Amsterdam, 27 June 2024
EMA/277177/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

EVKEEZA

Evinacumab

Procedure no: EMEA/H/C/005449/P46/008

Note

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

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

On 27 November 2023, the MAH submitted a completed paediatric study for

A Three-Part, Single-Arm, Open-Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Evinacumab in Pediatric Patients with Homozygous Familial Hypercholesterolemia" (R1500-CL-17100, EudraCT number: 2019-001931-30)

in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Evkeeza was approved in the EU on 17 June 2021 as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolaemia (HoFH) based on the results of the pivotal Phase 3, double-blind, placebo-controlled study R1500-CL-1629 supplemented with the Phase 3 open-label study R1500-CL-1719 (EMA/H/C/005449/0000). A marketing authorization under exceptional circumstances was granted on the basis that HoFH is encountered so rarely that it cannot reasonably be expected to provide comprehensive evidence in terms of efficacy and safety. A non-interventional post-authorisation safety study (PASS) was requested to be conducted to have some confirmatory understanding on, among others, long-term safety and the cardiovascular implications of treating these patients with evinacumab.

The initial paediatric investigation plan (PIP; EMEA-002298-PIP01-17) was agreed with the Paediatric Committee (PDCO) in December 2018, including a product-specific waiver for patients below the age of 5 years, which was agreed on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies are not feasible.

The measures specified in the PIP included 3 nonclinical studies relevant to cover the paediatric population from 5 years of age (a dose range finding juvenile toxicity study in rabbits, a definitive Good Laboratory Practice [GLP] IV study in juvenile rabbits, and an IV and subcutaneous [SC] toxicology study in juvenile rats), and 4 clinical studies, including the adolescent arm of the pivotal Phase 3, double-blind, placebo-controlled study R1500-CL-1629. The nonclinical studies and the first clinical study (R1500-CL-1629) were completed at the time of the initial MAA submission and a positive partial compliance check was confirmed ahead of this submission.

At the time of the initial MAA, 3 measures remained outstanding:

• PIP Study 5: R1500-CL-17100: A three-part single arm, open-label trial to evaluate the pharmacokinetics (PK), safety, and activity of evinacumab in children ≥ 5 to < 12 years of age with HoFH. The agreed date of completion within the PIP is May 2024.

• PIP Study 6: R1500-CL-1719: An open-label study to evaluate the long-term safety and efficacy of evinacumab in patients with HoFH. The study includes adult and adolescent patients ≥ 12 years of age. The agreed date of completion within the PIP is September 2023.

• PIP Study 7: R1500-CL-17100-Extrapolation: An extrapolation analysis to evaluate the use of evinacumab in the proposed pediatric indication in children ≥ 5 to < 12 years of age with HoFH. This measure was completed on 18 April 2023, with compliance verification confirmed on 16 May 2023.

The interim clinical study report (CSR) from Study R1500-CL-17100 (dated: 16 Sep 2022), supported by an updated interim analysis from Study R1500-CL-1719 (dated: 10 Nov 2022), as well as the R1500-CL-17100 extrapolation report, formed the basis of a type II variation that was submitted on 31 May 2023 to extend the therapeutic indication to include paediatric patients with HoFH aged 5 years and older (EMA/H/C/005499/II/0011). On 9 November 2023, the CHMP adopted a positive opinion (EMA/CHMP/489254/2023).

Prior to the submission of this type II variation, partial PIP compliance verification was confirmed for Studies R1500-CL-17100 and R1500-CL-1719, for all measures except those related to study completion (EMEA-C2-002298-PIP01-17-M05). In addition, full compliance was confirmed for Study 7, the R1500-CL-17100-Extrapolation.

The current review concerns the submission of the final clinical study report for the study “A Three-Part, Single-Arm, Open-Label Study to Evaluate the Efficacy, Safety, And Pharmacokinetics of Evinacumab in Pediatric Patients with Homozygous Familial Hypercholesterolemia” (R1500-CL-17100, EudraCT number: 2019-001931-30). The study has been completed in accordance with the paediatric investigation plan (Study 5, PIP EMEA 002298-PIP01-17-M04) agreed on December 2018. As Parts A and B of the study were complete at the time of the First- and Second-Step Analysis CSR, the Third-Step Analysis CSR consists of the final safety analysis and focuses on the results from Part C of the Study.

In order to provide a complete assessment of the study, to support this Article 46 submission, this Critical Expert Overview summarizes results from both the First- and Second-Step Analysis Interim CSR (previously submitted to the EMA within eCTD sequence 0027) and the Third-Step Analysis CSR (Final CSR provided within this submission).To support this Article 46 submission, a final integrated report is provided.

The MAH stated that the study “A Three-Part, Single-Arm, Open-Label Study to Evaluate the Efficacy, Safety, And Pharmacokinetics of Evinacumab in Pediatric Patients with Homozygous Familial Hypercholesterolemia” (R1500-CL-17100, EudraCT number: 2019-001931-30) is part of a clinical development program. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

In study R1500-CL-17100, Evkeeza was administered as an intravenous infusion over 60 minutes, Q4W. The recommended dose for patients aged between 5 and 11 years was 15 mg/kg, similar to the recommended dose for other age groups.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study R1500-CL-17100 “A Three-Part, Single-Arm, Open-Label Study to Evaluate the Efficacy, Safety, And Pharmacokinetics of Evinacumab in Pediatric Patients with Homozygous Familial Hypercholesterolemia”. The study design and interim study results have been assessed previously in the extension of indication variation procedure to include the paediatric population of in pediatric patients aged ≥ 5 to 11 years with HoFH (EMEA/H/C/005449/II/0011). Nevertheless for clarity, the design of the study is briefly described below.

2.3.2. Clinical study

A Three-Part, Single-Arm, Open-Label Study to Evaluate the Efficacy, Safety, And Pharmacokinetics of Evinacumab in Pediatric Patients with Homozygous Familial Hypercholesterolemia (R1500-CL-17100)

Description

The primary purpose of the R1500-CL-17100 study was to demonstrate the efficacy, safety, and tolerability of evinacumab in pediatric patients, aged 5 through 11 years, with HoFH. The study consisted of 3 parts: Part A (phase 1b), Part B (phase 3), and Part C (phase 3). Part A was a single-dose, open-label study to determine the safety, PK, and PD of evinacumab 15 mg/kg IV in 6 patients aged 5 to 11 years with HoFH. Part B was a 24-week, single-arm, open-label study to assess the efficacy and safety of evinacumab in 14 pediatric patients with HoFH. Part B began when PK data from all patients in Part A were sufficiently analyzed to determine the dose for Part B. Part C was an (open-label) extension of the study available to patients who completed Part A or Part B to continue to receive evinacumab (48-week treatment period and 24-week follow-up period).

Methods

Study participants

This study enrolled male and female participants aged 5 through 11 years diagnosed by genetic or clinical criteria with HoFH receiving any combination of lipid-lowering therapies.

Genetic Criteria:

- Documented functional mutation or mutations in both LDLR alleles

  Note: Patients who had null receptor mutations on both LDLR alleles, ie, double null, were eligible

OR

- Documented homozygous mutations in LDLRAP1, or homozygous or compound heterozygous mutations in Apo B or PCSK9

  Note: Patients who were double heterozygous, ie, mutations on different genes [LDLR/PCSK9 or LDLR/ Apo B] were eligible

Clinical Criteria:

- Untreated TC >500 mg/dL (>13 mmol/L) and triglycerides <300 mg/dL (<7.8 mmol/L)

AND

- Both parents with documented TC >250 mg/dL OR cutaneous or tendinous xanthoma in the study patient before age 10 years
- LDL-C >130 mg/dL at the screening visit
- Body weight ≥15 kg
- Receiving stable maximally tolerated therapy* at the screening visit
  *Maximally tolerated therapy could include a daily statin.

Note: Patients who were not able to be on a maximum daily statin were required to be on the appropriate dose for the patient or no statin, according to the investigator's judgment. Some examples of acceptable reasons for a patient taking a lower statin dose included but were not limited to: adverse effects on higher doses, lack of efficacy, regional practices, local prescribing information, concomitant medications. The reason(s) were required to be documented in the CRF.

- Willing and able to comply with clinic visits and study-related procedures
- Parent(s) or legal guardian(s) were required to provide the signed ICF. Patients ≥5 years of age (or above age determined by the IRB/EC and in accordance with the local regulations and requirements) must have also provided informed assent forms to enroll in the study, and sign and date a separate informed assent forms or ICF signed by the parent(s)/legal guardian(s) (as appropriate based on local regulations and requirements).

Treatments

R1500-CL-17100 was a 3-part, single-arm, open-label study that included Part A, Part B, and Part C as follows:

• Part A: phase 1b single arm, single dose PK/PD study

• Part B: phase 3, single-arm, 24-week, open-label efficacy, and safety study

• Part C: phase 3, 48-week treatment period and 24-week follow-up period

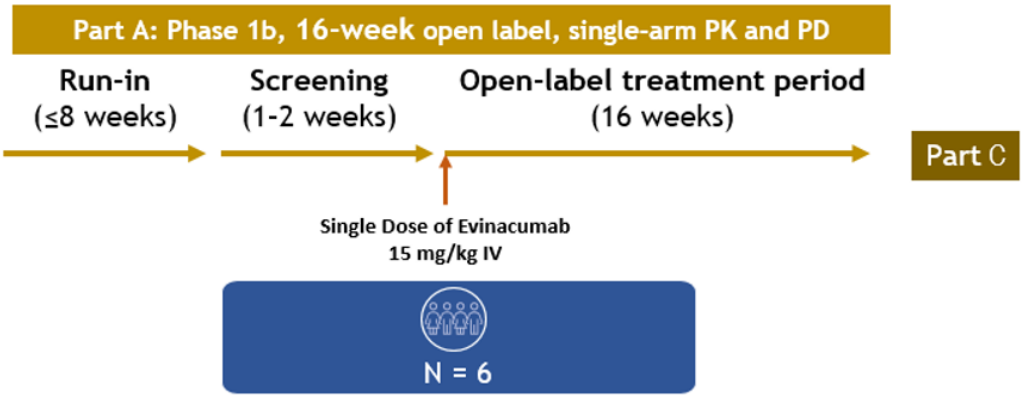
Note, for patients who entered a CUP or EAP, they were allowed to forgo the 24-week follow-up period after the last dose in Part C. In this situation, the EOT visit was their last visit.

Part A

Part A was a phase 1b single-dose, open-label study to determine the safety, PK, and PD of a single dose of evinacumab 15 mg/kg IV in 6 patients aged 5 to 11 years with HoFH. To ensure a distribution of body weight within Part A of the study, every effort was made to enroll 3 patients <25 kg and 3 patients ≥25 kg. Additionally, to ensure a distribution of ages, every effort was made to enroll 2 patients <10 years of age. All patients who successfully completed Part A were allowed to continue receiving evinacumab in Part C. Initially, patients from Part A who entered Part C received evinacumab 15 mg/kg IV Q4W. When PK data from all patients in Part A were sufficiently analyzed, the dose for Part B was determined using the cumulative data to date with evinacumab and data from Part A. If data from 6 patients was insufficient, up to 4 more patients could be enrolled to confirm the dose in Part B, but this was deemed unnecessary. The dose for Part B was also to be the final dose in Part C. The dose for Part B (and final dose in Part C) remained at 15 mg/kg IV Q4W.

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

Figure 1: Study Flow Diagram Part A

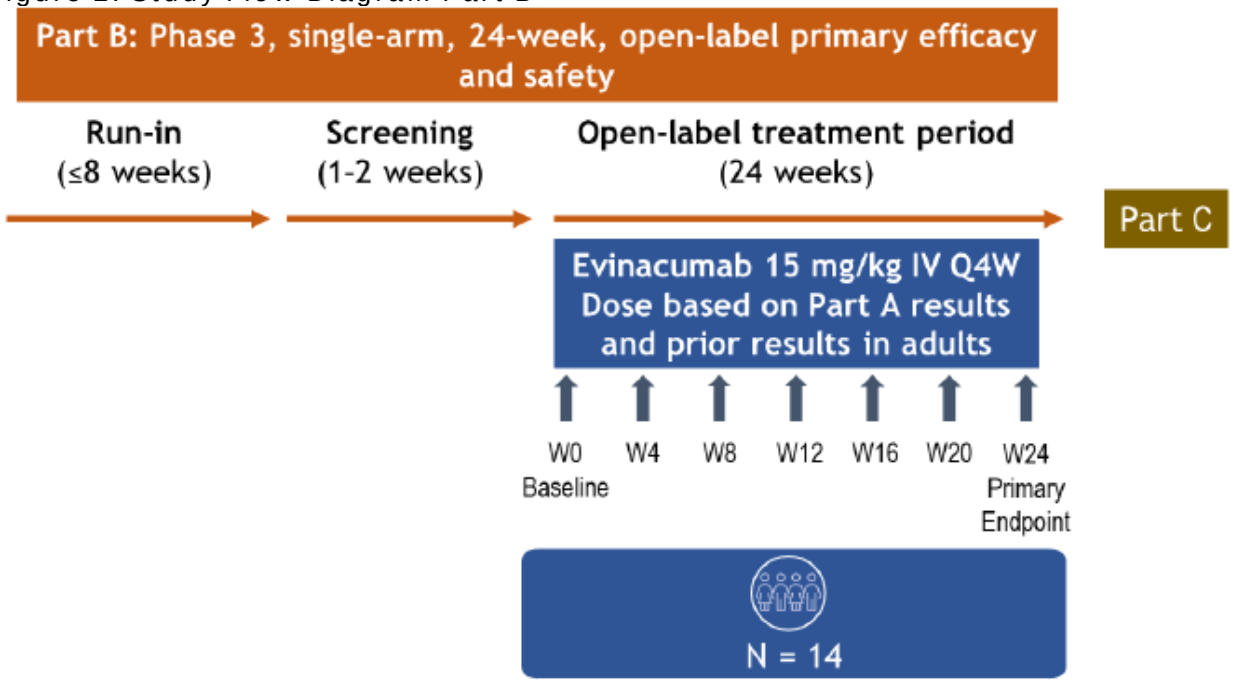


Part B

Part B was a phase 3 single-arm, open-label study to assess the efficacy and safety of evinacumab in pediatric patients (age 5 to 11 years) with HoFH. Part B began once dose-selection for Part B was completed. Part B enrolled 14 pediatric patients. Patients enrolled into Part B did not include patients from Part A. Upon completion of Part B, all patients continued into Part C.

Part B consisted of up to 4 periods: run-in; screening; 24-week open-label treatment; follow-up (Since all patients entered Part C, the follow-up period of Part B was not applicable). The study design for Part B is depicted below in Figure 2.

