14 November 2024
EMA/556932/2024
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: EVKEEZA

International non-proprietary name: Evinacumab

Procedure No. EMEA/H/C/005449/II/0015

Note

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

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List of abbreviations

ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ANGPTL3	angiopoietin-like protein 3
Apo B	apolipoprotein B
APOB	apolipoprotein B gene
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
$AUC_{tau.}$	area under the concentration-time curve over the dosing interval
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CASCADE	Cascade Screening for Awareness and Detection
CDC	Centers for Disease Control and Prevention
CI	confidence interval
cIMT	carotid intima-media thickness
CL	linear elimination clearance
C_{max}	maximum serum concentration
C_{min}	minimum [trough] serum concentration
CUP	compassionate use programme
CV	cardiovascular
CVD	cardiovascular disease
DBTP	double-blind treatment period
EAS	European Atherosclerosis Society
EC	European Commission
EL	endothelial lipase
EMA	European Medicines Agency
ESC	European Society of Cardiology
EU	European Union
FH	familial hypercholesterolaemia

FHBL2	familial combined hypobetalipidemia 2
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein-cholesterol
HEART	Hyperlipidaemia Education and Atherosclerosis Research Trust
HeFH	heterozygous familial hypercholesterolaemia
HICC	HoFH International Clinical Collaboration
HoFH	homozygous familial hypercholesterolaemia
IC_{50}	half-inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
I_{max}	maximal inhibitory effect
IV	intravenous(ly)
LD	lactation day
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein-cholesterol
LDLR	low-density lipoprotein receptor
LDLRAP1	LDLR adaptor protein 1
LMT	Lipid-modifying therapy
LOF	loss-of-function
LPL	lipoprotein lipase
MTTP	microsomal alanine transaminase triglyceride transfer protein
NICE	National Institute for Health and Care Excellence
NOAEL	no-observed-adverse-effect level
NPC1L1	Niemann-Pick C1-Like 1 Intracellular Cholesterol Transporter 1
OLTP	open-label treatment period
PASS	post-authorisation safety study
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic(s)
PDCO	Paediatric Committee
PI	prediction interval
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)

PND	postnatal day
PT	preferred term
Q12W	every 12 weeks
Q4W	every 4 weeks
Q2W	every 2 weeks
QW	every week
RMP	risk management plan
SAE	serious adverse event
SC	subcutaneous(ly)
SD	standard deviation
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglyceride
UK	United Kingdom
UKB	UK Biobank
ULN	upper limit of normal
US	United States
VLDL	very low-density lipoprotein
VPC	visual predictive check
V_{max}	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 8 April 2024 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 for EVKEEZA to include the treatment of paediatric patients with homozygous familial hypercholesterolaemia aged 6 months to less than 5 years, based on the results of population PK and population PK/PD model-based extrapolation reports (R1500-PM-23202-SR-01V2 and R1500-PM-23089-SR-01V2). 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 2.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement minor changes to sections 4.2, 4.4, and 4.7 of the SmPC, along with editorial changes to the SmPC.

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 was completed.

The PDCO issued an opinion on compliance for the PIP P/0087/2023.

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: N/A

Timetable	Actual dates
Submission date	8 April 2024
Start of procedure:	27 April 2024
CHMP Rapporteur Assessment Report	21 June 2024
PRAC Rapporteur Assessment Report	27 June 2024
Updated PRAC Rapporteur Assessment Report	4 July 2024
PRAC Outcome	11 July 2024
CHMP members comments	15 July 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 July 2024
Request for supplementary information (RSI)	25 July 2024
CHMP Rapporteur Assessment Report	17 October 2024
PRAC Rapporteur Assessment Report	18 October 2024
PRAC members comments	22 October 2024
PRAC Outcome	31 October 2024
CHMP members comments	4 November 2024
Opinion	14 November 2024

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 HoFH paediatric patients aged 6 months to less than 5 years and is seeking full approval under exceptional circumstances.

2.1.1. Problem statement

Disease or condition

Familial hypercholesterolaemia (FH), an inherited hyper-LDL cholesterolaemia, has been regarded as a Mendelian autosomal dominant disease caused by rare genetic mutation(s) in the LDLR or its associated genes. FH can be classified into heterozygous FH (HeFH) (caused by a deleterious mutation in an FH-related gene), polygenic FH (caused by LDL-associated common genetic variations), polygenic FH plus hypertriglyceridemia (caused by LDL- and TG-associated common genetic variations), or homozygous familial hypercholesterolaemia (HoFH) (caused by double deleterious mutations in FH-related genes) (Masana et al., 2019).

HoFH is an ultra-rare and serious genetic condition resulting in severe hypercholesterolaemia (> 10 mmol/L or > 400 mg/dL) leading to premature cardiovascular disease (CVD) and, in untreated patients, premature death (Cuchel et al., 2023b).

HoFH is primarily caused by mutations in the LDLR gene and less frequently by mutations in the proprotein convertase subtilisin/kexin type 9 (PCSK9), apolipoprotein B (APOB), and LDLR adaptor protein 1 (LDLRAP1) genes. More than 90% of HoFH results from LDLR mutations (Cuchel et al., 2014). These mutations can be classified as:

1. "Null/null" where little to no LDL binding and uptake activity exists (< 15% LDLR activity) (Etxebarria et al., 2015; Gaudet et al., 2017; Banerjee et al., 2019),
2. Genotypically "negative/negative" where mutations such as premature stop codons, frame shifts, splice site changes, small and large insertions/deletions, and copy number variations are predicted to result in LOF of both LDLR alleles (Chora et al., 2018), or
3. Genotypically "defective" where missense mutations (hypomorphs) result in some LDLR activity (> 15% LDLR activity).

The amount of residual LDLR activity that a patient has contributes to the severity of disease. Given the progressive nature of the disease, it is likely that patients who present with clinical manifestations and symptoms during infancy have the most severe genetic mutations, and therefore, extremely limited levels of functional LDLRs. The lower the activity, the more severe the disease and the harder to treat with the available treatment options.

Currently, there is no clinically available test that can reproducibly determine the amount of residual LDLR activity as compared with a normal LDLR protein. LDLR activity can be either assayed through in vitro experiments that assess the relationship between the mutant protein and receptor function, or by predicting the residual receptor function depending on the type of mutation(s) and its estimated effect on the protein. The null/null definition described above is based on results of in vitro experiments reported in the literature describing the residual LDLR activity associated with a particular mutation. A threshold of < 15% residual activity is considered "null" because there is variability in the different experimental methods used to assess the LDLR activity (Banerjee et al., 2019; Gaudet et al., 2017; Etxebarria et al., 2015). The negative/negative definition consists of mutations that would likely render the protein nonfunctioning or with minimal function. Evaluation of these mutations is important because there are many LDLR variants for which the LDLR function has not been experimentally characterized with in vitro assays. Patients who are LDLR null or negative develop xanthomas sooner than patients who are LDLR defective, and untreated patients who are LDLR null or negative rarely live past the second decade of life (Kolansky et al., 2008; Moorjani et al., 1993).

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 HoFH aged 6 months to less than 5 years for EVKEEZA, based on the results of population PK and population PK/PD model-based extrapolation reports (R1500-PM-23202-SR-01V2 and R1500-PM-23089-SR-01V2).

The indication applied for is:

Evkeeza is indicated as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and paediatric patients aged 6 months ~~5 years~~ and older with homozygous familial hypercholesterolaemia (HoFH).

The proposed dose is 15 mg/kg given by intravenous (IV) infusion every 4 weeks (Q4W).

Epidemiology

HoFH is a rare (~1 in 300,000 in the EU) and life-threatening genetic condition resulting in severely elevated LDL-C (> 10 mmol/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

HoFH is a progressive disease, which requires early diagnosis and treatment beginning in infancy for the best outcomes. The aetiology of the hypercholesterolaemia observed in patients with HoFH is the same for both adult and paediatric patients. 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). The diagnostic criteria for HoFH are the same regardless of age. Diagnosis of HoFH can be made based on genetic criteria or clinical criteria. HoFH can be diagnosed genetically by the identification of biallelic LOF mutations in the LDLR, APOB, or LDLRAP1 genes, biallelic gain-of-function mutations in the PCSK9 gene, or a combination of 2 of these types of mutations in a heterozygous state. Regardless of the underlying mutations, patients with HoFH have severe hypercholesterolaemia starting in infancy. An LDL-C level > 10 mmol/L or > 400 mg/dL is consistent with phenotypic HoFH (Cuchel et al., 2023b). However, the LDL-C criteria could be lower depending on the presence of positive family history and age of screening.

In addition to genetic criteria, HoFH can be diagnosed clinically. Skin xanthomas since infancy, frequently found in flexures of the wrist and ankles, are pathognomonic for HoFH. Additional phenotypic characteristics include premature CVD, aortic valve disease, and tendon xanthomas in the hands and Achilles' tendons. Tendon xanthomas are more prominent in HoFH than in heterozygous familial hypercholesterolaemia (HeFH), but typically become apparent later than skin xanthomas (Harada-Shiba et al., 2023). Clinical diagnostic criteria are generally consistent worldwide, and the diagnosis in children follows a similar framework as in adults.

Lifelong exposure to extremely elevated LDL-C leads to an exceedingly high risk of developing premature atherosclerosis as well as valvular and supravalvular stenosis. 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).

Moreover, Mortality associated with HoFH has been reported in children as young as 1.5 years of age (Fredrickson DS, 1972). Published case reports include death of a 2-year-old male; postmortem examination revealed advanced aortic root atheroma and aortic valve stenosis. This patient presented with almost complete occlusion of the left coronary artery and the first 0.5 cm of ramus interventricularis anterior and ramus circumflexus, and the right coronary artery showing a 90% stenosis of about 0.8 cm in length (Galiano et al., 2020). Myocardial infarction leading to death was reported in a 3-year-old patient with HoFH (Rose et al., 1982). Sudden death due to 98% stenosis in the left coronary artery was reported in a 4-year-old male with HoFH (Widhalm et al., 2011). A case report of fatal refractory asystolic cardiac arrest in a 4.5-year-old female also summarized an additional 7 published reports of early death from CVD in children < 5 years of age with HoFH (Gautschi et al., 2012).

Management

Treatment guideline for HoFH

Because 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. LDL-C levels (ie, the phenotype) and not the presence of a genetic diagnosis drives therapeutic decisions.

Due to the high CVD risk associated with HoFH and the lifelong exposure to elevated LDL-C, a very aggressive cholesterol-lowering approach should be initiated as early as possible, ideally at diagnosis, to prevent or delay the development of CVD (Cuchel et al., 2014; Wiegman et al., 2015; France et al., 2016; Cuchel et al., 2023b).

The importance of initiating lipid-lowering therapy at diagnosis was highlighted by a retrospective cohort study (HoFH International Clinical Collaborators NCT04815005), which demonstrated the association of multi-lipid lowering regimens with lower LDL C levels and better outcomes (Tromp et al., 2022).

Recommended treatment guidelines have been instituted, including:

- Both the European Atherosclerosis Society (EAS)/European Society of Cardiology (ESC) consensus panel on FH and the Hyperlipidaemia Education and Atherosclerosis Research Trust (HEART) United Kingdom (UK) consensus statement on HoFH recommend initiation of lipid-lowering therapy in patients with HoFH as soon as possible after diagnosis, with the goal of reducing LDL-C levels to < 1.8 mmol/L (< 70 mg/dL) in adults or < 3.0 mmol/L (< 115 mg/dL) in children (Wiegman et al., 2015; France et al., 2016; Mach et al., 2020; Cuchel et al., 2023b).
    - These recommendations for children are in line with the American College of Cardiology/American Heart Association clinical practice guidelines for the management

of cholesterol that suggest LDL-C levels should be kept under 3.4 mmol/L (< 130 mg/dL) at a minimum (Grundy et al., 2019).

- The UK National Institute for Health and Care Excellence (NICE) guideline for FH states that statins should usually be considered by the age of 10 years for children with FH. Furthermore, for children with exceptional circumstances (eg, family history of coronary heart disease in early adulthood), a higher dose of statin than is licensed for use in the appropriate age group, and/or more than 1 lipid-modifying drug therapy, and/or institution of a lipid-modifying drug therapy before the age of 10 years should be considered. For adults, NICE guidelines currently state that high-intensity statins should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (ie, LDL-C concentration before treatment) (NICE, 2008).
- The Guidelines for the Diagnosis and Treatment of Pediatric Familial Hypercholesterolaemia 2022, published by the official journal of the Japan Atherosclerosis Society and the Asian Pacific Society of Atherosclerosis and Vascular Diseases, states that FH is a high-risk condition for atherosclerotic diseases. Thus, early initiation of treatment is recommended, depending on LDL-C levels. Since LDL-C accumulation levels, over time, are believed to be associated with the development of ASCVD, and since FH is a high-risk condition for atherosclerotic disease, early initiation of treatment in children is recommended (Harada-Shiba et al., 2023). The Japan Atherosclerosis Society guidelines recommend “treatment of HoFH be proactively conducted because it is essential to lower LDL-C as early as possible” (Harada-Shiba et al., 2018). The target value for the management of paediatric FH is an LDL-C level of 3.6 mmol/L (140 mg/dL) (Harada-Shiba et al., 2023).
- According to the Canadian Cardiovascular Society (CCS), statin therapy is suggested to be considered usually between 8 and 10 years of age if LDL-C remains ≥ 4.9 mmol/L (189.5 mg/dL), or ≥ 4.1 mmol/L (158.6 mg/dL) with a family history of premature ASCVD or other CV risk factors or risk conditions (Brunham et al., 2018).

Current consensus guidelines for FH recommend specific screening measures for children (Lee et al., 2022; Harada-Shiba et al., 2023). Screening for FH is advised in children under 2 years of age if they have a positive family history of premature ASCVD or hypercholesterolaemia. Additionally, universal cholesterol screening is recommended for children between the ages of 5 and 11 years (Cuchel et al., 2023b).

The above guidelines also emphasize the importance of cascade screening for early diagnosis (Lee et al., 2022). Cascade screening, also known as family-based or cascade genetic testing, is a systematic approach used to identify individuals who are at risk of inheriting genetic conditions such as FH, including HoFH. This method involves testing family members of individuals who have already been diagnosed with the condition to identify other affected individuals within the family.

Current available therapies for HoFH

Attempts to lower cholesterol levels often require multiple lipid-lowering drugs and LDL apheresis, although none of the lipid-lowering medication is approved for treatment of children less than 5 years of age. 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

hypercholesterolaemia (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 (Ezetrol SmPC). 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. In addition, performing lipoprotein apheresis on young children can be challenging due to their small peripheral vessels, and may result in complications related to venous puncture, low blood flow, and low blood volume. Moreover, anxiety and emotional distress can affect patients' compliance with apheresis treatment.

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 5 years and older with homozygous familial hypercholesterolaemia (HoFH).

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

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 (EMEA/H/C/005449/0000).

In 2023, the CHMP adopted extension of the indication to include treatment of patients aged 5 years and older with homozygous familial hypercholesterolaemia (HoFH) based on based on data from an interim analysis of Study R1500-CL-17100, a 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 an interim analysis of the open-label extension study, R1500-CL-1719, which provided updated long-term safety and efficacy data from adolescent (and adult) patients treated with evinacumab. Additionally, an extrapolation analysis, including population pharmacokinetics (PK), population PK/pharmacodynamics (PD; population PK/PD), and simulations, based on data from multiple clinical studies was provided in support of the extension of indication to included aged 5 years and older (EMEA/H/C/005449/II/0011).

An overview of all the phase 1, 2, and 3 studies in the evinacumab clinical program is presented in Figure 1. The paediatric development program for patients aged 5 years and older is in line with the approved PIP, EMEA-002298-PIP01-17-M05 (PIP decision number P/0087/2023)(Table 1). Evaluation of evinacumab in patients of 6 months to 5 years (proposed extension of indication) was not included in the PIP; Previously, the PDCO agreed to a waiver for patients less than 5 years of age on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible.

Clinical studies enrolled patients from the following age groups:

- Adult, defined as ≥ 18 years of age (R1500-CL-1629, R1500-CL-1719)
- Adolescent, defined as ≥ 12 and < 18 years of age (R1500-CL-1629, R1500-CL-1719)
- Paediatric, defined as ≥ 5 and < 12 years of age (R1500-CL-17100)

Additionally, due to the high level of unmet medical need in paediatric patients < 5 years of age, and the fact that it would not be feasible to conduct a clinical trial in this age group, a model-based extrapolation approach was pursued to support clinical dosing in patients < 5 years of age. The modelling and simulation analyses supported clinical dosing in a fourth age group:

- Paediatric, defined as ≥ 6 months to < 5 years of age

Clinical data (LDL-C levels, and total PK and ANGPTL3 in serum) of paediatric patients < 5 years of age receiving evinacumab for the treatment of HoFH in a compassionate use program (CUP) have been obtained to support the assessment of clinical benefit and safety of evinacumab treatment in this age group. As of August 2024, data was available for 5 patients who had initiated evinacumab treatment via compassionate use before the age of 5 years.

Figure 1. Clinical studies in the evinacumab development program

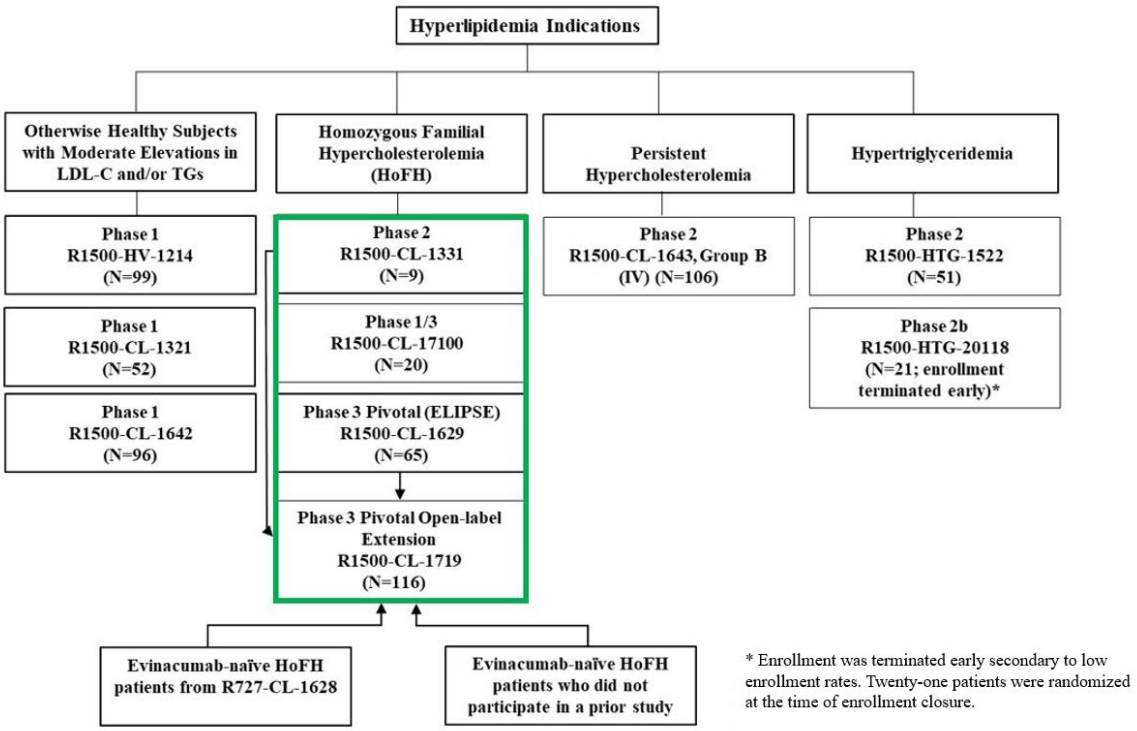


Table 1. Paediatric investigation plan

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, colourless 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, 70 mM L-arginine-HCl, 10 mM L-histidine, 3% (w/v) L-proline, and 0.1% (w/v) polysorbate 80.

There are two DP presentations: a 345 mg vial (2.7 mL fill volume with a 2.3 mL withdrawable volume in a 3 mL glass vial) and a 1,200 mg vial (9.0 mL fill volume with an 8.0 mL withdrawable volume in a 20 mL glass vial).

Table 1: Role of Excipients in the Evinacumab Drug Product Formulation

Excipient/Attribute	Contribution to Formulation
L-Histidine	Buffering agent to maintain the formulation pH at 6.0 at which the lowest rate of aggregation was observed in liquid state. Evinacumab was observed to have optimal stability at pH 6.0.
L-Histidine Monohydrochloride, Monohydrate[a]	
L-Arginine HCl	Viscosity reducer: the addition of L-arginine HCl reduces the viscosity of the formulation for administration.
L-Proline	Tonicity and stabilizing agent: the addition of L-proline reduces the rate of aggregation in the liquid state and maintains tonicity of the solution for administration.
Polysorbate 80	Stabilizing agent: the addition of polysorbate 80 reduces the rate of aggregation when the protein is handled and agitated as a liquid, and it protects against surface induced instability.
Water for Injection	Solvent

[a] Described as L-histidine hydrochloride hydrate in Japanese Pharmacopeia

Posology (from SmPC included in submission):

The recommended dose is 15 mg/kg body weight (bw) administered by intravenous infusion over 60 minutes once monthly (every 4 weeks).

2.2.1. Discussion on quality aspects

The Applicant wishes to extend the indication for EVKEEZA to include the treatment of paediatric patients with homozygous familial hypercholesterolaemia (HoFH) aged 6 months and older.

Considering a body weight of approximately 7.5 kg for a 6-month-old child (Reflection paper: formulation of choice for the paediatric population – EMEA/CHMP/PEG/194810/2005), the recommended dose of 15 mg/kg once monthly (every 4 weeks), gives a starting dose of 112.5 mg (0.75 ml) every 4 weeks, which is adequately covered by the smaller presentation (345 mg vial). The volume to be administered is acceptable considering the total body fluid contents of patients 6 months and older.

Excipients: No direct safety issues are foreseen with regards to the excipients. However, the formulation contains polysorbate 80, and in line with the Annex to the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668), revised in Apr 2024, the Applicant has included an appropriate safety warning in the package leaflet regarding this excipient.

2.3. Non-clinical aspects

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

2.3.1. Ecotoxicity/environmental risk assessment

In line with the original marketing authorisation application, a claim of exclusion from preparation of environmental risk assessment studies is made according to Section 2 of the 2006 CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (ERA Guideline) because evinacumab is a monoclonal antibody consisting of linked naturally occurring amino acids. Per the ERA

Guideline, “Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment.”

