EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 March 2026
EMADOC-1700519818-3004862
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: IMCIVREE

International non-proprietary name: Setmelanotide

Procedure No. EMA/VR/0000288021

Note

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

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List of abbreviations

Abbreviation	Definition
α	Alpha
ABPM	Ambulatory blood pressure monitoring
ADA	Anti-drug antibody
AgRP	Agouti-related peptide
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARC	Arcuate nucleus
AS	Alström Syndrome
AST	Aspartate aminotransferase
AU	Australia
AUCtau	Area under the concentration-time curve from time over the dosing interval
BBS	Bardet Biedl syndrome
BE	Belgium
BMI	Body mass index
BP	Blood pressure
BTD	Breakthrough therapy designation
CA	Canada
CeA	Central amygdala nucleus
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Apparent oral clearance
Cmax	Maximum concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CPHD	Combined pituitary hormone deficiency

CSR	Clinical study report
Ctrough	Trough concentration
CV	Coefficient of variation
CYP	Cytochrome P450
DE	Germany
DMH	Dorsomedical nucleus of the hypothalamus
DMV	Dorsal motor vagal nucleus
ECHO	The Energy Balance and Weight Loss in Craniopharyngioma-related or Other Hypothalamic Tumours in Hypothalamic Obesity trial
ECL	Electrochemiluminescence
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	End of treatment
ES	Spain
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FR	France
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP-1	Glucagon-like peptide receptor 1
GR	Greece
HDL	High-density lipoprotein
HO	Hypothalamic obesity
HR	Heart rate
IL	Israel
iPSP	Initial Paediatric Study Plan
ISI	Integrated Summary of Immunogenicity
ISR	Injection site reaction

ISS	Integrated Summary of Safety
IV	Intravenous
IWQOL-Kids	Impact of Weight on Quality of Life-Lite (11 to <18 year old)
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite Clinical Trial (≥18 years old
JP	Japan
LD	Lipodystrophy
LDL	low-density lipoprotein
LEPR	Leptin receptor
LHA	Lateral hypothalamus area
LOCF	Last observation carried forward
LSM	Least squares mean
LTE	Long-term extension
MC	Melanocortin
MC4	Melanocortin 4
MC4R	Melanocortin 4 receptor
MeA	Medial amygdala
Mes5	Mesencephalic trigeminal nucleus
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Multiple imputation
mITT	Modified intent-to-treat
mPEG-DSPE	N-(carbonyl-methoxypolyethylene glycol 2000)-1, 2-distearoyl-glycerol-3-phosphoethanolamine sodium salt
MPHD	Multiple pituitary hormone deficiency
MPO	Medical preoptic nucleus
MRI	Magnetic resonance imaging
MSH	Melanocyte stimulating hormone
MWPC	Meaningful within-person/patient change
NCOA1	Nuclear receptor coactivator 1
NIH	National Institutes of Health

NL	Netherlands
NTS	Nucleus of the solitary tract
ODD	Orphan Drug Designation
ONH	Optic nerve hypoplasia
OOPD	Office of Orphan Product Development
PCSK1	Proprotein convertase subtilisin/kexin type 1
PD	Pharmacodynamic
PK	Pharmacokinetic
POMC	Pro opiomelanocortin
PPL	POMC, LEPR, and PCSK1 deficiency (collectively)
PREA	Paediatric Research Equity Act
PSIS	Pituitary stalk interruption syndrome
PVH	Paraventricular hypothalamic nucleus
QD	Once daily
RCh	Retrochiasmatic area
RGDO	Rare Genetic Disease of Obesity
RH	Relative humidity
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SmPC	Summary of product characteristics
SMS	Smith-Magenis syndrome
sNDA	Supplemental New Drug Application
SOC	System organ class
SOD	Septo-optic dysplasia
SRC1	Steroid receptor coactivator 1
t1/2	Apparent terminal elimination half-life
TEAE	Treatment emergent adverse event

Tmax	Time to maximum concentration
UK	United Kingdom
US	United States
USPI	United States Prescribing Information
USPSTF	United States Preventive Services Task Force
VMH	Ventromedial hypothalamic nucleus
VTA	Ventral tegmental area
Vz/F	Apparent volume of distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Rhythm Pharmaceuticals Netherlands B.V. submitted to the European Medicines Agency on 24 July 2025 an application for a variation.

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include reduction in hunger (or hyperphagia) and BMI (Body Mass Index)/BMI z-score, improvement of metabolic parameters, and increase in energy expenditure in adults and children 4 years of age and above, following rapid and severe weight gain associated with hypothalamic injury and/or impairment for IMCIVREE, based on results from study RM-493-040 as well as supportive study RM-493-030. RM-493-040 is a phase 3, double blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of setmelanotide in patients with acquired hypothalamic obesity, while RM-493-030 is a phase 2, open-label 20-week study to evaluate the safety and efficacy of setmelanotide in subjects with hypothalamic obesity. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated. The Package Leaflet is updated accordingly. The RMP version 3.0 has also been submitted. In addition, the MAH took the opportunity to introduce editorial and administrative changes to the PI.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

IMCIVREE, was designated as an orphan medicinal product EU/3/23/2833 on 13 October 2023. IMCIVREE was designated as an orphan medicinal product in the following indication: Treatment of acquired hypothalamic obesity.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (EMA/PE/0000245434 – 06/05/2025) on the agreement of changes to the agreed paediatric investigation plan and to the deferral.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH received Protocol Assistance from the CHMP on 15/12/2022 (EMA/SA/0000104704). The Protocol Assistance pertained to the clinical aspects and in relation to paediatric development of the dossier. See section 2.3.1.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Karin Janssen van Doorn Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	24 July 2025
Start of procedure:	16 August 2025
CHMP Rapporteur's preliminary assessment report circulated on:	10 October 2025
PRAC Rapporteur's preliminary assessment report circulated on:	17 October 2025
PRAC RMP advice and assessment overview adopted by PRAC	30 October 2025
CHMP Rapporteur's updated assessment report circulated on:	6 November 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	13 November 2025
MAH's responses submitted to the CHMP on:	18 December 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	27 January 2026
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	30 January 2026
PRAC RMP advice and assessment overview adopted by PRAC	12 February 2026
CHMP Rapporteur's updated assessment report circulated on:	19 February 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 February 2026

Timetable	Actual dates
MAH's responses submitted to the CHMP on:	3 March 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	11 March 2026
CHMP Rapporteur's updated assessment report circulated on:	19 March 2026
CHMP opinion:	26 March 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Hypothalamic obesity is a devastating disease in which patients experience rapid, severe, and intractable weight gain and hyperphagia associated with hypothalamic injury and/or dysfunction. Acquired HO affects approximately 5,000 to 10,000 patients in the US and is believed to have similar incidence and prevalence in the EU and rest of world.