Figure 2: Study Flow Diagram Part B



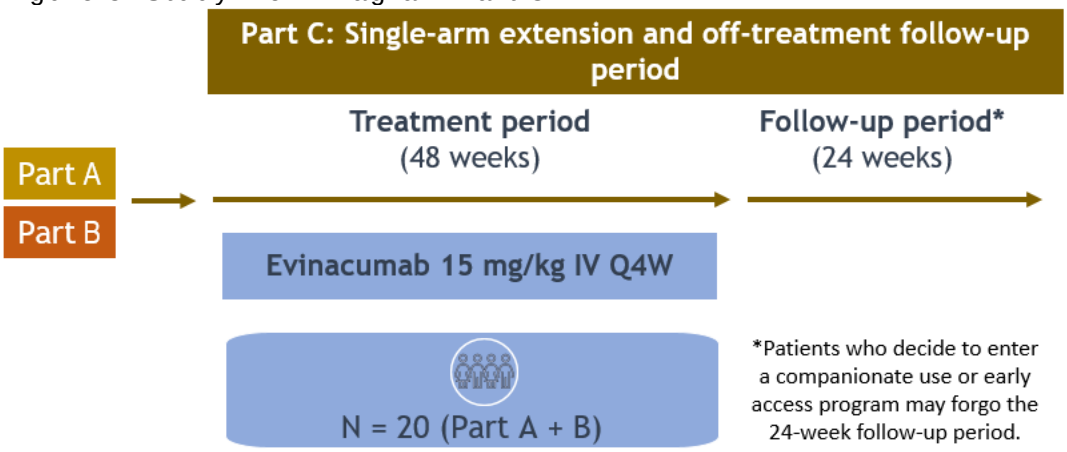
Part C

Part C was an extension period that consisted of the 20 patients who completed Part A or Part B. It consisted of 2 periods: a 48-week treatment period and a 24-week follow-up period after the last dose of study drug (Figure 3). Patients in Part C entered directly from Part A or Part B. The first visit (visit

1) in Part C could occur on the same day as the EOT visit in Part A (visit 11)/Part B (visit 11). Overlapping assessments completed at the EOT visit did not need to be duplicated during visit 1 in Part C.

All patients from Part A who entered Part C initially received open-label evinacumab 15 mg/kg IV Q4W. The final dose in Part C was the same as the dose in Part B, 15 mg/kg IV Q4W.

Figure 3: Study Flow Diagram Part C



Objective(s)

Part A

Primary objective:

- To assess the PK of evinacumab in pediatric patients with HoFH

Secondary objective:

- To evaluate the safety and tolerability of evinacumab administered IV in pediatric patients with HoFH

Part B

Primary objective:

- To demonstrate a reduction of LDL-C by evinacumab in pediatric (5 to 11 years of age) patients with HoFH

Secondary objectives:

- To evaluate the effect of evinacumab on other lipid parameters (ie, Apo B, non-HDLC, total cholesterol [TC], lipoprotein a [Lp(a)]) in pediatric patients with HoFH
- To evaluate the safety and tolerability of evinacumab administered IV in pediatric patients with HoFH
- To assess the PK of evinacumab in pediatric patients with HoFH
- To assess the immunogenicity of evinacumab in pediatric patients with HoFH over time
- To evaluate patient efficacy by mutation status

Exploratory objectives:

- To evaluate the efficacy of evinacumab in the extension of the study (Part C) in patients with HoFH

- To explore vascular changes using imaging techniques

Outcomes/endpoints

Part A

Primary endpoint:

- The PK parameters for evinacumab, including Cmax, AUC, and t1/2, following a single administration of evinacumab

Secondary endpoint:

- Incidence of TEAEs and other safety variables over time

Part B

Primary endpoint:

- The percent change in calculated LDL-C from baseline to week 24 (ITT estimand) in Part B. The primary efficacy endpoint is defined as: 100x (calculated LDL-C value at week 24 minus calculated LDL-C value at baseline) divided by calculated LDL-C value at baseline

Secondary endpoints:

- The percent change in Apo B from baseline to week 24 (ITT estimand)
- The percent change in non-HDL-C from baseline to week 24 (ITT estimand)
- The percent change in TC from baseline to week 24 (ITT estimand)
- The proportion of patients with ≥50% reduction in calculated LDL-C at week 24 (ITT estimand)
- The percent change in calculated LDLC from baseline to week 24 in patients who have negative/negative and null/null mutations (ITT estimand)
- The percent change in Lp(a) from baseline to week 24 (ITT estimand)
- The absolute change in LDL-C at week 24 (ITT estimand)

Exploratory endpoints:

- Percent change from baseline in LDL-C, Apo B, Non-HDL-C, Total Cholesterol, and Lp(a) over time
- Vascular changes via carotid intimamedia thickness at baseline and at 6-month intervals, as clinically indicated (for intra-patient comparison)

Sample size

For Part A, approximately 6 patients are planned. If data from 6 patients is insufficient, up to 4 more patients may be enrolled to confirm the dose in Part B.

For Part B, approximately 14 patients are planned. Patients for Part B will not include patients from Part A. Patients from Part A and Part B may enter Part C.

Randomisation and blinding (masking)

This was an uncontrolled, open-label study. To reduce bias, a central lab was used.

Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3,minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Data for patients in Part A and patients in Part B will be summarized and listed separately. Similar analyses will be performed for patients in Part A and patients in Part B, respectively, unless otherwise specified.

Efficacy analysis sets for Part B

Intent-to-treat (ITT): all patients who received at least 1 dose or part of a dose of study drug in Part B

Modified-intend-to-treat (mITT): all patients who received at least 1 dose or part of a dose of open-label study drug in Part B and have an evaluable primary efficacy endpoint. The endpoint is considered as evaluable when both of the following conditions are met:

1. Availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (i.e., baseline).
2. Availability of at least 1 calculated LDL-C value during the efficacy treatment period and within one of the analysis windows up to week 24. The efficacy treatment period is defined as the time from the first study drug administration up to 35 days after the last study drug administration in Part B.

Safety Analysis set (SAF): all patients who received at least 1 dose or part of a dose of study drug.

Part C Safety Analysis set: all patients who received at least 1 dose or part of a dose of study drug in Part C

Primary efficacy analysis for Part B

The percent change from baseline in calculated LDL-C at week 24 will be analysed in the ITT population using a pattern mixture model (PMM) approach. In the PMM approach, different imputation strategies will be applied to calculated LDL-C values missing during the on-treatment period (i.e., within the time period from the first study treatment administration up to the day of last study treatment administration +35 days in Part B) versus calculated LDL-C values missing due to treatment discontinuation after the on-treatment period (i.e., after the day of last study treatment administration +35 days in Part B).

This approach was discussed in detail in the interim report (EMEA/H/C/005449/II/0011).

Secondary efficacy analysis for Part B

For the secondary efficacy endpoints, descriptive summaries and analyses will be performed in the ITT population, using values obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand).

Results

Participant flow

A total of 23 patients were screened for study eligibility (3 patients screen-failed that included 2 who withdrew consent, and 1 due to “other” which was COVID-19).

A total of 6 patients were enrolled, treated and completed Part A of the study. All 6 patients continued to Part C. A total of 14 patients were enrolled, treated, and completed Part B of the study. All 14 patients continued to Part C. A total of 20 patients (6 patients from Part A, and 14 patients from Part B) were treated in Part C. All 20 patients completed the study.

The first patient first visit in Part A was on 29 June 2020 and the database lock for part C was at 30 June 2023.

Recruitment

During Part A (N=6), patients were treated at the following sites: Austria (N=2), Netherlands (N=1), and the United States (N=3). During Part B (N=14), patients were treated at the following sites: Australia (N=2), Austria (N=3), Netherlands (N=3), Taiwan (N=2), and the United States (N=4).

Baseline data

In the pooled Parts B and C population, 8/20 (40.0%) patients were male, and 12/20 (60.0%) patients were female. The mean (SD) age of patients in the pooled population was 9.0 (1.84) years at baseline, with an age range from ≥5 to <12 years and a median age of 9.0 years. A total of 11/20 (55.0%) patients were ≥5 to <10 years of age and 9/20 (45.0%) patients were ≥10 to <12 years of age.

Patients were White (14/20 [70.0%] patients), Black or African American (1/20 [5.0%] patient), Asian (2/20 [10.0%] patients), American Indian or Alaska Native (1/20 [5.0%] patient), and Other (2/20 [10.0%] patients). Concerning ethnicity, 18/20 (90.0%) patients were not Hispanic or Latino and 1/20 (5.0%) patient was Hispanic or Latino; ethnicity was not reported for the remaining 1 patient. The mean (SD) weight was 37.9 (13.08) kg, and the mean (SD) BMI was 18.8 (4.19) kg/m^2 (Table 1).

Table 1: Demographics and Baseline Characteristics for Pooled Data - Pool Parts B +C - Pooled Safety Analysis Set

	Part A Patients Evinacumab 15mg/Kg IV Q4W (N=6)	Part B Patients Evinacumab 15mg/Kg IV Q4W (N=14)	Total (N=20)
Age (years)			
n	6	14	20
Mean (SD)	8.8 (1.72)	9.1 (1.94)	9.0 (1.84)
Median	8.0	9.5	9.0
Q1 : Q3	8.0 : 11.0	8.0 : 11.0	8.0 : 11.0
Min : Max	7 : 11	5 : 11	5 : 11
Age group (years) [n(%)]			
n	6	14	20
>=5 to <10	4 (66.7%)	7 (50.0%)	11 (55.0%)
>=10 to <12	2 (33.3%)	7 (50.0%)	9 (45.0%)
Sex [n (%)]			
n	6	14	20
Male	2 (33.3%)	6 (42.9%)	8 (40.0%)
Female	4 (66.7%)	8 (57.1%)	12 (60.0%)
Race [n (%)]			
n	6	14	20
White	6 (100%)	8 (57.1%)	14 (70.0%)
Black or African American	0	1 (7.1%)	1 (5.0%)
Asian	0	2 (14.3%)	2 (10.0%)
American Indian or Alaska Native	0	1 (7.1%)	1 (5.0%)
Native Hawaiian or other Pacific Islander	0	0	0
Not Reported	0	0	0
Other	0	2 (14.3%)	2 (10.0%)
Ethnicity [n (%)]			
n	6	14	20
Hispanic or Latino	1 (16.7%)	0	1 (5.0%)
Not Hispanic or Latino	5 (83.3%)	13 (92.9%)	18 (90.0%)
Not Reported	0	1 (7.1%)	1 (5.0%)
Unknown	0	0	0
Weight (kg)			
n	6	14	20
Mean (SD)	32.8 (13.34)	40.1 (12.82)	37.9 (13.08)
Median	27.1	36.9	35.3
Q1 : Q3	23.5 : 43.0	32.2 : 43.9	28.2 : 43.7
Min : Max	21 : 55	20 : 69	20 : 69
Weight group (kg) [n(%)]			
n	6	14	20
<25	2 (33.3%)	1 (7.1%)	3 (15.0%)
>=25	4 (66.7%)	13 (92.9%)	17 (85.0%)
Height (cm)			
n	6	14	20
Mean (SD)	133.8 (16.58)	142.3 (11.08)	139.8 (13.14)
Median	128.1	142.1	140.7
Q1 : Q3	120.0 : 152.4	136.0 : 148.7	131.0 : 150.6
Min : Max	118 : 156	117 : 163	117 : 163
BMI (kg/m^2)			
n	6	14	20
Mean (SD)	17.3 (2.76)	19.5 (4.61)	18.8 (4.19)
Median	16.6	18.1	17.5
Q1 : Q3	15.3 : 18.4	15.7 : 22.4	15.7 : 22.3
Min : Max	15 : 22	14 : 30	14 : 30
BMI group (kg/m^2)			
n	6	14	20
<P5: Underweight	0	1 (7.1%)	1 (5.0%)
>=P5 to <P85: Healthy weight	5 (83.3%)	6 (42.9%)	11 (55.0%)
>=P85 to <P95: Overweight	0	1 (7.1%)	1 (5.0%)
>=P95: Obesity	1 (16.7%)	6 (42.9%)	7 (35.0%)

Source: PTT 14.4.1d

Baseline disease characteristics

The mean (SD) baseline calculated LDL-C in patients in Part A was elevated at 10.1 [5.75] mmol/L and 6.8 [2.35] mmol/L in patients in Part B, resulting in a mean (SD) baseline calculated LDL-C of 7.8 [3.86] mmol/L) in the pooled population in Part C. In Part A, B and C, results of other lipid parameters such as Apo-B, non-HDL-C, total C, and Lp(a) were also elevated consistent with the dyslipidemia of HoFH (Table 2).

Table 2: Lipid Parameters at Baseline – Quantitative Summary in SI Units for Pooled Data – Pool Parts B and C – Pooled Safety Analysis Set

Parameter (unit)	Part A Patients Evinacumab 15mg/Kg IV Q4W (N=6)	Part B Patients Evinacumab 15mg/Kg IV Q4W (N=14)	Total (N=20)
Calculated LDL-C (mmol/L)			
n	6	14	20
Mean (SD)	10.1 (5.75)	6.8 (2.35)	7.8 (3.86)
Median	7.9	6.1	6.2
Q1 : Q3	6.2 : 12.6	5.6 : 8.6	5.7 : 9.6
Min : Max	6 : 21	4 : 11	4 : 21
Apo-B (g/L)			
n	6	14	20
Mean (SD)	2.3 (1.04)	1.7 (0.47)	1.9 (0.71)
Median	1.9	1.6	1.6
Q1 : Q3	1.6 : 2.4	1.4 : 1.9	1.4 : 2.3
Min : Max	1 : 4	1 : 3	1 : 4
Non-HDL-C (mmol/L)			
n	6	14	20
Mean (SD)	10.7 (5.92)	7.3 (2.53)	8.3 (4.01)
Median	8.5	6.5	6.8
Q1 : Q3	6.5 : 13.3	6.0 : 8.9	6.0 : 10.4
Min : Max	6 : 21	4 : 12	4 : 21
TC (mmol/L)			
n	6	14	20
Mean (SD)	11.7 (5.83)	8.2 (2.29)	9.2 (3.90)
Median	9.6	7.5	7.7
Q1 : Q3	7.6 : 14.2	6.8 : 9.8	6.9 : 11.2
Min : Max	7 : 22	5 : 12	5 : 22
Fasting TG (mmol/L)			
n	6	13	19
Mean (SD)	1.1 (0.46)	1.0 (0.63)	1.0 (0.57)
Median	1.2	0.8	0.8
Q1 : Q3	0.6 : 1.5	0.6 : 1.3	0.6 : 1.4
Min : Max	1 : 2	0 : 2	0 : 2
ApoA1 (g/L)			
n	6	14	20
Mean (SD)	1.2 (0.20)	1.0 (0.23)	1.0 (0.23)
Median	1.1	1.0	1.0
Q1 : Q3	1.0 : 1.3	0.9 : 1.2	0.9 : 1.2
Min : Max	1 : 1	1 : 1	1 : 1
ApoB/ApoA1 (ratio)			
n	6	14	20
Mean (SD)	2.035 (1.1979)	1.880 (0.9927)	1.927 (1.0282)
Median	1.570	1.555	1.555
Q1 : Q3	1.330 : 2.140	1.300 : 2.120	1.305 : 2.130
Min : Max	1.21 : 4.39	0.79 : 4.16	0.79 : 4.39
Lp(a) (nmol/L)			
n	6	14	20
Mean (SD)	142.83 (236.386)	158.64 (142.516)	153.90 (169.284)
Median	28.00	106.00	68.00
Q1 : Q3	19.00 : 150.00	47.00 : 246.00	24.00 : 235.00
Min : Max	18.0 : 614.0	18.0 : 417.0	18.0 : 614.0
HDL-C (mmol/L)			
n	6	14	20
Mean (SD)	1.0 (0.23)	0.9 (0.33)	0.9 (0.30)
Median	0.9	0.8	0.9
Q1 : Q3	0.8 : 1.2	0.7 : 1.0	0.7 : 1.1
Min : Max	1 : 1	0 : 2	0 : 2

HoFH genotype and mutation status

HoFH diagnosis confirmed by either genetic or clinical criteria was specified in the protocol and was a requirement for inclusion in the study. Patients in Parts A and B were also genotyped as part of the study to identify or confirm known mutation(s) in LDLR, LDLRAP1, APOB or PCSK9 genes.

