EU RISK MANAGEMENT PLAN for EVKEEZA (Evinacumab)

RMP Version to Be Assessed as Part of This Application:

RMP version number:	2.1
Data lock point for the RMP:	25 April 2022
Date of final sign-off:	05 September 2024

Rationale for Submitting an Updated RMP:

The RMP for Evkeeza is being updated to support the extension of indication to patients aged 6 months and older with homozygous familial hypercholesterolaemia (HoFH) and to reflect the expanded study population of the Category 2 post-authorisation safety study (PASS) UX858-CL401.

Summary of Significant Changes in This RMP:

The following significant changes were introduced to the RMP:

- The indication and dosing instructions for Evkeeza were updated in Part I of the RMP to include patients aged 6 months and older with HoFH.
- The epidemiology of the indication was updated in Part II of the RMP to reflect on the inclusion of patients aged 6 months and older with HoFH.
- "Safety (including long-term) in children <5 years of age" was added as missing information for Evkeeza in Modules SVII and SVIII. This change was further reflected in Part III, Part V and Annex 2.
- The study population, milestones, and the list of addressed safety concerns of the Category 2 PASS UX858-CL401 were updated in Part III and Annexes 2 and 3 of the RMP for alignment with the therapeutic indication, i.e., including all patients with a clinical and/or a genetic diagnosis of HoFH who initiated treatment with commercially available evinacumab.
- All changes made to the body of the document were reflected in Part VI of the RMP.

Other RMP Versions Under Evaluation:

RMP version number:	Not applicable.
Submitted on:	Not applicable.
Procedure number:	Not applicable.

Details of Currently Approved RMP:

RMP version number:	1.2
Approved within procedure:	EMEA/H/C/005449/II/0011
Date of approval (opinion date):	09 November 2023

QPPV Name: Elena Alcaraz García

QPPV Oversight Declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
ANGPTL3	Angiopoietin-like 3
ASCVD	Atherosclerotic cardiovascular disease
ATC	Anatomical therapeutic chemical classification system
DBTP	Double-blind treatment period
DAC	Designated Activity Company
DNA	Deoxyribonucleic acid
EAS	European Atherosclerosis Society
EEA	European Economic Area
EL	Endothelial lipase
EPAR	European Public Assessment Report
ESC	European Society of Cardiology
EU	European Union
FH	Familial hypercholesterolaemia
FHSC	Familial Hypercholesterolaemia Studies Collaboration
GLP	Good Laboratory Practices
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolaemia
HoFH	Homozygous familial hypercholesterolaemia
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual case safety report
INN	International nonproprietary name
IV	Intravenous
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LLT	Lipid-lowering treatment
MACE	Major cardiovascular adverse event
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
NOAEL	No-observed-adverse-effect level
OLTP	Open-label treatment period
PASS	Post-authorisation Safety Study
PCSK9	Proprotein convertase subtilisin/kexin type 9

Abbreviation	Definition
PL	Package Leaflet
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
Q4W	Every 4 weeks
QPPV	Qualified person for pharmacovigilance
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SmPC	Summary of Product Characteristics
TG	Triglyceride
ULN	Upper limit of normal
VLDL	Very low-density lipoprotein

PART I PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Evinacumab
Pharmacotherapeutic group(s) (ATC code)	Other lipid modifying agents (C10AX17)
Marketing Authorisation Holder	Ultragenyx Germany GmbH
Medicinal products to which this RMP refers	1[a]
Invented name(s) in the European Economic Area (EEA)	EVKEEZA® 150 mg/ml concentrate for solution for infusion
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Evinacumab is a recombinant, fully human immunoglobulin G4 monoclonal antibody that binds and inhibits human angiopoietin-like protein 3 (ANGPTL3).
	Summary of mode 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 prominent 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.
	Important information about its composition: Evinacumab is produced by recombinant DNA technology in Chinese hamster ovary cell suspension culture. EVKEEZA contains 30 mg of proline in each mL. Proline may be harmful for patients with hyperprolinaemia type I or type II. EVKEEZA contains 1 mg of polysorbate 80 in each mL. Polysorbates may cause allergic reactions.
Hyperlink to the Product Information	Module 1.3.1

Indication(s) in the EEA	Current: EVKEEZA is indicated as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and paediatric patients aged 5 years and older with homozygous familial hypercholesterolaemia (HoFH). Proposed: EVKEEZA is indicated as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of patients aged 6 months and older with homozygous familial hypercholesterolaemia (HoFH).
Dosage in the EEA	Current: The recommended dose is 15 mg/kg administered by intravenous infusion over 60 minutes once monthly (every 4 weeks). No dose adjustment is required for paediatric patients aged 5 to 17 years. Proposed: The recommended dose is 15 mg/kg body weight administered by intravenous infusion over 60 minutes once monthly (every 4 weeks). No dose adjustment is required for paediatric patients aged 6 months to 17 years.
Pharmaceutical form(s) and strengths	Current and Proposed: Concentrate for solution for infusion (sterile concentrate). Clear to slightly opalescent, colourless to pale yellow solution. Each mL of concentrate for solution for infusion contains 150 mg of evinacumab.
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes

[a] Two presentations are available. One vial of 2.3 ml of concentrate which contains 345 mg of evinacumab and one vial of 8 ml of concentrate which contains 1,200 mg of evinacumab.

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Homozygous Familial Hypercholesterolaemia

HoFH is an ultra-rare genetic condition primarily caused by mutations in the LDLR gene, and less frequently by mutations in the proprotein convertase subtilisin/kexin type 9 (PCSK9), apolipoprotein B, and LDL receptor adaptor protein 1 genes; more than 90% of HoFH results from LDLR mutations (Cuchel, 2014).

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) (Banerjee, 2019; Etxebarria, 2015; Gaudet, 2017),
2. Genotypically "negative/negative" where mutations in stop codons, frame shifts, splice site changes, small and large insertions/deletions, and copy number variations result in the loss of function of both LDLR alleles (Chora, 2018), or
3. Genotypically "defective" where missense mutations (hypomorphs) result in diminished LDLR activity (>15% LDLR activity).

Regardless of the underlying mutations, lifelong exposure to extremely elevated LDL-C leads to an exceedingly high risk of developing premature atherosclerosis, as well as valvular and supravalvular stenosis.

Prevalence:

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) reported the prevalence of HoFH to be between 1 in 160,000 to 1 in 320,000 worldwide (Mach, 2020). The prevalence of HoFH can differ by country as methods used to identify cases vary (e.g., phenotypically, genotypic profiling, or calculation via the Hardy-Weinberg equilibrium).

Demographics of the Population in the Proposed Indication - Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease:

The rarity of HoFH means, in addition to the literature being based on either small case series or cohort studies, that information on the demographics of the disease is limited.

It is known that HoFH is an inherited disorder; thus, regions with isolated populations or higher rates of consanguineous marriages appear to have a higher prevalence of HoFH due to a founder effect for LDLR mutations (e.g., Afrikaaner-related populations in South Africa [1 in 30,000], Lebanese [1 in 100,000], and in the Horkuriku district of Japan [1 in 171,167]) (Raal, 2012).

Although the published literature commonly notes that HoFH should be diagnosed in children, adolescents, or young adults, a high percentage of HoFH patients are not diagnosed in childhood (Alonso, 2016). The literature notes that in studies with molecular confirmation of HoFH, there is a high variability in patient's age, cholesterol levels and cardiovascular disease.

The HoFH International Clinical Collaborators Interim report, which was presented at the 2018 EAS conference, reported limited demographic information on the first 220 patients with HoFH from 17 countries worldwide. In this report, the mean age at clinical diagnosis for HoFH was observed to be 17.7 years (± standard deviation [SD] ±17.4; range 1 to 79 years) (Hartgers, 2018). In a publication of the SAFEHEART registry, which included genetically identified HoFH patients (N = 31) from 2004 until 2015 living in Spain, the mean age of onset of treatment for these HoFH patients was 22.7 years (standard deviation [SD]±19.3) (Alonso, 2016).

Younger individuals with HoFH often harbor more severe mutations in the *LDLR* gene, with predicted very low or absent receptor activity and very high LDL-C (Reijman, 2023), often leading to earlier clinical diagnosis due to the early presence of xanthomas or cardiovascular events (Cuchel, 2023). On the other hand, diagnosis of milder HoFH cases may be delayed, as clinical phenotypes, such as xanthomas or cardiovascular events, occur later in life. As cascade and neonatal screening expands, it will enable early diagnosis of mild cases of HoFH who have lower baseline LDL-C; which in turn may lower the average LDL-C for very young children close to the level observed for older patients (Held, 2023; Henneman, 2015) and increase the number of patients with milder phenotypes diagnosed at a younger age.

Main Existing Treatment Options:

Patients with HoFH tend to be treated with multiple lipid-lowering treatment (LLTs) including statins, 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 paediatric population.

Treatment goals are to reduce LDL-C and the risk of atherosclerotic cardiovascular disease (ASCVD). The ESC/EAS Consensus Panel recommends that in patients with FH and at very high risk, an LDL-C reduction of at least 50% and an LDL-C goal of <55 mg/dL (1.42 mmol/L) should be considered (Mach, 2020). Due to the lifelong exposure to elevated LDL-C, aggressive lipid lowering therapy should be started as early as possible in childhood (Wiegman, 2015).