2.3.2. Discussion on non-clinical aspects

A complete assessment of the environmental risk of evinacumab has not been conducted, which was justified by the applicant on the basis that evinacumab is a natural substance. This is acknowledged.

2.4. Clinical aspects

2.4.1. Introduction

GCP

In the current application, the MAH, Ultragenyx Germany GmbH, is submitting a type II variation to extend the therapeutic indication for Evkeeza to include paediatric patients aged 6 months and older. The posology proposed for paediatric patients aged 6 months to 5 years old in the current extension of indication is similar to posology for HoFH patients ≤5 years of age.

A summary of individual studies in the adult, adolescent and paediatric 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) and the type II variation for extension of the indication to paediatric patients aged ≥5 to <12 years for evinacumab (EMEA/H/C/005449/0000 and EMEA/H/C/005449/II/0011, respectively).

The PK and PK/PD of evinacumab have been studied in 9 clinical studies to date (all completed):

- Three phase 1 studies in healthy adult subjects with elevated lipid levels (healthy subjects) (Studies R1500-HV-1214, R1500-CL-1321, and R1500-CL-1642)
- One phase 2 study in adult patients with persistent hypercholesterolaemia, including patients with HoFH (refractory hypercholesterolaemia) (Study R1500-CL-1643)
- One phase 2 study in adult patients with severe hypertriglyceridemia at risk for acute pancreatitis (Study R1500-HTG-1522)
- One phase 2 study in adult patients with HoFH (Study R1500-CL-1331)
- Three phase 3 studies in adult and adolescent patients with HoFH (Studies R1500-CL-1629, R1500-CL-1719), and paediatric patients (5 to < 12 years of age) with HoFH (R1500-CL-17100).

Population PK and population PK/PD analyses were conducted at MAA to assess the effect of intrinsic factors. The population PK analysis was initially conducted using pooled data from all Phase 1 studies in healthy subjects, and the Phase 2 (R1500-CL-1331) and Phase 3 (R1500-CL-1629 and R1500-CL-1719) studies in patients with HoFH, to support dosing in adult and adolescent patients; the pooled data set was later expanded to include data from the phase 3 R1500-CL-17100 study to characterise the PK of evinacumab in paediatric patients (*R1500-PM-23041-SR-01V1*).

In the current extension of indication, a model-based extrapolation analysis (including population PK, population PK/PD, and simulation analyses) of evinacumab PK and efficacy to paediatric patients with HoFH 6 months to <5 years was performed. Historical data contributing to the evinacumab clinical pharmacology program are provided, where relevant, to inform paediatric dosing and support the proposed labelling extension. In addition, supportive data is provided including PK and/or PD data of 3

paediatric patients who initiated evinacumab treatment before the age of 5 years for the treatment of HoFH, via the Ultragenyx or Regeneron compassionate use programs.

GCP

Not applicable. No clinical trials were performed.

2.4.2. Pharmacokinetics

Methodology

Bioanalyse

Evinacumab and ANGPTL3 concentrations were collected from one patient and were analysed using the bioanalytical assays used in the prior clinical trials (R1500-PK-19139-SR-01V1, R1500-PK-22070-SR-01V1, R1500-PM-23041-SR-01V1). The validation report of the bioanalytical methods used to analyse total evinacumab serum concentrations (REGN1500-AV-13001) and the methods to measure ANGPTL3 levels (REGN1500-MX-15060 and REGN1500-MX-15070) were assessed previously in the initial marketing application (EMEA/H/C/005449/0000) and were considered acceptable.

Total evinacumab concentration in serum
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.

Total ANGPTL3 concentration in serum
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.

The Applicant did not provide bioanalytical reports for the samples obtained from the patients included in the compassionate use program. Nevertheless, as the bioanalytical method was validated and the data is only supportive, this issue is not further pursued.

Population pharmacokinetic (and pharmacodynamic) model (R1500-PM-23089-SR-01V2)

Objectives
The objective of this analysis was to predict the PK of evinacumab and associated LDL-C reduction in a large virtual population of paediatric (6 months to <18 years) and adult patients with HoFH receiving weight-based dosing regimen of 15 mg/kg IV Q4W using model-based simulations and to compare the predicted metrics across age and body weight categories. Random sampling methods were applied to construct the population of 5000 virtual paediatric and adult patients with realistic distribution of demographic and disease characteristics (sex, age, body weight, baseline ANGPTL3, baseline LDL-C, and apheresis frequency).

Data
The population used in the simulation analyses reported herein comprised 5 groups of virtual patients with HoFH: 1000 patients aged 6 months to <2 years, 1000 patients aged 2 to <5 years, 1000

patients aged 5 to <12 years, 1000 adolescent patients aged 12 to <18 years, and 1000 adult patients aged ≥18 years and the maximum age observed in the analysis dataset.

For <18-year-old patients, age was randomly sampled from a uniform distribution within each age stratum. Sex was randomly assigned in the same proportions as those observed in the analysis dataset (that is, 49.6% of males and 50.4% of females; *R1500-PM-23041-SR-01V1*). Body weight was then randomly sampled within the 95% confidence interval of sex-specific weight-for-age growth models developed by the WHO (for patients aged <2 years) and Centres for Disease Control and Prevention (CDC) (for patients aged ≥2 years). For adult (≥18 years of age) patients, body weight was randomly re-sampled from the values observed in the analysis dataset. In patients ≥2 years of age, apheresis frequency was randomly assigned in the same proportions as those observed in the analysis dataset, regardless of age. No apheresis treatment was assumed in all patients <2 years (Luirink, 2019) (Lischka, 2022). Perfect compliance with the assigned apheresis treatment was assumed for all virtual patients (including no change or decrease in treatment frequency). Baseline ANGPTL3 was randomly sampled from an age-dependent distribution model fit to the data observed in the analysis dataset (using an exponential relationship between age and ANGPTL3, truncated at 5 years). The parameters of this model (including variability) were obtained by linear regression between the logarithm of baseline ANGPTL3 concentrations and the logarithm of age.

The proportions of male and female patients were approximately equal, and the average baseline body weight increased with increasing age, ranging from 9.92 kg in <2-year-old patients to 72 kg in adults. The average baseline ANGPTL3 concentration was approximately equal (~ 0.0675 mg/L) in patients aged <2 years, 2 to <5 years, and 5 to <12 years, then increased with increasing age till around 0.0838 mg/L in adult patients. The average baseline LDL-C concentration generally decreased with increasing age, ranging from 488 mg/dL in in patients aged <2 years to 258 mg/dL in adult patients. This was expected based on the previously identified covariate effect where increasing age was associated with a decrease in baseline LDL-C levels. This effect is possibly biased due to the fact that severe HoFH is earlier detected in paediatric patients that express more severe mutations in the LDLR gene which is associated with higher LDL-C levels due to early presence of disease-related events.

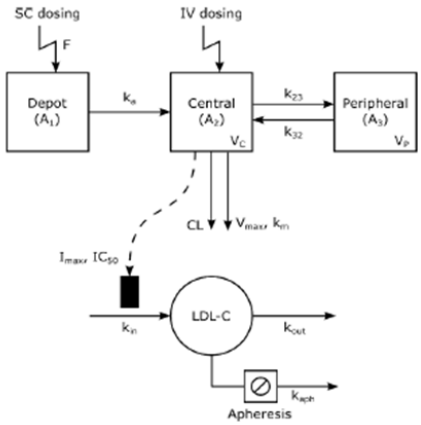
The Applicant did not provide any substantiation nor literature to support the equal baseline ANGPTL3 concentrations in the patients till the age of 12 years. Therefore, in the first round, the Applicant was requested to elaborate on the comparable ANGPTL3 levels in paediatric patients 6 months to <2 years and 2 to <5 years with paediatrics 5 to <12 years, while changes were observed in older age groups. In the second round, the Applicant provided the requested clarification on their approach of ANGPTL3 level determination in paediatrics patients with HoFH < 5 years of age. It is agreed that limited data and literature is available to substantiate any assumption for the (dis)similarity in ANGPTL3 expression in paediatric patients. ANGPLT3 levels were considered comparable between paediatric patients 5 to < 12 years of age and adolescents, which could also indicate comparable ANGPTL3 levels in paediatric patients below 5 years old. In addition, the typical exponential relationship obtained from the previous popPK/PD model (based on ANGPTL3 levels obtained from previous studies in older patients) can be considered generally in line with the observed ANGPTL3 expression observed in one patient from the compassionate use program (CUP). Even though, there is a statistically significant relationship between age and ANGPTL3 over the total analysis dataset, the difference in ANGPTL3 levels between paediatric patients >5 years and 5 to < 12 years of age is expected to be small and can therefore be considered irrelevant. Hence, sufficient comparability of ANGPTL3 expression between paediatric patients >5 years and 5 to < 12 years of age can be assumed based on the available data. The average baseline LDL-C concentration generally decreased with increasing age, ranging from 488 mg/dL in in patients aged <2 years to 258 mg/dL in adult patients, which was expected based on the previously identified covariate effect were increasing age was associated with a decrease in baseline LDL-C levels. This effect is possibly biased due to the fact that severe HoFH is earlier detected in paediatric patients that express

more severe mutations in the LDLR gene which is associated with higher LDL-C levels due to early presence of disease-related events.

Previous model description (R1500-PM-23041-SR-01V1)

The population PK model for evinacumab SC and IV administration in phase 1 adult participants and patients with HoFH aged ≥ 5 years was a 2-compartment model with first-order absorption after SC dosing and with dual linear and saturable (Michaelis-Menten) elimination (Figure 2). The disposition parameters CL, V_c, Q, and V_p were allometrically scaled on time-varying bodyweight, while V_{max} was dependent on baseline ANGPTL3 concentrations and differed in patients with HoFH compared to phase 1 adult participants. Baseline ANGPTL3 concentrations and disease status were estimated to have only marginal (≤ 5 %) effects on evinacumab exposures due to the saturation of V_{max}. In contrast, exposures varied with body weight more substantially: for instance, typical $AUC_{wk36-40}$ were predicted to decrease by 32.8% in a 19.7 kg individual and increase by 23% in a 152 kg individual compared to a typical 72 kg individual (*R1500-PM-23041-SR-01V1*).

The population PK/PD model for evinacumab effect on LDL-C concentrations in patients with HoFH aged ≥ 5 years 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 (Figure 2). The estimated baseline LDL-C concentrations were dependent on age, while I_{max} was dependent on body weight. In a 43-year-old, 72 kg patient with HoFH with a baseline ANGPTL3 concentration of 0.0908 mg/L and receiving weekly apheresis treatment, the typical %ΔLDL-C after 15 mg/kg IV Q4W administration was predicted to be 60.8%. A comparison to predicted values at the limits of the covariate ranges observed in the analysis dataset showed that %ΔLDL-C increased by approximately 18% in a typical 19.7 kg patient and 5-year-old patient. Conversely, %ΔLDL-C was predicted to decrease by 37% in a typical 152 kg patient and by 4.1% in a 75-year-old patient (*R1500-PM-23041-SR-01V1*).



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

Figure 2. Schematic representation of the model for evinacumab pharmacokinetics and effect on LCL-C.

Methods extrapolation analysis

The creation of the simulation dataset, data exploration, model-based exposure predictions, and result presentations in graphical and tabular outputs was performed using R version 4.2.1 (R Core Team, 2022). In particular, model-based exposure predictions were conducted using the R package version 1.0.6 (Baron, 2022).

The simulations relied on the 2 population PK and PK/PD models developed in phase 1 participants (for PK only) and paediatric (≥ 5 years of age) and adult patients with HoFH (*R1500-PM-23041-SR-01V1*) who received evinacumab and at least one other LMT. Several assumptions relative to the structure of the PK and PK/PD models were applied and tested for the extrapolation of evinacumab PK and its effects on LDL-C in paediatric patients include patients aged ≥6 months to <5 years:

1. PK1 assumed conventional fixed allometric exponents (Anderson and Holford, 2008): 0.75 for $\theta weight,CL$ and $\theta weight,Q$, and 1 for $\theta weight,VC$ and $\theta weight,VP$. This model parameterization assumed no maturation.
2. PK2 assumed alternative fixed allometric exponents proposed for allometric scaling of mAbs for first-in-human study design (Deng et al., 2011): 0.85 for $\theta weight,CL$ and $\theta weight,Q$, and 1 for $\theta weight,VC$ and $\theta weight,VP$. This model parameterization assumed no maturation.
3. PK3 assumed alternative fixed allometric exponents proposed for dose selection of therapeutic proteins (including mAbs) in paediatric patients and based upon the body weight-dependent changes in extracellular water fraction (Malik, 2021): 0.75 for $\theta weight,CL$ and $\theta weight,Q$, and 0.8 for $\theta weight,VC$ and $\theta weight,VP$. This model parameterization assumed no maturation.
4. PK4 was similar to Model PK1 but used age-specific allometric exponents for CL (Mahmood, 2020): 1.0 for individuals >3 months to 2 years of age, 0.9 for individuals >2 to 5 years of age, and 0.75 for individuals over 5 years of age.
5. PK5 was based upon allometric exponent estimates of the current evinacumab PK model. This model parameterization assumed no maturation.
6. PK6 implemented an allometric scaling approach identical to that used in model PK1 but assumed that CL changed over time by introducing a maturation function proposed by Robbie and colleagues. Half-life of maturation was 62.3 months, predicting ~ 99% maturation of CL by 30 years of age (Robbie et al., 2012).
7. PK7 was similar to PK6, except that the half-life of maturation was set so that ~ 99% maturation of CL was reached by 5 years of age.
8. PK8 was similar to PK6, except that the half-life of maturation was set so that ~ 99% maturation of CL was reached by 2 years of age

Under each of the 8 sets of assumptions, model-based simulations were performed to predict the individual evinacumab exposure metrics and %ΔLDL-C concentration-time profiles, assuming that each virtual patient in the population received 10 consecutive IV infusions of evinacumab at 15 mg/kg Q4W. Evinacumab exposure after the 1st, 6th, and 10th dose (including C_{max}, C_{min}, and $AUC_{wk36-40}$) and %ΔLDL-C at week 24 were summarised by age and weight groups.

The percentages of virtual patients achieving predicted absolute and relative LDL-C concentration targets at week 24 were calculated. The 2 absolute targets were LDL-C concentration at week 24 <110 mg/dL and <130 mg/dL as defined in the clinical practice guidelines set by the American College of Cardiology and the American Heart Association (Grundy, 2019) (Abdullah, 2018). The 130 mg/dL limit also aligns with the molar-unit target of 3.5 mmol/L defined in the guidelines set by the European Society of Cardiology and the European Atherosclerosis Society (Wiegman, 2015) (Mach, 2019). The 2 relative targets were magnitudes of reduction in %ΔLDL-C at week 24 >50% and >60%, which is based upon the European guidelines for management of familial hypercholesterolaemia in patients <10 years of age.

The Applicant considered the predicted exposures and LDL-C concentrations to be similar, and thus, the simulated results were generally summarised across scenarios PK1 to PK8 in a so-called 'composite model'. This summarisation, however, excluded results from the PK6 scenario, because the duration of CL maturation was deemed unrealistically long for this scenario (~30 years) and was not consistent with the lack of statistically significant effect of age on CL during the previous population PK analysis (*R1500-PM-23041-SR-01V1*), and the magnitude of LDL-C reduction was larger in patients <5 years of age in the PK6 scenario compared to the others.

A sensitivity analysis was performed through running these stochastic simulations using alternative simulation assumptions to assess the sensitivity of the predicted outcomes to the assumptions made in the main simulation series and explore an alternative dosing regimen:

1. LDL-C concentrations were simulated under the conditions used for the primary simulations, except that dose amounts were set as 20 mg/kg Q4W for <5-year-old patients and 15 mg/kg Q4W for ≥5-year-old patients;
2. LDL-C concentrations were simulated assuming that the effect of evinacumab matures over time for children below the age of 5 years, starting at approximately 50% of the maximum effect for 6-months-old patients. The half-life of maturation (ie, 11 months) was set so that ~99% maturation of I_{max} was reached by 5 years of age. The value of the maturation fraction (ie, 0.6600378) was set so that I_{max}(0.5 years) ≈ 0.5 × I_{max}(5 years) in a typical patient with median body weight according to the WHO/CDC growth charts. The weight effect on I_{max} was truncated at 19.7 kg, which was the minimum body weight observed in the analysis dataset and also larger than the median body weight for female or male children according to the WHO/CDC growth charts.
3. Lastly, simulations were performed in LMT naive patients that typically exhibit higher LDL-C concentrations at baseline. For these simulations, the estimates of the power relationship between age and baseline LDL-C concentrations estimated in the PK/PD model were replaced by estimates obtained by linear regression using the real-world data from the CASCADE (Cascade Screening for Awareness and Detection) FH registry (Cuchel, 2023). This registry includes a contemporary cohort of 67 patients with HoFH of all ages who are being treated and monitored in 1 of 20 lipid specialty clinics across the US.

Predictive performance extrapolation assumptions
An initial evaluation of the models associated with each of the 8 simulations scenarios described above was performed by visual predictive checks (VPC) to assess how each assumption set affected the model ability to adequately capture the observed evinacumab concentrations included in the original analysis dataset (*R1500-PM-23041-SR-01V1*). The analyses were not conducted for the models based upon the assumptions sets PK4, PK7 and PK8 because these models are virtually identical to the model based upon the PK1 assumptions.

The model modifications associated with the extrapolation assumptions had only marginal effects on the ability to describe the evinacumab concentrations observed in adolescent and adult subjects (both healthy volunteers and patients) included in the original analysis dataset. Small overpredictions of the peak concentrations in part B of Study R1500-CL-17100 (in patients 5 to < 12 years of age) were observed for all extrapolation assumptions, while almost neglectable overpredictions were observed in the assumption based upon the previous population PK model (i.e., PK5), which was expected. Overall, the data included in the original dataset was sufficiently described by the model including modifications related to the extrapolation exercise.

Population pharmacokinetic and pharmacodynamic model (R1500-PM-23202-SR-01V2)

Objectives

As of November 2023, LDL-C concentrations in serum have been collected in a small number (N = 3) of <5-year-old patients with HoFH receiving evinacumab via compassionate use. In addition, evinacumab and ANGPTL3 concentrations in serum were measured in 1 out of the 3 patients. The goals of the analysis are to compare these observed data to the predictions previously extrapolated from the population PK and PK/PD models and assess if the assumptions made in this previous extrapolation analysis are supported by the observed data.

Data

Data was initially available from three patients < 5 years of age treated with evinacumab via a compassionate use program in different countries. One patient was also treated with plasmapheresis at biweekly intervals at the start of treatment and at monthly intervals at Day 267 (week 38). Evinacumab and ANGPTL3 concentrations were only measured in one patient, while samples were collected in all patients for measurement of LDL-C concentrations at local laboratories. In the second round, the Applicant clarified that additional longer-term LDL-C data were available for the 3 patients; with data available for one patient up to week 72, for another patient up to week 62, and another patient up to week 90. Furthermore, since the initial submission of the variation in April, a few LDL-C data points have been made available to the Applicant for two additional HoFH patients < 5 years of age who initiated treatment with evinacumab via the compassionate use programs more recently. As of August 2024, LDL-C concentrations were available up to Week 16 for one patient and up to Week 12 for the other patient. All newly available LDL-C data were included in a revised analysis dataset that was used in additional model-based simulations to compare the revised observed data to evinacumab and LDL-C concentrations.

Methods

Model-based predictions were previously generated during an extrapolation analysis in virtual patients with HoFH who were assumed to perfectly comply to the 15 mg/kg IV Q4W dosing regimen and assigned apheresis frequencies (in ≥ 2-year-old patients only). Simulated data were summarized across 7 extrapolation assumptions for growth and maturation in a so-called 'composite model'. The population PK and PK/PD models and the methods and assumptions used for this extrapolation analysis are described in the *Quantitative Pharmacology Report R1500-PM-23089-SR-01V2* and the section *Population pharmacokinetic (and pharmacodynamic) model (R1500-PM-23089-SR-01V2)* of this assessment report.

The observed concentrations of evinacumab and LDL-C were graphically compared to the model-based predictions by overlaying the observed data with the median and 90% PI of simulated data in age-matched (6 months to <2 years; 2 to <5 years) or body weight-matched (<10 kg; 15 to <20 kg) groups. The observed data were also compared to new model-based simulations which used the models, methods, and assumptions described in *R1500-PM-23089-SR-01V2* but which reflected the actual dosing history (including skipped doses and dose reductions) and plasmapheresis history of the patients. Additionally, the ANGPTL3 concentration measured at baseline in one patient aged <5 years was compared to the baseline concentrations obtained in older patients included in the previous PK/PD analysis dataset (*R1500-PM-23041-SR-01V1*).

Pharmacokinetics in paediatric population

Extrapolation exercise

As no clinical study was performed in paediatric patients with HoFH aged <5 years, the existing population PK model (*R1500-PM-23041-SR-01V1*) was used to extrapolate evinacumab PK to these patients. For simulation purposes, a population of 5000 virtual patients was built to explore the variability in model-predicted exposures across a wide range of age and body weight. The population

included 1000 virtual patients in each of the 5 age groups (6 months to <2 years, 2 to <5 years, 5 to <12 years, 12 to <18 years, and ≥18 years). The distribution of baseline continuous and categorical descriptors of the virtual patients with HoFH included in the simulation dataset are summarized by age group in Table 2.

Table 2. Summary of baseline descriptors of virtual patients with homozygous familial hypercholesterolaemia included in the simulation dataset, stratified by age group.