In Part A, all 6 (100%) patients were diagnosed by genotyping and none by clinical diagnosis. The mean (SD) time from diagnosis to study randomization was 5.59 years (2.769). At baseline in Part A, 4 (66.7%) patients were categorized as having homozygous *LDLR* mutations (3 patients defective/defective and 1 patient negative/negative), 2 (33.3%) patients were categorized as having compound heterozygous *LDLR* mutations (1 patient with defective/negative, and 1 patient with negative/negative) (Table 3). Two patients (1 each with a homozygous *LDLR* mutation, and compound heterozygous *LDLR* mutation) were categorized as null/null, i.e., having LDLR activity <15%. Two patients with a negative/negative compound heterozygous *LDLR* mutation were confirmed to have a receptor-negative mutation in both *LDLR* alleles or *LDLRAP1* alleles.

In Part B, 13 (92.9%) patients were diagnosed by genotyping and 1 (7.1%) patient by clinical diagnosis. The mean (SD) time from diagnosis to study randomization was 5.38 years (2.957). At baseline in Part B, 4 (28.6%) patients were categorized as having homozygous *LDLR* mutations (3 defective/defective, and 1 negative/negative), 10 (71.4%) patients were categorized as having compound heterozygous *LDLR* mutations (5 patients with defective/negative, 3 patients with defective/negative, and 2 patients with negative/negative) (Table 3). One patient with a compound heterozygous *LDLR* mutation was categorized as null/null, i.e., having LDLR activity <15%.
One patient was confirmed to have a receptor-negative mutation in both *LDLR* alleles or *LDLRAP1* alleles.

Table 3: Genotype and Variant Categorization in LDLR for Part A and Part B - Safety Analysis Set

	Part A Total Evinacumab 15mg/Kg IV (N=6)	Part B Total Evinacumab 15mg/Kg IV Q4W (N=14)
Genotype State		
Homozygous	4 (66.7%)	4 (28.6%)
Compound Heterozygous	2 (33.3%)	10 (71.4%)
Homozygous (LDLR)	4 (66.7%)	4 (28.6%)
Defective/Defective	3 (50.0%)	3 (21.4%)
Negative/Negative	1 (16.7%)	1 (7.1%)
Homozygous (LDLRAP1)	0	0
Negative/Negative	0	0
Compound Heterozygous (LDLR)	2 (33.3%)	10 (71.4%)
Defective/Defective	0	3 (21.4%)
Defective/Negative	1 (16.7%)	5 (35.7%)
Negative/Negative	1 (16.7%)	2 (14.3%)
Double Heterozygous (LDLR and APOB)	0	0
Defective (LDLR)/Defective (APOB)	0	0
Negative (LDLR)/ Defective (APOB)	0	0

Source: PTT 14.4.8a

Lipid lowering treatment at baseline

Patients were required to maintain stable lipid-modifying therapy throughout the study. As depicted in Table 4, in the pooled population, 18 patients (90.0%) were taking any statin, and 10 (50.0%) were taking high-intensity statins; 5 patients were taking atorvastatin 40 to 80 mg daily and 5 patients were taking rosuvastatin 20 mg daily at baseline. Eight patients were taking low intensity statins; 5 patients were taking rosuvastatin 5 to 10 mg daily or other doses and 3 patients were taking simvastatin 30 to 40 mg daily. The most frequently used non-statin LLT was ezetimibe (19 patients [95.0%]). Two

patients (10.0%) were taking lomitapide (including 1 patient taking both ezetimibe and lomitapide at baseline). All 20 (100%) patients had a history of taking maximally tolerated LLT at baseline.

Table 4: Lipid Lowering Treatment (LLT) at Baseline for Pooled Data – Pooled Parts B and C – Pooled Safety Analysis Set

Number of patients with	Part A Patients Evinacumab 15mg/Kg IV Q4W (N=6)	Part B Patients Evinacumab 15mg/Kg IV Q4W (N=14)	Total (N=20)
Any statin	6 (100%)	12 (85.7%)	18 (90.0%)
Taking high intensity statin	4 (66.7%)	6 (42.9%)	10 (50.0%)
Atorvastatin daily dose (mg)			
10	0	0	0
20	0	0	0
40	1 (16.7%)	1 (7.1%)	2 (10.0%)
60	0	1 (7.1%)	1 (5.0%)
80	0	2 (14.3%)	2 (10.0%)
Other doses	0	0	0
Rosuvastatin daily dose (mg)			
5	0	1 (7.1%)	1 (5.0%)
10	0	2 (14.3%)	2 (10.0%)
20	3 (50.0%)	2 (14.3%)	5 (25.0%)
40	0	0	0
Other doses	1 (16.7%)	1 (7.1%)	2 (10.0%)
20 mg INTERMITTENT	0	1 (7.1%)	1 (5.0%)
40 mg once a week	1 (16.7%)	0	1 (5.0%)
Any non-statin LLT	6 (100%)	14 (100%)	20 (100%)
Any LLT	6 (100%)	14 (100%)	20 (100%)
Ezetimibe	6 (100%)	13 (92.9%)	19 (95.0%)
Lomitapide	0	2 (14.3%)	2 (10.0%)
Any non-statin LLT			
Any LLT			
PCSK9 inhibitor [1]	0	0	0

IV, Intravenous; LLT, Lipid lowering treatment; PCSK9, Proprotein convertase subtilisin/kexin type 9; Q4W, Every 4 weeks.
Note: High intensity statin corresponds to atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily
[1] Praluent (alirocumab) or Repatha (evolocumab)
Source: PTT 14.4.3d

In part C of the study, 12 patients (60.0%) had at least 1 apheresis treatment during the study period (Table 5); of which 7 (35.0%) had weekly treatment and 5 (20.0%) had treatment every 2 weeks. Changes of apheresis frequency were allowed during Part C (in contrast to Parts A and B), at the investigator's discretion. A total of 6 patients (30.0%) changed frequency, 4 changed once and 2 changed twice.

Table 5: Summary of Apheresis Occurrences During Study Treatment Period for Part C – Part C Safety Analysis Set

	Part C Total Evinacumab 15mg/Kg IV Q4W (N=20)
Patients with at least one apheresis treatment	12 (60.0%)
Frequency at start of Part C	
Weekly	7 (35.0%)
Bi-weekly	5 (25.0%)
Patients who changed frequency during the treatment period [1]	6 (30.0%)
Bi-weekly to Every 4 Weeks	2 (10.0%)
Bi-weekly to Weekly	1 (5.0%)
Weekly to Bi-weekly	4 (20.0%)
Weekly to Every 4 Weeks	1 (5.0%)
Treatment technique	
Double membrane filtration	2 (10.0%)
Immunoadsorption	1 (5.0%)
Heparin-induced LDL precipitation	1 (5.0%)
Direct adsorption of lipids	5 (25.0%)
Dextran sulfate adsorption (plasma)	3 (15.0%)
Dextran sulfate adsorption (whole blood)	0

IV, Intravenous; LDL, Low-density lipoprotein; Q4W, Every 4 weeks.
Source: PTT 14.4.5c
[1] A patient could have more than one change during treatment period. Bi-weekly denotes every 2 weeks.

Number analysed

The number of participants included in each part of the study is provided in Table 6. No patients were excluded from the ITT or SAF populations.

Table 6: Patient disposition for Part C (Part C Safety Analysis Set)

	Total Patients from Part A Evinacumab 15mg/Kg IV (N=6)	Total Patients from Part B Evinacumab 15mg/Kg IV Q4W (N=14)	Part C Total (Total Patients from Part A and Part B) Evinacumab 15mg/Kg IV Q4W (N=20)
Patients Treated in Part C	6 (100%)	14 (100%)	20 (100%)
Completed Part C treatment period (as per CRF)	6 (100%)	14 (100%)	20 (100%)
Completed Part C treatment period (derived)[1]	6 (100%)	14 (100%)	20 (100%)
Did not complete Part C treatment period (as per CRF)	0	0	0
Did not complete Part C treatment period due to COVID-19	0	0	0
Ongoing	0	0	0
Completed the study	6 (100%)	14 (100%)	20 (100%)
Did not complete the study	0	0	0
Ongoing in study	0	0	0

Pharmacokinetics

Pharmacokinetics Part A

Following a single dose of evinacumab 15 mg/kg IV in the 6 paediatric HoFH patients (5 received apheresis and 1 did not receive apheresis), the mean (SD) maximal total evinacumab concentrations in serum was 238 (90.8) mg/l. Thereafter, the concentration-time profiles of evinacumab can be generally described by a brief distribution phase followed by a linear beta elimination phase, and a terminal target-mediated elimination phase. A summary of PK parameters calculated from total evinacumab concentrations for patients in part A is presented in Table 7. Although other pharmacokinetic parameters, including t1/2, were specified in the protocol, derivation of these parameters is not meaningful for a drug exhibiting target-mediated elimination.

Based on the analyses from part A, a dose of 15 mg/kg IV Q4W was selected for part B of this study.

Table 7: Summary of pharmacokinetic parameters calculated from concentrations of 15 mg/kg total evinacumab in paediatric patients with HoFH in part A

	evinacumab 15mg/kg IV Q4W (N=6)			
Parameter (Units)	n	Mean (SD)	Median	Min : Max
AUC_{last} (day*mg/L)	6	4576 (1568)	4329	2207 : 6398
C_{max} (mg/L)	6	238 (90.8)	230	108 : 383

AUC_{last}, area under the plasma concentration-time curve from time zero to time of last measurable concentration; C_{max}, maximum serum concentration; IV, intravenously; Q4W, Every 4 weeks; n, Number of patients; N, Number of patients; SD, Standard deviation

Pharmacokinetics part B

Following 15 mg/kg Q4W dosing of evinacumab in part B, steady-state concentrations of total evinacumab in serum were reached between Weeks 8 and 12. The increase in exposures (AUC) of total evinacumab after the first dose and at steady-state was approximately 2-fold.

Population PK modeling was performed for evinacumab to generate individual steady-state exposure metrics based on empirical Bayesian estimates of PK parameters for paediatric patients with HoFH. A summary of predicted steady-state exposure metrics is presented in Table 8. Based on the population PK modelling, evinacumab exposures after 15 mg/kg IV infusions were predicted to be lower in paediatric patients compared to adolescents and adults which could most likely be explained by the difference in body weight.

The analysis of Part B and the population PK supported the continuation of 15 mg/kg IV Q4W in Part C.

Table 8: Summary of bayesian estimates of steady state exposure metrics for paediatric patients with HoFH receiving 15 mg/kg IV Q4W evinacumab in part B

	Evinacumab 15mg/kg IV Q4W (N=14)			
Parameter (Units)	n	Mean (SD)	Median	Min : Max
AUC_{ss} (day*mg/L)	14	7019 (2561)	7584	2153 : 10134
$C_{avg,ss}$ (mg/L)	14	251 (91.4)	271	76.9 : 362
$C_{max,ss}$ (mg/L)	14	429 (114)	461	186 : 559
$C_{min,ss}$ (mg/L)	14	172 (79.5)	185	33.1 : 277

AUC_{ss}, area under the serum concentration-time curve at steady state; $C_{avg,ss}$, average serum concentration at steady state $C_{max,ss}$, maximum serum concentration at steady state; $C_{min,ss}$, minimum serum concentration at steady state; IV, intravenously; Q4W, Every 4 weeks; n, Number of patients; N, Number of patients; SD, Standard Deviation

Pharmacokinetics part C

Concentrations of evinacumab were generally at steady state throughout the duration of part C. An increase in trough concentration was observed in participants who transitioned from part A to part C from Weeks 16 to 28, as participants resumed evinacumab administration. Trough evinacumab concentrations were generally consistent throughout the study in participants who transitioned from part B to part C. A slight increase from nominal Week 16 to nominal Week 28 was observed in participants that transitioned from part A to part C, when participants resumed evinacumab CSR therapy. A summary of evinacumab concentrations in part C is presented by time and apheresis status in Table 9.

Table 9: Summary of concentrations of total evinacumab in serum by time and summary of concentrations of total evinacumab in serum by time and apheresis status in participants aged 5 to 11 years old with HoFH (study R1500-CL-17100, Part C, PKAS)

		Concentrations of Total Evinacumab in Serum (mg/L)					
		Apheresis		No Apheresis		Overall	
Sampling Time Post First Dose (Week)	Time Point	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
16	Predose	5	0.325 (0.511)	1	--	6	0.271 (0.476)
	EOI	5	378 (294)	1	--	6	361 (266)
24	Predose	7	105 (65.0)	7	158 (43.5)	14	131 (59.8)
	EOI	5	339 (121)	6	411 (68.6)	11	378 (98.0)
28	Predose	5	99.5 (42.1)	1	--	6	95.0 (39.2)
	EOI	4	377 (159)	1	--	5	358 (144)
36	Predose	7	113 (62.4)	7	167 (40.3)	14	140 (57.7)
	EOI	6	345 (70.8)	7	420 (53.3)	13	385 (70.7)
40	Predose	5	93.1 (71.2)	1	--	6	88.4 (64.7)
	EOI	5	352 (100)	1	--	6	348 (90.0)
48	Predose	7	130 (67.3)	7	169 (37.6)	14	149 (56.1)
	EOI	7	357 (70.1)	7	508 (189)	14	433 (158)
52	Predose	5	120 (53.5)	1	--	6	111 (51.8)
	EOI	5	413 (127)	1	--	6	387 (131)
60	Predose	7	127 (74.4)	7	171 (30.1)	14	149 (59.1)
	EOI	7	362 (97.6)	7	411 (138)	14	387 (118)
64	Predose	5	117 (75.1)	1	--	6	105 (74.1)
72	Predose	7	123 (66.8)	7	199 (38.4)	14	161 (65.6)

n = Number of participants; SD = Standard deviation; EOI = End of infusion. Concentrations below the LLOQ (0.078 mg/l) were set to 0.

