abdominal pain upper on the same day. In 2 patients, Vomiting was reported (on study days 1, 350, and 377) in the absence of other concurrent events. None of the events were an infusion reaction or considered by the investigator to be related to evinacumab. In the pool of placebo-controlled studies (Pool 2) previously reported in the initial marketing authorization, Vomiting was not reported in any patients treated with either evinacumab or placebo. There is no apparent association with Vomiting and evinacumab, thus it is not considered an ADR.
- Fatigue: 3 (15.0%) patients experienced 4 events of Fatigue. In all 3 patients, Fatigue was reported in the absence of other concurrent events. None of the events were reported as an infusion reaction; however, 2 events in 1 patient (on study days 141 and 176) were considered by the investigator to be related to evinacumab and one event was reported the same day after the infusion in another patient (on study day 1). In the pool of placebo-controlled studies (Pool 2), Fatigue was reported in 4.3% of patients treated with evinacumab compared to 3.7% of patients treated with placebo as previously reported in the initial marketing authorization. Based on this information, a potential causal association between Fatigue and evinacumab exists and, thus, it will be considered an ADR.
- Rhinitis: 3 (15.0%) patients experienced 3 events of Rhinitis. In all 3 patients, Rhinitis was reported with concurrent events suggestive of a possible infection: one patient experienced Rhinitis with Cough on study day 361, one patient experienced Rhinitis with Body temperature increased and Oropharyngeal pain on study day 126, and one patient experienced Rhinitis with Oropharyngeal pain on study day 218. None of these events were considered by the investigator to be related to evinacumab. Overall, although rhinorrhoea is already considered an ADR, these events seem to be related to typical infections in paediatric patients and do not suggest a new ADR with evinacumab.
- Cough: 3 (15.0%) patients experienced 6 events of Cough. The majority of these events were reported along with other concurrent events occurring on the same day:
  - One patient experienced Cough with Rhinitis on study day 361.
  - One patient experienced Cough with Oropharyngeal pain and Pyrexia on study day 297.
  - One patient experienced Cough alone on study 96, with Oropharyngeal pain on study day 136, with Aortic stenosis on study day 162, and with Oropharyngeal pain on study day 277.

  None of these events were considered by the investigator to be related to evinacumab. In the pool of placebo-controlled studies (Pool 2) previously reported in the initial marketing authorization, Cough was reported in 2.6% of patients treated with evinacumab compared to 3.7% of patients treated with placebo. Overall, these events seem to be related to common infections in paediatric patients and do not suggest a new ADR with evinacumab.
- Rash: 2 (10.0%) patients experienced 3 events of Rash. One patient experienced 2 events of Rash considered by the investigator to be related to evinacumab with a potential alternative aetiology. The second patient experienced Rash on study day 290, which was considered by the investigator to not be related to evinacumab. No clear relationship with evinacumab and Rash has been identified, thus it is not an ADR.

In conclusion, the review of TEAEs in the R1500-CL-17100 paediatric study identified only 1 new ADR with evinacumab: Fatigue (15.0%) applicable only to patients aged ≥5 to <12 years of age.

Adult and Adolescent Patients (Pool 3)

For this application, safety data from updated Pool 3 were also screened for ADRs in the following manner:

1. AESIs were evaluated.
2. Given the larger sample size of Pool 3, all TEAEs at the PT level occurring in 5.0% or more of patients in the total evinacumab group were evaluated to identify any potential ADRs from the more commonly reported TEAEs.

Ad.1. Analysis of AESIs in the updated Pool 3 did not identify any new safety concerns (see below). There are no changes to the ADR profile for evinacumab based on review of updated Pool 3 data.

Ad. 2. The following TEAEs at the PT level occurred in 5.0% or more of patients in the Total Evinacumab group:

- Nasopharyngitis (33 [16.0%] patients)
- Headache (25 [12.1%] patients)
- Influenza like illness (22 [10.7%] patients)
- Urinary tract infection (20 [9.7%] patients)
- Arthralgia (16 [7.8%] patients)
- Back pain (16 [7.8%] patients)
- Corona virus infection (16 [7.8%] patients)
- Upper respiratory tract infection (16 [7.8%] patients)
- Gastroenteritis (13 [6.3%] patients)
- Nausea (13 [6.3%] patients)
- Cough (12 [5.8%] patients)
- Diarrhoea (12 [5.8%] patients)
- Toothache (11 [5.3%) patients)

Of these TEAEs, Nasopharyngitis, Influenza like illness, Back pain, and Nausea were previously identified in patients 12 years and older as ADRs in the placebo-controlled pool (Pool 2), as reported at the time of the initial marketing authorization.

As previously reported, with the exception of Corona virus infection and Upper respiratory tract infection, the remaining TEAEs (Headache, Urinary tract infection, Arthralgia, Gastroenteritis, Cough, Diarrhoea, and Toothache) were all more frequent in the placebo treatment group compared with the evinacumab treatment group in Pool 2 and thus were not considered ADRs.

As previously reported in Pool 2, Upper respiratory tract infection was reported in 3 (2.6%) patients in all evinacumab group compared with 0 patients in the placebo group and occurred in 7.8% patients in the Total Evinacumab group in Pool 3. Upper respiratory tract infection is commonly observed in clinical studies independent of underlying disease conditions and will not be considered an ADR. Moreover, Nasopharyngitis and Rhinorrhoea are already considered ADRs for evinacumab and encompass the general medical concept of upper respiratory tract symptoms.

With regards to Corona virus infection, evinacumab has not been associated with infections in general, and there is no biologic plausibility that it predisposes to COVID-19 infections. Pool 3 included data collected over a multiple month time period during the COVID-19 pandemic when there was considerable ongoing transmission of SARS-CoV-2. Thus, this is not considered an ADR.

Overall, there are no changes to the ADR profile for evinacumab based on review of updated Pool 3 data.

Serious adverse event/deaths/other significant events

Serious adverse events

Study R1500-CL-17100

In the paediatric R1500-CL-17100 study, there were no SAEs in Part A of the study. In the pooled population (Parts B+C), 1 (5.0%) patient experienced an SAE of tonsillitis that was considered by the investigator to be not related to study treatment.

Pool 3

In the Pool 3 Adolescent Population, 1 patient in the New Evinacumab group experienced 3 serious TEAEs (concurrent arteriovenous fistula site complication and vascular pseudoaneurysm, and gastroenteritis) that were considered by the investigator to be unrelated to study drug.

In the Pool 3 Total Population, 34 patients (16.5%) experienced at least one serious TEAE. Other than the single event of anaphylactic reaction (previously reported in an adult patient from study R1500-CL-1643), which was considered related to study drug, there were no additional serious TEAEs that appeared related from the updated Pool 3 analysis. Importantly, grouping of similar events was observed only for cardiac events, which reflect the underlying medical conditions of this patient population with HoFH.

Table 21. Number (%) of Patients with Serious TEAEs by Primary SOC and PT – Pool 3 Uncontrolled Studies (Open-label Safety Analysis Set Total Population)

Primary System Organ Class Preferred Term	**New Evin [1] (N=97)**	**Continue Evin [2] (N=109)**	**Total Evin 15 mg/kg (N=206)**
Patients with at least one serious TEAE	12 (12.4%)	22 (20.2%)	34 (16.5%)
Cardiac disorders	5 (5.2%)	13 (11.9%)	18 (8.7%)
Atrial fibrillation	2 (2.1%)	1 (0.9%)	3 (1.5%)
Coronary artery disease	0	3 (2.8%)	3 (1.5%)
Acute myocardial infarction	0	2 (1.8%)	2 (1.0%)
Angina pectoris	1 (1.0%)	1 (0.9%)	2 (1.0%)
Angina unstable	0	2 (1.8%)	2 (1.0%)
Aortic valve disease	0	2 (1.8%)	2 (1.0%)
Cardiac arrest	1 (1.0%)	0	1 (0.5%)
Cardiac failure chronic	1 (1.0%)	0	1 (0.5%)
Cardiac failure congestive	0	1 (0.9%)	1 (0.5%)
Cardiac valve disease	1 (1.0%)	0	1 (0.5%)
Coronary artery stenosis	0	1 (0.9%)	1 (0.5%)
Myocardial infarction	0	1 (0.9%)	1 (0.5%)
Palpitations	0	1 (0.9%)	1 (0.5%)
Supravalvular aortic stenosis	0	1 (0.9%)	1 (0.5%)
Eye disorders	0	1 (0.9%)	1 (0.5%)

Primary System Organ Class Preferred Term	New Evin [1] (N=97)	Continue Evin [2] (N=109)	Total Evin 15 mg/kg (N=206)
Cataract	0	1 (0.9%)	1 (0.5%)
Glaucoma	0	1 (0.9%)	1 (0.5%)
Gastrointestinal disorders	1 (1.0%)	1 (0.9%)	2 (1.0%)
Gastrointestinal motility disorder	1 (1.0%)	0	1 (0.5%)
Intestinal ischaemia	0	1 (0.9%)	1 (0.5%)
General disorders and administration site conditions	1 (1.0%)	1 (0.9%)	2 (1.0%)
Chest pain	1 (1.0%)	1 (0.9%)	2 (1.0%)
Hepatobiliary disorders	0	1 (0.9%)	1 (0.5%)
Gallbladder polyp	0	1 (0.9%)	1 (0.5%)
Infections and infestations	3 (3.1%)	2 (1.8%)	5 (2.4%)
Corona virus infection	1 (1.0%)	0	1 (0.5%)
Gastroenteritis	1 (1.0%)	0	1 (0.5%)
Oesophageal candidiasis	0	1 (0.9%)	1 (0.5%)
Pneumonia	1 (1.0%)	0	1 (0.5%)
Pyelonephritis	0	1 (0.9%)	1 (0.5%)
Injury, poisoning and procedural complications	2 (2.1%)	2 (1.8%)	4 (1.9%)
Arteriovenous fistula site complication	1 (1.0%)	0	1 (0.5%)
Cardiac procedure complication	0	1 (0.9%)	1 (0.5%)
Carotid artery restenosis	0	1 (0.9%)	1 (0.5%)
Cervical vertebral fracture	0	1 (0.9%)	1 (0.5%)
Rib fracture	1 (1.0%)	0	1 (0.5%)
Scapula fracture	1 (1.0%)	0	1 (0.5%)
Vascular pseudoaneurysm	1 (1.0%)	0	1 (0.5%)
Musculoskeletal and connective tissue disorders	0	1 (0.9%)	1 (0.5%)
Joint effusion	0	1 (0.9%)	1 (0.5%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Prostate cancer	0	1 (0.9%)	1 (0.5%)
Transitional cell carcinoma	1 (1.0%)	0	1 (0.5%)
Nervous system disorders	1 (1.0%)	1 (0.9%)	2 (1.0%)
Carotid artery stenosis	1 (1.0%)	0	1 (0.5%)
Ischaemic stroke	0	1 (0.9%)	1 (0.5%)
Psychiatric disorders	0	1 (0.9%)	1 (0.5%)
Mental status changes	0	1 (0.9%)	1 (0.5%)
Renal and urinary disorders	0	1 (0.9%)	1 (0.5%)
Nephrocalcinosis	0	1 (0.9%)	1 (0.5%)
Renal infarct	0	1 (0.9%)	1 (0.5%)

Primary System Organ Class Preferred Term	New Evin [1] (N=97)	Continue Evin [2] (N=109)	Total Evin 15 mg/kg (N=206)
Reproductive system and breast disorders	1 (1.0%)	0	1 (0.5%)
Ovarian cyst ruptured	1 (1.0%)	0	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	0	2 (1.8%)	2 (1.0%)
Dyspnoea	0	1 (0.9%)	1 (0.5%)
Pulmonary embolism	0	1 (0.9%)	1 (0.5%)
Vascular disorders	1 (1.0%)	2 (1.8%)	3 (1.5%)
Aortic stenosis	0	2 (1.8%)	2 (1.0%)
Peripheral artery stenosis	1 (1.0%)	0	1 (0.5%)

DBTP, double-blind treatment period; MedDRA, Medical Dictionary for Regulatory Activities; OLTP, open-label treatment period; PT, preferred term; TEAE, treatment-emergent adverse event; SOC, System Organ Class;
Open-label periods of studies: 1629, 1643, and 1719 (excluding patients who participated in the 1331 parent study).
MedDRA (Version 22.0) coding dictionary applied.
A patient who reported 2 or more TEAEs with the same preferred term is counted only once for that term.
A patient who reported 2 or more TEAEs with different preferred terms within the same system organ class is counted only once in that system organ class.
SOC is sorted alphabetically and PT sorted by decreasing frequency of the Total Evin doses group.
[1] Patients who were randomized to placebo in 1629/1643 DBTP and then received evinacumab in OLTP, or evin-naive patients enrolled in 1719.
[2] Patients who were randomized to evinacumab in 1629/1643 DBTP and also received evinacumab in OLTP.