Common therapies such as statins and PCSK9 inhibitors are dependent on increasing LDLR activity, and many HoFH patients are therefore refractory to these treatments due to defects at the LDLR locus. For example, statins reduce LDL-C by more than 50% in patients with heterozygous familial hypercholesterolaemia (HeFH) and polygenic forms of hypercholesterolaemia, but statins decrease LDL-C by only <15% to 30% in HoFH patients. In patients with little or no LDLR activity (including null/null and negative/negative mutations), statins provide minimal to no efficacy (<15% reduction) (Raal, 2000; Rader, 2003; Stein, 2017).

The addition of ezetimibe may further decrease LDL-C by 20% to 27% compared to statins alone, but patients with HoFH treated with a high dose statin and ezetimibe still remain far from their LDL-C goal and at substantial residual risk for coronary artery disease.

PCSK9 inhibitors provide an effective treatment option in patients with HeFH and polygenic causes of hypercholesterolaemia, but, similar to statins, are modestly effective in patients with HoFH. For example, treatment with alirocumab or evolocumab resulted in a mean reduction in LDL-C of approximately 30% compared to placebo (Blom, 2020; Raal, 2015). In the most difficult-to-treat patients with minimal residual LDLR function, on average alirocumab and evolocumab had minimal to no efficacy (<10% reduction) in lowering LDL-C (Blom, 2020; Raal, 2015; Raal, 2017).

Of the available drugs for HoFH, lomitapide provides the greatest reductions in LDL-C (up to 40% with the highest dose), but the drug is associated with dose-limiting safety issues that limit its efficacy (such as high rates of gastrointestinal side effects, hepatic steatosis, and abnormal liver function tests) (Cuchel, 2013; Raal, 2010). In an analysis of 1-year data from the Lomitapide Observational Worldwide Evaluation Registry project, the mean dose of lomitapide was 14.4 mg daily, which is well below the highest approved dose of 60 mg daily (Khoury, 2019). Additionally, lomitapide is not approved for paediatric patients and thus not an option for patients under 18 years of age.

The treatment of paediatric HoFH is a serious dilemma for physicians and caregivers because most lipid-lowering therapies are only approved for use in adolescents/adults and none are approved for the treatment of young children less than 6 years old. However, considering the very high risk of premature ASCVD, the limited availability of apheresis to specialized centres or to medical facilities able to provide the necessary equipment and trained staff, and the complications related to liver transplantation, children are often prescribed off-label lipid-lowering therapy on a compassionate use basis.

The majority of patients with HoFH could benefit from lipid apheresis (Goldberg, 2011) and in some European Union (EU) countries, this treatment modality is available and used, but this can be difficult in very young patients and can be limited by lack of access.

The procedure mechanically removes LDL-C from circulation and is efficacious in all patients with HoFH, regardless of their mutation status. However, the time-averaged reductions in LDL-C over an extended period (1 to 5 years) range between only 22% and 36% (Wang, 2016). It is also the only therapeutic option recommended in patients under 5 years of age. However, performing lipid apheresis on young children can be challenging due to their small peripheral vessels, and may result in complications related to venous puncture, low blood flow, and low blood volume. Moreover, anxiety and emotional distress can affect patients' compliance with apheresis treatment. While LDL apheresis is generally well tolerated, it may result in hypotension, hypocalcemia, allergic reactions, or an acute decrease in serum protein levels. In addition, the placement of an arteriovenous fistula for frequent vascular access may be required. Central venous catheters are an option to start apheresis in young children with severe HoFH; however, this type of access needs careful management to avoid infections and catheter displacement and should only be used when urgency overrules risks (Lischka, 2022).

Despite its benefits, many patients do not have access to a qualified apheresis centre, and the cost, tolerability, and burden of weekly or biweekly apheresis sessions (lasting 2 to 5 hours per session) are infeasible. A lipid-lowering treatment that could result in a decrease in frequency or discontinuation of apheresis would provide meaningful benefit to patients.

Finally, liver transplantation, which normalises cholesterol levels, can be used to treat HoFH, especially in children. However, this is a very invasive procedure with many issues, including a high risk of post-transplantation surgical complications and mortality, paucity of donors, and need for life-long treatment with immunosuppressive therapy. Accordingly, it is rarely used and viewed as a treatment option of last resort.

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 paediatric HoFH patients who lack treatment options.

Natural History of the Indicated Condition in the (Untreated) Population, Including Mortality and Morbidity:

HoFH is a life-threatening genetic condition, which is typically characterised clinically by untreated plasma cholesterol levels >13 mmol/L (>500 mg/dL), presence of cutaneous or tendon xanthomas before the age of 10 years old, and premature and progressive ASCVD (Cuchel, 2014). Historically, the literature notes that patients with HoFH have a significantly increased risk of experiencing a fatal myocardial infarction when compared to the general population, with one study reporting a finding of a 100-times greater risk for patients with HoFH (Naveen, 2019).

The first major cardiovascular event in patients with clinically diagnosed HoFH often occurs during adolescence (Al-Shaikh, 2002; Kolansky, 2008; Raal, 2011). Patients who are LDLR negative have worse outcomes, with angina pectoris, myocardial infarctions, and deaths reported in early childhood. If these patients are untreated, they rarely survive beyond their second decade of life. Patients that are LDLR-defective typically have a longer life expectancy, but they develop clinically significant ASCVD by the age of 30 years old (Cuchel, 2014).

Mortality associated with HoFH has been reported in children as young as 1.5 years of age (Stanbury, 1983). Published case reports include death of a 2-year-old male; postmortem examination revealed advanced aortic root atheroma and aortic valve stenosis (Galiano, 2020). Myocardial infarction leading to death was reported as early as 3 years of age in a patient with HoFH (Rose, 1982). Sudden death due to 98% stenosis in the left coronary artery was reported in a 4-year-old male with HoFH (Widhalm, 2011). A case report of fatal refractory asystolic cardiac arrest in a 4.5-year-old female also summarised an additional 7 published reports of early death from CVD in children <5 years of age with HoFH (Gautschi).

The interim analysis of 220 patients enrolled in the HoFH International Clinical Collaborators registry showed that the mean age at first myocardial infarction and aortic valve replacement was 35.7 years (range 17 to 53 years) and 33.8 years (range 5 to 69 years), respectively. The mean age of death in 15 (7%) patients entered in the registry posthumously was 42.2 years (range 13 to 87 years) with the leading cause of death being cardiovascular (66.7%) (Hartgers, 2018). Therefore, these data show that even with currently available treatment, the mean age at death of HoFH patients is well below the general European life expectancy, estimated to be 80.9 years (Eurostat, 2019).

Thompson et al. analysed data from two long-term retrospective surveys of patients from South Africa and the United Kingdom and identified 133 patients that were statin-naïve as of Jan 1990 and followed until death or the end of 2014 (Thompson, 2018). The results of their survival analysis show a significant association between on-treatment total cholesterol level and time to death. This analysis also concluded that the unadjusted comparison of patients who had one or more MACE while on treatment were older, more often Caucasian, and more likely to have pre-existing cardiovascular disease, as well as started LLT later in life and had less of a reduction in total cholesterol on treatment. The authors did note that patients with MACE were more often null/null or null/defective LDLR mutations, and there was no statistically significant difference in the risk of MACE by gender or pre-treatment total cholesterol.

In conclusion, patients with HoFH have extreme elevations in LDL-C levels from birth, which leads to accelerated atherosclerosis, premature death from acute coronary syndromes,

and is often associated with valvar and supra-valvar atheroma of the aortic root (Alonso, 2016; Rallidis, 1998).

Important Co-morbidities:

Due to the limited nature of studies conducted on this ultra-rare patient population, the specific frequency in which co-morbidities occur in patients with HoFH are not readily available in the literature.

It is known that the natural history and disease progression of HoFH in general includes ASCVD complications and/or MACE. Additional co-morbidities that are commonly referenced with an association with hypercholesterolaemia include hypertension and diabetes mellitus; however, the exact frequency is not known in patients with HoFH (Cuchel, 2014).

PART II: MODULE SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

The nonclinical programme for evinacumab was consistent with the International Council for Harmonisation (ICH) guidelines on the preclinical safety evaluation of biotechnology derived pharmaceuticals and the supporting studies were conducted under the Good Laboratory Practices (GLP), as appropriate.

The cynomolgus monkey, rabbit, and rat were considered to be the most appropriate species for toxicologic evaluation based on the in vitro binding data as well as the amino acid sequence homology between human, monkey, rabbit, and rat ANGPTL3.

The results of a comprehensive carcinogenicity risk assessment, including review of data from repeat-dose toxicology studies and supporting information regarding ANGPTL3 inhibition and ANGPTL3 loss of function available in the literature, indicate that chronic treatment with evinacumab does not pose an increased cancer risk. Based on this risk assessment, no further nonclinical studies (including no animal carcinogenicity studies) were considered necessary to assess the carcinogenic potential of evinacumab.

The full details on the evinacumab nonclinical development programme were provided in the initial Marketing Authorisation application Module 2.4 and 2.6.

Key Safety Findings from Nonclinical Studies and Relevance to Human Usage:

Toxicity

Reproductive/Developmental Toxicity

During embryofoetal and fertility/postnatal developmental studies conducted in rats, evinacumab-related effects were limited to decreases in serum TG levels in maternal and F_1 animals at ≥30 mg/kg. Because there were no evinacumab-related foetal malformations or impacts on fertility, the no-observed-adverse-effect level (NOAEL) for rat embryofoetal/developmental toxicity is 100 mg/kg/dose.