PK/PD

In participants who transitioned form both part A and part B, steady-state concentrations of evinacumab are consistent with an observed reduction in LDL-C in part C. In participants in part A, LDL-C returned to baseline as concentrations of evinacumab decreased following a single dose of evinacumab in part A. At the start of part C (week 16), LDL-C concentrations were near baseline, and upon resumption of evinacumab 15 mg/kg IV Q4W, declined by approximately 40% at week 40. A consistent reduction in LDL-C was observed from week 40 through the end of the study. In participants in part B transitioning to part C, LDL-C reductions were consistent with the observed reduction seen in part B, and this decrease in LDL-C was maintained throughout the duration of the study, consistent with steady-state evinacumab concentrations.

Despite the lower evinacumab exposures, the magnitude of LDL-C reduction was comparable across paediatric, adolescent, and adult HoFH patients.

Efficacy results

Pooled efficacy results represent analyses of pooled data from Part A patients during their participation in Part C and from Part B patients during their participation in Parts B and C. All patients treated in Parts A and B continued into Part C. The current report presents results for all patients to follow the efficacy and safety of evinacumab for up to 72 weeks (treatment: 24 weeks in Part B and 48 weeks in Part C). It is important to point out that, per protocol, patients were allowed by the investigator to change their apheresis frequency during Part C. Two patients changed their apheresis frequency twice; 1 patient changed from weekly to every 2 weeks at week 32 (Part C week 16) and back to weekly at week 44 (Part C week 28), the other from weekly to every 2 weeks at week 22 (Part C week 6) and then to every 4 weeks at week 44 (Part C week 28).

LDL-C

In the pooled population, treatment with evinacumab 15 mg/kg IV Q4W resulted in a decrease in LDL-C presented as calculated percent change from baseline. LDL-C decrease was already observed at week 4 and was maintained through week 72 (Figure 4, Table 10), except for increased LDL-C levels at week 36 and week 44 compared with other timepoints. The mean (SD) percent change from baseline in calculated LDL-C was -44.61% (20.966) at week 48 (n=16) and -40.65% (38.723) at week 72 (n=14).

Table 10: Calculated LDL-C Over Time for Pooled Data - Raw Data Description Pool Parts B + C Pooled Safety Analysis Set

	Part A Patients Evinacumab 15mg/Kg IV Q4W (n=6)			Part B Patients Evinacumab 15mg/Kg IV Q4W (n=14)			Total (n=20)		
Calculated LDL-C (mmol/L)	Value	Change from baseline	% change from baseline	Value	Change from baseline	% change from baseline	Value	Change from baseline	% change from baseline
Baseline									
N	6	6	6	14	14	14	20	20	20
Mean (SD)	10.127 (5.7539)			6.830 (2.3539)			7.819 (3.8609)		
Median	7.925			6.085			6.215		
Q1:Q3	6.190 : 12.560			5.570 : 8.570			5.660 : 9.620		
Min:Max	5.62 : 20.54			3.81 : 11.16			3.81 : 20.54		
Week 4									
N	-			13	13	13	13	13	13
Mean (SD)	-			4.292 (2.7676)	-2.599 (2.2449)	-38.25 (25.324)	4.292 (2.7676)	-2.599 (2.2449)	-38.25 (25.324)
Median	-			3.700	-2.900	-44.19	3.700	-2.900	-44.19
Q1:Q3	-			2.670 : 3.830	-3.860 : -1.820	-52.07 : -32.81	2.670 : 3.830	-3.860 : -1.820	-52.07 : -32.81
Min:Max	-			1.99 : 12.20	-6.14 : 2.57	-66.2 : 26.7	1.99 : 12.20	-6.14 : 2.57	-66.2 : 26.7
Week 8									
N	6	6	6	14	14	14	20	20	20
Mean (SD)	4.940 (3.8118)	-5.187 (2.5276)	-52.57 (14.777)	3.464 (2.6542)	-3.366 (2.4848)	-49.23 (28.769)	3.907 (3.0209)	-3.913 (2.5764)	-50.23 (25.024)
Median	3.435	-5.230	-57.94	2.655	-3.250	-60.01	2.710	-3.690	-59.00
Q1:Q3	2.590 : 5.310	-7.250 : -3.600	-60.58 : -39.58	2.200 : 2.930	-4.380 : -2.280	-69.15 : -47.40	2.280 : 4.080	-5.565 : -2.580	-65.60:-43.49
Min:Max	2.46 : 12.41	-8.13 : -1.68	-69.5 : -29.9	1.53 : 11.19	-8.49 : 1.56	-76.1 : 16.2	1.53 : 12.41	-8.49 : 1.56	-76.1:16.2

P value									
Week 12									
N	-	-	-	14	14	14	14	14	14
Mean (SD)				3.229 (2.0664)	-3.601 (2.3358)	-50.94(26.465)	3.229 (2.0664)	-3.601 (2.3358)	-50.94(26.465)
Median				2.395	-3.495	-58.20	2.395	-3.495	-58.20
Q1:Q3				1.970 : 2.850	-4.170 : -2.460	-64.38:-48.29	1.970 : 2.850	-4.170 : -2.460	-64.38:-48.29
Min:Max				1.71 : 8.65	-8.85 : 0.67	-80.0:17:2	1.71 : 8.65	-8.85 : 0.67	-80.0:17:2
Week 16									
N	6	6	6	13	13	13	19	19	19
Mean (SD)	5.225 (3.3571)	-4.902 (2.8586)	-47.72 (10.199)	3.572 (2.7052)	-3.345 (2.7294)	-46.63 (37.375)	4.094 (2.9380)	-3.836 (2.7909)	-46.98 (30.991)
Median	4.155	-4.050	-45.94	2.360	-3.420	-58.01	3.320	-3.420	-52.04
Q1:Q3	3.320 : 4.640	-8.160 : -2.300	-51.72 : -40.93	1.860 : 3.780	-4.580 : -2.570	-69.08 : -44.11	2.050 : 4.640	-5.360 : -2.300	-66.13 : -40.93
Min:Max	3.11 : 11.97	-8.57 : -2.28	-65.0 : -36.8	1.37 : 10.85	-7.38 : 1.94	-84.0 : 49.9	1.37 : 11.97	-8.57 : 1.94	-84.0 : 49.9
Week 20									
N	-	-	-	13	13	13	13	13	13
Mean (SD)				3.393 (2.3915)	-3.663 (1.9953)	-53.10 (21.092)	3.393 (2.3915)	-3.663 (1.9953)	-53.10 (21.092)
Median				2.360	-3.290	-54.25	2.360	-3.290	-54.25
Q1:Q3				2.050 : 3.260	-4.400 : -2.310	-67.83 : -46.19	2.050 : 3.260	-4.400 : -2.310	-67.83 : -46.19
Min:Max				1.71 : 9.71	-6.99 : 0.08	-80.0 : 0.8	1.71 : 9.71	-6.99 : 0.08	-80.0 : 0.8
Week 24									

N	6	6	6	14	14	14	20	20	20
Mean (SD)	5.892 (3.0393)	-4.235 (3.7939)	-37.37 (27.699)	3.414 (2.8456)	-3.416 (2.9096)	-48.32 (39.052)	4.157 (3.0543)	-3.662 (3.1191)	-45.04 (35.664)
Median	5.620	-3.520	-40.68	2.370	-3.640	-60.08	2.450	-3.640	-58.40
Q1:Q3	3.650 : 7.020	-7.720 : -1.970	-61.38 : -33.40	1.890 : 2.540	-4.270 : -2.310	-69.98 : -51.47	2.230 : 6.230	-4.840 : -2.295	-66.81 : -35.60
Min:Max	2.41 : 11.03	-9.51 : 0.83	-61.5 : 13.4	1.50 : 11.66	-8.67 : 2.17	-81.6 : 55.8	1.50 : 11.66	-9.51 : 2.17	-81.6 : 55.8
Week 28									
N	6	6	6	3	3	3	9	9	9
Mean (SD)	5.668 (2.7926)	-4.458 (3.3757)	-40.09 (19.477)	4.910 (1.9727)	-4.197 (1.9263)	-46.03 (11.770)	5.416 (2.4476)	-4.371 (2.8402)	-42.07 (16.750)
Median	5.180	-3.950	-47.86	4.790	-3.520	-47.37	4.870	-3.520	-47.37
Q1:Q3	3.910 : 5.650	-6.910 : -2.280	-50.64 : -36.83	3.000 : 6.940	-6.370 : -2.700	-57.08 : -33.65	3.910 : 5.650	-6.370 : -2.700	-50.64 : -36.83
Min:Max	3.08 : 11.01	-9.53 : -0.13	-55.0 : -2.3	3.00 : 6.94	-6.37 : -2.70	-57.1 : -33.7	3.00 : 11.01	-9.53 : -0.13	-57.1 : -2.3
Week 32									
N	6	6	6	9	9	9	15	15	15
Mean (SD)	5.428 (3.0088)	-4.698 (3.3563)	-43.19 (17.942)	2.503 (0.5611)	-3.583 (1.6530)	-56.67 (13.254)	3.673 (2.3692)	-4.029 (2.4298)	-51.28 (16.188)
Median	4.415	-4.300	-43.62	2.670	-3.030	-55.91	2.980	-3.030	-49.32
Q1:Q3	3.700 : 6.500	-7.050 : -1.660	-48.25 : -26.82	2.100 : 2.980	-4.040 : -2.440	-65.80 : -49.32	2.540 : 4.300	-6.060 : -2.130	-65.80 : -40.71
Min:Max	2.56 : 10.98	-9.56 : -1.32	-73.4 : -23.5	1.66 : 3.13	-6.91 : -1.66	-80.6 : -37.5	1.66 : 10.98	-9.56 : -1.32	-80.6 : -23.5
Week 36									
N	6	6	6	3	3	3	9	9	9
Mean (SD)	4.982 (3.0376)	-5.145 (3.3098)	-48.44 (16.452)	5.630 (2.4343)	-1.053 (3.9632)	1.13 (77.023)	5.198 (2.7117)	-3.781 (3.8677)	-31.92 (47.609)
Median	3.910	-4.855	-45.87	6.660	-2.850	-36.33	4.300	-2.850	-45.19

Q1:Q3	3.420 : 4.950	-7.610 : -2.670	-60.59 : -43.13	2.850 : 7.380	-3.800 : 3.490	-50.00 : 89.72	3.420 : 6.660	-6.890 : -2.670	-50.00 : -36.33
Min:Max	2.72 : 10.98	-9.56 : -1.32	-71.7 : -23.5	2.85 : 7.38	-3.80 : 3.49	-50.0 : 89.7	2.72 : 10.98	-9.56 : 3.49	-71.7 : 89.7
Week 40									
N	5	5	5	11	11	11	16	16	16
Mean (SD)	5.330 (2.4803)	-4.900 (4.4961)	-40.84 (20.961)	3.372 (2.1351)	-3.498 (1.7552)	-51.81 (18.953)	3.984 (2.3576)	-3.936 (2.8097)	-48.38 (19.602)
Median	4.040	-2.250	-36.06	2.670	-2.820	-44.88	3.430	-2.720	-44.72
Q1:Q3	3.990 : 4.920	-8.570 : -2.150	-52.73 : -34.73	2.070 : 3.600	-4.870 : -2.380	-66.29 : -42.73	2.265 : 4.480	-5.080 : -2.200	-64.97 : -38.18
Min:Max	3.99 : 9.71	-10.83 : -0.70	-68.2 : -12.5	1.45 : 8.42	-7.12 : -1.21	-83.1 : -12.6	1.45 : 9.71	-10.83 : -0.70	-83.1 : -12.5
Week 44									
N	6	6	6	3	3	3	9	9	9
Mean (SD)	6.553 (3.4792)	-3.573 (2.6247)	-32.44 (12.404)	5.467 (1.5761)	-1.217 (3.6519)	-2.10 (63.572)	6.191 (2.9124)	-2.788 (3.0047)	-22.33 (36.560)
Median	5.465	-2.900	-34.33	6.060	-2.020	-35.44	5.930	-2.120	-34.42
Q1:Q3	4.660 : 6.190	-6.370 : -1.240	-38.29 : -19.87	3.680 : 6.660	-4.400 : 2.770	-42.07 : 71.21	4.660 : 6.190	-4.400 : -1.240	-38.29 : -19.87
Min:Max	4.07 : 13.47	-7.07 : -0.96	-50.7 : -17.1	3.68 : 6.66	-4.40 : 2.77	-42.1 : 71.2	3.68 : 13.47	-7.07 : 2.77	-50.7 : 71.2
Week 48									
N	5	5	5	11	11	11	16	16	16
Mean (SD)	6.242 (3.1126)	-3.398 (3.2170)	-31.37 (9.135)	3.478 (2.4171)	-3.392 (2.0112)	-50.61 (22.323)	4.342 (2.8686)	-3.394 (2.3359)	-44.60 (20.961)
Median	4.580	-2.100	-31.53	2.490	-2.350	-52.60	3.615	-2.340	-41.75
Q1:Q3	4.430 : 6.580	-3.030 : -1.810	-33.93 : -29.01	2.100 : 3.680	-5.130 : -2.310	-65.47 : -38.97	2.240 : 5.305	-4.635 : -2.060	-61.54 : -32.73
Min:Max	4.09 : 11.53	-9.01 : -1.04	-43.9 : -18.5	1.30 : 9.58	-7.27 : -0.05	-84.8 : -0.5	1.30 : 11.53	-9.01 : -0.05	-84.8 : -0.5
Week 52									

