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-100471-PIP01-22-M01

Scope of the Application

Active Substance(s)

SETMELANOTIDE

Condition(s)

Treatment of appetite and general nutrition disorders

Pharmaceutical Form(s)

Solution for injection

Route(s) of Administration

SUBCUTANEOUS USE

Name / Corporate name of the PIP applicant

Rhythm Pharmaceuticals, Inc.

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Rhythm Pharmaceuticals, Inc. submitted to the licensing authority on 18/03/2022 16:19 GMT an application for a

The procedure started on 10/10/2022 12:16 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-100471-PIP01-22-M01

Of 08/11/2022 17:08 GMT

On the adopted decision for SETMELANOTIDE (MHRA-100471-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 for SETMELANOTIDE, Solution for injection , SUBCUTANEOUS USE .

This decision is addressed to Rhythm Pharmaceuticals, Inc., 222 Berkeley Street, 12th Floor, Boston, UNITED STATES OF AMERICA, MA 02116

ANNEX I

1. Waiver

1.1 Condition:

Treatment of appetite and general nutrition disorders The waiver applies / applied to: Paediatric Subset(s): The paediatric population from birth to less than 2 years of age Pharmaceutical form(s): Solution for injection Route(s) of administration: SUBCUTANEOUS USE Reason for granting waiver: on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

2. Paediatric Investigation Plan:

2.1 Condition(s):

Treatment of appetite and general nutrition disorders

2.2 Indication(s) targeted by the PIP:

Treatment of obesity and/or hyperphagia associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway

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

The paediatric population from 2 years to less than 18 years of age

2.4 Pharmaceutical Form(s):

Solution for injection

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	2	Study 1 Development of a formulation which does not contain DSPE/mPEG and which has a dose interval longer than 1 day (ideally 1 week). Study 2 Development of a device capable of accurate and reproducible delivery of the lowest dosing volume required.
Non-Clinical Studies	2	Study 3 (RM-493-TOX-023 and RM-493-TOX-024) Evaluation of mPEG-DSPE in rat and monkey brain from chronic toxicity studies by immunohistochemistry. The objective is to determine localisation of mPEG-DSPE in rat and monkey brain. Study 4 Evaluation of the absorption, distribution, metabolism and elimination of mPEG-DSPE in rat using 14C-mPEG-DSPE (labelled on mPEG only).
Clinical Studies	4	Study 5 (RM-493-012) Open-label, 1-year study to evaluate the pharmacokinetics, safety and efficacy of setmelanotide in children from 6 years to less than 18 years of age (and in adults) with Proopiomelanocortin (POMC) deficiency obesity. Study 6 (RM-493-014) Open-label, uncontrolled, 3-months study, to evaluate the pharmacokinetics, safety and efficacy of setmelanotide in

		children from 6 years to less than 18 years of age (and in adults) with rare genetic disorders of obesity. Study 7 (Study RM-493-015) Open-label, 1-year study to evaluate the pharmacokinetics, safety and efficacy of setmelanotide in children from 6 years to less than 18 years of age (and in adults) with leptin receptor (LEPR) deficiency obesity. Study 8 (RM-493-033) Added during procedure MHRA-100471-PIP01-22-M01. Open label, non-comparative study to assess the safety and activity of setmelanotide in obese children with Proopiomelanocortin (POMC) deficiency, prohormone convertase 1 (PCSK1) deficiency or leptin receptor (LEPR) deficiency and Bardet-Biedl syndrome, from 2 years to less than 6 years of age.
Extrapolation, Modeling & Simulation Studies	0	Not applicable
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:	31/12/2024
Deferral of one or more studies contained in the paediatric investigation plan:	Yes