Variable	Group or Statistic	6 months - < 2 years (n = 1000)	2 - < 5 years (n = 1000)	5 - < 12 years (n = 1000)	12 - < 18 years (n = 1000)	≥ 18 years (n = 1000)	Overall (n = 5000)
Sex, N (%)	Male	494 (49.4%)	484 (48.4%)	513 (51.3%)	476 (47.6%)	510 (51%)	2477 (49.5%)
	Female	506 (50.6%)	516 (51.6%)	487 (48.7%)	524 (52.4%)	490 (49%)	2523 (50.5%)
Baseline age (years)	Mean (SD)	1.26 (0.435)	3.49 (0.871)	7.94 (2)	14.5 (1.67)	42.1 (13.8)	13.9 (16.1)
	Median	1.25	3.52	8	14	40	8
	Min, Max	0.5, 2	2, 5	5, 11	12, 17	18, 75	0.5, 75
Baseline body weight (kg)	Mean (SD)	9.92 (1.58)	15.4 (2.5)	28.6 (8.42)	54.3 (11.1)	75 (20.3)	36.6 (27)
	Median	9.77	15.1	27.2	52.7	72	27.2
	Min, Max	6.49, 14.5	10.2, 24.4	14.9, 65.6	29.6, 93.3	42.4, 152	6.49, 152
Baseline ANGPTL3 concentration (mg/L)	Mean (SD)	0.0675 (0.0259)	0.0672 (0.0265)	0.068 (0.0262)	0.0705 (0.0269)	0.0838 (0.0329)	0.0714 (0.0285)
	Median	0.0632	0.063	0.0627	0.0657	0.0776	0.066
	Min, Max	0.0266, 0.149	0.0265, 0.151	0.0262, 0.151	0.0275, 0.157	0.0288, 0.208	0.0262, 0.208
Baseline LDL-C concentration (mg/dL)	Mean (SD)	488 (259)	478 (260)	426 (224)	346 (185)	258 (142)	399 (235)
	Median	432	423	374	303	224	345
	Min, Max	74.3, 1900	75, 1970	58.1, 1620	63.5, 1410	45.4, 1220	45.4, 1970
Baseline LDL-C concentration (mmol/L)	Mean (SD)	12.6 (6.7)	12.4 (6.72)	11 (5.78)	8.94 (4.77)	6.68 (3.67)	10.3 (6.08)
	Median	11.2	10.9	9.68	7.84	5.8	8.93
	Min, Max	1.92, 49.2	1.94, 51	1.5, 41.9	1.64, 36.4	1.17, 31.6	1.17, 51
Apheresis frequency, N (%)	No treatment	1000 (100%)	582 (58.2%)	562 (56.2%)	573 (57.3%)	579 (57.9%)	3296 (65.9%)
	Weekly	0 (0%)	192 (19.2%)	183 (18.3%)	207 (20.7%)	173 (17.3%)	755 (15.1%)
	Bi-weekly	0 (0%)	216 (21.6%)	240 (24%)	211 (21.1%)	235 (23.5%)	902 (18%)
	Monthly	0 (0%)	10 (1%)	15 (1.5%)	9 (0.9%)	13 (1.3%)	47 (0.94%)

ANGPTL3 = Angiopoietin-like protein 3; LDL-C = Low-density lipoprotein cholesterol; Max = Maximum; Min = Minimum; n = Number of patients; N = Number of records; SD = Standard deviation

Figure 3 illustrates the median and 90% prediction interval of evinacumab concentrations versus time profiles for the virtual patients included in the composite model (that is, simulations based upon extrapolation assumptions PK1, PK2, PK3, PK4, PK5, PK7, and PK8) stratified by age. The same simulations stratified on bodyweight were similar to the comparison presented in Figure 3.

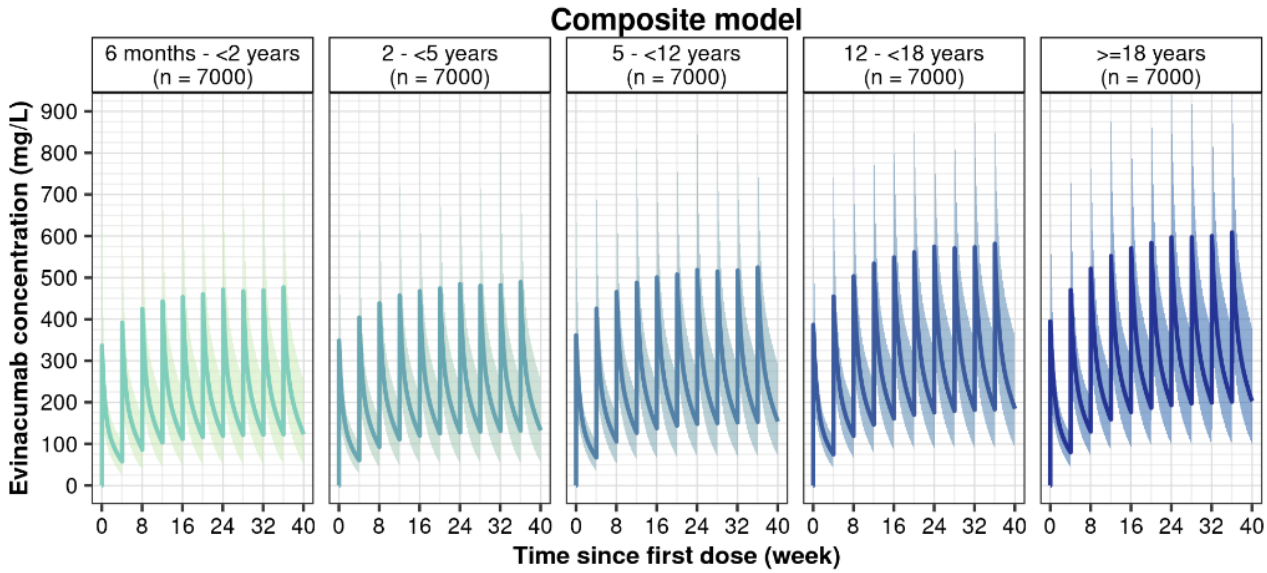


Figure 3. Median and 90% prediction interval of model-based predicted evinacumab concentrations in patients with homozygous familial hypercholesterolaemia after 15 mg/kg infusions every 4 Weeks, stratified by age Group and extrapolation scenario.

The distribution of individual exposure metrics associated with these simulated concentration versus time profiles are summarized by age group in *Table 3*.

Table 3. Summary of model-based predicted evinacumab exposure metrics for virtual patients with homozygous familial hypercholesterolaemia included in the composite model, stratified by age group.

Variable	Statistic	6 months - < 2 years (n = 1000)	2 - < 5 years (n = 1000)	5 - < 12 years (n = 1000)	12 - < 18 years (n = 1000)	≥ 18 years (n = 1000)	Overall (n = 5000)
Cmax,wk0-4 (mg/L)	Mean (SD)	362 (154)	372 (154)	385 (151)	405 (146)	417 (155)	388 (154)
	Median	336	349	361	386	395	365
	P5, P95	(155, 631)	(170, 660)	(190, 668)	(205, 657)	(206, 697)	(182, 664)
	N	7000	7000	7000	7000	7000	35000
Cmax,wk20-24 (mg/L)	Mean (SD)	481 (179)	495 (172)	528 (175)	576 (174)	606 (190)	537 (185)
	Median	460	474	508	561	584	517
	P5, P95	(227, 804)	(254, 815)	(281, 851)	(325, 878)	(330, 948)	(272, 869)
	N	7000	7000	7000	7000	7000	35000
Cmax,wk36-40 (mg/L)	Mean (SD)	499 (185)	513 (179)	548 (183)	600 (183)	631 (200)	558 (193)
	Median	477	490	525	582	609	536
	P5, P95	(238, 831)	(264, 844)	(292, 883)	(340, 918)	(343, 993)	(282, 905)
	N	7000	7000	7000	7000	7000	35000
Cmin,wk4 (mg/L)	Mean (SD)	60.8 (24.9)	62.4 (21.9)	68.7 (21.9)	77.1 (22.5)	81.5 (24)	70.1 (24.4)
	Median	58.1	61.1	67.8	75.2	80.3	68.8
	P5, P95	(25.2, 106)	(29, 101)	(35.6, 106)	(42.7, 118)	(45.2, 124)	(32.5, 113)
	N	7000	7000	7000	7000	7000	35000
Cmin,wk24 (mg/L)	Mean (SD)	130 (62.3)	135 (56.7)	156 (62.9)	186 (71)	205 (77.1)	163 (72.4)
	Median	120	128	149	177	194	152
	P5, P95	(50, 245)	(53.9, 240)	(69.5, 273)	(89.3, 325)	(98.7, 348)	(63.9, 299)
	N	7000	7000	7000	7000	7000	35000
Cmin,wk40 (mg/L)	Mean (SD)	135 (65.3)	141 (60.9)	164 (68.7)	197 (79.3)	217 (86.8)	171 (79.4)
	Median	124	133	155	185	203	158
	P5, P95	(51.9, 254)	(55.1, 254)	(71.2, 293)	(90.7, 358)	(101, 379)	(65.7, 322)
	N	7000	7000	7000	7000	7000	35000
AUCwk0-4 (mg x day/L)	Mean (SD)	3630 (1020)	3760 (951)	4040 (956)	4410 (977)	4610 (1060)	4090 (1060)
	Median	3590	3740	4010	4400	4570	4050
	P5, P95	(2020, 5360)	(2260, 5400)	(2530, 5650)	(2840, 6040)	(2890, 6390)	(2410, 5900)
	N	7000	7000	7000	7000	7000	35000
AUCwk20-24 (mg x day/L)	Mean (SD)	6300 (2190)	6560 (1990)	7320 (2170)	8390 (2380)	9030 (2610)	7520 (2510)
	Median	6020	6380	7180	8150	8820	7250
	P5, P95	(3280, 10300)	(3600, 10100)	(4200, 11200)	(4800, 12800)	(5270, 13900)	(3940, 12100)
	N	7000	7000	7000	7000	7000	35000
AUCwk36-40 (mg x day/L)	Mean (SD)	6490 (2270)	6770 (2110)	7590 (2340)	8750 (2620)	9450 (2900)	7810 (2710)
	Median	6200	6550	7400	8430	9100	7470
	P5, P95	(3390, 10600)	(3670, 10600)	(4290, 11800)	(4950, 13700)	(5360, 14800)	(4040, 12900)
	N	7000	7000	7000	7000	7000	35000

In the composite model, evinacumab exposures after 15 mg/kg Q4W dosing and overall accumulation were predicted to decrease at younger age and with decreasing body weight. For instance, the median predicted C_{min} at week 40 decreased from 203 mg/L in ≥18-year-old patients to 124 mg/L in 6-months to < 2-year-old patients. This trend was also seen before in the previous Type II variation related to the paediatric population ≥ 5 to 12 years old, which showed an increase of evinacumab exposure of approximately 23% and 35% for the paediatric population ≥ 5 to 12 years of age compared to adolescent and adult patients, respectively. As evinacumab is dosed based on bodyweight, this difference in exposure could most likely be explained by the difference in body composition between the patient groups. Previously, baseline ANGPTL3 was observed to be a significant descriptor of exposure: lower baseline ANGTPL3 in paediatric patients led to reduced V_{max} and thus an increased exposure. As ANGPTL3 is predicted to be similar between the paediatric patients, the pharmacological target of evinacumab (i.e., ANGPTL3) cannot explain the difference in exposure.

Sensitivity analysis

The simulations were repeated assuming that the dosing regimen was 20 mg/kg infusions Q4W for virtual patients aged <5 years and 15 mg/kg infusions Q4W for virtual patients aged ⩾5 years. The median and 90% prediction interval of evinacumab concentrations versus time profiles for the virtual

patients based on this assumption is provided in

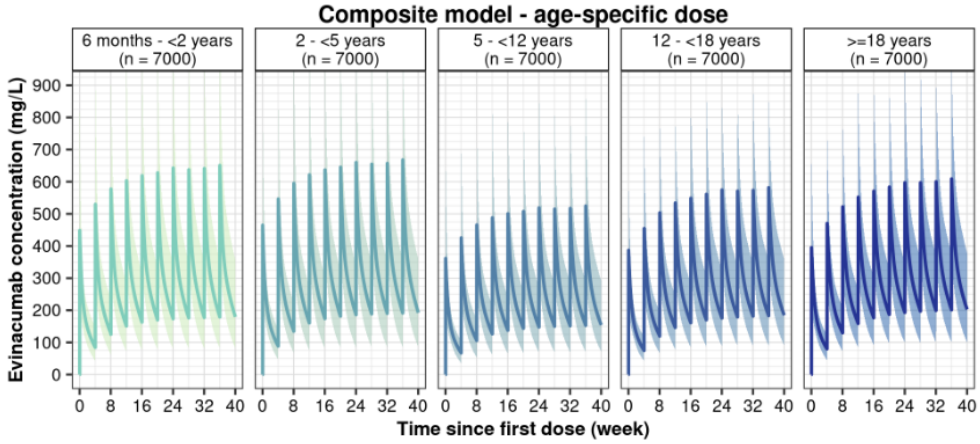


Figure 4. The same simulations stratified on bodyweight showed the same trend as seen in the comparison stratified on age.

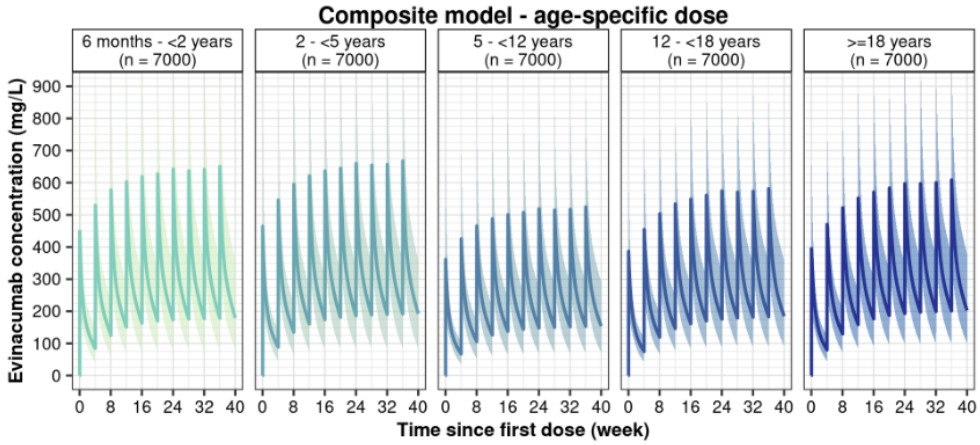


Figure 4. Median and 90% prediction interval of model-based predicted evinacumab concentrations in patients with homozygous familial hypercholesterolaemia after 20 mg/kg (for < 5-years-old patients) and 15 mg/kg (for ⩾ 5-years-old patients) infusions every 4 weeks, stratified by age group.

Using a 20 mg/kg instead of a 15 mg/kg Q4W dosing regimen in <5-year-old patients resulted in a 35-50% increase in median steady-state exposures, which could have caused a clinically relevant effect on LDL-C concentrations. Nevertheless, the LDL-C only slightly increased with the higher exposure and was thus considered not clinically relevant.

Furthermore, the simulations were repeated assuming that the inhibitory effect of evinacumab on LDL-C production matures over time for children below the age of 5 years, starting at approximately 50% of the maximum effect for 6-months-old patients. The median and 90% prediction interval of evinacumab concentrations versus time profiles for the virtual patients based on this assumption is provided in

Figure 5. The same simulations stratified on bodyweight showed the same trend as seen in the comparison stratified on age. The evinacumab exposure remained the same as in the extrapolation exercise discussed above, which was expected as the assumptions were related to the PK/PD model.

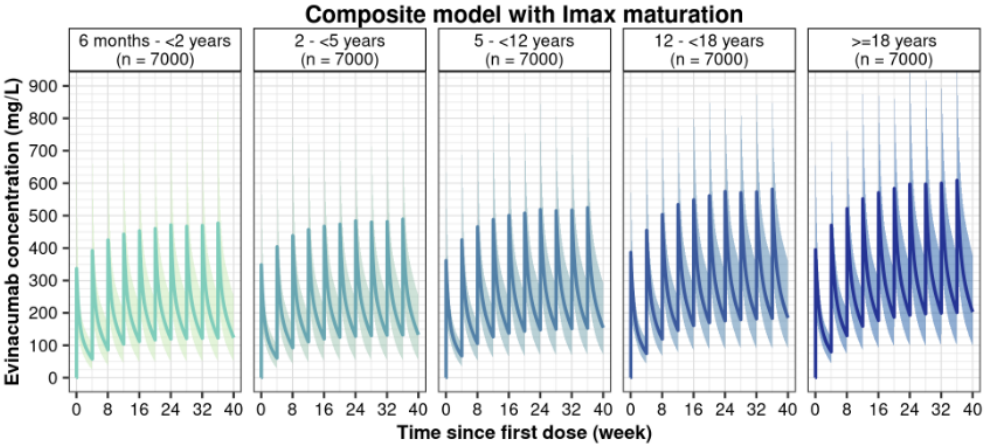


Figure 5. Median and 90% prediction interval of model-based predicted evinacumab concentrations in patients with homozygous familial hypercholesterolaemia after 15 mg/kg infusions every 4 week, stratified by age group – maturation of evinacumab effect.

Lastly, the simulations were repeated assuming that baseline LDL-C concentrations were reflective of the distribution determined in LMT naive patients rather than the distribution determined in patients already receiving LMT. The median and 90% prediction interval of evinacumab concentrations versus time profiles for the virtual patients based on this assumption is provided in

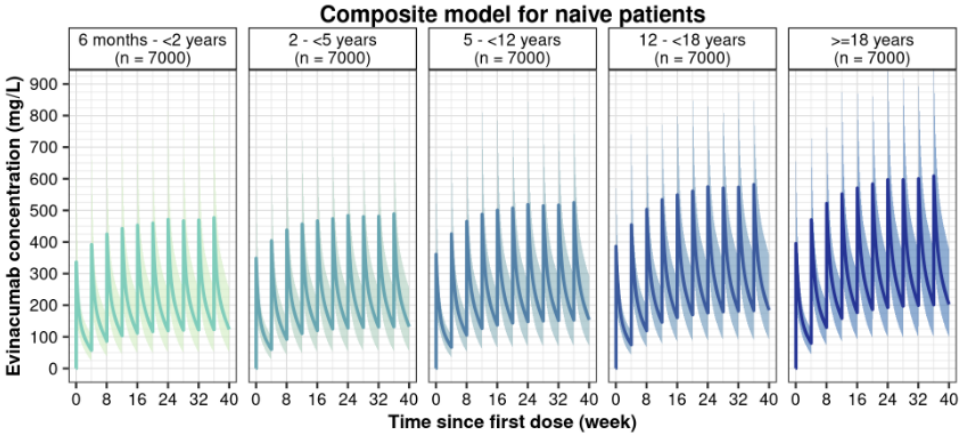


Figure 6. The same simulations stratified on bodyweight showed the same trend as seen in the comparison stratified on age. The evinacumab exposure remained the same as in the extrapolation exercise discussed above, which was expected as the assumptions were related to the PK/PD model.

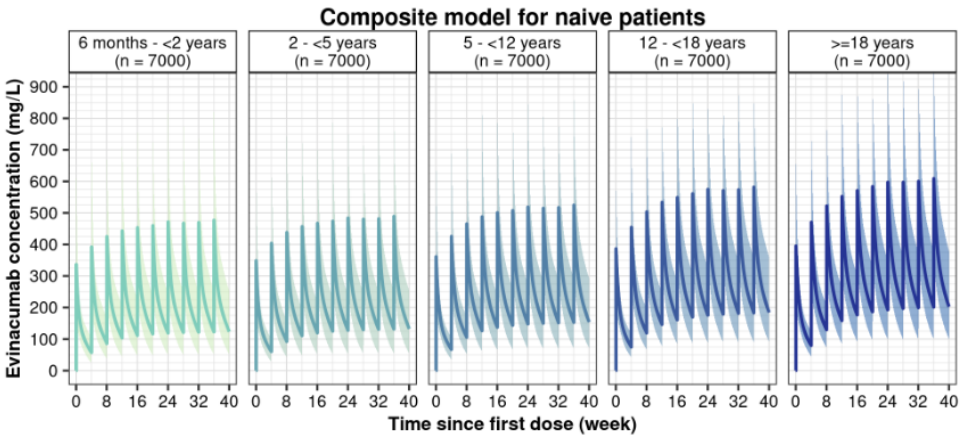


Figure 6. Median and 90% prediction interval of model-based predicted evinacumab concentrations in naïve patients with homozygous familial hypercholesterolaemia after 15 mg/kg infusions every 4 week, stratified by age group.

External qualification

As of August 2024, data was available from five paediatric patients < 5 years of age who were treated with evinacumab via compassionate use. Evinacumab exposure was characterised only in one patient. The observed evinacumab concentrations were compared with the 90% PI generated based upon the ideal 15 mg/kg IV Q4W dosing regimen and were stratified by age group (Figure 7

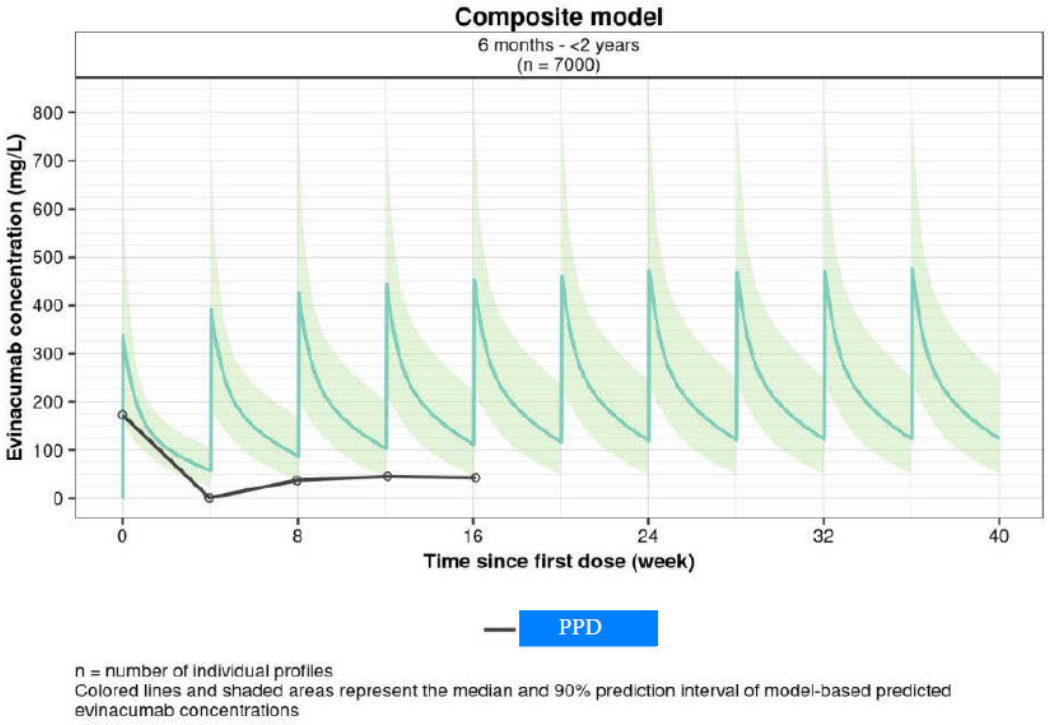


Figure 7). The comparison stratified on bodyweight were similar to the comparison presented in Figure 7.