In embryofoetal developmental studies in rabbits, embryofoetal toxicity was observed at dosages that induced maternal toxicity. Maternal toxicity consisted of early deaths, premature deliveries, and/or abortions at all dose levels; clinical signs and changes in body weight and food consumption also were observed. In addition, decreases in serum TG, HDL-C, and total cholesterol were seen, consistent with the pharmacology of evinacumab. Teratogenicity was observed in rabbit offspring at doses ≥5 mg/kg evinacumab. Based on the results of this rabbit study, a maternal NOAEL could not be determined, and the developmental NOAEL is considered to be 1 mg/kg/dose evinacumab.

- Relevance to human use: The clinical relevance of the rabbit findings to humans is unclear, based on lipid profile, as rabbits have significantly lower lipid levels than do humans at baseline (Yin, 2012), and therefore, may be uniquely sensitive to the lipid lowering effects of evinacumab during pregnancy. Further, it is also known that rabbits experience decreases in several lipid parameters during the third trimester of pregnancy (Zilversmit, 1972), whereas rats, and notably humans, experience increases (Abbassi-Ghanavati, 2009; Ghio, 2011; Liberati, 2004), a fact that may also limit the translational relevance of the rabbit data to human patients.

The findings in rabbits, without similar findings in rats, are of uncertain relevance to humans. Nevertheless, embryofoetal toxicity is considered an important potential risk of evinacumab (refer to Part II: Module SVII).

In the male fertility study in rabbits, there were no adverse findings related to the pharmacology of evinacumab. During the dosing period, prior to mating, there were 6 early evinacumab-related deaths caused by an anti-drug antibody (ADA)-related inflammatory response. Decreases in serum TG, HDL-C, and total cholesterol were observed, consistent with the pharmacology of evinacumab. Because there was no effect on male fertility observed, the NOAEL for this study is considered to be 300 mg/kg/dose, the highest dose level administered. Offspring from the untreated females presented with delayed ossification of caudal vertebrae. There were no teratogenic effects observed in the offspring in this study.

- Relevance to human use: None anticipated since this finding reflects normal variation in development and is not considered to be adverse (DeSesso, 2018).

The juvenile toxicity studies were conducted in rats and rabbits. In juvenile rats, exposure to evinacumab was well tolerated, with no adverse effects evident at any dose level. Based on the lack of adverse effects, the NOAEL in juvenile rats is considered to be 100 mg/kg/dose (IV or subcutaneous [SC]), which represented the highest dose administered.

Similarly, in a dose range finding study in juvenile rabbits, evinacumab-related effects were limited to those consistent with the intended pharmacology of evinacumab. During the subsequent GLP-compliant study in juvenile rabbits, administration of ≤300 mg/kg evinacumab once every 5 days via IV injection from postnatal day 21 through postnatal day 141 was well tolerated. The NOAEL is considered to be 300 mg/kg/dose, the highest dose evaluated.

- Relevance to human use: Juvenile toxicity studies in rats and rabbits did not identify any concerns for human paediatric use of evinacumab.

Other Toxicity-Related Information or Data

Anti-evinacumab antibody responses were generally low in monkeys and in rats (typically <25% of animals per study) and high in rabbits (typically >50%). Although ADA positivity correlated with lower evinacumab concentrations in serum, ADA did not impede the safety evaluation as exposure to total evinacumab was maintained throughout the dosing period in the majority of rats and monkeys at all dose levels, and in rabbits that received ≥30 mg/kg evinacumab.

- Relevance to human use: No impact on use in humans is anticipated.

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

Overall, a total of 243 patients have been treated with any IV dose of evinacumab in either placebo-controlled or open-label trials across all HoFH and non-HoFH study populations. Of these, 139 patients had HoFH, of which 138 patients were treated with evinacumab 15 mg/kg every 4 weeks (Q4W) for at least 24 weeks, 120 patients were treated for at least 52 weeks, and 78 patients were treated for at least 104 weeks.

From the pooled data analysis, a total of 223 patients with HoFH or persistent hypercholesterolaemia received any IV dose of evinacumab in clinical trials, with a total duration of exposure of 4,825.1 months (402.1 patient-years). The majority of these patients (216/223: 96.9%) had at least 24 weeks of exposure and 90.6% (202/223) had at least 48 weeks of exposure.

Of these 223 patients, 119 (51.0%) had HoFH. One-hundred and eighteen HoFH patients were treated with evinacumab at the intended commercial dose of 15 mg/kg IV Q4W for at least 24 weeks and 116 of these patients were treated for at least 48 weeks.

The integrated analysis strategy for the evinacumab clinical programme was divided into 3 distinct pooled data sets, as described below.

An overview of studies contributing to each integrated, pooled, analysis is provided in Table 1.

Safety data from the R1500-CL-17100 paediatric study, which included paediatric patients aged ≥5 to <12 years, were not included in any of the integrated data pools since the pooled data focused on patients aged ≥12 years of age and is presented separately.

Table 1: Listing of Studies Contributing to the Integrated (Pooled) Analysis

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

DBTP=double-blind treatment period; HoFH=homozygous familial hypercholesterolaemia; IV=intravenous; OLTP=open-label treatment period.

[a] The global pool includes exposure data from all IV dose regimens.

[b] Only data from Group B (IV treatment groups) of R1500-CL-1643 are included in the integrated safety analysis for this marketing application.

Source: Module 2.7.4 Table 10

- **Pool 1 (Global Pool):** The objective of this pool is to provide an accurate accounting of cumulative IV evinacumab exposure for each patient, taking into account a patient's participation in one or more studies. The studies included in this pool are R1500-CL-1331, R1500-CL-1629 (double-blind treatment period [DBTP] and open-label

treatment period [OLTP]), R1500-CL-1643 (DBTP and OLTP for Group B [IV treatment groups]), and R1500-CL-1719.

No safety analyses were conducted on this global pool due to the heterogeneity of study designs. Specifically, differing design elements (i.e., parallel group versus crossover, placebo-controlled versus uncontrolled, treatment duration, and dose regimens) have the potential to introduce reporting bias, which would affect the interpretability of the pooled safety analyses.

For details, refer to Table 2, Table 3, and Table 4 patient exposure and duration of cumulative exposure by age and sex. Table 5 presents the patient exposure for HoFH indication.

- **Pool 2 (Placebo-Controlled Studies):** This is the primary pool for the integrated analysis of safety. The objective of this pool is to identify potential drug-related events using the pooled placebo group data as an estimate of background event rates. This pool is considered to contain the least biased data reporting.

  It provides an integration of 24 weeks of data from the DBTP of the phase 3 study in patients with HoFH (R1500-CL-1629) and the completed IV portion of the phase 2 study in patients with persistent hypercholesterolaemia (R1500-CL-1643). The DBTP of these 2 studies have similar study design elements (e.g., assessments, schedule of assessments and common case report forms), which were pre-planned for the purpose of data integration.

  The safety data in this pool are divided into 3 treatment groups:

  - Placebo IV Q4W
  - Evinacumab 15 mg/kg IV Q4W
  - All evinacumab IV doses combined (5 mg/kg IV Q4W data from R1500-CL-1643 plus 15 mg/kg IV Q4W from the DBTP of both R1500-CL-1643 and R1500-CL-1629).

  Both IV doses of evinacumab were included in Pool 2 to increase the number of patients exposed to evinacumab. Analysis of the 15 mg/kg IV Q4W regimen alone is included because this is the intended dose for registration in HoFH patients. The summary of demographics and study treatment exposure in Pool 2 are presented in Table 6 and Table 7, respectively.

- **Pool 3 (Uncontrolled Studies):** The objective of this pool is to incorporate safety data from additional patients who received evinacumab in an open-label setting including long-term safety data.

  The uncontrolled studies pool is an integration of open-label evinacumab 15 mg/kg IV Q4W data in patients with HoFH (R1500-CL-1629 and R1500-CL-1719) or persistent hypercholesterolaemia (R1500-CL-1643). The OLTP of R1500-CL-1629 and R1500-CL-1643 and the open-label study R1500-CL-1719 have similar study design elements (e.g., assessments, schedule of assessments and common case report forms), which were pre-planned for the purpose of open label data integration.

  The open-label study R1500-CL-1331 is excluded from Pool 3 due to its study design, which is an unbalanced cross-over design with insufficient washout periods between treatments. Thus, the carry-over effect from each route of administration and dose of evinacumab cannot be quantified.

In this Pool 3 analysis, a total of 206 patients received IV doses of evinacumab. The mean (SD) number of study drug infusions in the total evinacumab group was 20.04 (10.166) with a mean (SD) duration of study drug exposure of 80.97 (41.189) weeks. The summary of study treatment exposure in Pool 3 is presented in Table 8.

The primary pool for safety analysis is Pool 2, while results from Pool 3 are included to corroborate the findings from Pool 2.

Pool 1 shows the overall patient exposure and demographic characteristics of patients treated with evinacumab within the clinical development programme.

Detailed information on the clinical development programme for evinacumab is available in the initial Marketing Authorisation application Module 2.5 and 2.7.4.

