22 April 2021
EMA/250315/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Evkeeza

International non-proprietary name: evinacumab

Procedure No. EMEA/H/C/005449/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANGPTL3	angiopoietin-like 3
ApoB	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUClast	Area under the concentration-time curve to last measurement
AUC$_T$	Area under the concentration-time curve to end of dosing
AUC$_T$(ss)	Area under the concentration-time curve at steady state to end of dosing
AUCtau	Area under the concentration-time curve calculated during the dosing interval
CAD	Coronary artery disease
CDRs	complementary-determining regions
CH	constant region of heavy chain
CHO	Chinese hamster ovary
CI	Confidence interval
cIMT	Carotid intima-media thickness
CK	Creatine kinase
CL	constant region of light chain
Cmax	Peak concentration
CNS	Central nervous system
CoA	certificate of analysis
CPP	critical process parameter
CQA	critical quality attribute
Ctrough	Last concentration in dosing interval
CV	column volume
CVD	Cardiovascular disease
DALA	Drug abuse liability assessment

DBTP	Double-blind treatment period
DP	Drug product
DTL	Drug tolerance limit
ECG	Electrocardiogram
EL	Endothelial lipase
ELISA	Enzyme-linked immunosorbent assay
F0	Maternal animals
F1	Offspring
FDS	formulated drug substance
GD	Gestation day
GHS	Geisinger Health System
GLP	Good Laboratory Practices
GMP	good manufacturing practices
GPP	general process parameters
GQA	general quality attributes
HbA1c	Glycosylated haemoglobin
HDL-C	High Density Lipoprotein Cholesterol
HeFH	Heterozygous familial hypercholesterolemia
His6	Hexahistidine
His10	Decahistidine
HoFH	homozygous familial hypercholesterolemia
ICH	International Conference on Harmonisation
IPC	in-process control
ITT	Intent-to-treat
IV	Intravenous
KD	Equilibrium dissociation constant
LD	Lactation day
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LDLRAP1	Low-density lipoprotein receptor adaptor protein 1
LLT	Lipid-lowering treatment
LOF	Loss of function

LoQ	list of questions
LPL	lipoprotein lipase
LS	Least squares
MCB	master cell bank
mFc	Mouse Fcγ domain
mmh	Myc-myc-hexahistidine
MMRM	Mixed-model repeated measures
MRHD	Maximum recommended human dose
MW	molecular weight
NCA	Noncompartmental analysis
NOAEL	No-observed-adverse-effect level
OLE	Open-label extension
OLTP	Open-label treatment period
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PK	Pharmacokinetics
PMM	Pattern mixture model
PND	Postnatal day
PPQ	process performance qualification
PT	Preferred term
QW	Once weekly
Q4W	Every 4 weeks
SBTP	Single-blind treatment period
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SMQ	Standard MedDRA query
SPR	surface plasmon resonance
TC	Total cholesterol
TCR	Tissue cross reactivity
TEAE	Treatment-emergent adverse event
TG	Triglycerides

TK	Toxicokinetics
TMC	Target-mediated clearance
TSE	transmissible spongiform encephalopathy
UKB	UK Biobank
ULN	Upper limit of normal
VH	variable region of heavy chain
VL	variable region of light chain
VLDL	Very low-density lipoprotein
VLDL-C	Very low-density lipoprotein cholesterol
WCB	working cell bank
WFI	water for injections

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Regeneron Ireland Designated Activity Company (DAC) submitted on 23 July 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Evkeeza, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 September 2019.

The applicant applied for the following indication: treatment of homozygous familial hypercholesterolemia (HoFH).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMEA-C1-002298-PIP01-17-M01 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0105/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

Applicant's request(s) for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active substance status

The applicant requested the active substance evinacumab contained in the above mentioned medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 March 2017	EMEA/H/SA/3489/1/2017/III	*Dr Amany N. El-Gazayerly and Dr Angeles Alonso*

The applicant received Scientific Advice on 23 March 2017 (EMEA/H/SA/3489/1/2017/III) for the development of an anti-ANGPTL3 monoclonal antibody intended for treatment of homozygous familial hypercholesterolemia. The Scientific Advice pertained to the following pre-clinical and clinical aspects:

- Appropriateness of envisaged toxicology programme
- Need for combination toxicology studies
- Need for a thorough QT study
- Need for drug-drug interaction studies
- Need for renal or hepatic impairment studies
- Pivotal phase 3 efficacy and safety study design: study duration, study population, sample size, primary and secondary efficacy endpoints, statistical analysis, need for active comparator
- Dose selection
- Safety database
- Evidentiary considerations for broadening the indication to patients with refractory hypercholesterolemia regardless of its genetic basis

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Alar Irs

The application was received by the EMA on	23 July 2020
Accelerated Assessment procedure was agreed-upon by CHMP on	25 June 2020
The procedure started on	10 September 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	10 November 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	16 November 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	18 November 2020
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their	

assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 November 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	8 December 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 January 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	18 February 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	23 February 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	2 March 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	18 March 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on (reverted to standard TT)	25 March 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	30 March 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 April 2021
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	20 April 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Evkeeza on	22 April 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The Applicant has submitted a Marketing Authorisation Application (MAA) for evinacumab (Evkeeza).

Evinacumab is proposed for use as an adjunct to diet and other low-density lipoprotein cholesterol (LDL-C) lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolemia (HoFH).

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

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

Mutations in LDLR are classified into the following subtypes:

1. "Null/null" where little to no LDL binding and uptake activity exists (<15% LDLR activity)

2. Genotypically "negative/negative" where mutations in stop codons, frame shifts, splice site changes, small and large insertions/deletions, and copy number variations (CNVs) result in the loss of function of both LDLR alleles

3. Genotypically "defective" where missense mutations (hypomorphs) result in diminished LDLR activity (>15% LDLR activity).

2.1.2. Epidemiology

The proposed target population for evinacumab is patients with HoFH (homozygous familial hypercholesterolaemia). HoFH is a rare (~1 in 300,000 in the EU) and life-threatening genetic condition resulting in severely elevated LDL-C (> 13mmol/L) from birth and premature cardiovascular disease (CVD). If left untreated, HoFH patients rarely live past the first or second decade of life. Moreover, even with the currently available lipid-lowering therapies, many patients still do not reach their target LDL-C goal and consequently are still at high risk for a CVD event. In a recent retrospective study in Italian patients with HoFH, 22% of the patients had a CVD event before age 20, and 16.7% died before age 21, despite starting lipid-lowering treatments early (Stefanutti 2019).

2.1.3. Biologic features

Regardless of the underlying mutations, this disorder is characterised by a markedly elevated plasma LDL cholesterol 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).

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2.1.4. Clinical presentation, diagnosis

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

2.1.5. Management

Attempts to lower cholesterol levels often require multiple lipid-lowering drugs and LDL apheresis. Despite these therapies, a majority of patients with this disorder do not reach guideline-recommended LDL cholesterol levels. Patients with HoFH are often treated with multiple lipid-lowering treatments (LLTs) including statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, ezetimibe, lomitapide, 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 pediatric population.

Statin therapy is the cornerstone treatment for LDL-C lowering and causes a 15-30% reduction in LDL-C in patients with HoFH. When ezetimibe is added to a statin, LDL-C reduces by 20%-27% compared to statin alone in patients with HoFH; nevertheless, it is acknowledged that HoFH patients treated with a high dose statin and ezetimibe likely remain far from their LDL-C goal.

Other lipid-lowering therapies, such as PCSK9 inhibitors could be used as well. 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.

Another available drug for HoFH is lomitapide, a selective inhibitor of microsomal transfer protein (MTP). Lomitapide causes reductions in LDL-C of 40%; however, optimal lomitapide treatment is limited by tolerability issues of gastrointestinal adverse events. Also, long-term safety, including, e.g. effects on the liver, is still uncertain.

Despite intensive drug therapy, most of the patients with HoFH cannot achieve their treatment LDL-C goal. Therefore, apheresis is an important adjunctive treatment for HoFH; a single treatment reduces LDL-C by 55%-70% relative to pre-treatment levels. However, apheresis may be burdensome, and its availability is limited. Also, only a temporal reduction in LDL-C is achieved.

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

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

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 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 is a new class of drug with a novel mechanism of action. 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 proposed for use as an adjunct to diet and other low-density lipoprotein cholesterol (LDL-C) lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolemia (HoFH).

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).

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the following conclusions.

"It was acknowledged that evinacumab is a medicinal product of major public health interest since the unmet medical need for additional lipid-lowering therapy in patients with HoFH might be fulfilled with evinacumab. It has sufficiently been made clear that here are currently available therapies do not satisfactory treatments reduce LDL-C levels (and consequently CV risk) for these patients, especially for those with null/null or negative/negative mutations for which LDLR dependent therapies show no to minimal benefit.

Evinacumab has a new mechanism of action, which is independent of the presence of LDLR. Evinacumab is a fully human monoclonal antibody against ANGPTL3, which plays a role in the regulation of lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL). Evinacumab leads to a reduction in LDL-C independent of the presence of an LDLR by promoting very low-density (VLDL) processing and clearance, thereby reducing the VLDL pool available to generate LDL-C, although the exact mechanism of the increased processing and clearance of VLDL remains undefined. Considering that 90% of the patients with HoFH have mutations in the LDLR gene in which LDLR dependent lipid-lowering therapies have no or minimal effect, this new LDLR independent pathway provides a new therapeutic innovation in the management of persistent elevated LDL-C in patients with HoFH. The MAA relies on the results of the pivotal placebo-controlled double-blind phase 3 study that consists of a 24-week double-blind treatment period and a 24-week open-label treatment period to evaluate treatment of evinacumab in 65 patients with HoFH. The design of the study appears appropriate to establish the LDL-C lowering effect of evinacumab in patients with HoFH. The sample size of 65 patients, of which 43 patients are treated with evinacumab can be considered limited, however, could be acceptable based on the rarity of the disease. Further, the 24 weeks double-blind placebo-control treatment period could be acceptable in this particular population of high unmet need. Single-arm open-label safety data have been evaluated for an additional 24 weeks, which may be regarded as limited but follows SAWP advice and general ICH requirements. Longer-term safety data will be generated during MAA, with an ongoing phase 3 single-arm open-label extension study.

In this pivotal phase 3 study, evinacumab seems to further reduce LDL-C levels by ~50% beyond that what can be achieved with current therapy, including apheresis. This substantial reduction in LDL-C was achieved regardless of the type of genetic mutations and background lipid-lowering therapy. The primary endpoint of LDL-C is a valid surrogate for cardiovascular risk reduction in line with the EMA guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/338966/2016). Due to the rarity of the disease, any long term CV outcome study seems not feasible, and one has to rely on surrogate parameters as LDL-C to provide some estimation of the possible effects. In line with previously approved therapies for HoFH, such an approach would be justified considering the very high cardiovascular risk for whom in these patients in line with previously approved therapies for HoFH and considering population seems not feasible because of the limited number of patients. A positive clinical outcome in HoFH patients by LDL-C lowering is supported by two retrospective studies showed that lipid-lowering therapy is associated with reduced risk for CV morbidity and mortality in patients with HoFH (Raal, 2011 and Thompson,2018). Moreover, large population-based studies revealed individuals with loss of function (LOF) mutations in ANGPTL3 have a lower risk of coronary artery disease (CAD) compared with non-carriers (Dewey, 2017), although this effect was marginal. Efficacy in LDL-C was supported by significant improvements in other parameters of the cholesterol profile, i.e. TC, ApoB, non-HDL-C. However, treatment with evinacumab also resulted in a 30% reduction in HDL-C at week 24 of which the impact on reverse cholesterol transport and atherosclerosis and subsequently risk for CVD events is uncertain. Despite this consideration, the LDL-

C treatment effect with evinacumab as based on the presented data is substantial and could likely outweigh the observed effect on HDL-C, although this may be subject for discussion during the MAA.

Overall, evinacumab is considered a medicinal product of major public health interest as it addresses a substantial unmet medical need and provides a therapeutic innovation for the management of LDL-C in patients with HoFH with the expectation of reduction of the very high cardiovascular risk. Further, the available efficacy and safety database seems limited but generally sufficient for the evaluation of the benefit/risk of evinacumab in the proposed indication, although some uncertainties have been identified, which includes the undefined mechanism of action, the lack of long term efficacy and safety data, a possible treatment-related serious event of anaphylaxis and the observed substantial reduction in HDL-C in HoFH patients treated with evinacumab. Nevertheless, it is not considered that these issues should withhold the current request, especially if these issues can appropriately be addressed during MAA."

However, during the assessment of this application the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as major objections have been identified that could not be handled in an accelerated timetable.

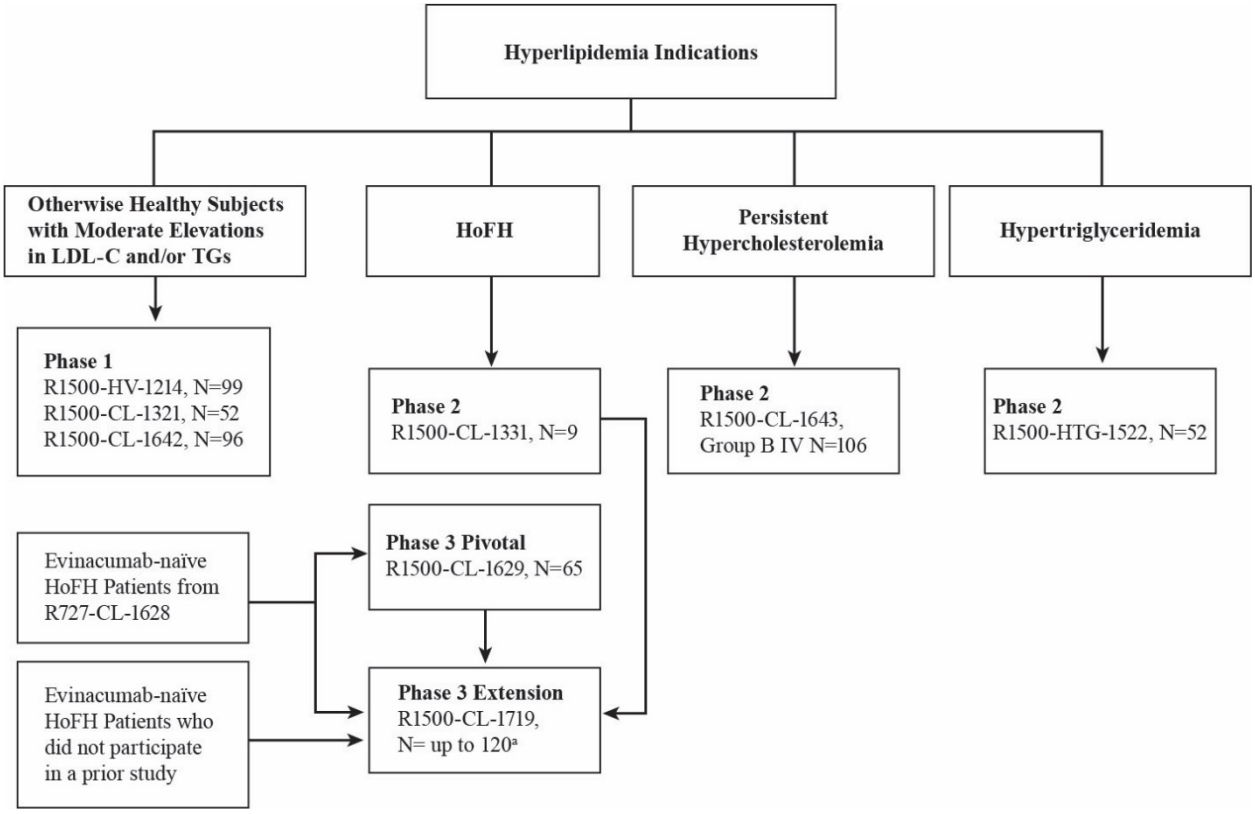
The applicant did not request consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of the above mentioned Regulation. However, as comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances was proposed by the CHMP after having consulted the applicant because the applied for indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence.

The development programme/compliance with CHMP guidance/scientific advice

Development programme

An overview of the phase 1, 2 and 3 studies in the evinacumab clinical program that is the basis of this application, is presented below. This figure shows the clinical studies in each phase for the target HoFH indication and other potential indications under evaluation and includes the total number of patients in the study and the number of patients exposed to evinacumab; these numbers reflect actual numbers for completed studies and planned numbers for studies that are ongoing. The phase 2 and 3 studies are described further in the sections below.

Figure 1 Clinical Studies in the Evinacumab Program



HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein-cholesterol; TG = triglyceride
N = number of randomised and treated patients (ie, the safety analysis set).
[a] At the data cutoff date, study R1500-CL-1719 was ongoing and open to enrollment. A total of 64 patients had enrolled.

Scientific advice

On 7 March 2017, the Applicant had a Scientific Advice meeting with the Scientific Advice Working Party (SAWP) of the Committee for Human Medicinal Products (CHMP) to discuss the Phase 3 HoFH study (R1500-CL-1629) and the overall development plan intended to support a marketing application. The CHMP adopted the advice proposed by the SAWP. A summary of the main points from the CHMP scientific advice is displayed below:

- The CHMP agreed that the completed chronic general toxicity and embryo-fetal development toxicity were acceptable for the MAA. However, they stated that considering the relative absence of toxicity in the chronic studies, the need for juvenile toxicity studies is not immediately apparent, and the CHMP does not recommend initiating juvenile toxicology studies unless the Applicant can justify otherwise.
- The CHMP agreed the following studies were not required to support registration:
    - drug-drug interaction studies
    - thorough QT study
    - renal or hepatic impairment studies
- The CHMP stated that the planned phase 3 HoFH study (R1500-CL-1629), could potentially support a marketing application in adults and adolescents with HoFH. Specifically, they did not

object to the duration of the controlled study, the patient population, including adolescents, sample size, the primary endpoint and statistical analysis approach, and the dose selection.

- The CHMP agreed with the proposed safety database planned in the marketing application.

Paediatric Investigation Plan

A Paediatric Investigation Plan has been agreed with the Paediatric Committee (PDCO).

Indication targeted by the PIP: Evinacumab is indicated as an adjunct to diet and other LDL-C lowering therapies for the treatment of patients with homozygous familial hypercholesterolemia (HoFH), including patients with double null/negative LDL-R mutations.

The subset of the paediatric population concerned by the paediatric development ranges from 5 years to less than 18 years of age.

Status of clinical studies:

Study 4 (R1500-CL-1629): Double-blind, randomised, placebo-controlled trial of 24 weeks to evaluate safety and efficacy of Evinacumab as an 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 (HoHF) on stable LMT, followed by a 24-week open-label treatment period to evaluate the 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). This study is completed.

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 HoHF. This study is ongoing.

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. This study is ongoing.

Date of completion of the paediatric investigation plan: May 2024.

2.2. Quality aspects

2.2.1. Introduction

The finished product Evkeeza is presented as a concentrate for solution for infusion for intravenous (IV) administration containing 150 mg/mL of evinacumab as active substance.

Other ingredients are: arginine hydrochloride, histidine hydrochloride monohydrate, proline, histidine, polysorbate 80 and water for injections (WFI).

The finished product is available in a Type I clear glass vial with an elastomeric stopper and aluminum seal cap with flip-off button. Evkeeza is supplied in two presentations as follows:

- One vial of 2.3 mL of concentrate containing 345 mg of evinacumab.
- One vial of 8 mL of concentrate containing 1,200 mg of evinacumab.

The product is to be diluted in an IV infusion bag containing sodium chloride 9 mg/mL (0.9%) or dextrose 50 mg/mL (5%) for infusion to deliver a final concentration of the diluted solution of 0.5 mg/mL to 20 mg/mL

2.2.2. Active Substance

General information

Evinacumab (INN) is a recombinant human IgG4 monoclonal antibody containing a serine-to-proline substitution within the hinge region of the Fc domain.

Evinacumab is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each covalently linked through a disulfide bond to a human kappa light chain.

Each heavy chain (453 amino acids) contains a serine-to-proline substitution at amino acid 234 (S228P, Eu numbering, designated IgG4P), within the hinge region of the Fc domain. There is a single N-linked glycosylation site (Asn303) in each heavy chain, located within the CH2 domain of the Fc constant region in the molecule. Based on the primary structure (in the absence of N-linked glycosylation), evinacumab has a molecular weight of 146.08 kDa ($C_{6480}H_{9992}N_{1716}O_{2042}S_{46}$), taking into account the formation of 16 disulfide bonds. The light chain consists of 214 amino acids.

The complementarity-determining regions (CDRs) within the heavy and light chain variable domains combine to form the binding sites of evinacumab to its target, which is angiopoietin-like 3 (ANGPTL3). Binding of evinacumab to ANGPTL3 blocks ANGPTL3 from inhibiting lipoprotein lipase (LPL) activity, which causes decreases in LDL-C and triglyceride (TG) levels i.e. evinacumab blockade of ANGPTL3 lowers TG and HDL-C by rescuing LPL and EL activities, respectively. Evinacumab leads to reduction in LDL-C independent of the presence of LDL receptor (LDLR) by promoting very low-density lipoprotein (VLDL) processing and clearance upstream of LDL formation.

Manufacture, process controls and characterisation

Manufacturer(s)

Evinacumab is manufactured at Regeneron Pharmaceuticals, Inc. (Regeneron Rensselaer), 81 Columbia Turnpike Rensselaer, NY 12144 USA. Testing sites and responsibilities are indicated. GMP compliance has been demonstrated.

Description of manufacturing process and process controls

Evinacumab is produced by a cell culture process with recombinant Chinese hamster ovary (CHO) cells that have been engineered to express evinacumab heavy and light chains. A narrative description of the cell culture process has been provided.

Evinacumab protein is expressed by the CHO cells and is secreted into the culture medium.

The unprocessed bulk is tested for mycoplasma and adventitious viruses which are controlled by acceptance criteria. The process is sufficiently controlled by in process controls (IPCs) and in-process monitoring.

The culture is harvested. The implemented controls are considered acceptable.

A narrative description of the downstream process (DSP) has been provided. The DSP represents a standard purification process for monoclonal antibodies consisting of standard chromatographic and

membrane based techniques and includes several steps ensuring adventitious agent safety. The material is finally compounded to ≥ 150 mg/mL with excipient buffer resulting in the evinacumab formulated active substance (also referred to as FDS) which is filtered and dispensed. FDS containers are stored until shipment to the finished product filling site.

Frozen bottles of FDS are shipped from Regeneron to the receiving site using validated procedures and qualified equipment under temperature-controlled conditions.

Adequate critical parameters and IPCs have been included. For some steps additional controls have been implemented (i.e. general process parameters (GPPs), general quality attributes (GQAs)), which have been included into the process flow tables as non-critical controls or monitors or are included in the process condition columns. This is considered acceptable.

Control of materials

For purchased compendial raw materials and excipients, Regeneron or a Regeneron-approved contract testing laboratory performs identity testing in addition to any tests specified in the individual raw material specification. For testing of non-compendial materials no contract laboratory is employed. Adequate safety information for biologically sourced materials has been provided in Module A.2 Adventitious Agents Safety Evaluation.

The evinacumab manufacturing process uses packed bed chromatography resins and different filters. Each lot of resin or filter received must meet the manufacturer specification and acceptance criteria as specified on the Certificate of Analysis (CoA). For resins Regeneron performs testing in accordance with in-house specifications.

The evinacumab manufacturing process uses single-use bioreactors (SUBs) containers. The source/vendor(s) of the SUBs have been provided. With regard to potential extractables and leachables a risk evaluation has been provided.

The evinacumab production cell line was developed using genetic technologies to the assurance of cell-substrate clonality and stability.

A traditional two-tiered cell banking system was established. Adventitious agent testing of Master Cell Bank (MCB) was conducted as per ICH Q5A requirements. No evidence of viral or microbial contamination was observed. A reduced adventitious agent testing of the evinacumab Working Cell Bank (WCB) was conducted compared to the MCB testing, which is considered acceptable. In addition, virus safety of WCB was also demonstrated. No evidence of viral or microbial contamination was observed.

Stability and homogeneity of the evinacumab production cell line have been evaluated by analysing cells from the master cell bank (MCB), working cell bank (WCB), and cells collected at the end of evinacumab production (end-of-production cells with appropriate methods).

New evinacumab WCBs will be manufactured from the same MCB in accordance with approved manufacturing records and using the same process steps. It is acceptable to introduce these new WCBs without regulatory filing provided successful qualification is performed as described.

Control of critical steps and intermediates

The IPC program, which includes process monitoring and verification activities to ensure that operational/performance parameters and quality attributes are maintained in a state of control with minimal risk to process and product, is considered adequate. Process parameters represent process inputs, whereas, quality attributes focus on process outputs. Determination of criticality for process parameters is based on the parameter's ability to impact any identified CQAs. CQAs and CPPs are

assigned acceptance criteria and critical action limits, respectively, in accordance with standard operating procedure (SOPs) and Regeneron policies.

Non-critical IPCs are classified as either GQAs or GPPs. Activities taken in case of excursions from acceptance criteria, critical action limits, and action limits are described. In particular, excursions from critical action limits and acceptance criteria are documented and investigated in accordance with a risk-based response strategy. This is acceptable. Non-critical IPCs are controlled by IPCs and in-process monitoring. The definition of non-critical IPCs and in-process monitoring is deemed acceptable. The action limits defined for evinacumab in-Process bioburden and endotoxin monitoring are adequate.

Process validation and/or evaluation

The validation of the evinacumab active substance manufacturing process included process performance qualification (PPQ) batches, extended hold times validation, Limit of *in vitro* cell age, column and filter (lifetime, cleaning and storage) validation, medium, feed and buffer validation, shipping validation and ongoing process verification.

Consecutive PPQ batches were manufactured and extended holds were performed for all PPQ batches. All validation criteria were met. Extended hold times during manufacturing steps were validated. Shipping validation of the FDS was performed.

Manufacturing process development

During the development of the manufacturing process and its control strategy quality by design (QbD) principles have been used. In general, the development and characterisation of the process steps is considered comprehensive.

An earlier process was used to manufacture materials used in non-clinical development as well as Phase I and II clinical trials. The commercial process was used to manufacture materials used in Phase II and III clinical trials.

A comparability study was performed in line with ICH Q5E. A process-development QA risk assessment report was provided, including a final list of preliminary QAs as well as justifications for selection. The approach is considered adequate. Any process parameter that had an impact on the final release CQA was deemed critical, in line with ICH Q8 (R2).

Characterisation

Elucidation of Structure and Other Characteristics

Characterisation of the evinacumab FDS was performed on several batches using state-of-the art methods. The selection of the FDS batches and methods used is considered adequate. Characterisation was performed extensively with a broad range of analytical techniques, including determination of primary, secondary, and tertiary structure, charge variants, purity, and potency. The characterisation of the structural aspects and biological activities is considered 'state of the art'.

Impurities

The impurities of evinacumab were divided into process- and product-related impurities. Results from leachable and extractable studies have been provided.

Process- and product-related impurities have been characterized and their control strategy described. This is considered adequate based on the characterisation studies.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The specifications for evinacumab active substance include tests for control of identity, purity and impurities, potency, and other general tests. The active substance release and shelf life specifications have been presented and discussed.

Release and shelf-life specifications for the FDS are largely identical to the specifications for the finished product.

Release and end-of-shelf-life specifications are set based on a holistic evaluation of clinical experience, safety concerns per regulations, manufacturing and clinical development data, statistical considerations derived from manufactured lots, and stability data. In general, the establishment of specifications is sufficiently justified.

Analytical methods

All analytical procedures are adequately described. Appearance, pH, osmolality, bioburden content, and endotoxin content comply with Ph. Eur. The compendial methods used to test FDS have been verified for use in accordance with USP and Ph. Eur. requirements. For non-compendial methods, clear system suitability criteria and assay validity criteria are defined. For each chromatographic or electrophoretic method, examples of chromatograms or electropherograms have been provided. The protein content is assayed by OD280 based on a fixed value of the extinction coefficient. The establishment of the coefficient has been described, and this extinction coefficient has been verified by an independent method.

Batch analysis

Release testing results for evinacumab active substance and FDS manufactured using an early manufacturing process, as well as FDS manufactured using the commercial manufacturing process have been provided. Batch-specific manufacturing details, study usage, and lot genealogy information for evinacumab manufactured via the commercial process have been presented.

Batch data has been presented for several lots. The results from the batch analysis data provided confirm the consistency of the commercial manufacturing process and the quality of the active substance.

Reference standards of materials

A two-tiered system with a primary and working reference standards (RS) has been established for evinacumab. The primary RS is used for the establishment of the working RSs and typically not used for routine testing. Qualification data demonstrated its suitability as primary RS. The qualification and stability acceptance criteria for future primary and working standards have been provided. An initial certification is applied, which is supported by annual stability testing and acceptable.

Container closure system

The container closure system (CCS) for evinacumab FDS is a bottle with a screw cap. Incoming CCS batches are sufficiently inspected, and suppliers approved and audited.

The CCS shows adequate protection against solvent loss, gas permeation, light as well as durability in shipment, taking the frozen storage condition of evinacumab FDS intro account.

Extractable and leachable studies were performed. Based on the review of data, no risk from extractables and leachables was identified.

Bovine tallow is included in the cap of the primary container. As stated, the tallow is produced according to the EMEA/410/01 rev.3 guidance.

The CCS materials are included in the Adventitious Agents Safety Evaluation and are concluded as safe.

Overall, the suitability and safety of the container closure system for use with evinacumab has been described in sufficient detail and is considered acceptable.

Evinacumab FDS is filled into the bottles, frozen and stored at the recommended storage conditions. Frozen bottles of FDS are packed on dry ice during routine shipment to the filler.

Stability

Stability studies were performed to evaluate the effects of long-term storage, temperature stress, light exposure, and freeze-thaw cycles on protein quality and to establish a shelf life, as well as recommend storage conditions for the active substance.

The evinacumab active substance stability program includes multiple batches. In line with ICH Q5C the batches were tested under long-term, accelerated and stress conditions. Furthermore, photostability, freeze-thaw cycle and forced degradation (including harsh chemical and temperature conditions) studies were performed. All acceptance criteria were met and only slight changes, possibly due to method variability, were detected. The data support the initial set

Overall, the analytical methods used are considered sufficiently sensitive and able to detect the main degradation pathways of evinacumab active substance.

Taken together, it can be concluded that the used analytical methods are sufficiently stable.

Based on the stability results the claimed shelf life for the active substance is considered acceptable.

Stability studies for the primary stability batches will continue through the final protocol time point. An adequate post-approval stability protocol has been provided, and it has been committed that all stability studies will be completed and that a minimum of one batch of evinacumab active substance will be put on long-term stability at the recommended storage condition every year that manufacturing of such batches occurs.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as a sterile, preservative free, concentrate for solution for infusion. Evkeeza finished product is supplied in vials containing 150 mg of evinacumab per ml as active substance. Other ingredients are: arginine hydrochloride, histidine hydrochloride monohydrate, proline, histidine, polysorbate 80 and water for injections (WFI). The qualitative and quantitative composition of the finished product is has been provided.

The product is available in a single-use 3 mL (345 mg, 2.3 mL extractable volume) or 20 ml (1200 mg, 8 mL extractable volume) glass (Type I) vial with a grey elastomeric stopper and a seal cap with a flip-off button.

Pharmaceutical development

The product has undergone a development process to optimize the formulation. The final commercial formulation (150 mg/mL evinacumab, histidine, arginine hydrochloride (arginine-HCl), proline, and polysorbate 80) shows adequate stability under long-term, accelerated and stress conditions.

Different fill volumes were tested for their impact on stability under stress conditions. The degradation profiles provided are comparable, demonstrating that the fill volume has no significant impact on the tested CQAs and that the research fill volume (5.0 mL fill volume in 20 mL glass vials) is comparable to the commercial fillings. Data from a formulation robustness study showed that minor variations in the excipient or evinacumab concentration or pH value does not significantly impact evinacumab quality parameters.

Overages

The evinacumab finished product does not include overages. To ensure that a 2.3 or 8.0 mL nominal volume can be delivered from the vials, there is an overfill. This is justified and appropriate.

Manufacturing process development

The selection of the final formulation of the evinacumab finished product has been sufficiently described and has been adequately justified. Multiple doses have been introduced for the new 150 mg/mL concentration. As stated, only the 345 mg and the 1,200 mg forms will be marketed.

An overview of changes implemented during the manufacturing processes has been provided. For all changes, their potential impact on the product quality was assessed. Changes in the manufacturing process between finished product forms were considered minor, with an anticipated low risk to product quality, and this can be accepted. A comparability study in line with ICH Q5E was provided demonstrating that all 150 mg/mL presentations are comparable. Also, a comparability study to the former presentation, used during clinical development, has been provided.

The manufacturing process has been described in detail. It consists of thawing/pooling/mixing, bioburden reduction filtration, sterilising filtration, aseptic filling/stoppering/capping/tray loading, and 100% visual inspection. Process parameters were adequately defined and ranked as CPPs or GPPs based on manufacturing experience gained during development or by manufacturer´s specification (e.g. filter integrity test parameters). Assigned parameter ranges were verified during PPQ testing.

Extractable and leachable studies were performed including worse-case conditions. Detected components or elements were evaluated according to ICH M7 or ICH Q3D. No unexpected extractable/leachable was found and the amounts detected in the leachable study do not raise a concern.

The container closure system has been sufficiently described. Extractable and leachable studies revealed no compounds potentially present in the finished product originating from the container closure materials at reasonable concentrations.

As to its nature evinacumab finished product cannot be finally sterilized by heat and does not include preservatives. Therefore, sterility is ensured by sterile filtration, release testing for sterility and endotoxins and container closure integrity (CCI). The vials and stoppers used are commonly employed as packaging for biotechnological products.

Compatibility

Evinacumab is administered by infusion, diluted in 0.9% sodium chloride injection or 5% dextrose infusion bags. Compatibility between the finished product and commonly used IV solutions, bags, pumps, IV sets and filters has been demonstrated under conditions expected during infusions. A microbial challenge and in-use stability study was included into the program. The data show that the

diluted evinacumab can be stored at room temperature up to 25°C for no more than 6 hours and 2°C to 8°C for no more than 24 hours.

Manufacture of the product and process controls

Manufacturer(s)

Information on the manufacturing sites used for evinacumab finished product including their responsibilities has been sufficiently provided. Sufficient GMP documentation has been provided.

Batch formula

There are two finished product forms: a 345 mg vial and a 1200 mg vial of evinacumab finished product. The finished product batch size range has been stated as number of vials for each finished product form (345 mg and 1200 mg). The batch formula for a typical batch size of each vial presentation (345 mg and 1200 mg) has been presented.

Description of manufacturing process and process controls

The evinacumab manufacturing process consists of thawing, pooling/mixing, bioburden reduction filtration, sterile filtration, aseptic filling, stoppering, capping, tray loading and 100% inspection of filled vials. The filled vials are transferred a facility where labelling and secondary packaging takes place.

A flow-diagram including incoming process components, process parameters and IPCs has been provided. Each step has been further described in sufficient detail. Process parameters and in process tests have been classified by criticality as general or critical during development. In this section only critical parameters and IPCs have been included. However, for some steps additional controls have been implemented (i.e. GPPs, GQAs), which are considered important to ensure a highly controlled state of the manufacturing process. Moreover, to have a good overview of the controls in place the GPPs and GQAs were included into section P.3.3 (flow-chart and description). The assigned ranges are considered adequate to ensure sufficient control of the manufacturing process.

No critical process parameters of IPCs have been identified for the secondary packaging which is considered adequate.

Controls of critical steps and intermediates

Critical steps during the manufacturing of the evinacumab finished product have been identified during manufacturing development. Adequate CPPs and IPCs are implemented to ensure a controlled state of the manufacturing process and of finished product quality attributes. For each process step a maximal processing time has been assigned and verified during process validation. A maximal processing time was implemented for this step based on data from the process validation runs.

Process validation and/or evaluation

The aseptic filling process was adequately validated. Container closure integrity is sufficiently controlled.

Media fills are performed to assure that the filling is operated under aseptic conditions. Data from the most recent fillings confirm that the filling line is appropriately controlled for aseptic filling of evinacumab finished product.

The validation of the evinacumab finished product was separated into two separate studies, one for each strength (1,200 mg and 345 mg). Several consecutive batches were tested in each study.

Overall, all predefined acceptance criteria were met, and the recorded data validate the assigned IPCs and CPPs set for the control of manufacturing.

Shipping validation was performed as a transport simulation qualification and as a real-world transport qualification. A brief summary has been provided, which is considered acceptable.

Product specification, analytical procedures, batch analysis

The release specifications for evinacumab finished product are largely identical to the specifications for the active substance. The finished product specifications for release and shelf life includes tests for appearance, pH, identity, potency, purity/impurities, endotoxin and sterility. The finished product release and shelf life specifications are summarised.

Some of the analytical procedures used for control testing of evinacumab finished product are also used for the active substance (appearance, colour, pH, total protein content, charge variant analysis, potency, purity and bacterial endotoxin). Specific analytical methods for the finished product cover product solution properties, identity, strength, potency, purity and performance properties.

A detailed discussion of each potential finished product impurity has been provided. The discussion includes details on the source of each impurity, actual levels of each impurity found in manufactured finished product lots, and details of the control strategy. The data are derived from in-process and release testing of the finished product PPQ lots, historical batch data from analysis of all lots produced to date, additional characterization testing of finished product lots manufactured using the commercial process, and studies performed on raw materials used in the manufacture of evinacumab.

A summary of the risk assessment for elemental impurities in line with ICH Q3D has been included. It can be concluded that the risk and the impact on patient safety associated with the presence of elemental impurities is negligible. Specific control on elemental impurities are considered not needed. This is agreed.

Upon request, the Applicant provided a risk assessment concerning the potential presence of nitrosamines in the product applying the principles outlined in the "Assessment report Procedure under Article 5(3) of Regulation EC (No) 726/2004" (EMA/369136/2020). The assessment was based on the risk factors identified within the revised EMA Questions and answers on nitrosamine impurities in human medicinal products (EMA/409815/2020). Based on this assessment the Applicant concluded that there is no risk associated with nitrosamines for Evkeeza finished product, and this conclusion can be agreed.

Analytical methods

Detailed method procedure descriptions for all analytical procedures used for release and stability testing have been provided. If the procedure is conducted according to a Pharmacopeial monograph and this monograph provides all details to reproduce the procedure, then a reference to the monograph is made. Validation and qualification information demonstrating that the non-compendial analytical procedures used for testing evinacumab finished product are suitable for their intended purpose have been provided.

Overall, the method descriptions are found acceptable and sufficiently detailed.

Batch analysis

Batch analyses from several lots have been provided and the results confirm compliance with the specifications. Overall the results comply well with the acceptance criteria and demonstrate a satisfactory batch to batch consistency.

Reference standards or materials

Reference is made to the respective active substance section, which is considered acceptable given that there is no major difference between the evinacumab active substance and finished product. A full description of the reference standard program can be found in the active substance section.