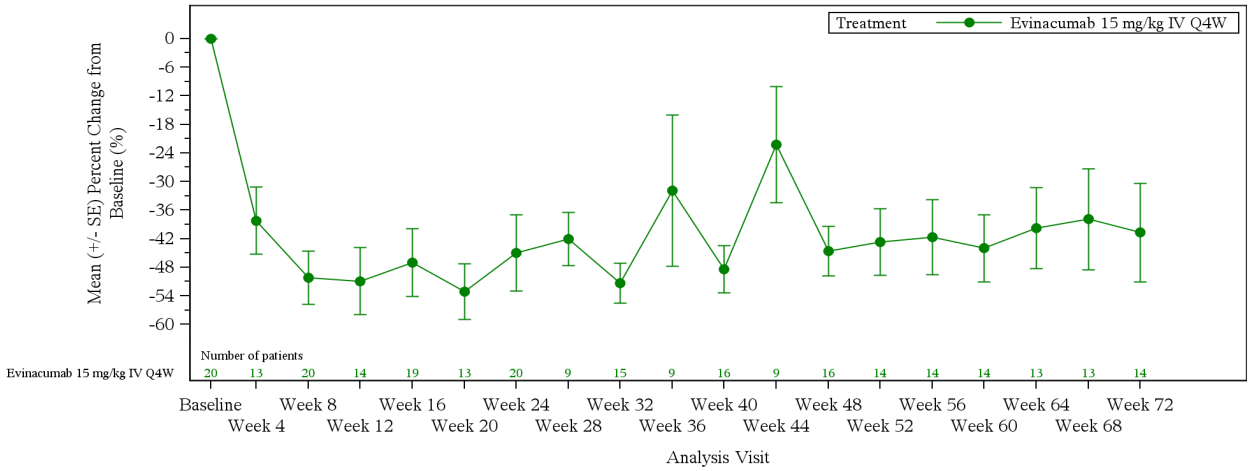
N	-	-	-	14	14	14	14	14	14
Mean (SD)				3.842 (2.1814)	-2.988 (2.0898)	-42.69 (25.959)	3.842 (2.1814)	-2.988 (2.0898)	-42.69 (25.959)
Median				3.275	-2.680	-46.50	3.275	-2.680	-46.50
Q1:Q3				2.050 : 5.230	-4.500 : -1.920	-58.52 : -33.68	2.050 : 5.230	-4.500 : -1.920	-58.52 : -33.68
Min:Max				1.32 : 9.25	-7.25 : 0.28	-84.6 : 7.2	1.32 : 9.25	-7.25 : 0.28	-84.6 : 7.2
Week 56									
N	-	-	-	14	14	14	14	14	14
Mean (SD)				3.920 (2.3590)	-2.910 (2.1153)	-41.74 (29.381)	3.920 (2.3590)	-2.910 (2.1153)	-41.74 (29.381)
Median				3.340	-2.555	-43.86	3.340	-2.555	-43.86
Q1:Q3				2.020 : 5.180	-4.220 : -2.200	-59.32 : -37.41	2.020 : 5.180	-4.220 : -2.200	-59.32 : -37.41
Min:Max				1.53 : 9.87	-7.04 : 1.29	-82.1 : 33.2	1.53 : 9.87	-7.04 : 1.29	-82.1 : 33.2
Week 60									
N	-	-	-	14	14	14	14	14	14
Mean (SD)				3.788 (2.2662)	-3.042 (2.0159)	-44.00 (26.298)	3.788 (2.2662)	-3.042 (2.0159)	-44.00 (26.298)
Median				3.330	-2.560	-43.28	3.330	-2.560	-43.28
Q1:Q3				2.100 : 4.580	-4.500 : -2.230	-61.15 : -40.04	2.100 : 4.580	-4.500 : -2.230	-61.15 : -40.04
Min:Max				1.48 : 9.61	-6.83 : 0.69	-79.7 : 17.7	1.48 : 9.61	-6.83 : 0.69	-79.7 : 17.7
Week 64									
N	-	-	-	13	13	13	13	13	13
Mean (SD)				4.077 (2.4751)	-2.806 (2.1836)	-39.82 (30.531)	4.077 (2.4751)	-2.806 (2.1836)	-39.82 (30.531)
Median				3.570	-2.390	-40.34	3.570	-2.390	-40.34

Q1:Q3				2.180 : 5.230	-3.910 : -2.070	-58.97 : -34.33	2.180 : 5.230	-3.910 : -2.070	-58.97 : -34.33
Min:Max				1.42 : 9.61	-7.15 : 1.34	-83.4 : 34.4	1.42 : 9.61	-7.15 : 1.34	-83.4 : 34.4
Week 68									
N	-	-	-	13	13	13	13	13	13
Mean (SD)				4.085 (2.5298)	-2.677 (2.2715)	-37.94 (38.091)	4.085 (2.5298)	-2.677 (2.2715)	-37.94 (38.091)
Median				3.290	-2.440	-44.61	3.290	-2.440	-44.61
Q1:Q3				2.020 : 6.480	-3.650 : -2.070	-55.08 : -36.32	2.020 : 6.480	-3.650 : -2.070	-55.08 : -36.32
Min:Max				1.30 : 8.47	-7.27 : 2.82	-84.8 : 72.5	1.30 : 8.47	-7.27 : 2.82	-84.8 : 72.5
Week 72									
N				14	14	14	14	14	14
Mean (SD)				3.832 (2.3320)	-2.998 (2.6209)	-40.65 (38.666)	3.832 (2.3320)	-2.998 (2.6209)	-40.65 (38.666)
Median				3.160	-2.795	-48.94	3.160	-2.795	-48.94
Q1:Q3				2.280 : 3.780	-3.930 : -2.230	-62.44 : -37.57	2.280 : 3.780	-3.930 : -2.230	-62.44 : -37.57
Min:Max				1.53 : 9.82	-7.38 : 2.92	-82.1 : 75.1	1.53 : 9.82	-7.38 : 2.92	-82.1 : 75.1

As previously presented in the first- and second-step analysis CSR, the percent change from baseline was more variable in Part C compared to Part B possibly due to including Part A participants with higher baseline LDL-C levels. A supplementary analysis of change from baseline in LDL-C among patients on apheresis at baseline was conducted. Overall, patients who were on apheresis but reduced apheresis frequency had substantially smaller absolute changes in LDL-C at weeks 24 and 48 compared to patients who were on apheresis but did not reduce frequency and to those without apheresis.

Patients in Part A had higher overall mean (SD) LDL-C at baseline (10.13 [5.75]) compared with patients in Part B (6.83 [2.35]). Although the absolute mean (SD) reduction in LDL-C was the same at week 48 for Part A (-3.40 [3.21]) and Part B patients (-3.39 [2.01]), there was a smaller percent reduction in LDL-C in patients in Part A (-31.37 [9.16]) compared with Part B (-50.61 [22.32]).

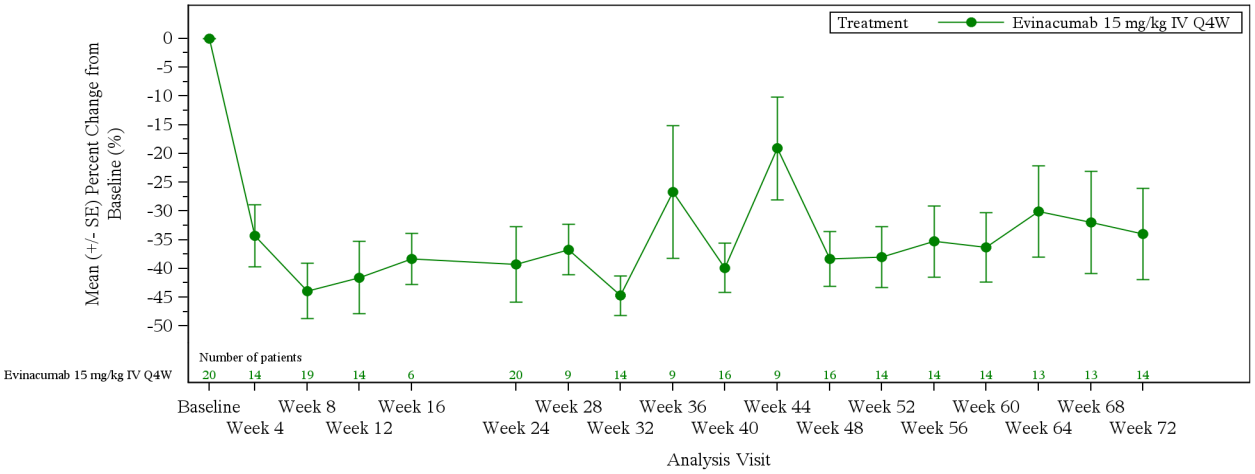
Figure 4: Calculated LDL-C Mean (±SE) Percent Change from Baseline Over Time (ITT Estimand) for Pooled Data – Raw Data Description Pooled Parts B and C - Pooled Safety Analysis Set



Apo-B

In the pooled population, treatment with evinacumab 15 mg/kg IV Q4W resulted in a decrease in Apo B presented as percent change from baseline (Figure 5). This decrease was observed from the first analysis visit at week 4 and the decrease was maintained throughout the study, except for increased Apo-B levels at week 36 and week 44 compared with other timepoints. The mean (SD) percent change from baseline in Apo B was -38.29% (19.134) at week 48 (n=16) and -34.02 (29.836) at week 72 (n=14).

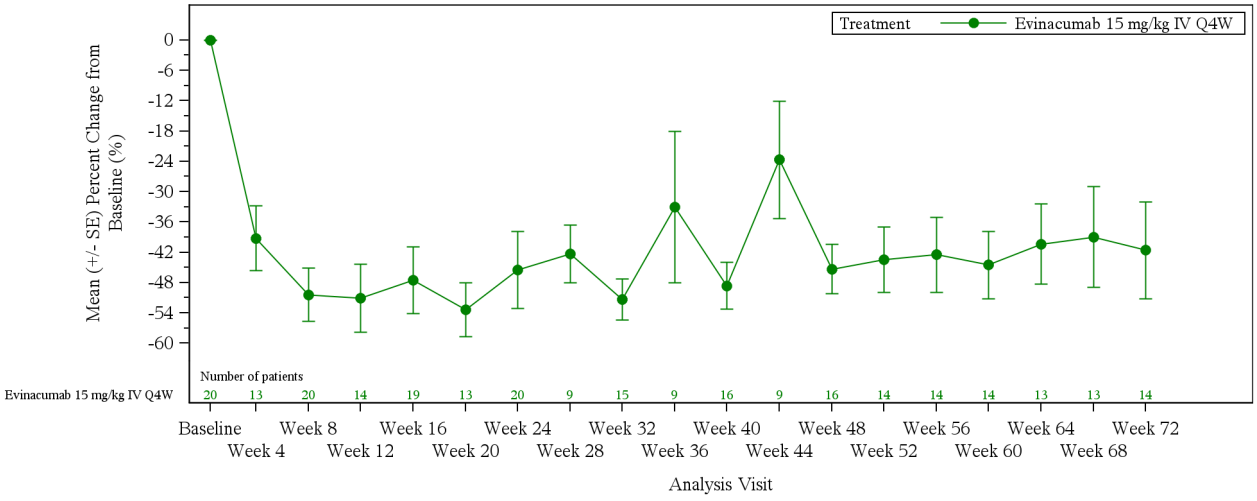
Figure 5: Apo B (±SE) percent change from baseline over time (ITT Estimand) for pooled data - Raw data description pooled parts B and C - pooled safety analysis set



Non-HDL-C

In the pooled population, treatment with evinacumab 15 mg/kg IV Q4W resulted in a decrease in non-HDL-C presented as percent change from baseline. This decrease was observed from the first analysis visit at week 4 and the decrease was maintained throughout the study, except for increased non-HDL-C levels at week 36 and week 44 compared with other timepoints (Figure 6). The mean (SD) percent change from baseline in non-HDL-C was -45.29% (19.72) at week 48 (n=16) and -41.62% (35.86) at week 72 (n=14).

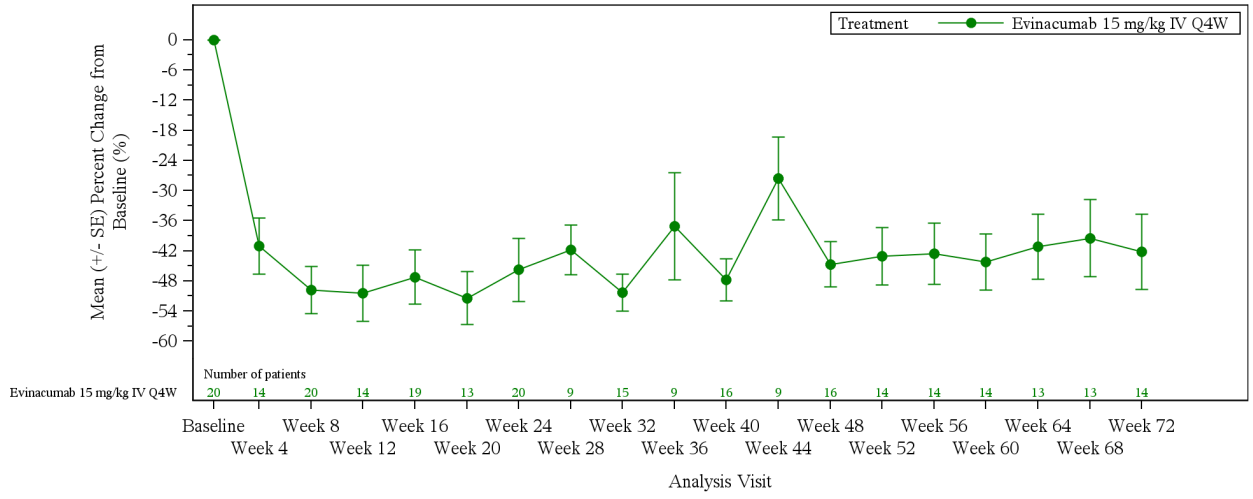
Figure 6: Non-HDL-C (±SE) Percent Change from Baseline Over Time (ITT Estimand) for Pooled Data – Raw Data Description Pooled Parts B and C – Pooled Safety Analysis Set



Total cholesterol

In the pooled population, treatment with evinacumab 15 mg/kg IV Q4W resulted in a decrease in total cholesterol presented as percent change from baseline. This decrease was observed from the first analysis visit at week 4 and the decrease was maintained throughout the study, except for increased total cholesterol levels at week 36 and week 44 (Figure 7). The mean (SD) percent change from baseline in TC was -44.74% (17.98) at week 48 (n=16) and -42.23 (28.16) at week 72 (n=14).