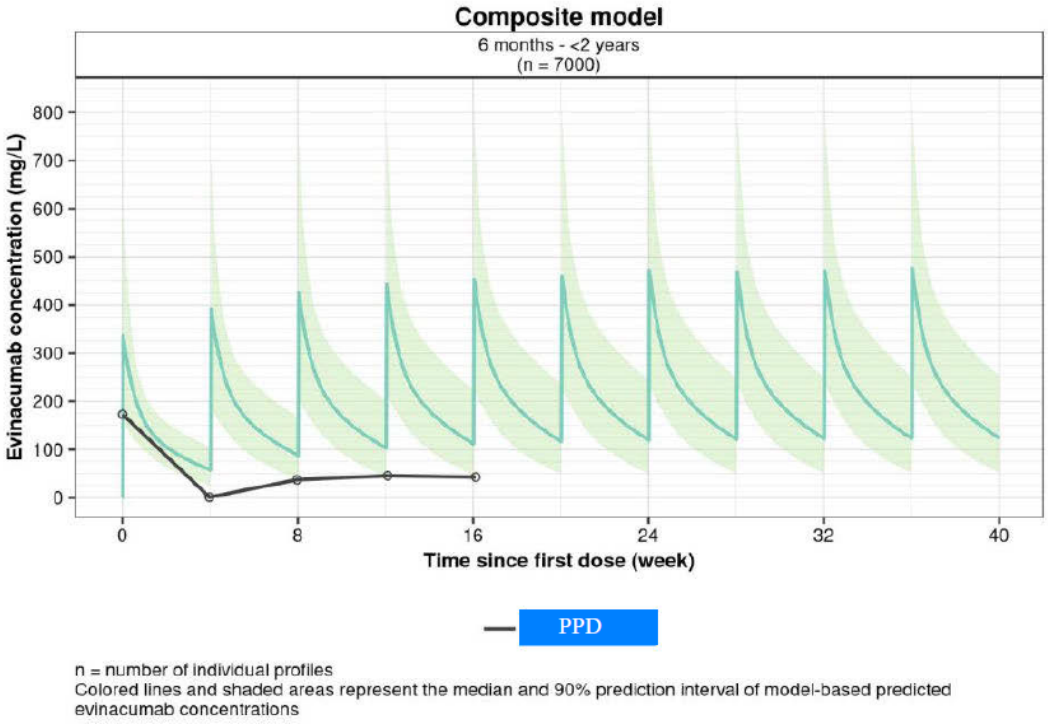


Figure 7. Comparison of observed and model-predicted evinacumab concentrations after 15 mg/kg infusions every 4 weeks, stratified by age group.

The observed evinacumab concentrations in the patient up to week 16 were generally within the 90% PI generated based upon the ideal 15 mg/kg IV Q4W dosing regimen. The trough concentration after the first dose, however, was found to be outside the 90% PI. This can be explained by the fact that this patient was treated with 7.5 mg/kg of evinacumab at the first infusion before increasing the dose to 15 mg/kg for all subsequent infusions, which is also confirmed by the VPC simulating the actual dosing of evinacumab for this patient.

Furthermore, for the later doses the evinacumab trough concentrations were near the lower limit of the 90% PI based upon 15 mg/kg of evinacumab, but remained within the PI. Therefore, population PK model sufficiently described the data of the patient. No later evinacumab concentrations were collected for this patient in order to minimize treatment burden for this very young patient and because it was expected a plateau was reached based on the earlier obtained data from patients ages 5 to < 12 years, which is considered acceptable.

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

No new pharmacodynamic studies has been conducted by the Applicant.

2.4.4. PK/PD modelling

Extrapolation exercise
The relationship between evinacumab pharmacokinetics and pharmacodynamics (LDL-C reduction) was evaluated in the population PK/PD extrapolation.

Simulated baseline LDL-C concentration was higher in paediatric patients compared to adolescent, and adult patients. This can be explained by the fact that the paediatrics that are included in the studies used to create the population PK model most likely have more severe HoFH which is earlier detected due to early presence of disease-related events.

Figure 8 illustrates the median and 90% prediction interval of %ΔLDL-C versus time profiles for the virtual patients included in the composite model stratified by age. The same simulations stratified on bodyweight showed the same trend as seen in the comparison stratified on age.

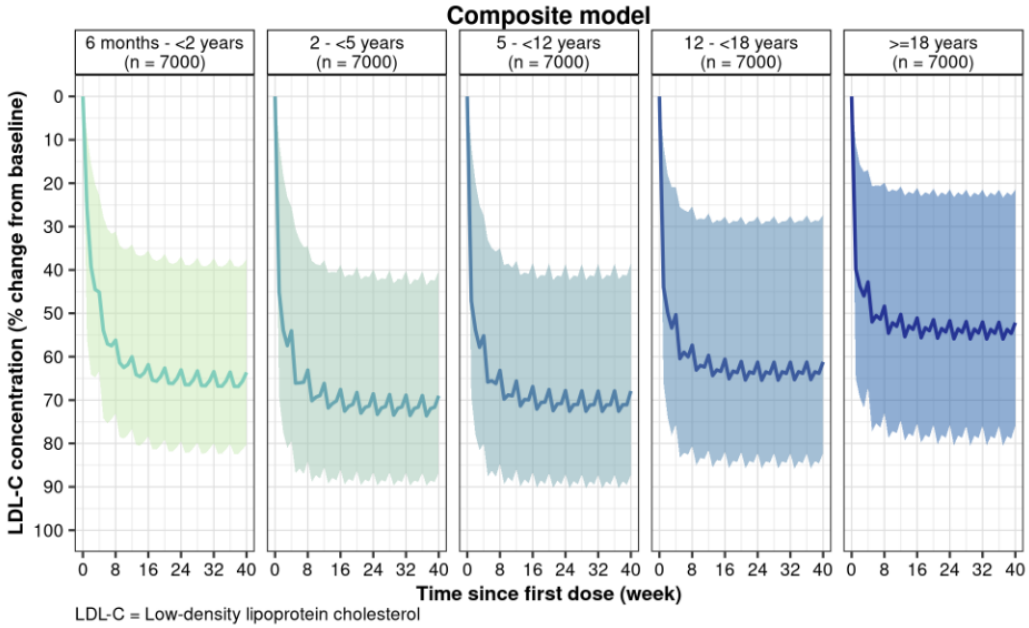


Figure 8. Median and 90% Prediction Interval of Model-Based Predicted Percent Change from LDL-C Baseline in Patients with Homozygous Familial Hypercholesterolaemia After 15 mg/kg Evinacumab Infusions Every 4 Weeks, Stratified by Age Group.

The percentages of virtual patients reaching the different targets which were described in the methodology for the extrapolation analysis are summarised in Table 4

Table 4.

Table 4. Predicted percentages of virtual patients with homozygous familial hypercholesterolaemia achieving clinical targets after 15 mg/kg evinacumab infusions every 4 week, stratified on age and weight group.

Variable	Category	n	Mean (SD) baseline LDL-C		Patients with LDL-C < 110 mg/dL (2.8 mmol/L) at Week 24	Patients with LDL-C < 130 mg/dL (3.4 mmol/L) at Week 24	Patients with %ΔLDL-C reduction > 50% at Week 24	Patients with %ΔLDL-C reduction > 60% at Week 24
			mg/dL	mmol/L				
Age	6 months - < 2 years	7000	488 (259)	12.6 (6.7)	26.3%	36.5%	82%	59.4%
	2 - < 5 years	7000	478 (260)	12.4 (6.71)	41.7%	52.3%	86.9%	72.3%
	5 - < 12 years	7000	426 (223)	11 (5.78)	46.6%	56.9%	84.5%	69.1%
	12 - < 18 years	7000	346 (184)	8.94 (4.77)	48.1%	57.6%	72%	52.6%
	≥ 18 years	7000	258 (142)	6.68 (3.66)	52.4%	63.9%	54.8%	31.1%
Weight	< 10 kg	3864	481 (266)	12.5 (6.87)	28.1%	37.4%	80%	55.7%
	10 - < 15 kg	6468	495 (262)	12.8 (6.77)	31.5%	42.7%	85.1%	67.3%
	15 - < 20 kg	4312	467 (251)	12.1 (6.49)	44.9%	54.3%	88.1%	74.5%
	20 - < 35 kg	4991	428 (224)	11.1 (5.79)	46.2%	56.9%	84.7%	69.3%
	35 - < 50 kg	4431	354 (196)	9.14 (5.06)	50.3%	61%	78.5%	59.3%
	50 - < 65 kg	5236	315 (164)	8.14 (4.24)	51.5%	61.2%	69.4%	47.1%
	65 - < 80 kg	3108	296 (170)	7.66 (4.39)	48.9%	60.1%	59.5%	37.8%
	≥ 80 kg	2590	244 (130)	6.31 (3.35)	47.8%	59.2%	39.4%	18.4%
Overall		35000	399 (235)	10.3 (6.08)	43%	53.4%	76%	56.9%

LDL-C = Low-density lipoprotein cholesterol; n = Number of patients; SD = Standard deviation

Despite the lower simulated evinacumab exposures in paediatrics, the predicted magnitude of LDL-C reduction was maintained and appeared even larger in paediatrics compared to adolescents and adults (61%, 67%, 66%, 59%, and 51% in patients 6 months to <2 years, 2 to <5 years, ≥5 to <12 years, ≥12 to <18 years, and ≥18 years, respectively). However, the predicted percentages of target attainment (e.g., LDL-C < 110 mg/dL) based upon absolute LDL-C concentrations decreased in

paediatrics: 26.3% and 41.7% of 6 months to < 2-year-old and 2 to < 5-year-old patients were predicted to achieve LDL-C < 110 mg/dL at week 24, whereas 52.4% of the virtual adult population achieved the target. The same pattern was seen for the LDL-C < 130 mg/dL target attainment. These differences between target attainment based on %ΔLDL-C and absolute LDL-C concentrations were expected as the baseline LDL-C in paediatrics is increased compared to adults, meaning a higher magnitude of reduction in %ΔLDL-C may not lead to target attainment based upon absolute LDL-C reduction.

Sensitivity analysis

The simulations were repeated assuming that the dosing regimen was 20 mg/kg infusions Q4W for virtual patients aged < 5 years and 15 mg/kg infusions Q4W for virtual patients aged ≥5 years. The percentages of virtual patients reaching the different targets described in the methodology for the extrapolation analysis under the assumption of age-specific dosing regimens are summarised in Table 5. The same predictions stratified on bodyweight showed a similar trend as seen in the predictions stratified on age.

Table 5. Predicted percentages of virtual patients with homozygous familial hypercholesterolaemia achieving clinical targets after 20 mg/kg (for < 5-years-old patients) and 15 mg/kg (for ⩾ 5-years-old patients) infusions every 4 weeks, stratified by age.

Variable	Category	n	Mean (SD) baseline LDL-C		Patients with LDL-C < 110 mg/dL (2.8 mmol/L) at Week 24	Patients with LDL-C < 130 mg/dL (3.4 mmol/L) at Week 24	Patients with %ΔLDL-C reduction > 50% at Week 24	Patients with %ΔLDL-C reduction > 60% at Week 24
			mg/dL	mmol/L				
Age	6 months - < 2 years	7000	488 (259)	12.6 (6.7)	33.6%	45%	86.5%	69.3%
	2 - < 5 years	7000	478 (260)	12.4 (6.71)	44.6%	55%	87.9%	76%
	5 - < 12 years	7000	426 (223)	11 (5.78)	46.6%	56.9%	84.5%	69.1%
	12 - < 18 years	7000	346 (184)	8.94 (4.77)	48.1%	57.6%	72%	52.6%
	≥ 18 years	7000	258 (142)	6.68 (3.66)	52.4%	63.9%	54.8%	31.1%

Using a 20 mg/kg dosing regimen in < 5-year-old patients only increased the number of patients achieving absolute LDL-C targets by approximately 3% to 9% and the number of patients achieving relative %ΔLDL-C targets by approximately 1% to 10%, despite the more substantial increase in exposures (approximately 40%). This suggests that exposures related to the 15 mg/kg Q4W dosing regimen were sufficient to achieve maximal ANGPTL3 target engagement, and thus, an increased dose in < 5-year-old patients will not provide clinically relevant attribution to LDL-C reduction.

Furthermore, the simulations were repeated assuming that the inhibitory effect of evinacumab on LDL-C production matures over time for children below the age of 5 years, starting at approximately 50% of the maximum effect for 6-months-old patients. The percentages of virtual patients reaching the different targets under the assumption of evinacumab maturation are summarised in Table 6. The same predictions stratified on bodyweight showed a similar trend as seen in the predictions stratified on age.

Table 6. Predicted percentages of virtual patients with homozygous familial hypercholesterolaemia achieving clinical targets after 15 mg/kg infusions every 4 weeks, stratified by age – maturation of evinacumab effect.

Variable	Category	n	Mean (SD) baseline LDL-C		Patients with LDL-C < 110 mg/dL (2.8 mmol/L) at Week 24	Patients with LDL-C < 130 mg/dL (3.4 mmol/L) at Week 24	Patients with %ΔLDL-C reduction > 50% at Week 24	Patients with %ΔLDL-C reduction > 60% at Week 24
			mg/dL	mmol/L				
Age	6 months - < 2 years	7000	488 (259)	12.6 (6.7)	15.3%	23.4%	56%	30.7%
	2 - < 5 years	7000	478 (260)	12.4 (6.71)	35.1%	44.8%	81%	62.5%
	5 - < 12 years	7000	426 (223)	11 (5.78)	46.6%	56.7%	84.3%	68.9%
	12 - < 18 years	7000	346 (184)	8.94 (4.77)	48.1%	57.6%	72%	52.6%
	≥ 18 years	7000	258 (142)	6.68 (3.66)	52.4%	63.9%	54.8%	31.1%

The predicted percentages of the 6 months to < 2-year-old virtual paediatrics patients that achieved the absolute LDL-C and the relative %ΔLDL-C targets decreased by approximately 10% and 30%, respectively, while the predicted percentages of the 2 to <5 years old virtual patients that achieved the LDL-C target remained comparable with a slight decrease of approximately 5% for absolute LDL-C and 10 percent for relative %ΔLDL-C. Nevertheless, as the baseline ANGPTL3 levels are predicted to remain largely similar between all paediatric age groups, such amounts of reduction in target attainment are not expected to be reflective of practical context.

Lastly, the simulations were repeated under the third assumption that baseline LDL-C concentrations were reflective of the distribution determined in LMT naive patients rather than the distribution determined in patients already receiving LMT. The percentages of virtual patients reaching the different targets are summarised for LMT naive patients in Table 7. The same predictions stratified on bodyweight showed a similar trend as seen in the predictions stratified on age.

Table 7. Predicted percentages of virtual lipid-modifying therapy naïve patients with homozygous familial hypercholesterolaemia achieving clinical targets after 15 mg/kg infusions every 4 weeks, stratified by age.

Variable	Category	n	Mean (SD) baseline LDL-C		Patients with LDL-C < 110 mg/dL (2.8 mmol/L) at Week 24	Patients with LDL-C < 130 mg/dL (3.4 mmol/L) at Week 24	Patients with %ΔLDL-C reduction > 50% at Week 24	Patients with %ΔLDL-C reduction > 60% at Week 24
			mg/dL	mmol/L				
Age	6 months - < 2 years	7000	864 (403)	22.3 (10.4)	4.67%	8.44%	81%	58.6%
	2 - < 5 years	7000	739 (353)	19.1 (9.14)	18.5%	25.7%	85.2%	69.6%
	5 - < 12 years	7000	663 (304)	17.1 (7.86)	25.6%	34.9%	85.8%	72.7%
	12 - < 18 years	7000	597 (278)	15.4 (7.18)	20.3%	31%	75.1%	59.7%
	≥ 18 years	7000	520 (242)	13.4 (6.26)	16%	23.3%	62%	40.5%

The effect of evinacumab on LDL-C in LMT naive patients was simulated as there is a substantial chance that these very young patients >5 years old did not receive any treatment before. Mean predicted baseline LDL-C concentrations were approximately 75% and 55% higher in 6 months to < 2-year-old and 2 to < 5-year-old respectively, LMT naive patients compared to the primary simulations, which was expected. Due to this increase of baseline LDL-C levels, target attainment based upon absolute LDL-C concentrations decreased over 50% in all age groups. Nevertheless, target attainment based upon relative %ΔLDL-C remained comparable to the predicted target attainment from the primary simulations.

External qualification

As of August 2024, data is available from five paediatric patients < 5 years of age were treated with evinacumab. ANGPTL3 was characterised only in one patient, while the corresponding effect on LDL-C

was measured in all five patients. In the initial submission, however, data was only available for three patients. The comparisons of observed and model-predicted %ΔLDL-C assuming the ideal 15 mg/kg IV Q4W dosing regimen and assigned apheresis frequencies are presented stratified by age group in Figure 9. The comparisons stratified on bodyweight were similar to those presented in Figure 9.

The ANGPTL3 concentration measured at baseline in one patient was compared with patients 5 to < 12 years of age in the analysis population in Figure 10.

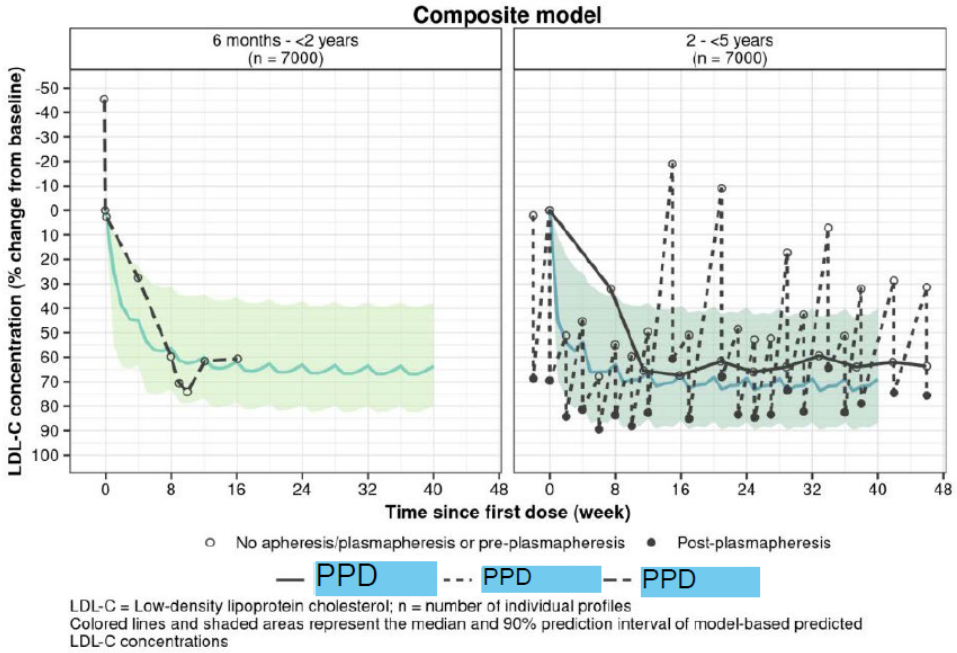


Figure 9. Comparison of observed and model-predicted change from LDL-C baseline concentrations after 15 mg/kg infusions every 4 weeks, stratified by age group.

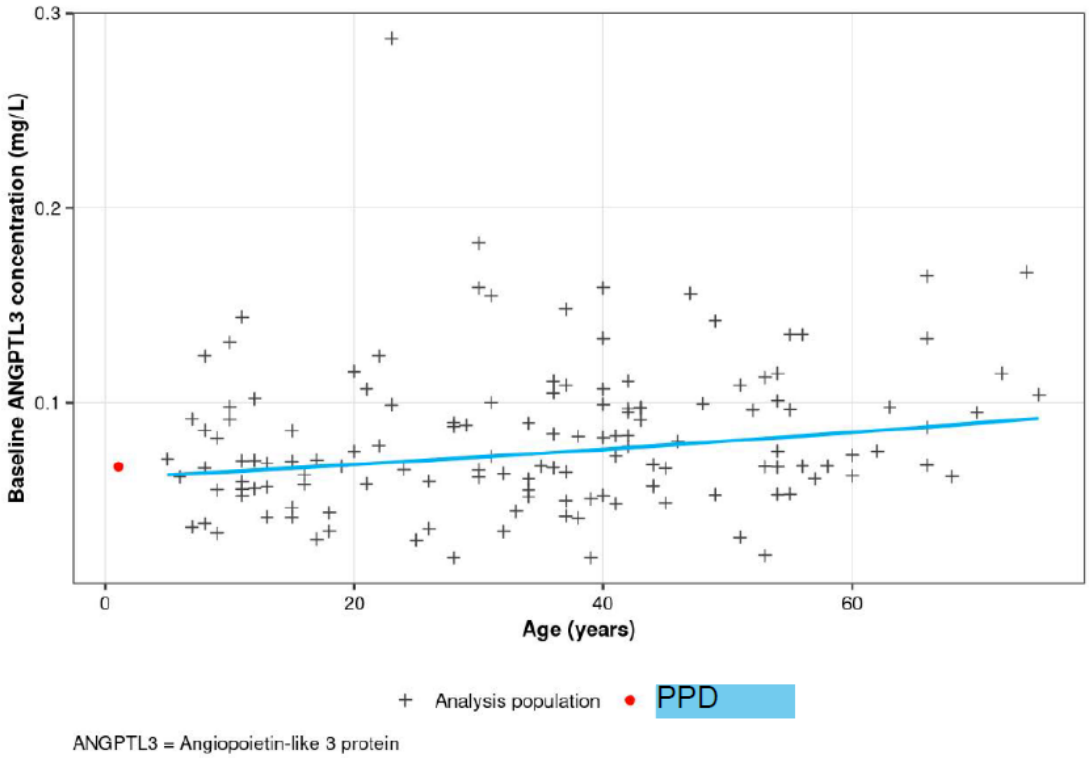


Figure 10. Comparison of ANGPTL3 concentrations at baseline in patients with homozygous familial hypercholesterolaemia.