Container closure system

The evinacumab finished product CCS consists of a 3 mL or 20 mL glass vial made of Type I clear glass, compliant with Ph. Eur. <3.2.1>, a chlorobutyl stopper and a 13 mm or 20 mm aluminium seal cap with flip-off buttons. The stopper material is manufactured to comply with Ph. Eur. <3.2.9>.

The glass vial and stopper are in immediate contact with the finished product and comply with applicable compendial requirements. All components are tested in-house according to SOPs. If a qualified supplier is used a reduced panel of testing will be employed.

Extractable studies were performed and a leachable study was started and is still ongoing until the end of shelf life. No risk from extractables and leachables was identified so far. Leachables will continue to be monitored through the end of shelf life according to the leachable study protocol.

Overall, the CCS is considered to provide sufficient finished product protection against microbial contamination and adequate for long-term storage as supported by stability studies performed with identical CCS materials. The control strategy in place for the CCS qualification is adequate.

Stability of the product

A shelf life of 36 months when stored between 2-8°C and protected from light is claimed for the finished product.

Stability studies were performed in accordance with ICH recommended long-term and accelerated storage conditions. Long-term stability data are available and at the recommended storage conditions, no changes were observed.

The overall photostability analysis indicates that evinacumab finished product is photosensitive and should be protected from light during storage. Appropriate storage instructions have been included in the proposed SmPC in regard to storage temperature and protection from light.

Based on the stability data provided a shelf life of 36 months for the finished product when stored between 2-8°C and protected from light is considered acceptable for the unopened vial. Once opened, the medicinal product should be diluted and infused immediately.

After dilution and from a microbiological point of view, the product should be used immediately. If not used immediately, it is the responsibility of the user to follow the in-use storage times and conditions prior to use.

If the diluted solution is not administered immediately, it may be stored temporarily either:

- under refrigeration at 2°C to 8°C for no more than 24 hours from the time of infusion preparation to the end of the infusion
or
- at room temperature up to 25°C for no more than 6 hours from the time of infusion preparation to the end of the infusion.

The Applicant commits to completing the stability studies of the primary evinacumab finished product batches at the long-term storage condition of 5 ± 3°C in accordance with the stability protocol provided.

Adventitious agents

Evkeeza is a recombinant monoclonal antibody produced in recombinant CHO cells. The purification of the antibody includes several steps for virus removal or inactivation, some of which have been validated for virus reduction. The final finished product is formulated with known excipients and there are no novel excipients.

TSE compliance

None of the materials used during preparation of MCB, WCB or during Evkeeza manufacture is of direct animal origin. None of the excipients in the final finished product is of animal origin. Animal-derived materials were used in cell line development. Their compliance with the TSE Guideline "Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" EMEA/410/01 Rev. 3 has been sufficiently demonstrated.

Virus safety

No materials of direct animal or human origin were used during cell banking or are used in the Evkeeza manufacturing process. None of the excipients is of human or animal origin. The MCB, WCB and an end-of-production cell bank have been tested sufficiently for adventitious viruses as well as retroviruses and according to ICH Q5A. Testing reports were provided for final assessment. Bulk harvests are routinely tested for adventitious viruses according to ICH Q5A. No viral contaminants have been found within the cell banks and in the bulk harvest of several batches tested so far except for retrovirus-like particles (RVLP). The presence of RVLP is well known for CHO cells and is acceptable because there is enough capacity in the purification process of Evkeeza to remove them.

The purification process includes several chromatography steps, a low pH treatment step and virus retentive filtration. Four of these steps have been validated in appropriately designed small scale studies for virus reduction using model viruses. It was shown that two of the steps were effective for removal of a wide range of viruses as all model viruses were reduced by more the 4 $\log_{10}$. Another step is effective for inactivation of enveloped viruses. Additionally, another chromatography step contributes to overall virus reduction. A retrovirus risk assessment was performed, demonstrating sufficient clearance for the CHO cell-derived RVLP.

In summary, the virus safety of Evkeeza has been sufficiently demonstrated.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The overall quality standard of the Module 3 Quality dossier presented in support of this application for evinacumab is adequate for Marketing Aurthorisation, with the descriptions of the manufacture and control of the active substance and finished product containing sufficient detail to permit an in-depth assessment of the marketing authorisation application.

Based on the review of the provided quality data the marketing authorisation application for Evkeeza is considered approvable from the quality point of view.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Evkeeza is considered acceptable when used in accordance with the conditions as defined in the SmPC.

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance is adequately described, controlled and validated. The active substance is well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated.

The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents' safety including TSE have been sufficiently assured.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended some points for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro characterisation of evinacumab binding

Affinity binding of evinacumab to ANGPTL3 of various species was assessed with surface plasmon resonance. Evinacumab binds with high affinity to human ANGPTL3 isoforms (KD<2 nM) and the ANGPTL3 full-length protein (KD<1 nM) Binding of evinacumab to rabbit and rat ANGPTL3 was shown to be in the low micromolar range (KD= 1.9µM for rabbit) and approximately 3 times higher for rat (KD = 670nM). Evinacumab bound to monkey ANGPTL3 with a KD of 2,6 nM. Thus, these species are considered to be responder species for evinacumab activity. This was further demonstrated in a functional assay where evinacumab promoted lipoprotein lipase (LPL) activity after blocking human ANGPTL3 (IC50 = 5.4-6.4 nM); monkey ANGPTL3 (IC50 = 20.7 nM); rat ANGPTL3 (IC50 = 9.8nM); and mouse ANGPTL3 (IC50 = 105.5 nM). No potentiation of LPL was observed when evinacumab was incubated with human or mouse ANGPTL4 or human ANGPTL5. Similarly, the ability of evinacumab to promote endothelial lipase activity (LIPG) was also demonstrated (potentiation LIPG activity after ANGPTL3 blockade with IC50 values of 96, 30, 61, and 84nM using human, monkey, rat and mouse ANGPTL3, respectively). The ability of evinacumab to induce ADCC, CDC or to activate complement was evaluated in human-derived HepG2 and Hep3B cells with or without the addition of exogenous human ANGPTL3. In contrast to positive control antibodies (including rituximab), evinacumab was unable to elicit ADCC, nor CDC responses. This is in line with evinacumab belonging to the IgG4 class of antibodies. Similarly, Evinacumab did not activate C1q, suggesting that evinacumab mediated complement activation is not likely.

Table 3.2.1.1. Overview of in vivo PD studies with evinacumab and main findings on lipid trafficking

Study number	***Mouse model***	***Dose (frequency, route, dose level)***	***Main effects on lipids***
REGN1500-MX-12022	C57Bl/6 (normolipidemic)	SD, SC, 5-10 mg/kg	↓TG, ↓Tchol, ↓HDl-C, non-HDL-C
REGN1500-MX-12022	ApoE$^{-/-}$ (hyperlipidemic)	SD, SC, 10 mg/kg	↓TG, ↓Tchol, ↓HDL-C, ↓non-HDL-c, ↓LDL-C, ↓VLDL-C, ↓VLDL-TG
REGN1500-MX-12022	Ldlr$^{-/-}$ (LDLR null)	SD, SC, 10mg/kg	↓TG, ↓Tchol, ↓HDL-C, ↓non-HDL-C, ↓LDL-C, ↓VLDL-C, ↓VLDL-TG, ↓LDL-TG
REGN1500-MX-12022	Db/Db (diabetic/obese)	SD, SC, 5-10 mg/kg	↓TG, ↓LDL-C, ↓non-HDL-C →Tchol, →HDL-C
REGN1500-MX-12022	C57Bl/6 WT, high fat diet	1QW, 8 weeks, SC, 25mg/kg	↓TG, ↓LDL-C, ↓HDL-C
REGN1500-MX-14032	Lipg$^{-/-}$ (EL null) and WT	SD, SC, 10 mg/kg	Lipg$^{-/-}$: ↓TG, WT: ↓TG, ↓HDL-C, ↓Tchol Lipg$^{-/-}$/WT: →LDL-C
R1500-PH-19183	Ldlr$^{-/-}$ (LDLR null)	1QW, 3 weeks, 25 mg/kg	↓TG, ↓Tchol, ↓HDL, ↓LDL, ↓VLDL
R1500-PH-19183	Ldlr$^{-/-}$ / Lipg$^{-/-}$ + Ldlr$^{-/-}$ (double ko)	SD, SC, 10 mg/kg	Ldlr$^{-/-}$: ↓TG, ↓Tchol, ↓LDL-C, ↓VLDL Lipg$^{-/-}$ + Ldlr$^{-/-}$: ↓TG

<u>In vivo mode of action and proof of concept of evinacumab mediated modification of lipid profiles</u>

The pharmacology of evinacumab was further investigated in vivo. The ability of evinacumab to reduce serum triglyceride levels after a single administration was evaluated in Lipg-/- mice, normolipidemic C57Bl/6 mice, hyperlipidemic ApoE-/- and Ldlr-/- mice, and diabetic dyslipidemic db/db mice. Furthermore, the effect of weekly evinacumab administration to C57Bl/6 mice fed a high-fat, high-cholesterol diet was evaluated (also see table 3.2.1.1.).

In normolipidemic C57Bl/6 mice, a single SC administration of 5, 10 or 25 mg/kg evinacumab, but not 1 mg/kg evinacumab, resulted in a dose-dependent reduction of circulating triglyceride levels (TG), total cholesterol (TChol), non-high-density cholesterol (non-HDL-C) and high-density cholesterol levels (HDL-C. Reductions in TG levels were profound and prolonged (up to 25 days in animals receiving 10 or 25 mg/kg evinacumab). LDL-C levels were not significantly altered after administration of evinacumab. Total ANGPTL3 levels were elevated in animals receiving evinacumab demonstrating the formation of antibody-ANGPTL3 complexes.

Administration of a single dose of evinacumab in Lipg-/- and wt-litter mates resulted in marked reductions of serum TG. Evinacumab also reduced T-Chol and HDL-C in wild-type littermates, but not in Lipg-/- mice, demonstrating that this is dependent on LPL activity. Evinacumab did not alter LDL-C in either wild-type nor Lipg-/- mice.

Administration of a single dose of 10 mg/kg evinacumab in hyperlipidemic ApoE knockout mice resulted in a significantly decreased level of TG, TChol, non-HDL-C and HDL-C and a trend towards decreased LDL-C compared to mice given control antibody.

A single administration of 10 mg/kg evinacumab in Ldlr knockout mice (a model for familial hypercholesterolemia) resulted in marked decreases in TG, LDL-C, total cholesterol, non-HDL-C and HDL-C compared to mice given control antibody, and was independent of LDLR.

In a subsequent series of experiments, evinacumab was shown to reduce TG, total cholesterol, VLDL, LDL, and HDL after 3 weekly administrations to Ldlr-/- mice. Following this, evinacumab was administered to a double knockout Ldlr-/- Lipg-/- mouse model, and therefore in the absence of both EL and LDLR. A single administration of 10 mg/kg evinacumab reduced levels of circulating TG compared with isotype control, consistent with the ability of evinacumab to indirectly upregulate LPL activity. The ability of evinacumab to reduce serum lipids was limited in Lipg-/- Ldlr-/- mice, demonstrating that the LDLR-independent cholesterol- and phospholipid-lowering effect of evinacumab is attributed to blocking ANGPTL3-mediated inhibition of EL. In a third study, ApoE-/- mice were used to assess lipid clearance because VLDL clearance is too rapid to adequately measure in Ldlr-/- mice. Animals were given 2 once-weekly doses of 10mg/kg evinacumab. VLDL and LDL from these animals were isolated, purified, labelled and reinjected in untreated ApoE-/- mice. Evinacumab-driven modifications on VLDL led to faster clearance of these particles, compared with VLDL from mice treated with isotype control. Evinacumab treatment had no impact on LDL clearance rates, suggesting that evinacumab-driven LDL-C reduction occurs through accelerated clearance of VLDL, upstream of LDL formation.

In further studies, a single dose of 5 or 10 mg/kg evinacumab was administered to db/db mice (mouse model of obesity, diabetes and dyslipidemia), which resulted in a marked decrease in serum TG and LDL-C and non-significantly reduced non-HDL-C. Total cholesterol or HDL-C was unaffected compared to mice given control antibody. Evinacumab and had no effect on hepatic lipase activity. However, and in contrast to C75Bl/6 and ApoE-/- mice, db/db mice were noted to have 2-5 times higher ANGPTL4 levels. It is considered by the applicant that this could account for reduced LPL activity in this model.

The ability of evinacumab to reduce serum lipids was evaluated in C57Bl/6 mice fed a high fat 'western' diet after repeated administration. Evinacumab was able to reduce serum TG levels, total cholesterol and LDL-C. HDL-C was also statistically significantly reduced. The reductions were maintained for 8 weeks, which was also the duration of the study. Administration of evinacumab had no effect on body weight, white adipose tissue or heart weight. There were no effects of weekly evinacumab administration on ALT/AST ratio or hepatic TG content at the end of the study.

<u>In vivo proof of concept on cardiovascular protection after prolonged administration of evinacumab</u>

Effects of evinacumab on atherosclerosis were evaluated in APOE*3Leiden.CETP mice, which is considered a well-established model. Mice were fed a Western diet and were administered weekly doses of evinacumab for 13 weeks. Consistent with other models, TG and lipid levels were markedly reduced, with the exception of HDL-C. Atherosclerotic lesion size and the area of the necrotic core was reduced in evinacumab treated animals compared to control animals. However, there were no significant differences in a number of lesions, undiseased segments or in lesion severity.

In the same model (APOE*3Leiden.CETP tg mice) animals were fed a western diet and atherosclerosis was induced for 13 weeks prior to treatment. Evinacumab was administered to animals alone or in combination with atorvastatin, alirocumab or both for 25 weeks. Combination treatment with atorvastatin and evinacumab or alirocumab and evinacumab significantly blocked the progression of established atherosclerosis in APOE*3Leiden.CETP mice. Triple treatment with evinacumab and

alirocumab on top of atorvastatin regressed atherosclerosis, also improved plaque phenotype, and reduced the proliferation of macrophages in the plaques.

The totality of evidence suggests that evinacumab is effective in dose-dependently lowering serum lipids in multiple mouse models. Evinacumab lowers serum lipids by inhibiting ANGPTL3 and promoting very-low-density lipoprotein (VLDL) processing and clearance upstream of LDL formation. The ability of evinacumab alone to reduce the progression of atherosclerotic plaques has been demonstrated in a relevant model of disease, but without reducing other relevant markers. In this animal model of atherosclerosis, combination treatment with approved lipid-lowering therapies blocked disease progression when given as a double combination or reversed it when given as a triple combination. The reduction of cardiovascular risk in the patient population at large should nevertheless be demonstrated clinically.

Secondary pharmacodynamic studies

The absence of secondary pharmacology studies is acknowledged. ADCC, CDC and complement activation has been assessed as part of the primary pharmacology.

Safety pharmacology programme

Formal safety pharmacology studies in accordance with ICH S7 are not required for monoclonal antibodies, which is in line with ICH S6(R1). Safety pharmacology endpoints were incorporated in repeat-dose toxicity studies, which did not suggest that evinacumab poses a risk to the cardiovascular system, respiratory system or the CNS.

2.3.3. Pharmacokinetics

Evinacumab single dose (IV and SC) pharmacokinetics were assessed in rats and monkeys. Repeat dose toxicokinetics of evinacumab were assessed from toxicology studies (IV and SC, QW) in studies up to 13 weeks in rats and 26 weeks in monkeys, in juvenile rats and rabbits and as part of the reproductive and developmental toxicology studies in pregnant rats and rabbits as well as in fetuses.

Methods of analysis

For the quantification of total evinacumab in rat, rabbit and monkey serum, enzyme-linked immunosorbent assay (ELISA) methods based on capture by mouse anti-human IgG4 monoclonal antibody and detection by biotinylated mouse anti-human immunoglobulin (Ig), kappa light chain specific, mAb were used. The provided validation reports demonstrate that the assays were sensitive, selective and suitable to assess evinacumab concentrations in serum. The lower and upper limits of quantitation (LLOQ and ULOQ) were in the range of 0.078 µg/ml - 5 µg/ml.

For the detection of antibodies against evinacumab, a non-quantitative, titer-based, bridging assay based on electrochemiluminescence was used. The assay detects ADA generated against the constant regions of a human IgG4 antibody (including evinacumab). Although it is noted that rats do not have IgG4, the ADA method was validated for the detection of ADA against REGN846 in monkey and rat serum, but was not validated for rabbit serum and neither for anti-REGN1500 (evinacumab)

antibodies. According to the applicant, sensitivity is approximately 9.2, 24.3, and 7.0 ng/mL in neat rat, rabbit, and monkey serum, respectively. The values mentioned for rat and monkey correspond to the sensitivity values for REGN846, but cannot simply be used for evinacumab. Drug tolerance is approximately 206, 153, and 257 µg/mL of evinacumab in rat, rabbit, and monkey serum. It is noted that the drug tolerance level was generally exceeded in the samples from the doses ≥30 mg/kg in all evaluated species, suggesting that the ADA response may be underestimated at these dose levels.

In addition, the presence of neutralizing antibodies has not been assessed.

Absorption

A single-dose pharmacokinetic study was performed in rats and Cynomolgus monkeys, with IV and SC doses of 1, 5 and 15 mg/kg bw. In both species, the PK of evinacumab is characterized by a brief distribution (IV) or absorption (SC) phase (Tmax was 36 to 72 hours in rat and 20-106 hours in monkey), followed by a linear beta elimination phase and a target-mediated clearance (TMC) phase, with a prolonged linear elimination phase (post-TMC phase) observed at very low concentrations. In line with the non-linear kinetics, plasma clearance decreased with increasing doses (from 1.27 to 0.32 ml/h/kg in rats and from 1.3 to 0.14 ml/h/kg in monkeys). Cmax followed an approximately proportional (IV) or greater than proportional (SC) increase with increasing dose. A greater than proportional increase in exposure (AUC) with increasing dose was observed. Terminal elimination half-life (T1/2) ranged from 84-146 hours in rats and 134 to 242 hours in monkeys.

The SC bioavailability of evinacumab was approximately 37-84% in rats and 39-82% in the monkey.

There were no apparent gender differences in exposure.

Multiple-dose toxicokinetic studies (IV and SC, QW) were performed in rat (5 and 13 weeks) and cynomolgus monkeys (5, 13 and 26 weeks) at dose levels of 10-100 mg/kg bw. Absorption of evinacumab was slow after multiple SC dosing, with Tmax ranging from 28-96h (but mostly between 48 and 72h). After repeated exposure, systemic exposure of evinacumab increased in an approximately dose-proportional manner. Accumulation ratios (based on AUC) in rat and monkey were low to moderate (1.3-5.1 for once-weekly IV and 1.7-4.7 for once-weekly SC) and increased with increasing study duration. Steady-state was achieved after approximately 7 weekly doses in the 13-week study in rats and after approximately 12 weekly doses in the 26-week study in monkeys.

Toxicokinetics were also assessed in juvenile toxicity studies and EFD in rats (administration every 3 or 7 days) and rabbits (administration every 3 or 5 days) as well as in the male fertility study in rabbits and the female fertility/PPND study in rats. Also in these studies, exposure increased in an approximately dose-proportional manner, although in the EFD studies in rabbits in which lower dose levels (1-100 mg/kg) were used, this was slightly greater than dose-proportional.

There were no consistent sex-related differences in evinacumab exposure following repeated IV or SC dosing.

Distribution

Formal tissue distribution and protein binding studies were not conducted with evinacumab, which is acceptable. Evinacumab has a normal volume of distribution (54.3-98.4 ml/kg in rat and 53.2 to 75.6 mL/kg in monkey), suggesting moderate extravascular distribution.

Fetal exposure to evinacumab was demonstrated in the Embryo-Fetal Development Studies in rat and rabbit, as well as in a PPND study in rats. In rats dosed 5-100 mg/kg bw once weekly (IV) from GD 6 to GD 18, the ratio of fetal and maternal total evinacumab concentration) at GD 21 ranged from 0.419 to 0.619. In an EFD study in rabbits, evinacumab was detected in fetuses from 3 of the 16 maternal females in the 10 mg/kg dose group and in fetuses from 7 of the 10 maternal females in the 30 mg/kg

dose group on GD 29. Concentrations in fetal serum were typically equal to or more than those observed in maternal serum, probably due to the large impact of ADAs. In a PPND study in rabbits, detectable concentrations of evinacumab were observed in all foetuses at GD21 as well as in all pooled samples from litters on PND7 and in 12 of 22 F1 animals through maturation day 63. In conclusion, fetal exposure was observed in rats as well as rabbits

In addition, in a male fertility study in rabbits, with doses up to 300 mg/kg, detectable concentrations of total evinacumab were observed in seminal plasma (median percentage of total evinacumab concentrations in seminal plasma relative to total evinacumab concentrations in serum was 0.6%).

Distribution to milk has not been investigated. However, since it is known that many immunoglobulins are excreted in human milk, this may also be expected for evinacumab.

Metabolism

No metabolism studies with evinacumab were conducted in animals. The absence of metabolism studies is in accordance with ICH S6(R1) and is agreed with.

Excretion

As evinacumab is a monoclonal antibody, no renal excretion is anticipated due to its molecular size. Therefore, no specific studies to measure excretion of evinacumab were conducted. The absence of excretion studies in accordance with ICH S6(R1) and is agreed with.

Immunogenicity

The immunogenicity of evinacumab in rats and monkeys was assessed in all PK and toxicity studies.

Positive ADA responses in the rat studies varied between 0 and 19% of treated animals (0-43% per dose group), with higher incidences at lower dose levels in the single-dose study, but independent from dose in the repeated dose studies. In general, the presence of ADA was associated with a corresponding reduction in exposure to evinacumab compared to that of ADA negative animals. In addition to the ADA positive animals, several ADA negative animals (especially from the higher dose groups) showed a decline in the concentration-time profiles consistent with the development of ADAs. It is noted that the majority of the measured concentrations of total evinacumab in dose groups (≥ 30 mg/kg) exceeded the DTL, suggesting that the actual amount of ADA positive animals may be much higher. Concentration values from animals considered to be impacted by ADA (either by positive ADA test or suspected concentration-time profile) were excluded from NCA.

Furthermore, although concentrations of evinacumab remain relatively high, it is not clear whether the presence of ADAs prevents binding of evinacumab to its target and thereby reduces efficacy (i.e. neutralizing ADAs).

In rabbit 2-88% of treated animals tested positive for ADA's (0-100% per dose group). The incidence of ADA was inversely dose-dependent across all dose groups following multiple dosing in adult rabbits, with a higher incidence of ADA observed at doses ≤30 mg/kg. In juvenile rabbits, the pattern was independent of dose. In animals that tested positive for ADA, the presence of ADA was typically associated with a corresponding reduction in evinacumab plasma concentrations. Also in rabbits, the majority of samples (especially ≥30 mg/kg) were above the DTL. For rabbits, however, presence of ADAs did not result in exclusion from analysis. It is noted that ADAs were also observed in 50-94% of control animals. No validation results have been provided for the assay in rabbit plasma (as was done for rat and monkey for another antibody).

In monkey, 3-28% of treated animals tested positive for ADAs (0-50% per dose group). The incidence of a positive ADA response was inversely dose-dependent across dose groups following a single dose, but dose-independent across dose groups following multiple doses. In animals that tested positive for

ADA, the presence of ADA was typically associated with a corresponding reduction in exposure to evinacumab. Although evinacumab concentrations were below the DTL in the majority of samples in the single-dose PK study, the majority of samples in the repeated dose studies had evinacumab concentrations exceeding the DTL, indicating that the presence of ADAs may be underestimated. Indeed, in addition to the ADA positive animals, also a low percentage of monkeys that tested negative in the ADA assay (≤17%) exhibited concentration-time profiles characteristic for ADA presence. Concentration values from animals considered to be impacted by ADA were excluded from NCA.

Pharmacokinetic drug interactions

Drug-drug interaction at the PK level is highly unlikely for this type of product since biotechnology-derived substances do not metabolize via CYP P450 enzymes. However, the mechanism of action may have an effect on CYP450 activities. The Pharmacokinetic Drug-Drug Interactions (DDI) will be assessed in the clinical AR.

2.3.4. Toxicology

Single dose toxicity

No single dose toxicology studies have been conducted.

Repeat dose toxicity

Repeated dose toxicity of evinacumab was studied in rats and monkeys, for up to 13 and 26 weeks respectively at doses up to 100 mg/kg/week. Both SC and IV slow bolus dosing was used in all studies; however, in the pivotal monkey 26-week study IV dosing was only performed with the control and high dose groups. However, since no adverse effects were seen in any of the studies, this is sufficient.

Rats: From the pharmacology studies, it was shown that evinacumab binds to the target ANGPTL3 of rats, and therefore rats are a suitable species for toxicology testing. However, there was no effect on cholesterol or triglyceride levels in the pivotal rat toxicology studies. No pharmacological or toxicological effects were seen in the rat studies, and therefore the NOAEL is set at 100 mg/kg/week IV, resulting in a safety margin of 4.6 based on AUC.

Monkey: Evinacumab is pharmacologically active in the cynomolgus monkey, as evidenced by decreases in triglyceride, total cholesterol and HDL-C levels. However, no consistent effects were seen on LDL-C levels, as only a few animals showed a decrease after treatment. There were no adverse effects in any of the monkey studies, resulting in a NOAEL of 100 mg/kg/week IV, and a safety margin of 14.7 based on AUC.

In addition to the general parameters investigated in the repeated dose studies, additional endpoints on the cardiovascular system, respiratory system and central nervous system were included to meet the requirements of safety pharmacology testing. Additionally, female menstrual cycle and male reproductive parameters were studied in the 26-week monkey study, without any adverse effects reported.

Genotoxicity and Carcinogenicity

No genotoxicity or carcinogenicity studies were performed. Considering the nature of the product, this is in line with guidance from ICH S6 and agreed. In a Carcinogenicity Risk Assessment it is concluded that blockade of ANGPTL3 is unlikely to contribute to an increased cancer risk.

Reproduction Toxicity

Female fertility: There were no effects on fertility or early embryonic development study in rats when dosed up to 100 mg/kg SC evinacumab every 3 days.

Males fertility: Evinacumab was not well tolerated in treated male rabbits, with 3 mortalities in both groups of 100 mg/kg and 300 mg/kg IV dosed every 5 days. Causes for mortality were haemorrhage, inflammation, interstitial nephritis of the kidney and dehydration. Surviving males had lower body weight gain, lower heart weights and marked kidney adverse effects. Lower fecundity index is likely due to lesser health status of the male animals. There is no paternal NOAEL. There was an increased incidence of unossified caudal vertebrae at the highest dose. However, this is unlikely to be treatment-related, since it is within historical controls for fetal incidence, and it is unlikely that evinacumab in sperm can elicit such an effect. Therefore, the NAOEL for fertility and early embryonic development is 300 mg/kg every 5 days. Overall, there is no effect on fertility or early embryonic development in female rats and male rabbits up to exposures 3.6- and 30-fold of the MHRD respectively, based on AUC.

In the embryofoetal development study in rats, pharmacological-related effects were seen in all dose groups (decreased triglyceride levels). Treatment-related findings on the offspring were only observed at the highest dose, where there was an increase in bipartite ossification of the thoracic centrum. This is a variation that is not considered of much relevance for human. Also noted was an increased incidence of absent innominate artery, but this effect is likely a background effect and not evinacumab-related since the incidence was within the historical control range. Due to these findings, the NOAEL for embryofetal development in the rat is 30 mg/kg, which is <1-fold human exposure.

Pregnant rabbits did not tolerate treatment with evinacumab well, resulting in decreases in maternal body weight, leading to mortalities, abortions and resorptions. The F1 generation was also effected by decreased body weight, and from a dose of 10 mg/kg domed head, cleft palate, flexed hindlimbs and ventricular dilatation of the brain were observed. The exposure at this dose is below the MHRD. The relevance of these findings for humans is unclear, due to the accompanying maternal toxicity, and the different lipid profile during pregnancy in rabbits compared to humans. Embryotoxicity has been identified as an important potential risk in the RMP.

There were no effects on pre- or postnatal development in rats when dosed up to 100 mg/kg SC every 3 days, leading to exposures of 3.6-fold of the MHRD, based on AUC.

The safety of evinacumab was assessed in both juvenile rats and juvenile rabbits. Evinacumab was administered to rats once weekly from PND21 through PND84. No test-article related changes with the exception of increased total protein and globulin levels in the 100 mg/kg IV and SC groups and A/G ratios were decreased as a result of increased protein load due to the dose. Histopathological evidence of injection site reactions was noted in animals given evinacumab via the SC route. These findings were fully reversible. Consistent with the intended pharmacology of evinacumab, and in contrast with adult rat toxicology studies, TG; HDL; and cholesterol levels were decreased all evinacumab groups. The NOAEL was considered to be 100mg/kg for either IV and SC routes, which was 5.1 times higher than the anticipated clinical exposure.

In the pivotal juvenile toxicity study, rabbits were given evinacumab once every 5 days from PND 21 through PND 141 via slow bolus IV injection. Animals received 0, 30, 100 or 300 mg/kg evinacumab. Mortality in this study was considerable. Eight animals in the control group were found dead or were euthanised, 5 animals in the 30 mg/kg group, 8 animals in the 100 mg/kg group, and 12 animals in the 300 mg/kg group. The applicant considers that these deaths were not evinacumab-related due to the findings in these animals and the absence of overt toxicity in the study. This is acknowledged. Apart from the expected findings of reduced TG and lipid levels, there were no remarkable evinacumab related findings. There were no evinacumab related effects on reproductive performance in males or females, intrauterine growth and survival or fetal morphology. The NOAEL was considered to be 300 mg/kg, which was 21.4 times higher than the anticipated clinical exposure.

In conclusion, apart from the intended pharmacological action, there were no adverse findings in juvenile animals. Therefore, there is no evidence that juvenile animals are more sensitive to evinacumab administration compared to adult animals.

Toxicokinetic data

Local Tolerance

Local tolerance of evinacumab has been evaluated in repeat dose toxicity studies. There are no findings to suggest that evinacumab will be an irritant or result in local tolerability issues.

Other toxicity studies

In a GLP compliant ex-vivo tissue cross-reactivity study, no specific evinacumab binding was observed in any human, cynomolgus monkey or rat tissue. In contrast, a positive control (rhAngPTL3) was positive for evinacumab binding, whereas there was no staining with a negative control (DLL3).

There was no evidence that evinacumab had immunotoxic potential in repeat dose toxicity studies. Furthermore, evinacumab did not affect haematological parameters in these studies.

2.3.5. Ecotoxicity/environmental risk assessment

A justification for not performing an environmental risk assessment studies was submitted in line with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (ERA Guideline) (1) 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." The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, evinacumab is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The totality of evidence suggests that evinacumab is effective in dose-dependently lowering serum lipids in multiple mouse models. In dyslipidemic, diabetic db/db mice, evinacumab caused a reduction in TG and LDL-C, without effect on total cholesterol or HDL-C. In this mouse strain, a significant increase in TG levels was observed in animals treated with control Ab compared to the pre-bleed values. Since the effect of evinacumab was presented as "% from control Ab" an increase in TG in the

control animals suggests a TG reduction in the evinacumab-treated groups, although the overall TG levels in the evinacumab-treated animals are not much different from the TG levels determined prior to treatment. The applicant clarified that in the baseline TG values in hyperlipidemic db/db mice were typically 200 - 230 mg/dl and that the baseline TG values determined in study REGN1500-MX-12022 were exceptionally low. In additional experiments in db/db mice, described in the Applicant's response, pre-bleed baseline values of TG in db/db mice were as expected. In these studies, evinacumab administered at 10 mg/kg SC either as single dose or repeated weekly doses led to a reduction of circulating TG of approximately 50% compared to control. These data confirm the TG reducing effect of evinacumab in hyperlipidemic db/db mice. Finally, it is noted that in study R1500-PH-19183 blood was collected from non-fasted mice, while in the previous studies, blood samples were generally collected after a 4-h fast. The Applicant clarified that in general the expression of ANGPTL3 is only minimally influenced by fasting or refeeding, and that levels of total cholesterol and LDL-C were not affected by fasting. Since study R1500-PH-19183 evaluated the effect of evinacumab on reduction of LDL-C, fasting was not warranted. In the previous studies, mice had been fasted to reduce the variability in TG levels while fasting per se had no effect on evinacumab efficacy in reducing levels of TG, cholesterol and LDL-C.

Generally, evinacumab lowered serum lipids by inhibiting ANGPTL3 and promoting very-low-density lipoprotein (VLDL) processing and clearance upstream of LDL formation. To add to this, recent literature describes ANGPTL8 as an additional angiopoietin-like protein involved in lipid metabolism [Zhang et al., 2014]. Together with ANGPTL3 and ANGPTL4, ANGPTL8 can regulate TG metabolism by inhibiting the activity of LPL [Fu et al., 2015; Quagliarini et al., 2012]. While ANGPTL8 is an atypical ANGPTL family member (due to the lack of the C-terminal domain), it maintains the N-terminal domain required for interaction with lipases. Thus, ANGPTL8 is a potential target for evinacumab. However, evinacumab did not bind to ANGPTL8 while it bound to its target ANGPTL3. Thus, the data show a lack of evinacumab reactivity with ANGPTL8.

The ability of evinacumab alone to reduce the progression of atherosclerotic plaques has been demonstrated in a relevant model of disease, but without reducing other relevant markers. In this animal model of atherosclerosis, combination treatment with approved lipid-lowering therapies blocked disease progression when given as a double combination or reversed it when given as a triple combination. The reduction of cardiovascular risk in the patient population at large should nevertheless be demonstrated clinically.

Pharmacokinetics and toxicokinetics were assessed in rats and monkeys and in the reproduction toxicity studies in rats and rabbits. The assay was not validated for rabbit serum. In all species, the presence of anti-drug-antibodies (ADA's) was detected. Based on the outcome of the ADA assay, several rats and monkeys (but not rabbits) have been excluded from NCA, for a better prediction of human PK. For calculation of the exposure margins, data from ADA-positive animals were not excluded. Drug tolerance level was generally exceeded at doses ≥30 mg/kg in all evaluated species, suggesting that the ADA response may be underestimated at these dose levels. However, concentration-time profiles suggest that the number of ADA-positive animals is limited and does not have a marked impact on exposure or safety assessment.

Rats (up to 13 weeks) and monkeys (up to 26 weeks) have been used as non-clinical species in the toxicology studies. There were no toxicological effects due to treatment with evinacumab. Both species are relevant since evinacumab binds to the target in both species. Although in the rat studies no pharmacological effect on LDL or triglyceride levels was evident, there was in increase in ANGPTL3 levels.

Exposure margins were recalculated by the applicant taking into account the difference in duration of exposure in animals vs. humans. Exposure margins based on Cmax and adjusted AUC lie within the

same order of magnitude, e.g. for the chronic toxicity study in cynomolgus, the Cmax-based margin is 10.3x and the AUC-based margin is 14.6x. For the repeat-dose toxicity studies, the recalculated AUC-based exposure margins also lie approximately in the same order of magnitude as the initially provided margins based on cumulative AUC (14.6x vs. 18.1x for the cynomolgus 26-week study; 4.56x vs. 3.1x for the rat 13-week study). The exposure margins derived are considered adequate to support the proposed use of evinacumab at 15 mg/kg once every 4 weeks.

Evinacumab was not well tolerated in the rabbits embryofetal development (EFD) studies. Treatment with evinacumab at doses below the MHRD resulted in a domed head, flexed hindlimbs and ventricular dilatation of the brain in both rabbit EFD studies, and cleft palate in one of the studies. Maternal toxicity was also present at the doses at which malformations were seen. The relevance of these findings for humans is unclear, due to the accompanying maternal toxicity, and the different lipid profile during pregnancy in rabbits compared to humans. Embryotoxicity has been identified as an important potential risk in the RMP, due to malformations seen in the rabbit EFD studies. Due to the severity of the disease and the importance of cholesterol in embryofoetal development, the advice for use during pregnancy introduced in section 4.6 of the SmPC: "not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk", is the most appropriate advice. In the male fertility study in rabbits, treatment-related microscopic findings were seen in the liver and the kidney. Non-adverse liver findings consisted of increased glycogen and minimal to moderate centrilobular vacuolation. Findings in the kidney of mesangio-proliferative glomerulonephritis and interstitial nephritis were considered adverse as these were considered the cause for the moribund conditions in individual animals sacrificed due to an ADA-related inflammatory reaction. The attribution of adversity to the observed kidney findings in the present study is acknowledged. Nevertheless, the relevance for humans is unclear. Direct evidence, e.g. by immunohistochemistry, that ADA-containing immune complexes contribute to the pathology not was provided. Nevertheless, taking into account that 5 of the 6 animals that were euthanised early/died were ADA-positive and that the microscopic findings were primarily observed in ADA-positive animals, it is agreed that these findings are related to the anti-drug antibody response and not relevant for the human risk assessment.

Finally, in both rabbit juvenile toxicity studies, several animals were found dead or were euthanised in extremis. The applicant did not consider the early deaths/euthanasia in extremis in juvenile rabbits as related to evinacumab. However, the cause of death remained undetermined for quite a number of cases. The applicant indicated that the CRO did not have a historical control database for juvenile rabbits. This is unfortunate; however, it is recognised that rabbits are not used routinely for toxicity studies in juvenile animals and that historical controls may not be available to the extent wished. Based on the fact that deaths were also observed in animals from the control group and based on the lack of adverse clinical finding or post-mortem histopathology, findings in surviving animals early deaths/euthanasia in juvenile rabbits were considered not related to evinacumab.