Figure 7: Total Cholesterol (TC) (±SE) Percent Change from Baseline Over Time (ITT Estimand) for Pooled Data – Raw Data Description Pooled Parts B and C - Pooled Safety Analysis Set

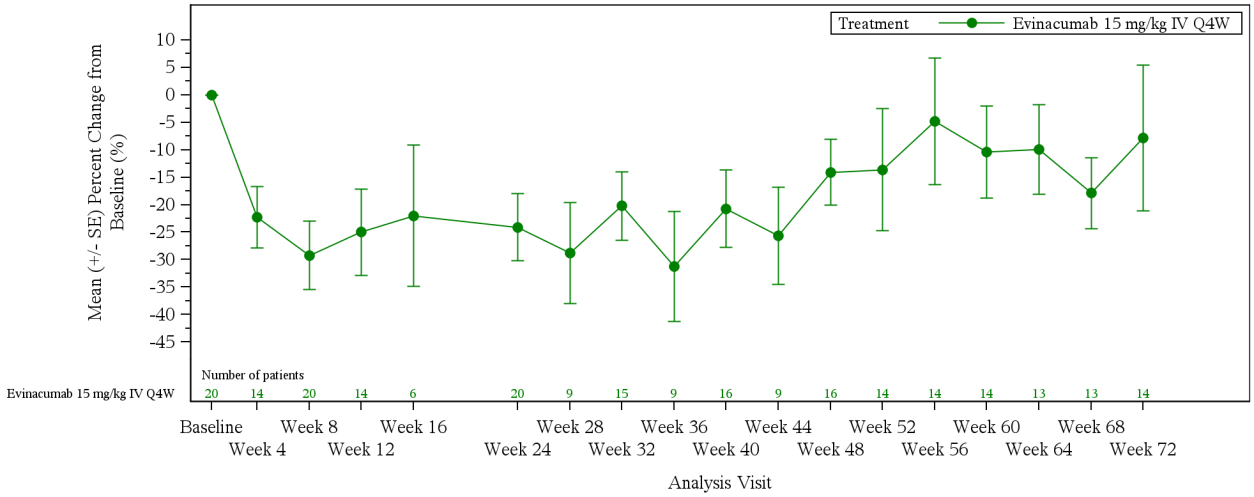


Lp(a)

In the pooled population, treatment with evinacumab 15 mg/kg IV Q4W resulted in a decrease in Lp(a) presented as percent change from baseline. This decrease was observed from the first analysis visit at

week 4, but throughout the study it was not maintained; Lp(a) levels rose during follow-up but remained somewhat lower than at baseline. The mean (SD) percent change from baseline in Lp(a) was -14.15 (23.92) at week 48 (n=16) and -7.78% (49.66) at week 72 (n=14)

Figure 8: Lp(a) (±SE) Percent Change from Baseline Over Time (ITT Estimand) for Pooled Data – Raw Data Description Pooled Parts B and C – Pooled Safety Analysis Set



Ultrasound imaging

In Study R1500-CL-17100, cIMT measurements were done at a limited number of study sites where carotid ultrasound was available and successful site qualification was completed. In the pooled population, mean (SD) baseline cIMT in 8/20 patients was 0.405 (0.0593) mm. In 6/20 patients at week 24, mean (SD) cIMT increased by 0.023 (0.0308) mm. In 3/20 patients at week 48, mean (SD) cIMT increased by 0.003 (0.0379) mm and in 2/20 patients at week 72, mean (SD) cIMT increased by 0.005 (0.0778) mm.

Subgroup analyses

Treatment effect (i.e. percent change in LDL-C) was assessed for the following subgroups: baseline LDL-C status (≥median; <median), lomitapide treatment (yes; no), and receptor characterization (defective/defective; negative/defective; negative/negative).

For baseline LDL-C status, the mean (SE) percent change in LDL-C status at week 24 and week 72 was greater among patients ≥median baseline LDL-C status -54.0 (13.7) and -52.4 (10.3) compared with patients < median baseline LDL-C status -42.6 (16.6) and-28.9 (17.7), respectively.

The mean (SE) percent change in LDL-C status at week 24 and week 72 was greater among patients not treated with lomitapide (n=18) -51.6 (10.3) and -42.1 (11.4) compared with patients treated with lomitapide (n=2) -28.4 (49.3) and -32.1 (34.0), respectively.

For receptor characterization, the mean (SE) percent change in LDL-C status at week 24 and week 72 was greater among patients who were negative/defective -66.6 (4.4) and -56.5 (8.1) or negative/negative -67.7 (6.5) and -50.8 (8.0), than in patients who were defective/defective -23.4 (20.6) and -22.3 (21.8), respectively.

The homogeneity of the treatment effect relative to baseline apheresis status (yes[n=12]; no [n=8]) was assessed by summarizing the percent change in Lp(a) from baseline at week 24 and week 72. There was no consistent trend visible. The mean (SE) percent change from baseline in Lp(a) at week 24 was greater among patients with baseline apheresis -43.7 (1.6) compared with those without-32.7 (1.4). At week 72, the change was greater among patients without baseline apheresis -16.9 (8.1) compared with those with baseline apheresis 1.3 (25.9).

Safety results

TEAE

Pooled Parts B and C includes Part A patients' data during their participation in Part C and Part B patients' data during their participation in Parts B and C. In the pooled population, all 20 (100.0%) patients had at least 1 TEAE. 2/20 (10.0%) patients experienced an SAE, and no patients had TEAEs resulting in treatment discontinuation, or death. No post-treatment AEs were reported.

Overall, all 20 (100.0%) patients experienced at least 1 TEAE during the study, of which the most frequently reported PTs were COVID-19 (15/20 [75.0%] patients), and Vomiting, Pyrexia, Headache, and Oropharyngeal pain (6/20 [30.0%] patients each). In the pooled population, TEAEs reported in ≥ 10% of patients (ie, 2 or more patients) are summarized in Table 11.

The most frequent TEAEs per patient-year were similar to the frequency of all TEAEs and included COVID-19, Pyrexia, Headache, Oropharyngeal pain, Vomiting, Diarrhoea, Cough, Abdominal pain upper, Fatigue, Abdominal pain, Nasopharyngitis, and Rhinitis.

Table 11: Number (%) of Patients with TEAEs that Occurred with PT ⩾10% by Primary SOC and PT - Pooled Parts B and C - Pooled Safety Analysis Set

Primary System Organ Class Preferred Term n(%)	Part A Patients Evinacumab 15mg/Kg IV Q4W (N=6)	Part B Patients Evinacumab 15mg/Kg IV Q4W (N=14)	Total (N=20)
Patients with at least one TEAE	6 (100%)	14 (100%)	20 (100%)
Gastrointestinal disorders	2 (33.3%)	8 (57.1%)	10 (50.0%)
Vomiting	1 (16.7%)	5 (35.7%)	6 (30.0%)
Diarrhoea	0	4 (28.6%)	4 (20.0%)
Abdominal pain	0	3 (21.4%)	3 (15.0%)
Abdominal pain upper	1 (16.7%)	2 (14.3%)	3 (15.0%)
Constipation	0	2 (14.3%)	2 (10.0%)
Nausea	0	2 (14.3%)	2 (10.0%)
General disorders and administration site conditions	2 (33.3%)	5 (35.7%)	7 (35.0%)
Pyrexia	2 (33.3%)	4 (28.6%)	6 (30.0%)
Fatigue	1 (16.7%)	2 (14.3%)	3 (15.0%)
Chest pain	1 (16.7%)	1 (7.1%)	2 (10.0%)
Infections and infestations	4 (66.7%)	11 (78.6%)	15 (75.0%)
COVID-19	4 (66.7%)	11 (78.6%)	15 (75.0%)

Nasopharyngitis	0	3 (21.4%)	3 (15.0%)
Rhinitis	2 (33.3%)	1 (7.1%)	3 (15.0%)
Investigations	1 (16.7%)	1 (7.1%)	2 (10.0%)
Body temperature increased	1 (16.7%)	1 (7.1%)	2 (10.0%)
Nervous system disorders	1 (16.7%)	5 (35.7%)	6 (30.0%)
Headache	1 (16.7%)	5 (35.7%)	6 (30.0%)
Respiratory, thoracic and mediastinal disorders	2 (33.3%)	6 (42.9%)	8 (40.0%)
Oropharyngeal pain	1 (16.7%)	5 (35.7%)	6 (30.0%)
Cough	2 (33.3%)	2 (14.3%)	4 (20.0%)
Skin and subcutaneous tissue disorders	1 (16.7%)	1 (7.1%)	2 (10.0%)
Rash	1 (16.7%)	1 (7.1%)	2 (10.0%)

Treatment-related TEAE

In the pooled population, 4/20 (20.0%) patients experienced TEAEs that were considered by the investigator to be related to study treatment. 1/20 (5.0%) patient experienced Fatigue, 1/20 (5.0%) patient experienced Abdominal pain and Nausea, 1/20 (5.0%) patient experienced Infusion site swelling, and 1/20 (5.0%) patient experienced Dermatitis contact and Rash. All TEAEs were considered mild, did not require an evinacumab dose change, and all events resolved/ recovered.

Serious AE

Two patients (10%) experienced SAEs. One patient experienced a SAE of tonsilitis that required hospitalisation and antimicrobial treatment, after which the patient recovered. The study drug was not changed, and the event was considered unrelated to the study drug by the investigator. The other patient experienced a mild intensity aortic valve stenosis, which required surgery and postoperative ICU stay. The study drug was not changed, and the event was considered unrelated to the study drug by the investigator.

HDL-C

In the pooled population, there was a decrease in mean HDL-C over time. Mean (SD) HDL-C at baseline was 34.9 (11.72) mg/dL. At week 48, mean (SD) change from baseline was -13.4 (8.55) mg/dL, and at week 72, mean (SD) change from baseline was -11.7 (11.10) mg/dL (Table 12).

Table 12: HDL-C - Descriptive Statistics Over Time During Treatment Period in Conventional Units for Pooled Data Pool Parts B + C Pooled Safety Analysis Set

	Part A Patients Evinacumab 15mg/Kg IV Q4W (N=6)	Part B Patients Evinacumab 15mg/Kg IV Q4W (N=14)	Total (N=20)
HDL Cholesterol (mg/dL)			
Baseline			
Observed Value			
n	6	14	20
Mean (SD)	38.7 (8.80)	33.3 (12.71)	34.9 (11.72)
Median	36.0	32.5	34.0
Q1 : Q3	31.0 : 48.0	26.0 : 39.0	26.5 : 42.5
Min : Max	30 : 51	12 : 59	12 : 59
Week 48			
Change from baseline			
n	5	11	16
Mean (SD)	-19.2 (4.15)	-10.8 (8.86)	-13.4 (8.55)
Median	-17.0	-9.0	-14.5
Q1 : Q3	-22.0 : -17.0	-20.0 : -6.0	-20.5 : -9.0
Min : Max	-25 : -15	-24 : 6	-25 : 6
Week 72			
Change from baseline			
n	0	14	14
Mean (SD)		-11.7 (11.10)	-11.7 (11.10)
Median		-10.0	-10.0
Q1 : Q3		-25.0 : -5.0	-25.0 : -5.0
Min : Max		-28 : 3	-28 : 3

AESIs

Anaphylactic reactions

No patient in the pooled population experienced an anaphylactic reaction.

Allergic reactions

In the pooled population, 3 patients (15%) experienced general allergic reactions; Rash (2 patients [10.0%]), Conjunctivitis allergic (1 patient [5.0%]), Dermatitis contact (1 patient [5.0%]), and Rhinitis allergic (1 patient [5.0%]). None of these reactions were serious, nor resulted in study treatment discontinuation.

Infusion reactions

One patient (5.0%) experienced an mild infusion-related AESI of Infusion site swelling. This did not result in discontinuation of the study treatment.

Hepatic disorders

No patient experienced a hepatic disorder AESI.

Liver function

Liver function parameters included alkaline phosphatase, ALT, AST, and bilirubin. The mean baseline for all parameters in all participants were within normal limits and the mean values over time remained within normal limits during the study. One patient had an LDH <LLN value that was out-of-range but was not considered clinically significant by the investigator. One patient's ALT increased from 54 U/L to 145 U/L at week 24 and this was classified as "Elevated ALAT", but not related to evinacumab treatment by the investigator. ALT remained moderately elevated at the following visits (62, 74 and 73 U/) and was considered resolved. The patients' bilirubin levels remained within normal range during this event. No additional patients with treatment-emergent PCSVs during the TEAE period according to baseline status were identified.

Symptomatic overdose

There were no cases of symptomatic overdose in the pooled population.

Neurocognitive events

There were no neurocognitive events in the pooled population.

Pancreatitis
There were no cases of pancreatitis in the pooled population.

New-onset diabetes and glucose
In the pooled population, all patients were confirmed to not have diabetes and none of the patients developed diabetes during the study. All patients met the PCSV criteria for glucose ≤70 mg/dL and <LLN (≤3.9 mmol/L and <LLN). The overall mean (SD) baseline HbA1C was 5.21% (0.291). Overall, no meaningful changes from baseline in HbA1C were observed with a mean (SD) change from baseline to week 72 of 0.16% (0.291).

Pregnancies
There were no cases of pregnancy in the pooled population.

Clinical laboratory evaluation
Metabolic function (albumin, creatinine kinase, C-reactive protein, glucose, and HbA1C)
Baseline mean value for all metabolic function parameters were within normal limits and remained within normal limits during the study. 2/20 (10.0%) patients had an out-of-range total protein value <LLN, including 1 patient with total protein 54 g/L at Part C week 40 and 1 patient with total protein 56 g/L at Part C week 48 (Listing 16.2.8.30). 1/20 (5.0%) patient had an out-of-range total protein value >ULN (83 g/L at Part C week 48) during the study. None were considered clinically meaningful by the investigator.

Electrolyte parameters (chloride, potassium, and sodium)
Out-of-range values were observed for bicarbonate <LLN for 9/20 (45.0%) patients, and for calcium <LLN for 4/20 (20.0%) patients and >ULN for 2/20 (10.0%) patients during the study. One patient met the PCSV criteria for sodium ≤129 mEq/L (≤129 mmol/L) at the Part B week 8 visit This patient's baseline sodium value was 138 mmol/L. Sodium returned to normal at the following week 12 visit at 141 mmol/L. At the Part B EOT week 24 visit, the patient's sodium was recorded at 137 mmol/L and remained within the normal range during Part C. One patient met the PCSV criteria for potassium ≥5.5 mmol/L at the Part C week 16 visit. The patient's baseline potassium value was 4.2 mmol/L. An increased potassium value of 5.8 mmol/L was recorded only at the Part C week 16 visit. At the Part C EOT week 48 visit, the patient's potassium was recorded at 4.3 mmol/L. Both findings were not associated with a TEAE.

Renal function (creatinine, uric acid and urea nitrogen)
Three (15.0%) patients met the PCSV criteria for creatinine ≥ 30% from baseline and 1 (5.0%) patient met the PCSV criteria for urate > 6.86 mg/dL. These findings were not associated with a TEAE.

Haematology
In the pooled population, a total of 6/20 (30.0%) had decreases in hematocrit. Three (15.0%) patients had decreases from baseline in hemoglobin of ⩾2.0 g/dL (⩾20 g/L). The majority of these were minor variations. Two patients had marked variations in hematocrit and haemoglobin, these were attributed by the investigator to their lipid apheresis therapy and were not associated with a TEAE.

PCSVs were observed in leukocytes (2 patients), basophils (2 patients), neutrophils (7 patients), lymphocytes (2 patient), monocytes (7 patients), and eosinophils (1 patient). Most were transient. One patient's neutrophils decreased, this was associated with TEAEs Dermatitis contact, Rash, Hypertension, Ear pain, Pyrexia, Oropharyngeal pain, and COVID-19. All TEAEs recovered and neutrophil levels returned to normal.