Table 2: Patient Exposure by Evinacumab Regimen (Pool 1)

Variable	5 mg/kg IV Q4W [a]	15 mg/kg IV Q4W [b]	Any Evinacumab IV
Patients	36	219	223
Total duration of exposure Patient-months	183.6	4641.4	4825.1
Total duration of exposure Patient-Years	15.3	386.8	402.1

IV=intravenous; Q4W=every 4 weeks.
Double-blind and open-label periods of phase 2 and 3 studies: R1500-CL-1331, R1500-CL-1629, R1500-CL-1643, and R1500-CL-1719. Patients from study R1500-CL-1643 can contribute to more than one dose regimen. Patients from study R1500-CL-1331 are assigned to 15 mg/kg Q4W.
[a] Double-blind period in study R1500-CL-1643.
[b] Double-blind period in studies R1500-CL-1629 and R1500-CL-1643. Open-label period in studies R1500-CL-1331, R1500-CL-1629, R1500-CL-1643, and R1500-CL-1719.
Source: Module 5.3.5.3 Pool 1 Table 1.2.1.1

At the DLP of this RMP, 76 patients (34.1% of exposed patients) have a duration of exposure of longer than 2 years (≥ 108 weeks).

Table 3: Duration of Cumulative Evinacumab Exposure (Pool 1)

Variable	5 mg/kg IV Q4W [a] (N=36)	15 mg/kg IV Q4W [b] (N=219)	Any Evinacumab IV (N=223)
Patient-year	15.3	386.8	402.1
Duration of evinacumab exposure			
≥1 day	36 (100%)	219 (100%)	223 (100%)
≥4 weeks	36 (100%)	219 (100%)	223 (100%)
≥8 weeks	34 (94.4%)	218 (99.5%)	220 (98.7%)
≥12 weeks	34 (94.4%)	214 (97.7%)	217 (97.3%)
≥24 weeks	28 (77.8%)	213 (97.3%)	216 (96.9%)
≥36 weeks	N/A	210 (95.9%)	211 (94.6%)
≥48 weeks	N/A	189 (86.3%)	202 (90.6%)
≥60 weeks	N/A	144 (65.8%)	173 (77.6%)
≥72 weeks	N/A	125 (57.1%)	141 (63.2%)
≥84 weeks	N/A	102 (46.6%)	102 (45.7%)

Variable	5 mg/kg IV Q4W [a] (N=36)	15 mg/kg IV Q4W [b] (N=219)	Any Evinacumab IV (N=223)
≥96 weeks	N/A	87 (39.7%)	87 (39.0%)
≥108 weeks	N/A	76 (34.7%)0	76 (34.1%)
≥120 weeks	N/A	72 (32.9%)	72 (32.3%)
≥132 weeks	N/A	60 (27.4%)	60 (26.9%)
≥144 weeks	N/A	44 (20.1%)	44 (19.7%)
≥156 weeks	N/A	28 (12.8%)	28 (12.6%)

IV=intravenous; N/A=not applicable; Q4W=every 4 weeks.

Double-blind and open-label periods of phase 2 and 3 studies: R1500-CL-1331, R1500-CL-1629, R1500-CL-1643, and R1500-CL-1719. Patients from study R1500-CL-1643 can contribute to more than one dose regimen. Patients from study R1500-CL-1331 are assigned to 15 mg/kg Q4W.

[a] Double-blind period in study R1500-CL-1643.

[b] Double-blind period in studies R1500-CL-1629 and R1500-CL-1643. Open-label period in studies R1500-CL-1331, R1500-CL-1629, R1500-CL-1643, and R1500-CL-1719.

Source: Module 5.3.5.3 Pool 1 Table 1.2.1.2

Table 4: Patient Exposure by Evinacumab Regimen: By Age and Sex (Pool 1)

Age Group (years)	Any Evinacumab IV (N=223)			5 mg/kg IV Q4W [a] (N=36)		15 mg/kg IV Q4W [b] (N=219)	
	Male	Female	Total of patients	Male	Female	Male	Female
≥12 to <18							
Patients	9	5	**14**	0	0	9	5
Total duration of exposure months	207.9	110.6	-	NA	NA	207.9	110.6
Total duration of exposure Patient-years	17.3	9.2	-	NA	NA	17.3	9.2
≥18 to <65							
Patients	88	94	**182**	11	17	87	91
Total duration of exposure months	2016.3	1929.9	-	536	86.1	1962.7	1843.8
Total duration of exposure Patient-years	168.0	160.8	-	4.5	7.2	163.6	153.6
≥65 to <75							
Patients	9	16	**25**	2	6	9	16
Total duration of exposure months	200.0	322.5	-	11.3	32.6	188.7	289.8
Total duration of exposure Patient-years	16.7	26.9	-	0.9	2.7	15.7	24.2

Age Group (years)	Any Evinacumab IV (N=223)			5 mg/kg IV Q4W [a] (N=36)		15 mg/kg IV Q4W [b] (N=219)	
	Male	**Female**	**Total of patients**	**Male**	**Female**	**Male**	**Female**
≥75							
Patients	1	1	**2**	0	0	1	1
Total duration of exposure months	8.3	29.5	-	NA	NA	8.3	29.5
Total duration of exposure Patient-years	0.7	2.5	-	NA	NA	0.7	2.5
Total of patients	**107**	**116**	**223**	**13**	**23**	**106**	**113**

IV=intravenous; NA=not applicable; Q4W=every 4 weeks.

Double-blind and open-label periods of phase 2 and 3 studies: R1500-CL-1331, R1500-CL-1629, R1500-CL-1643, and R1500-CL-1719. Patients from study R1500-CL-1643 can contribute to more than one dose regimen. Patients from study R1500-CL-1331 are assigned to 15 mg/kg Q4W.

[a] Double-blind period in study R1500-CL-1643.

[b] Double-blind period in studies R1500-CL-1629 and R1500-CL-1643. Open-label period in studies R1500-CL-1331, R1500-CL-1629, R1500-CL-1643, and R1500-CL-1719.

Source: TABLE 1.2.3.1 PATIENT EXPOSURE BY EVINACUMAB REGIMEN AND INTRINSIC FACTOR: AGE BY SEX; Global Pool; Double-blind and Open-label Safety Analysis Set

Table 5: Patient Exposure for Homozygous Familial Hypercholesterolaemia Indication: By Age and Sex (Pool 1)

Age Group (Years)	15 mg/kg IV Q4W [a]		
	Male	**Female**	**Total of Patients**
≥12 to < 18			
Patients	9	5	**14**
Total duration of exposure months	207.9	110.6	-
Total duration of exposure Patient-years	17.3	9.2	-
≥18 to < 65			
Patients	49	47	**96**
Total duration of exposure months	1474.6	1334.6	-
Total duration of exposure Patient-years	122.9	111.2	-
≥65 to < 75			
Patients	3	5	**8**
Total duration of exposure months	120.7	158.4	-
Total duration of exposure Patient-years	10.1	13.2	-
≥75			
Patients	0	1	**1**
Total duration of exposure months	NA	29.5	-
Total duration of exposure Patient-years	NA	2.5	-
Total of patients	**61**	**58**	**119**

IV=intravenous; NA=not applicable; Q4W=every 4 weeks.

Double-blind and open-label periods of phase 2 and 3 studies: R1500-CL-1331, R1500-CL-1629, and R1500-CL-1719.

Patients from study R1500-CL-1331 are assigned to 15 mg/kg Q4W.

[a] Double-blind period in studies R1500-CL-1629. Open-label period in studies R1500-CL-1331, R1500-CL-1629, and R1500-CL-1719.

Source: TABLE 1.2.6.1 PATIENT EXPOSURE FOR HOFH INDICATION BY INTRINSIC FACTOR: AGE BY SEX; Global Pool

Table 6: Summary of Demographics (Pool 2)

Variable	Placebo IV Q4W (N=54)	Evinacumab 15 mg/kg IV Q4W (N=81)	All Evinacumab IV Doses [a] (N=117)	Total (N=171)
Age (years)				
N	54	81	117	171
Mean (SD)	48.3 (14.78)	47.8 (15.07)	50.3 (14.13)	49.7 (14.32)
Median	50.0	49.0	53.0	52.0
Min : Max	12 : 76	15 : 75	15 : 75	12 : 76
Age group (years) [n (%)]				
N	54	81	117	171
≥12 to <18	1 (1.9%)	1 (1.2%)	1 (0.9%)	2 (1.2%)
≥18 to <45	21 (38.9%)	31 (38.3%)	35 (29.9%)	56 (32.7%)
≥45 to <65	25 (46.3%)	37 (45.7%)	61 (52.1%)	86 (50.3%)
≥65 to <75	5 (9.3%)	11 (13.6%)	19 (16.2%)	24 (14.0%)
≥75	2 (3.7%)	1 (1.2%)	1 (0.9%)	3 (1.8%)
Age group (years) [n (%)]				
N	54	81	117	171
<65	47 (87.0%)	69 (85.2%)	97 (82.9%)	144 (84.2%)
≥65	7 (13.0%)	12 (14.8%)	20 (17.1%)	27 (15.8%)
Sex [n (%)]				
N	54	81	117	171
Male	25 (46.3%)	39 (48.1%)	52 (44.4%)	77 (45.0%)
Female	29 (53.7%)	42 (51.9%)	65 (55.6%)	94 (55.0%)
Race [n (%)]				
N	54	81	117	171
White	43 (79.6%)	66 (81.5%)	99 (84.6%)	142 (83.0%)
Black or African American	2 (3.7%)	2 (2.5%)	2 (1.7%)	4 (2.3%)
Asian	5 (9.3%)	6 (7.4%)	7 (6.0%)	12 (7.0%)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Not Reported	0	2 (2.5%)	2 (1.7%)	2 (1.2%)
Other	4 (7.4%)	5 (6.2%)	7 (6.0%)	11 (6.4%)