2.3.7. Conclusion on the non-clinical aspects

The Applicant has adequately established the safety profile of evinacumab. No issues have been identified that would preclude a marketing authorisation from the nonclinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

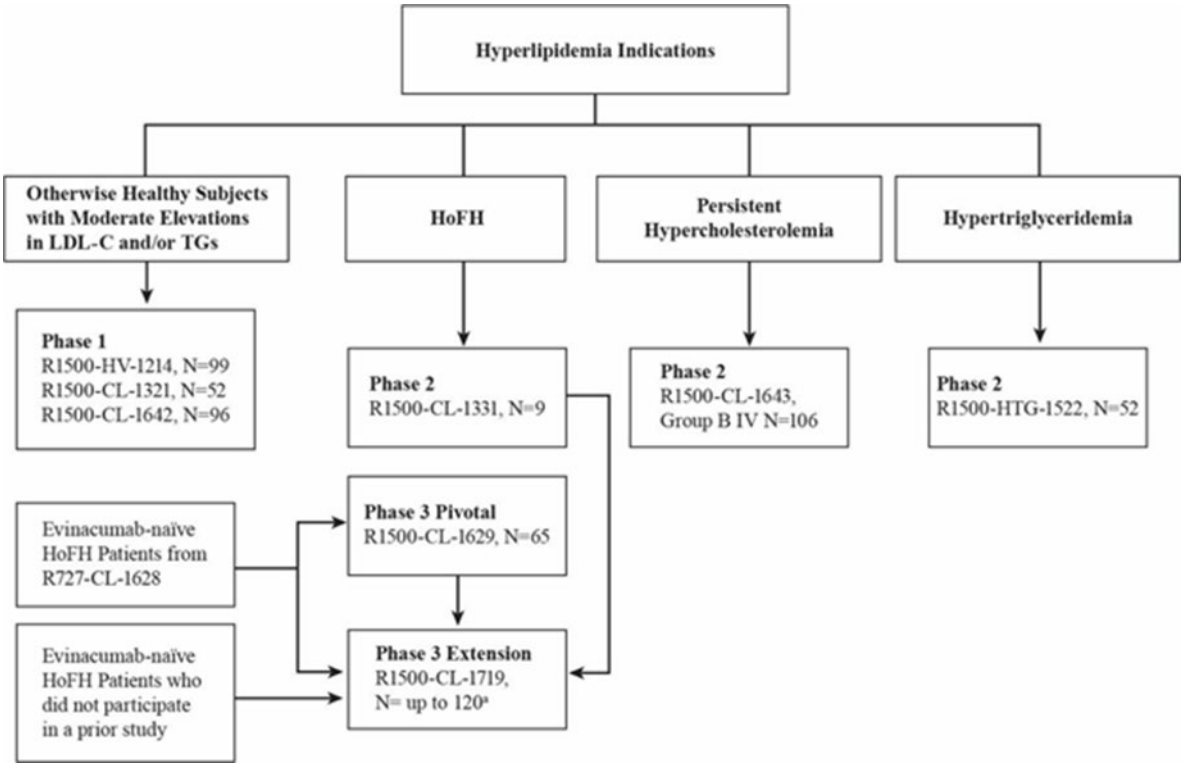


Figure 2. Clinical Studies in the Evinacumab Program

Table 1. Summary of clinical pharmacology program

Study	Study population	Objective	Study design and duration	Dose, route of administration and frequency	Number of patients	Sampling scheme
R1500-HV-1214	Group A: healthy subjects with moderate elevations in TGs (150 mg/dL to 450 mg/dL)	Characterise the PK profile of a single dose of evinacumab administered either SC or IV	Phase 1 randomised, double-blind, placebo-controlled, ascending single dose study of	Group A: 75 mg SC, 150 mg SC, 250 mg SC, 5 mg/kg IV, 10 mg/kg IV, 20 mg/kg IV,	Group A: evinacumab (n =62), placebo (n = 21)	Dense: Pre-dose, 0, 1, 2, 4, 8, 24, 48, and 72 h post-dose

	and/or LDL-C (≥ 100 mg/dL). Group B: adults with TGs ≥ 450 mg/dL. Group C: adults with TGs > 1000 mg/dL who are on LLTs.		safety, tolerability and bioeffect of evinacumab	placebo SC, placebo IV Group B: 10 mg/kg IV, placebo Group C: 250 mg SC, 20 mg/kg IV, placebo SC or IV	Group B: evinacumab (n = 5), placebo (n = 2) Group C: evinacumab (n = 6), placebo (n = 3)	
R1500-CL-1321	Healthy subjects with moderate elevations in TGs (150 to 500 mg/dL) and LDL-C (≥ 100 mg/dL)	Characterise the PK profile of multiple SC and IV doses of evinacumab	Phase 1 randomised, double-blind, placebo-controlled, multiple ascending dose study of the safety, tolerability, PK, immunogenicity, and PD effects of evinacumab.	Cohort 1: 150 mg SC QW x 8 doses, Cohort 2: 300 mg SC Q2W x 4 doses, Cohort 3: 300 mg SC QW x 8 doses, Cohort 4: 450 mg SC Q2W x 4 doses, Cohort 5: 450 mg SC QW x 8 doses, Cohort 6: 20 mg/kg IV Q4W x 2 doses, Placebo IV, Placebo SC	Evinacumab (n = 38), Placebo (n = 14)	Dense: Day -1, Day 1 pre- and end of infusion, 1, 2, 4, and 8, 24, 48 hours post infusion, Days 8, 15, and 22, 29: pre- and end of infusion, and 1, 2, 4,8 hours post-infusion, Days 36, 43, and 50, 57, 78, 99, 120, 141, 162, and 183
R1500-CL-1642	Healthy subjects with modest elevations in LDL-C (100 mg/dL to 160 mg/dL) and possibly modest elevations in TGs (150 mg/dL to 500 mg/dL)	To characterise the PK profile of total evinacumab following SC or IV doses of evinacumab	Phase 1 randomised, double-blind, placebo-controlled study to investigate the safety, tolerability and PK of evinacumab	Cohort 1: 300 mg or placebo SC x 1 dose, Cohort 2: 5 mg/kg or placebo IV Q4W x 2 doses, Cohort 3: 15 mg/kg or placebo IV Q4W x 2 doses, Cohort 4: 300 mg or placebo SC QW x 8 doses	Evinacumab (n = 72), Placebo (n = 24)	Pre-end of infusion on dosing days
R1500-CL-1331	Patients with HoFH who are not currently undergoing LDL apheresis therapy	To assess the PK and PD of varying doses and regimens of evinacumab	Phase 2 open-label, single-arm, proof-of-concept study to evaluate the safety and efficacy and multiple doses of evinacumab	Day 1: 250 mg SC x 1 dose, Day 15: 15 mg/kg IV x 1 dose, Day 85: 450 mg SC QW x 4 doses Open label extension: Week 26: 300 mg SC QW x 4	Evinacumab (n = 9)	Main Study Period: Day 15, 18, 22, 29,36, 43, 57, 71,85, 99, 127. OLE Period:

				doses, Week 38: 20 mg/kg IV x 1 dose, Week 58: 20 mg/kg IV Q12W		Day 183, 190, 197, 204, 211, 218, 225, 239, 253, 267, 274, 381, 288, 295, 309, 323, 351, 379, 407, 491, 575, 659, 743, 827, 911, 996, 1079, 1163, 1247, 1331 1499
R1500-HTG-1522	Patients with a history of fasting TG ≥1000 mg/dL, a fasting TG ≥500 mg/dL during screening, and a history of pancreatitis	To evaluate the total evinacumab and total ANGPTL3 concentrations, and ADA during the evinacumab treatment and follow-up periods	Phase 2, randomised, placebo-controlled, study to evaluate the efficacy and safety of repeated doses of evinacumab	Double-blind period: Evinacumab 15 mg/kg IV Q4W x 3 doses, Placebo Q4W x 3 doses Single-blind period: Evinacumab 15 mg/kg IV Q4W x 3 doses	Evinacumab (n = 35), Placebo (n = 16)	Sparse: Pre-dose and end of infusion
R1500-CL-1643	Patients with persistent hypercholesterolemia on background statins and PCSK9 inhibitor (80% HeFH)	To assess systemic serum concentrations of evinacumab in patients with primary hypercholesterolemia	Phase 2, randomised, double-blind, placebo-controlled, dose-ranging study	Group A: 300 mg SC QW, 300 mg SC Q2W, 450 SC QW, Placebo SC QW, Placebo SC Q2W Group B: 5 mg/kg IV Q4W, 15 mg/kg IV Q4W, Placebo IV Q4W	Evinacumab (n = 75), Placebo (n = 34)	Sparse: Pre-dose and end of infusion
R1500-CL-1629	Patients with HoFH	To determine concentrations of evinacumab in patients with HoFH	Phase 3, randomised, 24-week, double-blind, placebo-controlled study with a 24-week open-label extension period	15 mg/kg IV Q4W, Placebo IV Q4W	Evinacumab (n = 38), Placebo (n = 19)	Sparse: Pre-dose and end of infusion
R1500-CL-1719	Patients with HoFH	To determine concentrations of evinacumab in patients with HoFH	Phase 3 open-label safety and efficacy study including patients from study R1500-CL-1331 and study R1500-CL-1629, and evinacumab naïve patients.	15 mg/kg IV Q4W	Evinacumab (n = 64)	Dense: Pre-dose, 0, 1, 2, 4, 8, 24, 48, and 72 h post-dose

2.4.2. Pharmacokinetics

The pharmacokinetics of evinacumab have been characterised in 8 clinical trials, which included healthy subjects with elevated lipid levels, patients with heterozygous familial hypercholesterolemia (HeFH), patients with severe high triglycerides and patients with HoFH. The pharmacokinetics of evinacumab after single-dose and repeated dosages were investigated in both healthy subjects as patients with HoFH. In general, sparse samples were collected in patient studies, except for study **R1500-CL-1331** in which a dense sampling scheme was employed. Additionally, population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses were conducted to further characterise the clinical pharmacology of evinacumab. No in vitro permeability or drug-drug interaction studies have been conducted, because evinacumab is a monoclonal antibody. Furthermore, no clinical drug-drug interaction, hepatic or renal impairment studies have been conducted.

Analytical methods

Bioanalytical methods were developed for the determination of total evinacumab (i.e. free evinacumab + complex between evinacumab: AngPTL3 (target)), total AngPTL3 (i.e. free AngPTL3 and complex between evinacumab: AngPTL3) and evaluating immunogenicity. Total evinacumab was quantified in human serum using an enzyme-linked immunosorbent assay (ELISA). Samples were diluted with a mild acidic buffer to dissociate soluble target-drug complexes present in the serum samples to allow detection of total evinacumab. Total AngPTL3 concentrations were also determined using an ELISA bioanalytical method. Further, a bridging immunoassay has been developed and validated for the detection of anti-evinacumab antibodies in human serum samples, and a competitive ligand binding immunoassay has been developed and validated for the detection of anti-evinacumab neutralizing antibodies in human serum.

Pharmacokinetic data analysis

Noncompartmental PK parameters following the first dosing were calculated for individual subjects using Phoenix WinNonlin (version 6.3 or higher, Certara, L.P.) and linear trapezoidal method. In general, descriptive analyses were used to analyse the data.

Evaluation and Qualification of Models

Population pharmacokinetic model

A population pharmacokinetic analysis was conducted based on data of studies **R1500-CL-1629, R1500-CL-1719, R1500-HV-1214, R1500-CL-1321, R1500-CL-1642 and R1500-CL-1331.** The primary objectives of the population pharmacokinetics (PopPK) analyses were to: Estimate the population and individual pharmacokinetic (PK) parameters of evinacumab, estimate variability in PK parameters of evinacumab and, explore and characterise clinically relevant covariates that influence the pharmacokinetics. Evaluated covariates were sex, age, race, baseline body weight, baseline BMI, baseline albumin, disease type, concomitant anti-PCSK9 treatment, baseline total AngPTL3, baseline triglycerides.

A two-compartment model with parallel linear and non-linear elimination, implemented using a Michaelis-Menten equation, was determined as the most suitable structural model. An attempt to include target-mediated drug disposition, using either baseline triglycerides or baseline total AngPTL3, in the model was unsuccessful. Body weight was included in the model on central volume (power model: parameter estimate of 0.875) and on clearance (power model: assuming standard allometric scaling exponent fixed to a value of 0.75). Furthermore, disease state (healthy volunteer versus HoFH subjects) influenced Vmax and, also, baseline AngPTL3 influenced Vmax (power model). This final population pharmacokinetic model did not successfully converge using the IMPMAP estimation

algorithm. Therefore, the applicant re-estimated model parameters by setting CALPHA to 0.001 instead of the default value of 0.05.

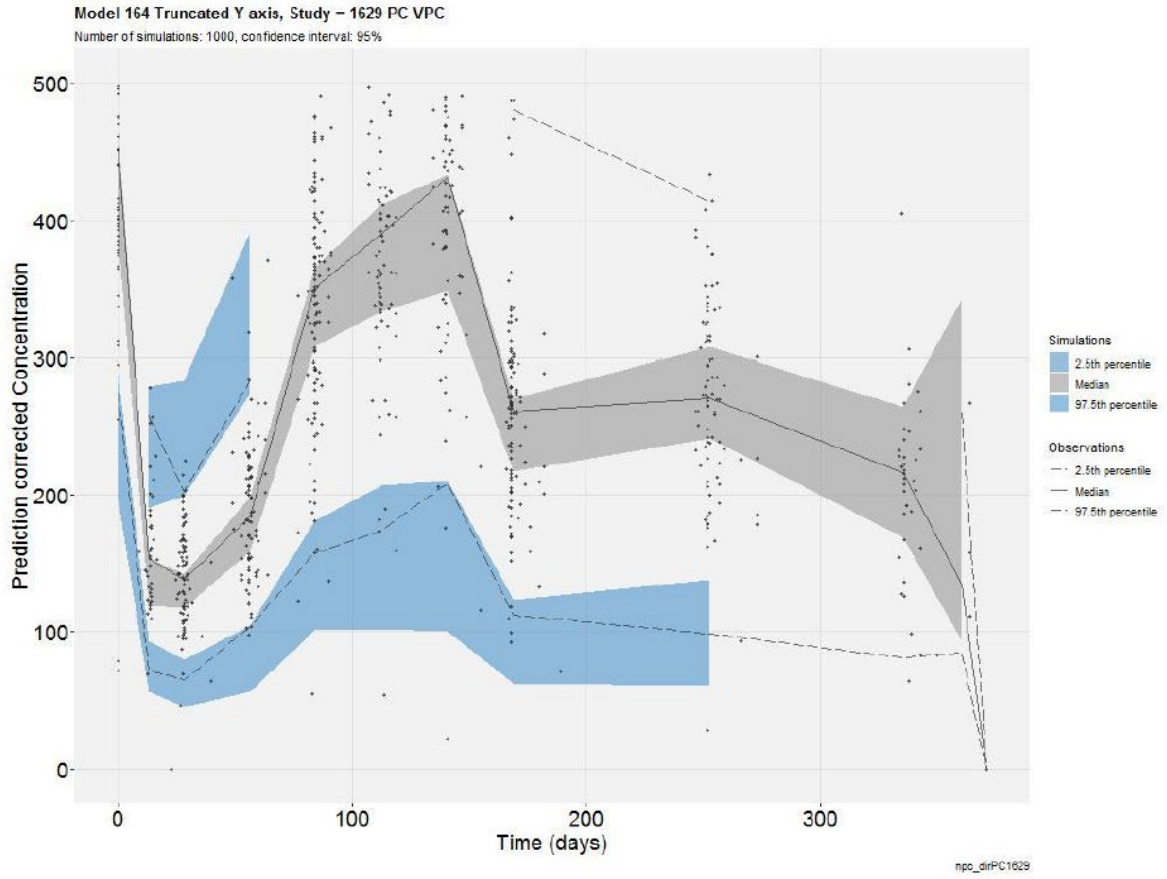
Table 2. Model parameters of the final population pharmacokinetic model

Parameter (units)	Population Estimate (RSE%)
PK Parameter	
Clearance (L/day for 74.1 kg subject)	0.0955 (3.40)
Central Volume (L for 74.1 kg subject)	2.56 (1.67)
KA (1/day)	0.181 (10.6)
F for SC dose	0.714 (1.55)
K23 (1/day)	0.109 (10.4)
K32 (1/day)	0.124 (10.4)
Vmax (mg/day)	3.16 (2.01)
Peripheral Volume (L for 74.1 kg subject, calculated)	2.56
Vss (L for 74.1 kg subject, calculated)	5.12
Km (mg/L)	1.02 (9.31)
Absorption lag time (days)	0.168 (8.20)
Covariates	
V~Weight	0.875 (5.37)
Linear Clearance ~ Weight	0.75 (Fixed)
Vmax ~AngPTL3	0.405 (9.98)
Vmax ~Disease state	-0.289 (24.7)
OMEGA Correlation Matrix (CV)	
σ (η(Cl))	0.355 (10.5)
σ (η(2,1))	0.213 (23.2)
σ (η(V))	0.213 (7.65)
σ (η(Ka))	0.686 (14.8)
σ (η(Alag1))	1.19 (5.55)
Residual error	
σ Additive (mg/L)	0.303 (9.01)
σ Proportional (CV)	0.189 (2.02)

PK = pharmacokinetic; RSE% = Percent relative standard error, CV = coefficient of variation

Bootstrap estimation of parameter position was not feasible for the final model due to long run times.

Figure 3. Prediction corrected visual predictive check (Study 1629)



Population pharmacokinetic/pharmacodynamic model

The objective of the population pharmacokinetic/pharmacodynamic analysis was to develop a model to quantify the concentration-response relationship of evinacumab on LDL-C reduction and to estimate the population and individual PD parameters. Data from three clinical studies (Phase II study **R1500-CL-1331** and Phase III studies: **R1500-CL-1629** and **R1500-CL-1719**) in patients with HoFH was used for this analysis. Covariates that were evaluated were: Concomitant medication or other lipid lower therapy (LLT): anti-PCSK9 treatment (evinacumab or evolocumab), statin, lipid apheresis therapy and baseline concentrations of LDL-C, total AngPTL3, triglyceride.

The population pharmacokinetic/pharmacodynamic model development was performed using a sequential approach. Firstly, individual PK parameters from the population pharmacokinetic model were used to calculate the evinacumab concentrations matching to the time points needed for the development of the population pharmacokinetic/pharmacodynamic model. Then, the population pharmacokinetic/pharmacodynamic relationship was analysed with the predicted PK data and observed PD data.

An indirect response model was used to link the evinacumab concentrations with LDL-C, via the inhibitory of production of response (LDL-C production). No baseline parameter was estimated, but baseline observations were used to initialise the LDL-C compartment. Interindividual variability was included in the model parameters for IC50 and Kin. The residual error was modelled using a combined error model. Using forward selection (ΔOFV decrease of 6.635 was used as criterium), race was

implemented on IMAX, baseline LDL on IC50 and baseline weight on IMAX. No covariates were removed during backward elimination (ΔOFV decrease of 10.8).

Absorption

Not applicable as evinacumab is administered as an intravenous injection.

Distribution

The distribution of evinacumab is primarily restricted to the vascular compartment. Based on the population pharmacokinetic analysis, the central volume of distribution (V2) was 2.56 L, and the peripheral volume of distribution (V3) was 2.25 L for a typical subject of 74.1 kg, resulting in a total volume of distribution of approximately 4.8 L for a typical subject of 74.1 kg.

Metabolism and Excretion

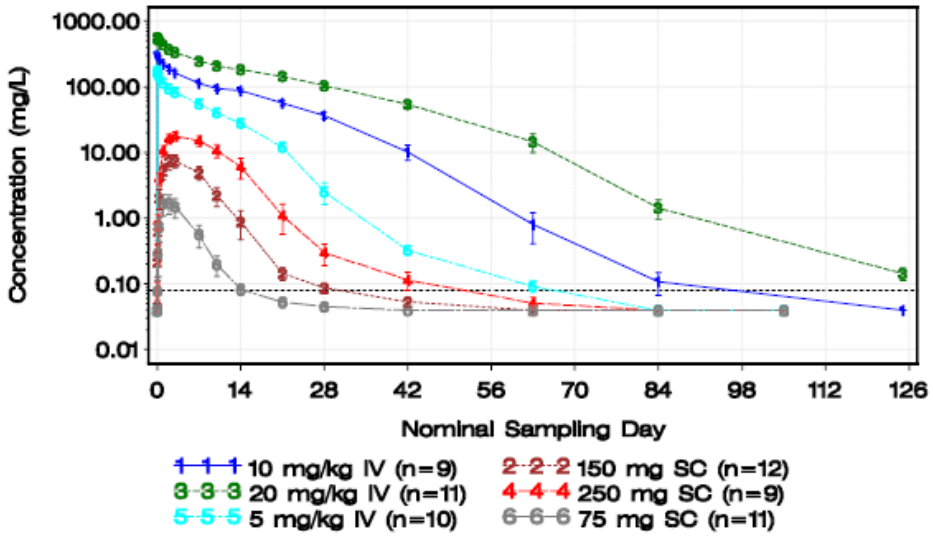
As a monoclonal antibody, evinacumab is not expected to be eliminated by the kidney or metabolized in the liver. The large molecular size of evinacumab is expected to preclude elimination via the kidney, and metabolism of evinacumab is expected to be limited to proteolytic catabolism to small peptides and individual amino acids. As a result, no metabolism/excretion studies were performed for evinacumab.

Population pharmacokinetic analysis indicated that elimination of evinacumab is best described by parallel linear, concentration-independent clearance and nonlinear, concentration-dependent, target-mediated clearance. The terminal elimination phase is described by target-mediated clearance leading to pronounced non-linear kinetics. As such, the half-life (t½) is not constant, and thus its estimation is dependent on the dosing regimen, and elapsed time after dosing, the specific concentration of evinacumab and free AngPTL3 at that timepoint.

Dose proportionality and time dependencies

Dose proportionality of evinacumab was evaluated in healthy volunteers after single-dose IV administration (study R1500-CL-1214, Figure 3). At baseline, the concentrations of total AngPTL3 were comparable across treatment arms, with mean values clustered around 0.1 mg/L. An increase in exposure to evinacumab with increasing doses was greater than dose-proportional. Following a single IV dose of evinacumab, an increase of approximately 7.1-fold in $AUC_{0\text{-last}}$ was observed with a 4-fold increase in dose from 5 mg/kg to 20 mg/kg. For patients with HoFH, only slightly greater than dose-proportional increases in exposure were predicted using the population pharmacokinetic model. Predicted exposure showed a 4.3-fold increase in mean steady-state $AUC_{0\text{-tau}}$ with a 3-fold increase in dose from 5 mg/kg IV to 15 mg/kg IV.

Figure 4. Mean (±SE) Log-Scaled Concentrations of Total evinacumab in Serum vs nominal time (Study R1500-CL-1214, Group A)



IV = Intravenous; SC = Subcutaneous
Concentrations below the lower limit of quantification (LLOQ, horizontal dotted line = 0.078 mg/L) are imputed as LLOQ/2 = 0.039 mg/L.

The accumulation ratio based on the observed Ctrough at week 4 versus week 24 after 15 mg/kg IV evinacumab in patients with HoFH was 2.9 (**Study R1500-CL-1629**). Steady-state is anticipated to be reached after approximately 12 to 16 weeks. The accumulation ratio based on predictions of AUC0-tau using the population pharmacokinetic model was approximately 2.0.

Intra- and inter-individual variability

Based on the population pharmacokinetic analysis, inter-individual variability in $C_{max,ss}$, $C_{min,ss}$ and $AUC_{0\text{-}Tau}$ was estimated to be 22.2%, 38.4% and 29.7% following 15 mg/kg evinacumab. No intra-individual variability was estimated for these summary statistics.

Pharmacokinetics in the target population

The pharmacokinetics of evinacumab were evaluated in two phase III studies (**R1500-CL-1629, R1500-CL-1719**) that used a sparse sampling scheme. The population pharmacokinetic analysis revealed that the V_{max} of the non-linear clearance pathway differed between healthy subjects and patients with HoFH, with the estimated V_{max} being 34% lower in patients. However, at a dose of 15 mg/kg IV Q4W, this difference is expected to have a minimal impact on the exposure of evinacumab, since the drug concentrations within the 4-week dosing interval are expected to be in a range where linear clearance dominates and the contribution of target-mediated drug disposition is minor.

Special populations

The impact of covariates on the pharmacokinetics of evinacumab has mainly been evaluated using the population pharmacokinetic model (**Table 3**). The influence of gender, age, race, body weight, body mass index, hepatic function (baseline albumin), disease type, concomitant anti-PCSK9 treatment,

baseline AngPTL3 and baseline triglycerides were evaluated in this analysis. Post-hoc estimates of $AUC_{0\text{-}tau}$, C_{max}, C_{trough} were presented for patients with extreme values of baseline covariates at baseline.

Table 3. Summary (Mean ± SD) of individual post-hoc estimates of exposure at steady state, stratified by categorised covariates.

Covariates	Categories	N	%	AUCtau(SS) mg*day/L	Ctrough(SS) mg/L	Cmax(SS) mg/L
Weight (kg)	≤60 kg	19	20.0	7898.6 (1181.4)	571.4 (87.2)	171.8 (40.1)
	60-80 kg	45	47.4	10395.8 (3200.1)	689.7 (146.7)	245.6 (102.7)
	> 80 kg	31	32.6	11590 (3099.4)	761.3 (163.7)	275.8 (91.9)
Angptl3 (mg/L)	≥ 0.08	48	50.5	9580.1 (2653.2)	659.5 (150.5)	217.6 (75.8)
	< 0.08	47	49.5	11007 (3446.1)	719.9 (158.9)	264.3 (109.7)
Age (years)	≥ 40	50	52.6	10600.5 (3477.6)	701.7 (180.4)	250.5 (104)
	< 40	45	47.4	9936.7 (2707.1)	675.7 (126.3)	229.8 (87.3)
LDL-C (mg/dL)	≥ 211	48	50.5	10195.1 (2816.3)	681.7 (137.9)	238.8 (87.4)
	< 211	47	49.5	10378.9 (3463.7)	697.2 (175.2)	242.6 (105.9)
Trig (mg/dL)	≥ 91	48	50.5	10247.5 (3126.5)	686.9 (147.4)	239.7 (97.2)
	< 91	47	49.5	10325.4 (3182.4)	692 (167.5)	241.7 (96.8)
PCSK9 inhibitor	No	33	34.7	10125.5 (3277.2)	691.9 (160.2)	233.1 (100.8)
	Yes	62	65.3	10371.5 (3084.8)	688.1 (156.3)	244.7 (94.7)
Statin	High	71	74.7	10566.3 (3042.5)	704 (156.6)	248.5 (93)
	Low/No	24	25.3	9456.8 (3332.2)	646.1 (152.6)	217.5 (105)
Apheresis	No	65	68.4	10554 (3163.8)	699.9 (160.2)	249.1 (97.2)
	Yes	30	31.6	9705.3 (3051.7)	666.7 (149.4)	222.6 (94)
Sex	Female	47	49.5	9267 (2447.8)	642.6 (134)	209.4 (72.7)
	Male	48	50.5	11283.8 (3430.9)	735.2 (165.2)	271.4 (107.3)
Race	White	68	71.6	10542.2 (3065.9)	697.7 (159)	249.4 (93.8)
	Other	27	28.4	9640.9 (3281.6)	668.6 (152.1)	218.8 (101.5)

Angptl3, Angiopoietin-like protein 3; AUC_{tau}, area under the concentration-time curve over the dosing interval; C_{max}, maximum concentration; C_{trough}, minimum concentration; PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9; Trig, fasting triglyceride
Note: Statin high: rosuvastatin (≥20 mg) or atorvastatin (≥40 mg), otherwise as "Low/No". Anti-PCSK9 treatments include alirocumab and evolocumab.

Data from phase 3 studies in patients with HoFH showed that apheresis did not reduce concentrations of evinacumab by a clinically meaningful extent, with mean reductions of approximately 20% in post-apheresis serum concentrations compared with pre-apheresis concentrations (**R1500-CL-1629** and **R1500-CL-1719**). Notably, the effect of apheresis on the concentrations of total AngPTL3 was greater, approximately 50% in reducing the total target concentrations in serum.

Trough concentrations at week 24 in study **R1500-CL-1629** showed no clear difference between HoFH patients taking or not taking high-intensity statins. Similar results were observed for patients taking or not taking PCSK9 inhibitor antibodies (e.g., alirocumab or evolocumab). Consistently, PopPK analysis did not identify concomitant PCSK9 inhibitor therapy as a significant covariate on PK of evinacumab.

Immunogenicity

Anti-drug antibodies were measured in all clinical studies. None of the patients treated with evinacumab exhibited treatment-emergent ADA responses in phase 1 clinical studies. None of the patients treated with evinacumab exhibited treatment-emergent ADA responses in either R1500-CL-1629 or R1500-CL-1719. In patients with severe hypertriglyceridemia (Study R1500-HTG-1522), one patient receiving evinacumab during the double-blind treatment period had a low-titer treatment-emergent ADA response that was negative in the NAb assay; there was no impact on the PK and efficacy of evinacumab in the patient.

Pharmacokinetic interaction studies

No in vitro, in silico or in vivo drug-drug interaction studies have been performed. The effects of concomitant medication have been explored in the population pharmacokinetic analysis.

Exposure relevant for safety evaluation

At steady-state, the mean C_{max} and $AUC_{0\text{-}tau}$ were estimated to be 690 (± 157) mg/L and 10286 (± 3138) mg*day/L, following a 15 mg/kg dose.

2.4.3. Pharmacodynamics

Mechanism of action

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

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

Primary and Secondary pharmacology

The pharmacodynamics (PD) of evinacumab have been studied in 8 clinical studies: three phase 1 studies in healthy subjects with elevated lipid levels, one phase 2 study in patients with HoFH, one phase 2 study in patients with persistent hypercholesterolemia, including patients with HeFH (refractory hypercholesterolemia), one phase 2 study in patients with severe hypertriglyceridemia (SHTG) at risk for acute pancreatitis, and two phase 3 studies in patients with HoFH.

Pharmacodynamic data were collected as follows:

- Total ANGPTL3 (Target): Systemic concentrations of total ANGPTL3 were assessed in all studies as a marker for target engagement.

In the bioanalysis total AngPTL3 was measured. This means that all AngPTL3 being measured consists of "free" AngPTL3 and AngPTL3 complexes with evinacumab. This indicates target binding, because the concentration of AngPTL3 increases and the AngPTL3-evinacumab complex is most likely broken down less quickly than AngPTL3. So a rise in "total" AngPTL3 doesn't indicate the actual rise in ANGPTL3 activity as the AngPTL3-evinacumab complex has no more AngPTL3 activity.

Pharmacodynamic assessments included the evaluation of lipid parameters.

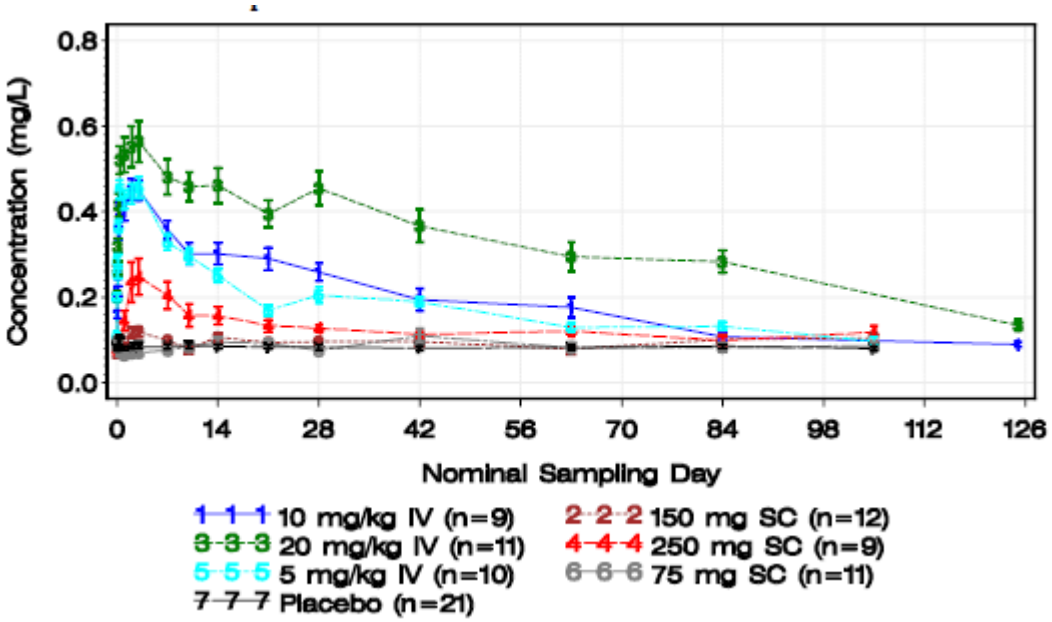
- Triglycerides (Pharmacodynamic Marker): Reduction in TG levels is a direct, rapid PD response to the inhibitory effect of evinacumab on ANGPTL3.

- Analysis of Efficacy (LDL-C) as a Pharmacodynamic Endpoint: The relationship between evinacumab concentration and its effect on LDL-C lowering was assessed through descriptive analyses and by PopPK/PD modelling.

Single dose

A single dose study Phase 1 in 99 healthy subjects **(R1500-HV-1214)** showed that following SC or IV injection of evinacumab, dose-dependent increases in total ANGPTL3 concentrations were observed. This indicates target binding. Mean maximal concentrations increased from 0.11 mg/L to 0.56 mg/L, as dose increased from 75 mg SC to 20 mg/kg IV. In general, the maximum concentration was reached before day 4, 72 hours following either IV or SC administration. Subsequently, concentrations of total ANGPTL3 declined, coinciding with the declining evinacumab concentrations. A plateau of total ANGPTL3 concentration curve was not clearly observed, indicating the absence of target saturation with meaningful duration at the highest dose tested, 20 mg/kg.

Figure 5. Mean (±SE) Concentrations of Total ANGPTL3 in Serum vs Nominal Time in Group A



Note: Group A (N=83) were otherwise healthy volunteers with elevations of TG (in mg/dL: 150≤ TG ≤450) and/or LDL-C (LDL-C ≥100 mg/dL) at baseline).

SC and IV doses of evinacumab induced reductions in TG, VLDL-C, HDL-C, total cholesterol, non-HDL-C, ApoA1, and ApoB. The reductions were dose-dependent. The highest reductions were seen with 10 and 20 mg/kg IV. For LDL-C, the peak reduction in LDL-C occurred approximately between day 11 and day 15 (see figure below). For HDL-C, approximately at day 15 (see figure below).

Figure 6. Mean Percent Change from Baseline in LDL-C (mg/dL, Direct Measure) (±SE) – All Subjects in Group

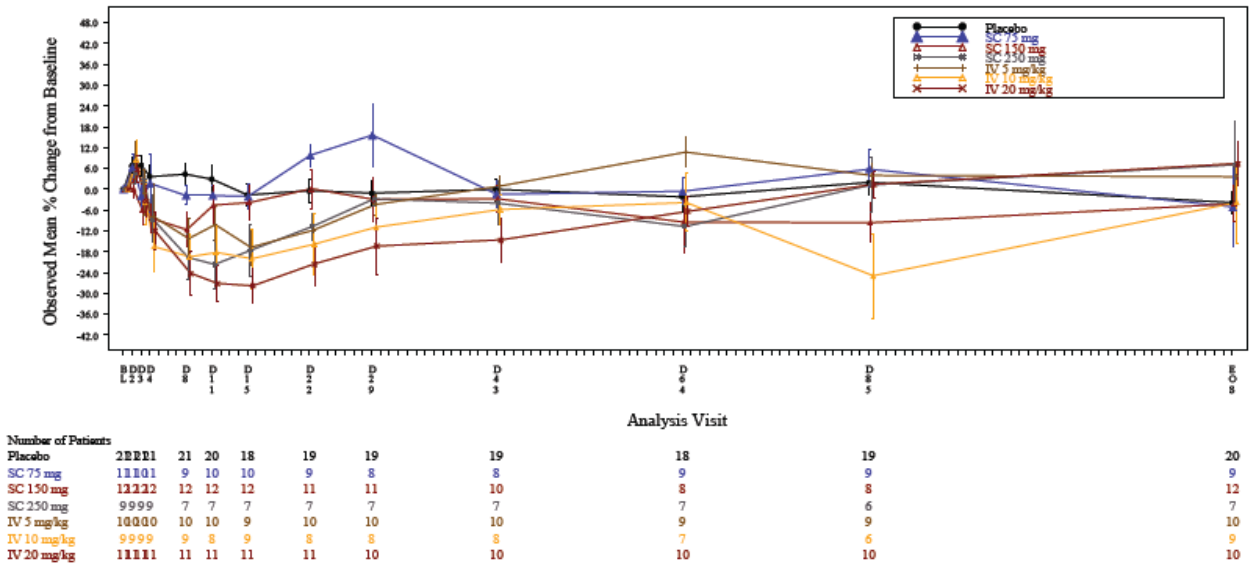
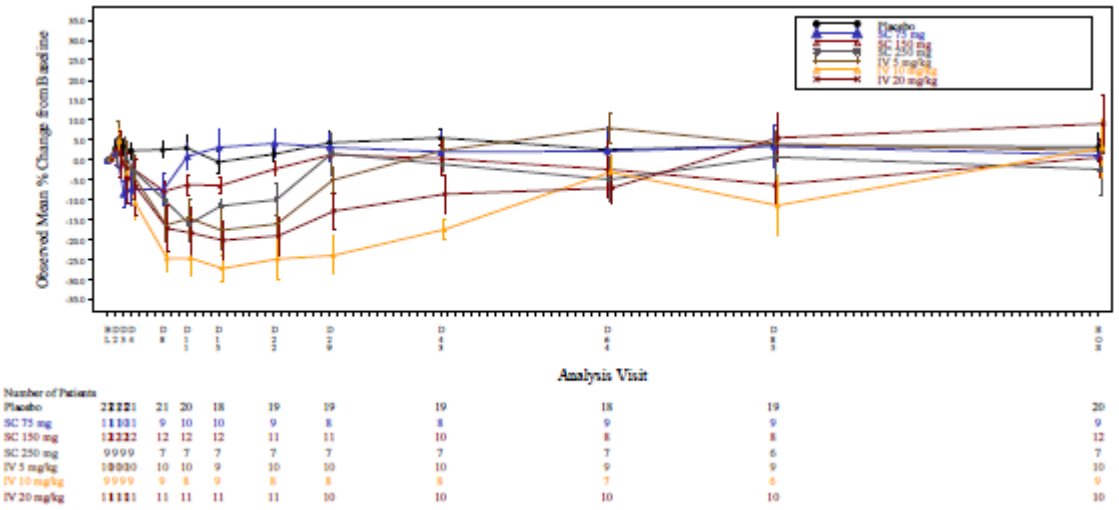


Figure 7. Mean Percent Change from Baseline in HDL-C (mg/dL) (±SE) – All Subjects in Group A



Multiple ascending dose

Study **R1500-CL-1321** was a multiple ascending dose, phase 1 study, conducted in 52 healthy subjects with elevated TGs (150 mg/dL to 500 mg/dL) and LDL-C (≥ 100 mg/dL), evaluating the safety, tolerability, PK, immunogenicity, and PD effects of evinacumab administered IV and SC.

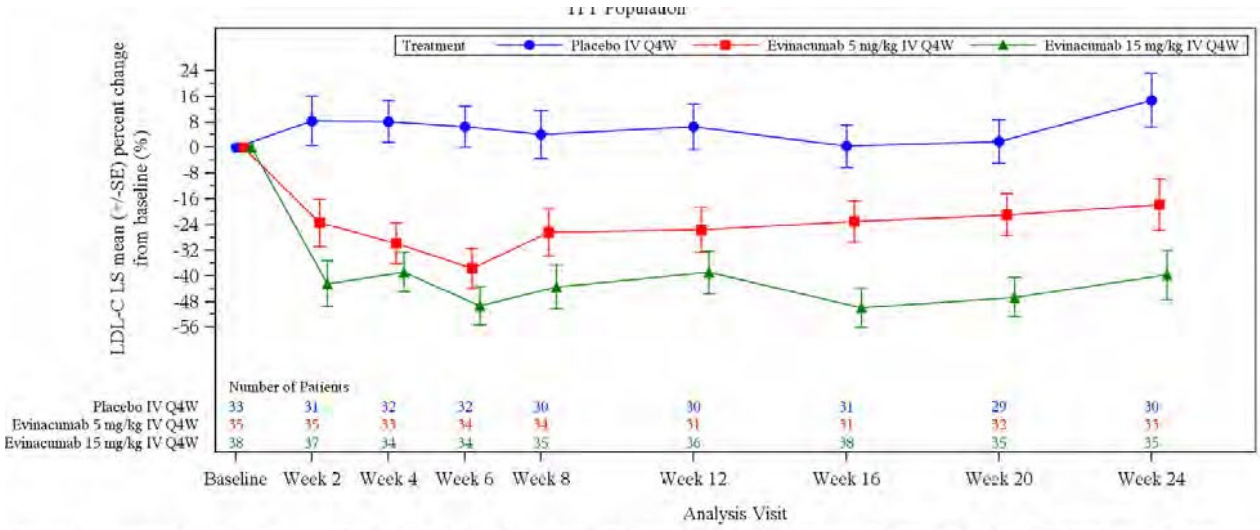
Greatest reductions of more than 40% in LDL-C was observed at 20 mg/kg IV as compared to other SC doses (up to -30%).