Gonadal Steroid Hormones and Gonadotropins - females
In the pooled population, the following fluctuations in hormone levels occurred: At baseline, the mean (SD) estradiol level was 12.7 (6.46) pg/mL, and at week 72, the mean (SD) change from baseline in

estradiol was 26.2 (30.58) pg/mL. At baseline, the mean (SD) FSH level was 3.16 (1.972) mIU/mL, and at week 72, the mean (SD) change from baseline in FSH was 1.14 (1.621) mIU/mL. At baseline, the mean (SD) LH level was 1.621 (3.2192) mIU/mL. At week 72, the mean (SD) change from baseline in LH was 3.510 (5.3106) mIU/mL. The baseline levels and fluctuations are within the range expected for female children aged 5-11, as judged by the investigator. There were no PCSVs in hormones.

Gonadal Steroid Hormones and Gonadotropins – males

In the pooled population, the following fluctuations in hormone levels occurred: At baseline, the mean (SD) FSH level was 1.35 (1.133) mIU/mL, and at week 72, the mean (SD) change from baseline in FSH was 0.46 (0.702) mIU/mL. At baseline, the mean LH (SD) level was 1.025 (1.7678) mIU/mL, and at week 72, the mean (SD) change from baseline in LH was 0.250 (0.8231) mIU/mL. At baseline, the mean (SD) testosterone level was 0.5056 (1.02987) ng/mL, and week 72, the mean (SD) change from baseline in testosterone was 0.3710 (1.09070) ng/mL. The baseline levels and fluctuations are within the range expected for male children aged 5-11, as judged by the investigator. There were no PCSVs in hormones.

Growth and development

All patients had a ≥5% weight increase (Table 13), which is, according to the investigator, in line with growth and development expectations. PCSVs were reported in SBP 7 patients (35.0%), DBP 7 patients (35.0%), and Pulse Rate ⩽50 bpm and decrease from baseline ⩾20 bpm in 1/20 (5.0%) and Pulse Rate ⩾120 bpm and increase from baseline ⩾20 bpm in 3 patients (15.0%). The majority of these were isolated, transient, and not associated with symptoms of hypotension or tachycardia.

In 3 patients, low DBD was reported concomitantly to COVID-19, and abnormal hepatic function (2 patients)

Table 13: Vital Signs – Number (%) of Patients with Treatment-Emergent PCSV During TEAE Period – Pooled Parts B and C (SI Units) – Pooled Safety Analysis Set

Parameter Treatment-emergent PCSV Category	Part A Patients Evinacumab 15mg/Kg IV Q4W (N=6)	Part B Patients Evinacumab 15mg/Kg IV Q4W (N=14)	Total (N=20)
Systolic Blood Pressure (mmHg)			
<=95 mmHg and decrease from baseline >=20 mmHg	2 (33.3%)	5 (35.7%)	7 (35.0%)
Diastolic Blood Pressure (mmHg)			
<=45 mmHg and decrease from baseline >=10 mmHg	1 (16.7%)	6 (42.9%)	7 (35.0%)
Pulse Rate (beats/min)			
<=50 bpm and decrease from baseline >=20 bpm	0	1 (7.1%)	1 (5.0%)
>=120 bpm and increase from baseline >=20 bpm	1 (16.7%)	2 (14.3%)	3 (15.0%)
Weight (kg)			
>=5% decrease from baseline	0	1 (7.1%)	1 (5.0%)
>=5% increase from baseline	6 (100%)	14 (100%)	20 (100%)

In the pooled population, cumulative height and weight changes were assessed over time. Overall, increases in height and weight were consistent with appropriate growth and development of children 5-11 years of age, as judged by the investigator. Baseline mean (SD) height was 139.78 (13.139) cm.

Height was assessed at 24 and 48 weeks and was available in the majority of patients (13/20) at week 24. At week 24, mean height (SD) was 146.28 (11.158) cm with a mean change from baseline of 4.08 cm. Overall, the mean baseline weight was 37.93 (13.078) kg. Weight was available for all patients at week 44 and had increased to 41.76 kg with a 3.83 (2.023) kg increase from baseline. The baseline mean (SD) height-for-age z-score was 0.624 (1.1576) and in 19/20 patients at week 24 was 0.857 (1.1697), with a mean change from baseline of 0.157. In all patients, the baseline mean (SD) weight-for-age z-score was 0.665 (1.0722) and at week 44 was 0.612 (1.0668), with a mean change from baseline of -0.052.

The potential effects of evinacumab on a child's development during childhood and early adolescence were monitored via Tanner staging. In the pooled population, 12/20 (60.0%) patients were rated as Tanner Stage 1, 6/20 (30.0%) patients were rated as Tanner Stage 2, and 2/20 (10.0%) patients were rated as Tanner Stage 3. Over the course of Parts B and C, 9/20 (45.0%) patients progressed ≥1 Tanner Stage, as depicted in Table 14. According to the investigator, this change is consistent with appropriate pubertal development in children 5-11 years old.

Table 14: Overall Change from Baseline in Tanner Assessments for Pooled Data – Pooled Parts B and C – Pooled Safety Analysis Set

	Part A Patients Evinacumab 15mg/Kg IV Q4W (N=6)	Part B Patients Evinacumab 15mg/Kg IV Q4W (N=14)	Total (N=20)
Overall Tanner Stage			
Baseline			
Overall Tanner Stage			
Stage 1	4 (66.7%)	8 (57.1%)	12 (60.0%)
Stage 2	1 (16.7%)	5 (35.7%)	6 (30.0%)
Stage 3	1 (16.7%)	1 (7.1%)	2 (10.0%)
Overall Tanner Stage Overview			
Change from baseline			
No change in tanner stages	3 (50.0%)	8 (57.1%)	11 (55.0%)
Tanner Stage >= 1	3 (50.0%)	6 (42.9%)	9 (45.0%)

Immunogenicity

Out of 20 participants included in the ADA analysis set, 2 (10%) had pre-existing immunoreactivity and 1 patient (5%) developed low titer, TE ADA. No participants with a detectable ADA response developed NAb. One participant in Part B developed low titer, TE ADA against evinacumab. ADA in this participant was detected only at the end of treatment visit in Part B, and was therefore initially categorized as an indeterminate response in Part B. After continuing to Part C, this participant tested negative for ADA at all subsequent time points. Therefore, on the bases of no consecutive ADA positive samples across Parts B and C, this participant was recategorized in the overall study population as having a transient ADA response.

Table 15: Summary of ADA Status, Category, Maximum Titer Category, and NAb Status in Participants Aged 5 to 11 Years Old with HoFH (Study R1500-CL-17100, Full Study, AAS)

ADA Status/Category Max. Titer Category NAb Status	Part A n (%)	Part B n (%)	Part C n (%)	Overall n (%)
ADA				
ADA Analysis Set	6 (100%)	14 (100%)	20 (100%)	20 (100%)
Negative	5 (83.3%)	12 (85.7%)	18 (90.0%)	17 (85.0%)
Pre-existing Immunoreactivity	1 (16.7%)	1 (7.1%)	2 (10.0%)	2 (10.0%)
Treatment-Boosted Response	0	0	0	0
Treatment-Emergent Response	0	1 (7.1%)	0	1 (5.0%)
Persistent	0	0	0	0
Indeterminate	0	1 (7.1%)	0	0
Transient	0	0	0	1 (5.0%)
TE & TB Maximum Titer Category				
Low (<1,000)	0	1 (7.1%)	0	1 (5.0%)
Moderate (1,000 to 10,000)	0	0	0	0
High (>10,000)	0	0	0	0
NAb				
NAb Analysis Set	6 (100%)	14 (100%)	20 (100%)	20 (100%)
NAb Negative	6 (100%)	14 (100%)	20 (100%)	20 (100%)
NAb Positive	0	0	0	0

ADA, Anti-drug antibody; n Number of participants; TE, Treatment-emergent; TB, Treatment-boosted.
Note: Percentages are based on ADA analysis set for ADA status, subcategories, and titer categories. Sub-category for treatment-emergent ADA response were not defined in part A. Percentages are based on NAb analysis set for NAb status. ADA baseline is classified based on the ADA category at Part A/B baseline. The overall column showed ADA results throughout the study.
Source: Appendix 16.1.14 R1500-CL-17100-CP-021 Table 6

2.3.3. Discussion on clinical aspects

This application concerns the submission of the final clinical study report for Study R1500-CL-17100 in accordance with Article 46 of Regulation (EC) No 1901/2006. Study R1500-CL-17100 is an open-label designed to demonstrate the efficacy, safety, and tolerability of evinacumab in paediatric patients, aged 5 through 11 years, with HoFH.

The design and conduct of the study and results up to 24 weeks of follow-up were assessed previously and considered acceptable (EMEA/H/C/005449/II/0011).

Pharmacokinetics

Pharmacokinetic data is available for all 20 included patients. Concentrations of evinacumab were generally at steady state throughout the duration of part C. The pharmacokinetic results are consistent with previous findings from part A and part B and do not give rise to new issues with regard to the pharmacokinetics of evinacumab in the adolescent patient population with HoFH. The pharmacokinetic results of this study are in support of the dose of evinacumab 15 mg/kg IV Q4W for children from 5 to less than 12 years of age with HoFH.

Efficacy

The pooled population comprised in total 20 patients; 6 patient who participated in Part A (dose finding, single administration of study product) and Part C of the study, and 14 patients who participated in Part B and Part C of the study. All 20 patients completed the study period, which is reassuring.

LDL-C

Treatment with evinacumab resulted in a substantial reduction in the primary endpoint of mean % change from baseline in LDL-C of -44.61% (20.966) at week 48 (n=16) and -40.65% (38.723) at week 72 (n=14). The reduction in LDL-C with evinacumab were observed as early as Week 4 and sustained over the study period of Part B and C. The degree of reduction was comparable to that observed in adolescent patients evaluated in Study R1500-CL-1719 (-50.77% [27.18]) at week 72. Within the evinacumab clinical program, LDL-C is used as a surrogate biomarker for cardiovascular risk reduction, which is acceptable, based on the existing unmet need for these patients and knowing that robust evaluation of any potential cardiovascular benefit with evinacumab seems difficult to achieve due to the rarity of the disease, especially in children. The finding on LDL-C was further supported by beneficial effects in other lipid parameters (Apo B, non-HDL-C and TC). Lp(a) levels initially reduced after initiation of evinacumab, but rose during follow-up. The lower magnitude of effect on Lp(a) is likely due to 2 outliers who showed large increases in Lp(a) at certain time points in combination with the small sample size and a high intervariability. Despite the number of patients in the study is too small to make firm conclusions on comparisons of the paediatric and adult populations, both reductions in LDL-C are considered clinically relevant.

The lower magnitude of effect on several lipid parameters at week 36 and week 44 can be explained by 1) the difference in number of patients with available assessments at Week 36 and 44 (n=9) and other visits (n> 13), and 2) the non-compliance with background lipid lowering therapies by 1 patient.

Carotid intima-media thickness (cIMT) was included in this study as exploratory endpoint. Small increases in cIMT were measured. As the number of patients with cIMT measurements over time was very small, and this was a single-arm study, interpretation of these findings is limited.

The subgroups analyses indicated that the effect of evinacumab was greater in patients with high baseline LDL-C levels, patients not treated with lomitapide and in patients with receptor status negative/ defective or negative/ negative. However, the number of patients in each subgroup was limited, and in the other groups, evinacumab also showed substantial LDL-C reduction and is therefore considered beneficial in all patient groups in this study.

Safety

In the pooled population, all 20 patients (100%) experienced at least one TEAE, which was more than the adolescent patients (85.7%) in the open-label Study R1500-CL-17100 and more than the patients in the pivotal Phase 3 study R1500-CL-1629 (65.9%). However, in the majority of patients (80%) in Study R1500-CL-17100, the TEAE were judged by the investigator to be unrelated to evinacumab treatment.

Four patients (20.0%) experienced TEAEs related to evinacumab, including fatigue, abdominal pain and nausea, infusion site swelling and dermatitis contact and rash. Fatigue, abdominal pain, nausea, and infusion site reactions are known ADRs from the initial MAA dossier and the interim report of Study R1500-CL-17100.

In total 2 patients (10.0%) experienced an SAE; one of tonsilitis and the other of aortic valve stenosis. Both were considered not to be related to the study drug. The percentage of patients with a SAE was in Study R1500-CL-17100 comparable to the initial MAA dossier (9.9%) No death were reported in Study R1500-CL-17100.

HDL-C

Similar to adolescent and adult patients in Study R1500-CL-1719 , a reduction of HDL-C was reported in Study R1500-CL-17100. At week 48, mean (SD) HDL-C had reduced 38.4 (72.9)%, which is generally consistent with the reductions observed in the Adult Population (28%) and the Adolescent

Population (49%) in Study R1500-CL-1719., and with the reduction in adults population in study R1500-CL-1629 (30%). Possibly, evinacumab increases the activity of endothelial lipase responsible for the hydrolysis of HDL-C particles. However, these HoFH patients are at very high cardiovascular risk and the lowering of HDL-C by evinacumab may likely not importantly offset the potential CV benefits from substantial lowering of LDL-C in these HoFH patients. Nonetheless, special efforts are still requested to better understand the CV impact of evinacumab treatment by the conduction of the requested PASS study in light of the MAA under exceptional circumstances, in which atherogenesis over time in patients with HoFH who are treated with evinacumab will be evaluated by cardiac imaging.

AESIs

In the pooled population, 3 patients (15%) experienced an allergic reaction, which is a similar percentage to the Total Population (adolescents and adults) in Study R1500-CL-1719 (13.6%). One patient (5%) in the current study experienced infusion site swelling, which is consistent with the frequency of 7.4% in the placebo-controlled studies in the initial MAA and is already included in the SmPC as ADR.

None of the patients in Study R1500-CL-17100 experienced hepatic disorders. Some increases in liver enzymes were observed, however, the frequency was low, and none of these TEAEs were serious or resulted in discontinuation of evinacumab.

The clinical laboratory evaluation of the safety of evinacumab in the study population did not raise any new safety issues. Vital signs and growth and development of the study population was as expected in this age group and did not raise safety issues.

Immunogenicity

The evaluation of anti-drug antibodies against evinacumab did not raise any new safety issues.

3. CHMP overall conclusion and recommendation

Treatment with evinacumab resulted in a substantial and clinically meaningful reduction in LDL-C in paediatric patients aged 5 through 11 years receiving maximally tolerated lipid lowering therapy, including maximally tolerated statin, ezetimibe, PCSK9 inhibitors, lomitapide, and/or lipoprotein apheresis, whereas no new safety issues have been identified. The efficacy and safety data was limited in terms of number of patients (n=20), but, consistent with results from other studies (R1500-CL-1719, R1500-CL-1629). Overall, the results do not raise new issues regarding the efficacy and safety of evinacumab in adolescent patients with HoFH.

The results of Study R1500-CL-17100 do not alter the positive benefit-risk ratio in paediatric patients aged 5 through 11 years with HoFH.

☒ Fulfilled:

No regulatory action required.

☐ Not fulfilled:

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. In the analysis of efficacy, increased levels of LDL-C, Apo-B, non-HDL-C and TC were measured at week 36 and week 44 compared with other timepoints, that do not fit in the expected effect of evinacumab. The Applicant is requested to clarify the increases at these time points.
2. The Applicant is requested to elaborate on the finding that the decrease in Lp(a) is not maintained throughout the study and almost returned to baseline levels at week 72.

The timetable is a 30 day response timetable with clock stop.

5. MAH responses to Request for supplementary information

1. In the analysis of efficacy, increased levels of LDL-C, Apo-B, non-HDL-C and TC were measured at week 36 and week 44 compared with other timepoints, that do not fit in the expected effect of evinacumab. The Applicant is requested to clarify the increases at these time points.

Applicant Response

The MAH acknowledges the Agency's comment. The increased levels of LDL-C, Apo-B, non-HDL-C, and TC at the Week 36 and Week 44 timepoints are considered to be explained by 2 confounding factors:

1. The number of patients with available assessments at Weeks 36 and 44, n = 9, was smaller than at most other visits (n ≥ 13),

2. One patient had markedly large percentage increases in LDL-C, Apo-B, non-HDL-C, and TC parameters at these visits, and was confirmed to be noncompliant with background lipid lowering therapies.

In order to provide longer term safety follow-up and more accurate estimation of the rate for common AEs, individual data across study parts was combined into an integrated data pool, as presented in the clinical study reports [Statistical Analysis Plan Version 1.0 / February 16, 2021].

The Pooled Parts B and C data included results from Part A patients during their participation in Part C, and Part B patients during their participation in Parts B and C. The designation of new Pooled visits was created programmatically based on reference start date of Part C for Part A patients and reference start date of Part B for Part B patients. As a result of this integration, the sample sizes at Pooled Weeks 36 and 44 were smaller due to differences in protocol-scheduled visits between Part A and Part B patients. Pooled Weeks 36 and 44 visits were aligned with protocol-scheduled visits for the 6 Part A patients during their participation in Part C; however, lipid assessments were not scheduled at Pooled Weeks 36 and 44 for the 14 Part B patients. Three Part B patients experienced delays to their protocol-scheduled visits at Weeks 32 and 40, and therefore, the data from these visits were included in Pooled Weeks 36 and 44 visits programmatically. Thus, data is available from 9 patients (6 patients from Part A + 3 patients from Part B) at Weeks 36 and 44, rather than for 13 or more patients at most other visits.

As detailed in Section 5.5.4 of the First and Second Step Analysis Interim CSR (dated 16 September 2022), 1 patient was non-compliant with background lipid-modifying therapy (LMT) at all study visits in Parts B and C. It is likely that this non-compliance impacted the measured LDL-C and other lipid results for this patient. Although this patient had increases from baseline in LDL-C, Apo-B, non-HDL-C, and TC throughout the study, some of the largest increases were observed at Weeks 36 and 44, for example, 90% and 71% respectively in LDL-C (Table 16).

Table 16. Percent change from baseline in LDL-C, Apo-B, non-HDL-C and TC for

	Percent Change from Baseline (%)			
Visit	**LDL-C**	**Apo B**	**non-HDL-C**	**TC**
Baseline	3.89 mmol/L	108 mg/dL	4.2 mmol/L	5.72 mmol/L
Week 4	-4.00	1.85	-4.32	-22.17
Week 8	8.67	5.56	8.02	-9.50
Week 12	17.33	15.74	15.43	-3.62
Week 16	50.00		43.83	18.55
Week 24	56.00	41.67	50.62	20.81
Week 36	**90.00**	**57.41**	**80.86**	**42.08**
Week 44	**71.33**	**44.44**	**64.81**	**34.84**
Week 52	7.33	-8.33	3.70	-8.14
Week 56	33.33	18.52	28.40	6.33
Week 60	18.00	17.59	16.05	-4.98
Week 64	34.67	37.96	30.25	7.24
Week 68	72.67	50.00	65.43	33.94
Week 72	75.33	50.00	66.67	36.65

Asessors' comment

The Applicant has adequately clarified the lower magnitude of effect on several lipid parameters at week 36 and week 44. First, the number of patients with available assessments at Week 36 and 44 (n=9) was smaller than at most other visist (n> 13). Secondly, 1 patient had large increases in LDL-C, Apo-B, non-HDL-C, and TC parameters at these visits due to being non-compliant with background lipid lowering therapies.

Issue resolved

2. The Applicant is requested to elaborate on the finding that the decrease in Lp(a) is not maintained throughout the study and almost returned to baseline levels at week 72.

Applicant Response

The MAH acknowledges the observation that the decrease in mean percent change from baseline in Lp(a) is not maintained throughout the study and almost returned to baseline levels at Week 72.

It is considered that this is likely due to the small sample size of the study (n = 20) and the higher between-patient variability of Lp(a) compared to other lipid parameters.

In contrast to other lipoproteins analyzed as secondary endpoints within this study, Lp(a) levels exhibit remarkable interindividual variability primarily influenced by the structural gene for apo(a), which displays significant polymorphism. Large cohort studies have revealed a staggering > 100-fold variance in Lp(a) levels, particularly pronounced among populations of European descent where levels skew positively. Typically, population Lp(a) levels are expressed as median values due to their non-normal distribution (Reyes-Soffer et al., 2022). Thus, one or two outliers can have a substantial impact on the mean.

Individual patients profile plots of absolute Lp(a) and percent change from baseline in Lp(a) presented in Figure 9 and Figure 10 show the high between-patient variability observed in the study.

As shown in Figure 10, there were 2 patients who experienced larger increases in percent change from baseline after Week 44, both of whom had approximately 100% increases at Week 72 (Table 17),

which is likely to have impacted the mean at this timepoint. As shown in Table 2, one patient had a Lp(a) level below the normal threshold (< 75 nmol/L) at baseline and their Lp(a) level doubled at Week 72, although the value (36 nmol/L) remains below the normal threshold. One patient also had a normal Lp(a) level at baseline (69 nmol/L); although this patient generally experienced decreases from baseline in Lp(a), there were some increases observed after Week 44, with a particularly high increase of 97% at Week 72. As both of these patients had baseline values below the normal threshold, the observed absolute changes are not expected to be clinically meaningful. However, the large percentage changes at certain timepoints have a significant impact on the mean, considering the small sample size.

Table 17. Absolute and Percent Change from Baseline in Lp(a) for Patients

Visit	[redacted]		[redacted]	
Baseline		18 nmol/L		69 nmol/L
	Percent change from Baseline (%)	**Absolute change from Baseline (nmol/L)**	**Percent change from Baseline (%)**	**Absolute change from Baseline (nmol/L)**
Week 4	22.22	4	-55.07	-38
Week 8	61.11	11	-46.38	-32
Week 12	38.89	7	-36.23	-25
Week 24	16.67	3	-46.38	-32
Week 32	-	-	10.14	7
Week 40	61.11	11	-34.78	-24
Week 48	38.89	7	26.09	18
Week 52	100.00	18	34.78	24
Week 56	127.78	23	-4.35	-3
Week 60	66.67	12	-5.80	-4
Week 64	22.22	4	27.54	19
Week 68	33.33	6	-31.88	-22
Week 72	100.00	18	97.10	67

The sample size of this small paediatric study limits the interpretation of the long-term impact of evinacumab on Lp(a) in patients with HoFH who are 5 to < 12 years of age, due to the high impact of the 2 outliers on the mean percentage change. However, the results from the R1500-CL-1719 study in adult and adolescent patients aged 12 years and older, which had a larger sample size, suggest a positive impact of evinacumab on Lp(a) long-term. As described in the R1500-CL-1719 Final CSR (dated 29 September 2023), although some variability in results was observed, reductions in Lp(a) with evinacumab were seen from Week 8 and were generally maintained through at least Week 120.

In conclusion, while it is acknowledged that the reduction in mean percent change in Lp(a) is not maintained at the Week 72 timepoint, the MAH considers that this is likely due to the small sample size, great inter-individual variability in Lp(a), and the impact of 2 outliers observed at certain timepoints, rather than reflecting the long-term effect of evinacumab on Lp(a).

Figure 9. Individual patient profile plots of absolute Lp(a) Pool Parts B + C — Pooled Safety Analysis Set

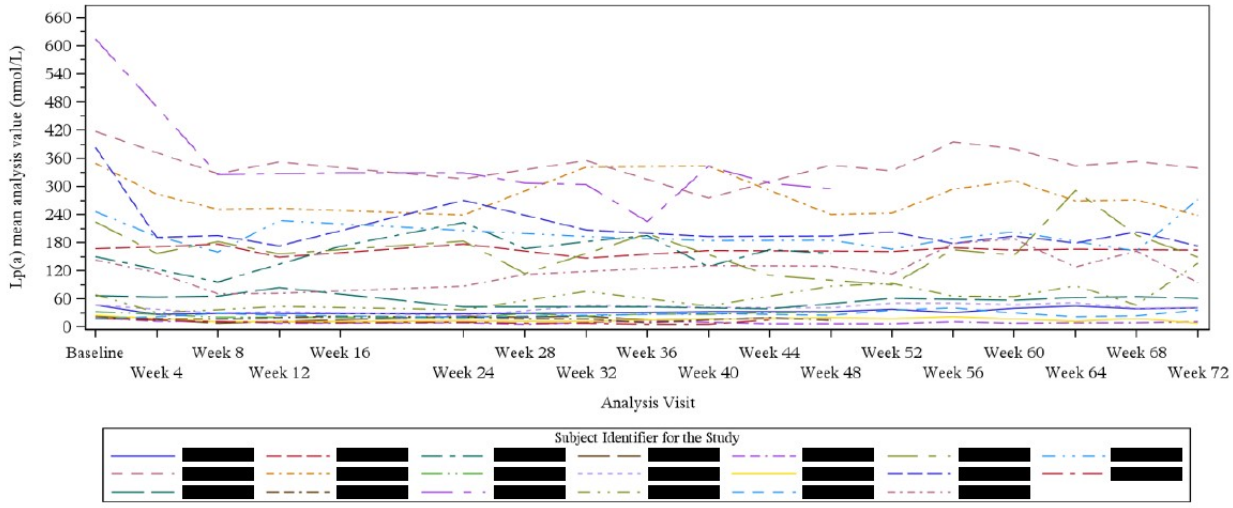
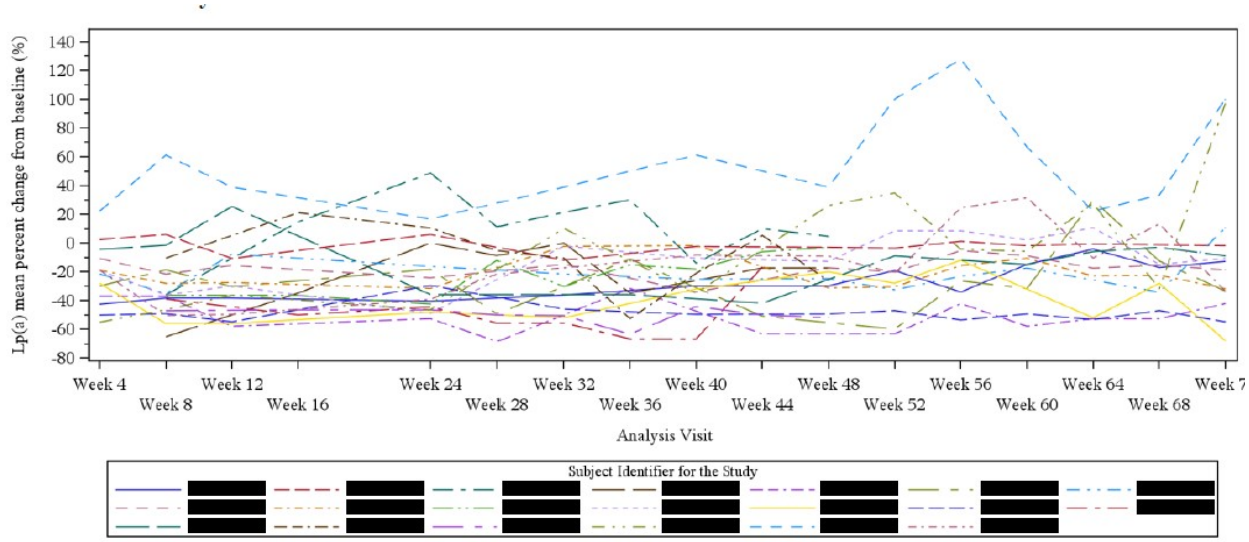


Figure 10. Individual patient profile plots of percent change from baseline in Lp(a) Pool Parts B + C — Pooled Safety



Asessors' comment

The Applicant has adequately elaborated on the observation that the decrease in Lp(a) was not maintained throughout Study R1500-CL17100. It is acknowledged that the lower magnitude of effect on Lp(a) from Week 44 till end of study is likely due to 2 outliers who showed large increases in Lp(a) at certain time points in combination with the small sample size and a high intervariability. According to the Applicant, the results from the R1500-CL-1719 study in adult and adolescent patients aged 12 years and older, which had a larger sample size, suggest a positive impact of evinacumab on Lp(a) long-term, which is reassuring although specific data on this have not been provided by the Applicant.

Issue resolved

Annex. Line listing of all the studies included in the development program

Non-clinical studies

Product Name: Evkeeza Active substance: evinacumab

Study title	Study number	Date of completion	Date of submission of final study report
A Pilot Subcutaneous or Intravenous (Slow Push) Injection Juvenile Toxicity Study of REGN1500 in Rabbits	R1500-TX-18035	03-Apr-2019	23-Jul-2020
R1500: A Subcutaneous or Intravenous (Bolus) Injection Juvenile Toxicity Study in Sprague Dawley Rats	R1500-TX-17094	04-Apr-2019	23-Jul-2020
R1500: An Intravenous (Slow Push) Injection Juvenile Toxicity Study in Rabbits	REGN1-TX-17093	18-May-2020	23-Jul-2020

Clinical Studies

Product Name: Evkeeza Active substance: evinacumab

Study title	Study number	Date of completion	Date of submission of final study report
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Evinacumab in Patients with Homozygous Familial Hypercholesterolemia	R1500-CL-1629 DBTP	LPLV: 10-Jun-2019	23-Jul-2020
An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of Evinacumab in Patients with Homozygous Familial Hypercholesterolemia	R1500-CL-1719	LPLV: 13-Apr-2023	11-Oct-2023
Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses of Evinacumab in Pediatric Patients with Homozygous Familial Hypercholesterolemia	R1500-PM-23041-SR-01V1 (R1500-CL-17100-Extrapolation)	18-Apr-2023	26-May-2023
A Three-Part, Single-Arm, Open-Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Evinacumab in Pediatric Patients with Homozygous Familial Hypercholesterolemia	R1500-CL-17100	LPLV: 30-May-2023	28-Nov-2023 Current submission