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

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Decision Cover Letter

Decision of the licensing authority to:

agree a paediatric investigation plan and grant a deferral and grant a waiver

MHRA-100317-PIP01-21

Scope of the Application

Active Substance(s)

Ralinepag

Condition(s)

Treatment of pulmonary arterial hypertension

Pharmaceutical Form(s)

Age-appropriate oral solid dosage form; Age-appropriate oral liquid dosage form

Route(s) of Administration

Oral use, Enteral use

Name / Corporate name of the PIP applicant

United Therapeutics Corporation

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, United Therapeutics Corporation submitted to the licensing authority on 25/03/2022 20:41 GMT an application for a Paediatric Investigation Plan

The procedure started on 31/08/2022 08:08 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 agree a paediatric investigation plan and grant a deferral and grant a waiver

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-100317-PIP01-21

Of 13/10/2022 14:33 BST

On the adopted decision for Ralinepag (MHRA-100317-PIP01-21) 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 a paediatric investigation plan

This decision applies to a Paediatric Investigation Plan for Ralinepag , Age-appropriate oral solid dosage form; Age-appropriate oral liquid dosage form , Oral use, Enteral use .

This decision is addressed to United Therapeutics Corporation , 55 TW Alexander Drive, Research Triangle Park, United States, 27709

ANNEX I

1. Waiver

1.1 Condition:

Treatment of pulmonary arterial hypertension The waiver applies / applied to: Paediatric Subset(s): The paediatric population from birth to less than 1 year of age Pharmaceutical form(s): Age-appropriate oral solid dosage form; Age-appropriate oral liquid dosage form Route(s) of administration: Oral use; Enteral use Reason for granting waiver: on the grounds that the specific medicinal product is likely to be unsafe.

2. Paediatric Investigation Plan:

2.1 Condition(s):

Treatment of pulmonary arterial hypertension

2.2 Indication(s) targeted by the PIP:

Treatment of World Health Organization (WHO) Group I pulmonary arterial hypertension (PAH) to improve exercise capacity and to delay clinical worsening in children from 1 years to less than 18 years of age.

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

The paediatric population from 1 years to less than 18 years of age

2.4 Pharmaceutical Form(s):

Age-appropriate oral solid dosage form; Age-appropriate oral liquid dosage form

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	2	Study 1 (ADP811-FD01) Development of an age-appropriate oral solid dosage form. Study 2 (ADP811-FD02) Development of an age-appropriate oral liquid dosage form.
Non-Clinical Studies	2	Study 3 (APD811- JAS01) Juvenile dose-finding toxicity study in rats. Study 4 (APD811- JAS02) Juvenile toxicity study in rats.
Clinical Studies	1	Study 5 (ROR-PH-201) Open-label, single-arm study to investigate the pharmacokinetics (PK), safety, tolerability, and pharmacodynamics (PD) of ralinepag in paediatric patients from 1 year to 18 years of age with pulmonary arterial hypertension (PAH).
Extrapolation, Modeling & Simulation Studies	2	Study 6 (ROR-PH-201-MS) Population PK/PD analysis to determine paediatric dosing and support extrapolation of efficacy for ralinepag from adults to children from 1 year to less than 18 years. Study 7 (ROR-PH-201-EX) Analysis of existing in-house and literature data on exposure-response relationships of ralinepag and compounds with a similar mode of action for the treatment of PAH to support extrapolation of efficacy from adults to paediatric patients from 1 years to less than 18 years of age with PAH.

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:	No
Date of completion of the paediatric investigation plan:	30/06/2026
Deferral of one or more studies contained in the paediatric investigation plan:	Yes