Studies with the proposed 15 mg/kg dose

Two studies with the proposed 15 mg/g dose were performed. In a repeated-dose phase 1 race study comparing Japanese with Caucasian patient with elevated LDL-C (n=72) **(study R1500-CL-1642**), a dose-dependent increase in ANGPTL3 and accompanied reductions in LDL-C, including IV doses of 5 mg/kg and 15 mg/kg (also some SC doses were evaluated) was shown after 28 weeks. Further, an

ongoing phase 2 dose-ranging study (n=106) in adult patients with refractory hypercholesterolemia (HeFH, or non-HeFH with a history of clinical atherosclerotic cardiovascular disease [ASCVD]; **study 1500-CL-1643**), showed a dose-dependent effect on ANGPTL3 concentrations and a dose-dependent reduction in LDL-C (15 mg/kg, 5 mg/kg, and placebo) during 24 weeks of treatment.

Figure 8. Calculated LDL-C LS Mean (+/- SE) Percent Change from Baseline Over Time up to week 24 (ITT Estimand): MMRM Analysis ITT Population in study 1500-CL-1643

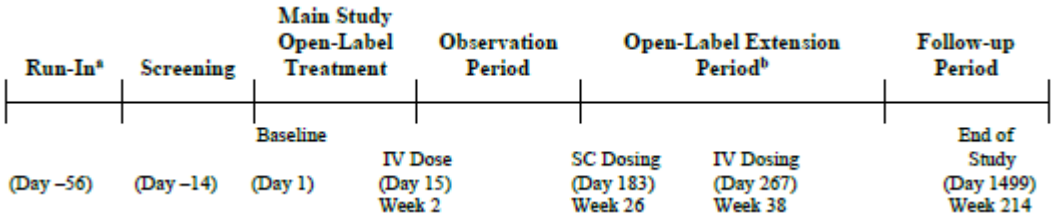


Least-squares (LS) means and standard error (SE) taken a MMRM model with the fixed categorical effects of treatment group, randomization strata (high-intensity statin [Yes/No] and HeFH status [Yes/No]), time point up to week 24, treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value-by-time point interaction.

Proof of concept phase 2 study in the HoFH population

Study **R1500-CL-1331** was an open-label, single-arm proof-of-concept study with nine patients with HoFH with background therapy of lipid-modifying therapies, including statins, ezetimibe, lomitapide, and evolocumab, but excluding apheresis.

Table 4. Study Flow diagram R1500-CL-1331



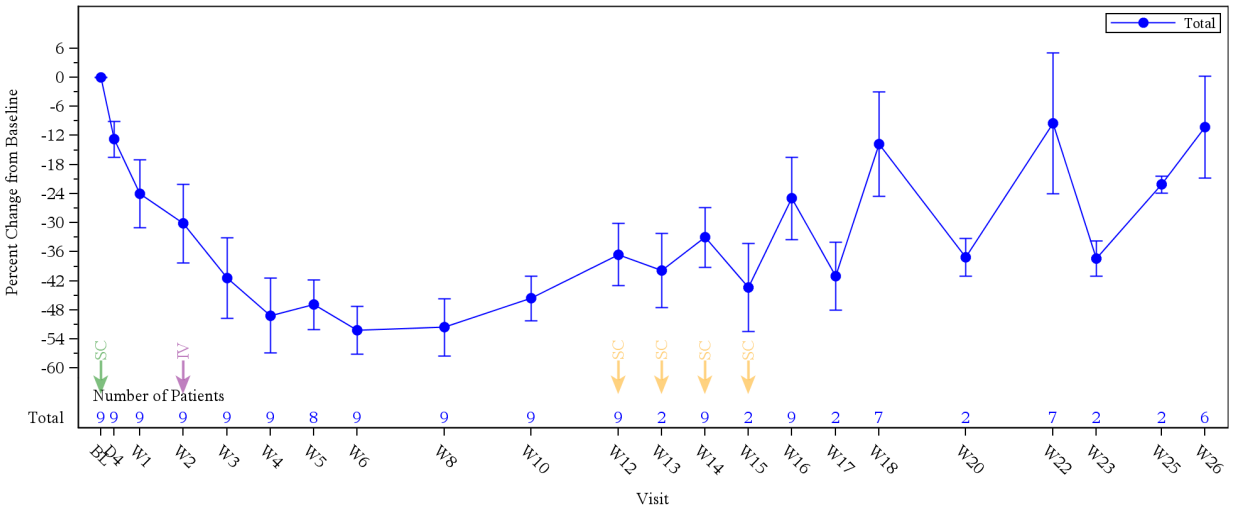
a Patients who require stabilization of their background LMT or washout of apheresis will enter a 4- to 6-week run-in period after signing informed consent but prior to screening. Patients underwent screening again at visit E1a prior to entering the OLE period if they did not go directly into the OLE period from visit 17/Wk 26 of the main study open-label treatment period
b The open-label extension treatment period as defined in the protocol is the same as the open-label extension period.

Several doses were subsequently investigated including 250 mg SC x 1 dose (week 0), 15 mg/kg IV x 1 dose (week 2), 450 mg SC QW x 4 doses (only 2 patients, then replaced by 15 mg/kg IV dose due to

better efficacy), 300 mg SC QW x 4 doses (week 26), 20 mg/kg IV x 1 dose (week 38), and 20 mg/kg IV every 12 weeks (Q12W) (week 58). In 2018, a new phase 3, open-label study (R1500-CL-1719) was initiated, and all patients from this study went into the new study, and this study was terminated.

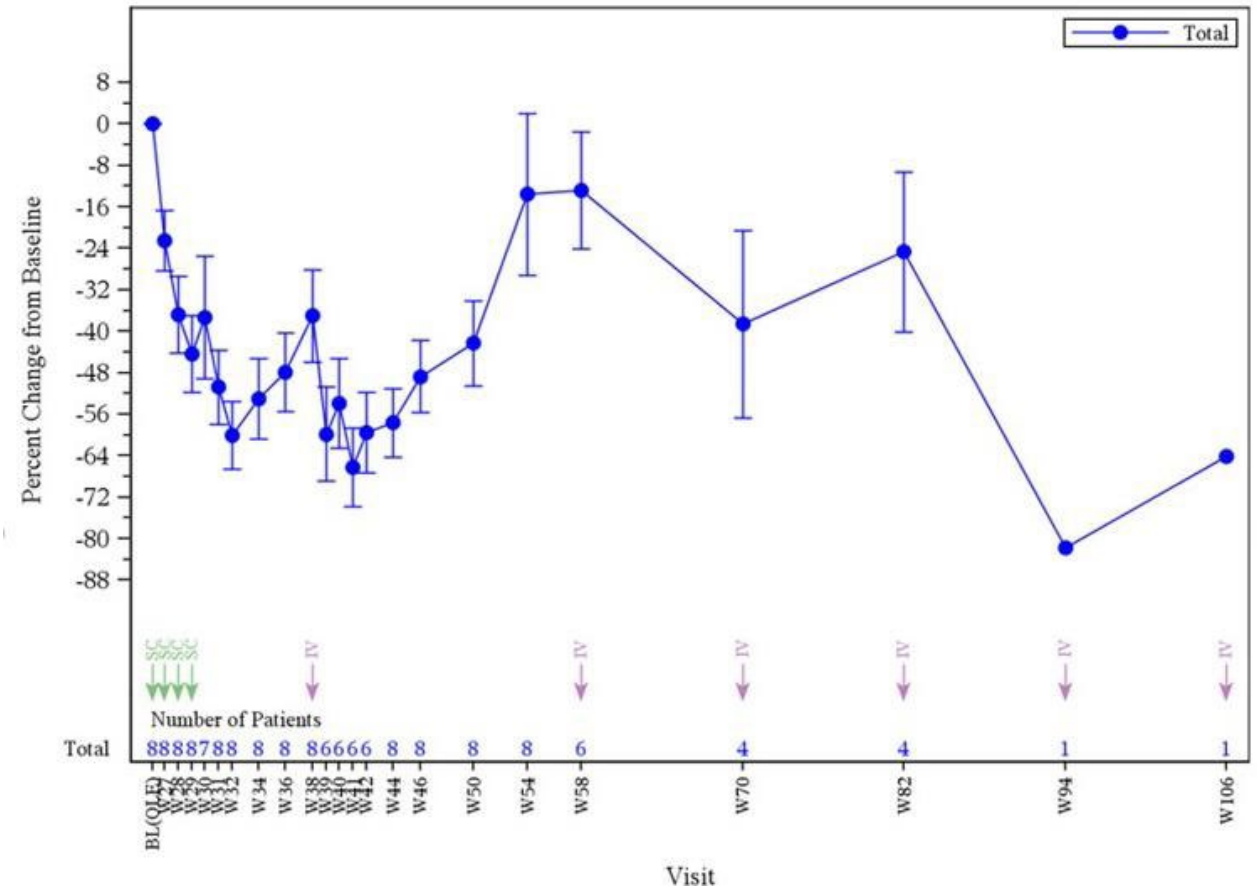
Increases of ANGPTL3 to levels of approximately 0.15 to 0.6 mg/dL were seen from baseline levels of 0-0.15 mg/dL after IV administration of 15 mg/kg. Reduction of ≥50% from baseline in LDL-C was seen in 7 patients, the remaining 2 (null/null) achieved a reduction of ≥25% in LDL-C.

Figure 9. R1500-CL-1331: Mean Percent Change (±SE) from Baseline in LDL-C Over Time in the Main Study Period (Efficacy Analysis Set)



Patients received a single dose of evinacumab 250 mg SC on Day 1 and 15 mg/kg IV at week 2. First 2 patients (patient ID: 124002001 and 124002002) also received a single dose of evinacumab 450 mg SC at weeks 12, 13, 14 and 15.

Figure 10. R1500-CL-1331: Mean Percent Change (±SE) from Baseline in LDL-C Over Time in the OLE Period (Efficacy Analysis Set)



Note: Not all patients entered the OLE period for R1500-CL-1331 directly from the main study due to the timing of the protocol amendment, all post OLE baseline visits are nominal per the schedule of events in the protocol. Eight of the 9 patients in the main study period transitioned into the OLE period. Three treatment regimens were evaluated in the OLE period: 300 mg SC QW x 4 doses at weeks 26, 27, 28, 29; 20 mg/kg IV x 1 dose at week 38; and 20 mg/kg IV Q12W starting at week 58. All patients completed the first two treatment regimens (evinacumab 300 mg SC QW x 4 doses at weeks 26, 27, 28, 29; evinacumab 20 mg/kg IV x 1 dose at week 38) and most patients transitioned into the phase 3 open-label study, R1500-CL-1719, during the third treatment regimen, evinacumab 20 mg/kg IV Q12W starting at week 58.

Study reports from clinical trials in intended populations suggest that LDL-R mutation status does not affect reductions in LDL-C significantly.

Due to the different mechanism of action of evinacumab, direct PD interactions with common lipid-lowering agents are not expected. This assumption is supported by population PK/PD analysis, where concomitant therapies were not found to be covariates.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Analytical methods

All method validation studies (total evinacumab, total AngPTL3, anti-drug antibodies and neutralising antibodies) have not been performed under good laboratory practice (GLP) regulations. Nonetheless, the bioanalytical methods appear to have been appropriately validated, and method validation is in line

with the Guideline on Bioanalytical Method Validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

Pharmacokinetic data analysis

Standard pharmacokinetic methods were used to estimate the pharmacokinetic parameters of evinacumab. In general, the population pharmacokinetic model has been used to determine pharmacokinetic parameters.

Evaluation and Qualification of Models

Population pharmacokinetic model

The applicant developed a bioanalytical method that measures total AngPTL3 (free AngPTL3 + complex of AngPTL3 and evinacumab). Therefore, baseline AngPTL3 is assumed to be a reflection of free circulating AngPTL3 without any presence of evinacumab; however, it should be noted that it is uncertain whether it is an adequate reflection of the amount of free AngPTL3 in the presence of evinacumab. The mechanism of action is to neutralise free AngPTL3, which results in the formation of an AngPTL3-evinacumab complex. Therefore, evinacumab concentrations during a treatment period should be able to neutralise all newly formed AngPTL3 per dosing interval. The applicant did not measure the amount of free evinacumab.

An attempt to fit a more mechanistic model (i.e. target-mediated drug disposition model using baseline triglycerides or baseline AngPTL3) was not successful. It is unclear how the imputation method for missing data in AngPTL3 affected this result, but this could also be due to the fact that total evinacumab was assumed to be the driver for the response (i.e. free evinacumab + complex of AngPTL3 and evinacumab), whereas, in theory, only free evinacumab can neutralise free AngPTL3. The applicant did not account for the fact that total evinacumab concentrations are being measured instead of free evinacumab concentrations. This results in an underestimation of the non-linear clearance pathway of evinacumab. The pharmacokinetics of the free evinacumab and the complex between evinacumab and AngPTL3 can be substantially different, which biases the results. As a result, the submitted population pharmacokinetic model is insensitive for the fluctuation in evinacumab clearance over time as the model does not account for any fluctuations in AngPTL3 concentrations over time. Thus, this model is not suitable for dosing recommendations or any future extrapolations. The applicant is advised in future applications to measure both free evinacumab and total evinacumab in study samples or fit adequate models that account for the target-mediated drug disposition in the case when only total concentrations are available.

The model can, however, be used to estimate pharmacokinetic parameters of total evinacumab concentrations and explain variability in the total evinacumab concentrations over time in the dataset it was built on as long as it is noted that the model does not account for variability over time caused by fluctuations in AngPTL3. The effect of this covariate is for the above-mentioned reasons most likely underestimated. Furthermore, the fact that both disease state and AngPTL3 affected non-linear elimination of total evinacumab could indicate that the AngPTL3 concentration (and also the fluctuation over time) is different between healthy volunteers and patients with HoFH, which could explain a different pharmacokinetic behaviour in patients as compared to healthy volunteers. The applicant has provided interpretable prediction-corrected visual predictive checks. These plots indicate that the model adequately predicts total concentrations of evinacumab for a typical patient included in study 1629.

Population pharmacokinetic/pharmacodynamic model

Free evinacumab neutralises serum AngPTL3, which is supposed to reduce LDL-C and triglyceride concentrations. Therefore, if all AngPTL3 is neutralised by evinacumab, a maximum reduction in LDL-C or triglycerides should also be achieved. The current indirect response model, however, assumes that the concentration of total evinacumab, which is measured as the combination of free evinacumab and the complex between AngPTL3 and evinacumab, is directly linked to LDL-C response. As a result, by increasing the total evinacumab concentration, even if no free AngPTL3 is present, the model assumes that an additional effect can be achieved. The model results and, in particular, the simulations should therefore be interpreted with caution and should not be used to support dosing recommendations.

Absorption

Not applicable as evinacumab is administered as an intravenous injection.

Distribution

It should be noted that the estimates of the volume of distribution are based on a typical subject of 74.1 kg. Weight was a covariate on the model parameter representing the volume of distribution in the central compartment. Therefore, patients with higher body weight are anticipated to have a higher volume of distribution and vice versa. Furthermore, these estimates are based on total evinacumab concentrations (i.e. free evinacumab + complex between evinacumab and AngPTL3). Therefore, these estimates provide a rough approximation of the approximate volume of distribution of free evinacumab.

Metabolism and Excretion

Evinacumab concentration-time profiles indicate both linear- and non-linear elimination pathways, of which the non-linear process could be explained by target-mediated elimination. This is likely as evinacumab neutralises soluble AngPTL3, which is a saturable process (i.e. evinacumab pharmacokinetics are linear in a state where no soluble free AngPTL3 is present in the circulation). Further, the linear elimination process is expected to be caused by non-specific cleavage to small peptides. The applicant indicates that the half-life is not constant in the terminal elimination phase as this is dependent on the dosing regimen, elapsed time after dosing, and the specific concentration at that time point (and of course the concentration of free AngPTL3). In the state of complete neutralisation of AngPTL3 and assuming the production of AngPTL3 is constant, half-life will be predictable and relatively constant at steady state.

Dose proportionality

The pharmacokinetics of evinacumab display target-mediated drug disposition pharmacokinetics. This implies that, if all AngPTL3 in the serum is neutralised, the pharmacokinetics become dose-proportional. For evinacumab, this translates in dose-proportional pharmacokinetics with higher dosages. Nonetheless, these estimates will need to be interpreted with caution as these are based on the total evinacumab concentration (i.e. free evinacumab + complex between evinacumab and AngPTL3) present in the serum.

Time dependency

It is anticipated that free evinacumab is more abundantly present in the systemic circulation compared to the complex between evinacumab and AngPTL3 as the amount of evinacumab administered with the 15 mg/kg dose exceeds the saturable non-linear elimination process over time, in particular at steady state. The complex between evinacumab and AngPTL3 could, however, be subject to extensive accumulation. The applicant is asked to discuss the potential for accumulation of the complex between evinacumab and AngPTL3 and, if applicable, the clinical consequences.

Intra- and inter-individual variability

The between-subject variability in $C_{max,ss}$, $C_{min,ss}$ and AUC_{0-Tau} of total evinacumab varies between 22 – 38%, which was estimated using the population pharmacokinetic model. The variability appears to be increased after repeated administration. No intra-individual variability was estimated for the summary statistics. However, based on the population pharmacokinetic model, after accounting for several covariates, the proportional error was estimated to have a coefficient of variation of approximately 19% (although some questions have been raised about the adequacy of the population pharmacokinetic model). The additive error was minimal 0.3 mg/L. Therefore, it can be expected that the intra-subject variability of evinacumab is in general minimal.

Pharmacokinetics in the target population

Both disease state and baseline AngPTL3 affected the non-linear clearance of total evinacumab in the population pharmacokinetic model. The different non-linear clearance is expected to be a result of differences in AngPTL3 concentrations (both at baseline and over time) between healthy subjects and patients with HoFH. Therefore, any difference in the pharmacokinetics of evinacumab between healthy subjects and patients with HoFH is expected to be a result of differences in AngPTL3 concentrations over time and possible body weight differences.

Special populations

The pharmacokinetics in special populations have been sufficiently characterised. Mainly body weight and AngPTL3 concentrations influence the pharmacokinetics of evinacumab. The influence of body weight has been accounted for by the body weight-based dosing regimen. Nonetheless, the implementation of allometric scaling in the current population pharmacokinetic model is questionable and additional analyses are requested. Furthermore, the influence of AngPTL3 was quantified using the population pharmacokinetic model. It should be emphasized that total AngPTL3 (i.e. free and bound) and total evinacumab (i.e. free and bound) have been measured in the bioanalytical method. The pharmacokinetics of free and bound evinacumab can be substantially different, and as a relatively high dose of evinacumab has been administered, the effect of AngPTL3 on the pharmacokinetics of free evinacumab could have been underestimated. The AngPTL3 concentration is age-independent.

Apheresis did not influence the pharmacokinetics of total evinacumab. It should, however, be noted that apheresis did influence the concentrations of total AngPTL3, which would reduce the non-linear target-mediated drug disposition of evinacumab. The linear elimination pathway is expected to dominate due to the high dose of evinacumab administered; therefore, the reduction of the non-linear clearance of evinacumab is most likely not clinically relevant. In addition, the fact that total AngPTL3 is reduced after apheresis could suggest that the complex between evinacumab and AngPTL3 is removed during apheresis. However, it would be expected that this is also reflected in the total evinacumab concentration. The applicant is asked to comment on this.

Immunogenicity

The probability of developing anti-drug antibodies for evinacumab appears to be minimal. One patient demonstrated a low-titer treatment-emergent ADA, but the neutralising antibody assay was negative, and the applicant stated that no influence on the pharmacokinetics or efficacy was observed.

Interactions

No drug-drug interactions are to be expected for evinacumab as evinacumab is not metabolised by specific enzymes. The only interactions that can be expected are drugs that influence the amount of circulating AngPTL3. Nonetheless, the influence of these interactions is expected to be low as the amount of free evinacumab is more abundantly present at steady state than the amount of bound evinacumab. This is in line with the results of the population pharmacokinetic analysis, which

demonstrated that the influence of statins and PCSK9 inhibitors was minimal as no clear difference in the pharmacokinetics of total evinacumab was observed.

Exposure relevant for safety evaluation

The steady-state exposures have been estimated with the population pharmacokinetic model.

Pharmacodynamics

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

TG and LDL-C were the main lipid parameters used to assess evinacumab's pharmacodynamics. Total ANGPTL3 was used as target engagement marker.

A single dose study demonstrates comparable ANGPTL3 concentrations and an approximately similar reduction in LDL-C with a 5 and 10 mg/kg dose and higher levels of ANGPTL3 and a slightly further reduction in LDL-C with a 20 mg/kg dose. Multiple-dose studies in different type of patients, including patients with elevated LDL-C levels, demonstrate a dose-dependent increase in ANGPTL3 concentrations for 5 and 15 mg/kg iv doses within 72 hours of initiating treatment. The onset of ANGPTL3 increase was within 72 hours of initiating therapy with a lagged effect on LDL-C (maximum effect at 11 to 15 days). Further, a reduction in HDL-C was observed. Generally, this provides some support for the proof of concept, although the exact mechanism is not exactly clear (see discussion above). Several studies have investigated the proposed 15 mg/kg dose, including the proof of concept study in 9 HoFH patients. Based on the results as discussed, the 15 mg/kg dose would be the appropriate dose to be further investigated in the clinical program. Any increased effect of the 20 mg/kg is too minimal in comparison to the 15 mg/kg dose.

As for genetic differences on PD, study reports from clinical trials in the intended population (HoFH) suggest that mutation status does not affect reductions in LDL-C significantly (see efficacy section).

Concomitant lipid-lowering therapies such as statins, PCSK-9 inhibitors and apheresis did not affect the pharmacodynamics of evinacumab (see efficacy section).

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of evinacumab, a recombinant human immunoglobulin-4 (IgG4) monoclonal antibody, have been sufficiently characterised throughout the presented clinical development programme. The recommended dose of evinacumab is 15 mg/kg administered as an intravenous infusion over 60 minutes every 4 weeks. With this relatively high dose, evinacumab displays dose-proportional pharmacokinetics at steady state. Evinacumab displays both linear and non-linear elimination, but at high evinacumab concentrations, the non-linear elimination pathway becomes

saturated. The non-linear elimination represents the target-mediated drug disposition, which is caused by the neutralisation of the target (i.e. angiopoietin-like protein 3 (AngPTL3)). Consequently, free AngPTL3 is the predominant factor influencing the pharmacokinetic profile of evinacumab. Upon complete neutralisation of free AngPTL3, the pharmacokinetics become linear. This is the case with the relatively high 15 mg/kg dose of evinacumab, which is sufficient to completely neutralise all AngPTL3 that is formed during the 4-week interval, which is derived from the absence of non-linear pharmacokinetic behaviour at steady state over the 4 weekly intervals. The applicant is however advised to study the free fractions of both evinacumab and AngPTL3 in combination with the total concentrations of both evinacumab and AngPTL3 in future clinical trials. It is anticipated that a lower dose could achieve similar results but would substantially reduce the burden for patients (e.g. shorter infusion times or less frequent dosing) and could be relevant for the SC formulation which demonstrates more non-linear pharmacokinetic behaviour.

Pharmacodynamics

The conducted phase 1 and 2 studies provide evidence for the general proof of concept of target engagement of ANGPTL3 with an associated lagged reduction in LDL-C levels. Although efforts have been made to demonstrate the mechanism of action, this is not fully understood especially in the HoFH setting with extremely elevated LDL-C levels.

In conclusion the application was considered approvable from clinical pharmacology point of view.

2.5. Clinical efficacy

The submission of evinacumab efficacy in HoFH consists of one pivotal phase 3 study (R1500-CL-1629) including a double-blind and an open-label part, and two supportive studies (R1500-CL-1331, a phase 2 proof-of-concept study and R1500-CL-1719, an ongoing phase 3 open-label extension study).

The pivotal phase 3 study (R1500-CL-1629) is described under Main study below, the ongoing R1500-CL-1719 study is described under supportive studies, and the phase 2 study R1500-CL-1331 is described under Pharmacodynamics.

Details of these studies are presented in the table below:

Table 5. Overview of Clinical Efficacy Studies for Evinacumab in the Treatment of Homozygous Familial Hypercholesterolemia

Study / Report Location/ Study Status	Study Population/ Analysis Sets	Primary objective	Study Design and Duration	Test prouct(s), Dosage Regimen, Route of Administration
R1500-CL-1629 DBTP **R1500-CL-1629 OLTP** DBTP: completed OLTP: completed Austria, France, Greece, Italy, the Netherlands, Japan, Australia, Canada, South	Male and female adults ≥18 years of age and adolescents (≥12 to <18 years old) with HoFH Evinacumab: 44 (actual) Placebo: 21 (actual)	To demonstrate the reduction of LDL-C by evinacumab 15 mg/kg IV in comparison to placebo after 24 weeks in patients with HoFH	Randomized, doubleblind, placebo-controlled and openlabel extension study DBTP: 24 weeks OLTP: 24 weeks	evinacumab or placebo solution in vial **DBTP:** Evinacumab 15 mg/kg IV Q4W for 24 weeks (n = 43) or matching placebo (n = 22) **OLTP:** Evinacumab 15 mg/kg IV Q4W for 24 weeks (n = 64)

Africa, Ukraine, USA (ELIPSE HoFH)				
R1500-CL-1719 Australia, Austria, Canada, France, Greece, Italy, the Netherlands, South Africa, Ukraine, USA Study ongoing	Male and female adults ≥18 years of age and adolescents (≥12 to <18 years old with HoFH). Includes patients from R1500-CL-1331, R1500- CL-1629, and R727-CL-1628[3] studies and evinacumab-naive patients Appr. 120 patients planned	To evaluate the longterm safety and tolerability of evinacumab 15 mg/kg IV administered Q4W in patients with HoFH Efficacy objective: to evaluate the effect of evinacumab on lipid parameters (ie, LDL-C, Apo B, non-HDL-C, TC, and TG)	Open-label study that consists of a run-in period (for patients who may require HoFH genotyping, patients whose background medical LLT has not been stable prior to screening, or those whose apheresis settings and/or schedule have not been stable for at least 8 weeks prior to screening), a screening period, an openlabel treatment period and a follow-up period	Evinacumab 15 mg/kg IV Q4W for up to approximately 4 years in appr. 120 patients (planned) (115 patients enrolled as of 28 Aug 2020)
R1500-CL-1331[1,2] USA, Canada, the Netherlands Study completed	Men and women ≥18 years of age diagnosed with HoFH All 9 patients who entered the main portion of the study and all 8 patients who entered the OLE were included in the safety analysis set (SAF) and efficacy analysis set.	To assess the reduction of LDL-C Within the context of this submission, this study only provided supportive information for efficacy.	Open-label, singlearm, proof-of-concept study (Phase 2) Main study period: up to 34 weeks Open-label extension period: up to 4 years	evinacumab or placebo lyophilized for reconstitution **Main Study Period:** Day 1: 250 mg SC, Day 15: 15 mg/kg IV, and Day 85: 450 mg SC QW x 4 doses[1] Open Label **Extension Period:** Week 26: 300 mg SC QW x 4 doses Week 38: 20 mg/kg IV x 1 dose Week 58: 20 mg/kg IV Q12W

1 The study was amended to remove the 450 mg SC dose regimen. Only 2 patients received this dose regimen.
2 Nine patients were enrolled, and all 9 patients completed the main study period. One patient withdrew from the study after completing the main study period and 8 patients continued into the OLE period. In the OLE period, all 8 patients received evinacumab 300 mg SC QW for 4 weeks and at least 1 dose of 20 mg/kg IV starting at week 38. Subsequently, patients transitioned into the phase 3 study, R1500-CL-1719, at various times during the OLE period
OLE - open-label extension; DBTP – double-blind treatment period; OLTP – open-label treatment period.
3 A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of alirocumab in patients with homozygous familial hypercholesterolemia

2.5.1. Dose response study(ies)

The dose-finding/pharmacology studies have already been discussed within the pharmacology section (see above).

2.5.2. Main study

Title of study

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Evinacumab in Patients with Homozygous Familial Hypercholesterolemia (ELIPSE-HoFH)

Methods

This study consisted of the following: up to 8-week run-in period (for patients who required homozygous familial hypercholesterolemia [HoFH] genotyping, for patients whose background medical lipid-modifying therapy [LMT] was not stable prior to screening or whose apheresis settings and/or schedule were not stable for at least 8 weeks prior to screening), a 2-week screening period, a 24-week double-blind treatment period (DBTP), a 24-week OLTP (open-label phase), and a 24-week follow-up period after the last dose of study drug for patients not entering an optional long-term, open-label study, R1500-CL-1719.

Randomization was stratified by apheresis treatment status (Yes, No) and region (Japan, Rest of World).

The efficacy of evinacumab was assessed by clinical laboratory evaluation of lipid levels at pre-specified time points throughout the study. Overall safety was assessed by monitoring and evaluation of treatment-emergent adverse events (TEAEs), physical examinations, electrocardiogram (ECG), and clinical safety laboratory tests at pre-specified time points. The potential emergence of anti-evinacumab antibodies was also evaluated.

Study Participants

The study planned to randomize approximately 57 patients at 30 multinational sites in 11 countries in Europe, Asia, North America, and Australia. Randomization was stratified by region (Japan, Rest of the World [ROW]) to ensure an appropriate balance in treatment assignment for the Japanese patients.

Key inclusion criteria

The study population consisted of patients with HoFH receiving stable LMT. HoFH was diagnosed by either genetic or clinical criteria:

Genetic criteria

1. Documented functional mutation or mutations in both LDLR alleles (Note: patients who have null receptor mutations on both LDLR alleles, i.e., double null, are eligible),

   OR

2. Presence of homozygous or compound heterozygous mutations in Apo B or PCSK9 (Note: patients who are double heterozygous, i.e., mutations on different genes (e.g., LDLR/PCSK9) and patients with homozygous LDLRAP1 mutations are eligible)

Clinical criteria

Untreated TC > 500 mg/dL (12.93 mmol/L) and TG <300 mg/dL (3.39 mmol/L),

AND

Both parents with documented TC > 250 mg/dL (6.47 mmol) or cutaneous or tendinous xanthoma before the age of 10 years

Lipid modifying therapies could include maximally tolerated daily statin, ezetimibe, PCSK9 inhibitor antibody or other lipid-lowering therapies, including lipoprotein apheresis. Subjects were expected to be on background LLT, including apheresis but were excluded when their LDL-C level was <70 mg/dL (1.81 mmol/L) at screening.

Subjects were to be >12 years of age or >18 years of age, depending on the applicable regulations per country.

Key exclusion criteria

Exclusion criteria designed to prevent confounding of efficacy results included background LLT, including apheresis, not stable for a sufficient period prior to screening, as well as the presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins.

Further, no pregnancies should occur on treatment, and highly effective birth control methods were mandatory, for men and women due to possible negative effects on the fetus seen in non-clinical studies.

Treatments

Patients were randomized 2:1 to receive evinacumab 15 mg/kg intravenously (IV) every 4 weeks (Q4W) or matching placebo IV Q4W starting on day 1. During the 24-week double-blind treatment phase, patients received evinacumab 15 mg/kg IV every 4 weeks (Q4W) or matching placebo IV Q4W. During the 24-week open-label treatment phase, all patients received open-label evinacumab 15 mg/kg IV Q4W. The last dose of double-blind study drug was administered at week 20. After completion of the DBTP, all patients entered a 24-week OLTP to receive open-label evinacumab 15 mg/kg IV Q4W.

Objectives

The following objectives and endpoints were specified:

Table 6. Objectives and endpoints

Objectives	**Endpoints/Estimands**
Primary	
The primary objective of the study was to demonstrate the reduction of LDL-C by evinacumab 15 mg/kg IV in comparison to placebo after 24 weeks in patients with HoFH	The primary endpoint was the percent change in calculated LDL-C from baseline to week 24 The primary endpoint was defined as: 100x (calculated LDL-C value at week 24 -calculated LDL-C value at baseline)/calculated LDL-C value at baseline (ITT estimand)
Secondary	
To evaluate the effect of evinacumab 15 mg/kg IV on other lipid parameters (ie, Apo B, non-HDL-C, and total cholesterol [TC]) in patients with HoFH	• Percent change in Apo B from baseline to week 24 (ITT estimand) • Percent change in non-HDL-C from baseline to week 24 (ITT estimand) • Percent change in TC from baseline to week 24 (ITT estimand) • Percent change in TG from baseline to week 24 (ITT estimand), • Percent change in Lp(a) from baseline to week 24 (ITT estimand) • Percent change in Apo CIII from baseline to week 24 (ITT estimand)

To evaluate the effect of evinacumab on LDL-C goal attainment	• The proportion of patients with ≥30% and ≥50% reduction in calculated LDL-C at week 24 (ITT estimand) • The proportion of patients with LDL-C <100 mg/dL (2.59 mmol/L) and <70 mg/dL (1.81 mmol/L) at week 24 (ITT estimand)
To assess the effect of evinacumab on patients meeting eligibility criteria for apheresis (using German and US apheresis criteria)	• The proportion of patients who meet EU apheresis eligibility criteria (see German Apheresis Working Group) at week 24 (ITT estimand) • The proportion of patients who meet US apheresis eligibility criteria (see US [National Lipid Association] Lipid Apheresis Criteria) at week 24 (ITT estimand)
To evaluate the safety and tolerability of evinacumab 15 mg/kg in patients with HoFH	Incidence of TEAEs
To determine concentrations of evinacumab in patients with HoFH	Total evinacumab concentrations in serum at selected time points
To evaluate the potential development of anti-evinacumab antibodies	ADA status (positivity, titer and neutralizing activity) over time
Other	
Genotyping was performed for all patients to identify mutations causing HoFH and to explore potential differences in efficacy and safety based on type of LDLR function variant	Response on each EQ-5D item, index score, and change of index score from baseline through week 24
To assess the effect of evinacumab on quality of life using the EQ-5D and HADS QOL questionnaires	Response on HADS from baseline through week 48

ADA, anti-drug antibody; Apo B, apolipoprotein B; HADS, Hospital Anxiety and Depression Scale; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; QOL, Quality of Life; TEAEs, treatment-emergent adverse events.

Outcomes/endpoints

The primary endpoint was the percent change in calculated LDL-C from baseline to week 24.

The secondary efficacy endpoints include assessments of other atherogenic lipoproteins or lipid parameters associated with an elevated risk of ASCVD (ApoB, TC, non-HDL-C, TG, and ApoB/ApoA1 ratio), the proportion of patients reaching predefined LDL-C targets, or proportion of patients meeting certain apheresis eligibility criteria (see also table above).

Randomisation and Blinding (masking)

Evinacumab IV (Q4W) or matching placebo IV Q4W for the 24-week double-blind treatment period (DBTP). The randomization was stratified by apheresis treatment (Yes, No) and by region (Japan, Rest of World).

Study patients, the principal investigators, and study site personnel were to remain blinded to all randomization assignments throughout the DBTP (up to week 24). Lipid results from blood samples collected after the randomization visit were not communicated to the sites, and the sponsor's operational team did not have access to these laboratory results until after completion of the DBTP and the first-step analysis. Although there is a slight colour difference between the drug product and placebo product for IV infusion bag preparation, the colour difference was not detectable when the investigational product is added to the IV infusion bag. Treatment assignment was not to be provided to site personnel, other than the unblinded study pharmacist, at any time during the conduct of the study, except in the case of a true emergency.

Statistical methods

The ITT population is defined as all randomized patients who received at least one dose or part of a dose of double-blind study drug. The modified ITT (mITT) population is defined as the all randomized population who took at least 1 dose or part of a dose of study drug and had an evaluable primary endpoint. The ITT and mITT population will be analyzed as randomized. The double-blind safety analysis set (SAF) considered for safety analyses will be the randomized population who received at least 1 dose or part of a dose of double-blind study drug and will be analyzed according to the treatment received.

The double-blind primary efficacy analysis will compare the evinacumab treatment group to placebo at week 24. The percent change from baseline in calculated LDL-C will be analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within week 2 to week 24 analysis windows will be used, and missing data are accounted for by the MMRM model. The model will include the fixed categorical effects of treatment group, randomization strata and region, time point, strata-by-time point interaction, and treatment by time point interaction, as well as, the continuous fixed covariates of baseline calculated LDL-C value and baseline value-by-time point interaction. The statistical testing of the comparison for the primary measure will be evaluated at a 2-sided significance level of 0.05. This model will be run with an unstructured correlation matrix to model the within-patient errors.

Robustness of the primary analysis statistical methods will be assessed through sensitivity analyses, including an on-treatment analysis using the mITT population, and a pattern mixture model (PMM) will be employed to assess the potential violation of the missing at random assumption.

Continuous secondary variables anticipated to have a normal distribution (i.e., lipids other than TG and Lp[a]) will be analyzed using the same MMRM model as for the primary endpoint. Continuous secondary efficacy endpoints anticipated to have a non-normal distribution (i.e., TG and Lp[a]), will be analyzed using a robust regression model. Binary secondary efficacy endpoints will be analyzed using stratified logistic regression with treatment group and randomization stratum as a main effect and corresponding baseline value(s) as a covariate. Missing values will be addressed using a multiple imputation approach. In order to address multiple key secondary efficacy endpoints, the overall type-I error will be controlled by the use of a hierarchical inferential approach. Inferential conclusions about key secondary parameters require statistical significance of the prior parameter within the hierarchy.

Results

Participant flow

Double-blind treatment period

Of the 75 patients who were assessed for eligibility, ten patients were excluded: eight did not meet the inclusion criteria, and two refused to participate. In total, 65 patients were randomized (22 patients to placebo and 43 patients to evinacumab). A total of 64 patients completed the 24-week DBTP. One patient from the placebo treatment group withdrew consent after receiving 1 dose of study drug and discontinued the study early.

Open-label treatment period

All 64 patients subsequently enrolled into the open-label part of the study, of which 62 patients completed the 24-week OLTP. One patient discontinued due to pregnancy (evinacumab). One patient (placebo) discontinued due to non-compliance with the protocol. This placebo patient (4.5%) had

incorrectly received evinacumab treatment at week 20, which was identified after the first DBL. Therefore, in the open-label treatment period, this subject was counted as former evinacumab.