Deaths

Study R1500-CL-17100

There were no deaths in the paediatric R1500-CL-17100 study.

Pool 3

As previously described in the initial marketing authorization, cardiac deaths occurred in 2 adults from the Pool 3 Total Population. Both deaths were assessed as unrelated to study treatment.

Adverse events of special interest

Protocol-defined AESIs in the paediatric R1500 CL-17100 study were the same as defined for the pivotal R1500-CL-1629, and the R1500-CL-1643 and R1500-CL-1719 studies.

The AESI categories were selected based on the physical-chemical nature of evinacumab (a monoclonal antibody), typical concerns for new drugs (eg, overdose or effects on pregnancy), or based on theoretical concerns with other lipid-lowering therapy (Table 22). The individual CSRs for the studies provide details on these AESIs as reported by Investigators.

Table 22. Summary of Adverse Events of Special Interest and Methods of Data Collection and Derivations

Adverse Event of Special Interest	Methods of Data Collection and Derivations
Anaphylactic reactions	As reported by the Investigator
General allergic events	SMQ “hypersensitivity” (broad and narrow) excluding the following PTs linked to local injection site reactions (“infusion site dermatitis”, “infusion site hypersensitivity”, “infusion site rash”, “infusion site urticaria”, “injection site dermatitis”, “injection site hypersensitivity”, “injection site

Adverse Event of Special Interest	Methods of Data Collection and Derivations
	rash", "injection site urticaria", "injection site vasculitis") plus "idiopathic angioedema"
Infusion reactions	As reported by the Investigator
Hepatic disorders	SMQ Drug-related hepatic disorder Potentially clinically significant value (PCSV)[a] Hy's law evaluation of drug-induced serious hepatotoxicity plot
Pregnancy	As reported by the Investigator
Symptomatic overdose with investigational medicinal product	As reported by the Investigator
Neurocognitive events	CMQ for neurocognitive events as defined based on Regulatory Agency request for another lipid-lowering program [b]
Neurologic events	As reported by the Investigator
New onset of diabetes (NOD)	No medical history of diabetes as specified in "Cardiovascular History and Cardiovascular Risk Factors" eCRF page AND one of the following criteria: Laboratory criteria: At least 2 values of hemoglobin A1C (HbA1c) ≥ 6.5% during the TEAE period. NOTE: For patients with only a single measurement available during the TEAE period, a single value ≥ 6.5% will be considered and qualify the patient as NOD by default. For patients with several HbA1c measurements but only with the last one ≥ 6.5%, this single value ≥ 6.5% will be considered and qualify the patient as NOD by default. OR Laboratory criteria: At least 2 values of fasting glucose ≥ 7.0 mmol/L (126 mg/dL). NOTE: For patients with only a single measurement available during the TEAE period, a single value ≥ 7.0 mmol/L (126 mg/dL) will NOT be considered and will NOT qualify the patient as NOD. For patients with several fasting glucose measurements but only with the last one ≥ 7.0 mmol/L (126 mg/dL), this single value ≥ 7.0 mmol/L (126 mg/dL) will NOT be considered and will NOT qualify the patient as NOD. OR HLT Diabetes mellitus (incl subtypes) OR Initiation of any new concomitant medication for hyperglycemia during the treatment period
Diabetes mellitus or diabetic complications	HLGT "diabetes complications" (including PTs pertaining to the secondary SOC included in the HLGT), HLT "diabetes mellitus (incl subtypes)", and HLT "carbohydrate tolerance analyses (incl diabetes)" excluding PTs "blood glucose decreased" and "Glycosylated haemoglobin decreased" and including the PTs "hyperglycaemia", "Hyperglycaemic unconsciousness", and "Hyperglycaemic seizure" from the HLT "Hyperglycaemic conditions NEC" Changes in diabetic medication dosage (specifically increases in dosage) or initiation of additional diabetic medication
Pancreatitis	As reported by the Investigator

Adverse Event of Special Interest	Methods of Data Collection and Derivations
Cataracts	HLT Cataract conditions
Immune complex diseases	SMQ (Narrow) Systemic lupus erythematous SMQ (Narrow) Vasculitis SMQ (Narrow) Guillain-Barre syndrome
Muscle events/Creatine kinase elevation	Laboratory data analyses (eg, PCSV[a]) All PTs under system organ class (SOC): Musculoskeletal and connective tissue disorders Rhabdomyolysis/myopathy (Narrow SMQ)

In the paediatric R1500-CL-17100 study, there were no cases of anaphylactic reactions, symptomatic overdose with investigational medicinal products, infusion reactions, pregnancy, NOD, muscle events, neurologic events, neurocognitive events, cataracts, pancreatitis, or immune complex TEAEs.

In the updated Pool 3 (Adolescent and/or Total Populations), there were no cases of anaphylactic reactions, symptomatic overdose with investigational medicinal products, neurologic events, pancreatitis, or immune complex TEAEs.

Select AESI categories are presented in the following subsections.

General allergic events

R1500-CL-17100

In Part A, a total of 2/6 (33.3%) patients experienced general allergic events TEAE. Both patients experienced mild allergic rhinitis.

In the pooled population (Parts B+C), 3 (15.0%) patients experienced general allergic TEAEs, including rash (2 [10.0%] patients), conjunctivitis allergic (1 [5.0%] patient), dermatitis contact (1 [5.0%] patient), and rhinitis allergic (1 [5.0%] patient). The events of dermatitis contact and rash were considered related to study treatment; however, alternate aetiologies were suspected. None of the general allergic TEAEs were serious, nor resulted in discontinuation of study treatment.

Pool 3

One patient in the Pool 3 Adolescent Population (7.1%) experienced general allergic TEAEs of dermatitis contact and seasonal allergy. All TEAEs were moderate in severity. None were considered by the investigator to be related to study treatment.

Consistent with data available at the time of the initial marketing authorization, general allergic TEAEs were reported in 28 (13.6%) patients in the updated Pool 3 Total Population. None of these events were fatal or serious or led to discontinuation of evinacumab treatment.

Of the reported general allergic TEAEs, the only PTs reported in more than 2 patients were pruritus, dermatitis contact, and rash. The majority of general allergic TEAEs were mild in severity. General allergic TEAEs considered moderate in severity included asthma, dermatitis contact, drug hypersensitivity, eczema, lip oedema, mouth ulceration, pruritus, pruritus generalized, rash, seasonal allergy, and urticaria chronic. The only severe general allergic TEAE reported was urticaria.

Five (2.4%) patients experienced a general allergic TEAE considered by the Investigator to be related to study treatment (data on file). These TEAEs included drug hypersensitivity, infusion related reaction, pruritus, pruritus generalised, and swelling face.

Infusion reactions

R1500-CL-17100

No paediatric patients experienced infusion reaction AESIs during the R1500-CL-17100 study.

Pool 3

One (7.1%) patient in the Adolescent Population experienced an infusion reaction (2 TEAEs of Cough and Dyspnoea). These events occurred 20 minutes into the 13th infusion resulting in discontinuation of the infusion. Both events were assessed as nonserious, mild in intensity, and unrelated to study drug. The events did not require treatment and recovered/resolved in 20 minutes time. The patient resumed study drug infusions the following month without incident and continued on treatment.

Infusion reactions TEAEs were reported in 13 (6.3%) patients in the updated Pool 3 Total Population. None of these events were fatal. One event of Acute MI was serious, and one event of headache led to discontinuation of evinacumab treatment.

Of the reported infusion reaction TEAEs, only the PTs asthenia and headache were reported in more than a single patient.

Hepatic disorders/liver enzyme elevations

R1500-CL-17100

No paediatric patient in R1500-CL-17100 experienced a hepatic disorder AESI during Part A or in the pooled population (Parts B+C). Although not included in the SMQ, 1 patient in Part A and 1 patient in the pooled population had a relevant TEAE of Alanine aminotransferase increased.

Pool 3

In the Pool 3 Adolescent Population, the following PTs were reported and are of note: Aspartate aminotransferase increased in 1 (7.1%) patient and Alanine aminotransferase increased in 1 (7.1%) patient.

In the updated Pool 3 Total Population, no patient experienced a hepatic disorder TEAE by SMQ.

Although not included in the SMQ, the following PTs were reported and are of note: Aspartate aminotransferase increased in 5 (2.4%) patients, Alanine aminotransferase increased in 5 (2.4%) patients, and Liver function test increased in 1 (0.5%) patient. None of these TEAEs were serious or led to any action taken with study treatment. Furthermore, no patient met the biochemical criteria for potential Hy's law in study R1500-CL-17100 or Pool 3.

Pregnancy

Five pregnancies reported in 4 adult patients: 3 female patients and 1 female partner of a male patient.

- One female received study drug while on Study R1500 CL 1629 during first trimester gestation, and later enrolled in Study R1500 CL 1719, and became pregnant a second time while exposed to evinacumab during first trimester of gestation.
- Two other female patients became pregnant while receiving evinacumab in Study R1500 CL 1719.
- One female partner of a male patient who received evinacumab in Study R1500 CL 1719 became pregnant.

Exposure to evinacumab was in the first trimester of gestation in all 5 pregnancies. All pregnancies were carried to term and resulted in delivery of a healthy baby with no reported embryofoetal toxicity or foetal anomaly.

Neurocognitive events

R1500-CL-17100

There were no neurocognitive events in Study R1500-CL-17100.

Pool 3

One adult patient in Pool 3 Total Population experienced a serious TEAE of mental status changes that was considered not related to study treatment by the Investigator.

New onset of diabetes

R1500-CL-17100

New onset diabetes (NOD) was evaluated in patients without diabetes at baseline through evaluation of TEAEs, laboratory parameters, and concomitant medications for hyperglycaemia. In Study R1500-CL-17100, all patients were without diabetes mellitus at baseline, and no patients developed NOD during the study.

Pool 3

In the Pool 3 Adolescent Population, 14 (100%) patients were without diabetes mellitus at baseline. None of these patients met the criteria for NOD. In the updated Pool 3 Total Population, 188 (91.3%) patients were without diabetes mellitus at baseline. Of these patients, 8 (4.3%) met the criteria for NOD during treatment with evinacumab. Five adult patients met the NOD criteria based on fasting glucose, 2 patients met the NOD criteria based on HbA1c, and 1 patient met the NOD criteria based on any HLT of diabetes mellitus (including subtypes).

Diabetes mellitus or diabetic complications (in patients with diabetes at baseline)

R1500-CL-17100

In Study R1500-CL-17100, no paediatric patient had diabetes mellitus at baseline.

Pool 3

In the Pool 3 Adolescent Population, no patient had diabetes mellitus at baseline. In the updated Pool 3 Total Population, 18 (8.7%) adult patients had diabetes mellitus at baseline as per medical history. Of these patients, 4 patients experienced a diabetic complication TEAE. Additionally, no clinically meaningful changes in mean HbA1c or fasting glucose were noted in paediatric patients from R1500-CL-17100 or in Pool 3. Potentially clinically significant values for hyperglycaemia were primarily isolated, transient, and returned to within normal limits at the next visit in most patients in Pool 3.

Cataracts

R1500-CL-17100

There were no cataract events in the paediatric study R1500-CL-17100.