Acquired HO develops after injury to the hypothalamus, most often as a result of a tumor (e.g., craniopharyngiomas, gliomas, pituitary adenomas, hamartomas), and/or the surgery or radiation therapy used to treat the tumor. Other rarer causes of injury may include inflammatory conditions involving the hypothalamus such as sarcoidosis or traumatic brain injury. Craniopharyngiomas currently represent the most common tumor associated with the development of acquired HO and account for 5% to 15% of paediatric intracranial tumors, and occur with 2 peaks of incidence, one during childhood (10 to 19 years of age [29%]) and the second in adulthood (30 to 49 years of age [25%]). In other disorders which may involve the hypothalamus, a subset of patients develop obesity which is hypothesized to be due to developmental abnormalities of the hypothalamus. These disorders include septo-optic dysplasia (SOD), optic nerve hypoplasia (ONH), childhood-onset combined pituitary hormone deficiency (CPHD) also called multiple pituitary hormone deficiency (MPHD) and pituitary stalk interruption syndrome (PSIS). Patients with these disorders often have a variable degree of endocrinopathies due to pituitary and or hypothalamic developmental abnormalities that may significantly impact growth, development, and survival.

Regardless of the underlying cause, patients with HO develop an aggressive form of obesity characterized by a high degree of sudden, severe, and sustained weight gain that has generally been unresponsive to lifestyle or medical intervention.

The weight gain in patients with HO is most dramatic in the first 6 to 12 months after injury and then continues for the next 8 to 12 years before plateauing. Hyperphagia may occur in approximately 50%

to 70% of patients along with lethargy due to decreased energy expenditure, and psychosocial disorders spanning from depression to aggressive behaviour are common. There is currently no approved effective treatment for HO.

Claimed therapeutic indication

At initial submission, the MAH proposed the wording of the new therapeutic indication as follows:

IMCIVREE is indicated for reduction in hunger (or hyperphagia) and BMI/BMI z-score, improvement of metabolic parameters, and increase in energy expenditure in adults and children 4 years of age and above, following rapid and severe weight gain associated with hypothalamic injury and/or impairment.

During the procedure, the MAH revised the proposed wording of the new therapeutic indication as follows:

IMCIVREE is indicated for the treatment of obesity and the control of hunger in adults and children 4 years of age and above with acquired hypothalamic obesity (aHO) due to hypothalamic injury or impairment.

2.1.2. About the product

Setmelanotide is a MC4R agonist that retains the specificity and functionality of the naturally occurring POMC-derived neuropeptide, α-melanocyte stimulating hormone (α-MSH), which is the endogenous ligand for the MC4R. Setmelanotide is more potent and has a much longer half- life (~10-12 hours in humans) than the short-lived α-MSH ligand.

The melanocortins (MC) are a family of peptide hormones (including adrenocorticotropin hormone [ACTH], α-MSH, β-MSH, and γ-MSH) that are all derived from the common precursor, POMC. The MCs regulate energy homeostasis and body weight.

The MC4R has been identified as the dominant MC receptor involved in regulation of body weight, hunger, and energy homeostasis. Setmelanotide has the potential to restore lost activity in the MC4R pathway by bypassing the defects upstream of the MC4R and directly activating MC4 neurons in the hypothalamus downstream of such defects (Figure). Thus, setmelanotide bypasses the upstream defects in this critical MC4R signalling pathway to re-establish weight and appetite control in patients with genetic, syndromic, and acquired diseases of obesity involving this pathway.

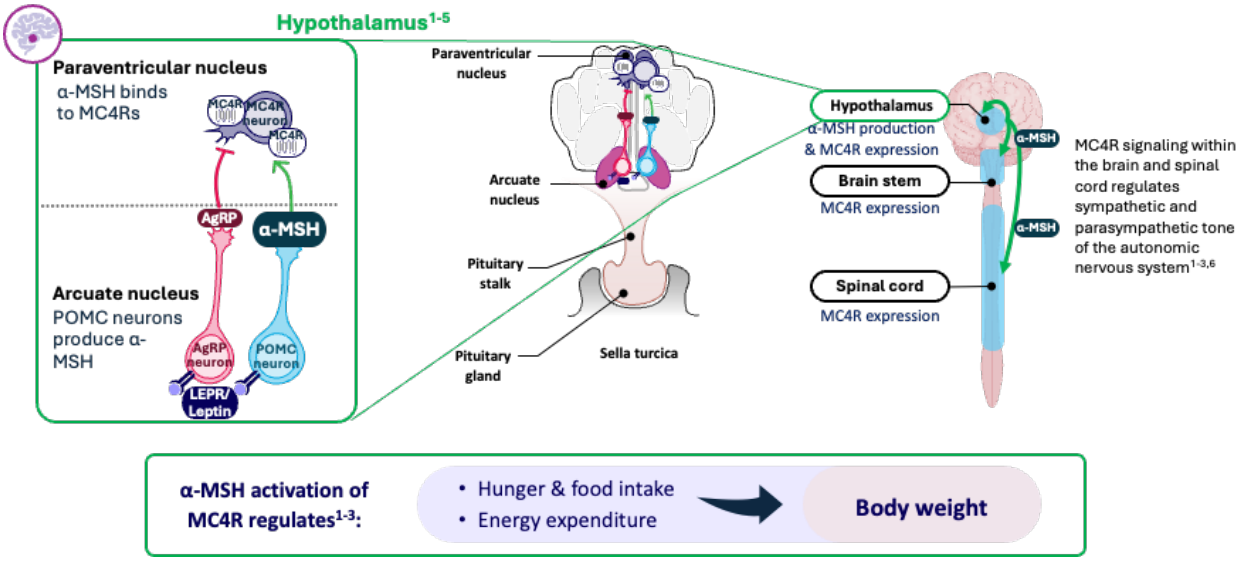


Figure 1: α-MSH Drives MC4R Pathway Signaling to Regulate Energy Balance and Body Weight

Abbreviations: α-MSH = α–melanocyte-stimulating hormone; AgRP = agouti-related peptide; LEPR = leptin receptor; MC4R = melanocortin-4 receptor; POMC = proopiomelanocortin.