While the number of patients included in the compassionate use program was small and thus the results should be approached carefully, the collected observations were generally consistent with the results generated from the prior model-based extrapolation exercise (*R1500-PM-23089-SR-01V2*). The magnitude of observed reduction from baseline LDL-C was generally consistent with the model-based predictions for two patients. However, for one patient, around week 15, 20, 29, 34, and after week 38, the LDL-C reduction was found to be outside the 90% PI, which could possibly be explained by the fact that the model is able to predict the LDL-C reduction effect only after the combination of evinacumab treatment and apheresis in the case of this patient. The model predicts the observed data points after plasmapheresis sufficiently, as all these observed data points are found within the 90% PI.

In the second round, the Applicant provided additional simulations using the additional LDL-C data of all five patients. For these simulations, a subgroup of 1000 virtual patients was created for each real patient, using the actual dosing history (including skipped doses and dose reductions), plasmapheresis history, and prior LMT therapy (or lack thereof) of the real patient associated to the subgroup. A comparison of observed and model-predicted % change from LDL-C baseline stratified by actual dosing and plasmapheresis history and concomitant lipid-modifying therapy (Figure 11). Model-predicted LDL-C concentrations were based upon simulations assuming variability in patient characteristics and model parameters.

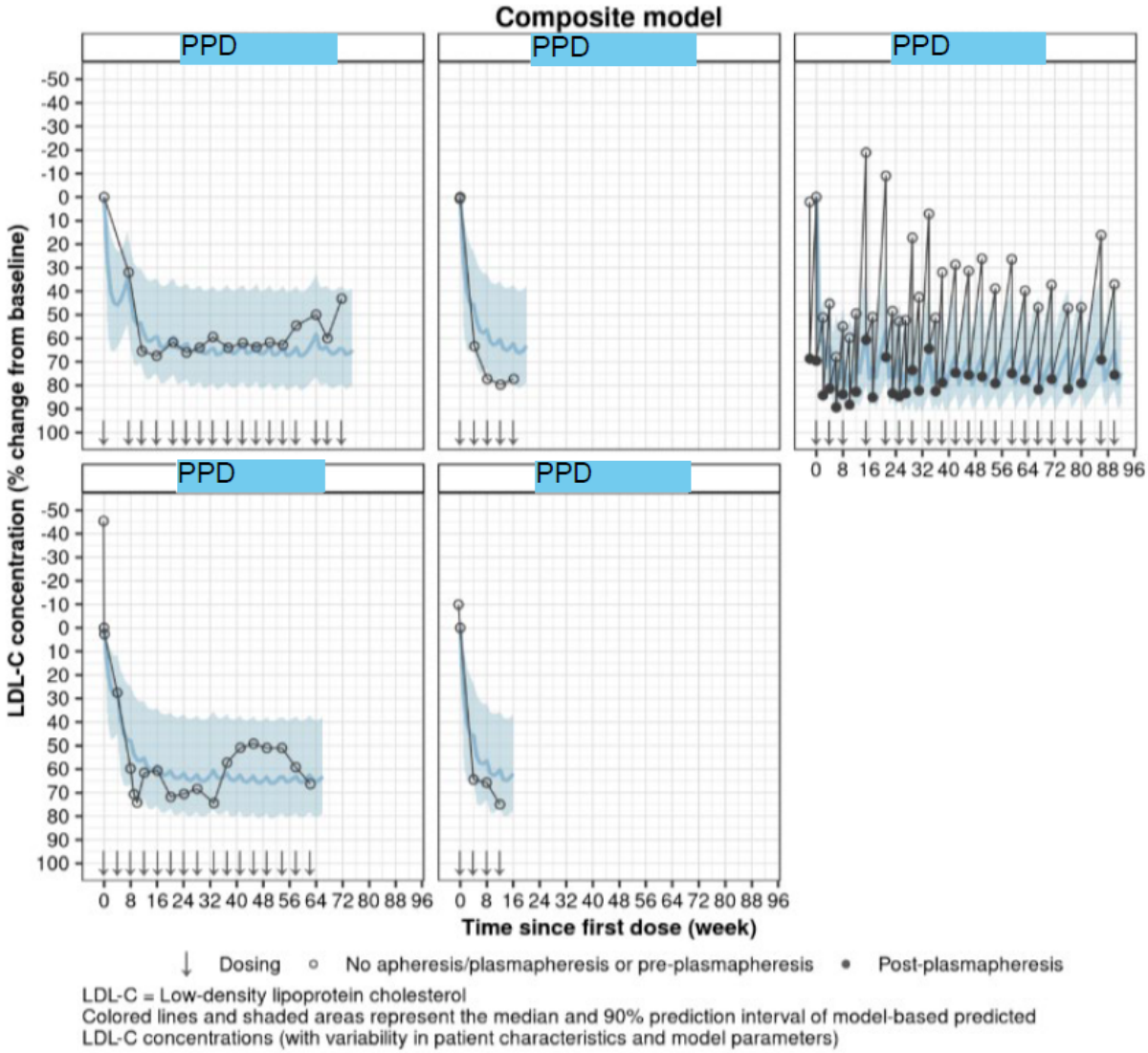


Figure 11. Observed and Model-predicted Percent Change from LDL-C Baseline versus Time Accounting for Variability in Virtual Patient Characteristics and Model Parameters and Using Actual Patient Dosing, Plasmapheresis History, and Concomitant Lipid-Modifying Therapy.

The additional observed LDL-C levels (both in terms of LDL-concentrations and %change in LDL-C baseline) for all five patients were generally within the 90% PI using the composite model.

The ANGPTL3 concentration measured at baseline in one patient was approximately at the centre of the range of values observed at baseline in patients 5 to < 12 years of age, which seems to be consistent with the extrapolation exercise where a lack of change in the expression of ANGPTL3 was simulated.

The alternative assumption of implementing a maturation of an evinacumab inhibitory effect between the age of 6 months and 5 years, which was tested in a sensitivity analysis, resulted in lower magnitudes of LDL-C reduction in the paediatric patients below 5 years old.

2.4.5. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of evinacumab in paediatric patients < 5 years have been appropriately evaluated.

As no clinical study was performed in paediatric patients with HoFH aged <5 years, the existing population PK model (R1500-PM-23041-SR-01V1) was used to extrapolate evinacumab PK to these patients. Random sampling methods were applied to construct 5000 virtual patients to predict the PK of evinacumab and associated LDL-C reduction in a virtual population of paediatric (6 months to < 5 years) patients with HoFH using model-based simulations (*R1500-PM-23089-SR-01V2*). The methodology used for the extrapolation exercise was considered adequate. In the composite model, evinacumab exposures after 15 mg/kg Q4W dosing and overall accumulation were predicted to decrease at younger age and with decreasing body weight, which was consistent with previous findings (*EMEA/H/C/005449/II/0011*).
Furthermore, additional explored assumptions (i.e. higher dose regimen for paediatrics >5 years old, maturation of the effect of evinacumab, and LMT naïve patients) indicated that only for scenario 1 of the sensitivity analysis, evinacumab concentrations were elevated compared to the initial simulation, which was expected.

In a compassionate use program, five HoFH patients <5 years old treated with evinacumab were analysed as an external qualification of the extrapolation exercise (*R1500-PM-23202-SR-01V2*), which is considered accurate. However, as the number of patients from whom data is available is limited, the results should be approached carefully. Evinacumab exposure was only measured in one patient up to week 16, and these observed evinacumab concentrations were generally within the 90% PI generated based upon the ideal 15 mg/kg IV Q4W dosing regimen. Only the trough concentration after the first dose was found to be outside the 90% PI, which can be explained by the fact that one patient was treated with 7.5 mg/kg of evinacumab at the first infusion before increasing the dose to 15 mg/kg for all subsequent infusions. Overall, the population PK model sufficiently described the data of one patient. Evinacumab concentrations at later time points were not collected in order to minimize treatment burden for this very young patient and because it was expected a plateau was reached based on the earlier obtained data from patients ages 5 to < 12 years.

Pharmacodynamics

No new pharmacodynamic studies in support of this application has been conducted by the Applicant. Although the proof of concept studies previously demonstrated 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.

PK/PD modelling

The pharmacokinetic and pharmacodynamic (LDL-C reduction) relationship of evinacumab in paediatric patients < 5 years has been sufficiently evaluated.

In the primary simulations, baseline LDL-C were predicted to increase with decreasing age, which was expected due to these paediatric patients having more severe HoFH and was consistent to previous findings in the application for extension of the indication to paediatric patients aged ≥5 to <12 years (*EMEA/H/C/005449/II/0011*). The average baseline ANGPTL3 concentration was simulated to be approximately equal (~ 0.0675 mg/L) in patients aged < 2 years, 2 to < 5 years, and 5 to < 12 years, then after increased with increasing age.
Despite the lower simulated evinacumab exposures in paediatric patients, the reduction in LDL-C was

predicted to be elevated in paediatric patients compared to adults. The sensitivity analysis indicated that the higher dosing (i.e. 20 mg/kg) with evinacumab corresponding to increased exposure did not result in an appreciable increase in LDL-C reduction. Furthermore, the magnitude reduction in target attainment resulting from evinacumab effect maturation are not expected to be reflective of practical context. LMT naïve patients are predicted to have higher LDL-C baseline levels, which is considered accurate, and thus more LMT naïve paediatric patients do not achieve the absolute LDL-C target compared to patients that received treatment before. Nevertheless, %ΔLDL-C was comparable between LMT naïve paediatric patients and paediatric patients from the primary simulations, and this is thus acceptable.

In a compassionate use program, the collected observations were generally consistent with the results generated from the prior model-based extrapolation exercise. The magnitude of observed reduction from baseline LDL-C was generally consistent with the model-based predictions for two patients. However, for one patient, around week 15, 20, 29, 34, and after week 38, the LDL-C reduction was found to be outside the 90% PI, which could possibly be explained by the fact that the model is able to predict the LDL-C reduction effect only after the combination of evinacumab treatment and apheresis in the case of one patient. The model predicts the observed data points after plasmapheresis sufficiently, as all these observed data points are found within the 90% PI.
In the second round, the Applicant provided additional LDL-C data for one patient up to week 72, for one patient up to week 62, and for one patient up to week 90. Furthermore, a few LDL-C data points have been made available for two additional patients who initiated treatment with evinacumab via the compassionate use programs (for one patient, data available up to Week 16; and for one patient , data available up to Week 12). The additional observed LDL-C levels (both in terms of LDL-concentrations and %change in LDL-C baseline) for all five patients were generally within the 90% PI using the composite model.

ANGPTL3 concentration measured at baseline in one patient was approximately at the centre of the range of values observed at baseline in patients ≥5 to <12 years of age, which seems to be supportive of the extrapolation exercise. Implementing maturation of the inhibitory effect of evinacumab between the age of 6 months and 5 years resulted in predictions with lower magnitudes of LDL-C reduction in the paediatric patients below 5 years old, which was inconsistent with the data observed in the three patients. Therefore, maturation of the effect of evinacumab is considered unlikely in practical context.

2.4.6. Conclusions on clinical pharmacology

To support the extension of the therapeutic indication for evinacumab to include paediatric patients aged 6 months to <5 years with homozygous familial hypercholesterolaemia (HoFH), an extrapolation analysis (including population pharmacokinetic, population pharmacokinetic/pharmacodynamic, and simulations analyses) was provided.

The extrapolation exercise sufficiently described the PK and PD of evinacumab in the youngest paediatric population. Evinacumab exposure after 15 mg/kg Q4W dosing is simulated to be decreased in paediatric patients <5 years compared to the older paediatric, adolescent and adult patients, which is most likely explained by the difference in body composition. Furthermore, LDL-C baseline levels were predicted to be increased in these 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.

2.5. Clinical efficacy

The primary evidence to support clinical dosing in this age group comes from a model-based extrapolation analysis, which was developed using population pharmacokinetics (PK) and population PK/pharmacodynamics (PD; population PK/PD) modelling and simulations (based on previously observed data in older children, adolescent, and adult patients), together with assumptions on the biological development and pathophysiological circumstances in younger children with HoFH. In addition, supportive data is provided detailing the clinical experience of 5 paediatric patients who initiated evinacumab treatment before the age of 5 years for the treatment of HoFH, via the Ultragenyx or Regeneron compassionate use programs.

As the aetiology of HoFH is the same for adult, adolescent, and paediatric patients, clinical monitoring data from compassionate use patients provides information on the efficacy of evinacumab in a real-world setting to aid the assessment of benefit/risk within the population of HoFH patients aged 6 months to 5 years.

2.5.1. Extrapolation concept

To support use of evinacumab in patients aged 6 months to 5 years with HoFH, an extrapolation analysis (including population PK, population PK/ PD, and simulation analyses) has been conducted.

There are several considerations that justify the overall approach to extrapolate data from older populations 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 hypercholesterolaemia observed in patients with HoFH is the same for both adult and paediatric patients. Hypercholesterolaemia 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

Evinacumab is a human IgG4 monoclonal antibody that binds human ANGPTL3 and decreases circulating LDL-C and TG levels. Expressed primarily in the liver, ANGPTL3 plays a prominent role in the regulation of lipid metabolism by inhibiting LPL and EL (Merkel et al., 2002; Wang and Eckel, 2009; Shimamura et al., 2007). Evinacumab reduces LDL-C independent of the presence of the LDLR by promoting VLDL processing and clearance upstream of LDL-C formation. The mechanism through which evinacumab acts is the same regardless of patient age due to the same underlying disease processes.

This is also supported non-clinically where studies examining the pharmacology of evinacumab in adult, juvenile, and newborn animals demonstrated consistent lipid-lowering effects irrespective of animal age.

As a monoclonal antibody, the disposition and elimination of evinacumab includes both a non-linear saturable target-mediated pathway and a linear non-saturable proteolytic catabolism pathway. At higher systemic concentrations of evinacumab, sufficient to saturate the target-mediated pathway, the PK of evinacumab is mainly governed by the linear elimination pathway. Evinacumab is not expected to interact with CYP450 enzymes or drug transporters, which may be affected by genetic or physiological factors. Population PK analyses identified body weight as the main source of intrinsic PK variability, with lower body-weight patients showing a decrease in exposure. The predicted mean steady state trough concentration in paediatric patients (5 to < 12 years of age) was lower, but within the range observed in adolescent and adult patients.

Similar exposure (efficacy/ safety) response

Non-clinical data

The evinacumab toxicology studies that were conducted to support paediatric administration in patients of all ages are summarized in Table 8. Evinacumab exposure was well tolerated in juvenile rats and rabbits, with drug-related findings limited to pharmacologically anticipated decreases in TG, HDL-C, and/or cholesterol that were generally reversible upon discontinuation of dosing, consistent with general repeat-dose effects observed in older animals. During the reproductive phase of the GLP juvenile rabbit study, there were no evinacumab-related effects on female reproductive performance, intrauterine growth and survival, or foetal morphology. Therefore, the NOAEL is considered to be 100 and 300 mg/kg/dose in juvenile rats and rabbits, respectively, the highest doses administered.

Table 8. Summary of Toxicology Studies Supporting Evinacumab Dosage and Administration in Patients from 6 Months to Less than 5 Years of Age

Study Type and Duration (Compliance)	Study Number	Species	Evinacumab Dose (mg/kg) (Route of Administration)
Reproductive and Developmental Toxicology Studies			
Female fertility and early embryonic development to implantation and pre- and postnatal development study (GLP)	R1500-TX-17096	Sprague Dawley rat	0, 30, and 100 (SC) *NOAEL 100 mg/kg (SC)*
Juvenile Toxicology			
PND 21 through PND 84 with a minimum 56-day recovery period (GLP)	R1500-TX-17094	Sprague Dawley rat	0, 30,100 (SC), and 100 (IV) [a] *NOAEL 100 mg/kg (SC and IV)*
Nonpivotal PND 21 through PND 96 (non-GLP)	R1500-TX-18035	New Zealand White rabbit	0, 30, 100, 300 (SC), and 100 (IV) [a] *NOAEL not set per study design; doses informed Study R1500-TX-17093*
PND 21 through PND 144, followed by a female reproductive phase[b] (GLP)	R1500-TX-17093	New Zealand White rabbit	0, 30, 100, and 300 (IV) [a] *NOAEL 300 mg/kg (IV)*

A short summary of the key juvenile studies supporting dosing in paediatric subjects 6 months to < 5 years of age is provided below. Comprehensive information was previously reported. Please note that only administration by IV route is intended for the administration of evinacumab in this population:

1. Study R1500-TX-17096 – Combined Fertility/Early Embryonic Development Study and Prenatal and Postnatal Development in Sprague Dawley Rats: In this study, groups of pregnant female rats (F0) were administered evinacumab SC (0, 30, or 100 mg/kg) once every 3 days beginning 2 weeks prior to pairing, and continued to gestational day 21 (to examine embryofoetal effects), or extended through the post-gestational period until lactation day (LD) 21 (a range roughly equivalent from newborn to 2 years of age). Exposure to evinacumab was well tolerated by the F0 cohort as well as F1 pups postnatally, with no dose limiting evinacumab-related adverse effects observed. Continuous exposure to evinacumab was maintained in F0 females throughout the treatment period, and importantly, detectable concentrations were observed in more than half of the F1 pups postnatally (implying exposure via lactation). Evinacumab-related decreases in serum TGs, HDL-C, LDL-C, and TC were observed in F1 offspring of F0 females that received ≥ 30 mg/kg evinacumab. Drug-related, statistically significant decreases in mean sperm concentration were observed in F1 animals administered 100 mg/kg; however, this was not considered adverse as no effect on reproductive indices was observed. Therefore, based on the lack of adverse effects, the NOAEL for all animals was considered to be 100 mg/kg SC, the highest dose evaluated.
2. Study R1500-TX-17094 – Toxicology Study in Juvenile Rats; 63 days Dosing and 8-week Recovery: During this juvenile toxicity study conducted in 21-to-84 day-old rats (equivalent to approximately 2 years of age in children at time of treatment initiation),

exposure to evinacumab was well tolerated, with no adverse effects evident at any dose level. Evinacumab-related effects were consistent with the intended pharmacology of evinacumab and consisted of decreases in serum TG, HDL-C, and mean cholesterol levels, which were generally reversible at the end of the recovery period. Based on the lack of adverse effects, the NOAEL in juvenile rats is considered to be 100 mg/kg/dose IV or SC, the highest doses administered.

3. Study R1500-TX-18035 – A Study in Juvenile Rabbits to Guide Dose Selection of Study 17093: In this completed dose-range finding pilot study (non-GLP), juvenile rabbits were administered control article or evinacumab once every 5 days from PND 21 to PND 96 (equivalent to approximately 2 years of age in children at time of treatment initiation). Dosages were administered SC (30, 100, or 300 mg/kg) or IV (300 mg/kg). Exposure to evinacumab was well tolerated and there was no dose limiting evinacumab-related adverse effects. Evinacumab-related effects were consistent with the intended pharmacology of evinacumab and consisted of decreases in serum TGs, HDL-C, and/or cholesterol.

4. Study R1500-TX-17093 – A 17-week Study in Juvenile Rabbits: Administration of ≤ 300 mg/kg evinacumab once every 5 days via IV injection from PND 21 through PND 141 (equivalent to approximately 2 years of age in children at time of treatment initiation) was well tolerated and did not produce any adverse test article-related findings. Evinacumab-related effects were limited to decreases in serum TGs, HDL-C, LDL-C, and TC; these changes were reversible and consistent with the intended pharmacology of evinacumab. All incidences of animal mortality and moribundity that were noted during this treatment phase, the recovery period which followed between PND 142 and 352, or the subsequent reproductive phase, were not considered related to evinacumab-treatment. In addition, during the reproductive phase of the study, there were no evinacumab-related effects on female reproductive performance, intrauterine growth and survival, or foetal morphology. Therefore, based on the lack of adverse effects, the NOAEL was considered to be 300 mg/kg/dose, the highest dose evaluated.

Clinical data

Multiple dose administration of evinacumab 15 mg/kg IV Q4W over 24 weeks in paediatric patients 5 to < 12 years of age 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 achieved in the paediatric population (5 to < 12 years of age) 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 5 to < 12 years of age were sufficient to achieve maximal target engagement (Wiegman et al., 2023).

Given the consistency of effect seen in adults, adolescents, and paediatric patients 5 years of age and older, and the similarity in the disease across ages, it would be expected that similar reductions in LDL-C would also be observed in HoFH patients of 6 months to < 5 years of age.

Data are available from 5 patients < 5 years treated with evinacumab via a compassionate use program. Evinacumab and ANGPTL3 concentrations were only measured in one patient, while the corresponding effect on LDL-C was measured in all five patients. The collected LDL-C observations were generally consistent with the results generated from the model-based extrapolation exercise (*R1500-PM-23089-SR-01V2*) showing the predicted magnitude of LDL-C reduction was maintained and appeared even larger in paediatrics compared to adolescents and adults.

Human genetic evidence

The safety of ANGPTL3 inhibition by evinacumab is supported by human genetic evidence. Genetic studies of individuals with biallelic ANGPTL3 LOF mutations show that long-term disruption of ANGPTL3 due to naturally occurring genetic variants is not associated with any increase in adverse clinical outcomes, or has been shown to have a negative impact on foetal or early childhood development. There have been no reports of increased risk of liver disease, tumours, impact on growth/development in children, or any morbidity or clinical condition associated with LOF mutations in ANGPTL3 beyond the clinical lipid phenotype. Therefore, it is reasonable to conclude that LOF mutations in ANGPTL3 (FHBL2, OMIM #605019) is a benign condition, and it is expected that ANGPTL3 inhibition by evinacumab would pose no safety concerns (related to its mechanism of action) in any age group.

Evinacumab safety profile in patients aged 5 years and older

Similar to what has been observed in adult and adolescent patients, evinacumab treatment was well-tolerated in 20 paediatric patients 5 to < 12 years of age in Study R1500-CL-17100, with the majority of treatment-emergent adverse events (TEAEs) being mild to moderate in severity. Due to the consistency of the safety profile observed in paediatric patients 5 to < 12 years of age, adolescents, and adults, as well as the available non-clinical data, and human genetic evidence, the safety profile in paediatric patients 6 months to < 5 years of age is also expected to be consistent.

Fatigue is the only additional adverse drug reaction (ADR) for patients 5 to < 12 years of age, which was based on the 3 paediatric patients in Study R1500-CL-17100 who experienced 4 non-serious events of fatigue of mild severity. These events were reported in the absence of other concurrent events, no action was taken (dose was not changed as a result of the events), and fatigue was considered recovered/resolved. Notably, Asthenia is already considered as an expected ADR in patients > 12 years of age. Other than an ADR of fatigue, no safety findings were identified in the paediatric program that had not previously been identified in the adult and adolescent program, and no significant safety findings of special importance to children have been identified throughout the clinical development program.