Pool 3

No patient in the Adolescent Population experienced a cataract TEAE. One adult patient in the Continue Evinacumab group experienced a cataract TEAE of moderate severity that was considered not related to study treatment by the Investigator.

Muscle events/creatine kinase elevation

R1500-CL-17100

In Part A, no patients experienced TEAEs in the Musculoskeletal and connective tissue disorders SOC. In the pooled population (Parts B+C) 1 patient (5.0%) experienced a TEAE of Pain in extremity. No patients in R1500-CL-17100 experienced a TEAE of Rhabdomyolysis or Myopathy SMQ. No PCSV values for CK were reported in Study R1500-CL-17100.

Pool 3

Three patients in the Adolescent population experienced TEAEs in the Musculoskeletal and connective tissue disorders SOC. The TEAEs of arthralgia, arthritis, musculoskeletal pain, and myalgia were reported in 1 patient each. The events of arthralgia and arthritis were reported as moderate. All events were considered unrelated to study treatment by the Investigator.

TEAEs in the Musculoskeletal and connective tissue disorders SOC were reported in 53 (25.7%) patients in the Pool 3 Total Population. No patient experienced a TEAE leading to discontinuation of study treatment in this SOC. One patient experienced a serious TEAE of joint effusion, which was considered not related to study treatment. The only severe TEAEs in this SOC were joint effusion and haemarthrosis (1 patient each). Moderate TEAEs in this SOC were reported in 28 (13.6%) patients. The PTs assessed as moderate in > 1 patient were back pain (10 patients), arthralgia (7 patients), and bursitis, muscle spasms, musculoskeletal pain, myalgia, pain in extremity, and tenosynovitis (2 patients each). The TEAEs in this SOC reported in ≥5% of patients in the Total Evinacumab group were Arthralgia (7.8%) and Back pain (7.8%). In the updated Pool 3 Total Populations, no patient experienced a TEAE in the Rhabdomyolysis/myopathy SMQ.

Additionally, in the Pool 3 Adolescent Population, 2 patients experienced a CK elevation >3 upper limit of normal (ULN) and ≤5 ULN. Two patients experienced a CK elevation > 5 x ULN and < 10 x ULN. In the updated Pool 3 Total Population, 10 patients experienced a CK elevation > 5 x ULN and ≤ 10 x ULN, and 6 patients experienced a CK elevation > 10 x ULN. In Pool 3, most CK elevations > 10 x ULN were attributed to strenuous exercise.

Laboratory findings

Immunogenicity

R1500-CL-17100

One patient in Part A and 1 patient in Part B had detectable pre-existing ADAs against evinacumab at the start of treatment, and one patient in Part B developed a low titer of treatment-emergent ADAs (Table 23). None of the patients with ADAs had positive NAb results.

The LDL-C response profiles of the 1 ADA-positive patient lay within the distribution of the LDL-C response profiles of ADA-negative patients, suggesting that the positive ADA results did not affect the LDL-C responses for these patients.

There was no apparent effect of treatment-emergent ADA or NAb on the safety, efficacy, or PK of evinacumab.

Table 23. Summary of ADA Status, Category, Maximum Titer Category, and NAb Status by Study Part in Paediatric Patients with HoFH (Study R1500-CL-17100)

ADA Status/Category Max. Titer Category NAb Status	Part A n (%)	Part B n (%)
ADA		
ADA Analysis Set	6 (100%)	14 (100%)
Negative	5 (83.3%)	12 (85.7%)
Pre-existing Immunoreactivity	1 (16.7%)	1 (7.1%)
Treatment-Boosted Response	0	0
Treatment-Emergent Response	0	1 (7.1%)
Persistent	NA	0
Indeterminate	NA	1 (7.1%)
Transient	NA	0
TE & TB Maximum Titer Category		
Low (<1,000)	0	1 (7.1%)
Moderate (1,000 to 10,000)	0	0
High (>10,000)	0	0
NAb		
NAb Analysis Set	6 (100%)	14 (100%)
NAb Negative	6 (100%)	14 (100%)
NAb Positive	0	0

n = Number of patients
Note: Percentages are based on ADA analysis set.

Haematology

R1500-CL-17100

No notable trends in haematology parameters were evident during the paediatric study R1500-CL-17100.

In R1500-CL-17100 Part A, one patient had a decrease in haematocrit (as well as haemoglobin) and was diagnosed with the AE of Iron Deficiency 7 days later. At the next visit, the haematocrit increased. Four patients had decreases in neutrophils that were transient and normalized 1-2 visits later.

In the R1500-CL-17100 pooled population (Parts B+C), a total of 6/20 (30.0%) had decreases in haematocrit. Three (15.0%) patients had decreases from baseline in haemoglobin of ≥2.0 g/dL (≥20 g/L). The majority of these were minor variations. However, one patient had marked variations in haematocrit and corresponding haemoglobin values. The investigator attributed these variations to lipid apheresis treatments and changes in blood volume, and no associated TEAEs were reported.

Potentially clinically significant values were observed in leukocytes (2 patients), basophils (2 patients), neutrophils (6 patients), lymphocytes (1 patient), monocytes (2 patients), and eosinophils (1 patient). Most of these were transient. Decreases in neutrophils were noted in 1 patient for 3 of 4 visits over a 4-month period. These findings were associated with TEAEs of Dermatitis contact, Rash, Hypertension, Ear pain, Fever, Throat pain, and COVID-19. All TEAEs were noted to be recovered/resolved and the neutrophil count returned to normal.

Pool 3

There were no clinically meaningful changes from baseline in any haematology parameters (red blood cells, platelets, or white blood cells) in adolescents or adults from updated Pool 3.

In the Pool 3 Adolescent Population, 2/14 (14.3%) of patients in the Total Evinacumab group had a decrease in haemoglobin ≥1.5 g/dL from baseline, and 1 patient in the Continue Evinacumab group had a decrease in haemoglobin ≥2 g/dL from baseline. One adolescent patient had a potentially

clinically significant values (PCSV) for leukocytes; there were no other PCSV values for WBCs in this population.

In the updated Pool 3 Total Population, there was a notable number of patients with PCSVs for haemoglobin. Specifically, 14.3% of patients in the Total Evinacumab group had a decrease in haemoglobin ≥1.5 g/dL from baseline. The majority of the decreases in haemoglobin were transient and resolved at subsequent assessments and there were no TEAEs reported in the SOC of Investigations regarding abnormal haemoglobin values.

In Pool 3, there were a notable number of patients with PCSVs for monocytes. Although 17.6% of patients in the Total Evinacumab group had PCSVs related to an increase in monocytes, values in these patients were transient and generally below 1.0 x 109/L. Importantly, there were no TEAEs reported in the SOC of Investigations for abnormal monocyte values

Clinical chemistry

HDL-C

R1500-CL-17100

In the R1500-CL-17100 paediatric study (Part B), mean (SD) baseline HDL-C was 0.86 mmol/L (33.3 [12.71] mg/dL). At Week 24, mean (SD) value for HDL-C was 0.50 mmol/L (19.5 [5.73] mg/dL), representing a mean (SD) change from baseline of −0.36 mmol/L (−13.8 [11.31] mg/dL).

Pool 3

In the Pool 3 Adolescent Population, the mean (SD) baseline HDL-C was 1.041 (0.3141) mmol/L. At Week 24, mean (SD) value for HDL-C was 0.593 (0.1365) mmol/L, representing a mean (SD) change from baseline of −0.481(0.2755) mmol/L. Decreases in mean HDL-C levels were generally consistent throughout the OL treatment period.

In the updated Pool 3 Total Population, the mean (SD) baseline HDL-C was 1.262 (0.4520) mmol/L. At Week 24, mean (SD) value for HDL-C was 0.911 (0.3948) mmol/L, representing a mean (SD) change from baseline of −0.370 (0.3225) mmol/L. Decreases in mean HDL-C levels were generally consistent throughout the OL treatment period.

Routine serum chemistry

R1500-CL-17100

In the paediatric study R1500-CL-17100, there were no clinically meaningful changes from baseline in metabolic or renal function parameters in R1500-CL-17100 Part A. No patients met the PCSV criteria for sodium, potassium, or chloride. In the R1500-CL-17100 pooled population (Parts B+C), one patient met the PCSV criteria for sodium ≤129 mq/L (≤129 mmol/L), but this finding was not associated with a TEAE.

Pool 3

In the updated Pool 3, there were no clinically meaningful changes from baseline in metabolic function, electrolytes, renal function, or liver function parameters.

Vital signs, physical findings and other observations related to safety

Vital signs and body weight

Study R1500-CL-17100

In R1500-CL-17100, no notable trends in vital signs were observed in the study.

In R1500-CL-17100 Part A, PCSVs for vital signs and weight were transient, and most were not associated with TEAEs. In the R1500-CL-17100 pooled population (Parts B+C), the most notable PCSV occurred in weight. A total of 19/20 (95.0%) patients had an increase of ≥5% in weight from baseline, which is consistent with growth and development expectations in a paediatric population.

There were also PCSVs in systolic blood pressure (6/20 [30.0%] patients), diastolic blood pressure (4/20 [20.0%] patients), and pulse rate (3/15 [15.0%] patients). The majority of these were isolated, transient decreases and not associated with symptoms of hypotension or tachycardia.

Pool 3

In the Pool 3 Adolescent Population, there were no clinically meaningful trends over time in vital signs. Potentially clinically significant values regarding a decrease in diastolic blood pressure were observed in 50.0% of patients in the Total Evinacumab group. All PCSVs regarding changes in blood pressure and pulse rate were transient and none were reported as TEAEs.

Potentially clinically significant values regarding changes in body weight were observed for both increases and decreases in weight. The majority (78.6%) of patients experienced PCSVs of ≥5% increase from baseline in body weight, which is consistent with growth and development expectations in an adolescent population.

For the updated Pool 3 Total Population, there were no clinically meaningful trends over time in vital signs or body weight. Potentially clinically significant values regarding a decrease or increase in systolic blood pressure were observed in 16.5% and 16.0% of patients in the Total Evinacumab group, respectively. All PCSVs regarding changes in blood pressure and pulse rate were transient and none were reported as TEAEs.

PCSVs regarding changes in body weight were observed for both increases and decreases in weight. There were 2 patients with PCSVs regarding a decrease in body weight that were also reported as TEAEs.

Tanner stages and hormones

Study R1500-CL-17100

At baseline in the pooled (Parts B+C) population, 12/20 (60.0%) patients were rated as Tanner Stage 1, 6/20 (30.0%) patients were rated as Tanner Stage 2, and 2/20 (10.0%) patients were rated as Tanner Stage 3. Over the course of Parts B and C, 9/20 (45.0%) patients progressed ≥ 1 Tanner Stage. These changes were considered consistent with appropriate pubertal development in children 5-11 years old.

Gonadal steroid hormones and gonadotropins were also evaluated for females and males. Baseline hormone levels and fluctuations were within the range expected for female and male children aged ≥5 to <12 years. There were no PCSVs in hormones.

Study R1500-CL-1719

In Study R1500-CL-1719, Tanner stage results in the Adolescent Population were consistent with appropriate continuation of maturation and development. At study enrollment, the mean (SD) age in patients comprising the Adolescent Population was 14.4 (1.82) years; at study enrollment, the 5 female patients ranged in age from 12 to 16 years and the 9 male patients ranged in age from 12 to 17 years.

Over the course of treatment, Tanner stage results in the Adolescent Population were consistent with continuation of maturation and development in these younger patients. Of the 7 male patients that were evaluable over the course of the study, 5 reached overall Tanner stage 5 by Week 72 compared with 1 patient at baseline; the remaining 2 male patients at Week 72 were at overall Tanner stages 3 and 4 (1 patient each). By Week 72, all 4 evaluable female patients had reached overall Tanner stage 4 compared with 1 patient at baseline.

Baseline hormone levels and fluctuations were within the range expected for children aged 12 to <18 years at study enrollment.

Discontinuation due to adverse events

Study R1500-CL-17100

No patient in the R1500-CL-17100 paediatric study experienced TEAEs that led to permanent treatment discontinuation during the study.