1. Baldini 2019; 2. Dimitri 2022; 3. Hill 2017; Hochberg 2010; 5. Roth 2011b; 6. Sohn 2013.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH received Protocol Assistance on the development of Setmelanotide for the Treatment of obesity and acquired defects in the MC4 pathway due to injury to the hypothalamus from the CHMP on15/12/2022 (EMA/SA/0000104704). The Protocol Assistance pertained to the following Clinical aspects:

• the proposed patient population; the proposed Phase 3 study, if positive, could support submission of a Type II Variation for this patient population; the inclusion of these younger patients (aged 4 to <6 years) and the dosing regimen proposed for patients aged 4 to <12years; this approach to support the key secondary endpoint pertaining to the reduction of hunger in patients ≥12 years of age: If the trial results pertaining to "most hunger" are positive in patients aged ≥12 years, consistent with prior indications;

• the inclusion of these younger patients (aged 4 to <6 years) and the dosing regimen proposed for patients aged 4 to <12 years; the proposed plan to better define PK in HO patients;• the Phase 2 data from Study RM-493-030 demonstrating a positive benefit-risk balance combined with the established safety profile of setmelanotide and the plan for generating comprehensive post-approval evidence via the proposed placebo-controlled trial, are adequate to support a Type II Variation for the use of setmelanotide in the described patient population with hypothalamic obesity.

2.1.4. General comments on compliance with GCP

See section 2.2.3.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP. An updated environmental risk assessment has been submitted.

2.2.1. Ecotoxicity/environmental risk assessment

Setmelanotide has a log Kow (logD) below 4.5. Therefore, a definitive assessment of setmelanotide for PBT/vPvB is not necessary.

Calculation of the Predicted Environmental Concentration (PEC) was derived using the refined Fpen values (0.00008) for Bardet-Biedl syndrome (BBS), loss-of-function biallelic proopiomelanocortin (POMC), including PCSK1, deficiency and biallelic leptin receptor (LEPR) deficiency and for the proposed new indication.

The combined PECSURFACEWATER for setmelanotide from the use of IMCIVREE 10 mg/mL solution for injection for all indications has been calculated to be 0.00012 µg/L, that is 83 times lower than the Phase I action limit of 0.01 µg/L. Overall, the preclinical safety data reveal no special hazards for the environment from the active substance, setmelanotide.

IMCIVREE 10 mg/mL solution for Injection contains 10 mg/mL setmelanotide and 100 mg/mL mPEG-DSPE. Since the combined Phase I PECSURFACEWATER for setmelanotide has been calculated to be 0.00012 µg/L, the PECSURFACEWATER for mPEG-2000-DSPE is 0.0012 µg/L and this is 8 times lower than the action limit used for active substances.

Furthermore, PK, mass balance, and tissue distribution studies, as well as toxicity studies done with mPEG-2000-DSPE did not reveal potential for accumulation or adverse effects.

Those data indicated that mPEG-2000-DSPE use as an excipient in IMCIVREE 10 mg/mL solution does not present any environmental risk.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of setmelanotide.

2.2.3. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID	Phase	Country	Study Title	Study Population	Status
Pivotal					
RM-493-040	3	CA, DE, NL, UK, US, JP	A Phase 3, Double Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Setmelanotide in Patients with Acquired Hypothalamic Obesity	Patients with acquired hypothalamic obesity	Ongoing
Confirmatory					
RM-493-030	2	US	A Phase 2, Open-Label 20-Week Study to Evaluate the Safety and Efficacy of Setmelanotide in Subjects with Hypothalamic Obesity	Patients with acquired hypothalamic obesity aged 6-40 years.	Completed
RM-493-022	N/A (Ext. Study)	Global	Long-term Extension Trial of Setmelanotide (RM-493) for Patients Who Have Completed a Trial of Setmelanotide for the Treatment of Obesity Associated with Genetic Defects Upstream of the MC4 Receptor in the Leptin-Melanocortin Pathway	Obesity associated with genetic defects upstream of the MC4R in the leptin melanocortin pathway	Completed
RM-493-042	N/A (Ext. Study)	Global	Open-Label Extension Study of Setmelanotide in Patients with a Rare Genetic, Syndromic or Acquired Disease of the MC4R Pathway	Patients with a rare genetic, syndromic, or acquired disease of the MC4R pathway	Ongoing

2.2.4. Pharmacokinetics

The pharmacokinetics (PK) of setmelanotide have previously been characterised in healthy subjects and patients with rare diseases of obesity in multiple clinical studies.

This application adds PK data from two recent clinical studies (Studies RM-493-022 and RM-493-040) conducted in patients with hypothalamic obesity (HO). The approved commercially available subcutaneous (SC) setmelanotide formulation was used in both clinical studies.

A previously developed setmelanotide population PK model (RPI0104F) was updated with new data from patients with HO ranging from 4 years of age to adult (≥18 years of age).

Study RM-493-040

The pivotal study RM-493-040 assessed setmelanotide doses in HO patients 4 years old and older. SC Setmelanotide 0.5 mg QD or placebo equivalent was administered as the starting dose for all patients. After the initial dose, patients´ daily doses were escalated each week in increments of either 0.5 or 1.0 mg to achieve the individual patient's therapeutic regimen detailed in the dosing scheme based on the patient's age and weight.

Predose trough concentrations were obtained at multiple study visits (week 1, week 12, week 24, end of treatment (after 52 weeks on a therapeutic regimen)) for assessment of drug exposure upon long-term multiple dosing. A modest increase in Ctrough was observed over week 12 and week 24 across all age groups (<12 years, ≥12 to <18 years, and ≥18 years) suggesting slight accumulation of setmelanotide following multiple dosing. Ctrough values at each dose level were broadly similar between Japanese (n=12) and non-Japanese patients.