Protocol deviations

Table 7. Protocol Deviations – Randomized Patients

	Placebo IV Q4W (N=22)	Evinacumab 15 mg/kg IV Q4W (N=43)
Patients with any protocol deviations	20 (90.9%)	40 (93.0%)
Any important protocol deviations	11 (50.0%)	21 (48.8%)
Any minor protocol deviations	17 (77.3%)	39 (90.7%)
Types of important protocol deviations		
Category 1: Inclusion/Exclusion criteria deviation but randomized	0	0
Category 2: Inadequate Informed consent administration	0	1 (2.3%)
Category 3: Randomization and drug allocation errors	1 (4.5%)	0
Category 4: Procedural irregularities	8 (36.4%)	10 (23.3%)
Category 5: Patients developed withdrawal criteria but were not	0	0
withdrawn		
Category 6: Patients received prohibited medications/procedures	2 (9.1%)	6 (14.0%)
Category 7: other	2 (9.1%)	8 (18.6%)

IV, intravenous; Q4W, every 4 weeks.
Note: Percentages were calculated using the number of patients randomized as denominator. All protocol deviations presented here are for data collected up to the data cut-off point and include DBTP and OLTP

Among the most common important deviations of "procedural irregularities", the most common were "procedure performed outside of window"; specifically, apheresis procedure not performed per the patient schedule (10 evinacumab patients [23.3%]; 6 placebo patients [27.3%]), and LDL-C measurement taken after apheresis treatment (1 evinacumab patient [2.3%]; 2 placebo patients [9.1%]). Further, for patients in the evinacumab treatment group, 3 patients (7.0%) were being treated with background PCSK9 inhibitor antibodies whose regimens were not stable for at least 8 weeks prior to screening, and 3 patients (7.0%) did not have their background medical LMT stable for at least 4 weeks before the screening visit (week -2).

Recruitment

In total, 22 patients (33.8%) were randomized and treated at sites located in European Union (EU) member countries (Austria, France, Greece, Italy, and the Netherlands [13 females and 9 males; mean age: 33.3 years]) and 10 patients (15.4%) were randomized and treated at sites in Japan (5 females and 5 males; mean age 49.5 years). The remaining 33 randomized patients (50.7%) were from non-EU member countries (Australia [4 patients, 6.2%], Canada [3 patients, 4.6%], South Africa [8 patients, 12.3%], Ukraine [8 patients, 12.3%], and the United States [US] [10 patients, 15.4%].

First patient, first visit was 18 Jan 2018. Week 24 last patient/last visit for the double-blind treatment period was 10 Jun 2019 [DBTP]). The database lock date for the double-blind treatment period was 29 Jul 2019.

For the subsequent open-label extension the last patient/last visit was 26 Nov 2019. Database lock date for the analyses was 16 Jan 2020.

Conduct of the study

Several protocol amendments were made during the study period. Some changes involved changing global protocol into country-specific versions (mainly adding or removing adolescents from the inclusion criteria), clarifications, or minor changes.

From Amendment 4, as reflected in the exclusion criteria, no pregnancies should occur on treatment and highly effective birth control methods were mandatory, for men and women. This due to possible negative effects on the foetus seen in non-clinical studies. Women of childbearing potential should use effective contraception during treatment with evinacumab and for at least 5 months after the last dose of evinacumab.

Baseline data

Baseline demographics

Demographic and clinical characteristics of the patients at baseline are given in the following table:

Table 8. Demographic Characteristics – ITT Population – DBTP

	Placebo IV Q4W (N=22)	Evinacumab 15 mg/kg IV Q4W (N=43)	Total (N=65)	P-Value
Age (years)				
N	22	43	65	0.1531
Mean (SD)	36.7 (11.52)	44.3 (16.78)	41.7 (15.54)	
Median	39.5	41.0	41.0	
Q1 : Q3	30.0 : 44.0	30.0 : 55.0	30.0 : 53.0	
Min : Max	12 : 55	15 : 75	12 : 75	
Age group (years) [n (%)]				
N	22	43	65	0.2089
≥12 to <18	1 (4.5%)	1 (2.3%)	2 (3.1%)	
≥18 to <45	16 (72.7%)	23 (53.5%)	39 (60.0%)	
≥45 to <65	5 (22.7%)	11 (25.6%)	16 (24.6%)	
≥65 to <75	0	7 (16.3%)	7 (10.8%)	
≥75	0	1 (2.3%)	1 (1.5%)	
Age group (years) [n (%)]				
N	22	43	65	0.0436
<65	22 (100%)	35 (81.4%)	57 (87.7%)	
≥65	0	8 (18.6%)	8 (12.3%)	
Sex [n (%)]				
N	22	43	65	0.7936
Male	11 (50.0%)	19 (44.2%)	30 (46.2%)	
Female	11 (50.0%)	24 (55.8%)	35 (53.8%)	
Race [n (%)]				
N	22	43	65	0.8535
White	17 (77.3%)	31 (72.1%)	48 (73.8%)	
Black or African American	0	2 (4.7%)	2 (3.1%)	
Asian	4 (18.2%)	6 (14.0%)	10 (15.4%)	
American Indian or Alaska Native	0	0	0	
Native Hawaiian or Other Pacific Islander	0	0	0	
Not Reported	0	2 (4.7%)	2 (3.1%)	
Other	1 (4.5%)	2 (4.7%)	3 (4.6%)	
Ethnicity [n (%)]				
N	22	43	65	0.8440
Hispanic or Latino	1 (4.5%)	1 (2.3%)	2 (3.1%)	
Not Hispanic or Latino	20 (90.9%)	38 (88.4%)	58 (89.2%)	
Not Reported	1 (4.5%)	4 (9.3%)	5 (7.7%)	
Weight (kg)				
N	22	43	65	0.3824
Mean (SD)	71.5 (23.32)	73.3 (19.28)	72.7 (20.57)	
Median	66.7	71.0	70.0	

Q1 : Q3	53.4 : 76.2	60.2 : 82.9	60.2 : 82.1	
Min : Max	48 : 151	42 : 124	42 : 151	
Height (cm)				
N	22	43	65	0.3974
Mean (SD)	169.5 (11.84)	166.8 (8.71)	167.7 (9.88)	
Median	165.6	166.0	166.0	
Q1 : Q3	162.0 : 177.0	160.0 : 172.3	161.5 : 174.0	
Min : Max	151 : 198	151 : 186	151 : 198	
BMI (kg/m2)				
N	22	43	65	0.1720
Mean (SD)	24.6 (5.69)	26.1 (5.86)	25.6 (5.80)	
Median	23.6	25.5	24.3	
Q1 : Q3	21.5 : 25.5	21.7 : 30.0	21.7 : 28.2	
Min : Max	16 : 40	18 : 46	16 : 46	
BMI group (kg/m2)				
N	22	43	65	0.3492
<30	19 (86.4%)	32 (74.4%)	51 (78.5%)	
≥30	3 (13.6%)	11 (25.6%)	14 (21.5%)	

BMI, body mass index; DBTP, double-blind treatment period; ITT, intent-to-treat; Q4W, every 4 weeks; SD, standard deviation.
Note: p-values comparing baseline data between treatment groups (evinacumab vs placebo) are provided for descriptive purpose, as a screening tool using Fisher exact test for qualitative data and the asymptotic one-way analysis of variance (ANOVA) test for Wilcoxon scores (Kruskal-Wallis test) for continuous data.

Stratification

Patients in both treatment groups were evenly distributed with respect to their apheresis treatment status (yes/no) and their regions (Japan (n=10)/ROW). Twenty-two patients were studied in the EU.

Table 9. Randomization Stratification Factors as per the Interactive Voice Response System – ITT Population

	Placebo IV Q4W (N=22)	**Evinacumab 15 mg/kg IV Q4W (N=43)**	**Total (N=65)**
Apheresis treatment status			
N	22	43	65
Yes	8 (36.4%)	14 (32.6%)	22 (33.8%)
No	14 (63.6%)	29 (67.4%)	43 (66.2%)
Region			
N	22	43	65
Japan	4 (18.2%)	6 (14.0%)	10 (15.4%)
Rest of the World	18 (81.8%)	37 (86.0%)	55 (84.6%)

ITT, intent-to-treat; IV, intravenously; Q4W, every 4 weeks

Overall, 12 patients (18.5%) were on weekly treatment and 10 patients (15.4%) were on bi-weekly treatment of apheresis with a similar frequency in both groups.

Lipid Parameters at Baseline

Among all patients in the DBTP, the mean (SD) baseline calculated LDL-C was 6.6 [4.28] mmol/L.

Table 10. Lipid Parameters at Baseline– ITT Population

SI units	**Placebo IV Q4W (N=22)**	**Evinacumab 15 mg/kg IV Q4W (N=43)**	**Total (N=65)**	**P-Value**
Calculated LDL-C (mmol/L)				
n	22	43	65	0.7498
Mean (SD)	6.4 (3.98)	6.7 (4.47)	6.6 (4.28)	

Median	5.1	5.4	5.2	
Q1 : Q3	3.6 : 8.4	3.9 : 8.8	3.9 : 8.6	
Min : Max	1 : 16	1 : 23	1 : 23	
Apo B (g/L)				
n	22	43	65	0.9723
Mean (SD)	1.8 (0.99)	1.7 (0.83)	1.7 (0.88)	
Median	1.3	1.5	1.5	
Q1 : Q3	1.2 : 2.2	1.1 : 2.2	1.2 : 2.2	
Min : Max	0 : 5	1 : 5	0 : 5	
Non-HDL-C (mmol/L)				
n	22	43	65	0.7237
Mean (SD)	7.0 (4.09)	7.3 (4.47)	7.2 (4.32)	
Median	5.4	5.8	5.6	
Q1 : Q3	4.1 : 8.9	4.3 : 9.4	4.3 : 9.0	
Min : Max	2 : 17	2 : 24	2 : 24	
Total-C (mmol/L)				
n	22	43	65	0.9282
Mean (SD)	8.2 (3.90)	8.4 (4.42)	8.3 (4.22)	
Median	6.6	6.8	6.6	
Q1 : Q3	5.5 : 10.5	5.5 : 10.2	5.5 : 10.2	
Min : Max	3 : 18	3 : 25	3 : 25	
Fasting TG (mmol/L)				
n	22	43	65	0.5281
Mean (SD)	1.6 (1.63)	1.3 (0.77)	1.4 (1.14)	
Median	1.2	1.0	1.1	
Q1 : Q3	0.7 : 2.1	0.7 : 1.6	0.7 : 1.8	
Min : Max	0 : 8	0 : 4	0 : 8	
Apo-A1 (g/L)				
n	22	43	65	0.7237
Mean (SD)	1.3 (0.34)	1.3 (0.32)	1.3 (0.33)	
Median	1.2	1.2	1.2	
Q1 : Q3	1.1 : 1.5	1.0 : 1.4	1.1 : 1.4	
Min : Max	1 : 2	1 : 2	1 : 2	
Apo B/Apo-A1 (ratio)				
n	22	43	65	0.5650
Mean (SD)	1.56 (1.189)	1.45 (0.911)	1.49 (1.006)	
Median	1.11	1.32	1.26	
Q1 : Q3	0.90 : 1.86	0.95 : 1.87	0.94 : 1.86	
Min : Max	0.3 : 4.6	0.3 : 5.9	0.3 : 5.9	
Lp(a) (nmol/L)				
n	22	43	65	0.9227
Mean (SD)	103.4 (109.43)	111.3 (114.40)	108.7 (111.95)	
Median	53.0	59.0	57.0	
Q1 : Q3	32.0 : 134.0	22.0 : 173.0	29.0 : 166.0	
Min : Max	2 : 472	5 : 462	2 : 472	
HDL-C (mmol/L)				
n	22	43	65	0.5696
Mean (SD)	1.2 (0.42)	1.1 (0.39)	1.2 (0.39)	
Median	1.1	1.1	1.1	
Q1 : Q3	0.8 : 1.6	0.8 : 1.4	0.8 : 1.4	
Min : Max	1 : 2	0 : 2	0 : 2	

Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; DBTP, double-blind treatment period; HDL-C, high-density lipoprotein cholesterol; ITT, intent-to-treat; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; Q4W, every 4 weeks; TGs, triglycerides.

History of HoFH

Patients could enter the study based on either clinical criteria or genotyping done prior to study entry: 44 patients (67.7%) were diagnosed by genotyping and 21 patients (32.3%) by clinical criteria.

Table 11. History of HoFH – ITT Population – DBTP

	Placebo IV Q4W (N=22)	Evinacumab 15 mg/kg IV Q4W (N=43)	Total (N=65)
HoFH			
Confirmation of diagnosis	22 (100%)	43 (100%)	65 (100%)
By Genotyping	15 (68.2%)	29 (67.4%)	44 (67.7%)
By Clinical diagnosis	7 (31.8%)	14 (32.6%)	21 (32.3%)
Time from HoFH diagnosis (years) [1]			
n	22	43	65
Mean (SD)	10.65 (12.537)	16.15 (14.562)	14.29 (14.058)
Median	5.49	15.38	9.23
Q1 : Q3	2.26 : 12.00	2.20 : 27.03	2.26 : 25.00
Min : Max	0.1 : 38.0	0.0 : 47.6	0.0 : 47.6

HoFH, homozygous familial hypercholesterolemia; ITT, intent-to-treat; IV, intravenous; Q4W, every 4 weeks; SD, standard deviation.
Note: A patient can be counted in several categories.

[1] Time from diagnosis to study randomization.

Cardiovascular History

A large proportion had a history of cardiovascular disease or CV risk factors (95% vs 88%) with a large proportion with CHD (55% vs 51%), respectively for evinacumab and placebo.

Prior and Concomitant Medications/Procedures

Lipid-Lowering Treatment

At baseline, 93.8% of the total patients were on a statin, and 76.9% were on a high-intensity statin regimen. The main reason for patients not being on a high-intensity statin regimen was due to tolerability issues related to muscle symptoms. In addition to statins, the most frequently used LLT included PCSK9 inhibitors (50 patients [76.9%]), ezetimibe (49 patients [75.4%]), and apheresis (22 patients [33.8%]). Fourteen patients were on lomitapide at baseline.

Most patients were on at least 3 lipid-lowering therapies. The most common reason patients were not on ezetimibe was due to lack of access, and the most common reason patients were not on a PCSK9 inhibitor was due to lack of efficacy.

Table 12. Lipid-Lowering Treatment (LLT) At Baseline – ITT Population

	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W
Number of patients with	(N=22)	(N=43)
Any statin	20 (90.9%)	41 (95.3%)
Taking high intensity statin	16 (72.7%)	34 (79.1%)
Atorvastatin daily dose (mg)		
10	0	1 (2.3%)
20	0	0
40	2 (9.1%)	8 (18.6%)
80	3 (13.6%)	15 (34.9%)
Other doses	1(4.5%)	1 (2.3%)
Rosuvastatin daily dose (mg)		
5	0	0
10	0	0
20	5 (22.7%)	4 (9.3%)
40	5 (22.7%)	7 (16.3%)
Other doses	2 (9.1%)	0
Any non-statin LLT	20 (90.9%)	43 (100%)

Any LLT	20 (90.9%)	43 (100%)
Ezetimibe	16 (72.7%)	33 (76.7%)
Lomitapide	3 (13.6%)	11 (25.6%)
PCSK9 inhibitor [1]	16 (72.7%)	34 (79.1%)
Alirocumab	10 (45.5%)	17 (39.5%)
Evolocumab	6 (27.3%)	17 (39.5%)

Note: High intensity statin corresponds to atorvastatin 40 or 80 mg daily or rosuvastatin 20 to 40 mg daily.
[1] Praluent (alirocumab) or Repatha (evolocumab).

Numbers analysed

The double-blind efficacy analysis set comprised all 65 patients. The open-label efficacy analysis set comprised all 64 patients of the open-label safety set.

Outcomes and estimation

Primary efficacy results (LDL-C)

Treatment with evinacumab resulted in a statistically significant decrease in percent change from baseline calculated LDL-C at week 24 with LS mean difference of -49.0% (95% CI: -65.0% to -33.1%) (-47.1% for evinacumab vs 1.9% for placebo). The absolute mean change in LDL-C was approximately -3.48 mmol/L.

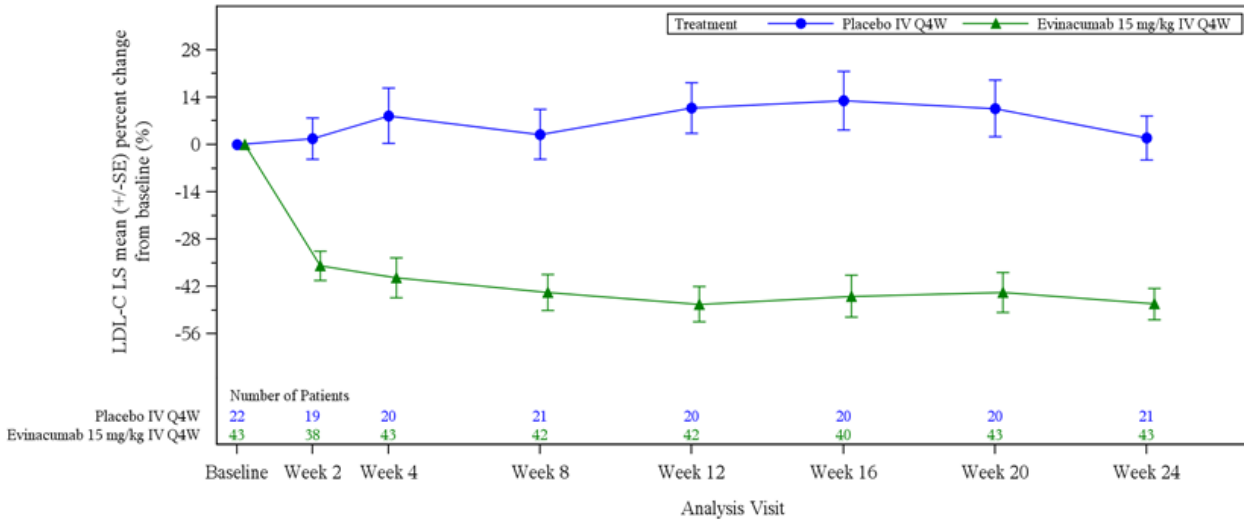
Table 13. Percent Change from Baseline in Calculated LDL-C at Week 24 (ITT Estimand): MMRM Analysis – ITT Population

Calculated LDL Cholesterol	Placebo (N=22)	Evinacumab (N=43)
Baseline (mmol/L)		
n	22	43
Mean (SD)	6.386 (3.9807)	6.721 (4.4651)
Median	5.140	5.390
Min : Max	1.01 : 15.67	1.19 : 23.49
Week 24 percent change from baseline (%)		
LS mean (SE)	1.9 (6.5)	-47.1 (4.6)
LS mean difference (SE) vs Placebo	-49.0 (8.0)	
95% CI	(-65.0 to -33.1)	
p-value vs Placebo	<.0001	

ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; MMRM, mixed-effect model repeat measurement; SD, standard deviation.

Reductions in LDL-C with evinacumab were observed as early as the first post-baseline measurement at week 2, and the reductions were maintained throughout the 24-week DBTP.

Figure 11. Calculated LDL-C LS Mean (±SE) Percent Change from Baseline Over Time (ITT Estimand): MMRM Analysis – ITT Population



Note: Least-squares (LS) means and standard error (SE) taken from a mixed-effect model with repeated measures (MMRM) model with the fixed categorical effects of treatment group, randomization strata (apheresis [Yes/No] and region [Japan, Rest of World]), time point, treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value-by-time point interaction.

Secondary endpoints

The summary key secondary efficacy endpoints in the ITT Population, as analysed according to hierarchical testing, is given in the table below.

Table 14. Summary of Key Secondary Efficacy Analyses (ITT Population)

Key Secondary Endpoint	Placebo (N=22)	Evinacumab (N=43)	Comparison (Evinacumab vs Placebo)	P-value
1. ApoB % change from baseline to WK24	LS mean: -4.5%	LS mean: -41.4%	Diff: -36.9%	<0.0001
2. non-HDL-C % change from baseline to WK24	LS mean: 2.0%	LS mean: -49.7%	Diff: -51.7%	<0.0001
3. TC % change from baseline to WK24	LS mean: 1.0%	LS mean: -47.4%	Diff: -48.4%	<0.0001
4. Pts with ≥30% reduction in LDL-C at WK24	18.2%	83.7%	Odds ratio: 25.2	<0.0001
5. Pts with ≥50% reduction in LDL-C at WK24	4.5%	55.8%	Odds ratio: 24.2	0.0028
6. LDL-C absolute change from baseline to WK24	LS mean: -2.6	LS mean: -134.7	Diff: -132.1	<0.0001
7. Met US apheresis eligibility criteria at WK24 [1]	22.7%	7.0%	Odds ratio: 0.1	**0.0845**
8. LDL-C <100 mg/dL (2.59 mmol/L) at WK24	22.7%	46.5%	Odds ratio: 5.7	0.0203 [3]
9. Met EU apheresis eligibility criteria at WK24 [2]	77.3%	32.6%	Odds ratio: 0.1	0.0004 [3]

[1] A patient met the US apheresis eligibility criteria if LDL-C was ≥300 mg/dL (7.77 mmol/L).
[2] A patient with primary CVD prevention met EU apheresis criteria if LDL-C was >160 mg/dL (4.2 mmol/L) or LDL-C was >120 mg/dL (3.1 mmol/L) for a patient with secondary CVD prevention.
[3] The p-value is nominal for descriptive purpose only.

Other endpoints

- HDL-C

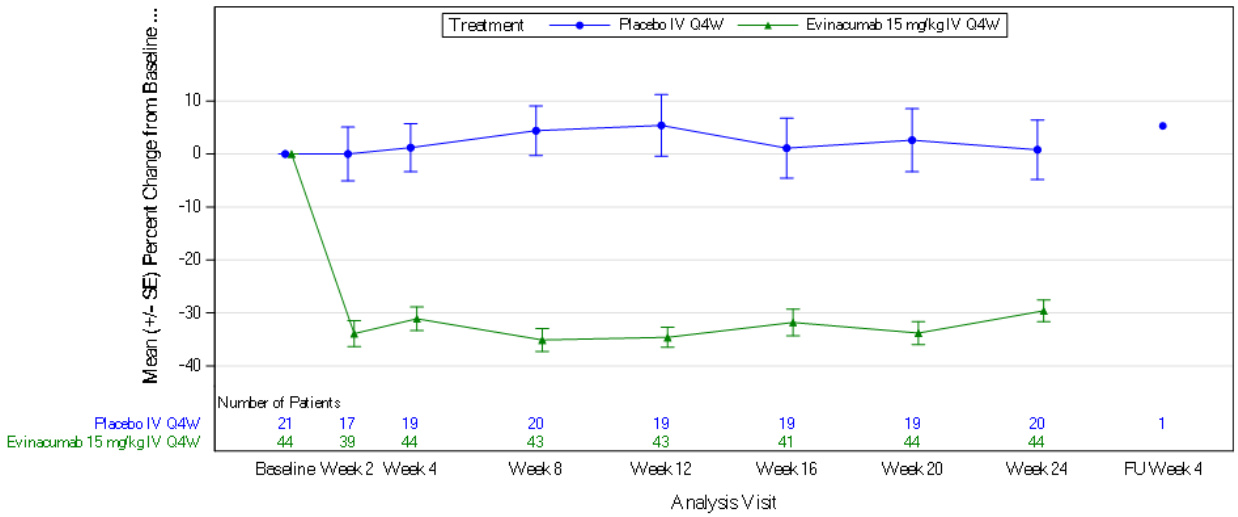
Evinacumab reduced HDL-C levels vs placebo (-30% vs +0.8%) from a baseline level from 1.14 mmol/L to 0.80 mmol/L.

Table 15. HDL-C on Week 24 in SI Unit - Raw Data Description Double-blind Safety Analysis Set - DBTP

	Placebo IV Q4W (N=21)			Evinacumab 15 mg/kg IV Q4W (N=44)		
HDL Cholesterol (mmol/L)	Value	Change from Baseline	Percent Change from Baseline	Value	Change from Baseline	Percent Change from Baseline
Baseline						
n	21	NA	NA	44	NA	NA
Mean (SD)	1.181 (0.4234)			1.135 (0.3836)		
Median	1.110			1.075		
Q1 : Q3	0.830 : 1.550			0.840 : 1.360		
Min : Max	0.52 : 1.86			0.44 : 2.33		
Week 24						
n	20	20	20	44	44	44
Mean (SD)	1.185 (0.4742)	-0.007 (0.2490)	0.79 (25.050)	0.799 (0.3046)	-0.336 (0.2148)	-29.58 (13.519)
Median	1.025	-0.040	-2.30	0.800	-0.310	-31.58
Q1 : Q3	0.870 : 1.580	-0.185 : 0.180	-15.17 : 11.19	0.555 : 0.920	-0.450 : -0.180	-38.73 : -22.20
Min : Max	0.47 : 2.20	-0.51 : 0.57	-32.9 : 73.1	0.26 : 1.55	-0.85 : 0.15	-58.7 : 10.7

Table 14.9.3.11a (week 24)

Figure 12. HDL-C Mean (±SE) Percent Change from Baseline Over Time (On-treatment Estimand) – Raw Data Description – Double-Blind Safety Analysis Set – DBTP



DBTP: Double-blind treatment period.
On-treatment period is up to the day of last dose of study treatment +35 days.

- TG

There was a larger percent change from baseline in fasting TG in the evinacumab treatment group (-55.0%) than in the placebo treatment group (-4.6%; p<0.001).

- Proportion of patients with LDL-C <1.81 mmol/L

The proportion of patients with calculated LDL-C <1.81 mmol/L at week 24 based on an ITT analysis was greater in the evinacumab treatment group (27.9%) than in the placebo treatment group (4.5%; p=0.0209).

- Other lipid parameters

Greater reductions were observed for evinacumab vs placebo for apolipoprotein CIII (Apo CIII), apo A1, while the reduction in Lp(a) could not be maintained at week 24.

Ancillary analyses

Sensitivity Analysis of the Primary Endpoint

Results of the sensitivity analyses were consistent and similar in magnitude to the primary efficacy analysis.

Genotyping and Mutation Subgroup Analyses

Table 16. Percent Change from Baseline in Calculated LDL-C at Week 24 (ITT Estimand): Subgroup Analysis According to HoFH Genotyping – ITT Population

HoFH Genotyping Percent change from baseline in calculated LDL-C at Week 24	Placebo IV Q4W (N=22)	Evinacumab 15 mg/kg IV Q4W (N=43)
Homozygous[1, 2]		
N	8	22
LS mean (SE)	12.0 (10.6)	-52.4 (6.6)
LS mean difference (SE) vs Placebo		-64.4 (12.6)
95% CI		(-89.6 to -39.2)
p-value vs Placebo		<0.0001
Compound Heterozygous [2]		
N	8	12
LS mean (SE)	-7.5 (11.2)	-51.2 (8.6)
LS mean difference (SE) vs Placebo		-43.7 (14.2)
95% CI		(-72.2 to -15.2)
p-value vs Placebo		0.0033
Double Heterozygous [1, 2]		
N	1	2
LS mean (SE)	-25.2 (30.1)	-50.6 (21.8)
LS mean difference (SE) vs Placebo		-25.4 (36.8)
95% CI		(-99.2 to 48.3)
p-value vs Placebo		0.4922
Other [2]		
N	5	7
LS mean (SE)	6.0 (13.9)	-22.7 (12.2)
LS mean difference (SE) vs Placebo		-28.7 (17.9)
95% CI		(-64.6 to 7.1)
p-value vs Placebo		0.1141
Negative/negative		
N	7	5
LS mean (SE)	11.9 (12.0)	-36.9 (14.4)
LS mean difference (SE) vs Placebo		-48.7 (18.1)
95% CI		(-85.0 to -12.4)
p-value vs Placebo		0.0094
Null/null		
N	6	15
LS mean (SE)	16.2 (12.4)	-43.4 (8.0)
LS mean difference (SE) vs Placebo		-59.6 (14.5)
95% CI		(-88.6 to -30.5)
p-value vs Placebo		0.0001
Not Negative/negative		
N	15	38
LS mean (SE)	-2.6 (8.0)	-48.5 (5.0)
LS mean difference (SE) vs Placebo		-45.9 (9.3)
95% CI		(-64.6 to -27.2)
p-value vs Placebo		<.0001
Not Null/null		
N	16	28
LS mean (SE)	-3.8 (7.7)	-49.1 (5.7)
LS mean difference (SE) vs Placebo		-45.3 (9.5)
95% CI		(-64.3 to -26.2)
p-value vs Placebo		<.0001

CI, confidence interval; HoFH, homozygous familial hypercholesterolemia; LDL-C, ITT, intent-to-treat; IV,intravenous; LDL-C, low-density lipoprotein cholesterol; LS, least squares; Q4W, every 4 weeks; MMRM, mixed-effect model repeat measurement; SE, standard error.

Background lipid lowering therapies

Table 17. Efficacy Results at Week 24 by Background Lipid Lowering Therapies

	Placebo	Evinacumab	Placebo	Evinacumab
Background Lipid Lowering Therapies				
	Statin		***No Statin***	
N	19	41	2	2
LDL-C % change, mean (SD)	2.17 (32.338)	-47.29 (30.579)	-5.70 (22.687)	-46.24 (11.007)
	Ezetimibe		***No Ezetimibe***	
N	16	33	5	10
LDL-C % change, mean (SD)	-1.95 (30.579)	-53.07 (20.965)	12.20 (34.136)	-28.02 (45.515)
	PCSK9 Inhibitor		***No PCSK9 Inhibitor***	
N	15	34	6	9
LDL-C % change, mean (SD)	1.73 (30.337)	-49.45 (31.870)	0.65 (36.224)	-38.93 (20.068)
	Apheresis		***No Apheresis***	
N	8	14	13	29
LDL-C % change, mean (SD)	-7.32 (34.260)	-46.15 (18.149)	6.80 (29.221)	-47.77 (34.445)
	Lomitapide		***No Lomitapide***	
N	3	11	18	32
LDL-C % change, mean (SD)	-17.22 (47.620)	-49.64 (22.549)	4.53 (28.387)	-46.42 (32.308)

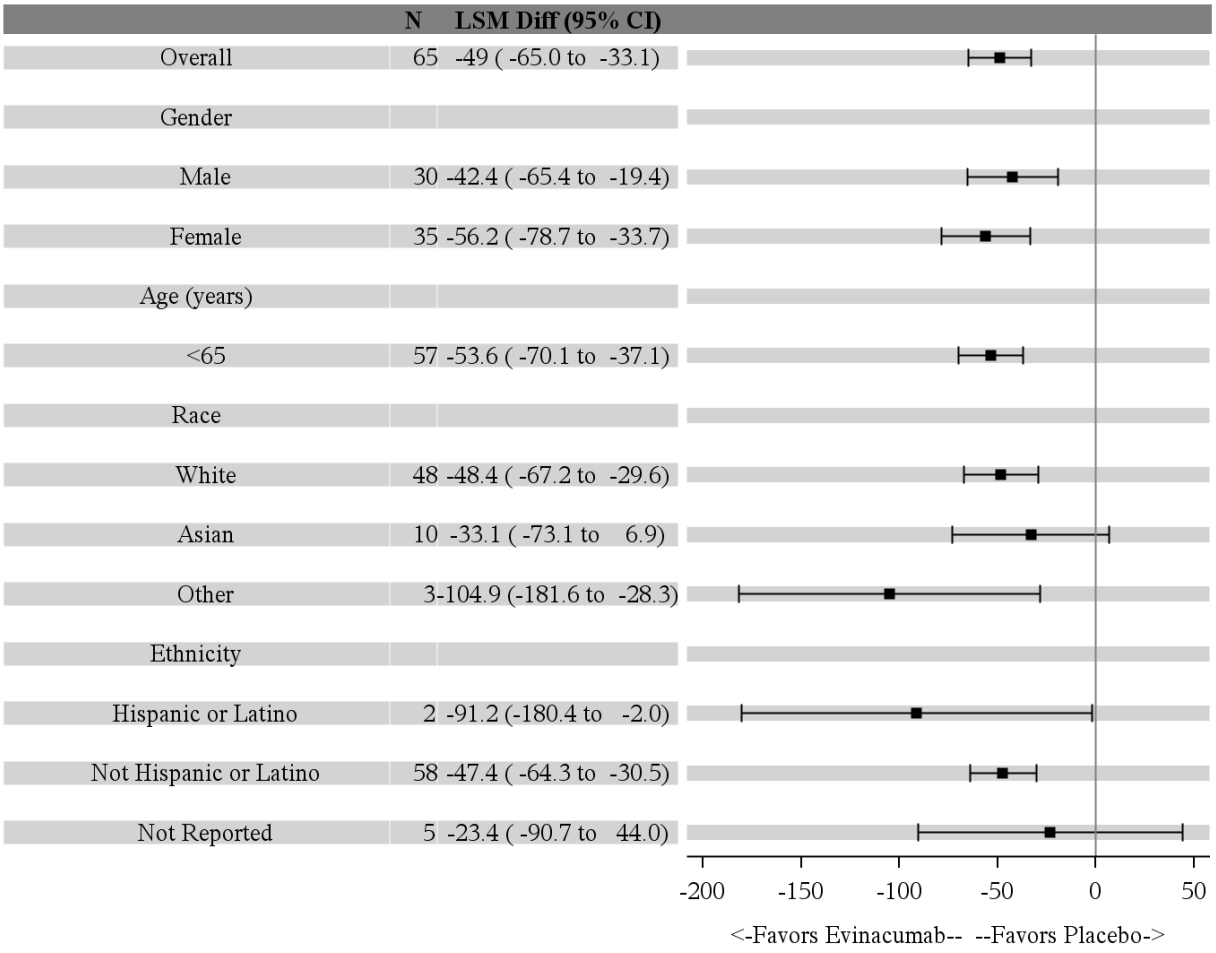
Adolescent Subgroup Analyses

Two adolescents, both null/null, were enrolled with 1 patient randomized to each treatment group. The baseline LDL-C was 10.39 mmol/L for the patient in the evinacumab treatment group and 3.63 mmol/L for the patient in the placebo group. The percent change from baseline in LDL-C at week 24 for the evinacumab-treated adolescent was -73.3%, with an associated absolute change in LDL-C of -7.62 mmol/L. There was a +60% change for the patient treated with placebo, with an associated absolute change in LDL-C of +2.17 mmol/L (reduction in LDL-C was seen in the open-label phase when treated with evinacumab, see further below). More data in adolescents (total 13) are available from the ongoing open-label study R1500-CL-1719 (see section supportive studies).

Demographic and Stratification Factor Subgroup Analyses

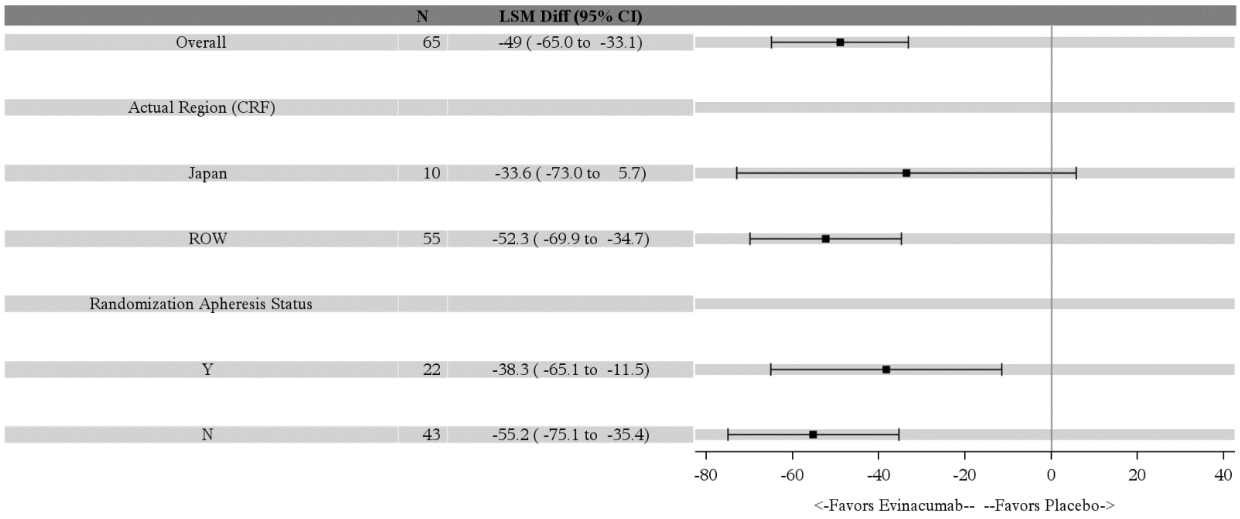
The following figures display the percent change from baseline in calculated LDL-C at week 24 in the ITT analysis as forest plots according to demographic characteristics and stratification factors.

Figure 13. Percent Change from Baseline in Calculated LDL-C at Week 24 (ITT Estimand): Subgroup Analysis According to Demographic Characteristics – Forest Plot – ITT Population



CI, confidence interval; ITT, intent-to-treat; LSM, least squares means.

Figure 14. Percent Change from Baseline in Calculated LDL-C at Week 24 (ITT Estimand): Subgroup Analysis According to Actual Region (CRF) and Randomization Apheresis Status– Forest Plot – ITT Population



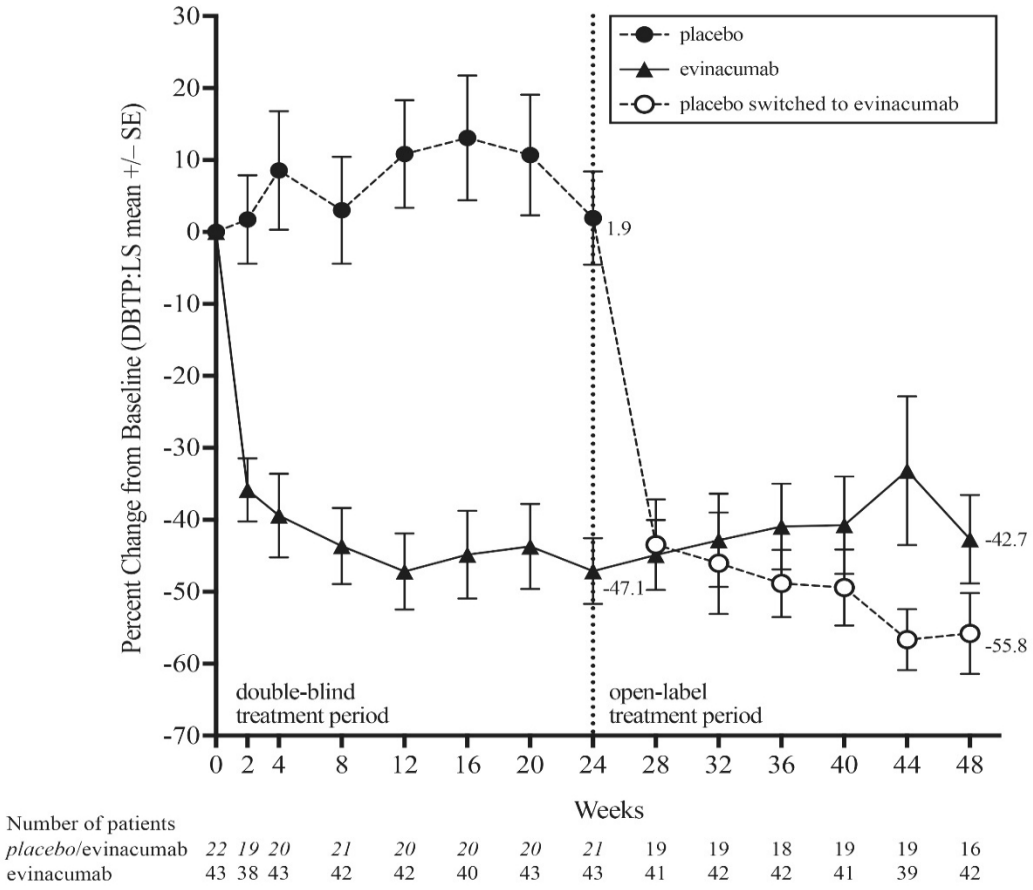
Note: Least-squres (LS) means difference and 95% confidence interval (CI) taken from mixed-effect model with repeated measures (MMRM) analysis.