Pool 3

No patient in the Pool 3 Adolescent Population experienced TEAEs leading to discontinuation of study treatment.

Three patients in the updated Pool 3 Total Population experienced events leading to discontinuation of study treatment. One patient experienced the TEAE of headache, and 2 patients discontinued study treatment due to pregnancy, which was considered as an AESI per protocol.

Post marketing experience

As detailed in Evkeeza periodic benefit-risk evaluation report #4 (PBRER #4: reporting period of 12 Aug 2022 - 11 Feb 2023), submitted to EMA on 20 April 2023, no new information became available during the reporting interval that would impact the known benefit-risk profile of evinacumab in the approved indication.

In terms of signal and risk evaluation, no signals were identified, or validated as safety concerns during this reporting interval.

With regards to the important potential risk of embryofetal toxicity, no case reports indicative of embryofetal toxicity or congenital anomaly events were identified from the totality of the pregnancy outcome reports [i.e., from spontaneous post-marketing sources and solicited data sources (post-marketing patient support program [MYRARE], clinical trials, EAP and CUPs with evinacumab)] that were reviewed in the reporting interval. No relevant information for this safety concern was identified from other available sources.

With regards to missing information on safety of long-term use (e.g., >2 years), as of the DLP of PBRER #4, additional data on longer treatment exposure with evinacumab was available from the clinical study R1500-CL-1719. Overall, 61.2% (71/116) of patients had been treated with evinacumab for more than 104 weeks. Safety of long-term use (e.g. >2 years) remains a missing information topic for evinacumab and will be monitored through clinical trials (R1500-CL-1719, open-label extension study), routine pharmacovigilance activities, a planned category 2 long-term registry PASS [1500-CL-2161/UX858-CL401], and published literature review. Any relevant information will be described in future PBRERs.

With regards to missing information on use in pregnant or breastfeeding women, the global safety database was searched using the SMQ Pregnancy and neonatal events for case reports of pregnancy received from any sources including spontaneous post-marketing sources and solicited data sources (post-marketing patient support program [MYRARE], clinical trials, and CUPs with evinacumab). During the reporting interval, one initial case report of pregnancy was received. Follow-up information has been requested and will be reported in the next PBRER. No pregnancy outcome report was consistent with human embryofoetal toxicity and evinacumab exposure. No relevant information regarding foetal toxicity with evinacumab use was identified from other available sources. No reports of evinacumab use during breastfeeding were received from any sources. Use in pregnant or breastfeeding women remains a missing information topic for evinacumab and will be monitored through clinical trial data, routine pharmacovigilance, additional activities (a planned category 2 long-term PASS [R1500-CL-2161/UX858-CL401] and an ongoing FDA PMR Study [R1500-CL-2162]), and published literature. Any relevant information will be discussed in future PBRERs.

Finally, with regards to new information on the risk of systemic hypersensitivity reactions (including anaphylaxis and infusion reactions), which were not categorized as important, 4 initial cases (1 spontaneous and 3 solicited) reporting 11 events were retrieved from the global safety database using the above SMQ search strategy, during the reporting interval. No follow-up information was received during the reporting interval. All 4 cases were non-serious. The risk of systemic hypersensitivity reaction (including anaphylaxis and infusion reactions) is properly described in the 'Warning & Precautions' and 'Contraindications' sections of the prescribing information for evinacumab with no changes necessary.

Based on all available safety and efficacy data for evinacumab, the overall benefit-risk balance remains positive in the approved indication. The safety profile of evinacumab remains stable and consistent with safety data observed in clinical trials. It will continue to be monitored through pharmacovigilance activities in place.

2.6.1. Discussion on clinical safety

Main safety information on the use of evinacumab in patients with HoFH aged 5 -⩽11 years is based on the pivotal Study R1500-CL-17100, an ongoing Phase 1b/3 single-arm, open-label study designed to evaluate the long-term safety and efficacy of evinacumab in paediatric (⩾5 to <12 years) patients with HoFH. Additionally, three updated integrated pooled safety analyses have been provided. Pool 2 (R15-CL-1629 DBTP and R1500-CL-1643) was the primary pool for the integrated analysis of safety to support the initial MAA and will not be discussed here as no updates are available. Therefore, in this assessment report, the focus is only on updated integrated analysis for Pool 3 (and global exposure of Pool 1). Pool 3 is an integration of open-label evinacumab 15 mg/kg IV Q4W data in adolescent and adult patients with HoFH (R1500-CL-1629 and R1500-CL-1719) and adults with persistent hypercholesterolemia (R1500-CL-1643), which had similar study design elements. For Pool 3, the safety results were presented using the following analysis populations, i.e. Adolescent Population (all participants ⩾12 but <18 years of age at screening), Adult Population (all participants ⩾18 years of age at screening) and the Total Population (all participants enrolled, i.e. the Adult Population and the Adolescent Population). The Pool 3 Adolescent Population is actually the Adolescent Population of R1500-CL-1719, since no adolescents were enrolled in Study R1500-CL-1643 in persistent hypercholesterolemia. Therefore, all patients in the Pool 3 Adolescent Population were HoFH patients.

Patient exposure

In the initial MAA dossier, a total of 76 HoHF patients had been exposed to evinacumab 15 mg/kg IV Q4W for at least 24 weeks and 51 HoFH patients for at least 48 weeks, with placebo-controlled safety

data for at least 24 weeks available for only 38 HoFH from study R1500-CL-1629, including 1 adolescent. Safety data on persistent hypercholesterolemic patients (study R1500-CL-1643) increased the available exposure data with 29 patients exposed to evinacumab 15 mg/kg IV Q4W and 28 patients to evinacumab 5 mg/kg IV Q4W for at least 24 weeks. Overall, the safety data in HoFH patients during the initial MAA was very limited, but expected considering the rarity of the disease. Therefore, Evkeeza has been granted a MAA under exceptional circumstances. Consequently, a non-interventional post-authorisation safety study (PASS) was requested in order to generate confirmatory data on, among others, long-term safety and the cardiovascular implications of treating patients with evinacumab. In this respect, it was expected that the ongoing 4 years open label study R1500-CL-1719 and a PASS agreed as specific obligation in the context of the MA under exceptional circumstances should provide some additional data to further evaluate long-term safety.

Since the start of the clinical development program for evinacumab till the latest data cut-off, a total of 243 patients have been treated with any IV dose of evinacumab in either placebo-controlled or open-label trials (Pool 1). Of these, 139 patients had HoFH, of whom 138 patients were treated with evinacumab 15 mg/kg Q4W for at least 24 weeks, 120 patients for at least 52 weeks, and 78 patients were treated for at least 104 weeks, respectively.
In the pooled population of study R1500-CL-17100, a total of 20 paediatric patients were exposed to evinacumab with a mean (SD) duration of 51.63 (5.28) weeks of whom 5 patients were exposed to evinacumab for at least 56 weeks. Pooled Parts B+C results are reported cumulatively and include data from Part A patients during their participation in Part C and data from Part B patients during their participation in Parts B and C.
In the Pool 3 Adolescent Population, a total of 14 patients who participated in R1500-CL-1629 and/or R1500-CL-1719 were exposed to evinacumab with a mean (SD) duration of 97.22 (25.36) weeks of whom 14 adolescent HoFH patients were exposed for at least 52 weeks and 3 adolescent HoFH for at least 104 weeks. Regarding the Total Population in Pool 3 (adolescent and adult), a total of 206 HoFH patients were exposed to evinacumab with a mean (SD) duration of 80.97 (41.19) weeks of which 103 HoFH patients were exposed for at least 52 weeks and 67 HoFH patients for at least 104 weeks.
Overall, the exposure data has substantially increased compared with the exposure data during the initial MAA. Nevertheless, the exposure data in paediatric HoFH patients aged 5-⩽ 11 years of age of a total of 20 patients exposed to evinacumab with a mean (SD) duration of 51.63 (5.28) weeks of which 5 patients were exposed to evinacumab for at least 56 weeks, is very limited, but expected considering the rarity of the disease.

Adverse events
During Part A and in the pooled (Parts B + C) population of R1500-CL-17100, a high proportion of patients experienced at least one TEAE (83.3% and 95.0%, respectively), which appeared somewhat higher as observed during the initial MAA (65.9%). However, the majority of the TEAEs were classified as mild or moderate in severity, which is reassuring. Additionally, there were no patients with TEAEs resulting in treatment discontinuation or death in Part A and the pooled population. There was only one SEA reported in the pooled population that was considered by the investigator to be unrelated to study. The most frequent TEAEs were vitamin D deficiency, cough, oropharyngeal pain, and rhinitis allergic (2 patients each (33.3%) in Part A and COVID 19 (15/20 (75.0%) patients), and pyrexia (5/20 (25.0%) patients) in the pooled (Parts B + C) population. The AEs considered treatment-related by the investigator were reported in 1 (8.2%) patient in Part A (infusion site reaction) and in 3 (15.0%) patients in the pooled (Parts B + C) population (fatigue, abdominal pain and nausea, and dermatitis contact and rash). Infusion site reactions, abdominal pain, and nausea are already known ADRs from the initial MAA dossier.
In the Pool 3 Adolescent Population, TEAEs were also frequently reported (85.7%), however, no

patient had a TEAE leading to discontinuation of study treatment, TEAE considered related to study treatment, or death. One patient experienced 3 serious TEAEs (concurrent arteriovenous fistula site complication and vascular pseudoaneurysm, and gastroenteritis) that were considered by the investigator to be unrelated to study drug.

In the Pool 3 Total Population, 80.6% of the HoFH patients experienced any TEAEs. Overall, the safety profile of the Pool 3 Total Population was consistent to that of Pool 2 (previously assessed during initial MAA). Treatment-emergent AEs that occurred in ⩾ 5% of patients in the Pool 3 Total Population that did not occur in ⩾ 5% of patients in any treatment group in Pool 2 were abdominal pain, blood creatine phosphokinase increased, chest pain, corona virus infection, cough, gastroenteritis, oropharyngeal pain, pyrexia, toothache, upper respiratory tract infection, and urinary tract infection. However, the majority of these were mild or moderate in severity and were considered not related to study drug by the investigator.

To identify (new) ADRs, the Applicant focussed on AEs of special interest (AESIs), SAEs and TEAEs at the PT level occurring in 2 (10%) or more patients in the pooled (Parts B + C) population of the pivotal study R1500-CL-17100 and on AESIs and TEAEs at the PT level occurring in 5.0% or more patients in Pool 3, which is considered acceptable. Based on these evaluations, only fatigue was identified as a new ADR, which is endorsed. However, the Applicant was requested to justify why the ADR fatigue is applicable only to patients aged 5-⩽ 11 years since in the placebo-controlled studies in adults a slightly higher frequency of fatigue events was reported in the evinacumab group compared with the placebo group (4.3% vs. 3.7%). Moreover, considering the MoA and the disease similarity between adult, adolescents and paediatric HoFH patients, a difference in causal association is not expected. In the response, the Applicant highlighted that there was a close association of administration of the drug and the onset of events and that there were two fatigue events in one patient which was considered by the investigator treatment related. As there is no controlled data in paediatric patients aged 5 to <12 years, the causal relationship of fatigue in the paediatric population could not be ruled out according to the Applicant.