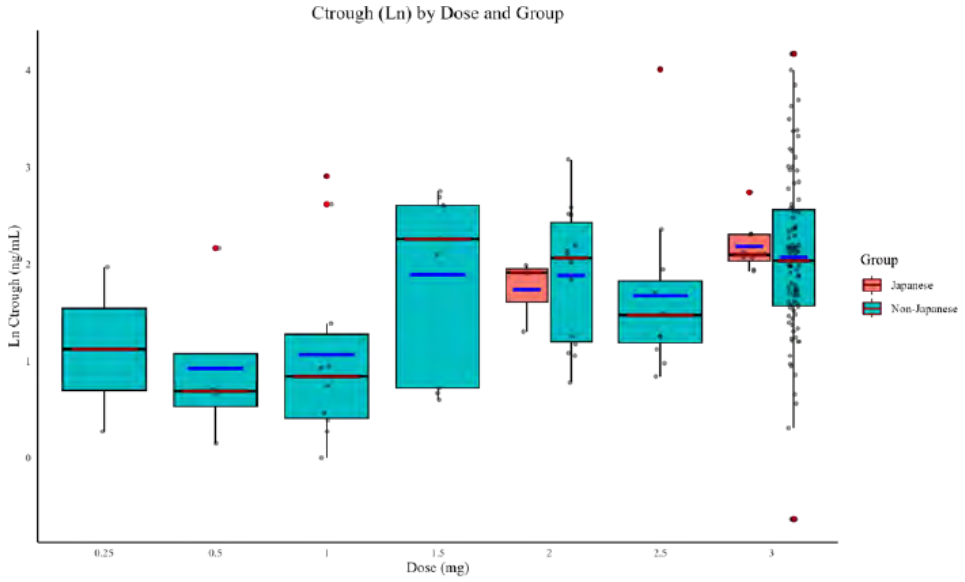


Figure 2. Boxplots of Ctrough vs Dose for Japanese and Non-Japanese Patients
(Median and mean values are presented by red and blue lines, respectively. All visits pooled by dose level)

In addition, non-compartmental PK analysis was performed on the subset of patients from Japan. In this subset, PK samples were collected pre-dose and at several time points (up to 24h) post-dose at week 1 and after 4 weeks on a therapeutic dose.

Table 1. Summary of PK Parameters in Japanese Patients by Treatment and Visit

Race	Dose (mg)	Age Group	Visit	Statistics	AUClast (h*ng/mL)	Cmax (ng/mL)	Tmax (h)	Clast (ng/mL)	Tlast (h)
Japanese	0.50	>= 18 Years	1	N	8	8	8	8	8
				Mean	71.5	6.80	5.79	1.57	18.9
				SD	19.2	1.49	2.28	0.603	5.67
				CV%	26.8	22.0	39.4	38.5	30.1
				Min	39.9	5.06	1.97	1.05	11.8
				Median	73.7	6.87	5.73	1.29	22.4
				Max	96.1	9.58	9.50	2.56	23.4
				Geometric Mean	69.0	6.66	NC	1.47	NC
Japanese	3.00	>= 18 Years	5	N	1	1	1	1	1
				Mean	352	39.4	5.93	22.9	11.5

Study RM-493-022

Patients who completed treatment in a previous trial (index trial) of setmelanotide and wished to continue with setmelanotide treatment were considered for eligibility to enter this long-term extension trial. Patients began this extension trial on the same dose of setmelanotide that they were taking

when they completed their index trial. Setmelanotide plasma PK was assessed in all patients for trough (pre-dose) concentrations measured prior to dose administration in the clinic.

For the subset of HO patients on a stable dose (4 consecutive weeks at the same dose level) of setmelanotide participating at selected trial centers in the US, additional blood samples for non-compartmental PK analysis were collected at the following times: pre-dose and at 1, 2, 4, 6, 8, 10, and 12 hours post-dose for assessment of PK in this patient population. At a minimum, samples were to be collected at 1, 2, 4, 6, and 12 hours post-dose.

The geometric mean AUClast, AUCinf, and Cmax was 340 h*ng/mL, 448 h*ng/mL, and 35.7 ng/mL, respectively. These values compare favorably to those found in healthy obese subjects wherein the mean steady state Cmax and area under the concentration - time curve from time over the dosing interval (AUCtau) for 3.0 mg QD was 37.9 ng/mL and 495 h*ng/mL, respectively.

Table 2. Summary of Pharmacokinetic Parameters by Treatment and Visit for HO Substudy Patients (PK Parameter Population)

Visit	Dose (mg)	Statistic	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	C_{last} (ng/mL)	T_{last} (h)	$T_{½}$ (h)
HO PK Sub-Study	3.00	N	7*	3**	8	8	8	8	3**
		Mean	365	534	42.9	5.25	22.2	10.8	6.47
		SD	129	316	23.7	2.82	10.6	3.54	2.54
		CV%	35.4	59.2	55.4	53.6	47.5	32.9	39.3
		Min	146	181	9.01	2.00	6.25	2.00	3.87
		Median	398	631	45.4	5.00	22.4	12.0	6.58
		Max	549	790	85.8	10.0	38.3	12.0	8.95
		Geometric Mean	340	448	35.7	NC	19.3	NC	6.11

N: Number of observations; SD: Standard Deviation; CV%: Coefficient of Variation; Min: Minimum, Max: Maximum; NC = Not calculated; HO: Hypothalamic obesity

*AUC_{last} was excluded from descriptive statistics for Subject 44-001 since only 0 to 2 hours samples were available

**If λ_z cannot be measured (e.g.: fewer than 3 non-zero concentrations in the terminal elimination phase or Rsq adjusted < 0.8), the PK parameters derived from λ_z were not included in the summary statistics and half-life was not calculated.

2.2.5. PK/PD modelling

The setmelanotide population PK analysis (RPI0105), which built on a prior analysis (RPI0104F), used an expanded dataset. In total, the analysis dataset included 513 subjects pooled from 12 clinical studies: 330 subjects with RGDO, 102 subjects with HO, and 81 subjects with neither RGDO nor HO. The PK data were predominantly from 314 adults (≥18 years old) and 122 adolescents (12 to <18 years old). The dataset also included 64 children 6 to <12 years old and 13 children <6 years old. All data in subjects with moderate or severe renal impairment came from adults plus one subject in the 12 to <18 years age group. No subjects in the youngest age groups (<4 and 4 to <6 years) had renal impairment.