Open-Label efficacy (additional 24 weeks after pivotal double-blind study phase)

In the overall open-label population (N=64), a mean (SD) absolute reduction of 3.479 mmol/L [3.0386]) in LDL-C was seen from baseline to week 48 with evinacumab treatment, corresponding to a 46.3% reduction, which is in line with the reduction observed in the DBTP.

Similar reductions in LDL-C were seen between patients converted from placebo to evinacumab during the OLTP (see figure below).

Figure 15. Calculated LDL-C LS Mean Percent Change from Baseline Over Time Through Week 24, and Observed Mean Percent Change from Week 28 Through Week 48 in Study ELIPSE-HoFH



Of the 2 adolescent patients treated in the double-blind period, LDL-C reductions at week 48 were 35.7% and 72.3% for the double-blind placebo patient and evinacumab patient, respectively. More data in adolescents (total 13) are available from the ongoing open-label study R1500-CL-1719 (see section supportive studies).

HDL-C remained reduced with a 30% reduction at week 48 (reduction of 0.36 mmol/L).

Effects on other lipid parameters were consistent with those observed in the double-blind phase.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. The summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit-risk assessment.

Table 18. Summary of efficacy for trial R1500-CL-1629 (ELIPSE-HoFH)

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Evinacumab in Patients with Homozygous Familial Hypercholesterolemia			
Study identifier	Protocol number: R1500-CL-1629 EudraCT number: 2017-001388-19 ClinicalTrials.gov Identifier: NCT03399786		
Design	R1500-CL-1629 was a phase 3 study that consisted of a 24-week randomized, double-blind, placebo-controlled, parallel-group treatment period, then a 24-week, single-arm, open-label treatment period to evaluate the efficacy and safety of evinacumab in patients with Homozygous Familial Hypercholesterolemia (HoFH)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks Double-Blind Treatment Period Up to 8 weeks run-in period 24 weeks Open-Label Treatment Period
Hypothesis	Superiority of evinacumab over placebo in reducing respective lipid values		
Treatments groups	Evinacumab		Evinacumab 15 mg/kg IV Q4W. 24 weeks. n=43
	Placebo		Placebo IV Q4W. 24 weeks. n=22
Endpoints and definitions	Primary endpoint	% change in calculated LDL-C from baseline to week 24	Percent change in calculated LDL-C from baseline to week 24 (ITT estimand)
	Key Secondary Efficacy Endpoint	% change in Apo B from baseline to week 24	Percent change in Apo B from baseline to week 24 (ITT estimand)
	Key Secondary Efficacy Endpoint	% change in non-HDL-C from baseline to week 24	Percent change in non-HDL-C from baseline to week 24 (ITT estimand)
	Key Secondary Efficacy Endpoint	% change in TC from baseline to week 24	Percent change in TC from baseline to week 24 (ITT estimand)
	Key Secondary Efficacy Endpoint	% of patients achieving ≥ 30% reduction in LDL-C at week 24	The proportion of patients with ≥30% reduction in calculated LDL-C at week 24 (ITT estimand)

	Key Secondary Efficacy Endpoint	% of patients achieving ≥ 50% reduction in LDL-C at week 24	The proportion of patients with ≥50% reduction in calculated LDL-C at week 24 (ITT estimand)
	Key Secondary Efficacy Endpoint	Absolute change in LDL-C (mmol/L) from baseline to week 24	Absolute change in LDL-C (mmol/L) from baseline to week 24
	Key Secondary Efficacy Endpoint	% of patients with LDL-C <100 mg/dL (2.59 mmol/L) at week 24	The proportion of patients with LDL-C <100 mg/dL (2.59 mmol/L) at week 24 (ITT estimand)
	Key Secondary Efficacy Endpoint	% patients that met EU apheresis eligibility criteria at week 24	The proportion of patients who meet EU apheresis eligibility criteria (see German Apheresis Working Group in notes under Key Secondary Analysis) at week 24 (ITT estimand)
Database lock	The database lock for the primary efficacy analysis was 29 July 2019		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent-to-treat (ITT) in all randomised patients with homozygous familial Hypercholesterolaemia who received at least one or part of a dose of double blind study drug. Time point: 24 weeks		
Descriptive statistics and estimate variability	Treatment group	Placebo	Evinacumab
	Number of subjects	22	43
	% change in calculated LDL-C from baseline to week 24 (LS mean (SE))	1.9 (6.5)	-47.1 (4.6)
Effect estimate per comparison	**Primary endpoint**	Comparison groups	Evinacumab versus placebo

	% change in calculated LDL-C from baseline to week 24 (LS mean (SE))	% change from baseline versus placebo	-49.0
		95% CI	-65.0 to -33.1
		P-value	<0.0001
Notes	ITT estimand: patients in ITT population whose lipid values obtained within the week 24 analysis window were included in the analysis, regardless of adherence to treatment and subsequent therapies. Statistical model: the analysis used a mixed-effect model with repeated measures (MMRM) approach including the treatment group, randomization strata, timepoint, treatment-by-timepoint, and strata-by-timepoint interaction, as well as the continuous baseline calculated LDL-C value and baseline value-by-timepoint interaction. This model also applies to other similar key secondary endpoints.		
Analysis description	**Key Secondary Analysis**		
Analysis population and time point description	Intent-to-treat (ITT) in patients with homozygous familial Hypercholesterolaemia. Time point: 24 weeks		
Descriptive statistics and estimate variability	Treatment group	Placebo	Evinacumab
	Number of subjects	22	43
	% change in Apo B from baseline to week 24 (LS mean (SE))	-4.5 (4.8)	-41.4 (3.3)
	% change in non-HDL-C from baseline to week 24 (LS Mean (SE))	2.0 (5.4)	-49.7 (3.8)
	% change in TC from baseline to week 24 (LS Mean (SE))	1.0 (4.2)	-47.4 (3.0)
	% of patients achieving ≥ 30% reduction in LDL-C at week 24	18.2	83.7
	% of patients achieving ≥ 50% reduction in LDL-C at week 24	4.5	55.8

	Absolute change in LDL-C (mmol/L) from baseline to week 24 (LS Mean (SE))	-0.07 (0.46)	-3.48 (0.32)
	% of patients with LDL-C <100 mg/dL (2.59 mmol/L) at week 24	22.7	46.5
	% patients that met EU apheresis eligibility criteria at week 24	77.3	32.6
Effect estimate per comparison	**Key secondary endpoint** % change in Apo B from baseline to week 24 (LS mean (SE))	Comparison groups	Evinacumab versus placebo
		% change from baseline versus placebo	-36.9 (5.9)
		95% CI	(-48.6 to -25.2)
		P-value	<0.0001
	Key secondary endpoint % change in non-HDL-C from baseline to week 24 (LS Mean (SE))	Comparison groups	Evinacumab versus placebo
		% change from baseline versus placebo	-51.7 (6.6)
		95% CI	(-64.8 to -38.5)
		P-value	<0.0001
	Key secondary endpoint % change in TC from baseline to week 24 (LS Mean)	Comparison groups	Evinacumab versus placebo
		% change from baseline versus placebo	-48.4 (5.1)
		95% CI	(-58.7 to -38.1)
		P-value	<0.0001
	Key secondary endpoint % of patients achieving ≥ 30% reduction in LDL-C at week 24	Comparison groups	Evinacumab versus placebo
		Ratio of odds versus placebo*	25.2
		95% CI	(5.7 to 110.5)
		P-value	<0.0001
	Key secondary endpoint % of patients achieving ≥ 50%	Comparison groups	Evinacumab versus placebo
		Ratio of odds versus placebo*	24.2

	reduction in LDL-C at week 24	95% CI	(3.0 to 195.6)
		P-value	0.0028
	Key secondary endpoint Absolute change in LDL-C (mmol/L) from baseline to week 24 (LS Mean (SE))	Comparison groups	Evinacumab versus placebo
		Change from baseline versus placebo	-3.42 (0.56)
		95% CI	(-4.53 to -2.30)
		P-value	<0.0001
	Key secondary endpoint % of patients with LDL-C <100 mg/dL (2.59 mmol/L) at week 24	Comparison groups	Evinacumab versus placebo
		Ratio of odds versus placebo*	5.7
		95% CI	(1.3 to 24.9)
		P-value	0.0203**
	Key secondary endpoint % patients that met EU apheresis eligibility criteria at week 24	Comparison groups	Evinacumab versus placebo
		Ratio of odds versus placebo*	0.1
		95% CI	(0.0 to 0.3)
		P-value	0.0004**
Notes	A patient was considered to have met the EU Apheresis Eligibility Criteria if they fulfilled the criteria set forth by the German Apheresis Working Group (Thompson, 2010): treatment was required for primary CVD prevention and LDL-C was >160 mg/dL (4.2 mmol/L) or if treatment was required for secondary CVD prevention and LDL-C was >120 mg/dL (3.1 mmol/L). * The estimate of odds ratio was obtained by combining the logarithm of odds ratio from logistic regression model analyses of datasets generated by the multiple imputation approach. **Select key secondary efficacy endpoints are presented, the p-value is nominal for descriptive purpose only as statistical hypothesis testing terminated prior to analysis of the endpoint in the hierarchy."		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Elderly

		Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**

R1500-CL-1629 (double-blind)		7	1	0
R1500-CL-1719 (interim)		2	0	0

The number of patients older than 65 years included in the clinical studies is limited (n=10). In study R1500-CL-1629 DBTP at week 24, the LDL-C change from baseline vs placebo was -53.6% in the <65 years group (n=35) and -28.9% in the ≥65 years group (n=8, all evinacumab).

Gender

Evinacumab treatment resulted in a slightly higher reduction in LDL-C in female compared with male (-56.2% and -42.4%, respectively).

Supportive study(ies)

Phase 3 study R1500-CL-1719 (Phase 3, Open-Label, ongoing)

Study R1500-CL-1719 is an ongoing open-label study to evaluate the long-term safety and efficacy of evinacumab in patients ≥12 years of age and adults with HoFH, receiving maximally tolerated lipid-modifying therapy (LMT), including lipoprotein apheresis. Overall (data cut-off date 28 Aug 2020), 117 patients had been enrolled, 70 patients participated in previous evinacumab studies.

Mean (SD) percent change from baseline in LDL-C at week 24 is -43.7% (SD 38; n=81). Reductions from baseline were observed at week 24 in other atherogenic lipid parameters, including a 37%, 46%, 44% and 47% reductions in ApoB, non-HDL-C, TC, and TG. There was a 30% mean reduction in HDL-C from baseline to week 24. Decreases were similar between the New Evinacumab (-47.7% [23]) (n=45) and Continue Evinacumab (-41.7% [44]) (n=70) groups.

At the time of the data cut-off date, 13 adolescents have been included (2 from the placebo-controlled study) with mean duration of treatment of 34.5 weeks ranging from 4 to 61 weeks with 11 patients treated for more than 24 weeks, and 3 more than 48 weeks. Week 24 data are available for 9 patients and demonstrate a reduction in LDL-C of -52.4% (SD 29). This was -67% for adolescents with the null/null variant(n=4) and -40.6% for the non-null/null variants (n=5). Secondary lipid parameters showed substantial reductions in ApoB (-49%), non-HDL-C (-55%), TC (-54%), TG (-52%), although also a reduction in HDL-C was observed (-41%) with an absolute change of 0.42 mmol/L.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The main clinical program consists of a phase 3 placebo-controlled double-blind study including a 24-week double-blind treatment period (evinacumab 15 mg/kg IV every 4 weeks (Q4W) or matching placebo IV Q4W, randomised 2:1) and a 24-week open-label period on evinacumab 15 mg/kg IV Q4W in the targeted population of an intended 65 patients with HoFH. Further, a phase 2 study has been performed in the targeted population of 9 HoFH patients. A placebo-controlled 16-24 weeks study in patients with severe hypercholesterolemia (n=106) could provide further support for the evaluation of the lipid-lowering effect of evinacumab. Further support will be generated from an ongoing open-label study which included both treated and untreated evinacumab patients and intended treatment of up to 4 years. Nevertheless, the clinical programme is currently very limited, especially with regards to the

target population included in the proposed indication but is reasonable considering the very low prevalence (and availability) of these types of patients.

The proposed study population included in the pivotal study is considered appropriate. The HoFH diagnosis had to be genetically or clinically confirmed by specific criteria, which seems appropriate. Further, the population had to receive optimal lipid-lowering therapy (statin, ezetimibe, PCSK9 inhibitor antibody or other lipid-lowering therapies, including apheresis). Inclusion of adolescent HoFH ≥12 years of age is understood considering the high unmet medical need also present in children due to early aged onset of disease, the similarity in disease characteristics with adults and the weight-based dosing as applied. The current study has also been included in the paediatric investigational plan (PIP), amongst other studies.

It was stressed that no pregnancies should occur on treatment and highly effective birth control methods were mandatory, for men and women due to possible negative effects on the foetus seen in non-clinical studies.

The primary endpoint of percent change LDL-C from baseline to week 24 was considered acceptable and sufficiently long to provide reliable, stable data on the evaluation of LDL-C reduction for 6 times administration of evinacumab. Key secondary endpoints evaluation of other lipid parameters (i.e., ApoB, non-HDL-C, and total cholesterol [TC]), the proportion of patients with ≥30% and ≥50% reduction in LDL-C, proportion of patients with LDL-C < 2.6 mmol/L, and on eligibility criteria for apheresis, as well as additional endpoints, including e.g. HDL-C and TG, were considered appropriate to provide a decent understanding on the effects of evinacumab on the overall lipid profile. The open-label extension period of 24 weeks could provide valuable information on the maintenance of effect over almost a year's treatment period. With this clinical program, the assumed clinical benefit was based on the LDL-C surrogate which was considered 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. Nevertheless, to address and confirm that the LDL-C reduction with evinacumab translates into CV benefit is considered valuable, in particular in the context of a new mechanism of action of evinacumab and available inconsistent/incomplete findings on atherosclerosis evaluation in non-clinical studies.

The analysis populations and the primary and secondary analyses were considered acceptable. Missing data handling assuming random missingness is not preferred, however considering the small amount of missing data and suitable sensitivity analysis (e.g. PMM), this was not considered of concern. However, the primary analysis follows a treatment policy strategy, which is not entirely agreed. In the analysis, data is assumed to be missing at random, and this corresponds more with a hypothetical strategy. Again, as the amount of missing data is minimal, this was not further pursued, and the strategy was acceptable. In general, the defined estimand and sensitivity analysis were agreed. However, this would require that background treatment (LMT and apheresis) remains stable. Since this was not the case for all patients, this could have had an impact on the analysis. However, in a post-hoc analysis, the applicant showed this did result in a slightly lower treatment effect but did not change the conclusions.

Efficacy data and additional analyses

Of the enrolled 65 patients, 43 patients were treated with evinacumab and 22 with placebo. All patients remained in the study during the placebo-controlled period and all patients, except one, completed the 48 treatment period.

A sufficient representation of the EU setting was available with 22 patients (33.8%) included from the EU (Austria, France, Greece, Italy, and the Netherlands). Patients were on appropriate background

therapy at the start of study inclusion; 94% were on statins, 73-76% on ezetimibe, 73-79% on PCSK9 inhibitors, 14-26% on lomitapide, and 34% on apheresis. Baseline characteristics (also according to stratification factors) between the groups were fairly similar for this small study for baseline lipid parameters, type of HoFH diagnosis (clinical criteria or genotyping), CV history, and types of LLT. Mean baseline LDL-C level for the total study population was 6.6 mmol/L. Patients with null/null or negative/negative mutations had a higher mean baseline LDL-C, 8.1 mmol/L and 7.5 mmol/L, respectively.

A substantial treatment effect was observed with evinacumab at week 24, as a significant difference in LDL-C between the evinacumab vs placebo of -49.0% (95% CI: -65.0% to -33.1%; mean difference from baseline of -47.1% vs 1.9%, respectively) was observed. This corresponds to a clinically relevant absolute mean change in LDL-C of -3.48 mmol/L, with an effect already starting at week 2. This corresponded to the results already obtained in the phase 2 study in 9 HoFH patients treated with the proposed 15 mg/kg dose. Results of the sensitivity analyses were consistent and similar in magnitude to the primary efficacy analysis. The key secondary endpoint outcomes were in support of the primary endpoint with a significant lowering of all lipid parameters (TC -48.4%, ApoB -36.9%, non-HDL-C -51.7%), except that HDL-C (-30%) was also reduced (see further below).

Further, the lipid-lowering effect was maintained during the additional 24 weeks open-label treatment period with an approximately 50% reduction in LDL-C at week 48 for both evinacumab prolonged treatment patients, while former placebo patients confirmed the previous effect demonstrated in the double-blind phase. Moreover, the effect appeared consistent among several subgroups including genetic mutation variants, regardless of the type of background therapy, and amongst gender, region, and race subgroups.

Moreover, similar results, although very limited, were obtained in adolescents (both null/null genotype). For the one treated with evinacumab LDL-C reduction at week 24 was -73.3%. For the one treated with placebo, this was +60%, however, at week 48 (treated for 24 weeks with evinacumab), the reduction was -35.7% from baseline for this patient. Of note, for the adolescent already treated with evinacumab, this was -72.32% at week 48. These data were reinforced by the availability of efficacy results of an additional 11 adolescents as included in the ongoing open-label study (with 2 adolescents included in pivotal study this gives total of 13 adolescents) demonstrating comparable efficacy of -52% at week 24 for data as available for 9 patients. This is sufficient to consider this population as part of the target population.

Further support for the LDL-C lowering effect comes from a study in adult patients with refractory hypercholesterolemia (HeFH, or non-HeFH with a history of clinical atherosclerotic cardiovascular disease), in which treatment with evinacumab 15 mg/kg confirmed the results as obtained in HoFH patients with a statistically significant decrease in LDL-C at week 16 of -49.9% as compared to placebo. Further, a lower dose of evinacumab 5 mg/kg showed a much lower effect on LDL-C vs placebo (-23.5% at week 16). Further, support for longer-term efficacy data in HoFH patients beyond 48 weeks of evinacumab treatment comes from the ongoing study R1500-CL-1719. Currently, data are available with a cut-off date of 28 Aug 2020, with 117 patients being enrolled. The study further confirmed the LDL-C lowering effect who continued evinacumab treatment with a maintained decrease in LDL-C of -43%.

However, in the pivotal study (as well in other submitted studies), treatment with evinacumab resulted in a 30% reduction in HDL-C at week 24, with HDL-C reaching below normal levels of 0.799 mmol/L. This could likely be to the effect of evinacumab on the endothelial lipase (EL) responsible for the hydrolysis of HDL-C particles. However, the impact of this for reverse cholesterol transport, especially in the setting of this diseased population with extremely high elevated cholesterol, is somewhat uncertain. Further, the potential impact on cardiovascular risk remains unclear, especially since recent

findings challenged a clear correlation between HDL-C targeted treatment (increase in HDL-C) and improvement in cardiovascular risk. The cardioprotective association with LOF variants in ANGPTL3 may suggest that this may overall provide a cardiovascular protective effect with evinacumab. However, extrapolation to current findings may be complicated as the current diseased HoFH population substantially deviated from the LOF population based on the extremely elevated LDL cholesterol levels, and the loss of function in the LDL receptor. Overall, the lowering of HDL-C by evinacumab may likely not importantly offset the potential CV benefits from substantial lowering of LDL-C, although efforts should be made to better understand the CV impact of evinacumab treatment post-approval.

Additional efficacy data needed in the context of a MA under exceptional circumstances

Due to the rarity of the HoFH population (~1 in 300,000 in the EU), it may be challenging if not unfeasible to provide comprehensive data of a robust confirmation on morbidity (CV benefit) and mortality. Anticipating that the level of evidence is considerably less than what would normally be required for a standard approval (with expected robust confirmatory data post-approval), a different regulatory approach was foreseen and needed to be followed. As comprehensive data on safety and efficacy of the product are not available, and the application meets the applicable requirements, a marketing authorisation under exceptional circumstances was proposed by the CHMP during the assessment with the main reason that *indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence* (see EMEA/357981/2005).

Consequently, specific obligation was agreed and included in Annex IIE to form the basis for annual reassessment in the context of MA under exceptional circumstances. 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. This was felt important considering the not completely understood new mechanism of action of evinacumab also in relation to the limited understanding of the implications of the observed potential off target effect of HDL-C reduction.

The following objectives were agreed for the PASS: to evaluate the long term safety outcomes (i.e., hospitalisations, death, and MACE) in patients with Homozygous Familial Hypercholesterolemia (HoFH) who are ≥12 years old and treated with evinacumab, to evaluate the frequency and outcomes of pregnancy in female patients with HoFH treated with evinacumab and to evaluate the atherosclerosis process over time in patients with HoFH who are treated with evinacumab and undergo cardiac imaging. The MAH should conduct and submit the results of this study based on data from a registry in patients with HoFH. Patients included in the existing disease registry: European Atherosclerosis Society (EAS) FH Studies Collaboration (FHSC) Registry were agreed to be the source population for this study.

Further, any evaluation of vascular damage by imaging of the atherosclerosis process will be of particular interest as a confirmation between LDL-C lowering surrogate effect and the proposed longer-term monitoring for MACE events.

The outline specifying the objectives and the design of the proposed PASS study were agreed within current procedure. The draft protocol will be submitted for assessment within 3 months after product approval, and annual study reports will follow within the annual reassessment.

2.5.4. Conclusions on the clinical efficacy

In the pivotal phase 3 study, evinacumab 15 mg/kg 4QW demonstrated a substantial and consistent reduction in LDL-C and other lipid parameters on top of existing therapy options in a limited number of 43 patients with HoFH, including one adolescent, compared to 22 placebo-treated patients. The ongoing long-term study provides data of maintenance of effect in the longer term. Data in adolescents are consistent with the overall data. There is some uncertainty on the effect of a lowering of HDL-C by evinacumab treatment. However, this does likely not offset the potential CV benefits from substantial lowering of LDL-C, although efforts should be made to better understand the CV impact of evinacumab treatment post-approval.

To address this uncertainty related to efficacy aspect in the context of a MA under exceptional circumstances, a PASS study including MACE as one of the endpoints and vascular damage by imaging of the atherosclerosis process through routine clinical practice data generation was agreed. The approval under exceptional circumstances was considered acceptable.

2.6. Clinical safety

The safety evaluation is displayed based on the following:

- the pivotal study in HoFH patients (R1500-CL-1629),
- a combined pool of placebo-controlled data including the pivotal study R1500-CL-1629 (a phase 3 study in HoFH patients) and a phase 2 study in patients with persistent hypercholesterolemia (R1500-CL-1643)), including data on placebo, the 15 mg/kg dose and the 5 mg/kg dose.
- and an open-label pool including safety data of the 15 mg/kg dose as used in HoFH patients from the extension phase of the pivotal study R1500-CL-1629 and the ongoing open-label study R1500-CL-1719 and data from the ongoing open-label phase from patients with persistent hypercholesterolemia (R1500-CL-1643). This both includes patients already treated to any of the placebo-controlled phases as newly included patients.

Patient exposure

A total of 199 patients received any IV dose of evinacumab, with a total duration of exposure of 9556 weeks, or 183.3 patient-years (**Table 19**). The majority of these patients (174 patients, 87.4%) had a least 24 weeks of exposure, and 126 patients (63.3%) had at least 48 weeks of exposure (**Table 20**). Of these 199 patients, 95 (47.7%) had HoFH. Seventy-six HoFH patients were treated with evinacumab 15 mg/kg IV Q4W for at least 24 weeks, and 51 of these patients were treated for at least 48 weeks.

Table 19. Patient Exposure by Evinacumab Regimen - Global Pool (Double-Blind and Open-Label Safety Analysis Set)

	5 mg/kg IV Q4W [1]	15 mg/kg IV Q4W [2]	Any Evinacumab IV
Patients	36	195	199
Total duration of exposure Weeks	798.4	8757.6	9556.0

	5 mg/kg IV Q4W [1]	15 mg/kg IV Q4W [2]	Any Evinacumab IV
Total duration of exposure Patient-Years	15.3	168.0	183.3

Double-blind and open-label periods of phase 2 and 3 studies: 1331, 1629, 1643, and 1719.
Patients from study 1643 can contribute to more than one dose regimen.
Patients from study 1331 are assigned to 15 mg/kg Q4W.
[1] Double-blind period in study 1643.
[2] Double-blind period in studies 1629 and 1643. Open-label period in studies 1331, 1629, 1643, and 1719.

Table 20. Duration of Cumulative Evinacumab Exposure – Pool 1 Global Pool (Double-Blind and Open-Label Safety Analysis Set)

	5 mg/kg IV Q4W [1] (N=36)	15 mg/kg IV Q4W [2] (N=195)	Any Evinacumab IV (N=199)
Patient-year	15.3	168.0	183.3
Duration of evinacumab exposure			
>= 1 day	36 (100%)	195 (100%)	199 (100%)
>= 4 weeks	36 (100%)	195 (100%)	199 (100%)
>= 8 weeks	34 (94.4%)	187 (95.9%)	189 (95.0%)
>= 12 weeks	34 (94.4%)	181 (92.8%)	184 (92.5%)
>= 24 weeks	28 (77.8%)	171 (87.7%)	174 (87.4%)
>= 36 weeks	N/A	132 (67.7%)	142 (71.4%)
>= 48 weeks	N/A	105 (53.8%)	126 (63.3%)
>= 60 weeks	N/A	40 (20.5%)	60 (30.2%)
>= 72 weeks	N/A	20 (10.3%)	28 (14.1%)
>= 84 weeks	N/A	5 (2.6%)	5 (2.5%)
>= 96 weeks	N/A	2 (1.0%)	2 (1.0%)
>= 108 weeks	N/A	0	0

Double-blind and open-label periods of phase 2 and 3 studies: 1331, 1629, 1643, and 1719.
Patients from study 1643 can contribute to more than one dose regimen.
Patients from study 1331 are assigned to 15 mg/kg Q4W.
[1] Double-blind period in study 1643.
[2] Double-blind period in studies 1629 and 1643. Open-label period in studies 1331, 1629, 1643, and 1719.

Pivotal study (R1500-CL-1629)

In R1500-CL-1629 DBTP, the mean (SD) number of study drug infusions was similar between the evinacumab group (5.95 [0.211] infusions) and placebo group (5.62 [1.161] infusions), as was the duration of study drug exposure (24.14 [1.003] weeks in the evinacumab group; 22.78 [4.633] weeks in the placebo group). A total of 38 patients (86.4%) in the evinacumab group and 17 patients (81.0%) in the placebo group completed the DBTP with 24 weeks of study drug exposure.

In R1500-CL-1629 OLTP, a total of 43 patients (97.7%) who received evinacumab during the 24 weeks DBTP and continued in the 24 weeks OLTP completed the open-label treatment period.

Placebo-Controlled Pool

The mean (SD) number of study drug infusions and the duration of study drug exposure were comparable between the groups (5.7 [1.02-1.06] in the all evinacumab and placebo groups and 5.8 [0.84] in the evinacumab 15 mg/kg group) (Table 65). The proportion of patients who completed the DBTP with 24 weeks of study drug exposure was 81.2% (95 patients) in the all Evinacumab IV Doses

group, 82.7% (67 patients) in the evinacumab 15 mg/kg IV group and 81.5% (44 patients) in the placebo group.

Uncontrolled Pool

The mean (SD) number of study drug infusions in the Total Evinacumab group was 8.30 (3.087) with a mean (SD) duration of study drug exposure of 33.45 (12.377) weeks (**Table 21**).

Table 21. Summary of Study Treatment Exposure – Pool 3 Uncontrolled Studies (Open-Label Safety Analysis Set)

	New Evin [1] (N=73)	Continue Evin [2] (N=109)	Total Evin 15 mg/kg (N=182)
Total number of study treatment infusions			
n	73	109	182
Mean (SD)	7.56 (3.528)	8.80 (2.655)	8.30 (3.087)
Median	8.00	8.00	8.00
Min : Max	1.0 : 12.0	1.0 : 15.0	1.0 : 15.0
Duration of study drug exposure (weeks)			
n	73	109	182
Mean (SD)	30.48 (14.254)	35.44 (10.551)	33.45 (12.377)
Median	30.29	32.43	32.29
Min : Max	4.1 : 50.1	4.1 : 59.4	4.1 : 59.4
Duration of study drug exposure by category [patient, n (%)]			
>=1 day to <4 weeks	0	0	0
>=4 weeks to <8 weeks	7 (9.6%)	1 (0.9%)	8 (4.4%)
>=8 weeks to <12 weeks	3 (4.1%)	1 (0.9%)	4 (2.2%)
>=12 weeks to <16 weeks	2 (2.7%)	0	2 (1.1%)
>=16 weeks to <20 weeks	2 (2.7%)	1 (0.9%)	3 (1.6%)
>=20 weeks to <24 weeks	5 (6.8%)	4 (3.7%)	9 (4.9%)
>=24 weeks to <28 weeks	9 (12.3%)	22 (20.2%)	31 (17.0%)
>=28 weeks to <32 weeks	10 (13.7%)	16 (14.7%)	26 (14.3%)
>=32 weeks to <36 weeks	9 (12.3%)	12 (11.0%)	21 (11.5%)
>=36 weeks to <40 weeks	1 (1.4%)	7 (6.4%)	8 (4.4%)
>=40 weeks to <44 weeks	6 (8.2%)	13 (11.9%)	19 (10.4%)
>=44 weeks to <48 weeks	5 (6.8%)	12 (11.0%)	17 (9.3%)
>=48 weeks	14 (19.2%)	20 (18.3%)	34 (18.7%)

Open-label periods of studies: 1629, 1643, and 1719 (excluding patients who participated in the 1331 parent study).
[1] Patients who were randomized to placebo in 1629/1643 DBTP and then received evinacumab in OLTP, or Evin-naive patients enrolled in 1719.
[2] Patients who were randomized to evinacumab in 1629/1643 DBTP and also received evinacumab in OLTP.

Based on updated data (cut-off of 28 August 2020) from study R1500-CL-1719, the mean duration of evinacumab treatment administration in study R1500-CL-1719 for all patients was 52.7 weeks, ranging from 4.1 to 132.1 weeks. There were 110 and 58 patients that had greater than 24 and 48 weeks of treatment exposure, respectively.

Adverse events

Pivotal study

In R1500-CL-1629 DBTP, TEAEs were frequently reported; however, the percentage of subjects with any TEAE was lower in the evinacumab 15 mg/kg IV Q4W group (65.9%) compared with the placebo

group (81.0%) (**Table 22**). The most frequent AEs (≥5.0% of the patients) with a greater incidence with evinacumab compared with placebo were influenza-like illness (11.4% vs 0 patients) and rhinorrhea (6.8% vs 0 patients). The incidence of AEs considered by the investigator related to study drug was higher in the evinacumab group compared with the placebo group (11.4% (n=5) vs 4.8% (n=1), respectively). The drug-related AEs in the evinacumab group included infusion site pruritus (2 patients), pyrexia, vascular pain and muscular weakness (1 patient), gastroenteritis, nasopharyngitis and epistaxis (1 patient), and upper respiratory tract inflammation and nasopharyngitis (1 patient). One patient in the placebo group had treatment-related TEAEs of face oedema and infusion site hypoesthesia.

Table 22. Number (%) Patients with TEAEs that Occurred with PT ≥5% by Primary System Organ Class and PT (Double-Blind Safety Analysis Set – DBTP)

Primary System Organ Class Preferred Term	Placebo IV Q4W (N=21)	Evinacumab 15 mg/kg IV Q4W (N=44)
Patients with at least one TEAE	17 (81.0%)	29 (65.9%)
Gastrointestinal disorders	5 (23.8%)	7 (15.9%)
Toothache	2 (9.5%)	2 (4.5%)
General disorders and administration site conditions	3 (14.3%)	9 (20.5%)
Influenza like illness	0	5 (11.4%)
Infections and infestations	6 (28.6%)	12 (27.3%)
Nasopharyngitis	5 (23.8%)	7 (15.9%)
Urinary tract infection	2 (9.5%)	0
Investigations	2 (9.5%)	0
Aspartate aminotransferase increased	2 (9.5%)	0
Musculoskeletal and connective tissue disorders	2 (9.5%)	7 (15.9%)
Myalgia	2 (9.5%)	0
Nervous system disorders	5 (23.8%)	5 (11.4%)
Headache	5 (23.8%)	4 (9.1%)
Respiratory, thoracic and mediastinal disorders	1 (4.8%)	8 (18.2%)
Rhinorrhoea	0	3 (6.8%)

DBTP, double-blind treatment period; IV, intravenous; PT, preferred term; Q4W, every 4 weeks; SOC, system organ class; TEAE, treatment-emergent adverse event.
MedDRA (Version 22.0) coding dictionary applied.

Placebo-Controlled Pool

In the placebo-controlled studies pool, the percentage of patients with any TEAE was comparable between the treatments groups (~74%)(**Table 23**). The most frequent AEs (≥5.0% of the patients) with a higher incidence (≥2.0% difference) with all evinacumab IV doses compared with placebo were nausea (5.1% vs 1.9%), influenza-like illness (7.7% vs 5.6%), pain in extremity (5.1% vs 0), and dizziness (6.0% vs 0%). These events were also experienced by more patients (≥2.0% difference) in the evinacumab 15 mg/kg group than the placebo group, with the exception of influenza-like illness which was higher compared with the placebo group although no ≥2.0% difference. Additionally, more patients (≥2.0% difference) in the evinacumab 15 mg/kg group experienced nasopharyngitis compared with placebo (16.0% vs 13.0%, respectively). None of the TEAEs of nausea, influenza-like illness, pain in extremity, or dizziness were serious or severe. The majority of TEAEs were classified as mild or moderate in intensity.

The incidence of drug-related AEs was higher in the evinacumab groups compared with the placebo group (10.3% (n=12) in the all evinacumab IV doses group, 11.1% (n=9) in the evinacumab 15 mg/kg IV group vs 7.4% (n=4) in the placebo group). The drug-related TEAEs which occurred in > 1 patient in any evinacumab treatment group were infusion site pruritus (n=2 (2.5%), both in the 15 mg/kg IV evinacumab group) and nasopharyngitis (n=2 (2.5%), both in the 15 mg/kg IV evinacumab group). Drug-related TEAEs which occurred in a single patient treated with evinacumab and none of the placebo patients included nausea, influenza illness, pyrexia, anaphylactic reaction, drug hypersensitivity, gastroenteritis, muscular weakness, epistaxis, nasal congestion, visual impairment, fatigue, upper respiratory tract inflammation.

Table 23. Number (%) of Patients with TEAEs (by Primary SOC and PT) that Occurred in ≥5% of Patients – Pool 2 Placebo-Controlled Studies (Double-Blind Safety Analysis Set)

Primary System Organ Class Preferred Term	Placebo IV Q4W (N=54)	Evinacumab 15 mg/kg IV Q4W (N=81)	All Evinacumab IV Doses [1] (N=117)
Patients with at least one TEAE	40 (74.1%)	60 (74.1%)	87 (74.4%)
Gastrointestinal disorders	11 (20.4%)	17 (21.0%)	28 (23.9%)
Nausea	1 (1.9%)	4 (4.9%)	6 (5.1%)
Diarrhoea	3 (5.6%)	2 (2.5%)	3 (2.6%)
General disorders and administration site conditions	9 (16.7%)	19 (23.5%)	27 (23.1%)
Influenza like illness	3 (5.6%)	6 (7.4%)	9 (7.7%)
Infections and infestations	10 (18.5%)	26 (32.1%)	36 (30.8%)
Nasopharyngitis	7 (13.0%)	13 (16.0%)	16 (13.7%)
Musculoskeletal and connective tissue disorders	11 (20.4%)	17 (21.0%)	28 (23.9%)
Back pain	2 (3.7%)	3 (3.7%)	6 (5.1%)
Myalgia	6 (11.1%)	2 (2.5%)	6 (5.1%)
Pain in extremity	0	3 (3.7%)	6 (5.1%)
Arthralgia	3 (5.6%)	2 (2.5%)	4 (3.4%)
Nervous system disorders	12 (22.2%)	14 (17.3%)	20 (17.1%)
Headache	11 (20.4%)	9 (11.1%)	11 (9.4%)
Dizziness	0	5 (6.2%)	7 (6.0%)
Vascular disorders	4 (7.4%)	5 (6.2%)	9 (7.7%)
Hypertension	3 (5.6%)	0	3 (2.6%)

Double-blind treatment periods of placebo-controlled studies: 1629 and 1643
MedDRA (Version 22.0) coding dictionary applied. TEAE: Treatment Emergent Adverse Events; SOC: System organ class, PT: preferred term.
A patient who reported 2 or more TEAEs with the same preferred term is counted only once for that term.
A patient who reported 2 or more TEAEs with different preferred terms within the same system organ class is counted only once in that system organ class.
SOC is sorted alphabetically and PT sorted by decreasing frequency of the All Evinacumab IV Doses group.
[1] Evinacumab doses include 5 mg/kg (1643 only) and 15 mg/kg.

Uncontrolled Pool

In the uncontrolled pool, 68.1% patients in the total evinacumab group experienced at least 1 TEAE (58.9% in the new evinacumab and 74.3% in the continue evinacumab groups). The TEAEs of nasopharyngitis, back pain, myalgia, and headache observed in the uncontrolled pool occurred in comparable proportions as those observed in the placebo-controlled pool. Ten patients experienced

AEs considered by the investigator related to study drug, all of which occurred on 1 patient with the exception of muscle spasms (2 patients). Six of the 10 patients experienced treatment-related events of infusion reactions (1 patient each with drug hypersensitivity, pruritus generalized, malaise and muscle spasm, 1 patient with infusion-related reaction and asthenia, and 1 patient with feeling hot, swelling face, headache and paraesthesia).