Regarding the adult and adolescent population, although the clinical pattern of AEs of fatigue was similar between adults (and adolescents) and patients aged 5 to < 12 years, data of the placebo-controlled studies in the adults and adolescents (DBTP of R1500-CL-1629 and R1500-CL-1643) showed a risk difference for fatigue of 0.5% with a 95% CI [-5.7% ; 6.6%] (n=5 (4.3%) and n=2 (3.7%) for the evinacumab and placebo group, respectively), which corresponds to an absence of risk difference. Based on the above, the Applicant argued that fatigue should only be considered an ADR for paediatric patients aged 5 to < 12 years. However, the incidence in fatigue between the adult (+adolescent) population and the paediatric population did not differ much according to CHMP. Additionally, asthenia is currently already stated as the ADR table in section 4.8 of the SmPC based on the data of the placebo-controlled studies in adults and adolescents. The Applicant clarified that the events of asthenia and fatigue were recorded as different verbatim terms as reported by clinical investigators. It is however unclear if the differences between the two types of recordings were clinically relevant. In other words, whether the investigators intentionally rejected one term and used the other term instead. Additionally, fatigue has a broader definition and also includes asthenia (according to Pelicier, 1994). Based on the above, the Applicant was requested to include fatigue in the ADR table in section 4.8 of the SmPC. Subsequently, the extra information in “Description of selected adverse reactions” under the table should describe that fatigue, which is then mentioned in the table, is only observed in a certain age group according to the available data. In the response, the Applicant has updated section 4.8 of the SmPC as requested by CHMP. The Applicant also highlighted that the ADR fatigue may occur within an undefined timeframe, which was acknowledged by CHMP. Therefore, the specification “after infusion” may be misleading and may lead to confusion, since fatigue is expected to be experienced shortly after the infusion, which is not necessarily the case. As such, it was agreed that the ADR fatigue should be stated without any additional information regarding the timing with the infusion.

In this respect, every ADR should be included in the ADR table in section 4.8 and that no new ADRs (ADRs not mentioned in the table) should only be described in “Description of selected adverse reactions” under the table.
Further, no new ADRs were identified based on screening of updated Pool 3 data from adolescents and adults.

AEs of special interest
Special attention has been given to certain AESIs, including anaphylactic reactions, general allergic events, infusion reactions, hepatic disorders, neurocognitive events, neurologic events, new onset of diabetes (NOD), diabetes mellitus or diabetic complications, pancreatitis, cataracts, immune complex diseases, and muscle events/creatine kinase elevation.
In the pivotal study R1500-CL-17100, there were no events of anaphylactic reactions, infusion reactions, NOD, muscle events, neurologic events, neurocognitive events, cataracts, pancreatitis, or immune complex TEAEs. In the Pool 3 Total Population, there were no cases of anaphylactic reactions, neurologic events, pancreatitis, or immune complex TEAEs.

General allergic events. The incidence in general allergic events in Study R1500-CL-17100 (33% and 15.0% in Part A and Part B, respectively) appeared higher compared with the Pool 3 Total Population (13.6%) and the placebo-controlled Pool 2 (~11), however, the events were not serious, did not result in discontinuation of study treatment and were considered not related to study drug. More specifically, two (33.3%) patients in Part A (both allergic rhinitis) and 3 (15.0%) patients in the pooled (Parts B + C) population (rash (2 (10.0%) patients), conjunctivitis allergic (1 (5.0%) patient), dermatitis contact (1 (5.0%) patient), and rhinitis allergic (1 [5.0%] patient) experienced general allergic events TEAE of which none were serious or resulted in discontinuation of the study drug. Only 1 patient experienced a general allergic TEAE considered by the investigator to be related study drug where this patient experienced 2 separate episodes of mild rash and 1 episode of dermatitis contact with possible alternative aetiologies including starch for the Rash and poison ivy contact for the dermatitis contact.
In the updated Pool 3, none of the general allergic TEAEs were serious or led to discontinuation of study drug. Five patients in the Pool 3 Total population experienced general allergic TEAEs considered related to study drug, including hypersensitivity, infusion related reaction, pruritus, pruritus generalised, and swelling face. However, as evinacumab is a monoclonal antibody, there may be the potential for hypersensitivity reactions. Overall, the paediatric HoFH patients aged 5-⩽ 11 years appears not to be at increased risk for allergic reactions.
Infusion reactions. No paediatric patients experienced infusion reaction AESIs during the R1500-CL-17100 study. In the Pool 3 Total Population, the percentage of patients with an infusion reaction was 6.3% which is consistent with the frequency of 7.4% in the placebo-controlled studies in the initial MAA (Pool 2). Infusion site reaction, infusion related reaction and anaphylaxis are currently already stated as ADRs in the labelling.
Hepatic disorders/ liver enzyme elevations. No patient experienced a hepatic disorder TEAE by or met patient met the criteria for Hy’s Law in both study R1500-CL-17100 or Pool 3. Some increases in liver enzymes were observed, however, the frequency was low, and none of these TEAEs were serious or resulted in discontinuation of study drug.
Neurocognitive events. With respect to neurocognitive events, one (0.49%) adult patient in Pool 3 Total Population experienced a serious TEAE of mental status changes that was considered not related to study treatment by the investigator.
New onset of diabetes/diabetic complications. No patients in the pivotal Study R1500-CL-17100 or in the Pool 3 Adolescent Population had diabetes mellitus at baseline and no patients developed new onset of diabetes (NOD) during the studies. In the Pool 3 Total Population, 8 out of 188 (4.3%) patients without diabetes mellitus at baseline developed NOD during evinacumab treatment, however,

the frequency was similar as that observed in the placebo-controlled studies in the initial MAA (Pool 2) (7.4%). With respect to diabetic complications, 4 out of 18 adult patients who had diabetes mellitus at baseline experienced a diabetic complication TEA, however no clinically meaningful changes in mean HbA1c were reported in these patients.
Cataracts. One (0.49%) adult patient in the Pool 3 Total Population experienced a cataract TEAE of moderate severity that was considered by the investigator not related to study.
Muscle events/creatine kinase elevation. In paediatric patients from R1500-CL-17100 or in adolescent or adult patients in Pool 3, no serious muscle TEAEs, including rhabdomyolysis/myopathy were reported. In Study R1500-CL-17100, one (5.0%) patient experienced an event of pain in extremity. In the Pool 3 Adolescent Population, 53 (25.7%) patients experienced muscle events, which is consistent with that observed in the placebo-controlled studies in the initial MAA (21.0%). The most common (⩾ 5% of patients) TEAEs were arthralgia (7.8%) and back pain (7.8%). Pain in extremity and back pain are already known ADRs from the initial MAA dossier.

Overall, the safety data provided suggested that evinacumab was not associated with any new safety concerns related to hepatic TEAE or liver enzymes, neurologic or neurocognitive events, glycaemic control or diabetes in patients with or without diabetes at baseline, cataracts, pancreatitis, immune complex TEAEs, and muscle events/creatine kinase elevation. However, the open-label designs of the studies and the frequencies in the different AESIs are limited, making firm conclusions difficult.
These observations are supported by a genetic study of 650 carriers of ANGPTL3 LOF variants, which shows no association with any apparent increase in adverse clinical outcomes, including liver disease, type 2 diabetes mellitus, neurological diseases, risk of cancer or overall mortality. Nevertheless, the safety results of carriers of ANGPTL3 LOF variants are difficult to extrapolate to HoFH patients treated with evinacumab, among other things since the lipid profile between both populations are very different with severely elevated LDL-C levels in HoFH, while ANGPTL3 is suggested to play an important role in lipid metabolism. Additionally, in the genetic study, almost all patients were heterozygous ANGPTL3 LOF variants whereas, with evinacumab treatment, all ANGPTL3 in the serum is neutralised mimicking complete loss of ANGPTL3 function. Consequently, higher reductions in different lipid parameters were observed in HoFH patients treated with evinacumab compared with LOF variants compared with (LDL-C:-48.3% vs -10%, and HDL-C -41.9% vs -7%, respectively).

Serious AEs
The percentage of patients experiencing SAEs in paediatric patients with HoFH aged 5 - ⩽ 11 years was relatively low (n=1 (5.0%)), not considered related to study drug and lower to that observed in adults and adolescents the initial MAA dossier (9.9%), which is reassuring. Also the Pool 3 Adolescent and Total Population did not show any patterns indicative of a new safety signal; all SAEs were considered not related to study treatment, with the exception of a single event of an anaphylactic reaction which is already a known ADR from the initial MAA dossier.

Deaths
No deaths were reported in the pivotal study R1500-CL-17100 in in paediatric patients with HoFH aged 5 - ⩽ 11 years. Two deaths were reported in Pool 3 Total Population (both adults), but not considered related to study treatment, which has already been discussed during the initial MAA.

Laboratory findings
A low level of immunogenicity of anti-drug antibody has been observed (n=1) in study R1500-CL-17100), which was low-titer, Nab negative and did not affect the LDL-C response. However, in Study R1500-CL-17100, 1 patient in Part A and 1 patient in Part B had detectable pre-existing anti-drug antibodies (ADAs) against evinacumab at the start of treatment. The Applicant adequately clarified that

the presence of pre-existing ADA responses can be attributed to a variety of factors, including sensitivity of the assay and cross-reactivity with other proteins. Further, it is stated that the ADA assay used in the evinacumab program is highly sensitive which allows for the detection of very low levels of antibodies, however, also increases the potential of detecting false positive responses. Nevertheless, these pre-existing ADA responses did not result in any safety or efficacy concerns in relation to evinacumab.
Furthermore, no trends indicative of clinically important treatment-related laboratory abnormalities, including haematology parameters, renal and hepatic function parameters, blood glucose (see also AESIs) were observed with evinacumab.

However, in the pivotal study (consistent with other submitted studies), treatment with evinacumab resulted in a -41.9% reduction in HDL-C at week 24, with HDL-C reaching below normal levels of 0.50 mmol/L. As also discussed during the initial MAA, this unfavourable effect could likely be to the effect of evinacumab on the endothelial lipase (EL) responsible for the hydrolysis of HDL-C particles. However, the impact of this for reverse cholesterol transport, especially in the setting of this diseased population with extremely high elevated cholesterol, is somewhat uncertain. Further, the potential impact on cardiovascular risk remains unclear, especially since recent findings challenged a clear correlation between HDL-C targeted treatment (increase in HDL-C) and improvement in cardiovascular risk. The cardioprotective association with LOF variants in ANGPTL3 may suggest that this may overall provide a cardiovascular protective effect with evinacumab. However, extrapolation to current findings may be complicated as the current diseased HoFH population substantially deviated from the LOF population based on the extremely elevated LDL cholesterol levels, and the loss of function in the LDL receptor. Overall, the lowering of HDL-C by evinacumab may likely not importantly offset the potential CV benefits from substantial lowering of LDL-C in these HoFH patients at very high cardiovascular, although special efforts are still requested to better understand the CV impact of evinacumab treatment post-approval by the conduction of the requested PASS study in light of the MAA under exceptional circumstances, in which the atherosclerosis process over time in patients with HoFH who are treated with evinacumab and undergo cardiac imaging.
It has to be noted that with the submission of this type II variation to extend the therapeutic indication of Evkeeza, the Applicant is proposing to adjust the age range of the PASS study to align with the therapeutic indication, thereby including patients aged 5 years and above, which is supported.

Vital signs

There were no trends indicative of important vital signs abnormalities, including systolic/diastolic blood pressure and heart rate, observed. Evaluations of growth and pubertal development (Tanner stage) and gonadal steroid hormones in paediatric patients from R1500-CL-17100 and the Pool 3 Adolescent Population showed that the changes were consistent with growth and development expectations in these populations, although the number of patients is limited (n=34) making firm conclusions difficult.

Discontinuation due to AEs

The percentage of patients who discontinued due to AEs was low; Only 3 (1.46%) patients in the Pool 3 Total Population and none in Study R1500-CL-17100 discontinued study drug, indicating that the drug is well tolerated.

Post marketing experience

Post-marketing data did not reveal any additional safety concerns.

2.6.2. Conclusions on clinical safety

Generally, evinacumab displays an acceptable safety profile in paediatric HoFH patients aged 5-≤ 11 consistent to those observed in adult and adolescent HoFH patients, with very few patients discontinuing treatment. However, the safety data of evinacumab in HoFH paediatric patients aged 5-≤ 11 is very limited, which is expected, considering the rarity of the disease. No new safety signal has been identified with the exception of a new ADR fatigue, which has been added as ADR in the table in section 4.8 of the SmPC.