		Number		Percent	
	SUBJ	OBS	BLQ	OBS	BLQ
Patient population					
RGDO	330	6329	224	71.6	2.5
HO	102	424	30	4.8	0.3
non-RGDO/non-HO	81	1748	82	19.8	0.9
Age group (years)					
<4	5	45	4	0.5	0.0
4 to <6	8	88	0	1.0	0.0
6 to <12	64	778	25	8.8	0.3
12 to <18	122	2258	80	25.6	0.9
18+	314	5332	227	60.3	2.6
Renal function					
Normal	391	6305	240	71.3	2.7
Mild impairment	95	1719	67	19.5	0.8
Moderate impairment	19	347	16	3.9	0.2
Severe impairment	8	130	13	1.5	0.1
All data	513	8501	336	96.2	3.8

HO: acquired hypothalamic obesity; RGDO: rare genetic diseases of obesity

Setmelanotide PK was well described by a one-compartment model with zero-order input, the same compartmental structure used in the previous analysis. Also consistent with the previous analysis, IIV was estimated on CL/F, V/F, and D2, and a combination model was used to describe the RUV. The final parameter estimates for the structural model parameters were similar to those previously estimated (Table 3); the estimated setmelanotide typical value of CL/F was 7.19 L/h (previously 7.15 L/h), the typical value of V/F was 73.1 L (previously 75.2 L), and the typical value of D2 was 5.82 h (previously 5.23 h). Two notable adjustments were made to the previous model during development of the final covariate model. First, a subject-level random effect on the additive residual error was implemented. The addition of the ETA on RUV incidentally allowed for better characterization of the setmelanotide half-life compared to the previous PK analysis. Second, the effect of age on CL/F was removed from the final covariate model. The combination of the correlation between eGFR and age (-0.52) and spurious trends in ETAs versus age diagnostics prompted the removal of the covariate effect from the model.

In the final PK covariate model, setmelanotide CL/F was found to decrease with decreasing renal function as quantified by eGFR. Consequently, setmelanotide exposures generally increased with declining renal function, and dose adjustments are potentially required as the severity of renal impairment increases. Setmelanotide clearance was allometrically scaled to actual body weight, and volume of distribution to ideal body weight using the fixed allometric exponents of 0.75 and 1, respectively. No other covariates, including patient population (RGDO, HO, non-RGDO/non-HO), explained the significant variability in setmelanotide PK.

Table 3. final model fixed and random effect parameter estimates

			Estimate	95% CI
Structural model parameters				
CL/F (L/h)	$\exp(\theta_1)$	Apparent clearance	7.19	6.86, 7.53
V/F (L)	$\exp(\theta_2)$	Apparent volume of distribution	73.1	70.1, 76.3
D2 (h)	$\exp(\theta_3)$	Duration of zero-order absorption	5.82	5.44, 6.23
Covariate effect parameters				
CL/F ~ weight	θ_5	Weight effect on CL/F	0.750	FIXED
CL/F ~ eGFR	θ_9	Estimated glomerular filtration rate effect on CL/F	0.572	0.456, 0.689
CL/F ~ sex	$\exp(\theta_{10})$	Female effect on CL/F	0.937	0.890, 0.987
CL/F ~ HO	$\exp(\theta_{11})$	HO effect on CL/F	0.970	0.902, 1.04
CL/F ~ non-RGDO/non-HO	$\exp(\theta_{12})$	Non-RGDO/non-HO effect on CL/F	0.939	0.871, 1.01
V/F ~ ideal body weight	θ_6	Ideal body weight effect on V/F	1.00	FIXED
F ~ formulation	$\exp(\theta_{13})$	Unpreserved or missing formulation effect on bioavailability	0.929	0.886, 0.974
D2 ~ formulation	$\exp(\theta_7)$	Unpreserved or missing formulation effect on D2	1.07	0.904, 1.27

		Estimate	95% CI	Shrinkage (%)
Interindividual variance parameters				
IIV-CL/F	$\Omega_{(1,1)}$	0.0784 [CV%=28.6]	0.0637, 0.0931	12.2
IIV-V/F	$\Omega_{(2,2)}$	0.0699 [CV%=26.9]	0.0507, 0.0890	27.1
IIV-D2	$\Omega_{(3,3)}$	0.221 [CV%=49.7]	0.172, 0.269	24.0
IIV-RUV	$\Omega_{(4,4)}$	1.61 [CV%=200]	1.33, 1.90	10.2
Interindividual covariance parameters				
V/F-CL/F	$\Omega_{(2,1)}$	−0.00552 [Corr=−0.0746]	−0.0196, 0.00854	-
D2-CL/F	$\Omega_{(3,1)}$	0.0169 [Corr=0.128]	−0.00782, 0.0416	-
D2-V/F	$\Omega_{(3,2)}$	0.00978 [Corr=0.0787]	−0.0106, 0.0301	-
RUV-CL/F	$\Omega_{(4,1)}$	−0.175 [Corr=−0.493]	−0.224, −0.127	-
RUV-V/F	$\Omega_{(4,2)}$	0.121 [Corr=0.359]	0.0596, 0.182	-
RUV-D2	$\Omega_{(4,3)}$	0.132 [Corr=0.221]	0.0211, 0.243	-
Residual variance				
Proportional	$\Sigma_{(1,1)}$	0.0359 [CV%=19.0]	0.0323, 0.0396	5.66
Additive	$\Sigma_{(2,2)}$	2.63 [SD=1.62]	1.89, 3.36	5.64

Model evaluation

Prediction-corrected VPCs were generated for setmelanotide concentration over time after dose and stratified by formulation, age group (adult versus paediatric), renal function, and patient population. Given PK data were limited for children with impaired renal function, this analysis assumed that the renal-function–PK relationships identified predominantly in adult patients also applied to paediatric patients.