Variable	Placebo IV Q4W (N=54)	Evinacumab 15 mg/kg IV Q4W (N=81)	All Evinacumab IV Doses [a] (N=117)	Total (N=171)
Ethnicity [n (%)]				
N	54	81	117	171
Hispanic or Latino	3 (5.6%)	4 (4.9%)	11 (9.4%)	14 (8.2%)
Not Hispanic or Latino	50 (92.6%)	73 (90.1%)	102 (87.2%)	152 (88.9%)
Not Reported	1 (1.9%)	4 (4.9%)	4 (3.4%)	5 (2.9%)
Site region				
N	54	81	117	171
Europe	28 (51.9%)	41 (50.6%)	55 (47.0%)	83 (48.5%)
Japan	4 (7.4%)	6 (7.4%)	6 (5.1%)	10 (5.8%)
North America	16 (29.6%)	22 (27.2%)	39 (33.3%)	55 (32.2%)
Rest of World	6 (11.1%)	12 (14.8%)	17 (14.5%)	23 (13.5%)
BMI (kg/m^2)				
N	54	81	117	171
Mean (SD)	27.2 (5.78)	27.6 (5.66)	27.9 (5.35)	27.7 (5.48)
Median	25.7	27.2	27.4	27.1
Min : Max	16 : 40	18 : 46	18 : 46	16 : 46
BMI group (kg/m^2)				
N	54	81	117	171
<30	39 (72.2%)	56 (69.1%)	79 (67.5%)	118 (69.0%)
≥30	15 (27.8%)	25 (30.9%)	38 (32.5%)	53 (31.0%)

BMI=body mass index; IV=intravenous; Max=maximum; Min=minimum; Q4W=every 4 weeks; SD=standard deviation.

Double-blind treatment periods of placebo-controlled studies R1500-CL-1629 and R1500-CL-1643.

[a] Evinacumab doses include 5 mg/kg (R1500-CL-1643 only) and 15 mg/kg.

Source: Module 5.3.5.3 Pool 2 Table 1.2.1

Table 7: Summary of Study Treatment Exposure (Pool 2)

Variable	Placebo IV Q4W (N=54)	Evinacumab 15 mg/kg IV Q4W (N=81)	All Evinacumab IV Doses [a] (N=117)
Total number of study treatment infusions			
N	54	81	117
Mean (SD)	5.70 (1.057)	5.80 (0.843)	5.71 (1.018)
Median	6.00	6.00	6.00
Min : Max	1.0 : 6.0	1.0 : 6.0	1.0 : 6.0
Duration of study drug exposure (weeks)			
N	54	81	117
Mean (SD)	23.03 (4.232)	23.50 (3.415)	23.09 (4.105)
Median	24.14	24.14	24.14
Min : Max	4.1 : 25.7	4.1 : 25.7	4.1 : 25.7
Duration of study drug exposure by category [patient, n (%)]			
≥1 day to <4 weeks	0	0	0
≥4 weeks to <8 weeks	2 (3.7%)	1 (1.2%)	3 (2.6%)
≥8 weeks to <12 weeks	0	2 (2.5%)	2 (1.7%)
≥12 weeks to <16 weeks	1 (1.9%)	0	2 (1.7%)
≥16 weeks to <20 weeks	1 (1.9%)	0	0
≥20 weeks to <24 weeks	6 (11.1%)	11 (13.6%)	15 (12.8%)
≥24 weeks	44 (81.5%)	67 (82.7%)	95 (81.2%)

IV=intravenous; Q4W=every 4 weeks; Max=maximum; Min=minimum; SD=standard deviation.
Double-blind treatment of placebo-controlled studies: R1500-CL-1629 and R1500-CL-1643.
[a] Evinacumab doses include 5 mg/kg (R1500-CL-1643 only) and 15 mg/kg.
Source: Table 1.3.1 Summary of Study Treatment Exposure, Pool 2

Table 8: Summary of Study Treatment Exposure (Pool 3)

Variable	New Evinacumab [a] (N=97)	Continue Evinacumab [b] (N=109)	Total Evinacumab 15 mg/kg (N=206)
Total number of study treatment infusions			
N	97	109	206
Mean (SD)	21.26 (9.325)	18.95 (10.787)	20.04 (10.166)
Median	21.00	12.00	13.50
Min : Max	2.0 : 39.0	2.0 : 41.0	2.0 : 41.0
Duration of study drug exposure (weeks)			
N	97	109	206
Mean (SD)	85.91 (37.648)	76.57 (43.806)	80.97 (41.189)
Median	84.14	48.29	53.57
Min : Max	8.1 : 156.0	8.1 : 163.9	8.1 : 163.9
Duration of study drug exposure by category [patient, n (%)]			
≥1 day to <4 weeks	0	0	0
≥4 weeks to <8 weeks	0	0	0
≥8 weeks to <12 weeks	1 (1.0%)	1 (0.9%)	2 (1.0%)
≥12 weeks to <16 weeks	0	0	0
≥16 weeks to <20 weeks	0	1 (0.9%)	1 (0.5%)
≥20 weeks to <24 weeks	0	2 (1.8%)	2 (1.0%)
≥24 weeks to <28 weeks	1 (1.0%)	0	1 (0.5%)
≥28 weeks to <32 weeks	1 (1.0%)	1 (0.9%)	2 (1.0%)
≥32 weeks to <36 weeks	0	0	0
≥36 weeks to <40 weeks	1 (1.0%)	2 (1.8%)	3 (1.5%)
≥40 weeks to <44 weeks	1 (1.0%)	9 (8.3%)	10 (4.9%)
≥44 weeks to <48 weeks	5 (5.2%)	21 (19.3%)	26 (12.6%)
≥48 weeks to <52 weeks	26 (26.8%)	30 (27.5%)	56 (27.2%)

DBTP=double-blind treatment period; OLTP=open-label treatment period; SD=standard deviation.
Open-label periods of studies R1500-CL-1629, R1500-CL-1643, and R1500-CL-1719 (excluding patients who participated in the R1500-CL-1331 parent study).
[a] Patients who were randomised to placebo in R1500-CL-1629/ R1500-CL-1643 DBTP and then received evinacumab in OLTP, or evinacumab-I patients enrolled in R1500-CL-1719.
[b] Patients who were randomised to evinacumab in R1500-CL-1629/ R1500-CL-1643 DBTP and also received evinacumab in OLTP.
Source: Module 5.3.5.3 Pool 3 Table 1.3.1

Study R1500-CL-17100 was not included in the integrated pooled analysis because this study focuses on a paediatric population (patients aged 5-11 years) with HoFH and is described separately:

R1500-CL-17100: This study consists of 3 parts:

- Part A: Phase 1b, single-dose pharmacokinetic/pharmacodynamic study; consists of up to 4 periods: Run-in Period, Screening Period, Single-dose OLTP, 16-week Observation Period, and Follow-up Period (Follow-up Period is for patients who do not enter Part C).
- Part B: Phase 3, OL efficacy and safety study; consists of up to 4 periods: Run-in Period; Screening Period; 24-week OLTP, and Follow-up Period (Follow-up Period for patients who do not enter Part C).
- Part C: Phase 3, OLE efficacy and safety study for Parts A and B; consists of 2 periods: 48-week OLTP and 24-week Follow-up Period.

A total of 20 patients were enrolled and treated within this study. The mean (SD) age of patients in the population was 9.0 (1.84) years at baseline, with an age range from ≥5 to <12 and a median age of 9.0 years.

All 6 (100%) patients in Part A received a single infusion of evinacumab 15 mg/kg IV. Patients in Part B (N=14) had a mean (SD) number of infusions of 6.00 (0.000) over a mean (SD) duration of study drug exposure of 24.17 (0.639) weeks. Pooled data includes data from Part A patients during their participation in Part C and data from Part B patients during their participation in Parts B and C. In the pooled population (patients from part B and C), patients had a mean (SD) number of infusions of 12.75 (1.482) over a mean (SD) duration of study drug exposure of 51.63 (5.283) weeks.

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criteria	Reason for Exclusion	Is it Considered to be Included as Missing Information?	Rationale if not considered as missing information
Age < 5 years of age	HoFH is a very rare condition and diagnosed patients under 5 years of age are even more rare. Therefore, a clinical trial in paediatric patients below 5 years of age was not considered feasible. Recruiting the number of patients necessary to carry out a dedicated clinical study would be extremely challenging. A waiver in the Paediatric Investigation Plan was granted by the Paediatric Committee at the EMA in paediatric patients below 5 years of age.	Yes	-
Uncontrolled hypertension History of a myocardial infarction, unstable angina leading to hospitalisation, coronary artery bypass graft surgery, percutaneous coronary intervention, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischaemic attack, valve replacement surgery, carotid revascularisation,	These exclusion criteria were considered due to methodological reasons, to prevent biases affecting the efficacy/safety endpoint evaluation or because they could result in an increased risk of premature study discontinuation.	No	The safety profile of evinacumab in these sub-populations of patients is not expected to differ from the general safety profile seen in HoFH patients.