However, similar as in the initial dosser, there is some uncertainty on the effect of a lowering of HDL-C by evinacumab treatment. This does likely not offset the potential CV benefits from substantial lowering of LDL-C in HoFH patients who are at very high cardiovascular risk, although efforts are still requested to better understand the CV impact of evinacumab treatment by the conduction of the requested PASS study in light of the MAA under exceptional circumstances, in which the atherosclerosis process over time is studied in patients with HoFH who are treated with evinacumab and undergo cardiac imaging.

2.6.3. PSUR cycle

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

2.7. Risk management plan

The MAH submitted an updated RMP version (1.1) and subsequent version 1.2 with this application. The (main) proposed RMP changes were the following:

- Part I, Product Overview: Change of MAH
- Part I, Product Overview: Proposed indication for Evkeeza to include the treatment of paediatric patients aged from 5 years to 11 years with homozygous familial hypercholesterolaemia (HoFH).
- Part II, module SIII: Update on clinical exposure to include exposure from completed and, ongoing adult/ adolescent studies, as well as paediatric study
- Part II, module SV: Update on post-authorisation exposure
- Part II, module SVII: Identified and Potential Risks (no impact on summary of safety concerns)
- Part III Pharmacovigilance Plan (no impact on summary of safety concerns)
- Minor administrative formatting updates without change in data (marked as such throughout the RMP)

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 is acceptable. The CHMP endorsed this advice without changes.

The CHMP endorsed the RMP version 1.2 with the following content:

Safety concerns

The Summary of the safety concerns has not been changed.

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Embryofoetal toxicity
Missing information	Safety of long-term use (e.g., >2 years) Use in pregnant or breast-feeding women

Considering the data in the safety specification, the safety concerns listed above are appropriate.

Pharmacovigilance plan

Routine pharmacovigilance

Routine pharmacovigilance including signal management and reporting of adverse reactions will continue to be implemented.

Additional pharmacovigilance activities

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances.				
UX858-CL401: An observational study to evaluate the long-term effects of evinacumab treatment in patients with homozygous familial hypercholesterolemia (HoFH) Ongoing;	– To evaluate the long-term safety outcomes in patients with HoFH who are ≥12 years old [a] and treated with evinacumab. – To evaluate the	Embryofoetal toxicity Safety of long-term use (e.g., >2 years) Use in pregnant or breast-feeding women (note that pregnancy	Protocol submission	Adopted by Pharmacovigilance Risk Assessment Committee (PRAC) on 07 Apr 2022. Statistical analysis plan (SAP) was submitted on 20 Sep 2022 together with an updated protocol. On 14 Apr 2023, a positive PRAC outcome has been received for the PASS protocol and SAP.

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
MAH: Ultragenyx Germany GmbH	frequency and outcomes of pregnancy in female patients with HoFH who are treated with evinacumab. – To evaluate changes in the atherosclerosis process over time in patients with HoFH who are treated with evinacumab and undergo cardiovascular imaging (as data allow). – To evaluate the frequency of cardiovascular imaging of patients with HoFH.	information will be evaluated in the proposed long-term safety study to address the potential risk of embryofoetal toxicity)	Annual study reports	Submitted with the annual reassessment.
			Start of data collection End of data collection Final report of study results	Jul 2023 Dec 2028 Jun 2029

HoFH=homozygous familial hypercholesterolaemia, ICSR=individual case safety report, MAH=marketing authorisation holder.

[a] Of note, although the current study population includes patients who are 12 years and older and have a diagnosis of HoFH, the study population may be adjusted and expanded if the approved indication for evinacumab extends to cover other patient groups.

Overall conclusions on the PhV Plan

There are still outstanding issues regarding the RMP but a preliminary view is that:

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety Concern	Routine Risk Minimisation Activities
Embryofoetal toxicity	**Routine risk communication** – SmPC Sections 4.6 and 5.3 – PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk** Recommendation that women of childbearing potential should use effective contraception during treatment with evinacumab and for at least 5 months after the last dose is included in SmPC Section 4.6 and PL Section 2. **Other routine risk minimisation measures beyond the Product Information** – SmPC Section 4.2 **Legal status** Evinacumab is subject to restricted medical prescription. Treatment with Evinacumab should be initiated and monitored by a physician experienced in the treatment of lipid disorders.
Safety of long-term use (e.g., >2 years)	**Routine risk communication** None **Routine risk minimisation activities recommending specific clinical measures to address the risk** None **Other routine risk minimisation measures beyond the Product Information** None. **Legal status** Restricted medical prescription.
Use in pregnant or breast-feeding women	**Routine risk communication** – SmPC Sections 4.6 and 5.3 – PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk** Recommendation that women of childbearing potential should use effective contraception during treatment with evinacumab and for at least 5 months after the last dose is included in SmPC Section 4.6 and PL Section 2.

Safety Concern	Routine Risk Minimisation Activities
	It is unknown whether evinacumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which decrease to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, evinacumab could be used during breast-feeding if clinically needed is included in SmPC Section 4.6 and PL Section 2 as recommendation on use of evinacumab for breast-feeding women. **Other routine risk minimisation measures beyond the Product Information** – SmPC Section 4.2 **Legal status** Evinacumab is subject to restricted medical prescription. Treatment with Evinacumab should be initiated and monitored by a physician experienced in the treatment of lipid disorders.

Additional risk minimisation measures

None proposed

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Annex II and the Package Leaflet have been updated accordingly.

Changes are also made to the PI to bring it in line with the current QRD template version 10.3.

Please refer to Attachment 1 which includes all changes to the Product Information.

2.8.1. User consultation

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

The number of changes made in the package leaflet is small, and the changes do not fundamentally alter the layout or presentation of the information in the package leaflet.

Furthermore, the safety profile of Evkeeza in patients aged ⩾5 to <12 years old is generally consistent with that observed in adult and adolescent patients, with the inclusion of fatigue as a possible side effect with increased frequency in children aged ⩾5 to <12 years old. The MAH does not consider that this additional text would alter the ability of patients and care givers to locate and understand the information presented.

In addition, evinacumab will be administered by healthcare professionals only, and it is considered likely that for patients aged ⩾5 to <12 years old, parents or carers of children will be responsible for reviewing and understanding the information, rather than the patients themselves.

In the original User Test, 7 of the 20 participants included were parents or carers of children, and therefore, it is considered that the functionality of the package leaflet for parents or carers has already been adequately tested.

The MAH considers that the patient leaflet is presented in accordance with the QRD Product information Template guidelines (28 September 2022/ version 10.3) and that no further changes to the patient leaflet are required in support of this type II variation. Furthermore, the MAH considers that the changes made do not alter the Patient Leaflet sufficiently to require a new User Test.

The CHMP is in agreement with the conclusions of the MAH. The justification for not performing a full user consultation on the package leaflet is considered acceptable.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Evkeeza (evinacumab) is still (since July 2021) included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is a biological product that is not covered by the previous category and authorised after 1 January 2011;
- It has a PASS imposed either at the time of authorisation or afterwards; [REG Art 9(4)(cb), Art 10a(1)(a), DIR Art 21a(b), Art 22a(1)(a)];
- It is approved under exceptional circumstances [REG Art 14(8), DIR Art (22)]

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic life-threatening condition resulting in severely elevated LDL-C (> 13mmol/L) leading to premature cardiovascular disease (CVD) and, in untreated patients, premature death. The prevalence of HoFH is estimated 1/160,000 to 1/320,000 patients worldwide.

If left untreated, HoFH patients rarely live past the first or second decade of life, with one study indicating the mean age of the first ASCVD event at 12.8 years and an average age of ASCVD death of 17.7 years (Raal 2011). Further, a recent retrospective study in Italian and Chinese patients with HoFH showed that despite starting lipid-lowering treatments early (mean age of 5.6 year, Italian cohort, and 10.7 year, Chinese cohort), 22% (Italian cohort) and 45% (Chinese cohort) of the patients had a CVD event before age 20 and 16.7% (Italian cohort) and 31.8% (Chinese cohort) had died before age 21 (Stefanutti 2019).

The goal of therapy in patients with HoFH is to reduce LDL-C, thereby reducing atherogenesis and subsequently reducing CVD events and mortality. Currently, patients with HoFH tend to be treated with multiple lipid-lowering therapies (LLT) but are not able to achieve guideline-recommended LDL-C targets.

3.1.2. Available therapies and unmet medical need

Attempts to lower cholesterol levels often require multiple lipid-lowering drugs and LDL apheresis. Despite these therapies, a majority of patients with this disorder does not reach guideline-recommended LDL cholesterol levels. Patients with HoFH are often treated with multiple lipid-lowering treatments (LLTs) including statins, evolocumab, ezetimibe, and lipid apheresis; however, these treatments are largely ineffective for patients either due to LDLR mutations, problems with tolerability, and/or they are not available for the paediatric population.

Statin therapy is the cornerstone treatment for LDL-C lowering in the paediatric population aged 6 years and older and causes a 50% reduction in patients with HeFH, however only a 15-30% reduction in LDL-C is reached in patients with HoFH. The safety and efficacy of ezetimibe in children with HoFH aged less than 18 years have not been established. Further, lomitapide is not approved for use in paediatric patients.

Evolocumab, a PCSK9 inhibitor, is indicated for paediatric HoFH patients aged 10 years and older. Anti-PCSK9 therapy on top of maximally tolerated lipid-lowering therapy resulted in a mean reduction in LDL-C of approximately 30% compared to placebo. Of note, only evolocumab is currently approved for patients with HoFH; use of alirocumab in patients with HoFH is considered off label.

Apheresis is an important adjunctive treatment for HoFH; a single treatment reduces LDL-C by 55%-70% relative to pre-treatment levels. However, apheresis may be burdensome, and its availability is limited. Also, only a temporal reduction in LDL-C is achieved.

Liver transplantation can be used to treat HoFH, although it is rarely used and considered as a last resort treatment option due to the many disadvantages, including a high risk of post-transplantation surgical complications and mortality, the paucity of donors, and the need for life-long treatment with immunosuppressive therapy.

Due to the limitations of currently available treatments, there exists a high unmet medical need for new therapeutic options that reduce LDL-C and the inevitable risk for premature ASCVD in paediatric patients with HoFH. The unmet medical need is particularly severe for paediatric HoFH patients with null/null or negative/negative mutations where currently available LLTs provide little benefit in lowering LDL-C and for paediatric HoFH patients who lack treatment options.

3.1.3. Main clinical studies

The paediatric development program in line with the approved EF PIP, EMEA-002298-PIP01-17-M05 (PIP decision number P/0087/2023) as also indicated by the partial compliance check by the EMA (EMA/145021/2023). EMA decision dated 16 May 2023: Studies R1500-CL-17100 and R1500-CL- 1719 are confirmed to be compliant as set out in the EMA's Decision (P/0087/2023) of 10 March 2023.

Study R1500-CL-17100 is an ongoing 3-part, phase 1b/3 single-arm open-label study evaluating the efficacy, safety and pharmacokinetics of 15 mg/kg IV Q4W evinacumab in a total of 20 paediatric patients with HoFH aged ≥5 to <12 years, on top of maximal stable lipid lowering therapy. The study composed of 3 parts: Part A (pharmacokinetics/pharmacodynamics [PK/PD]), Part B (24-week primary efficacy and safety) and Part C (48-week treatment period and 24-week follow-up period).

The results of the pivotal phase 1b/3 study R1500-CL-17100 was supplemented with efficacy and safety results from updated interim analysis of the ongoing open-label study R1500-CL-1719 in HoFH adults and adolescents aged 12 years and older, and an extrapolation analysis (including population PK, population PK/PD, and simulation analyses).

3.2. Extrapolation

To support use of evinacumab in patients ≥5 to <12 years of age with HoFH, an extrapolation analysis (including population PK, population PK/PD), and simulations analyses) has been conducted.

There are several considerations that justify the overall approach to extrapolate efficacy from adults as outlined in outlined in the CHMP "*Reflection paper on the use of extrapolation in the development of medicines for paediatrics*" (EMA/189724/2018) and the draft "*ICH guideline E11A on paediatric extrapolation*" (EMA/CHMP/ICH/205218/2022). Development of a paediatric extrapolation concept requires an understanding of the factors that influence the similarity of disease, the pharmacology of the drug and the response to therapy as well as the safety of use in all the relevant populations.