Due to the consistency of the safety profile observed in paediatric patients 5 to < 12 years of age, adolescents, and adults, and the other factors presented above, the safety profile in paediatric patients 6 months to < 5 years of age is also expected to be generally consistent.

2.5.2. Dose response study(ies)

The dose selection for the initial phase 3 studies was based on the totality of data from the phase 1 and 2 studies. Results from the adult and adolescent phase 3 studies R1500-CL-1629 and R1500-CL-1719 confirmed the selection of 15 mg/kg IV Q4W as the appropriate dosing regimen for adult and adolescent populations.

The collective results from the aforementioned phase 1, phase 2, and adult and adolescent phase 3 studies were used to inform the paediatric clinical pharmacology program for evinacumab. Results from the phase 1b/3 R1500-CL17100 study and multiple model-based simulations, along with the observed safety profile, supported the selection of the 15 mg/kg IV Q4W as the appropriate proposed dose for LDL-C lowering in the paediatric population 5 years of age and above.

A model-based extrapolation analysis was performed to predict the PK of evinacumab and associated LDL-C reduction in a virtual population of patients less than 5 years of age with HoFH based on previously observed data in older children, adolescent, and adult patients, an integrated PK/PD model, and assumptions on the biological development and pathophysiological circumstances in younger children with HoFH. The lowest body weight in the virtual population was ~ 6 kg. Under the simulation

assumptions after dosing with 15 mg/kg Q4W, evinacumab exposures and overall accumulation were predicted to be lower with younger age and lower weight. Furthermore, the magnitude of reduction in percent change in LDL-C was predicted to be generally comparable between paediatric patients 6 months to < 5 years of age, adolescents and adults, suggesting that the trend observed in absolute LDL-C concentrations was related to the higher baseline LDL-C concentrations at younger age rather than a decrease in evinacumab exposure.

Increasing the dose in patients < 5 years of age to 20 mg/kg Q4W infusions was not predicted to provide a substantial improvement in LDL-C reduction over the 15 mg/kg Q4W dosing regimen recommended in patients ≥ 5 years of age, despite a 35-50% increase in median steady-state exposures. This is primarily explained by the fact that trough concentrations are predicted to be above the half-inhibitory concentration (IC50) (32.5 mg/L) in most patients of all age groups at 15 mg/kg Q4W, indicating that full inhibition of LDL-C production is already achieved at this dose regimen.

These findings support the selection of the 15 mg/kg IV Q4W as the appropriate proposed dose for LDL-C lowering in the paediatric population of 6 months to less than 5 years of age.

2.5.3. Main study(ies)

Compassionate use program

As indicated above, supportive data is provided detailing the clinical experience of 5 paediatric patients who initiated evinacumab treatment before the age of 5 years for the treatment of HoFH, via the Ultragenyx or Regeneron compassionate use programs. Details of the compassionate use program is provided below.

Methods

Study participants

To be eligible for compassionate use, patients must (1) have a serious or life-threatening disease that does not have satisfactory alternative treatment options available; (2) have a condition that does not have satisfactory alternative treatment options available or has exhausted all reasonable available therapeutic options typically used to treat the disease; and (3) be unable to participate in an ongoing clinical trial. The compassionate use program provides access to evinacumab treatment when an unsolicited request is made by an individual patient's responsible physician after obtaining patient or caregiver consent.

Compassionate use requests are evaluated on a case-by-case basis. The patient's responsible physician must provide adequate documentation to demonstrate that the patient meets the eligibility criteria listed above. Documentation may include, but is not limited to, a summary of the patient's medical history, clinical status, and rationale for treatment with evinacumab. The responsible physician must also obtain appropriate country-specific Health Authority approval and/or local Institutional Review Board/Ethics Committee approval for compassionate use of the investigational medicine.

Patients that receive evinacumab via compassionate use are generally reflective of the overall patient population with HoFH that would be expected to receive evinacumab should the marketing authorization be extended to include paediatric patients < 5 years of age.

Treatments

All compassionate use patients were treated with evinacumab 15 mg/kg IV Q4W.

Efficacy parameters

Standard of care assessments (which could include physical exam, total cholesterol [TC], LDL-C, other laboratory assessments, imaging, and radiological assessments) were collected according to standard practice for HoFH at each patient's site.

LDL-C was the primary efficacy parameter and similar to previous clinical studies, percent change in LDL-C from baseline over time was calculated for all compassionate use patients.

In addition to standard of care assessments, additional assessments were recommended to be performed at 6-month intervals at the discretion of the responsible physician (Table 9).

Table 9. Suggested Patient Monitoring

Assessment	Suggested Frequency
• Informed consent	Prior to starting treatment
• Patient age, sex, weight in kg • Medical history including cardiovascular history (onset of aortic stenosis, MI, stroke, etc), any imaging • Family history including onset of cardiovascular history in family • Surgical history • Allergies	Prior to starting treatment
• Vital signs • Physical examination, including height measurement • Medications and specifically HoFH medication (statins, ezetimibe, PCSK9 inhibitors, lomitapide, apheresis, plasmapheresis, liver transplant) if applicable and duration on treatment	Per standard of care for HoFH,
• Weight for drug preparation • Treatment with evinacumab • Assess for adverse events • Allergies	Every 4 weeks
• Safety laboratory tests, including hematology, chemistry, liver enzymes, creatine phosphokinase, and urinalysis [a]	Recommended monthly for the first 6 months, and subsequently every 3 months
• Total Cholesterol • LDL-C <u>At Responsible Physicians' discretion for patients less than 5 years of age and with caregiver consent</u>: • Serum total evinacumab and total ANGPTL3: (3 mL blood - into 3 mL red-top vacutainer tube). See also	Lipid Panel including LDL-C: Day 1 (Baseline), Weeks 4, 8, 12, and 16 PK: Predose/EOI on Day 1 (Baseline), Weeks 4, 8, 12, and 16 ANGPTL3: Predose only at the same time points
• Imaging and radiological assessments	Every 6 months or at responsible physician's discretion

[a] Safety laboratory tests were recommended only for patients in the USA in the Regeneron CUP

CUP, compassionate use program; EOI, end of infusion; HoFH, homozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; PK, pharmacokinetics

Results

Participant flow

As of the initial submission of this variation in April 2024, three patients less than 5 years of age received evinacumab via compassionate use (Table 10). During the variation procedure further LDL-C data points have been made available for two additional patients who initiated treatment with

evinacumab via the compassionate use programs (for one patient, data available up to Week 16; and for another patient, data available up to Week 12).

Table 10. Overview of Compassionate Use Patients less than 5 years of age

Patient	Evinacumab dose	Baseline LDL-C (mmol/L)	Other clinical conditions	Concomitant medication/ therapy	Data available
Patient 1	15 mg/kg IV Q4W[a]	22.6	-	None	LDL-C, Serum PK/ ANGPTL3
Patient 2	15 mg/kg IV Q4W	11.6	xanthomas	Plasma-pheresis, rosuvastatin, and ezetimibe	LDL-C
Patient 3	15 mg/kg IV Q4W	9.1	xanthomas	atorvastatin and ezetimibe	LDL-C
Patient 4	15 mg/kg IV Q4W	15.3	xanthomas on bilateral heels	rosuvastatin and ezetimibe	LDL-C
Patient 5	15 mg/kg IV Q4W	6.2	xanthomas on left gluteal region and left knee	rosuvastatin and ezetimibe	LDL-C

[a] Patient 1 received 7.5 mg/kg evinacumab at the first dose at the responsible physician's discretion.
ANGPTL3, angiopoietin-like protein 3; LDL-C, low-density lipoprotein cholesterol; PK, pharmacokinetics

Baseline data

Patient 1

A patient started receiving evinacumab via CUP. This patient has a homozygous mutation in the LDLR gene. The patient was not receiving any other lipid lowering medications or apheresis due to very young age. The patient's LDL-C value was 22.6 mmol/L (872 mg/dL) at Day 1 (pre-dose) of evinacumab treatment.

Patient 2

A patient started receiving evinacumab via CUP. The diagnosis of this patient was confirmed by genetic criteria as the patient was reported to have homozygous pathologic/functional variants in the LDL receptor gene. The patient presented with xanthomas prior to evinacumab treatment. This patient was receiving plasmapheresis Q2W, rosuvastatin 20 mg/day, and ezetimibe 10 mg/day. The patient's LDL-C value was 11.4 mmol/L (440.4 mg/dL) pre-plasmapheresis and 3.6 mmol/L (140.8 mg/dL) post-plasmapheresis at Screening (Day -14), and 11.6 mmol/L (449.7 mg/dL) pre-plasmapheresis and 3.5 mmol/L (136.9 mg/dL) post-plasmapheresis at Day 1 (pre-dose).

Patient 3

A patient started receiving evinacumab via CUP. The diagnosis of this patient was reported by the responsible physician to have been confirmed by clinical criteria. The patient presented with

xanthomas prior to evinacumab treatment. At the time that the request for compassionate use of evinacumab was submitted, the patient was not receiving lipoprotein apheresis or plasmapheresis, and was receiving treatment with atorvastatin, alirocumab, and ezetimibe. According to the information available from the compassionate use request, the patient started atorvastatin 20 mg/day. The responsible physician later added ezetimibe 10 mg/day and alirocumab 75 mg Q4W, due to the limited effect seen with atorvastatin 20 mg/day. The patient's LDL-C value was 9.1 mmol/L (350 mg/dL) at Day 1.

Patient 4

A patient started receiving evinacumab via CUP after being diagnosed by the responsible physician based on clinical criteria (total cholesterol of 25.4 mmol/L [984 mg/dL] and non-HDL cholesterol of 24.8 mmol/L [957 mg/dL]. The patient presented with xanthomas on bilateral heels prior to evinacumab treatment. This patient was not receiving lipoprotein apheresis or plasmapheresis, and was receiving treatment with rosuvastatin 10 mg/day and ezetimibe 10 mg/day. The patient's LDL-C value was 15.2 mmol/L (586 mg/dL) at Screening (Day -1), and 15.3 mmol (590 mg/dL) at Day 1.

Patient 5

A patient started receiving evinacumab via CUP. The patient was diagnosed with HoFH based on clinical criteria (elevated total cholesterol and LDL-C). The patient presented with xanthomas on the left gluteal region and left knee prior to evinacumab treatment. This patient was not receiving lipoprotein apheresis or plasmapheresis, and was receiving treatment with rosuvastatin 20 mg/day, and ezetimibe 10 mg/day. The patient's LDL-C value was 6.8 mmol/L (262 mg/dL) at Screening (Day -4), and 6.2 mmol (238 mg/dL) at Day 1.

Conduct of study

To capture data on clinical outcomes of evinacumab treatment for patients less than 5 years of age in a real-world setting, Ultragenyx, in collaboration with Regeneron, prepared an Excel spreadsheet to collect patient characteristics, evinacumab dosing information, lipid data, and LDL-C and PK/ANGPTL3 sample collection information (if available) for patients less than 5 years of age in the CUP. The responsible physician at each compassionate use patient's site was requested to record patient data in the Excel spreadsheet. Due to the timing of the development of the Excel spreadsheet, and so as not to cause any delay in the treatment of these patients, safety and efficacy data were obtained retrospectively from two patients: Patient 2 and Patient 3. Prospective data was obtained for Patient 1, as treatment for this patient initiated after availability of the Excel spreadsheet. Site personnel uploaded the spreadsheet completed by the responsible physician into a folder within the Box GxP system at Ultragenyx. Permissions to Box GxP were linked to a specific individual at the site identified as the responsible person to upload patient data. Separate folders were created for each site, and access to each of the folders was restricted to individual sites to maintain personal data protection.

For PK/ANGPTL3 data collection, serum samples from one patient were shipped to Regeneron Bioanalytical once all samples were collected. Regeneron uploaded the bioanalytical data in the Box GxP system at Ultragenyx.

All data uploaded to Box was cross-checked against information obtained informally from the responsible physician. Additional clarifications from the responsible physician were sought when needed.

Data obtained for this report is based on available data from the use of evinacumab in the real world, and therefore, it is more difficult to achieve the same level of certainty and standardisation of data obtained in a prospectively designed clinical study. Despite this, Ultragenyx and Regeneron have taken

every effort to confirm the accuracy of the limited data available through the CUP to ensure the quality of the data presented within this report.

Outcomes and estimation

LDL-C

Patient 1

This patient received evinacumab 15 mg/kg IV Q4W (120 mg) after receiving a half dose at their initial infusion (7.5 mg/kg; 60 mg) at the responsible physician's discretion to ensure the patient tolerated the drug before receiving a full dose. The patient's LDL-C value was 22.6 mmol/L (872 mg/dL) at Day 1 (predose). On evinacumab monotherapy, the LDL-C level of this patient decreased to 8.9 mmol/L (343 mg/dL) after 4 infusions (-60.7% change from baseline) (Table 11). The patient maintained this substantial reduction in LDL-C levels up to Week 33 when an increase was observed at the following visit (Week 37). Despite this slight increase between Weeks 37 and 54, which may be attributed to changes in diet, the reduction of 66.3% in LDL-C observed at Week 62 is considered substantial and close to reduction observed prior to Week 37.

Table 11. Clinical Data for Compassionate Use Patient 1

Visit	Evinacumab Treatment	Total Cholesterol		Calculated LDL-C		% Change in LDL-C from Baseline (Day 1 Predose)
		mmol/L	mg/dL	mmol/L	mg/dL	
Day -14 to -1 (Screening)		33.6	1300	32.8	1268	-
Baseline (Day 1; Predose)	7.5 mg/kg IV	24.1	933	22.6	872	-
Day 1 (End of Infusion)		22.8	883	22.0	849	-2.6
Week 4 (Day 29; Predose)	15 mg/kg IV	18.3	709	16.3	632	-27.5
Week 8 (Day 57)	15 mg/kg IV	10.3	399	9.3	351	-59.7
Week 9 (Day 64)		8.5	327	6.6	256	-70.6
Week 10 (Day 71)		7.7	298	5.8	225	-74.2
Week 12 (Day 85; Predose)	15 mg/kg IV	9.8	379	8.7	335	-61.6
Week 16 (Day 113; Predose)	15 mg/kg IV	10.1	389	8.9	343	-60.7
Week 20 (Day 141)	15 mg/kg IV	7.4	286	6.4	246	-71.8
Week 24 (Day 169)	15 mg/kg IV	7.6	293	6.6	257	-70.5
Week 28 (Day 197)	15 mg/kg IV	8.1	313	7.1	276	-68.3
Week 33 (Day 232)	15 mg/kg IV	6.5	251	5.8	223	-74.4
Week 37 (Day 260)	15 mg/kg IV	10.6	410	9.6	373	-57.2
Week 41 (Day 288)	15 mg/kg IV	12.1	468	11.1	428	-50.9
Week 45 (Day 316)	15 mg/kg IV	12.6	487	11.5	443	-49.2
Week 49 (Day 344)	15 mg/kg IV	12.0	464	11.0	427	-51.0
Week 54 (Day 376)	15 mg/kg IV	12.0	464	11.0	427	-51.0
Week 58 (Day 405)	15 mg/kg IV	10.2	396	9.2	356	-59.2

Week 62 (Day 436)	15 mg/kg IV	8.6	331	7.6	294	-66.3

Patient 2

This patient received evinacumab 15 mg/kg IV Q4W; evinacumab infusions were aligned so that the patient also underwent plasmapheresis at visits when they received evinacumab (Table 12). The patient's LDL-C value was 11.4 mmol/L (440.4 mg/dL) preplasmapheresis and 3.6 mmol/L (140.8 mg/dL) postplasmapheresis at Screening (Day -14), and 11.6 mmol/L (449.7 mg/dL) preplasmapheresis and 3.5 mmol/L (136.9 mg/dL) postplasmapheresis at Day 1 (predose).

Five dose interruptions occurred during treatment in the compassionate use program. The patient had elevated LDL-C values at Week 15 (13.8 mmol/L [534.8 mg/dL] pre-plasmapheresis and 4.6 mmol/L [176.7 mg/dL] post-plasmapheresis), Week 21 (12.7 mmol/L [490.3 mg/dL] pre-plasmapheresis and 3.7 mmol/L [144.2 mg/dL] post-plasmapheresis), and Week 34 (10.8 mmol/L [417.6 mg/dL] pre-plasmapheresis and 4.2 mmol/L [160.5 mg/dL] post-plasmapheresis), which occurred 1 to 3 weeks after missed doses at Weeks 12, 19, and 33, respectively.

After the ninth dose at Week 38, at the discretion of the responsible physician, considering the LDL-C reductions observed at that point, the patient's plasmapheresis schedule changed from Q2W to Q4W in an attempt to increase patient compliance with treatment. No changes were made in the doses of rosuvastatin and ezetimibe; evinacumab treatment also continued at Q4W. The reduced frequency in plasmapheresis resulted in a decrease in the magnitude of percentage LDL-C reduction from baseline at Weeks 42 and 46.

Furthermore, the responsible physician observed and reported regression of the patient's xanthomas during the CUP, with complete resolution after approximately 1 year of evinacumab treatment.

Even with instances of missed doses and alterations to the plasmapheresis schedule, this patient saw reduced LDL-C values up to the last reported dose at Week 90 (-37.1% change from baseline preplasmapheresis). In addition, the reduction observed in plasmapheresis frequency represents a benefit to this patient as it reduces the overall treatment burden.

The patient received treatment via compassionate use up to Week 90.

Table 12. Clinical data for Compassionate Use Patient 2

Visit	Evinacumab Treatment	Plasma-pheresis	Calculated LDL-C Pre-plasmapheresis		% Change in LDL-C from Pre-plasmapheresis Baseline (Day 1)	Calculated LDL-C Post-plasmapheresis	
			mmol/L	mg/dL		mmol/L	mg/dL
Day -14		Yes	11.4	440	-	3.6	141
Baseline (Day 1)	15 mg/kg IV	Yes	11.6	450	-	3.5	137
Week 2 (Day 15)		Yes	5.7	220	-51.2	1.8	71
Week 4 (Day 29)	15 mg/kg IV	Yes	6.4	246	-45.3	2.2	84
Week 6 (Day 43)		Yes	3.7	144	-67.9	1.2	48
Week 8 (Day 57)	15 mg/kg IV	Yes	5.2	203	-54.9	1.9	73
Week 10 (Day 71)		Yes	4.7	181	-59.8	1.4	53
Week 12 (Day 85)		Yes	5.9	227	-49.5	2.0	78
Week 15 (Day 106[a])	15 mg/kg IV	Yes	13.8	535	+18.9	4.6	177

Visit	Evinacumab Treatment	Plasma-pheresis	Calculated LDL-C Pre-plasmapheresis		% Change in LDL-C from Pre-plasmapheresis Baseline (Day 1)	Calculated LDL-C Post-plasmapheresis	
			mmol/L	mg/dL		mmol/L	mg/dL
Week 17 (Day 120)		Yes	5.7	220	-51.0	1.7	67
Week 21 (Day 148[a])	15 mg/kg IV	Yes	12.7	490	+9.0	3.7	144
Week 23 (Day 162)		Yes	6.0	232	-48.5	1.9	75
Week 25 (Day 176[b])	15 mg/kg IV	Yes	5.5	212	-52.8	1.8	69
Week 27 (Day 190)		Yes	5.6	215	-52.3	1.9	75
Week 29 (Day 204)	15 mg/kg IV	Yes	9.6	372	-17.3	3.1	119
Week 31 (Day 218)		Yes	6.7	258	-42.6	2.1	80
Week 34 (Day 239[a])	15 mg/kg IV	Yes	10.8	418	-7.1	4.2	160
Week 36 (Day 253)		Yes	5.7	219	-51.3	2.0	79
Week 38 (Day 267[c])	15 mg/kg IV	Yes	7.9	306	-32.0	2.4	95
Week 42 (Day 295)	15 mg/kg IV	Yes	8.3	321	-28.7	3.0	114
Week 46 (Day 323)	15 mg/kg IV	Yes	8.0	309	-31.4	2.8	110
Week 50 (Day 351)	15 mg/kg IV	Yes	8.6	331.8	-26.2	2.8	107
Week 54 (Day 379)	15 mg/kg IV	Yes	7.1	275.3	-38.9	2.4	94
Week 59 (Day 414)	15 mg/kg IV	Yes	8.6	330.6	-26.4	2.9	113
Week 63 (Day 442)	15 mg/kg IV	Yes	7.0	271.1	-39.7	2.6	101
Week 67 (Day 470)	15 mg/kg IV	Yes	6.2	239.0	-46.9	2.1	82
Week 71 (Day 498)	15 mg/kg IV	Yes	7.3	281.9	-37.3	2.7	102
Week 76 (Day 533)	15 mg/kg IV	Yes	6.2	238.2	-47.1	2.2	83
Week 80 (Day 561)	15 mg/kg IV	Yes	6.2	239.4	-46.9	2.4	94
Week 86 (Day 603)[a]	15 mg/kg IV	Yes	9.8	377.0	-16.2	3.6	139
Week 90 (Day 631)	15 mg/kg IV	Yes	7.3	283.1	-37.1	2.8	110

[a] An evinacumab dose was missed prior to this visit. The patient missed scheduled doses on Week 12 (Day 85), Week 19 (Day 134), Week 33 (Day 232), and Week 84 (Day 589), which were later administered on Week 15 (Day 106), Week 21 (Day 148), Week 34 (Day 239), and Week 86 (Day 603), respectively.
[b] The patient received a partial dose after experiencing nausea and vomiting during the infusion.
[c] The plasmapheresis schedule of the patient was changed from every 2 weeks to every 4 weeks.

Patient 3

This patient received evinacumab 15 mg/kg IV Q4W (Table 13). The patient's LDL-C value was 9.1 mmol/L (350 mg/dL) at Day 1 (predose).

At Week 12 (Day 81), the patient had an LDL-C value of 3.1 mmol/L (121 mg/dL). The patient maintained reduced LDL-C values up to the last reported dose at Week 72 (Day 503) (-43.1% change from baseline). The patient received treatment via compassionate use up to Week 72.