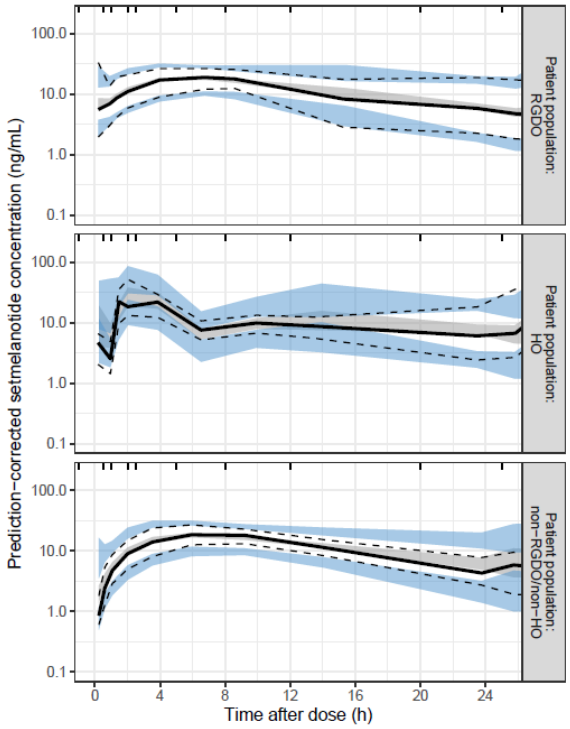


Figure 3. Prediction-corrected visual predictive check (VPC); stratified by patient population.

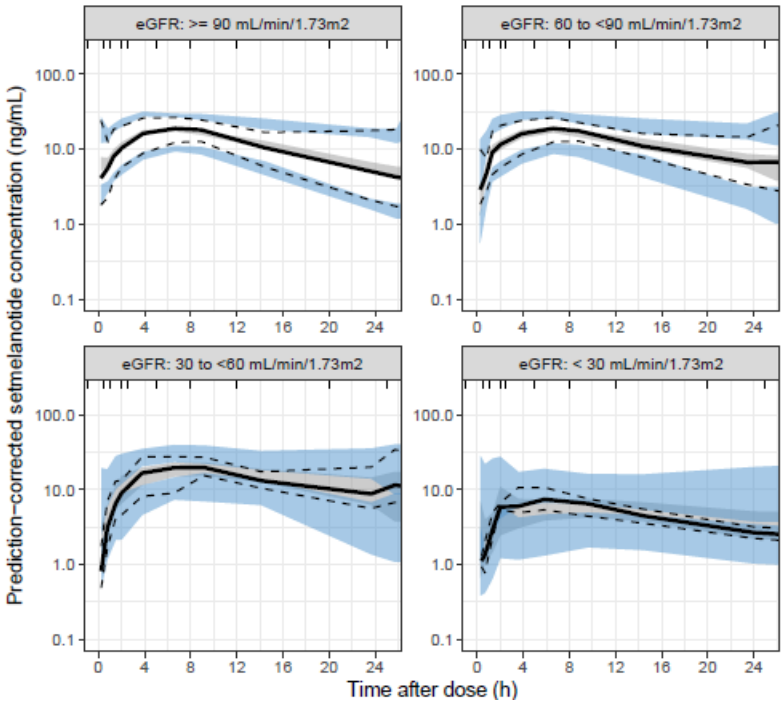


Figure 4. Prediction-corrected visual predictive check (VPC); stratified by renal function.

Simulations

The final population PK model was used to simulate setmelanotide exposures in adult and paediatric patients with HO and varying levels of renal function. The resulting exposures were then compared with simulations for adults with RGDO and normal renal function who received the approved maximum dose (3 mg once daily).

For paediatric patients 4 to<6 years old with normal renal function or mild renal impairment weighing<25 kg, the matching dose was between 0.5 and 1 mg. For paediatric patients weighing 25 to <30 kg, the matching dose was 1.0 mg. For patients 6 to <12 years old with normal renal function or mild renal impairment, the matching dose was between 1.0 mg and 2.0 mg. For patients 12 years old and older with normal renal function or mild renal impairment, the matching dose was between 2.0 mg and 3.0 mg. In patients with HO and moderate to severe renal impairment, reduced doses across all weight and age groups resulted in exposures within the reference range.

Simulated exposures in patients with HO were slightly higher than exposures in patients with RGDO; this difference was mediated through different weight distributions in patients with HO (median weight: 95.1 kg) compared to patients with RGDO (median weight: 118 kg). Adults with HO and normal renal function had an approximately 20% probability of exceeding the 95th percentile of the adult reference distribution.

An amended version of the population PK modelling report (dated 1 December 2025) was provided during the first round of questions to correct the PK simulation tables and figures to accurately reflect the final model (with the effect of age on CL/F removed from the covariate model). The probability that setmelanotide exposure in patients with HO, with and without renal impairment, exceeded the upper-bound (95th-percentile) reference range of adults with RGDOand normal renal function was summarized by weight band for paediatric patients aged 4 to <6 years and by age group for patients ≥6 years old (Table 4).

Table 4. PK Simulation: Probability (%) that setmelanotide exposure in paediatric subjects (4 to <6 years old) with HO, with and without renal impairment, exceeded the upper 3 mg

reference bound in adults with RGDO and normal renal function; stratified by weight group and dose.

	<20 kg			20 to <25 kg				25 to <30 kg			
	0.5 mg	1.0 mg	1.5 mg	0.5 mg	1.0 mg	1.5 mg	2.0 mg	0.5 mg	1.0 mg	1.5 mg	2.0 mg	2.5 mg
Renal function: Normal												
AUC,ss (ng*hr/mL)	0.6	43.8	89.0	0.1	19.2	73.0	93.6	0.0	9.3	54.8	87.8	97.3
Cmax,ss (ng/mL)	0.1	47.4	95.5	0.0	20.6	84.5	98.8	0.0	11.2	71.0	96.4	99.7
Cmin,ss (ng/mL)	3.5	35.0	59.9	0.6	17.2	41.5	61.0	0.3	10.8	30.3	47.4	60.4
Renal function: Mild impairment												
AUC,ss (ng*hr/mL)	1.9	58.7	94.4	0.4	30.7	81.3	97.5	0.2	18.6	68.5	92.7	98.5
Cmax,ss (ng/mL)	0.2	57.4	97.5	0.0	30.1	88.8	99.0	0.1	17.9	79.2	97.8	99.9
Cmin,ss (ng/mL)	6.8	47.5	72.4	1.9	27.9	55.9	71.5	0.9	19.7	44.9	61.5	72.3
Renal function: Moderate impairment												
AUC,ss (ng*hr/mL)	13.1	87.0	99.3	4.7	70.0	96.2	99.7	1.8	52.9	92.1	99.2	99.8
Cmax,ss (ng/mL)	2.6	82.5	99.7	0.4	61.3	97.2	99.9	0.3	44.5	93.5	99.7	100.0
Cmin,ss (ng/mL)	28.9	78.6	91.6	16.8	63.4	83.8	91.3	10.2	52.2	75.5	86.5	91.8
Renal function: Severe impairment												
AUC,ss (ng*hr/mL)	57.5	99.3	100.0	34.1	96.6	99.9	100.0	20.8	91.3	99.8	100.0	100.0
Cmax,ss (ng/mL)	24.5	98.2	100.0	7.5	92.3	100.0	100.0	3.4	81.8	99.5	100.0	100.0
Cmin,ss (ng/mL)	75.3	97.2	99.3	58.0	94.3	98.3	99.3	44.5	88.7	96.5	98.7	99.2