Disease similarity

HoFH is an ultra-rare and serious genetic condition, which requires early diagnosis and treatment beginning in infancy for the best outcomes. The of the hypercholesterolemia observed in patients with HoFH is the same for both adult and paediatric patients. Hypercholesterolemia is a consequence of the abnormal lipoprotein metabolism due to mutations in the key genes, mutations in the low-density lipoprotein receptor (LDLR) gene and less frequently by mutations in the proprotein convertase subtilisin/kexin type 9 (PCSK9), apolipoprotein B (APOB), and LDL receptor adaptor protein 1 (LDLRAP1) genes, and the markedly diminished hepatic LDL-C clearance from plasma. Additional phenotypic characteristics include premature CVD, aortic valve disease, and tendon xanthomas in the hands and Achilles' tendons.

As the aetiology of HoFH is the same for both adult and paediatric patients, the overarching goal of therapy is also the same, to lower LDL-C, and subsequently the risk of ASCVD:

- The EAS/European Society of Cardiology (ESC) consensus panel on FH recommends initiation of lipid-lowering therapy in patients with HoFH as soon as possible after diagnosis, with the goal of reducing LDL-C levels to <2.5 mmol/L (<100 mg/dL) in adults or <3.5 mmol/L (<135mg/dL) in children (Cuchel et al., 2014; Wiegman et al., 2015).
- The ESC/EAS Consensus panel recommends that in patients with FH and at very high risk, an LDL-C reduction of at least 50% and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered (Mach et al., 2020).

Similar drug pharmacology

The extrapolation study showed that patients achieve steady-state evinacumab concentrations that are sufficient for maximal ANGPTL3 engagement, resulting in comparable LDL-C reductions across paediatric, adolescent, and adult HoFH patients.

In the paediatric population receiving a dosing regimen of 15 mg/kg IV Q4W, PK and PD data consistently described a profile consisting of both linear, non-saturable, and non-linear, target mediated elimination, consistent with that previously reported for adolescents and adults.

At lower concentrations insufficient to saturate the target-mediated pathway, exposure increased in a greater than dose proportional manner. At higher systemic concentrations of evinacumab, sufficient to saturate the target-mediated pathway, the PK of evinacumab trended towards a linear and dose-proportional profile driven by the non-saturable protein catabolism process. Coincident with the observation of systemic concentrations sufficient to achieve linear PK, was evidence of maximal target engagement, as assessed by total ANGPTL3 concentrations, and a maximal PD effect on lipid parameters.

The main source of intrinsic PK variability identified by population PK analysis was body weight. Lower body weights (including in paediatric patients) showed a decrease in exposure. Model-based simulations based upon post-hoc Bayesian estimates predicted that mean steady-state exposures were 30% (for Cmin) to 38% (for Cmax) lower in paediatric patients ≥5 to <12 years compared to adult patients ≥18 years after 15 mg/kg IV administrations Q4W. Despite lower exposures in paediatric patients, comparable LDL C reductions were observed and predicted by the population PK/PD model in paediatric, adolescent, and adult populations at week 24, supporting the 15 mg/kg IV dosing regimen across these populations.

Baseline ANGPTL3 and disease status (patients with HoFH versus healthy participants) were descriptors of the variability in the Vmax of the saturable elimination pathway but had marginal influence on evinacumab exposures at clinically relevant doses, due to the pathway saturation. None of the other demographic characteristics (age, race, or gender) had a relevant effect on the PK of evinacumab.

Similar exposure response

In the paediatric Study R1500-CL-17100, the mean percent LDL-C reductions at Week 4 after single-dose evinacumab administration in Part A (approximately −26.0%) and Part B (approximately −38.3%) were consistent with the percent LDL-C reductions at Week 4 previously reported for adults from Study R1500-CL-1331 (approximately −30.1%) and adults and adolescents from the DBTP of Study R1500-CL-1629 (approximately −39.6%). Multiple dose administration of evinacumab 15 mg/kg IV Q4W over 24 weeks in the paediatric population resulted in lower steady-state evinacumab concentrations relative to those observed in the adult population. Despite these lower exposures, at 24 weeks, the 48.3% LDL-C reduction in the paediatric population was comparable to the 47.1% LDL C reduction observed in the adult and adolescent population in the Study R1500 CL-1629 DBTP, suggesting that the steady-state evinacumab concentrations in paediatric patients were sufficient to achieve maximal target engagement.

Similarity of treatment response across age groups was also demonstrated using model-based simulations to estimate the percentage of patients predicted to achieve LDL-C concentrations <2.8 mmol/L (or <110 mg/dL) and <3.4 mmol/L (or <130 mg/dL) by Week 24 following 15 mg/kg Q4W infusions. The threshold of <3.4 mmol/L (<130 mg/dL) was achieved by more than half of all virtual patients in all age and weight groups, despite baseline LDL-C concentrations being higher in the 5 to <12 age group (422 mg/dL on average) than in adults (255 mg/dL on average), with the percentage of target attainment ranging from 56.4% in patients ≥5 to <12 years of age to 67.4% in adult patients. Regarding safety, evinacumab displays an acceptable safety profile in paediatric HoFH patients aged 5-≤ 11 consistent to those observed in adult and adolescent HoFH patients.

Discussion

Similarity of disease, the pharmacology of the drug and the response to therapy as well as the safety of use in all the relevant populations has been adequately justified based on the totality of the data. Therefore, extrapolation of data from adults is acceptable.

3.3. Favourable effects

Primary endpoint. Evinacumab demonstrated a substantial reduction in LDL-C from baseline to Week 24 -48.3% (95% CI 68.8 to 27.8) in paediatric patients ≥5 to <12 years of age, which corresponds to an absolute mean change in LDL-C of approximately -3.416 mmol/L. The reduction in LDL-C with evinacumab were observed as early as Week 1 and sustained over 24 weeks.

Other endpoints. The LDL-C lowering effect was further supported by the beneficial effects in secondary cholesterol measurements (e.g. Apo-B, non-HDL-C, Total-C, and Lp(a)). At Week 24, 78.6% of the patients had a ≥50% reduction in LDL-C at Week 24.

Subgroups. The LDL-C lowering effect appears generally consistent among subgroups, including age, patients receiving apheresis yes or no (-47.9% and -48.8 %, respectively) and the most difficult to treat patients with null/null (-57.2%) and negative/negative (-67.7%) mutations.

Supportive study R1500-CL-1719. The LDL-C lowering effect at 24 weeks observed in paediatric patients with HoFH aged 5-≤ 11 years of age in study R1500-CL-17100 (-48.3%) was generally consistent with that observed in adolescents of the OL study R1500-CL-1719 (-55.4%) and with that observed in the total population (adolescents and adults) in OL study R1500-CL-1719 (-43.6%). Also in the OL study R1500-CL-1719, the primary endpoint results were further supported by the beneficial effects in secondary cholesterol measurements (e.g. Apo-B, non-HDL-C, Total-C, and fasting TGs).

3.4. Uncertainties and limitations about favourable effects

Mechanism of action. Although the proof of concept studies demonstrates that evinacumab as a human monoclonal antibody inhibits ANGPTL3, which leads to a reduction in LDL-C, the exact mechanism of action in HoFH patients remains not completely understood. Based on more recent studies, it is hypothesized that especially endothelial lipase (EL) rather than LPL, plays a more crucial role in the reduction of LDL-C via VLDL processing. Any potential for liver fat accumulation seems unlikely, as evinacumab seems not to interfere in blocking pathways in the assembly of VLDL particles in the liver with fat accumulation as a possible result.

Exploratory endpoint. No beneficial effect on cIMT was found, which can be attributed to the limited number of patients and the short follow-up of 24 weeks; In 4 (28.6%) patients with matching baseline and 24-week follow-up cIMT measurements, the change from baseline was 0.025 (0.0311) mm.

Long-term effect. The mean % change from baseline in LDL-C at week 48 in Part C of -39.71% was lower compared with that observed at Week 24 in Part B (-48.3%), which was highly likely due to the low number of patients and non-compliance to other lipid lowering therapies. Also, in the supportive study R1500-CL-1719, the total population (adolescents and adults), showed maintenance of LDL-C reduction of -30.8% for up to approximately 120 weeks (over 2.5 years), although the effect size was smaller compared with the LDL-C reduction at week 24 of (-43.6%).

3.5. Unfavourable effects

Adverse events. During Part A of the study and in the pooled (Parts B + C) population of study R1500-CL-17100, a high proportion of patients experienced at least one TEAE (83.3% and 95.0%, respectively), which appeared somewhat higher as observed during the initial MAA (65.9%). However, the majority of the TEAEs were classified as mild or moderate in severity. The most frequent TEAEs were vitamin D deficiency, cough, oropharyngeal pain, and rhinitis allergic (2 patients each (33.3%) in Part A and COVID 19 (15/20 (75.0%) patients), and pyrexia (5/20 (25.0%) patients) in the pooled (Parts B + C) population. The AEs considered treatment-related by the investigator were reported in 1 (8.2%) patient in Part A (infusion site reaction) and in 3 (15.0%) patients in the pooled (Parts B + C) population (fatigue, abdominal pain and nausea, and dermatitis contact and rash).

In the Pool 3 Adolescent Population and the Total Population, TEAEs were also frequently reported (85.7% and 80.6%, respectively), however, consistent to the frequently of the placebo-controlled

studies in the initial MAA (Pool 2)(81.2%). The majority of these were mild or moderate in severity and were considered not related to study drug by the investigator.

ADRs. Fatigue was identified as a new ADR and was included in the ADR table in section 4.8 of the SmPC.

Adverse events of special interest.

The incidence of *general allergic events* in Study R1500-CL-17100 (33% and 15.0% in Part A and Part B, respectively) appeared higher compared with the Pool 3 Total Population (13.6%) and the placebo-controlled Pool 2 (~11), however, the events were not serious, did not result in discontinuation of study treatment and were considered not related to study drug. So, the paediatric HoFH patients aged 5-≤ 11 years appears not to be at increased risk for allergic reactions. No paediatric patients experienced *infusion reaction* during the R1500-CL-17100 study. In the Pool 3 Total Population, the percentage of patients with an infusion reaction was 6.3% which is consistent with the frequency of 7.4% in the placebo-controlled studies in the initial MAA (Pool 2). Infusion site reaction, infusion related reaction and anaphylaxis are currently already stated as ADRs in the labelling. Further, the safety data, although limited, was not indicative of any new safety concerns related to hepatic TEAE or liver enzymes, neurologic or neurocognitive events, glycaemic control or diabetes in patients with or without diabetes at baseline, cataracts, pancreatitis, immune complex TEAEs or muscle events/creatine kinase elevation.

Serious AEs. The percentage of patients experiencing SAEs in paediatric patients with HoFH aged 5 - ≤ 11 years was relatively low (n=1 (5.0%)), not considered related to study drug and lower to that observed in adults and adolescents the initial MAA dossier (9.9%), which is reassuring. Also the Pool 3 Adolescent and Total Population did not show any patterns indicative of a new safety signal; all SAEs were considered not related to study treatment, with the exception of a single event of an anaphylactic reaction which is already a known ADR from the initial MAA dossier.

Deaths. No deaths were reported in study R1500-CL-17100 in the Pool 3 Total Population in paediatric patients with HoFH aged 5 - ≤ 11 years. Two deaths were reported in Pool 3 Total Population (both adults), but not considered related to study treatment, and already discussed during the assessment of the initial MAA.

Immunogenicity. A low level of immunogenicity of anti-drug antibody has been observed (n=1) in study R1500-CL-17100), which was low-titer, Nab negative and did not affect the LDL-C response.

Laboratory findings. No trends indicative of clinically important treatment-related laboratory abnormalities, including haematology, renal and hepatic function parameters, blood glucose, were observed.

Vital signs. There were no trends indicative of important vital signs abnormalities, including systolic/diastolic blood pressure, heart rate, growth and pubertal development (Tanner stage) observed.