Adverse events of special interest

General allergic events

Pivotal study

In R1500-CL-1629 DBTP, the percentage of patients experiencing a general allergic event was lower in the evinacumab 15mg/kg IV dose group compared with placebo in R1500-CL-1629 (5 patients (9.1%) vs 3 patient (14.3%) and in all cases, the event was comprised of a single patient (asthma, rash, rhinitis allergic, urticaria for the evinacumab group). None of the events was serious, of severe intensity or led to study treatment discontinuation.

Placebo-Controlled Pool

In the placebo-controlled pool, the incidences in allergic events were comparable between the treatment groups (11.1% (n=13) for all evinacumab IV doses, 11.1% (n=9) for evinacumab 15 mg/kg IV group and 11.1% (n=6) for the placebo group (**Table 24**), with no clear differences between single term AEs. The only serious general allergic TEAE was an anaphylactic reaction reported in a patient treated with evinacumab 15 mg/kg IV. Two (1.7%) patients in the all evinacumab IV doses group (anaphylactic reaction (15 mg/kg) and rash (5 mg/kg) and 1 (1.9%) patient in the placebo group (pruritus), discontinued study treatment due to a general allergic TEAE.

Table 24. Number (%) of Patients with AESI: General Allergic Events TEAE(s) by CMQ and PT – Pool 2 Placebo-Controlled Studies (Double-Blind Safety Analysis Set)

Preferred Term	Placebo IV Q4W (N=54)	Evinacumab 15 mg/kg IV Q4W (N=81)	All Evinacumab IV Doses [1] (N=117)
Patients with at least one general allergic event TEAE	6 (11.1%)	9 (11.1%)	13 (11.1%)
Asthma	0	2 (2.5%)	2 (1.7%)
Conjunctivitis	0	1 (1.2%)	2 (1.7%)
Rash	0	1 (1.2%)	2 (1.7%)
Anaphylactic reaction	0	1 (1.2%)	1 (0.9%)
Drug hypersensitivity	1 (1.9%)	1 (1.2%)	1 (0.9%)
Lip swelling	0	0	1 (0.9%)
Pruritus	2 (3.7%)	1 (1.2%)	1 (0.9%)
Rhinitis allergic	0	1 (1.2%)	1 (0.9%)
Seasonal allergy	0	0	1 (0.9%)
Urticaria	0	1 (1.2%)	1 (0.9%)
Dermatitis	1 (1.9%)	0	0
Dermatitis contact	1 (1.9%)	0	0
Face oedema	1 (1.9%)	0	0
Generalised oedema	1 (1.9%)	0	0

Double-blind treatment periods of placebo-controlled studies: 1629 and 1643
MedDRA (Version 22.0) coding dictionary applied. TEAE: Treatment-emergent adverse event. SMQ: standard MedDRA query, PT: preferred term.

Note: General allergic events TEAE(s) defined by using SMQ =hypersensitivity| (broad and narrow) excluding the following preferred terms linked to local injection site reactions (=infusion site dermatitis|, =infusion site hypersensitivity|, =infusion site rash|, =infusion site urticaria|, =injection site dermatitis|, =injection site hypersensitivity|, =injection site rash|, =injection site urticaria|, =injection site vasculitis|) plus =idiopathic angioedema|
A patient who reported 2 or more TEAEs with the same preferred term is counted only once for that term.
PT sorted by decreasing frequency of severe AEs in all evinacumab doses group.
[1] Evinacumab doses include 5 mg/kg (1643 only) and 15 mg/kg.

Uncontrolled Pool

In the uncontrolled studies pool, a lower percentage of patients experienced general allergic TEAEs with evinacumab compared with the placebo-controlled studies pool (4.9% in the total evinacumab 15 mg/kg group). In the updated data from study 7019, allergic reactions were reported in 13 (11.3%) of the patients with mostly pruritus (3.5%), eczema (1.7%) and rash (1.7%).

Infusion reactions

Pivotal study

In R1500-CL-1629 DBTP, infusion reaction TEAEs were reported more frequently in the evinacumab group compared with the placebo group (6.8% (n=3) vs 4.8% (n=1), respectively). For evinacumab, these were 2 patients (4.5%) with infusion site pruritis and 1 patient (2.3%) each with pyrexia (2.3%), muscular weakness (2.3%), and vascular pain (2.3%); the same patient experienced the pyrexia, muscular weakness, and vascular pain.

Placebo-Controlled Pool

Infusion reaction TEAEs were reported more frequently in the evinacumab groups compared with the placebo group (7.7% (n=9) for all evinacumab IV doses, 7.4% (n=6) for evinacumab 15 mg/kg IV group vs 3.7% (n=2) in the placebo group. The only infusion reaction TEAE reported in more than a single patient in any treatment group was infusion site pruritus (2 [1.7%] patients in the All Evinacumab IV Doses group and 0 in the placebo group). Both patients who experienced infusion site pruritus received evinacumab 15 mg/kg IV. The only serious infusion reaction TEAE was an anaphylactic reaction reported in a patient treated with evinacumab 15 mg/kg IV. Two (1.7%) patients in the all evinacumab IV doses group discontinued study treatment due to an infusion reaction TEAE (anaphylactic reaction and rash) compared to 0 in the placebo group (see also above).

Uncontrolled Pool

Infusion reactions TEAEs were reported in 8 (4.4%) patients in the total evinacumab group. None of these events was fatal or serious or led to discontinuation of evinacumab treatment. In the updated data from study 7019, infusion reactions were reported in 6 (5.2%) patients with asthenia (1.7%) and headache (1.7%) as mostly reported.

Hepatic disorders/ liver enzyme elevations

No patients in any treatment group experienced a hepatic disorder regardless of the pool. The percentage of patients who showed liver function test abnormalities were low and approximately similar between the treatment groups (**Table 25**). In the uncontrolled pool, these abnormalities were reported with similar low frequency.

Table 25. Liver Function - Number (%) of Patients with Treatment-Emergent PCSV During TEAE Period (Conventional Units) – Pool 2 Placebo-Controlled Studies (Double-Blind Safety Analysis Set*)*

Parameter Treatment-emergent PCSV Category	Placebo IV Q4W (N=54)	Evinacumab 15 mg/kg IV Q4W (N=81)	All Evinacumab IV Doses [1] (N=117)
Alanine Aminotransferase			
>2 ULN and <=3 ULN and <=2 ULN at baseline	1/53 (1.9%)	1/81 (1.2%)	2/117 (1.7%)
>3 ULN and <=5 ULN and <=3 ULN at baseline	1/53 (1.9%)	0/81	0/117
>5 ULN and <=10 ULN and <=5 ULN at baseline	0/53	1/81 (1.2%)	1/117 (0.9%)
>10 ULN and <=20 ULN and <=10 ULN at baseline	0/53	0/81	0/117
>20 ULN and <=20 ULN at baseline	0/53	0/81	0/117
Aspartate Aminotransferase			
>2 ULN and <=3 ULN and <=2 ULN at baseline	1/53 (1.9%)	2/81 (2.5%)	2/117 (1.7%)
>3 ULN and <=5 ULN and <=3 ULN at baseline	2/53 (3.8%)	0/81	0/117
>5 ULN and <=10 ULN and <=5 ULN at baseline	0/53	1/81 (1.2%)	1/117 (0.9%)
>10 ULN and <=20 ULN and <=10 ULN at baseline	0/53	0/81	0/117
>20 ULN and <=20 ULN at baseline	0/53	0/81	0/117
Bilirubin			
>1.5 ULN - <=2 ULN and =< 1.5 ULN at baseline	1/53 (1.9%)	1/81 (1.2%)	1/117 (0.9%)
>2 ULN and <=2 ULN at baseline	0/53	0/81	0/117
Alkaline Phosphatase			
>1.5 ULN and <=1.5 ULN at baseline	0/53	0/81	0/117
ALT and Total Bilirubin			
(ALT >3 ULN and Total Bilirubin >2 ULN) and (ALT <=3 ULN or Total Bilirubin <=2 ULN) at baseline	0/53	0/81	0/117

Double-blind treatment periods of placebo-controlled studies: 1629 and 1643
PCSV: Potentially clinically significant value. TEAE: Treatment-emergent adverse event.
Note: The number (n) represents the subset of the total number of patients who met the criterion at least once during the TEAE period. The denominator (/N1) for each parameter within a treatment group is the number of patients who had that parameter assessed post-baseline (not missing) during the TEAE period. For PCSV including condition based only on change from baseline the denominator is restricted on patients having (not missing) baseline and a post-baseline values during the TEAE period.
A patient who had 2 or more post-baseline PCSVs for the same test criteria is counted only once and presented by the worst PCSV.
Patients can be counted in more than one category within a laboratory test.
Double-blind TEAE period is defined from the day of the first dose of double-blind study treatment administration to the day of the last dose of double-blind study treatment administration + 168 days (24 weeks) for those patients not proceeding into the OLTP or up to the day before the first dose of open-label study treatment administration for those patients proceeding into the OLTP.
[1] Evinacumab doses include 5 mg/kg (1643 only) and 15 mg/kg.

Muscle events/creatine kinase (CK) elevation

Pivotal study

In R1500-CL-1629 DBTP, muscle-related AEs were more frequently reported in the evinacumab group compared with the placebo group (15.9% (n=7) vs 9.5% (n=2), respectively). The muscle-related AEs in the evinacumab included arthralgia, back pain, muscle spasms, muscular weakness, musculoskeletal chest pain, myalgia intercostal, neck pain, and pain in extremity. None of these events occurred in more than 1 patient. Further, no meaningful changes from baseline in CK were observed, with a mean (SD) change from baseline to week 24 of -13.7 U/L (91.51) in the evinacumab treatment group and -20.1 U/L (284.34) in the placebo treatment group.

Placebo-Controlled Pool

The incidence in muscle-related AEs was slightly higher in the evinacumab groups compared with the placebo group (23.9% (n=28) in the all evinacumab IV doses group, 21.0% (n=17) in the evinacumab 15 mg/kg IV group and 20.4% (n=11) in the placebo group (**Table 26**). The muscle-related TEAEs reported in ≥3% of patients in either evinacumab treatment group and at a higher frequency than placebo included back pain (5.1% all evinacumab, 3.7% evinacumab 15 mg/kg, 3.7% placebo) and pain in extremity (5.1% all evinacumab, 3.7% evinacumab 15 mg/kg, 0% placebo). In contrast, the following TEAEs in this SOC were reported in ≥3% of patients in the placebo group and at a higher frequency than either evinacumab treatment group: myalgia (5.1% all evinacumab, 2.5% evinacumab 15 mg/kg, 11.1% placebo) and arthralgia (3.4% all evinacumab, 2.5% evinacumab 15 mg/kg, 5.6% placebo). Further, no meaningful changes from baseline in CK were observed, with a mean (SD) change from baseline to week 24 of 5.0 (96.04) U/L in the All Evinacumab IV Doses group, 4.4 (104.09) U/L in the evinacumab 15 mg/kg IV group, and -10.1 (176.74) U/L in the placebo group. Additionally, no clinically meaningful differences between treatment groups were noted for PCSVs in CK (**Table 27**).

Table 26. Number (%) of Patients with AESI: Muscle Event TEAE(s) by Primary SOC and PT – Pool 2 Placebo-Controlled Studies (Double-Blind Safety Analysis Set)

Primary System Organ Class Preferred Term	Placebo IV Q4W (N=54)	Evinacumab 15 mg/kg IV Q4W (N=81)	All Evinacumab IV Doses [1] (N=117)
Patients with at least one musculoskeletal and connective tissue disorders TEAE	11 (20.4%)	17 (21.0%)	28 (23.9%)
Musculoskeletal and connective tissue disorders	11 (20.4%)	17 (21.0%)	28 (23.9%)
Back pain	2 (3.7%)	3 (3.7%)	6 (5.1%)
Myalgia	6 (11.1%)	2 (2.5%)	6 (5.1%)
Pain in extremity	0	3 (3.7%)	6 (5.1%)
Arthralgia	3 (5.6%)	2 (2.5%)	4 (3.4%)
Neck pain	0	2 (2.5%)	2 (1.7%)
Flank pain	1 (1.9%)	1 (1.2%)	1 (0.9%)
Intervertebral disc protrusion	0	1 (1.2%)	1 (0.9%)
Limb discomfort	0	1 (1.2%)	1 (0.9%)
Muscle spasms	0	1 (1.2%)	1 (0.9%)
Muscular weakness	1 (1.9%)	1 (1.2%)	1 (0.9%)
Musculoskeletal chest pain	0	1 (1.2%)	1 (0.9%)
Myalgia intercostal	0	1 (1.2%)	1 (0.9%)
Rotator cuff syndrome	1 (1.9%)	0	1 (0.9%)
Spinal osteoarthritis	0	1 (1.2%)	1 (0.9%)
Bursitis	1 (1.9%)	0	0
Facet joint syndrome	1 (1.9%)	0	0
Muscle discomfort	1 (1.9%)	0	0
Musculoskeletal pain	1 (1.9%)	0	0

Double-blind treatment periods of placebo-controlled studies: 1629 and 1643
MedDRA (Version 22.0) coding dictionary applied. TEAE: Treatment-emergent adverse event.
Note: Muscle event TEAEs defined by PTs under SOC: musculoskeletal and connective tissue disorders

Primary System Organ Class Preferred Term	Placebo IV Q4W (N=54)	Evinacumab 15 mg/kg IV Q4W (N=81)	All Evinacumab IV Doses [1] (N=117)

A patient who reported 2 or more TEAEs with the same preferred term is counted only once for that term.
A patient who reported 2 or more TEAEs with different preferred terms within the same system organ class is counted only once in that system organ class.
SOC is sorted alphabetically and PT sorted by decreasing frequency of the All Evinacumab IV Doses group.
[1] Evinacumab doses include 5 mg/kg (1643 only) and 15 mg/kg.

Table 27. Metabolic Function - Number (%) of Patients with Treatment-Emergent PCSV During TEAE Period (Conventional Units) – Pool 2 Placebo-Controlled Studies (Double-Blind Safety Analysis Set)

Parameter Treatment-emergent PCSV Category	Placebo IV Q4W (N=54)	Evinacumab 15 mg/kg IV Q4W (N=81)	All Evinacumab IV Doses [1] (N=117)
Creatine Kinase			
>3 ULN and <=5 ULN and <=3 ULN at baseline	0/53	1/81 (1.2%)	1/117 (0.9%)
>5 ULN and <=10 ULN and CPK =< 5 ULN at baseline	1/53 (1.9%)	2/81 (2.5%)	2/117 (1.7%)
>10 ULN and <=10 ULN at baseline	1/53 (1.9%)	1/81 (1.2%)	1/117 (0.9%)

Double-blind treatment periods of placebo-controlled studies: 1629 and 1643
PCSV: Potentially clinically significant value. TEAE: Treatment-emergent adverse event.
Note: The number (n) represents the subset of the total number of patients who met the criterion at least once during the TEAE period. The denominator (/N1) for each parameter within a treatment group is the number of patients who had that parameter assessed post-baseline (not missing) during the TEAE period. For PCSV including condition based only on change from baseline, the denominator is restricted on patients having (not missing) baseline and a post-baseline values during the TEAE period.
A patient who had 2 or more post-baseline PCSVs for the same test criteria is counted only once and presented by the worst PCSV.
Patients can be counted in more than one category within a laboratory test.
Double-blind TEAE period is defined from the day of the first dose of double-blind study treatment administration to the day of the last dose of double-blind study treatment administration + 168 days (24 weeks) for those patients not proceeding into the OLTP, or up to the day before the first dose of open-label study treatment administration for those patients proceeding into the OLTP.
[1] Evinacumab doses include 5 mg/kg (1643 only) and 15 mg/kg.

Uncontrolled Pool

Muscle-related AEs were reported in 28 (15.4%) patients in the total evinacumab group. The only muscle-related AEs reported in ≥3% of patients in the total evinacumab group was back pain (4.9%). CK elevations >5 × upper limit of normal (ULN) were reported in 5 patients, which either returned to toward baseline while continuing study treatment or were considered resolved if reported as a TEAE. Further, most CK elevations >5 x ULN were attributed to strenuous exercise. In the updated data from study 7019, muscle related events were frequently observed (21.7%). Some patients reported increased CK levels, 4.4% > 3 x ULN and ≤ 5 x ULN, 3.5% > 5 x ULN and ≤ 10 x ULN, and 0.9% > 10 x ULN, which is slightly higher than in the other studies.

Diabetes

Placebo-Controlled Pool

No patient in any treatment group experienced a new-onset of diabetes. Two patients in the all evinacumab group compared to one patient in the placebo group met the criteria for new-onset

diabetes. However, one patient who received evinacumab 15 mg/kg IV in the R1500-CL-1629 DBTP already had HbA1c ≥ 6.5% at baseline, suggesting that the patient was diabetic prior initiating study treatment. Additionally, the second patient who received evinacumab 5 mg/kg IV had baseline and post-baseline fasting glucose levels near to the cut-off values for diabetes, i.e. borderline diabetic patients and high likely did not reflect true new-onset diabetes.

With respect to diabetic complications, potentially clinically significant values for hyperglycemia were reported in 11 patients (9.4%) in the all evinacumab group, including 7 patients (8.6%) in the evinacumab 15 mg/kg group, compared to 2 patients (3.8%) patients in the placebo group. Most of these values were isolated, transient, and returned to within normal limits at the next visit except in 3 patients. These 3 patients (1 in the evinacumab 5 mg/kg group and 2 in the 15 mg/kg group) had more than a single fasting glucose value >126 mg/dL. Two of these 3 patients met the criteria for consideration of NOD (see above). The other patient was diabetic at baseline and had no diabetic complication TEAEs.

Uncontrolled Pool

Three patients met the criteria for new-onset diabetes; however, patient narratives did not suggest true new-onset diabetes. PCSVs for hyperglycemia (at least 1 fasting glucose ≥ 126 mg/dL with baseline < 126 mg/dL) were reported in 6.4% of patients in the total evinacumab group. Most of these values were isolated, transient, and returned to within normal limits at the next visit.

Other AESIs

The limited data provided does not suggest any safety concerns for evinacumab related with cataracts and neurologic events. Additionally, no cases of symptomatic overdose, neurocognitive events, pancreatitis, or immune complex TEAEs were reported in any safety set.

Adverse drug reactions

In order to identify ADRs from the evinacumab clinical data, the placebo-controlled studies pool safety data were screened as follows:

- Adverse events of specific interest for evinacumab as a monoclonal antibody or base on theoretical concerns with lipid-lowering

- All TEAEs at the PT level occurring in 3.0% or more of patients in the all evinacumab IV doses group or evinacumab 15 mg/kg group with a 1.0% or greater frequency than the placebo group were reviewed

- For each TEAE at the PT level, risk differences between the all Evinacumab IV doses group and placebo group and the evinacumab 15 mg/kg IV group and placebo group were evaluated to identify each TEAE for which the lower bound of the 95% CI was ≥0.1%.

Safety data from the uncontrolled studies pool were screened in the same manner with the exception of risk differences evaluation.

Based on this review, the following ADRs have been identified: nasopharyngitis, influenza-like Illness, dizziness, back pain, nausea, abdominal pain, constipation, rhinorrhea, and asthenia.

Additionally, systemic hypersensitivity reactions, including anaphylaxis and infusion reactions, have been reported and, as such, included in the labelling.

Table 28. Adverse Drug Reactions Occurring in ≥2% Patients Treated with Evinacumab – Pool 2 Placebo-Controlled Studies

Adverse Drug Reaction	Evinacumab[1] (n=117)	Placebo (n=54)
Nasopharyngitis	16 (13.7%)	7 (13.0%)
Influenza like illness	9 (7.7%)	3 (5.6%)
Dizziness	7 (6.0%)	0
Back pain	6 (5.1%)	2 (3.7%)
Nausea	6 (5.1%)	1 (1.9%)
Abdominal pain	4 (3.4%)	1 (1.9%)
Constipation	4 (3.4%)	0
Rhinorrhea	4 (3.4%)	0
Asthenia	3 (2.6%)	0

[1.] Includes patients treated 15 mg/kg Q4W IV or 5 mg/kg Q4W IV.

Serious adverse event/deaths/other significant events

Pivotal study

The incidence of SAEs was higher in the evinacumab groups compared with the placebo groups; 2 patients (4.5%) in the evinacumab group vs 0 patient (0%) in the placebo group

Placebo-Controlled Pool

Ten patients (8.5%) in all Evinacumab IV doses group experienced 13 serious TEAEs. In the 15 mg/kg IV group, 8 patients (9.9%) experienced 9 serious TEAEs. In the placebo group, 1 patient (1.9%) experienced 1 serious TEAE (**Table 29**). One serious TEAE of an anaphylactic reaction was considered to be related to study drug; the remaining serious TEAEs did not appear to be related to evinacumab. In most cases, the event could be attributed to the patient's underlying medical history, concomitant medication, or injuries.

Table 29. Number (%) of Patients with Serious TEAEs by Primary SOC and PT – Pool 2 Placebo-Controlled Studies (Double-Blind Safety Analysis Set)

Primary System Organ Class Preferred Term	Placebo IV Q4W (N=54)	Evinacumab 15 mg/kg IV Q4W (N=81)	All Evinacumab IV Doses [1] (N=117)
Patients with at least 1 serious TEAE	1 (1.9%)	8 (9.9%)	10 (8.5%)
Cardiac disorders	0	2 (2.5%)	3 (2.6%)
Coronary artery disease	0	1 (1.2%)	2 (1.7%)
Atrial fibrillation	0	1 (1.2%)	1 (0.9%)
Immune system disorders	0	1 (1.2%)	1 (0.9%)
Anaphylactic reaction	0	1 (1.2%)	1 (0.9%)
Infections and infestations	0	1 (1.2%)	1 (0.9%)
Urosepsis	0	1 (1.2%)	1 (0.9%)

Primary System Organ Class Preferred Term	Placebo IV Q4W (N=54)	Evinacumab 15 mg/kg IV Q4W (N=81)	All Evinacumab IV Doses [1] (N=117)
Injury, poisoning and procedural complications	0	1 (1.2%)	2 (1.7%)
Tendon rupture	0	0	1 (0.9%)
Tibia fracture	0	1 (1.2%)	1 (0.9%)
Investigations	0	1 (1.2%)	1 (0.9%)
Alanine aminotransferase increased	0	1 (1.2%)	1 (0.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (1.2%)	1 (0.9%)
Glioblastoma	0	1 (1.2%)	1 (0.9%)
Nervous system disorders	0	0	1 (0.9%)
Hypertensive encephalopathy	0	0	1 (0.9%)
Syncope	0	0	1 (0.9%)
Psychiatric disorders	0	1 (1.2%)	1 (0.9%)
Suicide attempt	0	1 (1.2%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	1 (1.9%)	0	0
Dyspnoea exertional	1 (1.9%)	0	0
Vascular disorders	0	1 (1.2%)	1 (0.9%)
Peripheral arterial occlusive disease	0	1 (1.2%)	1 (0.9%)

Double-blind treatment periods of placebo-controlled studies: 1629 and 1643
MedDRA (Version 22.0) coding dictionary applied. TEAE: Treatment Emergent Adverse Events; SOC: System organ class, PT: preferred term.
A patient who reported 2 or more TEAEs with the same preferred term is counted only once for that term.
A patient who reported 2 or more TEAEs with different preferred terms within the same system organ class is counted only once in that system organ class.
SOC is sorted alphabetically and PT sorted by decreasing frequency of the All Evinacumab IV Doses group.
[1] Evinacumab doses include 5 mg/kg (1643 only) and 15 mg/kg.

Uncontrolled Pool

In the uncontrolled pool, 15 patients (8.2%) in the Total Evinacumab group experienced 20 serious TEAEs. The majority of serious TEAEs were cardiovascular in nature, or occurred in the context of a cardiac event, reflecting the patients' underlying medical history. In the updated data from study 7019, serious adverse events were limited with unstable angina (2 (1.7%)), aortic valve disease (2 (1.7%)), and chest pain (2 (1.7%)) as most reported.

Deaths

No deaths were observed in patients treated with evinacumab or placebo. In the updated data from study 7019, two deaths were reported, very likely because of MI, and unrelated to study drug.

Adjudicated cardiovascular events

Pivotal study

In R1500-CL-1629 DBTP, there were no positively adjudicated cardiovascular events.

In R1500-CL-1629 OLTP, 2 patients experienced positively adjudicated CV events. One patient experienced TEAEs of cardiac procedure complication and acute myocardial infarction and underwent a coronary artery bypass graft and percutaneous coronary intervention, which were adjudicated to non-fatal myocardial infarction and ischemia-driven coronary revascularization procedure. Another patient experienced a TEAE of coronary artery disease and underwent a coronary artery bypass graft, which

was adjudicated to ischemia-driven coronary revascularization procedure. All of these events were serious, severe in intensity, considered unrelated to the study drug, and were recorded to be recovered/resolved.

Placebo-Controlled Pool

In the placebo-controlled studies pool, there were 2 patients with cardiovascular events that were positively adjudicated (1 event each in the evinacumab 5 mg/kg and 15 mg/kg IV dose groups). Both events were ischemia-driven coronary revascularization procedures in patients with a prior medical history of ischemic heart disease.

Uncontrolled Pool

In the uncontrolled studies pool, a total of 3 patients in the total evinacumab group experienced positively adjudicated CV events, all of whom were in the continue evinacumab group. In addition to the 2 patients described above in the open-label period of the pivotal study, 1 patient had a serious TEAE of palpitations that was positively adjudicated to ischemia-driven coronary revascularization procedure. In the updated data from study 7019, 1 patient (0.9%) had unstable angina requiring hospitalization, and 4 (3.5%) patients had ischemia-driven coronary revascularization (and 2 patients died likely due to MI).

Laboratory findings

Haematology

Placebo-Controlled Pool

There were no clinically meaningful changes from baseline in any haematology parameters (red blood cells, platelets, or white blood cells) nor clinically meaningful differences between the evinacumab and placebo groups with respect to the number of patients with haematology abnormalities that fell into the predefined potentially clinically significant value (PCSV) categories for red blood cells, platelets, leukocytes, basophils, eosinophils, lymphocytes, and neutrophils in the R1500-CL-1629 DBTP and the placebo-controlled pool. However, a higher incidence in patients with potentially clinically significant variables related to monocytes was observed with evinacumab treatment compared with placebo (12% (n=14) in the all evinacumab IV doses group, 13.6% (n=11) in the 15 mg/kg group and 5.7% (n=3) in the placebo group).

Uncontrolled Pool

In the uncontrolled studies pool, a comparable high incidence in PCSVs related to monocytes was observed (~11.0% in all evinacumab groups). The majority of these elevations were singular or transient events with resolution towards baseline with continued evinacumab treatment and therefore did not appear to be related to evinacumab treatment according to the Applicant.

Clinical chemistry

There were no clinically meaningful changes from baseline or difference PCSVs in metabolic function, electrolytes, renal function or liver function parameters observed in the pivotal study, the placebo-controlled pool and the uncontrolled pool.

For details on metabolic, liver and renal function, please see AEs of special interest.

Vital signs

Evinacumab treatment did not result in any clinically meaningful changes in vital signs or ECG parameters.

Safety in special populations

Gender

TEAEs were more frequently reported in female patients than in male patients (85.7% vs 61.5% in the all evinacumab IV doses group, respectively). Moreover, the incidence in TEAEs in females treated with evinacumab was also higher compared to placebo female patients (85.7% vs 79.3, respectively), whereas the incidence in TEAEs in males was lower in the all evinacumab IV doses group compared with placebo (61.5% vs 68.0%, respectively). Nevertheless, the most frequent AEs with a higher incidence with evinacumab compared with placebo observed in both female and male were in general similar as those found in the total placebo-controlled population.

Elderly

No dosage adjustment is required for elderly patients. Three patients were aged ≥75 years in the placebo-controlled pool and 2 patients in the uncontrolled pool, therefore, no subgroup analyses were performed for patients ≥75 years of age. Nevertheless, subgroup analyses showed a higher incidence in any TEAE compared with placebo with advancing age.

Placebo-controlled Pool

Of the 171 total patients in the placebo-controlled pool, 142 were aged ≥18 to <65 years. In this subgroup of patients, 68 patients (70.8%) in the all evinacumab IV doses group (including 48 [70.6%] in the 15 mg/kg group) and 35 patients (76.1%) in the placebo group reported at least 1 TEAE. Preferred terms reported by a greater percentage of patients in the all evinacumab IV doses group than in the placebo group were similar to those seen in the total placebo-controlled pool population. Twenty-four of the 171 total patients were aged ≥65 to <75 years. In this subgroup of patients, 17 patients (89.5%) in the all evinacumab IV doses group (including 10 [90.9%] in the 15 mg/kg group) and 3 patients (60.0%) in the placebo group reported at least 1 TEAE. No safety concerns were identified from these TEAEs in patients aged ≥65 years.

Uncontrolled Pool

Of the 182 total patients in the uncontrolled pool, 153 were aged ≥18 to <65 years, and 24 were aged ≥65 to <75 years. In the subgroup of ≥18 to <65 years, 102 patients (66.7%) experienced at least 1 TEAE in the total evinacumab 25 mg/kg group of which 64 patients (72.7%) in the continue evinacumab and 38 (58.5%) in the new evinacumab groups. In the subgroup of ≥65 to <75 years, 19 patients (79.2%) experienced at least 1 TEAE in the total evinacumab 25 mg/kg group of which 15 patients (78.9%) in the continue evinacumab and 38 (80.0%) in the new evinacumab groups.

Adolescents

Placebo-controlled Pool

Of the 171 total patients in the placebo-controlled pool, only 2 patients were aged ≥12 to <18 years (all HoFH patients): 1 patient in the evinacumab 15 mg/kg group, who experienced 1 TEAE of influenza-like illness and 1 patient in the placebo group, who experienced 3 TEAEs of abdominal pain, nasopharyngitis, and headache.

Uncontrolled Pool

In the updated data from study 7109, 13 adolescent patients have been included.

Immunological events

No treatment-emergent or treatment-boosted anti-drug antibody responses were observed in R1500-CL-1629, the placebo-controlled studies pool, or the uncontrolled studies pool.

Please see section AESI for information on general allergic reactions.

Safety related to drug-drug interactions and other interactions

As a monoclonal antibody, evinacumab is not anticipated to interact with cytochrome P450 (CYP) or drug transporters, and drug-drug interactions between evinacumab and other drugs is not anticipated. Thus, no drug-drug interaction studies have been conducted.

Discontinuation due to adverse events

Pivotal study

Both in the double-blind period and in the open-label period of the pivotal study, no patients experienced a TEAE leading to discontinuation of study treatment.

Placebo-Controlled Pool

Four patients in the all evinacumab group (3.4%) vs 1 (1.9%) for placebo discontinued the treatment due to TEAE, with no single adverse event occurring in more than one patient and without any clear pattern (**Table 30**).

Table 30. Number (%) of Patients with TEAEs Resulting in Permanent Treatment Discontinuation by Primary SOC and PT – Pool 2 Placebo-Controlled Studies (Double-Blind Safety Analysis Set)

Primary System Organ Class Preferred Term	Placebo IV Q4W (N=54)	Evinacumab 15 mg/kg IV Q4W (N=81)	All Evinacumab IV Doses [1] (N=117)
Patients with at least one TEAE resulting in permanent treatment discontinuation	1 (1.9%)	2 (2.5%)	4 (3.4%)
Immune system disorders	0	1 (1.2%)	1 (0.9%)
Anaphylactic reaction	0	1 (1.2%)	1 (0.9%)
Metabolism and nutrition disorders	1 (1.9%)	0	0
Calcium deficiency	1 (1.9%)	0	0
Musculoskeletal and connective tissue disorders	1 (1.9%)	0	0
Arthralgia	1 (1.9%)	0	0
Myalgia	1 (1.9%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (1.2%)	1 (0.9%)
Glioblastoma	0	1 (1.2%)	1 (0.9%)
Nervous system disorders	1 (1.9%)	0	1 (0.9%)
Headache	1 (1.9%)	0	1 (0.9%)
Skin and subcutaneous tissue disorders	1 (1.9%)	0	1 (0.9%)
Rash	0	0	1 (0.9%)

Primary System Organ Class Preferred Term	Placebo IV Q4W (N=54)	Evinacumab 15 mg/kg IV Q4W (N=81)	All Evinacumab IV Doses [1] (N=117)
Pruritus	1 (1.9%)	0	0

Double-blind treatment periods of placebo-controlled studies: 1629 and 1643
MedDRA (Version 22.0) coding dictionary applied. TEAE: Treatment Emergent Adverse Events; SOC: System organ class, PT: preferred term.
A patient who reported 2 or more TEAEs with the same preferred term is counted only once for that term.
A patient who reported 2 or more TEAEs with different preferred terms within the same system organ class is counted only once in that system organ class.
SOC is sorted alphabetically and PT sorted by decreasing frequency of the All Evinacumab IV Doses group.
[1] Evinacumab doses include 5 mg/kg (1643 only) and 15 mg/kg.

Uncontrolled Pool

One patient discontinued treatment due to a TEAE in the uncontrolled pool.

Supportive study in patients with severe hypertriglyceridemia

R1500-HTG-1522 is an ongoing, phase 2 randomized, placebo-controlled trial to evaluate the safety and efficacy of evinacumab in adult patients with severe hypertriglyceridemia at risk for acute pancreatitis. Patients in this study were randomized to receive 15 mg/kg IV or placebo Q4W in a 12 weeks double-blind treatment period, then all patients received 15 mg/kg IV Q4W in a 12 week, single-blind treatment period, followed by a 24-week, off-drug, follow-up period.

A total of 25 (71.4%) patients in the evinacumab treatment group (n=35) and 11 (68.8%) patients in the placebo treatment group (n=16) experienced at least 1 TEAE. Most frequently reported AEs were abdominal pain (5 versus 2 patients), headache (4 versus 1), constipation (3 versus 0. Two discontinuations due to AEs (evinacumab group only) were reported (influenza-like illness and pancreatitis acute). No deaths were reported.

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

The safety assessment primarily focuses on the double-blind treatment period (DBTP) of the individual pivotal study R1500-CL-1629 (HoFH subset) and placebo-controlled studies pool (HoFH and persistent hypercholesterolemia subset), as the HoFH group includes patients proposed to be indicated and the persistent hypercholesterolemia subset provides additional safety data due to the number of patients and comparative study design elements. Considering that HoFH patients and persistent hypercholesterolemia generally have similar patient characteristics, with elevated LDL-C as key characteristic, the integrations of safety data are appropriate.

Patient exposure. For the proposed target group of HoFH, a very limited number of patients has been exposed to the proposed evinacumab 15 mg/kg IV Q4W dose, i.e. 76 HoFH patients for at least 24 weeks and 51 HoFH patients for at least 48 weeks, with placebo-controlled safety for at least 24 weeks available for only 38 HoFH from the pivotal study. Placebo-controlled safety data on HoFH are supported by safety data on persistent hypercholesterolemic patients (study R1500-CL-1643), which increased the available exposure data with 29 patients exposed to evinacumab 15 mg/kg IV Q4W and 28 patients to evinacumab 5 mg/kg IV Q4W for at least 24 weeks, which still remains limited, especially, considering that evinacumab is intended for life-long treatment. In the uncontrolled studies

pool, 58 patients were exposed to evinacumab for ≥ 48 weeks. Overall, the safety data in HoFH patients is very limited; however, expected considering the rarity of the disease. Nevertheless, an ongoing 4 years open label study R1500-CL-1719 and a PASS agreed as specific obligation in the context of MA under exceptional circumstances could provide some additional data to further evaluate long-term safety.

Adverse events. In the DBTP of the pivotal study, TEAEs were frequently reported, however, the percentage of subjects with one or more adverse events was lower in evinacumab 15 mg/kg (65.9%) compared with placebo (81.0%). In the placebo-controlled studies pool, the percentage of patients with any TEAE was similar between the treatments groups (~74%), which is reassuring.

In the DBTP of the pivotal study, the most frequent AEs (≥ 5.0% patients) with a higher incidence with evinacumab 15 mg/kg compared with placebo were influenza-like illness (11.4% vs 0%) and rhinorrhea (6.8% vs 0 patients). In the placebo-controlled studies pool, the most frequent AE (≥ 5.0% patients) with a higher incidence (≥ 2.0% difference) with all evinacumab compared with placebo were nausea (5.1% vs 1.9%), influenza-like illness (7.7% vs 5.6%), pain in extremity (5.1% vs 0), and dizziness (6.0% vs 0%). These events were also more frequently reported (≥ 2.0% difference) in evinacumab 15 mg/kg compared with placebo, with the exception of influenza-like illness (<2.0% difference). Additionally, the percentage of patients who experienced nasopharyngitis was greater (≥ 2.0% difference) in the evinacumab 15 mg/kg group than the placebo group (16.0% vs 13.0%). Therefore, although the safety data of the 5 mg/kg IV Q4W data from the study in persistent hypercholesterolemic patients (R1500-CL-1643) has not been presented separately, a clear dose-dependent appearance of adverse events was not observed. In the uncontrolled studies pool, the TAEs occurred in comparable proportions as observed in the placebo-controlled studies pool.

AEs of special interest. *General allergic events.* No difference between treatment groups were noted for general allergic TEAEs (SMQ "hypersensitivity" excluding the PT linked to local injection site reactions). The percentage of patients experiencing a general allergic event was lower in evinacumab 15mg/kg compared with placebo in the pivotal study (9.1% (n=5) vs 14.3% (n=3), respectively) and comparable across the groups in the placebo-controlled studies pool (~11%). General allergic events reported in more than a single patient in any treatment group included asthma, (1.7% (n=2) all evinacumab vs 0% placebo), conjunctivitis (1.7% (n=2) vs 0%), rash (1.7% (n=2) vs 0%), and pruritus (0.9% (n=1) vs 3.7%(n=2)). None of the adverse events was a SAE, with the exception of one anaphylactic reaction in one persistent hypercholesterolemic patient on evinacumab 15 mg/kg Q4W, which was considered related to study drug. Consequently, anaphylactic reaction as ADR is included in section 4.8 of the SmPC,. In the uncontrolled studies pool, a comparable proportion of patients experienced general allergic TEAEs with evinacumab. Moreover*, anti-evinacumab antibodies* were not reported in any of the safety analysis sets.

Infusion reactions. Infusion reaction TEAEs were reported more frequently with treatment with evinacumab compared with placebo; 3 patients (6.8%) in the evinacumab group vs 1 patient (4.8%) in the placebo group in the pivotal study and 9 patients (7.7%) in the all evinacumab group and 6 patients (7.4%) in the evinacumab 15 mg/kg IV group vs 2 patients (3.7%) in the placebo group in the placebo-controlled studies pool. In the pivotal study, the infusion reactions with evinacumab treatment included infusion site pruritis, pyrexia, muscular weakness, and vascular pain. In the placebo-controlled pool, the only infusion reaction TEAE reported in more than a single patient in any treatment group was infusion site pruritus (2 patients who received 15mg/kg evinacumab vs 0 in the placebo group). There was one serious infusion reaction TEAE of anaphylactic reaction which is already discussed above. In the uncontrolled studies pool, 8 patients (4.4%) experienced infusion reactions of which none were reported in more than a single patient.