	6 to <12 years old				12 to <18 years old				18+ years old			
	0.5 mg	1.0 mg	2.0 mg	3.0 mg	0.5 mg	1.0 mg	2.0 mg	3.0 mg	0.5 mg	1.0 mg	2.0 mg	3.0 mg
Renal function: Normal												
AUC,ss (ng*hr/mL)	0.0	0.9	33.0	74.5	0.0	0.0	2.2	22.7	0.0	0.0	1.4	16.05
Cmax,ss (ng/mL)	0.0	0.9	50.4	90.8	0.0	0.0	2.6	33.4	0.0	0.0	1.1	20.25
Cmin,ss (ng/mL)	0.0	1.6	17.9	35.1	0.0	0.1	3.7	15.6	0.0	0.1	3.4	13.8
Renal function: Mild impairment												
AUC,ss (ng*hr/mL)	0.1	1.8	42.0	81.9	0.0	0.0	4.3	32.8	0.0	0.0	2.9	27.5
Cmax,ss (ng/mL)	0.0	1.5	57.1	93.7	0.0	0.0	4.5	39.4	0.0	0.0	1.5	26.95
Cmin,ss (ng/mL)	0.1	3.0	25.1	45.1	0.0	0.1	7.2	24.4	0.0	0.1	7.6	25.65
Renal function: Moderate impairment												
AUC,ss (ng*hr/mL)	0.1	11.8	73.2	95.6	0.0	0.2	24.1	67.3	0.0	0.1	18.0	59.75
Cmax,ss (ng/mL)	0.0	5.9	79.7	97.9	0.0	0.0	14.3	62.9	0.0	0.0	7.0	52.1
Cmin,ss (ng/mL)	1.2	17.3	54.5	75.5	0.0	2.8	30.4	57.2	0.0	1.9	28.1	55.25
Renal function: Severe impairment												
AUC,ss (ng*hr/mL)	3.0	43.6	95.2	99.7	0.0	5.7	65.0	93.3	0.0	4.3	56.5	89.5
Cmax,ss (ng/mL)	0.1	25.6	94.2	99.9	0.0	0.9	44.4	86.9	0.0	0.4	32.6	81.7
Cmin,ss (ng/mL)	11.9	54.3	87.8	95.0	1.1	21.4	70.8	89.8	0.7	19.8	68.8	87.7

2.2.6. Pharmacodynamics

Mechanism of action

Setmelanotide is a selective MC4 receptor agonist. MC4 receptors in the brain are involved in regulation of hunger, satiety, and energy expenditure. In MC4 receptor pathway diseases associated with insufficient activation of the MC4 receptor, setmelanotide is believed to re-establish MC4 receptor pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure.

Primary and Secondary Pharmacology

The immunogenicity of setmelanotide was assessed across multiple studies, including the pivotal Phase 3, Study RM-493-040. Original assay method development, validation, and results of testing for anti-setmelanotide and anti-alpha-melanocyte stimulating hormone (alpha-MSH) are in the original submission.

Antibodies to setmelanotide

The immunogenicity assay for antibodies to setmelanotide (RM-493) for the study RM-493-040 utilized a revised electrochemiluminescence (ECL) assay. No antibodies to setmelanotide were detected in patients 2 to <6 years old in Study RM-493-033 using the same new ECL ADA methodology, with the exception of one subject who was confirmed positive with a titer of 8 at Bridging Visit 4 followed by two visits negative for ADA. For study RM-493-040, 42 out of 583 samples were tested as potentially positive in the screening assay (interim analysis). However, no samples were confirmed as positive. In conclusion, no patients were positive for anti-setmelanotide antibodies to date for Study RM-493-040.

Antibodies to alpha-MSH

In addition, the immunogenicity assay for antibodies to alpha-MSH utilized a revised ECL in the study RM-493-040. An interim final bioanalytical has been submitted. Ninety-one out of 583 samples were tested as potentially positive in the screening assay. Only 12 samples confirmed positive and were tested in the titer assay. These 12 samples were positive at >MRD.

2.2.7. Discussion on clinical pharmacology

Setmelanotide PK was previously characterised in healthy volunteers and patients with rare genetic diseases of obesity. As such, the PK of setmelanotide are known to be body weight dependent with higher exposure in patients with lower body weight. Given the results of a renal impairment PK study, systemic exposure is also known to be higher and clearance to be lower with worsening renal function.

To extend the indication to adult and paediatric patients (≥ 4 years of age) with hypothalamic injury (HO), a pivotal Phase 3 study RM-493-040 was performed in this population and sparse PK samples were collected. A previously developed setmelanotide popPK model (RPI0104F) was updated with PK data from this pivotal study and the extension study RM-493-022 to support the proposed dosing.

Overall, the large majority of data used for model building and validation came from adults with a minority of data coming from paediatric subjects <6 years old. Compared to the previous popPK

analysis, no additional subjects with severe renal impairment and only 1 additional (adult) subject with moderate renal impairment was included in the current analysis. All patients <6 year of age included had normal renal function.