Criteria	Reason for Exclusion	Is it Considered to be Included as Missing Information?	Rationale if not considered as missing information
endovascular procedure or surgical intervention for peripheral vascular disease within 3 months prior to the screening visit History of New York Heart Association Class IV heart failure within 12 months before screening			
Uncontrolled endocrine disease Thyroid-stimulating hormone level >1.5 × upper limit of normal (ULN) for patients not on thyroid replacement therapy Patients with diabetes mellitus whose disease is poorly controlled or newly diagnosed	These exclusion criteria were due to methodological reasons, to prevent biases on the efficacy/ safety endpoint evaluation and because they could result in an increased risk of premature study discontinuation.	No	The safety profile of evinacumab in these sub-populations of patients is not expected to differ from the general safety profile seen in HoFH patients.
Pregnant or breast-feeding women	These exclusion criteria were considered due to methodological considerations, to prevent any potential direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development in the absence of information on the use of evinacumab during pregnancy or lactation in humans.	Yes	Not applicable.
Estimated glomerular filtration rate <30 mL/min/1.73 m^2	These exclusion criteria were considered due to methodological reason, to prevent biases on the	No	The safety profile of evinacumab in HoFH patients with renal or hepatic impairment is not expected to differ from the

Criteria	Reason for Exclusion	Is it Considered to be Included as Missing Information?	Rationale if not considered as missing information
Alanine aminotransferase or aspartate aminotransferase >3 × ULN	efficacy/safety endpoint evaluation.		general safety profile seen in HoFH patients. As a monoclonal antibody, evinacumab is not expected to undergo significant renal or hepatic elimination.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Because of the prevalence of the disease, the clinical development programme for evinacumab included a limited number of subjects. Such a programme is unlikely to detect certain types of adverse reactions, including less frequent adverse reactions. Moreover, the clinical development programme is unlikely to detect adverse reactions with long latency or those caused by prolonged or cumulative exposure (due to limited duration of clinical studies).

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme. Five cases of evinacumab-exposed pregnancy occurred within the clinical development programme (refer to Part II: Module SVII).
Breastfeeding women	Not included in the clinical development programme.

Type of Special Population	Exposure
Patients with relevant comorbidities: • Patients with hepatic impairment	Patients with moderate or severe hepatic impairment were not included in the clinical development programme due to methodological reason, to prevent biases on the efficacy/safety endpoint evaluation. The effects of evinacumab in patients with mild hepatic impairment were not investigated since evinacumab is not expected to undergo significant hepatic elimination.
• Patients with renal impairment	Patients with severe renal impairment were not included in the clinical development programme due to methodological reason, to prevent biases on the efficacy/safety endpoint evaluation. The effects of evinacumab in patients with mild/moderate renal impairment were not investigated since evinacumab is not expected to undergo significant renal elimination.
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable.

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Information on actual patient exposure in post-marketing is not available. For the purpose of providing an estimated number of patient exposure, the following points are considered:

- Patient-years are calculated based on the actual number of vials sold/supplied. Each 2.3 mL vial contains 345 mg of evinacumab, and each 8 mL vial contains 1,200 mg of evinacumab.
- It is estimated that the recommended dosage of 15 mg/kg of evinacumab administered Q4W is followed for all patients.
- It is estimated that the entire vial contents are administered, and no medicinal product is discarded.
- An average patient weight of 60 kg is assumed.
- 13 represents the number of doses of evinacumab each patient is administered per year if the recommended dosage 15 mg/kg evinacumab Q4W is followed.

$$\text{Patient-years} = \frac{\text{number of vials sold} \times \text{vial size (mL)} \times \text{vial strength (mg/mL)}}{60\ \text{kg} \times 15\ \text{mg/kg} \times 13}.$$

SV.1.2 Exposure

Cumulatively since the international birth date until 11 Feb 2023, the overall estimated post-marketing exposure to evinacumab is 207.5 patient-years.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Based on the molecular structure, pharmacokinetics and known mechanism of action of evinacumab, there is unlikely to be potential for misuse for illegal purposes.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

- Known risks that require no further characterisation and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member State where the product is authorised):

Systemic hypersensitivity reactions (including anaphylaxis) and infusion reactions

Serious systemic hypersensitivity reactions were reported infrequently in clinical trials, with 2 events of anaphylaxis of moderate intensity.

Infusion reactions were reported more frequently in patients treated with evinacumab (7.7%) compared to patients treated with placebo (3.7%), whereas general allergic events were reported at a similar frequency in the evinacumab group and the placebo group, and the incidence of these events was below 5% in the open-label pooled dataset.

All foreign proteins (including monoclonal antibodies) have a known potential to induce hypersensitivity reactions, which may be life-threatening, especially if not identified early and managed by treatment discontinuation and timely intervention, including use of supportive care or emergency measures.

Evinacumab is an intravenous medicinal product intended to be administered in a setting where infusions can be given with the appropriate measures for the management of such reactions as part of standard clinical practice. As such, this risk will be further monitored via routine pharmacovigilance activities.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk:

- None

Important Potential Risk:

- **Embryofoetal Toxicity**

Risk-benefit impact: The nonclinical studies in rabbits, but not in rats, showed reproductive toxicity of evinacumab with unknown clinical relevance to humans due to the lower baseline lipid levels in rabbits compared to humans during pregnancy (Yin, 2012).

Since human immunoglobulin G (IgG) antibodies are known to cross the placenta barrier, evinacumab has the potential to be transmitted from the mother to the developing foetus and evinacumab may cause foetal harm when administered to pregnant women. At the DLP of this RMP, there have been 5 pregnancies in clinical trial subjects, with no pregnancy outcome reports of embryofoetal toxicity, congenital malformations or abnormalities in any of these

newborns. All reported pregnancy outcomes reported delivery of a healthy newborn with no observations of embryofoetal toxicity.

In the absence of comprehensive data on use of evinacumab during pregnancy, the potential impact on pregnancy or foetal development is unknown.

Missing Information:

- **Safety of Long-Term Use (e.g., >2 Years)**

Risk-benefit impact:

The experience with administration of evinacumab is currently limited. At the DLP of this RMP, 76 patients from clinical studies (34.1% of exposed patients) had a duration of exposure of longer than 2 years (≥108 weeks).

In addition to the observed safety data across the evinacumab programme, there is also supportive safety information for ANGPTL3 inhibition through human genetic studies in individuals with loss-of-function *ANGPTL3* variants (Module 5.3.5.4. Cardiovascular Risk and Other Clinical Phenotypes in People with Loss-of-Function Genetic Variants in ANGPTL3). These populations did not have an increased risk of liver disease, type 2 diabetes, neurological diseases, or adverse cardiovascular outcomes, and were not associated with risk of cancer, overall mortality, age at parental death, or any other disease outcome. This implies that there is likely no increased risk of any of these events with evinacumab.

Although there are real-world data for the absence of risks outlined above (e.g., adverse cardiovascular outcomes or cancer) in patients with loss-of-function mutations in *ANGPTL3*, there is limited information available on long-term safety of evinacumab treatment in HoFH patients from the evinacumab clinical development programme. No new safety concerns were identified in patients who had treatment exposure of 2 years or longer.

- **Use in pregnant or breast-feeding women**

Risk-benefit impact: There is currently only limited experience with the use of evinacumab during pregnancy and no experience with the use during breast-feeding. The nonclinical studies in rabbits but not rats showed reproductive toxicity of evinacumab with unknown clinical relevance to humans.

At the DLP of this RMP, there have been 5 pregnancies in clinical trial subjects, with no pregnancy outcome reports of embryofoetal toxicity, congenital malformations or abnormalities in any of these newborns.

It is currently not known whether evinacumab is excreted in human milk and as such, a risk to the breastfed newborn/infant cannot be excluded. It is known that antibodies are present in human milk (Czosnykowska-Łukacka, 2020).

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Since there are limited data available for the paediatric patients with HoFH below 5 years of age treated with EVKEEZA, “safety (including long-term) in children <5 years of age” is added as missing information for EVKEEZA. The rationale is provided below.

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

Rationale:

There is currently limited experience with the use of evinacumab in children <5 years of age. Only a limited number of patients below 5 years of age have been exposed to evinacumab within the compassionate use programme.

The results of a model-based extrapolation analysis predict that paediatric patients aged 6 months to less than 5 years who receive evinacumab 15 mg/kg Q4W would experience a similar or higher magnitude of percent change in LDL-C at week 24 compared to adults while plateauing at higher absolute LDL-C concentrations at week 24.

In addition, given that the mechanism through which evinacumab acts is the same regardless of patient age due to the same underlying disease processes, and the observed similar safety profiles between adults, adolescent, and older paediatric patients, no difference in the safety profile of paediatric patients 6 months to <5 years of age is expected.

No new safety concerns have been identified in the patients below the age of 5 that received evinicumab via the compassionate use programme. Based on the available post-marketing data, there have been no significant differences seen in the safety profile of Evkeeza in the paediatric population compared to the adult population.

Refer to SVII.3.2 for details of this missing information.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Potential Risk: Embryofoetal Toxicity

Potential Mechanisms:

The mechanism is not yet established for evinacumab in humans as clinical relevance of findings seen in rabbits is unclear, giving the different lipid profiles in humans and rabbits during pregnancy.

Human IgG antibodies are known to cross the placenta barrier; therefore, evinacumab has the potential to be transmitted from the mother to the developing foetus.

Evidence Source(s) and Strength of Evidence:

The nonclinical development programme showed reproductive toxicity associated with evinacumab in rabbits, but not in rats (refer to Part II: Module SII).

In rabbits, the embryofoetal toxicity was observed at doses that induced maternal toxicity. Maternal toxicity (premature neonatal death, foetal loss and/or premature delivery) was observed at all doses and foetal findings (soft tissues and skeletal malformations) were observed at all but the lowest dose (1 mg/kg). Mean systemic exposure measured during the gestation period in rabbits was below that measured at maximum recommended human dose of 15 mg/kg Q4W.

The clinical relevance of these findings from reproduction studies is unclear, as rabbits have significantly lower lipid levels than do humans at baseline (Yin, 2012), and therefore, may be uniquely sensitive to the lipid-lowering effects of evinacumab during pregnancy.