Table 13. Clinical data for Compassionate Use Patient 3

Visit	Evinacumab Treatment	Calculated LDL-C		% Change in LDL-C from Baseline
		mmol/L	mg/dL	
Baseline (Day 1)	15 mg/kg IV	9.1	350	-
Week 8 (Day 53)	15 mg/kg IV	6.2	238	-32.0
Week 12 (Day 81)	15 mg/kg IV	3.1	121	-65.4
Week 16 (Day 112)	15 mg/kg IV	2.9	114	-67.4
Week 21 (Day 147)	15 mg/kg IV	3.5	134	-61.7
Week 25 (Day 175)	15 mg/kg IV	3.1	119	-66.0
Week 29 (Day 203)	15 mg/kg IV	3.3	126	-64.0
Week 33 (Day 231)	15 mg/kg IV	3.7	142	-59.4
Week 38 (Day 263)	15 mg/kg IV	3.3	126	-64.0
Week 42 (Day 294)	15 mg/kg IV	3.4	133	-62.0
Week 46 (Day 323)	15 mg/kg IV	3.3	127	-63.7
Week 50 (Day 351)	15 mg/kg IV	3.5	134	-61.7
Week 54 (Day 379)	15 mg/kg IV	3.4	130	-62.9
Week 58 (Day 407)	15 mg/kg IV	4.1	159	-54.6
Week 64 (Day 449)	15 mg/kg IV	4.5	175	-50.0
Week 68 (Day 473)	15 mg/kg IV	3.6	140	-60.0
Week 72 (Day 503)	15 mg/kg IV	5.1	199	-43.1

Patient 4

This patient received evinacumab 15 mg/kg IV Q4W (Table 14). The patient's LDL-C value was 15.2 mmol/L (586 mg/dL) at Screening (Day -1) and 15.3 mmol/L (590 mg/dL) at Day 1. On evinacumab therapy, the LDL-C level of this patient decreased to 3.5 mmol/L (134 mg/dL) after 4 infusions (-77.3% change from baseline at Week 16).

Table 14. Clinical Data for Compassionate Use Patient 4

Visit	Evinacumab Treatment	Total Cholesterol		Calculated LDL-C		% Change in LDL-C from Baseline
		mmol/L	mg/dL	mmol/L	mg/dL	
Screening (Day -1)		16.3	629	15.2	586	-
Baseline (Day 1)	15 mg/kg IV	16.3	630	15.3	590	-
Week 4 (Day 29)	15 mg/kg IV	6.4	246	5.6	216	-63.4
Week 8 (Day 57)	15 mg/kg IV	4.2	164	3.5	134	-77.3

Week 12 (Day 85)	15 mg/kg IV	3.9	149	3.1	120	-79.7
Week 16 (Day 113)	15 mg/kg IV	4.1	159	3.5	134	-77.3

Patient 5

This patient received evinacumab 15 mg/kg IV Q4W (Table 15). The patient's LDL-C value was 6.8 mmol/L (262 mg/dL) at Screening (Day -4), and 6.2 mmol (238 mg/dL) at Day 1. On evinacumab therapy, the LDL-C level of this patient decreased to 1.5 mmol/L (60 mg/dL) after 3 infusions (-75% change from baseline at Week 12).

Table 15. Clinical Data for Compassionate Use Patient 5

Visit	Evinacumab Treatment	Total Cholesterol		Calculated LDL-C		% Change in LDL-C from Baseline
		mmol/L	mg/dL	mmol/L	mg/dL	
Screening (Day -4)		8.0	309	6.8	262	-
Baseline (Day 1)	15 mg/kg IV	7.3	282	6.2	238	-
Week 4 (Day 29)	15 mg/kg IV	2.9	112	2.2	85	-64.4
Week 8 (Day 57)	15 mg/kg IV	2.7	104	2.1	82	-65.7
Week 12 (Day 85)	15 mg/kg IV	2.1	81	1.5	60	-75.0

2.5.4. Discussion on clinical efficacy

Introduction

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 based on data from the pivotal phase 3 double-blind placebo-controlled study R1500-CL-1629 and an interim analysis from the long-term, open-label safety and efficacy extension study R1500-CL-1719 (EMEA/H/C/005449/0000). An exceptional circumstances marketing authorization was granted on the basis that the indication is encountered so rarely that it cannot reasonably be expected to provide comprehensive evidence. In 2023, the CHMP adopted extension of the indication to include treatment of patients aged 5 years and older with HoFH based on based on data from Study R1500-CL-17100, a Phase 1b/3 single-arm, open-label study in paediatric (≥5 to <12 years) patients with HoFH, and an interim analysis of the ongoing open-label extension study, R1500-CL-1719. Additionally, an extrapolation analysis, including population pharmacokinetics (PK), population PK/pharmacodynamics (PD; population PK/PD), and simulations, based on data from multiple clinical studies was provided in support of the extension of indication to included aged 5 years and older (EMEA/H/C/005449/II/0011). These studies were performed in accordance with the PIP.

In the current application, an extension of the indication is proposed to include HoFH paediatric patients aged 6 months to less than 5 years, a population that was not considered to be needed to be investigated (waiver) according to the PIP. The primary evidence to support the use of evinacumab in this young population comes from a model-based extrapolation analysis, which was developed using population pharmacokinetics (PK) and population PK/pharmacodynamics (PD; population PK/PD) modelling and simulations (based on previously observed data in older children, adolescent, and adult patients) (R1500-PM-23202-SR-01V2 and R1500-PM-23089-SR-01V2), together with assumptions on the biological development and pathophysiological circumstances in younger children with HoFH. In

addition, supportive data is provided detailing the clinical experience of 5 paediatric patients who initiated evinacumab treatment before the age of 5 years for the treatment of HoFH, via the Ultragenyx or Regeneron compassionate use programs. This approach is considered acceptable, considering the rare nature of the disease. Therefore, a clinical trial in this very young age group is not considered feasible.

It has to be noted that evaluation of evinacumab in patients of 6 months to 5 years (proposed extension of indication) was not included in the PIP: Previously, the PDCO agreed to a waiver for patients less than 5 years of age on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible.

Extrapolation plan

The extrapolation concept has adequately been discussed by the Applicant. The extrapolation analysis took into consideration the principles as 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, which has been assessed below.

Disease similarity

It is acknowledged that the aetiology of the hypercholesterolaemia observed in patients with HoFH, i.e. mutation in key genes in lipoprotein metabolism, is the same for both adult and paediatric patients and that the overarching goal of therapy is also the same, i.e. to lower LDL-C, and subsequently the risk of ASCVD.

Similar drug pharmacology

Population PK and PK/PD models were developed in earlier applications using PK data from paediatric (≥ 5 years of age) and adult patients with HoFH (R1500-PM-23041-SR-01V1). Extrapolation simulations, performed in support of the extension of indication to paediatric patients from ≥6 months to 5 years old, predicted that regardless of the decreased exposures in paediatric patients, LDL-C reductions were simulated to be comparable between paediatric patients, adolescents and adults. This extrapolation study showed that patients receiving 15 mg/kg IV dosing 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. For further discussion on PK references is made to the pharmacology section.

Similar exposure response

All five paediatric patients aged < 5 years showed substantial reductions in LDL-C levels after initiating evinacumab treatment; Patient 1 had a 60.7% reduction in LDL-C at Week 16; Patient 2 had a 31.4% reduction at Week 46 and plasmapheresis frequency was reduced during the treatment period; Patient 3 had a 63.7% reduction in LDL-C at Week 46; Patient 4 had a 77.3% reduction in LDL-C at Week 16; Patient 5 had a 75.0% reduction in LDL-C at Week 12. Patient 2 a had a lower magnitude of effect compared to the other patients due to a change in frequency of apheresis treatment. Generally, the percent LDL-C reductions in these young patients with HoFH were higher than those previously reported for adults and adolescents from Study R1500-CL-1629 (47.1% at week 24) and paediatric patients aged ≥ 5 years to 11 (48.3% at week 24) from Study R1500-CL-17100, despite the lower predicted evinacumab concentrations. This observation can be explained by higher LDL-C baseline levels at younger age (22.6 mmol/L for patient 1, 11.6 mmol/L (pre-plasmapheresis) for Patient 2, 9.1

mmol/L for Patient 3, 15.3 mmol/L for Patient 4, and 6.2 mmol/L for Patient 5) compared with a mean of 6.8 mmol/L in paediatric patients aged ≥ 5 to 11 years in Study R1500-17100 and a mean of 6.61 mmol/L in adults and adolescents from Study R1500-CL-1629). Younger patients with HoFH are more likely to have higher LDL-C levels at baseline since 1) they are more often treatment naïve or receiving suboptimal lipid-lowering therapy or 2) younger individuals with HoFH often have more severe mutations in the LDLR gene (very low or no LDLR activity), which often leads to earlier clinical diagnosis due to the early presence of xanthomas or CV events.

Model-based simulations based on the previously developed population PK and PK/PD models (R1500-PM-23041-SR-01V1) predicted that the evinacumab exposures after 15 mg/kg IV administrations Q4W were lower in paediatric patients <5 years compared to paediatric patients ≥5 to <12 years. Despite these lower exposures in paediatric patients, comparable LDL-C reductions were simulated at week 24. Additional simulations with a 20 mg/kg dosing regimen predicted that while evinacumab exposures increased with 35 to 50%, the LDL-C reduction only increased by approximately 5%, indicating the steady-state evinacumab concentrations in paediatric patients were sufficient to achieve maximal target engagement. 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.

Regarding safety, no new safety concerns have been identified in the five HoFH patients aged 6 months to 5 years that received evinacumab via the compassionate use program. However, firm conclusions cannot be made due to the very limited data in terms of number of patients, treatment duration, and the fact that that physicians were asked to report only SAE in the CUP. In support of safe use of evinacumab in very young HoFH patients aged 6 months to 5 years, the Applicant provided and discussed the results of the non-clinical reproductive and developmental toxicology study 1500-TX-17096 and the juvenile toxicology studies R1500-TX-17094, R1500-TX-18035, and R1500-TX-17093. The data of these studies have already been assessed previously during the initial MAA and revealed no specific safety concerns. Overall, treatment with evinacumab in juvenile animals was considered safe, which appears to be reassuring in terms of development and maturation toxicity, although uncertainty remains because of limited clinical data.

Moreover, the Applicant highlighted that the safety of ANGPLT3 inhibition is also supported by human genetic evidence. Individuals with ANGPTL3 LOF mutations show that long-term disruption of ANGPTL3 due to naturally occurring genetic variants is not associated with any increase in adverse clinical outcomes, or has been shown to have a negative impact on foetal or early childhood development. Furthermore, the Applicant argued that as individuals with ANGPTL3 LOF mutations experience disruption of ANGPTL3 from conception, it is reasonable to conclude, that LOF mutations in the *ANGPTL3* gene is a benign condition and therefore, it is expected that ANGPTL3 inhibition by evinacumab would pose no safety concerns (related to its mechanism of action) in any age group. However, as previously indicated by CHMP in the initial MAA, since the phenotype of patients with LOF mutations in ANGPLT3 in terms of lipid profile is not comparable with that of patients with HoFH, the data on ANGPTL3 LOF mutation can only be considered as supportive.

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 considered acceptable.

Design and conduct of clinical studies

Dose selection

The approved dosing regimen in adults and paediatric patients aged 5 years and older is 15 mg/kg IV Q4W. A model-based extrapolation analysis was performed to predict the PK of evinacumab and associated LDL-C reduction in a virtual population of patients aged 6 months to 5 years with HoFH based on previously observed data in older children, adolescent, and adult patients, an integrated population PK and PK/PD model, and assumptions on the biological development and pathophysiological circumstances in younger children with HoFH. These model-based simulations predicted lower evinacumab exposures with the 15 mg/kg IV Q4W regimen in patients with a younger age and lower weight. Nevertheless, the effect on LDL-C was predicted to be comparable or even higher in the paediatric population compared with adolescent and adult HoFH patients, which is confirmed by observational data from five patients who received 15 mg/kg IV Q4W in the CUP. The relatively greater magnitude of LDL-C reduction in HoFH patients aged 6 months to < 5 years can be explained by the higher LDL-C baseline levels at younger age (see also “similar exposure response” section in the extrapolation plan above). The model-based simulations also predicted that increasing the dose to 20 mg/kg Q4W infusions in HoFH patients aged 6 months to 5 years does not provide a substantial improvement in LDL-C reduction over the 15 mg/kg Q4W dosing regimen recommended in patients ≥ 5 years of age, despite a 35-50% increase in median steady-state exposures, which is acknowledged.

Overall, it can be concluded that dose adjustment is not required in paediatric patients aged 6 months to 5 years and that the 15 mg/kg IV Q4W dose regimen is appropriate for all HoFH patients regardless of age.

Compassionate use program (CUP)

No clinical trial in this very young age group has been conducted since this is not considered feasible due to the rarity of the disease. Instead, efficacy data of five HoFH paediatric patients who started evinacumab treatment before the age of 5 years via a CUP have been provided.

To be eligible for compassionate use, patients must (1) have a serious or life-threatening disease that does not have satisfactory alternative treatment options available; (2) have a condition that does not have satisfactory alternative treatment options available or has exhausted all reasonable available therapeutic options typically used to treat the disease; and (3) be unable to participate in an ongoing clinical trial. The compassionate use program provides access to evinacumab treatment when an unsolicited request is made by an individual patient’s responsible physician after obtaining patient or caregiver consent. All compassionate use patients were treated with evinacumab 15 mg/kg/ IV Q4W.

Standard of care assessments (e.g. physical exam, total cholesterol [TC], LDL-C, other laboratory assessments, imaging, and radiological assessments) were collected according to standard practice for HoFH at each patient’s site. Similar as previous clinical studies, LDL-C was the primary efficacy parameter, which was expressed as percent change in LDL-C change from baseline over time. Within the evinacumab clinical program, LDL-C is used as a surrogate biomarker for cardiovascular risk reduction, which is acceptable as already indicated above.

Efficacy data and additional analyses

As of the initial submission of this variation in April 2024, three HoFH patients less than 5 years of age received evinacumab for the treatment of hypercholesterolaemia via CUP. During the variation procedure, further LDL-C data points were made available for two additional patients who initiated

treatment with evinacumab via the compassionate use programs (Patient 4, data available up to Week 16; and Patient 5, data available up to Week 12). The efficacy results of all five HoFH patients are described below.

Patient 1

A HoFH patient started evinacumab. This patient was not receiving any other lipid lowering medication or apheresis and the patient's LDL-C levels was 22.6 mmol/L at Day 1 (pre-dose) of evinacumab treatment. At first infusion the patient received a half dose (7.5 mg/kg; 60 mg) at the physician's discretion to ensure that the patients tolerated evinacumab after which the patients received four infusions of the proposed dose of 15 mg/kg IV Q4W. Treatment with evinacumab resulted in a substantial reduction in LDL-C of 60.7% from baseline at week 16, which corresponds to an absolute change in LDL-C of -8.9 mmol/L, which can be regarded as clinically relevant. The effect on LDL-C was further supported by a reduction in total cholesterol of 58%. During treatment with evinacumab at Week 37 and 54 there were some fluctuations in LDL-C response which was caused by not complying with the dietary recommendations. After following the dietary recommendations, treatment with evinacumab resulted in a reduction of 66.3% at Week 62, indicating maintenance of effect.

Patient 2

A HoFH patient started evinacumab. The patient was receiving plasmapheresis Q2W, rosuvastatin 20 mg/day, and ezetimibe 10 mg/day and this patient's LDL-C level was 11.6 mmol/L pre-plasmapheresis and 3.5 mmol/L post-plasmapheresis at Day 1 (pre-dose). Furthermore, the patient presented with xanthomas prior to evinacumab treatment. Treatment with evinacumab resulted in a substantial reduction in LDL-C of 51.3% from baseline at Week 38, which corresponds to an absolute change in LDL-C of -5.9 mmol/L. At Week 38 (after the 9th dose), at the discretion of the responsible physician, considering the LDL-C reductions observed at that point, the patient's plasmapheresis schedule changed from Q2W to Q4W in an attempt to increase patient compliance with treatment. This resulted in reduction in LDL-C of 31.4% from baseline at Week 46, which corresponds to an absolute change in LDL-C of -3.6 mmol/L, which can still be regarded as clinically relevant. The LDL-C lowering effect maintained up to at least Week 90 (-37.1%). The patient received treatment via compassionate use up to Week 90. Additionally, the patient's xanthomas completely resolved after approximately one year of evinacumab treatment. During evinacumab treatment, five dose interruptions occurred which resulted in elevated LDL-C values at Week 15, 21, 34, and 86. The dose interruption were considered unrelated to treatment (see safety for details). No other efficacy parameters have been provided.

Patient 3

A HoFH patient started evinacumab. The patient was receiving atorvastatin, alirocumab, and ezetimibe at the time of CUP request and the patient's LDL-C level was 9.1 mmol/L at Day 1 (pre-dose). Treatment with evinacumab resulted in a substantial reduction in LDL-C of 63.7% from baseline at Week 46, which corresponds to an absolute change in LDL-C of -5.8 mmol/L, which can be regarded as clinically relevant. No other efficacy parameters have been provided. The LDL-C lowering effect maintained up to at least Week 72 (-43.1%). The patient received treatment via compassionate use up to Week 72.

Patient 4

A HoFH patient started evinacumab. The patient presented with xanthomas on bilateral heels prior to evinacumab treatment. The patient was not receiving lipoprotein apheresis or plasmapheresis, but was receiving treatment with rosuvastatin 10 mg/day and ezetimibe 10 mg/day at baseline and the patient's LDL-C value was 15.3 mmol (590 mg/dL) at Day 1 (pre-dose). Treatment with evinacumab resulted in a substantial reduction in LDL-C of 77.3% from baseline at Week 16, which corresponds to

an absolute change in LDL-C of -11.8 mmol/L, which can be regarded as clinically relevant. No other efficacy parameters have been provided.

Patient 5

A patient started evinacumab . The patient presented with xanthomas on the left gluteal region and left knee prior to evinacumab treatment. The patient was not receiving lipoprotein apheresis or plasmapheresis, but was receiving treatment with rosuvastatin 20 mg/day, and ezetimibe 10 mg/day and their LDL-C value was 6.2 mmol at Day 1 (pre-dose). Treatment with evinacumab resulted in a substantial reduction in LDL-C of 75.0% from baseline at Week 12, which corresponds to an absolute change in LDL-C of -4.7 mmol/L, which can be regarded as clinically relevant. No other efficacy parameters have been provided.

Overall, all five HoFH paediatric patients showed substantial reductions in LDL-C levels after initiating evinacumab treatment. Generally, the percent LDL-C reductions in these young patients with HoFH were higher than those previously reported for adults and adolescents from Study R1500-CL-1629 (47.1% at week 24) and paediatric patients aged ≥ 5 years to 11 (48.3% at week 24) from Study R1500-CL-17100, despite the lower predicted evinacumab concentrations. This observation can be explained by higher LDL-C baseline levels at younger age (22.6 mmol/L for Patient 1, 11.6 mmol/L (pre-plasmapheresis) for Patient 2, 9.1 mmol/L for Patient 3, 15.3 mmol/L for Patient 4, and 6.2 mmol/L for Patient 5) compared with a mean of 6.8 mmol/L in paediatric patients aged ≥ 5 to 11 years in Study R1500-17100 and a mean of 6.61 mmol/L in adults and adolescents from Study R1500-CL-1629). Nevertheless, very limited efficacy (and safety) data is available in support of the proposed HoFH paediatric population of 6 months to 5 years of age.

2.5.5. Conclusions on the clinical efficacy

In the CUP, all five HoFH patients showed substantial reductions in LDL-C levels after treatment with evinacumab: Patient 1 had a 60.7% reduction in LDL-C at Week 16; Patient 2 had a 31.4% reduction at Week 46 and plasmapheresis frequency was reduced from Q2W to Q4W during the treatment period; Patient 3 had a 63.7% reduction in LDL-C at Week 46; Patient 4 had a 77.3% reduction in LDL-C at Week 16; Patient 5 had a 75.0% reduction in LDL-C at Week 12. Data up to Week 62, 90, and 72 were available for Patient 1, Patient 2 and Patient 3, respectively, which showed maintenance of effect. Generally, the % LDL-C reductions in these young patients with HoFH were higher than those previously reported for adults and adolescents, which can be explained by higher LDL-C baseline levels. Additionally, in one patient resolution of xanthomas was reported.

Nevertheless, very limited efficacy (and safety) data are available in support of the proposed HoFH paediatric population of 6 months to 5 years of age. The evidence for this application mainly relies on extrapolation of data from the adult and paediatric patients aged 5 years and older population thereby using model-based extrapolation analysis, particularly in terms of HoFH patients aged less than 1 year since no clinical data is available for these patients.

2.6. Clinical safety

Introduction

The safety profile of evinacumab was established based on the data obtained from paediatric patients ≥ 5 years of age, adolescents, and adults from the clinical development program. For this application,

supportive safety information is provided from five paediatric patients who initiated treatments with evinacumab before the age of 5 years through compassionate use.

For all patients being treated under the compassionate use agreements, the applicant required responsible physicians to submit notifications of all SAEs and pregnancies to the applicant and to relevant health authorities per local regulations.

Physicians were asked to provide seriousness, causality, and expectedness assessments for each reported SAE. SAE reports had to be as complete as possible, at minimum including the SAE term(s); patient identifier; seriousness criteria; date of event onset; causality assessment (causal relationship between the Medicinal product and the event); and expectedness assessment per the evinacumab Investigator's Brochure (version applicable at the time of onset) for each reported SAE term and Medicinal product; and name of the reporter (Physician). Information not available at the time of the initial report was to be documented in a follow-up report. Additional information included SAE stop date(s), outcome for each reported SAE, dates when medicinal product was first received and the last dose prior to event onset, and action taken with medicinal product as a result of the SAE.

Patient exposure

Five patients < 5 years of age have been treated with evinacumab 15 mg/kg Q4W via compassionate use. Results of clinical monitoring, including safety information, is available up for Patient 1 up to ~62weeks, Patient 2 up to ~90 weeks, and Patient 3 up to ~72 weeks. Both Patient 2 and Patient 3 received treatment via compassionate use up to Week 90 and Week 72, respectively. During the variation procedure, further efficacy and safety data have been made available for two additional patients who initiated treatment with evinacumab via the compassionate use programs (Patient 4, data available up to Week 16; and Patient 5, data available up to Week 12).

Adverse events

Patient 1

No SAEs have been reported for this patient.

Patient 2

No SAEs have been reported for this patient.