Tolerability. Evinacumab seems to be well tolerated; none in Study R1500-CL-17100 and only 3 (1.46%) patients in the Pool 3 Total Population and discontinued study drug.

Post marketing experience. Post-marketing data did not reveal any additional safety concerns; however, any details or discussion have not been provided.

3.6. Uncertainties and limitations about unfavourable effects

Exposure. Exposure data has substantially increased compared with the initial MAA dossier. Since the start of the clinical development program for evinacumab till the latest data cut-off, a total of 243 patients have been treated with any IV dose of evinacumab in either placebo-controlled or open-label trials (global exposure). Of these, 139 patients had HoFH, of whom 138 patients were treated with evinacumab 15 mg/kg Q4W for at least 24 weeks, 120 patients were treated for at least 52 weeks, and 78 patients were treated for at least 104 weeks. Nevertheless, the exposure data in paediatric HoFH patients aged 5-≤ 11 years of age of a total of 20 patients exposed to evinacumab with a mean (SD) duration of 51.63 (5.28) weeks of whom 5 patients were exposed to evinacumab for at least 56 weeks, remains very limited, which is however expected considering the rarity of the disease.

HDL-C. In the pivotal study (consistent with other submitted studies), treatment with evinacumab resulted in a -41.9% reduction in HDL-C at week 24, with HDL-C reaching below normal levels of 0.50 mmol/L. This is likely due to potentiating of the endothelial lipase with increased HDL-C hydrolysis. However, the consequences of the lower than normal HDL-C levels for e.g. cholesterol reverse transport are not exactly clear. Further, the clinical implications in terms of cardiovascular risk increase is unknown, especially since recent findings challenged a clear correlation between HDL-C targeted treatment (increase in HDL-C) and improvement in cardiovascular risk.

3.7. Effects Table

Effects Table for evinacumab in the HoFH paediatric population aged **5-≤** 11 years (data cut-off: 02 Jun 2022 Part C R1500-CL-study 17100)

Effect	Short description	Unit	Treatment (n=14)	Control	Uncertainties (Unc) / Strength of evidence (SoE)	References
Favourable Effects						
LDL-C	Change from baseline to week 24	%	-48.3%	N.A	SoE: Clinical relevant change of -3.416 mmol/L Effect size consistent with the HoFH patients of double-blind placebo-controlled study R1500-CL-1629 (−47.1%), the Adolescent population and Total Population of the OL study R1500-CL-1719 (-55.4% and -43.6%) Substantial changes observed in other lipid parameters (Apo-B, non-HDL-C, TC, Lp(a)) UnC: Effect was lower long-term: -39.71% at week 48 in Part C	R1500-CL-17100
Effect	**Short description**	**Unit**	**Treatment (n=20)**	**Control**	**Uncertainties / Strength of evidence**	**References**
Unfavourable Effects						
HDL-C	Change from baseline to week 24	%	-41.9%	N.A	SoE: effect consistent with other submitted studies UnC: HDL-C reaching below normal levels of 0.50 mmol/L; effect on CV risk unclear	Pooled (Parts B + C) population of R1500-CL-17100
Infusion		N (%)	0	N.A		

reactions						
Muscle related AEs		N (%)	1 (5)	N.A	SoE: effect consistent with other submitted studies	
Anti-evinacumab antibodies		N (%)	1 (5)	N.A	SoE: low titer response, transient, and no neutralizing antibodies	

3.8. Benefit-risk assessment and discussion

3.8.1. Importance of favourable and unfavourable effects

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic life-threatening condition resulting in severely elevated LDL-C (> 13mmol/L) leading to premature cardiovascular disease (CVD) and, in untreated patients, to premature death. Therefore, it is recommended to initiate lipid-lowering therapy in patients with HoFH as soon as possible after diagnosis. In children, testing for HF is recommended from the age of 5 or earlier if HoFH is suspected (Mach et al. 2020).

If left untreated, HoFH patients rarely live past the first or second decade of life, with one study indicating the mean age of the first event at 12.8 years and an average age of ASCVD death of 17.7 years (Raal 2011). Further, a recent retrospective study in Italian and Chinese patients with HoFH showed that despite starting lipid-lowering treatments early (mean age of 5.6 year, Italian cohort, and 10.7 year, Chinese cohort), 22% (Italian cohort) and 45% (Chinese cohort) of the patients had a CVD event before age 20 and 16.7% (Italian cohort) and 31.8% (Chinese cohort) had died before age 21 (Stefanutti 2019). Despite lipid lowering therapies, a majority of patients with this disorder do not reach guideline-recommended LDL cholesterol levels. Therefore, there is an unmet medical need for additional LDL-C lowering therapies. According to the ESC guideline (2019), the goals for treatment of children with FH > 10 years of age should be LDL-C < 3.5 mmol/L and at younger ages ≥ 50% reduction of LDL-C.

In 2021, Evkeeza has been approved for the indication: "*EVKEEZA is indicated* as an *adjunct to diet and other LDL-C lowering therapies for the treatment of adults and adolescent patients aged 12 years and older with HoFH* as a MA under exceptional circumstances. A non-interventional post-authorisation safety study (PASS) was requested at the time in order to generate confirmatory data on the cardiovascular implications of treating these patients with evinacumab.

This extension of the indication is based on interim results from an ongoing Phase 1b/3 single-arm, open-label study R1500-CL-17100 in paediatric (≥5 to <12 years) patients with HoFH, supplemented with supportive information from an updated interim analysis of an ongoing open-label study R1500-CL-1719 in adolescent (and adult) patients with HoFH, and an extrapolation analysis (including population PK, population PK/PD, and simulation analyses) to include treatment paediatric HoFH patients aged 5 to ≤ 11 years. The paediatric development program is in line with the approved EF PIP, EMEA-002298-PIP01-17-M05 (PIP decision number P/0087/2023) as also indicated by the partial compliance check by the EMA (EMA/145021/2023). EMA decision dated 16 May 2023: Studies R1500-CL-17100 and R1500-CL- 1719 are confirmed to be compliant as set out in the EMA's Decision (P/0087/2023) of 10 March 2023. Evinacumab demonstrated a substantial reduction in LDL-C from baseline to Week 24 of -48.3% (95% CI: 68.8 to 27.8) in paediatric patients ≥5 to <12 years of age on top of maximally stable lipid lowering therapies including statins, ezetimibe, lomitapide, and lipoprotein apheresis, which corresponds to an absolute mean change in LDL-C of approximately -3.416 mmol/L. The reductions in LDL-C with evinacumab were observed as early as Week 1 and

sustained over 24 weeks. The changes in LDL-C are considered to be clinically relevant as LDL-C is an important surrogate endpoint with potential benefits in terms of cardiovascular outcome. The degree of reduction was comparable to that observed in adult and adolescent patients evaluated in the initial MAA. The longer-term period demonstrated maintenance of effect, although the effect size at week 48 in Part C of -39.71% was lower compared with that observed at week 24 in part B most likely due to the small number of patients who contributed to this data (Part C is still ongoing) and reduced compliance to concomitant lipid lowering therapies. However, the LDL-C lowering effect is still considered clinically relevant. The LDL-C lowering effect appears generally consistent among subgroups, including age, patients receiving apheresis yes or no (-47.9% and -48.8 %, respectively) and the most difficult to treat patients with null/null (-57.2%) and negative/negative (-67.7%) mutations. Further, the LDL-C lowering effect was further supported by the beneficial effects in secondary cholesterol measurements (e.g. Apo-B, non-HDL-C, Total-C, and Lp(a)).

However, consistent with submitted studies in the initial MAA, treatment with evinacumab also demonstrated a substantial decrease in HDL-C (- 41.9%) to less than normal levels of HDL-C, for which the clinical consequences are currently not clear, especially in the setting of the HoFH population. The consequences for e.g. reverse cholesterol transport, and any potential causative relation to CV risk remains uncertain. Although recent understanding challenges the reverse relationship between HDL-C increase and CV risk reduction, some evidence (but not all e.g. gene associated low HDL-C levels) suggest that low levels of HDL-C have been associated with CV risk. Some reassurance has been provided based on effects as seen in ANGPTL3 loss-of-function patients; however, extrapolation to the HoFH population seems complex due to phenotype differences. Overall, the lowering of HDL-C by evinacumab may likely not importantly offset the potential CV benefits from substantial lowering of LDL-C in these patients at very high cardiovascular risk, although special efforts still have to be made to better understand the CV impact of evinacumab treatment by the conduction of the requested PASS study in light of the MAA under exceptional circumstances, in which the atherosclerosis process over time in patients with HoFH who are treated with evinacumab and undergo cardiac imaging will be evaluated. Moreover, the Applicant is proposing to adjust the age range of this PASS to align with the indication, thereby including patients aged 5 years and above, which is considered appropriate. The Applicant committed to providing a revised protocol of the PASS UX858-CL401 be within 3 months of positive CHMP opinion of the present extension of indication application.

The safety data of evinacumab in paediatric HoFH patients aged 5 -≤ 11 years is generally limited both in terms of number (n=20) as well as duration of treatment (only 5 patients were exposed for at least 56 weeks. The limited number of patients is expected considering the rarity of the disease. Nevertheless, the ongoing Part C of the pivotal study will provide some additional data to further address this as well as the already mentioned PASS study which has evaluation of long-term safety outcomes as one of the objectives and the age range will be adjusted to HoFH patients aged 5 years and above. Overall, evinacumab displays an acceptable safety profile in paediatric HoFH patients aged 5-≤ 11 consistent to those observed in adult and adolescent HoFH patients, with very patients discontinuing treatment. No new safety signal has been identified with the exception of a new ADR fatigue which was included in the ADR table of section 4.8 of the SmPC.

3.8.2. Balance of benefits and risks

Evinacumab has demonstrated a substantial and clinically meaningful reduction in LDL-C in paediatric HoFH patients aged 5-≤11 years on top of existing lipid lowering therapy options including statins, ezetimibe, lomitapide, and lipoprotein apheresis, which could likely address the high unmet medical need for these patients. Although a substantial decrease in HDL-C (- 41.9%) to less than normal levels of HDL-C were observed as also noted and discussed in the initial MAA, for which the clinical

consequences are currently not clear. It was considered that the lowering of HDL-C by evinacumab may likely not importantly offset the potential CV benefits from substantial lowering of LDL-C in these patients at very high cardiovascular risk. Evinacumab 15 mg/kg administered every 4 weeks by infusion has an acceptable safety profile and is well-tolerated, which is considered important for an intended lifelong treatment. The Benefit Risk balance is positive in the extended indication with treatment of patients from 5 years and older, although uncertainties remain, and further data will be provided post-approval to address these.

3.8.3. Additional considerations on the benefit-risk balance

None.

3.9. Conclusions

The overall Benefit Risk balance of evinacumab for paediatric HoFH patients aged 5-≤11 years is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include the treatment of paediatric patients with homozygous familial hypercholesterolaemia (HoFH) aged 5 years and older for EVKEEZA, based on interim results from study R1500-CL-17100, as well as supportive information from an updated interim analysis of study R1500-CL-1719, and an extrapolation analysis (including population PK, population PK/PD, and simulation analyses). R1500-CL-17100 is an ongoing multicentre, three-part, single-arm, open-label study evaluating the efficacy, safety, and tolerability of evinacumab in paediatric patients aged ≥ 5 to 11 years with HoFH. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Annex II and the Package Leaflet are updated in accordance. Version 1.2 of the RMP was agreed during the procedure. In addition, the marketing authorisation holder took the opportunity to introduce minor editorial changes to the PI. Furthermore, the PI is brought in line with the latest QRD template version 10.3.

Amendments to the marketing authorisation

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'EMEA-H-C-005449-II-0011'

Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 09 November 2023.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information (CCI) in "track changes" and with detailed justification by 24 November 2023. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 24 November 2023. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If a revised RMP is being approved as part of this procedure, please send to the EMA Procedure Assistant one redacted PDF document containing the RMP body, Annex 4 and Annex 6, as applicable, together with a redacted RMP file that can show the content that is proposed for redaction, and the signed RMP Publication Declaration, by 24 November 2023.