There is a limited amount of data from the use of evinacumab in pregnant women.

Characterisation of the Risk:

Frequency, Severity and Nature of Risk

Not yet established as there are no adequate or well-controlled trials of evinacumab in pregnant women.

- **Pool 1 (Global; Clinical Trial Exposure):**

Cumulatively, a total of 5 pregnancies have been reported within the evinacumab clinical trial programme. This includes 4 pregnancies in 3 female patients (including 1 female who received study drug during the first trimester while in study R1500-CL-1629 during the DBTP who later enrolled in study R1500-CL-1719 and became pregnant a second time while exposed to evinacumab during first trimester of gestation) and 1 pregnancy in the female partner of a male patient who received evinacumab. The pregnancy outcomes for the 4 pregnancies in 3 female patients exposed to evinacumab and the pregnancy in a female partner of a male patient exposed to evinacumab included full term delivery with no reports of embryofoetal toxicity or other abnormalities. Exposure to evinacumab was in the first trimester of gestation in all 5 pregnancies.

- **Pool 2 (Placebo-controlled studies):**

No reports of pregnancy.

Risk Factors and Risk Groups:

Any woman of childbearing potential who receives evinacumab has a potential risk of embryofoetal toxicity.

Preventability:

All women of childbearing potential must use effective contraception during evinacumab treatment and at least 5 months after the last dose. This is based on the elimination of evinacumab in patients with HoFH treated with a dose of 15 mg/kg IV Q4W. It is estimated to take approximately 19 weeks for the concentration of evinacumab to decline from the last dose at a steady state to reach a systemic concentration below the lower limit of quantitation.

Adherence to these recommendations should limit the evinacumab exposure during pregnancy and prevent any potential adverse effects on foetal development.

Evinacumab should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus.

Impact on the Risk-Benefit Balance of the Product:

The nonclinical studies in rabbits, but not in rats, showed embryofoetal toxicity of evinacumab with unknown clinical relevance to humans. Since human IgG antibodies are known to cross the placenta barrier, evinacumab has the potential to be transmitted from the mother to the developing foetus and evinacumab may cause foetal harm when administered to pregnant women. In the absence of comprehensive data on use of evinacumab during pregnancy, the potential impact on pregnancy or foetal development is unknown and remains to be elucidated.

Public Health Impact:

Not yet established for evinacumab.

SVII.3.2 Presentation of the Missing Information

Missing Information: Safety of Long-Term Use (e.g., >2 Years)

Evidence Source:

The experience with administration of evinacumab in clinical trials is limited. At the DLP of this RMP, 76 patients from clinical studies (34.1% of exposed patients in the development program) had a duration of exposure of longer than 2 years (≥ 108 weeks). The safety profile of evinacumab for patients who have received evinacumab treatment for 2 years or longer is consistent with the safety profile of evinacumab for patients with shorter periods of treatment.

In addition to the observed safety data across the evinacumab programme, there is also supportive safety information for ANGPTL3 inhibition through human genetic studies in individuals with loss-of-function *ANGPTL3* variants (Module 5.3.5.4. Cardiovascular Risk and Other Clinical Phenotypes in People with Loss-of-Function Genetic Variants in ANGPTL3). These populations did not have an increased risk of liver disease, type 2 diabetes, neurological diseases, or adverse cardiovascular outcomes, and were not associated with risk of cancer, overall mortality, age at parental death, or any other disease outcome. This implies that there is likely no increased risk of any of these events with evinacumab.

Although there are real-world data for the absence of risks outlined above (e.g., adverse cardiovascular outcomes or cancer) in patients with loss-of-function mutations in *ANGPTL3*, there is limited information available on long-term safety of evinacumab treatment in HoFH patients from the evinacumab clinical development programme.

Population in Need of Further Characterisation:

The long-term data are needed to confirm the safety data collected for evinacumab from the clinical development programme. The safety profile of evinacumab with long-term use will continue to be monitored.

Missing Information: Use in Pregnant or Breast-feeding Women

Evidence Source:

There is limited experience with the use of evinacumab during pregnancy. Cumulatively, 5 pregnancies have been reported for evinacumab, from clinical trials, for which there are reported pregnancy outcomes.

The nonclinical development programme showed reproductive toxicity associated with evinacumab in rabbits, but not in rats with unknown relevance to human use due to the lower baseline lipid levels in rabbits compared to humans during pregnancy (Yin, 2012) (refer to Part II: Module SII).

There is no experience with the use of evinacumab during breast-feeding. It is unknown whether evinacumab is excreted in human or animal breast milk. It is known that antibodies are secreted in human milk (Czosnykowska-Łukacka, 2020). However, the low concentrations of monoclonal antibodies found in the breast milk of women treated with various monoclonal antibodies are considered negligible to cause any adverse effects in breastfed children (LaHue, 2020; Matro, 2018).

Anticipated Risk/Consequence of the Missing Information:

The use of evinacumab may adversely affect the course of pregnancy and foetal development, based on the nonclinical findings.

It is currently not known whether evinacumab is excreted in human milk and as such, a risk to the breast-fed newborn/infant cannot be excluded.

Missing Information: Safety (Including Long-term) in Children <5 Years of Age

Evidence Source:

To date, a limited number of patients below 5 years of age have been exposed to evinacumab within the compassionate use programme. No new safety concerns were identified in this patient population treated with evinacumab.

Given that the mechanism through which evinacumab acts is the same regardless of patient's age due to the same underlying disease processes, and with the observed similar safety profiles of Evkeeza between adult, adolescent, and paediatric patients above 5 years of age, no difference in the safety profile of Evkeeza is expected in the paediatric patients below 5 years of age.

Anticipated Risk/Consequence of the Missing Information:

The limited data available to date do not indicate any differences in the safety profile of Evkeeza in paediatric patients below 5 years of age. However, the safety profile of evinacumab in children below 5 years of age will continue to be monitored via routine pharmacovigilance activities and as part of the post-authorisation safety study (PASS) UX858-CL401 (refer to Part III.2).

PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Table 9: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Embryofoetal toxicity
Missing information	Safety of long-term use (e.g., >2 years) Use in pregnant or breast-feeding women Safety (including long-term) in children <5 years of age

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance will continue to be implemented for Evkeeza.

The pharmacovigilance plan does not include any routine pharmacovigilance activities beyond signal management and reporting of adverse reactions.

III.2 Additional Pharmacovigilance Activities

III.2.1 Post-authorisation (EMA) Safety Study (PASS)

Study Short Name and Title:

UX858-CL401: An observational study to evaluate the long-term effects of evinacumab treatment in patients with homozygous familial hypercholesterolaemia (HoFH)

Rationale and Study Objectives:

HoFH is an ultrarare and life-threatening disease.

At present, there is no cure for HoFH, and the treatment regimen for HoFH is complex and presents major therapeutic challenges. Evinacumab is intended for chronic, lifelong use, understanding long-term effects in the overall population of patients receiving treatment will be informative to patients, caregivers, prescribers, as well as payers. The existing EAS FH Studies Collaboration (FHSC) Global FH Registry provides an established source to obtain data on the long-term effects of evinacumab in real-world use for analysis.

UX858-CL401 is a 5-year, international, observational, retrospective cohort study using data collected by the existing EAS FHSC Global FH Registry.

The study objectives include:

- To evaluate the long-term safety outcomes in patients with HoFH treated with evinacumab.[1]
- To evaluate the frequency and outcomes of pregnancy in female patients with HoFH who are treated with evinacumab.
- To evaluate changes in the atherosclerosis process over time in patients with HoFH who are treated with evinacumab and undergo cardiovascular imaging (as data allow).
- To evaluate the frequency of cardiovascular imaging of patients with HoFH.

[1] The study population will be aligned with local regulatory approvals in each participating country, and therefore, the study population may be adjusted and expanded if the indication(s) for evinacumab extends to cover other patient groups.

List of Addressed Safety Concerns:

- Embryofoetal toxicity
- Safety of long-term use (e.g., >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).
- Safety (including long-term) in children <5 years of age

Study Design:

A 5-year observational cohort study using data collected by the existing EAS FHSC Global FH Registry

Study Population:

Patients included in the existing EAS FHSC Global FH Registry are the source population for the study analyses. To address the study objectives, the following cohorts will be established:

- Safety Analysis Cohort: The evinacumab cohort will include patients who have a diagnosis of HoFH,[1] initiated commercially available evinacumab, and have received evinacumab treatment during the analysis year.
- Pregnancy Analysis Cohort: The pregnancy cohort will include female patients from the evinacumab cohort.
- Imaging Cohort: The imaging cohort will include all patients from the evinacumab cohort who have at least one report of cardiovascular imaging during their pre-treatment period and at least one report of cardiovascular imaging during the follow-up period while exposed to evinacumab.
- Historical Cohort: The historical cohort will include HoFH patients without exposure to evinacumab, as identified from the existing registry from the immediate 5 years preceding market approval and commercial availability of evinacumab.

Milestones:

The protocol was initially adopted by Pharmacovigilance Risk Assessment Committee (PRAC) on 07 Apr 2022. The Statistical Analysis Plan (SAP) and revised protocol were submitted on 20 Sep 2022 and a positive PRAC outcome has been received for the PASS protocol and SAP on 14 Apr 2023. Annual study reports will be submitted with the annual reassessment, with final study report expected Jun 2029.

