MHRA
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Canary Wharf
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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-M03

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 05/08/2025 14:47 BST an application for a Modification

The procedure started on 17/09/2025 15:12 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-M03

Of 10/10/2025 10:09 BST

On the adopted decision for SETMELANOTIDE (MHRA-100471-PIP01-22-M03) 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 SETMELANOTIDE, Solution for injection , SUBCUTANEOUS USE .

This decision is addressed to Rhythm Pharmaceuticals, Inc, 222 Berkeley Street, Boston, UNITED STATES OF AMERICA, MA02116

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. Pharmaceutical form(s): Solution for injection Route(s) of administration: SUBCUTANEOUS USE Reason for granting waiver: On the grounds 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	1	Study 1 This study was deleted during procedure MHRA-100471-PIP01-22-M03. 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	6	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) (This study was added during procedure MHRA-100471-PIP01-22-M01) 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	Clinical Studies continued: Study 9 (RM-493-035) (This study was added during procedure MHRA-100471-PIP01-22-M03) Randomised, double-blind, placebo-controlled study to assess the efficacy and safety of setmelanotide in patients with heterozygous gene variant in the POMC gene or PCSK1 gene, heterozygous gene variant in the LEPR gene, homozygous, heterozygous, or compound heterozygous variant in the NCOA1 (SRC1) gene, or homozygous, heterozygous, or compound heterozygous variant in the SH2B1 gene, or chromosomal 16p11.2 deletion encompassing the SH2B1 gene in children from 6 years of age to less than 18 years of age (and in adults). Study 10 (This study was added during procedure MHRA-100471-PIP01-22-M03) Open-label study to assess the safety and activity of setmelanotide in obese children with heterozygous gene variant in the POMC gene

		or PCSK1 gene, heterozygous gene variant in the LEPR gene, homozygous, heterozygous, or compound heterozygous variant in the NCOA1 (SRC1) gene, or homozygous, heterozygous, or compound heterozygous variant in the SH2B1 gene, or chromosomal 16p11.2 deletion encompassing the SH2B1 gene from 2 years to less than 6 years of age.

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:	31/12/2030
Deferral of one or more studies contained in the paediatric investigation plan:	Yes