Hepatic disorders/liver enzyme elevations. Treatment with evinacumab was not associated with safety concerns related to the liver. No patients in any treatment group experienced a hepatic disorder regardless of the pool, and the percentage of patients who met the pre-defined definition for liver function test abnormalities were low and approximately similar between the treatment groups, which is reassuring. Although, liver fat fraction, in addition to liver enzyme evaluation, has not been examined.

Muscle events/creatine kinase (CK) elevation. The incidence of muscle-related TEAE was higher in the evinacumab groups compared with the placebo group; 15.9% (n=7) vs 9.5% (n=2), respectively, in the pivotal study and 23.9% (n=28) in the all evinacumab group and 21.0% (n=17) in the evinacumab 15 mg/kg group and 20.4% (n=11) in the placebo group in the placebo-controlled studies pool. In the pivotal study, these AEs included arthralgia, back pain, muscle spasms, muscular weakness, musculoskeletal chest pain, myalgia intercostal, neck pain, and pain in extremity, of which none occurred in more than 1 patient. In the placebo-controlled studies pool, back pain (5.1% all evinacumab and 3.7% evinacumab 15 mg/kg vs 3.7% placebo) and pain in extremity (5.1% all evinacumab and 3.7% evinacumab 15 mg/kg vs 0% placebo) were reported with higher frequency (≥ 3.0%) for evinacumab, while myalgia (5.1% all evinacumab and 2.5% evinacumab 15 mg/kg vs 11.1% placebo) and arthralgia (3.4% all evinacumab and 2.5% evinacumab 15 mg/kg vs 5.6% placebo) were reported with a higher frequency in the placebo group. In the uncontrolled pool, the only muscle-related AEs (≥3.0%) in the total evinacumab group was back pain (4.9%) and, therefore, did not reveal new muscle-related AEs. back pain, and pain in extremity was included as ADRs in section 4.8 of the SmPC.

New onset of diabetes mellitus, diabetes mellitus or diabetic complications. The limited data provided suggested that evinacumab is not associated with safety concerns related to glycemic control or diabetes in patients with or without diabetes at baseline.

Furthermore, the limited data provided does not suggest any safety concerns for evinacumab related to cataracts and neurologic events. Furthermore, no cases of symptomatic overdose, neurocognitive events, pancreatitis, or immune complex TEAEs were reported in any safety set.

These observations are somewhat supported by a genetic study of 650 carriers of ANGPTL3 LOF variants, which shows no association with any apparent increase in adverse clinical outcomes, including liver disease, type 2 diabetes mellitus, neurological diseases, risk of cancer or overall mortality. Nevertheless, the safety results of carriers of ANGPTL3 LOF variants are difficult to extrapolate to HoFH patients treated with evinacumab, among other things since the lipid profile between both populations are very different with severely elevated LDL-C levels in HoFH, while ANGPTL3 is suggested to play an important role in lipid metabolism. Additionally, in the genetic study, almost all patients were heterozygous ANGPTL3 LOF variants whereas, with evinacumab treatment, all ANGPTL3 in the serum is neutralised mimicking complete loss of ANGPTL3 function. Consequently, higher reductions in different lipid parameters were observed in HoFH patients treated with evinacumab compared with LOF variants compared with (LDL-C:-49% vs -10%, TG: - 50% vs -30.2%, and HDL-C -30% vs -7%, respectively).

Adverse drug reactions. In order to identify ADRs from the evinacumab clinical data, the placebo-controlled studies pool safety were screened for AESIs, all AE at the PT level occurring in ≥3.0% of patients in both evinacumab groups, and risk differences (lower bound of the 95% CI was ≥0.1%) between the evinacumab groups and placebo for each AE at the PT level. Safety data from the uncontrolled studies pool were screened in the same manner with the exception of risk differences evaluation. Based on frequency differences with placebo, the following ADRs have been identified: nasopharyngitis, influenza-like illness, dizziness, back pain, nausea, abdominal pain, constipation, rhinorrhea, and asthenia. Further, evaluation of AE of interest identified infusion reactions with a slight

frequency difference for infusion site pruritus as an ADR. Additionally, based on the exposure-time relationship, a single patient reporting of anaphylaxis has been included as ADR.

The incidence of AEs considered by the investigator related to study drug was higher in the evinacumab groups compared with the placebo groups; 11.4% (n=5) vs 4.8% (n=2), respectively, in the pivotal study and 10.3% (n=12) in all evinacumab IV and 11.1% (n=9) in the evinacumab 15 mg/kg vs 7.4% (n=4) in placebo in the placebo-controlled studies pool. In the pivotal study, the drug-related AEs in the evinacumab group included infusion site pruritus (2 patients), pyrexia, vascular pain and muscular weakness (1 patient), gastroenteritis, nasopharyngitis and epistaxis (1 patient), and upper respiratory tract inflammation and nasopharyngitis (1 patient). In the placebo-controlled studies pool, the most common drug-related AEs (>1 patient) in the evinacumab groups were infusion site pruritus (n=2 (2.5%), both in the 15 mg/kg IV evinacumab group), and nasopharyngitis (n=2 (2.5%), both in the 15 mg/kg IV evinacumab group).

In the placebo-controlled studies pool, upper respiratory tract infection was more frequently reported in evinacumab treated patients (2.6%) compared with 0 patients in placebo and in 6.0% in the total evinacumab group in the uncontrolled studies pool. Upper respiratory tract infection is considered an ADR and included in the labelling.

Serious AEs. The incidence of SAEs was higher in the evinacumab groups compared with the placebo groups; 2 patients (4.5%) in evinacumab vs none in the placebo group in the pivotal study and 10 patients (8.5%) in all evinacumab and 8 patients (9.9%) in evinacumab 15 mg/kg vs 1 patient (1.9%) in placebo in the placebo-controlled studies pool. However, no pattern indicative for a safety signal could be identified among the SAEs, which is reassuring. Moreover, all SAEs were considered not related to study treatment, with the exception of one anaphylactic reaction event which was included in section 4.8 of the SmPC. In the uncontrolled pool, 15 patients (8.2%) in the total evinacumab group experienced 20 serious TEAEs of which the majority were cardiovascular related, reflecting the patients' underlying medical history.

Deaths. No deaths were observed in patients treated with evinacumab or placebo, regardless of the safety analysis set. Two deaths were reported in the ongoing open-label study, but not considered related to treatment.

Adjudicated cardiovascular events. Cardiovascular events and deaths are of interest, and a harmful effect should at least be excluded prior to registration for a new pharmacological class according to the *EMA Guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/748108/2013)*. However, due to the rarity of HoFH, exclusion of a detrimental effect of evinacumab in the target population seems not feasible, as such, no comprehensive data regarding cardiovascular safety could be provided and therefore remains uncertain and will continue to be evaluated post-authorisation. No positively adjudicated cardiovascular events were reported in the DBTP of the pivotal study; however, an imbalance in the incidence in positively adjudicated CV events has been reported in the placebo-controlled studies pool (2 patients treated with evinacumab (1 event each in the evinacumab 5 mg/kg and 15 mg/kg IV dose groups) vs none for placebo). Additionally, in the uncontrolled studies pool, a limited number of less than 10 patients experienced adjudicated CV events. Overall, firm conclusion on cardiovascular safety cannot be made due to the limited number of patients and cardiovascular events.

Laboratory findings. No clinically meaningful differences with respect to red blood cells, platelets, leukocytes, basophils, eosinophils, lymphocytes, monocytes and neutrophils were observed in the R1500-CL-1629 DBTP, the placebo-controlled studies pool and the uncontrolled studies pool.

With respect to clinical chemistry, please see AESIs.

Vital Signs. Evinacumab treatment did not result in any clinically meaningful changes in vital signs or ECG parameters.

Safety in special populations. *Gender.* The safety profile observed in both male and female were in general similar as those found in the total placebo-controlled studies population.

Elderly. Patients > 75 of age are underrepresented in the clinical development program (3 patients in the placebo-controlled pool and 2 patients in the uncontrolled studies pool). Further, the incidence in any AE showed slightly higher event rates compared with placebo with advancing age, likely due to the underlying disease and circumstances.

Adolescents. No specific safety concerns are identified in the 13 investigated adolescents.

Hepatic and renal impairment. Safety information regarding use of evinacumab in patients with hepatic impairment and patients with renal impairment has not been provided and is not available. Nevertheless, this issue is not pursued as evinacumab is not expected to undergo significant hepatic or renal elimination (see PK assessment).

Discontinuation due to AEs. AEs leading to discontinuations were not reported in the pivotal study and only one in the uncontrolled pool, which is reassuring. In the placebo-controlled studies pool, AEs leading to discontinuations were infrequent, however, slightly higher in the evinacumab group (4 patients (3.4%) in all evinacumab and 2 patients (2.5%) in evinacumab 15 mg/kg vs 1 patient (1.9%) in placebo). Nevertheless, no pattern with respect to type of AE leading to discontinuation of study drug could be observed.

Supportive study. Currently, a phase 2 randomized, placebo-controlled study, R1500-HTG-1522, to evaluate the efficacy and safety of evinacumab in adult patients with severe hypertriglyceridemia is ongoing. The available safety data from this study did not identify new safety signals with evinacumab treatment, which was considered reassuring.

Additional safety data needed in the context of a MA under exceptional circumstances

As comprehensive data on safety and efficacy of the product are not available, however the application meets the applicable requirements, a marketing authorisation under exceptional circumstances was proposed by the CHMP during the assessment, after having consulted the applicant. As specific obligation a non-interventional post-authorisation safety study (PASS) was requested to be conducted (please, see also Discussion on Clinical Efficacy)**.**

The following objectives were agreed for the PASS: (1) to evaluate the long term safety outcomes (i.e., hospitalisations, death, and MACE) in patients with Homozygous Familial Hypercholesterolemia (HoFH) who are ≥12 years old and treated with evinacumab, (2) to evaluate the frequency and outcomes of pregnancy in female patients with HoFH treated with evinacumab and (3) to evaluate the atherosclerosis process over time in patients with HoFH who are treated with evinacumab and undergo cardiac imaging. The MAH agreed to conduct and submit the results of this study based on data from a registry in patients with HoFH. Patients included in the existing disease registry: European Atherosclerosis Society (EAS) FH Studies Collaboration (FHSC) Registry were agreed to be the source population for this study.

2.6.2. Conclusions on the clinical safety

Generally, evinacumab displays an acceptable safety profile comparable to that of placebo, with low discontinuations due to AEs. No pattern indicative for a safety signal could be identified among the

SAEs, although one serious event of an anaphylactic reaction has been reported which was considered related to study drug. However, the safety data of evinacumab in HoFH patients is very limited, which is expected, considering the rarity of the disease. Nevertheless, even with the inclusion of safety data of evinacumab in persistent hypercholesterolemic patients, the safety package remains limited, especially considering that evinacumab is intended for life-long treatment. Due to the rarity of HoFH, exclusion of a detrimental effect in the target population seemed not feasible, as such, cardiovascular safety remains an uncertainty. The safety profile for adolescents is in line with that of the overall population.

To address the uncertainties related to the long term safety in the context of a MA under exceptional circumstances, a PASS study including MACE as one of the endpoints is proposed as a Specific Obligation to the marketing authorisation.

2.7. Risk Management Plan

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

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances.				
"Evaluation of the Long-Term Effects of Evinacumab Treatment in Patients with Homozygous Familial Hypercholesterolemia (HoFH)" Planned	– To evaluate the long-term safety outcomes in patients with HoFH who are ≥12 years old and treated with evinacumab. – To evaluate the frequency and outcomes of pregnancy in female patients with HoFH who are treated with evinacumab. – To evaluate the atherosclerosis process over time in patients with HoFH who are treated with evinacumab and undergo cardiac imaging (as data allow). – To evaluate the frequency of cardiac imaging of patients with HoFH.	Embryofoetal toxicity Safety of long-term use (eg, >2 years) Use in pregnant or breast-feeding women (note that pregnancy information will be evaluated in the proposed long-term safety study to address the potential risk of embryofoetal toxicity)	• Protocol concept submission • Annual study reports	Three months after marketing authorisation approval Submitted with the annual reassessment.

HoFH=homozygous familial hypercholesterolaemia.

Risk minimisation measures

Safety Concern	Risk Minimisation Measures
Embryofoetal toxicity	**Routine risk minimisation measures**: – SmPC Sections 4.6 and 5.3 – PL Section 2 Recommendation that women of childbearing potential should use effective contraception during treatment with evinacumab and for at least 5 months after the last dose is included in the SmPC Section 4.6 and PL Section 2. – SmPC Section 4.2 Legal status: Evinacumab is subject to restricted medical prescription. Treatment with Evinacumab should be initiated and monitored by a physician experienced in the treatment of lipid disorders. **Additional risk minimisation measures**: None
Safety of long-term use (e.g., >2 years)	**Routine risk minimisation measures**: Restricted medical prescription **Additional risk minimisation measures**: None
Use in pregnant and breast-feeding women	**Routine risk minimisation measures**: – SmPC Sections 4.6 and 5.3 – PL Section 2 Recommendation that women of childbearing potential should use effective contraception during treatment with evinacumab and for at least 5 months after the last dose is included in the SmPC Section 4.6 and PL Section 2. It is unknown whether evinacumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which decrease to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, evinacumab could be used during breast-feeding if clinically needed is included in SmPC Section 4.6 and PL Section 2 as recommendation on use of evinacumab for breast-feeding women. – SmPC Section 4.2 Legal status:

Safety Concern	Risk Minimisation Measures
	Evinacumab is subject to restricted medical prescription. Treatment with Evinacumab should be initiated and monitored by a physician experienced in the treatment of lipid disorders. **Additional risk minimisation measures**: None

PL=package leaflet; SmPC=summary of product characteristics

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 11.02.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that evinacumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers evinacumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. 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 AND*

- *It has a PASS imposed; [REG Art 9(4)(cb), Art 10a(1)(a),] AND*

- *It is approved under exceptional circumstances [REG Art 14(8)].*

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

Evinacumab is indicated for use as an adjunct to diet and other low-density lipoprotein cholesterol (LDL-C) lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolemia (HoFH).

Homozygous familial hypercholesterolemia (HoFH) is an ultra-rare (~1 in 300,000 in the EU) 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 genetic disorder is most often caused by the presence of loss-of-function variants in the low-density lipoprotein (LDL) receptor, which leads to low or absent hepatic clearance of LDL cholesterol from the circulation. Genetic alterations that cause a virtually complete absence of LDL-receptor expression (null homozygotes) result in higher LDL cholesterol levels than alterations that partially reduce LDL-receptor activity with either two non-null alleles or one null and one non-null allele (nonnull homozygotes).

The **goal of therapy** in patients with HoFH is to reduce LDL-C, which is believed to reduce atherogenesis and subsequently reducing CVD events and mortality. This is based on a large body of evidence, especially based on statin therapy, which demonstrates that reduction of LDL-C is associated with reduction in CV death and overall mortality; however, any of such association has not been robustly demonstrated in HoFH patients.

Evinacumab is a **human monoclonal antibody** against angiopoietin-like protein 3 (ANGPTL3), which play a role in the regulation of lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL). This would lead to a reduction in LDL-C independent of the presence of an LDL receptor by promoting very low-density lipoprotein (VLDL) processing and clearance, thereby reducing the VLDL pool available to generate LDL-C. Any further details on the mechanism of action, in particular in the setting of HoFH with extremely elevated cholesterol levels have not been provided.

3.1.2. Available therapies and unmet medical need

HoFH patients should be treated with intensive LDL-C lowering drug therapy to lower their highly increased LDL-C levels. Currently, available registered therapies include statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and lomitapide. Non-pharmacological therapies include lipid apheresis and liver transplantation.

Statin therapy is the cornerstone treatment for LDL-C lowering and causes a limited 15-30% reduction in LDL-C in patients with HoFH.

Ezetimibe on top of statins can reduce LDL-C by 20%-27% compared to statin alone.

PCSK9 inhibitors on top of maximally tolerated lipid-lowering therapy can result in a reduction in LDL-C of approximately 30%. Only evolocumab is currently approved for patients with HoFH; use of alirocumab in patients with HoFH is considered off label.

Lomitapide, a selective inhibitor of microsomal transfer protein (MTP) causes reductions in LDL-C of approximately 40%, however, optimal lomitapide treatment is limited by tolerability issues of gastro-intestinal adverse events. Also, long term safety including e.g. effects on the liver, is still uncertain.

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

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 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, HoFH are generally sub-optimally treated resulting in remaining increased levels of LDL-C (with increased CV risk), as such, there is still an unmet medical need for new treatment options for HoFH, especially for HoFH patients with null/null or negative/negative mutations where currently available LDL-R dependent lipid lowering therapies (i.e. statins and PCSK9 inhibitors) provide no to little benefit in lowering LDL-C.

3.1.3. Main clinical studies

The main evidence was provided by the pivotal phase 3 study **R1500-CL-1629 (ELIPSE – HoFH)** which compared the reduction of LDL-C by evinacumab 15 mg/kg IV Q4W (N=44) to placebo (N=21) after 24 weeks in patients with HoFH (with background therapy of lipid-modifying therapies, including statins, ezetimibe, lomitapide, evolocumab, and apheresis), followed by an **open-label extension period (ELIPSE – OLE)** for 24 weeks were all subjects received evinacumab 15 mg/kg IV Q4W. The primary endpoint was the percent change in calculated LDL-C from baseline to week 24. Important secondary endpoints included other lipid parameters, including ApoB, TC, non-HDL-C, TG, and ApoB/ApoA1.

Additional safety data was provided by the phase 2, randomized, double-blind, placebo-controlled, dose-ranging R1500-CL-1643, in adult patients with persistent hypercholesterolemia (HeFH, or non-HeFH with a history of clinical atherosclerotic cardiovascular disease [ASCVD]; 80% HeFH)(R1500-CL-1643). The study consisted of a 16-week DBTP for the SC dose groups (300 mg QW or Q2W, 450 mg QW) or 24-week DBTP for the IV dose groups (5mg/kg Q4W (N=36) or 15 mg/kg Q4W (N=39)), and a 48-week OLTP for the IV dose groups. In the integrated safety data pools only the safety data of IV administration of evinacumab 5 and 15 m/kg Q4W has been included.

Furthermore, in addition to the open-label treatment phases of the pivotal study R1500-CL-1629 and study R1500-CL-1643, open-label evinacumab 15 mg/kg IV Q4W safety data is derived from the ongoing **phase 3 open-label study in HoFH patients, R1500-CL-1719,** both for more extended treatment with evinacumab as for new evinacumab treatment naïve patients.

3.2. Favourable effects

LDL-C reduction. Evinacumab demonstrated a clinically significant reduction in LDL-C of 49.0% as compared to placebo background therapy (-47.1% vs +1.9%; 95% CI, –65.0 to –33.1; P<0.001) in a limited population of patients (n= 65 with 2:1 ratio) with genetically or clinically confirmed HoFH on optimal lipid-lowering therapy with a baseline LDL-C level of 6.7mmol/L (absolute change -3.5 mmol/L). A reduction in LDL-C was observed as early as week 2 and was maintained throughout the 24-week double-blind treatment period. Moreover, the effect was maintained throughout an additional 24 weeks open-label single-arm extension (-46.3%).

Other endpoints. The LDL-C lowering effect was supported by other lipid parameters, including ApoB (37%), non-HDL-C (-52%), TC (-48%), and TG (-50%). Further, also other secondary endpoints were in support of the main findings, e.g. 47% vs 23% achieved LDL-C levels <2.6 mmol/L, 56 vs 5% achieved ≥50% reduction in LDL-C, and 33% vs 77% met EU apheresis eligibility criteria, respectively.

Subgroups. Even though the number of included patients were limited, the effect appears consistent among many subgroups including stratification factors of Japan vs rest of the world, apheresis background therapy (n=22) or not (n=43) and other subgroups of, e.g. HoFH genotyping, (among which n=21 were null/null and n=12 were negative/negative). Moreover, the LDL-C lowering effect appears consistent across the range of background therapies, including statins, ezetimibe, lomitapide, and PCSK9 inhibitors.

Adolescents. Currently 13 adolescent patients have been included in the clinical program and support the main findings. Although the inclusion of two adolescents (both null/null genotype) in the pivotal, placebo-controlled study is limited, 13 adolescent patients (with 11 patients being evinacumab naïve) have been included in the ongoing open-label study R1500-CL-1719. LDL-C reduction at week 24 for the single adolescent patient treated with evinacumab was -73.3% and was maintained during 48 weeks (-72.32%). For the placebo-treated adolescent the effect on LDL-C was +60% during the first 24 weeks, but efficacy was shown during the subsequent evinacumab 24 weeks treatment period of -35.7% reduction in LDL-C. Efficacy was also demonstrated in the ongoing open-label study R1500-CL-1719 with a reduction in LDL-C of -52.4% (SD 29) at 24 weeks (baseline LDL-C of 7.8 mmol/L) and irrespective of the genetic variant for null/null (n=4; -67%) and non-null/null (n=5; -40.6%) patients. Secondary lipid parameters are supportive for the primary analysis.

3.3. Uncertainties and limitations about favourable effects

Clinical outcomes. Evinacumab has demonstrated to clinically significantly reduce LDL-C level, an established surrogate marker for CV disease, but its impact on clinical outcomes has not been formally tested. CV events were only rarely observed, although this was higher for evinacumab than placebo (2 patients vs none), this could be related to the underlying disease with increased CV risk and thus may not be unexpected and likely imbalanced due to chance finding. Any data on a treatment effect on atherosclerosis is also not available, while non-clinical data in mice models currently do not show any clear, consistent/complete effects on atherosclerosis.

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 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.

HDL-C. A substantial reduction in HDL-C has been observed of -30% vs 0.8% for evinacumab and placebo, respectively, to lower than normal levels of HDL-C (from a baseline level of 1.14 mmol/L to 0.80 mmol/L). This is likely due to potentiating of the endothelial lipase with increased HDL-C hydrolysis. However, the consequences of the lower than normal HDL-C levels for e.g. cholesterol reverse transport are not exactly clear. Further, the clinical implications in terms of cardiovascular risk increase is unknown, especially since recent findings challenged a clear correlation between HDL-C targeted treatment (increase in HDL-C) and improvement in cardiovascular risk.

3.4. Unfavourable effects

Adverse events. In the pivotal study, the most frequently reported AEs (≥5.0% patients) with a higher incidence in the evinacumab 15 mg/kg IV Q4W group compared with the placebo group were **influenza-like illness** (11.4% vs 0%) and **rhinorrhea** (6.8% vs 0%). A generally comparable safety profile was observed when the placebo-controlled safety data of the pivotal study (HoFH patients) was increased by placebo-controlled data from study R1500-CL-1643 (persistent hypercholesterolemic patients), i.e. placebo-controlled studies pool. In this pool, most frequent AE (≥5.0% patients) with a higher incidence (≥2.0% difference) with all evinacumab compared with placebo were **nausea** (5.1% vs 1.9%), **influenza-like illness** (7.7% vs 5.6%), **pain in extremity** (5.1% vs 0), and **dizziness** (6.0% vs 0%).

Adverse events of special interest. Infusion reactions were more frequently reported with evinacumab vs placebo in the pivotal study (6.8% vs 4.8%, respectively). The infusion reactions with evinacumab treatment included **infusion site pruritis**, **pyrexia**, **muscular weakness**, and **vascular pain**. Also, in the placebo-controlled studies pool, infusion reactions were reported more frequently in the evinacumab groups compared with placebo (7.7% all evinacumab and 7.4% evinacumab 15 mg/kg vs 3.7% placebo). **Infusion site pruritus** was the only reported infusion reaction AE reported in more than 1 patient (2 patients for evinacumab 15mg/kg vs 0 for placebo). None of the infusion reactions were serious, with the exception of an **anaphylactic reaction** in one persistent hypercholesterolemic patient on evinacumab 15 mg/kg IV Q4W.

Anti-evinacumab antibodies were not reported in any of the safety analysis sets. Additionally, no differences with respect to general allergic TEAES (SMQ "hypersensitivity" excluding the PT linked to local injection site reactions) were observed between the treatment groups in the different safety analysis sets.

Muscle-related AEs were more frequently reported in the evinacumab group than the placebo group in the pivotal study (15.9% vs 9.5%, respectively). These AEs with evinacumab treatment included **arthralgia**, **back pain**, **muscle spasms**, **muscular weakness**, **musculoskeletal chest pain**, **myalgia intercostal**, **neck pain**, **and pain in extremity**, of which none occurred in more than 1 patient. Also, in the placebo-controlled studies pool, muscle-related were reported more frequently in the evinacumab groups compared with the placebo group, although less evident (23.9% all evinacumab and 21.0% evinacumab 15 mg/kg vs 20.4% placebo). **Back pain** (5.1% all evinacumab, and 3.7% evinacumab 15 mg/kg vs 3.7% placebo) and **pain in extremity** (5.1% and 3.7% vs 0%,

respectively) were reported with a higher frequency (≥3.0%) for evinacumab, while myalgia (5.1% all evinacumab and 2.5% evinacumab 15 mg/kg vs 11.1% placebo) and arthralgia (3.4% all evinacumab and 2.5% evinacumab 15 mg/kg vs 5.6% placebo) were reported with a higher frequency in the placebo group.

Other AEs of special interest. The limited data provided suggested that evinacumab is not associated with safety concerns related to glycemic control or diabetes in patients with or without diabetes at baseline. Furthermore, the limited data provided does not suggest any safety concerns with cataracts and neurologic events. Furthermore, no cases of symptomatic overdose, neurocognitive events, pancreatitis, or immune complex TEAEs were reported in any safety set.

Serious adverse events. The incidence of SAEs was higher in the evinacumab groups compared with the placebo group both in the pivotal study (4.5% vs 0%) and the placebo-controlled pool (8.5% all evinacumab and 9.9% evinacumab 15 mg/kg vs 1.9% placebo). However, no pattern indicative for a safety signal could be identified among the SAEs and all SAEs were considered not related to study treatment, except for one anaphylactic reaction event.

Deaths. No deaths were observed in patients treated with evinacumab or placebo.

Tolerability. Generally, evinacumab seems to be well tolerated. No patients experienced AEs leading to discontinuation of study treatment in the pivotal study, whereas in the placebo-controlled studies pool, these were also limited (4 patients (3.4%) all evinacumab vs 1 patient (1.9%) placebo). Further, for only 3 patients, discontinuations due to AE were observed in the uncontrolled studies pool.

Adolescents. Safety data is available for 13 adolescents HoFH patients; one patient each in the evinacumab 15 mg/kg and the placebo group in the pivotal study, and for 13 (2 of those were also from the controlled phase) in the ongoing open-label study (mean duration 35 weeks). The safety profile is consistent with the overall population.

3.5. Uncertainties and limitations about unfavourable effects

Exposure. For the proposed target group of HoFH, a very limited number of patients has been exposed to the proposed evinacumab 15 mg/kg IV Q4W dose, i.e. 76 HoFH patients for at least 24 weeks and 51 HoFH patients for at least 48 weeks, with placebo-controlled safety data for at least 24 weeks available for only 38 HoFH patients. Placebo-controlled safety data on HoFH are supported by safety data on persistent hypercholesterolemic patients (study R1500-CL-1643), which increased the available exposure data with 29 patients exposed to evinacumab 15 mg/kg IV Q4W and 28 patients to evinacumab 5 mg/kg IV Q4W for at least 24 weeks, which still remains limited.

Adjudicated cardiovascular events. No positively adjudicated cardiovascular events were reported in the double-blind period of the pivotal study; however, a small imbalance in the incidence in positively adjudicated CV events has been reported in the placebo-controlled studies pool (2 patients treated with evinacumab [1 event each in the evinacumab 5 mg/kg and 15 mg/kg IV dose groups] vs none for placebo). Additionally, in the uncontrolled studies pool, three patients experienced adjudicated CV events. Nevertheless, a firm conclusion on cardiovascular safety cannot be made due to the limited number of patients and cardiovascular events.

Hepatic disorders/liver enzyme elevations. No patients in any treatment group experienced a hepatic disorder regardless of the pool, and the percentage of patients with liver function test abnormalities were low (1-2%) and approximately similar between the treatment groups. However, liver fat fraction in addition to liver enzyme evaluation, has not been examined.

Elderly. The incidences in any AEs showed that more safety issues occur in patients with advancing age, although these could be attributed to the underlying disease and condition. Patients above 75 years of age were underrepresented in the clinical development program (3 patients in the placebo-controlled pool and 2 patients in the uncontrolled studies pool).

3.6. Effects Table

Effects Table for evinacumab indicated as an adjunct to diet and other LDL-C lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with HoFH (data cut-off: R1500-CL-1629 [29 July 2019]), and in adults with HeFH (data cut-off: R1500-CL-1643 [24 September 2019]).

Table 31. Effects of evinacumab indicated as an adjunct to diet and other LDL-C lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with HoFH (data cut-off: R1500-CL-1629 [29 July 2019]), and in adults with HeFH (data cut-off: R1500-CL-1643 [24 September 2019])

Effect	Short Description	Unit	Treatment (n=43)	Control (n=22)	Uncertainties/ Strength of evidence	References
Favourable Effects						
LDL-C	Change from baseline at week 24	%	-47.1	+1.9	**SoE**: Difference -49.0%; P<0.0001, Clinical relevant change of -3.5 mmol/L, Substantial changes observed in other lipid parameters (ApoB, non-HDL-C, TC, TG), Effect maintained after 48 weeks: 46.3% **Unc**: Decrease in HDL-C to 0.80 mmol/L observed (-29% vs 0.8%); clinical meaning unclear, No CV events evaluation available (2 events vs 0 events)	R1500-CL-1629
Unfavourable Effects						
Infusion reactions	-	n (%)	3 (6.8)	1(4.8)	**SoE**: Similar trend in the placebo-controlled studies pool (7.7% all evi, 7.4% evi 15 mg/kg vs 3.7% placebo)	R1500-CL-1629
Anaphylaxis	-	n (%)	1 (2.7)*	0	**Unc**: *Only observed in one persistent hypercholesterolemic patient. None in the HoFH study	R1500-CL-1643
Muscle-related AEs		n (%)	7 (15.9)	2 (9.5)	**SoE**: Similar, but less evident trend in the placebo-controlled studies pool (23.9% all evi, 21.0% evi 15 mg/kg vs 20.4% placebo)	R1500-CL-1629

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Evinacumab has demonstrated a substantial and consistent reduction in LDL-C and other lipid parameters, on top of existing therapy options, including statins, ezetimibe, lomitapide, PCSK9 inhibitors, and apheresis for patients with HoFH. Efficacy was demonstrated in other types of patients with hypercholesterolemia as well. This is considered of clinical relevance as LDL-C is an important surrogate endpoint with potential benefits in terms of cardiovascular outcome.

However, treatment with evinacumab also demonstrated a decrease in HDL-C to less than normal levels of HDL-C, for which the clinical consequences are currently not clear, especially in the setting of the HoFH population. The consequences for e.g. reverse cholesterol transport, and any potential causative relation to CV risk remains uncertain. Although recent understanding challenges the reverse relationship between HDL-C increase and CV risk reduction, some evidence (but not all e.g. gene associated low HDL-C levels) suggest that low levels of HDL-C have been associated with CV risk.

Current data does not allow to provide reasonable conclusions on the overall CV treatment benefit based on these seemingly opposing lipid effects, due to very limited occurrence of CV events, although it is anticipated that the CV benefit as potentially be derived from LDL-C lowering will possibly not be completely offset by the HDL-C effect. Some reassurance has been provided based on effects as seen in ANGPTL3 loss-of-function patients; however, extrapolation to the HoFH population seems complex due to phenotype differences. Further, due to the rarity of the disease, any possibility to provide comprehensive cardiovascular results based on a robust clinical cardiovascular outcome study is unlikely to be feasible. Considering this limitation, a marketing authorisation under exceptional circumstances was considered appropriate as the date supporting the authorisation were not considered comprehensive. In this context, the PASS study was imposed as specific obligation and will form the basis for annual reassessment. Data on the impact of evinacumab on the atherosclerosis process (e.g. vascular outcome evaluation using imaging techniques of atherosclerosis burden (such as MRI, monitoring of coronary calcium content, etc.) and CV treatment effect was agreed to be provided post-approval through the PASS study imposed as specific obligation.

Evinacumab is administered by infusion and infusion reactions with a serious adverse event of anaphylaxis related to infusion of evinacumab have been observed. Any other (systemic) hypersensitivity reactions are not identified, including a lack of drug antibody formation. Further, muscle-related events were also associated with evinacumab treatment, which are generally typical for lipid-lowering treatment, and it cannot be excluded that this could to some part be possibly related to intensive LLT background therapy. Despite these typical adverse events as observed, evinacumab generally appears to be well tolerated, as most of the patients could be treated for at least a year with evinacumab, which can be considered relevant for a drug intended for life-long treatment.

The safety data of evinacumab in HoFH patients is generally limited both in terms of the number of patients exposed as well as the limited duration of treatment (also after the inclusion of safety data from persistent hypercholesterolemic patients). The ongoing 4 years study could provide some additional data to further address this, and as already mentioned a registry-based study to further evaluate long-term safety has been agreed as a specific obligation.

The applicant is applying for use in adults and adolescent patients aged 12 years and older. Sufficient data is currently available in adolescents to make a comparable benefit risk balance assessment in line with the analysis done for limited number of adult patients. Treatment of adolescent patients is of particular importance, considering the high unmet medical need in children due to early aged onset of the disease.

3.7.2. Balance of benefits and risks

Evinacumab has demonstrated a substantial clinical meaningful reduction in LDL-C on top of existing therapy options including statins, ezetimibe, lomitapide, PCSK9 inhibitors, and apheresis for patients with HoFH which could likely address the high unmet medical need for these patients. Although a cardiovascular benefit cannot be robustly demonstrated for this rare disease, any efforts for addressing this uncertainty post-approval are warranted, especially as the implications of a reduction in HDL-C cannot be sufficiently anticipated. Sufficient number of adolescents have been included in the

development program to accept including "adolescent patients aged 12 years and older" to the target population as proposed. Evinacumab administered every 4 weeks by infusion has an acceptable safety profile and is well-tolerated, which is considered important for an intended lifelong treatment. The B/R balance is positive, although uncertainties remain, and further data will be provided post-approval to address these as best as possible. In this respect, anapproval under exceptional circumstances was considered the most appropriate status for this marketing authorisation and was accepted by the applicant.

3.7.3. Additional considerations on the benefit-risk balance

There is a large body of epidemiological evidence demonstrating a strong positive correlation and causal relationship between LDL-C and CV risk. In addition, the surrogacy of LDL-C has particularly been established based on clinical trials showing that LDL-lowering therapy with statins reduces risk for CHD. Data from other types of medicinal products have reinforced this correlation, however, the body of clinical evidence for this correlation for each of these separate medicinal product groups (e.g. PCSK9, ezetimibe) is far less extensive than for statins.

The data available for evinacumab were considered not comprehensive. In accordance with the *EMA guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/748108/2013, Rev. 3)* recommendations, the requirement of clinical studies showing beneficial outcome on morbidity and mortality during registration largely depends on the mechanism of action and the pharmacological class of the medicinal product and the target population and is not foreseen for a new HMG-CoA reductase inhibitor. Until clinical trial data are available, it should be specifically mentioned in the Summary of product characteristics (SmPC) that beneficial effects on mortality and morbidity have not been evaluated. However, any statement that beneficial effects on mortality and morbidity have not been evaluated, as proposed, does not completely waive for requirements to investigate it further post-authorisation. Generating such level of evidence would not be different for evinacumab to consider this medicinal product for a full approval. Any support from data in a loss of function (LOF) genetic variant of ANGPTL3 is not considered sufficient to completely replace such comprehensive data package, especially considering the challenges to extrapolate such genetic LOF phenotype CV risk associations to 1) a different phenotype of HoFH and 2) treatment induced changes in the lipid profile CV (alteration) associations. However, due to the rarity of the HoFH population (~1 in 300,000 in the EU), it may be challenging if not unfeasible to provide such comprehensive data of a robust confirmation on morbidity and mortality. Anticipating that the level of evidence is considerably less than what would normally be required for a standard approval, as discussed above, a MA under exceptional circumstances will be granted with the main reason that *indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence* (see EMEA/357981/2005).

As a consequence, a specific obligation was agreed and included in Annex IIE to form the basis for annual reassessment in the context of MA under exceptional circumstances. This SOB is a non-interventional post-authorisation safety study (PASS). This was considered important given the not completely understood new mechanism of action of evinacumab also in relation to the limited understanding of the implications of the observed potential off target effect of HDL-C reduction.

The following objectives were agreed for the PASS: to evaluate the long term safety outcomes (i.e., hospitalisations, death, and MACE) in patients with Homozygous Familial Hypercholesterolemia (HoFH) who are ≥12 years old and treated with evinacumab, to evaluate the frequency and outcomes of pregnancy in female patients with HoFH treated with evinacumab and to evaluate the atherosclerosis process over time in patients with HoFH who are treated with evinacumab and undergo cardiac imaging. The MAH should conduct and submit the results of this study based on data from a registry in

patients with HoFH. Patients included in the existing disease registry: European Atherosclerosis Society (EAS) FH Studies Collaboration (FHSC) Registry were agreed to be the source population for this study. Inclusion of safety outcomes including MACE, death, and hospitalizations in a defined cohort of patients aged 12 years and older who have a diagnosis of HoFH and initiated evinacumab and have received evinacumab treatment during the analysis year, is of interest to increase the understanding on long term impact of evinacumab on these outcomes.

Further, any evaluation of vascular damage by imaging of the atherosclerosis process is of particular interest as a confirmation between LDL-C lowering surrogate effect and the proposed long-term monitoring for MACE events.

It was agreed to submit a draft protocol synopsis for assessment within 3 months after product approval, and annual reports will be submitted as part of annual reassessment.

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available, and the application meets the applicable requirements, a marketing authorisation under exceptional circumstances was proposed by the CHMP during the assessment, after having consulted the applicant.

The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because the applied for indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence. Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate.

3.8. Conclusions

The overall B/R of Evkeeza is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Evkeeza is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	**Due date**
Non-interventional post-authorisation safety study (PASS): In order to evaluate the long term safety outcomes in patients with Homozygous Familial Hypercholesterolemia (HoFH) who are ≥ 12 years old and treated with evinacumab as well as the frequency and outcomes of pregnancy in female patients with HoFH treated with evinacumab and to evaluate the atherosclerosis process over time in patients with HoFH who are treated with evinacumab and undergo cardiac imaging, the MAH should conduct and submit the results of a study based on data from a registry in patients with HoFH.	Annual study reports will be submitted with the annual reassessment.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that evinacumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0105/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

No significant studies in the agreed paediatric investigation plan PIP P/0105/2020 have been completed, in accordance with Article 45(3) of Regulation (EC) No 1901/2006, after the entry into force of that Regulation.