Tabulated summary of planned pharmacovigilance study programme is provided in Annex 2.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 10: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances.				
UX858-CL401: An observational study to evaluate the long-term effects of evinacumab treatment in patients with homozygous familial hypercholesterolaemia (HoFH) Ongoing; MAH: Ultragenyx Germany GmbH	– To evaluate the long-term safety outcomes in patients with HoFH [a] treated with evinacumab. – To evaluate the frequency and outcomes of pregnancy in female patients with HoFH who are treated with evinacumab. – To evaluate changes in the atherosclerosis process over time in patients with HoFH who are treated with evinacumab and undergo cardiovascular imaging (as data allow). – To evaluate the frequency of cardiovascular imaging of patients with HoFH.	Embryofoetal toxicity Safety of long-term use (e.g., >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) Safety (including long-term) in children <5 years of age	Protocol submission	Adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on 07 Apr 2022. Statistical analysis plan (SAP) was submitted on 20 Sep 2022 together with an updated protocol. On 14 Apr 2023, a positive PRAC outcome has been received for the PASS protocol and SAP.
			Start of data collection	Jul 2023
			End of data collection	Dec 2028
			Registration in EU PAS Register	Jun 2022 (completed)
			Interim report 1	Jun 2025
			Interim report 2	Jun 2026
			Interim report 3	Jun 2027
			Interim report 4	Jun 2028
			Final report of study results	Jun 2029

EU PAS=European Union electronic Register of Post-Authorisation Studies; HoFH=homozygous familial hypercholesterolaemia, ICSR=individual case safety report, MAH=marketing authorisation holder.

[a] The study population will be aligned with local regulatory approvals in each participating country, and therefore, the study population may be adjusted and expanded if the indication(s) for evinacumab extends to cover other patient groups.

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

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

Safety Concern	Routine Risk Minimisation Activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk Recommendation that women of childbearing potential should use effective contraception during treatment with evinacumab and for at least 5 months after the last dose is included in SmPC Section 4.6 and PL Section 2. It is unknown whether evinacumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which decrease to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, evinacumab could be used during breast-feeding if clinically needed is included in SmPC Section 4.6 and PL Section 2 as recommendation on use of evinacumab for breast-feeding women. **Other routine risk minimisation measures beyond the Product Information** – SmPC Section 4.2 **Legal status** Evinacumab is subject to restricted medical prescription. Treatment with Evinacumab should be initiated and monitored by a physician experienced in the treatment of lipid disorders.
Safety (including long-term) in children <5 years of age	**Routine risk communication** – SmPC Sections 4.2, 4.8, 5.1, and 5.2 – PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk** None **Other routine risk minimisation measures beyond the Product Information** **Legal status** Evinacumab is subject to restricted medical prescription. Treatment with evinacumab for patients <5 years of age should be initiated and monitored by a physician experienced in the treatment of lipid disorders.

IgG=immunoglobulin; PL=package leaflet; SmPC=summary of product characteristics.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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	**Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting:** None **Additional pharmacovigilance activity:** – Post-authorisation safety study UX858-CL401, final CSR due Jun 2029
Safety of long-term use (e.g., >2 years)	**Routine risk minimisation measures**: Restricted medical prescription **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	**Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting:** None **Additional pharmacovigilance activity:** – Post-authorisation safety study: UX858-CL401, final CSR due Jun 2029

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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** 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	**Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting:** None **Additional pharmacovigilance activity:** – Post-authorisation safety study UX858-CL401, final CSR due Jun 2029 (Note that pregnancy information will be evaluated in the post-authorisation safety study to address the potential risk of embryofoetal toxicity)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Safety (including long-term) in children <5 years of age	**Routine risk minimisation measures**: – SmPC Sections 4.2, 4.8, 5.1, and 5.2 – PL Section 2 **Legal status** Evinacumab is subject to restricted medical prescription. Treatment with evinacumab for patients <5 years of age should be initiated and monitored by a physician experienced in the treatment of lipid disorders. **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting:** None **Additional pharmacovigilance activity:** – Post-authorisation safety study UX858-CL401, final CSR due Jun 202

CSR=clinical study report; PL=package leaflet; SmPC=summary of product characteristics.

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR EVKEEZA (EVINACUMAB)

This is a summary of the risk management plan (RMP) for EVKEEZA. The RMP details important risks of EVKEEZA, how these risks can be minimised, and how more information will be obtained about EVKEEZA's risks and uncertainties (missing information).

EVKEEZA's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how EVKEEZA should be used.

This summary of the RMP for EVKEEZA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of EVKEEZA's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

EVKEEZA is authorised for the treatment of adult and paediatric patients aged 6 months and older with homozygous familial hypercholesterolaemia (see SmPC for the full indication). It contains evinacumab as the active substance and it is given by IV route.

Further information about the evaluation of EVKEEZA's benefits can be found in EVKEEZA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/evkeeza).

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of EVKEEZA, together with measures to minimise such risks and the proposed studies for learning more about EVKEEZA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of EVKEEZA is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of EVKEEZA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of EVKEEZA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	Embryofoetal toxicity
Missing information	Safety of long-term use (e.g., >2 years) Use in pregnant or breast-feeding women Safety (including long-term) in children <5 years of age

II.B Summary of Important Risks

Important Potential Risk: Embryofoetal Toxicity	
Evidence for linking the risk to the medicine	The nonclinical development programme showed reproductive toxicity associated with evinacumab in rabbits, but not in rats. In rabbits, the embryofoetal toxicity was observed at doses that induced maternal toxicity. Maternal toxicity (premature neonatal death, foetal loss and/or premature delivery) was observed at all doses and foetal findings (soft tissues and skeletal malformations) were observed at all but the lowest dose (1 mg/kg). Mean systemic exposure measured during the gestation period in rabbits was below that measured at maximum recommended human dose of 15 mg/kg Q4W. The clinical relevance of these findings from reproduction studies is unclear, as rabbits have significantly lower lipid levels than do humans at baseline (Yin, 2012), and therefore, may be uniquely sensitive to the lipid lowering effects of evinacumab during pregnancy. There is a limited amount of data from the use of evinacumab in pregnant women. Cumulatively, at the DLP of this RMP, 5 pregnancy case reports have been received, which were from clinical trial exposure and pregnancy outcomes have been reported. These included 4 pregnancies in 3 female patients (1 female patient had 2 pregnancies)

Important Potential Risk: Embryofoetal Toxicity	
	who received evinacumab, and 1 pregnancy in the female partner of a male patient who received evinacumab.
Risk factors and risk groups	Any woman of childbearing potential who receives evinacumab has a potential risk of embryofoetal toxicity.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.6 and 5.3 PL Section 2 Recommendation for women treated with evinacumab 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 Evinacumab is subject to restricted medical prescription. SmPC Section 4.2 includes treatment with Evinacumab should be initiated and monitored by a physician experienced in the treatment of lipid disorders. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activity:** Study UX858-CL401 (category 2 long-term post-authorisation safety study) See Section II.C of this summary for an overview of the post-authorisation development plan.

Yin W, Carballo-Jane E, McLaren DG, Mendoza VH, Gagen K, Geoghagen NS, et al. Plasma lipid profiling across species for the identification of optimal animal models of human dyslipidemia. J Lipid Res 2012, 53(1): 51-65.

Missing Information: Safety of Long-Term Use (e.g., >2 Years)	
Risk minimisation measures	**Routine risk minimisation measures:** Restricted prescription medicine **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activity:** Study UX858-CL401 (category 2 long-term post-authorisation safety study) See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Use in Pregnant or Breast-Feeding Women	
Risk minimisation measures	**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 Evinacumab is subject to restricted medical prescription. SmPC Section 4.2 includes treatment with Evinacumab should be initiated and monitored by a physician experienced in the treatment of lipid disorders. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activity:** Study UX858-CL401 (category 2 long-term post-authorisation safety study) (Note that pregnancy information will be evaluated in the long-term post-authorisation safety study to address the potential risk of embryofoetal toxicity) See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Safety (Including Long-term) in Children <5 Years of Age	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.8, 5.1, and 5.2 PL Section 2 Evinacumab is subject to restricted medical prescription. SmPC Section 4.2 includes treatment with Evinacumab should be initiated and monitored by a physician experienced in the treatment of lipid disorders. **Additional risk minimisation measures:** None

Missing Information: Safety (Including Long-term) in Children <5 Years of Age	
Additional pharmacovigilance activities	**Additional pharmacovigilance activity:** Study UX858-CL401 (category 2 long-term post-authorisation safety study) See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

Study UX858-CL401: An observational study to evaluate the long-term effects of evinacumab treatment in patients with homozygous familial hypercholesterolaemia (HoFH)

Purpose of the study:

The study includes the following objectives:

1. Evaluate the long-term safety outcomes in patients with HoFH treated with evinacumab[2].
2. Evaluate the frequency and outcomes of pregnancy in female patients with HoFH who are treated with evinacumab.
3. Evaluate changes in the atherosclerotic process over time in patients with HoFH who are treated with evinacumab and undergo cardiovascular imaging (as data allow).
4. Evaluate the frequency of cardiovascular imaging of patients with HoFH.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no other studies required for EVKEEZA.

[2] The study population will be aligned with local regulatory approvals in each participating country, and therefore, the study population may be adjusted and expanded if the indication(s) for evinacumab extends to cover other patient groups.

PART VII ANNEXES

LIST OF ANNEXES

ANNEX 1 EUDRAVIGILANCE INTERFACE

ANNEX 2 TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

ANNEX 3 PROTOCOLS FOR PROPOSED, ON-GOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 5 PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

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ANNEX 8 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME