MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

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Decision Cover Letter

Decision of the licensing authority to:

accept change(s) to the agreed paediatric investigation plan and to the deferral

MHRA-100521-PIP01-22-M01

Scope of the Application

Active Substance(s)

Evinacumab

Condition(s)

Treatment of elevated cholesterol

Pharmaceutical Form(s)

Concentrate for solution for infusion

Route(s) of Administration

INTRAVENOUS

Name / Corporate name of the PIP applicant

Ultragenyx Germany GmbH

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Ultragenyx Germany GmbH submitted to the licensing authority on 25/04/2022 19:00 BST an application for a Modification

The procedure started on 05/05/2022 15:48 BST

1. The licensing authority, having assessed the application in accordance with the Human Medicines Regulations 2012, decides, as set out in the appended summary report:

to accept change(s) to the agreed paediatric investigation plan and to the deferral

2. The measures and timelines of the paediatric investigation plan are set out in the Annex I.

This decision is forwarded to the applicant, together with its annex and appendix.

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Final Decision Letter

MHRA-100521-PIP01-22-M01

Of 19/05/2022 12:35 BST

On the adopted decision for Evinacumab (MHRA-100521-PIP01-22-M01) in accordance with the Human Medicines Regulations 2012.

The licensing authority, in accordance with the Human Medicines Regulations 2012, has adopted this decision:

Agreement on modification of a paediatric investigation plan (including modification of a waiver or deferral included in that paediatric investigation plan)

This decision applies to a Modification for Evinacumab, Concentrate for solution for infusion , INTRAVENOUS .

This decision is addressed to Ultragenyx Germany GmbH, Rahel-Hirsch-Str. 10, Berlin, GERMANY, 10557

ANNEX I

1. Waiver

1.1 Condition:

Treatment of elevated cholesterol The waiver applies / applied to: Paediatric Subset(s): The paediatric population from birth to less than 5 years of age Pharmaceutical form(s): Concentrate for solution for infusion Route(s) of administration: Intravenous use Reason for granting waiver: on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible.

2. Paediatric Investigation Plan:

2.1 Condition(s):

Treatment of elevated cholesterol

2.2 Indication(s) targeted by the PIP:

Evinacumab is indicated as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of patients with homozygous familial hypercholesterolemia (HoFH), including patients with double null/negative low-density lipoprotein-receptor (LDL-R) mutations.

2.3 Subset(s) of the paediatric population concerned by the paediatric development:

The paediatric population from 5 years to less than 18 years of age

2.4 Pharmaceutical Form(s):

Concentrate for solution for infusion

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	0	Not applicable
Non-Clinical Studies	3	Study 1 (R1500-TX-18035) Dose range-finding juvenile toxicity study to inform dose selection for Study 2. Study 2 (REGN1-TX-17093) A 17-Week Intravenous Study in Juvenile Rabbits with a 31-week Recovery Period. Study 3 (R1500-TX-17094) Intravenous and Subcutaneous Toxicology Study in Juvenile Rats.
Clinical Studies	3	Study 4 (R1500-CL-1629) Double-blind, randomised, placebo controlled trial of 24 weeks to evaluate safety and efficacy of Evinacumab as add-on to lipid modifying therapies (LMT) in children from 12 years to less than 18 years of age (and adults) with insufficiently controlled homozygous familial hypercholesterolaemia (HoFH) on stable LMT, followed by a 24 week open label treatment period to evaluate safety and a 24-week follow-up period after the last dose of study drug for those patients who choose not to enter the open-label long term safety study (Study 6). Study 5 (R1500-CL-17100) A three-part, single arm, open-label trial to evaluate pharmacokinetics, safety and activity of Evinacumab in children from 5 years to less than 12 years of age with HoHF. Study

		6 (R1500-CL-1719) Open-label, long term trial to evaluate safety and activity of Evinacumab in children from 12 years to less than 18 years of age (and adults) with HoFH following completion of Study 4 or are evinacumab naïve and directly enrolled into this study.
Extrapolation, Modeling & Simulation Studies	1	Study 7 (R1500-CL-17100-Extrapolation) Extrapolation study to evaluate the use of Evinacumab in the proposed paediatric indication in children from 5 to less than 12 years of age with HoFF.
Other Studies	0	Not applicable
Other Measures	0	Not applicable

3. Follow-up, completion and deferral of a PIP:

Concerns on potential long term safety and efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	31/05/2024
Deferral of one or more studies contained in the paediatric investigation plan:	Yes