Additionally, three events that were not considered as SAEs were mentioned by the responsible physician via informal channels. The patient complained of infrequent brief episodes of generalized abdominal pain with no associated symptoms. The event was not considered related to evinacumab treatment by the responsible physician/clinical team. On another occasion, the patient had an episode of vomiting during treatment (the patient received both evinacumab and plasmapheresis at this visit) and evinacumab infusion was stopped. Following both events, evinacumab treatment resumed as scheduled; subsequent evinacumab treatments occurred without recurrence of symptoms. Finally, the responsible physician noted the patient had progressive iron-deficient anemia. As long-term plasmapheresis can also cause iron deficiency anemia (Medical Advisory Secretariat, 2007; Compton et al., 2018), the applicant considers this event related to plasmapheresis treatment.

Patient 3

No SAEs have been reported for this patient.

Patient 4

No SAEs have been reported for this patient.

Patient 5

No SAEs have been reported for this patient.

Post marketing experience

As of the last Evkeeza Periodic Safety Update Report (PSUR) #6 (covering the period 12 August 2023 to 11 February 2024, the data cut-off for the report), no safety signals were identified, ongoing, or closed. There were no changes to the important identified or potential risks for Evkeeza and there was no new significant information relevant to the safety concerns of embryofoetal toxicity, safety of long-term use [e.g., > 2 years], or use in pregnant or breastfeeding women). The PRAC Recommendation was received on 06 September 2024; PRAC considers that the risk-benefit balance of medicinal products containing evinacumab remains unchanged and therefore recommends the maintenance of the marketing authorisation of Evkeeza.

Cumulatively through 11 February 2024, there were five post-marketing cases involving patients < 18 years of age, as summarized below. Of the five paediatric cases, none were serious. Two cases were associated with off-label use in population younger than the age approved at the time of reporting and no AEs were reported. The remaining three cases involved non-serious events, four expected and three unexpected events.

There was one case in a patient < 5 years of age:

- A literature case from North America involving product use in a patient who experienced abdominal pain while using Evkeeza 15 mg/kg for HoFH. Medical history included xanthomas. Concomitant medications included an unspecified statin and ezetimibe and treatment with plasmapheresis. After 3 months of Evkeeza treatment, the patient experienced unexplained intermittent abdominal pain, and treatment with Evkeeza was temporarily interrupted and outcome was not provided. The abdominal pain was considered non-serious and possibly related to Evkeeza. Abdominal pain is an expected event for Evkeeza.

There were four cases in patients aged 5 to < 18 years:

- One literature case from Europe involved a 10-year-old patient who underwent an allogeneic hematopoietic stem cell transplant (HSCT) for acute lymphoblastic leukaemia. This patient used Evkeeza off-label for life-threatening refractory hypertriglyceridemia due to the concomitant use of ruxolitinib and sirolimus for chronic graft-versus-host disease (GVHD). No other AEs were reported.
- One case involved a patient who used Evkeeza -off label for familial hypercholesterolaemia and experienced product leakage out of the tubing and therefore only received a partial dose since the infusion was stopped (non-serious events). No other AEs were reported.
- One case involved a patient who was treated with Evkeeza for HoFH (unknown dose, once a month) and experienced non-serious events of pain (onset unknown, outcome unknown), vomiting (onset unknown, outcome resolved), nausea (occurring same day post infusion and a day after, outcome unknown), upper abdominal pain (occurring same day post infusion, outcome unknown) and hypersomnia (occurring same day post infusion, outcome unknown). No information regarding patient's medical history or concomitant medications was provided. Causality for all reported events was

assessed as related to drug. The events of nausea and upper abdominal pain are expected for Evkeeza and the events of pain and hypersomnia are unexpected.

- One case involved a patient who was treated with Evkeeza for HoFH (unknown dose and frequency) experienced non-serious events of body aches (onset unknown, outcome unknown) and nausea (onset unknown, outcome unknown). No information regarding patient's medical history or concomitant medications was provided. Causality for both events was assessed as related to drug. The event of nausea is expected for Evkeeza and the event of body aches is unexpected.

Based on available post-marketing data, there have been no significant differences seen in the safety profile of Evkeeza in the paediatric population compared to the adult population.

The safety profile of Evkeeza is accurately reflected in the Summary of Product Characteristics (SmPC) and no changes to the SmPC are deemed necessary based on data available as of the last reporting interval (12 August 2023 to 11 February 2024) and in the context of the cumulative experience to date.

A comprehensive analysis of information collected during the last reporting interval (12 August 2023 to 11 February 2024) in the context of cumulative efficacy and safety data confirms the positive benefit-risk profile of evinacumab. The safety profile of evinacumab will continue to be monitored via routine pharmacovigilance.

2.6.1. Discussion on clinical safety

The safety profile of evinacumab was established based on the data obtained from paediatric patients ≥ 5 years of age, adolescents, and adults from the clinical development program. Since the start of the clinical development program for evinacumab, a total of 243 patients have been treated with any IV dose of evinacumab in either placebo-controlled or open-label trials. 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. Generally, evinacumab displays an acceptable safety profile in adults and paediatric patients aged 5 years and older with HoFH, with very few patients discontinuing treatment. Although, due to the limited program, uncertainties may exist and specific post-approval obligations have been imposed including follow-up of cardiovascular safety for patients ≥ 12 years of age (see further below). Based on frequency differences with placebo the following ADRs have been identified in the initial MAA application: nasopharyngitis, upper respiratory tract infection, anaphylaxis, influenza like illness, dizziness, back pain, pain in extremity, nausea, abdominal pain, constipation, rhinorrhoea, infusion related reaction, infusion site reactions and asthenia. In the previous extension of indication application to include paediatric patients aged 5 to 12 years, fatigue has been identified as a new ADR.

In addition to the previous extension of indication application, no new safety data from the clinical development program has been provided. For this application, supportive safety information is provided from five paediatric patients who initiated treatments with evinacumab before the age of 5 years through compassionate use. Results of clinical monitoring, including safety information, is available up for Patient 1 up to ~62 weeks, Patient 2 up to ~90 weeks, and Patient 3 up to ~72 weeks. During the variation procedure, further safety data have been made available for two additional patients who initiated treatment with evinacumab via the compassionate use programs (Patient 4, data available up to Week 16; and Patient 5, data available up to Week 12). In the CUP, the physicians were asked to report only SAEs and provide seriousness, causality, and expectedness assessments for each reported SAE. Based on the data in the CUP, no new safety concerns have been identified in the five patients below the age of 5 that received evinacumab. None of the five patients experienced SAEs.

One patient experienced three events (abdominal pain, nausea, and iron-deficiency anaemia) that were considered not related to evinacumab, which is reassuring.
However, firm conclusions, particularly on growth and pubertal development, cannot be made due to the very limited data in terms of number of patients, treatment duration and the fact that physicians were asked to report only SAE in the CUP. Additionally, very limited safety data are available in support of the proposed HoFH paediatric population of 6 months to 5 years of age.
In support of safe use of evinacumab in HoFH patients aged 6 months to 5 years, the Applicant provided and discussed the results of the non-clinical reproductive and developmental toxicology study 1500-TX-17096 and the juvenile toxicology studies R1500-TX-17094, R1500-TX-18035, and R1500-TX-17093. The data of these studies have already been assessed previously during the initial MAA and revealed no specific safety concerns. Overall, treatment with evinacumab in juvenile animals was considered safe, which appears to be reassuring in terms of development and maturation toxicity, although uncertainty remains because of limited clinical data.

In the clinical development program, treatment with evinacumab resulted in significant reduction in HDL-C of ~42% with HDL-C reaching below normal levels of 0.50 mmol/L. Unfortunately, data on HDL-C was not available in the CUP. The reduction in HDL-C observed in clinical studies 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 are unknown, especially since recent findings challenged a clear correlation between HDL-C targeted treatment (increase in HDL-C) and improvement in cardiovascular risk. Nevertheless, special efforts have previously been requested to evaluate the long-term safety outcomes and 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 long-term safety and the atherosclerosis process over time in patients with HoFH who are treated with evinacumab.

Further, 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 HoFH paediatric patients aged 6 months to 5 years: No new safety concerns have been identified in the five patients below the age of 5 that received evinacumab via the CUP. However, firm conclusions, particularly on growth and pubertal development, cannot be made due to the very limited data in terms of number of patients, treatment duration, and the fact that that physicians were asked to report only SAE in the CUP.

Based on the clinical development program, 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 long-term safety and the atherosclerosis process over time will be studied in patients with HoFH who are treated with evinacumab. 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 6 months to 5 years and above, which is supported.

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 with this application.

With this application the MAH initially submitted a RMP version 2.0. The proposed changes were mainly made to support the extension of indication to patients aged 6 months and older with HoFH and to reflect the expanded study population of the Category 2 post-authorisation safety study (PASS) UX858-CL401.

With the response to the RSI, the MAH submitted RMP version 2.1 (dated 05 Sep 2024). In the version the Applicant has, as requested, added "safety (including long-term) in children < 5 years of age" as topic of missing information in the summery of safety concern. Relevant parts of the RMP have been updated accordingly.

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

The PRAC considered that the risk management plan version 2.1 is acceptable. The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content:

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 Safety (including long-term) in children <5 years of age

Pharmacovigilance plan

Category 2 PASS UX858-CL401 were updated in Part III and Annexes 2 and 3 for alignment with the therapeutic indication, i.e., including all patients with a clinical and/or a genetic diagnosis of HoFH who initiated treatment with commercially available evinacumab.

The proposed update is endorsed and in line with the corresponding amendment of the PASS protocol in procedure EMEA/H/C/PSA/S/0112.

This section was also updated in line with the addition of "Safety (including long-term) in children <5 years of age" as missing information in the safety concerns.

Risk minimisation measures

This section was updated in line with the addition of "Safety (including long-term) in children <5 years

of age" as missing information in the safety concerns.

2.8. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement minor changes to sections 4.2, 4.4, 4.7 and 5.3 of the SmPC, along with editorial changes to the SmPC.

Changes are made to the Opinion Annex II conditions (description of specific obligation).

Please refer to Attachment 1 which includes all agreed 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. The MAH does not consider that the 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 ⩾6 months to <5 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 (Version 10.4, 02/2024) 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 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 hypercholesterolaemia (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, with the aim to reduce atherogenesis and subsequently to reduce 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, although none of the lipid-lowering medication is approved for treatment of children less than 5 years of age. 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 (Ezetrol SmPC). 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 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 primary evidence to support the use of evinacumab in HoFH paediatric patients aged 6 months to 5 years comes from a model-based extrapolation analysis, which was developed using population pharmacokinetics (PK) and population PK/pharmacodynamics (PD; population PK/PD) modelling and simulations (based on previously observed data in older children, adolescent, and adult patients) (R1500-PM-23202-SR-01V2 and R1500-PM-23089-SR-01V2), together with assumptions on the biological development and pathophysiological circumstances in younger children with HoFH. In addition, supportive data are provided detailing the clinical experience of five paediatric patients who initiated evinacumab treatment before the age of 5 years for the treatment of HoFH, via the Ultragenyx or Regeneron compassionate use programs.

The evaluation of evinacumab in patients of 6 months to 5 years (proposed extension of indication) was not included in the PIP: Previously, the PDCO agreed to a waiver for patients less than 5 years of age on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible.

3.2. Extrapolation

The extrapolation concept has adequately been discussed by the Applicant. The extrapolation analysis took into consideration the principles 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, which has been assessed below.

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 hypercholesterolaemia observed in patients with HoFH is the same for both adult and paediatric patients. Hypercholesterolaemia 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

Population PK and PK/PD models were developed in earlier applications using PK data from paediatric (≥ 5 years of age) and adult patients with HoFH (R1500-PM-23041-SR-01V1). Extrapolation simulations, performed in support of the extension of indication to paediatric patients from ≥6 months to 5 years old, predicted that regardless of the decreased exposures in paediatric patients, LDL-C reductions were simulated to be comparable between paediatric patients, adolescents and adults. This extrapolation study showed that patients receiving 15 mg/kg IV dosing 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.

Similar exposure response

All five paediatric patients aged < 5 years showed substantial reductions in LDL-C levels after initiating evinacumab treatment; Patient 1 had a 60.7% reduction in LDL-C at Week 16; Patient 2 had a 31.4% reduction at Week 46 and plasmapheresis frequency was reduced during the treatment period; Patient 3 had a 63.7% reduction in LDL-C at Week 46; Patient 4 had a 77.3% reduction in LDL-C at Week 16; Patient 5 had a 75.0% reduction in LDL-C at Week 12. Patient 2 had a lower magnitude of effect compared to the other patients due to a change in frequency of apheresis treatment. Generally, the percent LDL-C reductions in these young patients with HoFH were higher than those previously reported for adults and adolescents from Study R1500-CL-1629 (47.1% at week 24) and paediatric patients aged ≥ 5 years to 11 (48.3% at week 24) from Study R1500-CL-17100, despite the lower predicted evinacumab concentrations. This observation can be explained by higher LDL-C baseline levels at younger age (22.6 mmol/L for patient 1, 11.6 mmol/L (pre-plasmapheresis) for patients 2, 9.1 mmol/L for patient 3, 15.3 mmol/L for patient 4, and 6.2 mmol/L for patient 5) compared with a mean of 6.8 mmol/L in paediatric patients aged ≥ 5 to 11 years in Study R1500-17100 and a mean of 6.61 mmol/L in adults and adolescents from Study R1500-CL-1629). Younger patients with HoFH are more likely to have higher LDL-C levels at baseline since 1) they are more often treatment naïve or receiving suboptimal lipid-lowering therapy or 2) younger individuals with HoFH often have more severe mutations in the LDLR gene (very low or no LDLR activity), which often leads to earlier clinical diagnosis due to the early presence of xanthomas or CV events.

Model-based simulations based on the previously developed population PK and PK/PD models (R1500-PM-23041-SR-01V1) predicted that the evinacumab exposures after 15 mg/kg IV administrations Q4W were lower in paediatric patients <5 years compared to paediatric patients ≥5 to <12 years. Despite

these lower exposures in paediatric patients, comparable LDL-C reductions were simulated at week 24. Additional simulations with a 20 mg/kg dosing regimen predicted that while evinacumab exposures increased with 35 to 50%, the LDL-C reduction only increased by approximately 5%, indicating the steady-state evinacumab concentrations in paediatric patients were sufficient to achieve maximal target engagement. 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.

Regarding safety, no new safety concerns have been identified in the five HoFH patients aged 6 months to 5 years that received evinacumab via the compassionate use program. However, firm conclusions cannot be made due to the very limited data in terms of number of patients, treatment duration, and the fact that that physicians were asked to report only SAE in the CUP. In support of safe use of evinacumab in very young HoFH patients aged 6 months to 5 years, the Applicant provided and discussed the results of the non-clinical reproductive and developmental toxicology study 1500-TX-17096 and the juvenile toxicology studies R1500-TX-17094, R1500-TX-18035, and R1500-TX-17093. The data of these studies have already been assessed previously during the initial MAA and revealed no specific safety concerns. Overall, treatment with evinacumab in juvenile animals was considered safe, which appears to be reassuring in terms of development and maturation toxicity, although uncertainty remains because of limited clinical data.

Moreover, the Applicant highlighted that the safety of ANGPLT3 inhibition is also supported by human genetic evidence. Individuals with ANGPTL3 LOF mutations show that long-term disruption of ANGPTL3 due to naturally occurring genetic variants is not associated with any increase in adverse clinical outcomes,or has been shown to have a negative impact on foetal or early childhood development. Furthermore, the Applicant argued that as individuals with ANGPTL3 LOF mutations experience disruption of ANGPTL3 from conception, it is reasonable to conclude, that LOF mutations in the *ANGPTL3* gene is a benign condition and therefore, it is expected that ANGPTL3 inhibition by evinacumab would pose no safety concerns (related to its mechanism of action) in any age group. However, as previously indicated by CHMP in the initial MAA, since the phenotype of patients with LOF mutations in ANGPLT3 in terms of lipid profile is not comparable with that of patients with HoFH, the data on ANGPTL3 LOF mutation can only be considered as supportive.

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 considered acceptable.

3.3. Favourable effects

Efficacy parameters. The evaluation of efficacy is based on data obtained from five HoFH paediatric patients aged < 5 years via a CUP. Treatment with evinacumab resulted in a substantial reduction in LDL-C in all these patients.: Patient 1 had a 60.7% reduction in LDL-C at Week 16; Patient 2 had a 31.4% reduction at Week 46 and plasmapheresis frequency was reduced during the treatment period; Patient 3 had a 63.7% reduction in LDL-C at Week 46; Patient 4 had a 77.3% reduction in LDL-C at Week 16; Patient 5 had a 75.0% reduction in LDL-C at Week 12. Data up to Week 62, 90, and 72 were available for Patient 1, Patient 2, and Patient 3, respectively, which showed maintenance of effect. Generally, the percentage of LDL-C reductions in these young patients with HoFH were higher than those previously reported for adults and adolescents, which can be explained by higher LDL-C baseline

levels. In patient 1, the effect on LDL-C was further supported by a reduction in total cholesterol of 58%. Additionally, in one patient, resolution of xanthomas was reported.

3.4. Uncertainties and limitations about favourable effects

Population. Very limited efficacy (and safety) data is available in support of the proposed HoFH paediatric population of 6 months to 5 years of age.

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.

3.5. Unfavourable effects

Adverse events. None of the five patients experienced SAEs. One patient experienced three events (abdominal pain, nausea, and iron-deficiency anaemia) which were considered not related to evinacumab.

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

3.6. Uncertainties and limitations about unfavourable effects

Exposure. Results of clinical monitoring, including safety information, is available up to ~62 weeks, up to ~90 weeks, and to ~72 weeks for three patients. Further safety data have been made available for up to 16 weeks and up to 12 weeks for two additional patients.

HDL-C. No data on HDL-C of the five patients in the CUP was available. In the clinical development program, treatment with evinacumab resulted in significant reduction in HDL-C of ~42% with HDL-C reaching below normal levels of 0.50 mmol/L. This reduction 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

Not applicable

3.8. Benefit-risk assessment and discussion

3.8.1. Importance of favourable and unfavourable effects

Homozygous familial hypercholesterolaemia (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 HoFH 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). As available lipid lowering therapies provide only limited efficacy in HoFH, 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 HoFH > 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, since the level of evidence in terms of efficacy and safety was considerably less than what would normally be required for a standard approval. A non-interventional post-authorisation safety study (PASS) was requested to be conducted to have some confirmatory understanding on the cardiovascular implications of treating these patients with evinacumab. In 2023, the indication was extended to adult and paediatric patients aged 5 years and older with HoFH.

In the current application, an extension of the indication is proposed to include HoFH paediatric patients aged 6 months to less than 5 years. The primary evidence to support the use of evinacumab in this young population comes from a model-based extrapolation analysis. In addition, supportive data of five paediatric patients, who initiated evinacumab treatment before the age of 5 years for the treatment of HoFH, via a CUP is provided. This approach is considered acceptable, considering the rare nature of the disease and that therefore a clinical trial in this very young age group is not considered feasible. It has to be noted that evaluation of evinacumab in patients of 6 months to 5 years (proposed extension of indication) was not included in the PIP: Previously, the PDCO agreed to a waiver for patients for 5 years of age.

Overall, the five HoFH patients in the CUP showed that treatment with evinacumab resulted in substantial reductions in LDL-C of 31.4% to 77.3%. One patient (31.4%) a had a lower magnitude of effect compared to the other patients (60.7-77.3%) due to a change in frequency of apheresis treatment. 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 higher than those previously reported for adults and adolescents from Study R1500-CL-1629 (47.1% at week 24) and paediatric patients aged ≥ 5 years to 11 (48.3% at week 24) from Study R1500-CL-17100, despite the lower predicted evinacumab plasma concentrations. This observation can be explained by higher LDL-C baseline levels at younger age. Regarding safety, evinacumab displays an acceptable safety profile in HoFH paediatric patients aged 6 months to 5 years, with no new safety concerns have been identified in the five patients below the age of 5 that received evinacumab via the CUP. However, firm conclusions, particularly on growth and pubertal development, cannot be made due to the very limited data in terms of number of patients, treatment duration and the fact that physicians were asked to report only SAEs in the CUP. Furthermore, very limited efficacy and safety data are available in support of the proposed HoFH paediatric population of 6 months to 5 years of age. Therefore, as also indicated by the Applicant, the evidence for this application mainly relies on extrapolation of data from the adult and paediatric patients aged 5 years and older population thereby using model-based extrapolation analysis, particularly in terms of HoFH patients aged less than 1 year since no clinical data is available for these patients.

There are several considerations that justify the overall approach to extrapolate efficacy from older populations as 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 pediatric extrapolation*" (EMA/CHMP/ICH/205218/2022). These include demonstration of similarity of disease, the pharmacology of the drug and the response to therapy as well as the safety of use in all relevant population, which has been adequately justified based on the totality of data in the submitted dossier.

3.8.2. Balance of benefits and risks

The benefit comes from the model-based approach of extrapolating efficacy from older populations including both paediatric and adult patients in accord with the respective guidelines suggesting for comparable efficacy despite some lower exposure in comparison to adults. Further, substantial efficacy was observed in a limited number of five patients confirming on external validity of the model. No new safety issues were identified in the five patients investigated through a CUP program, although such data are limited. Nevertheless, based on the totality of data, the safety profile can be considered acceptable for the entire proposed and already registered population, despite remaining uncertainties, e.g. long term CV safety for which a PASS is ongoing.

Overall, the benefit-risk balance is positive for extending the indication with patients aged 6 months and older, although uncertainties remain, and further data will be provided post-approval to address these as best as possible.

3.8.3. Additional considerations on the benefit-risk balance

Not applicable

3.9. Conclusions

The overall benefit-risk of evinacumab for paediatric HoFH patients aged 6 months and older 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 accepted		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 for EVKEEZA to include the treatment of paediatric patients with homozygous familial hypercholesterolaemia aged 6 months to less than 5 years, based on the results of population PK and population PK/PD model-based extrapolation reports (R1500-PM-23202-SR-01V2 and R1500-PM-23089-SR-01V2). 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 2.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement minor changes to sections 4.2, 4.4, 4.7 and 5.3 of the SmPC, along with editorial changes to the SmPC.

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

Amendments to the marketing authorisation

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0087/2023 and the results of these studies are reflected in the SmPC and, as appropriate, the Package Leaflet.

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 ‘Evkeeza-H-C-005449-II-0015’

Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 14 November 2024

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 29 November 2024. 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 29 November 2024. 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 29 November 2024.