The dosing scheme applied in study RM-493-033 was identical to the dosing scheme proposed in the SmPC, except for renal impaired subjects. The use of setmelanotide was not permitted in patients <12 years with severe renal impairment (RI) and the maximum dose was limited to 1.5 mg for older severe RI patients, if included in the study.

Although the final model estimated effect of HO on CL/F suggested similar PK between patients with RGDO and HO, simulations among adults with normal renal function, predicted slightly higher exposures in patients with HO compared to patients with RGDO when receiving the same fixed dose. This difference is attributed to differences in weight distributions: enrolled patients with HO generally weighed less than those with RGDO. More pronounced deviations from the adult RGDO reference range (i.e., higher exposure) were predicted in younger patients and those with concomitant renal impairment, in line with the known effect of body weight and renal impairment on clearance. Given the very limited clinical data in children <6 years (n=2) and in patients with renal impairment, the adequacy of the proposed posology was questioned. Of note, an increased incidence of serious adverse events (SAEs) was observed in HO patients in the pivotal study and the Applicant was asked to explore if this could be related to higher setmelanotide exposure. See section 2.4.

Following several analyses across the predefined age groups (4 to <6, 6 to <12, 12 to <18, ≥18) in study RM-493-40, no consistent relationship between Ctrough and the occurrence of SAEs was identified in any age group, noting that for the age group 4 to <6, no firm conclusions can be drawn due to limited number of patients. Furthermore, the CHMP agreed that the proposed starting doses for each age group/renal impairment group are predicted to lie within the RGDO exposure reference range. Upward titration to doses that are predicted to largely exceed the reference range is only allowed in patients who show an insufficient clinical response and have no prior tolerability issues. With regard to the age group 4 to <6 year-old, the CHMP also agreed that the dose may be individually adjusted based on both tolerability and efficacy for these patients, and despite limited data.This information is reflected in the SmPC and is considered acceptable by the CHMP to guide the individual dose titration based on tolerability and clinical response. Additionally, the adapted dosing regimen for severe RI patients has been extended to moderate RI patients with HO to further reduce risks.

Immunogenicity

The immunogenicity of setmelanotide was assessed across multiple studies, including the pivotal Phase 3, Study RM-493-040. The CHMP agreed with the update in section 5.1 of the SmPC to reflect the immunogenicity data without identified effects, subsection 'pharmacodynamic effects.' As interim results were submitted, the MAH committed to provide an updated version of the ISI with final results from the treatment phase of the main study and further discussion on in Q2 2026, which was considered acceptable by the CHMP. Since additional samples will also be collected in the bridging phase, the CHMP recommended to provide the results from the bridging phase of the study in an

updated version of the ISI when available and consider a further update of the Product Information at this timepoint.

ADA assay

Similarly to clinical study RM-493-033, a new revised ECL ADA assay had been used in pivotal study RM-493-040 in comparison to the previous clinical trials. As a result of the current interim analysis, no patients were positive for anti-setmelanotide antibodies. While it was observed in the interim bioanalytical report that a quite significant number of patient samples were reported as re-assayed, the MAH has clarified that the vast majority of samples were considered as repeated only in that they confirmed positive in the screening assay and progressed to confirmatory analysis. These samples were therefore not true repeated samples and this justification was considered acceptable by the CHMP.

Anti-alpha-MSH antibody assay

A new revised and validated ECL anti-alpha MSH antibody assay has been used in pivotal clinical study RM-493-040. Four patients on 143 enrolled patients in the study RM493-040 had at least one sample timepoint with a confirmed positive result for antibodies to alpha-MSH with a titre greater than or equal to the minimum required dilution (MRD). The incidence in the patients treated with setmelanotide is 4/94 setmelanotide treated patients, i.e., 4%. It was observed in the interim bioanalytical report that a quite significant number of patient samples were reported as re-assayed. The MAH however clarified that, like ADA analysis (see above), these were not true repeated analysis.

2.2.8. Conclusions on clinical pharmacology

The MAH submitted an updated popPK analysis to support the proposed dosing in adult and paediatric patients with HO aged ≥ 4 years. Though the maximum doses in patients <6 years and in renal impaired patients do not match with the RGDO reference range, the titrated dose escalation practice in patients who need additional clinical effect and have no prior tolerability issues, is considered acceptable from clinical perspective. The information on immunogenicity is adequately reflected in the Product Information and further updates are expected once the final results are available.

2.3. Clinical efficacy

2.3.1. Main study

STUDY RM-493-040 - A PHASE 3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF SETMELANOTIDE IN PATIENTS WITH ACQUIRED HYPOTHALAMIC OBESITY

INTERIM ANALYSIS (DATA CUTOFF = 26 MARCH 2025)

Methods

This was a Phase 3, double-blind, multi-center, placebo-controlled, randomized 2:1 (active to placebo), registrational trial, designed to assess the efficacy and safety of setmelanotide on weight loss and hunger in patients ≥4 years of age with acquired HO. Approximately 120 patients (at least 12 from sites

in Japan) aged 4 years and older were planned to be enrolled at up to 35 clinical sites in North America, the UK, Europe, and Japan.

Setmelanotide 0.5 mg once daily (QD) or the placebo equivalent was administered as the starting dose for all patients. After the initial 0.5 mg dose, patients dose escalated each week in increments of either 0.5 or 1.0 mg to achieve the individual patient's therapeutic regimen. The target therapeutic regimen varied by age (and weight for patients <6 years of age) and ranged from a maximum of 1.5 to 3.0 mg QD. During the treatment period efficacy and safety assessments were performed approximately every 4 weeks via either in-clinic visits or at-home telehealth visits.

The end-of-treatment (EOT) visit occurred after 52 weeks on a therapeutic regimen, which was the final planned week of dosing with study treatment. At the EOT visit, patients who completed 52 weeks on a therapeutic regimen and completed assessments through the EOT visit could be eligible to enter an open label long-term extension (LTE) study or attend Bridging visits with open-label setmelanotide if the LTE was not yet available. For patients who did not receive setmelanotide following the EOT visit, a safety follow-up visit (SFV) was conducted approximately 2 weeks after the last dose of study treatment.

Study participants

Inclusion criteria :

1. Patient has documented evidence of acquired HO defined as:

– Diagnosis of craniopharyngioma or other brain lesion affecting the hypothalamic region and has undergone surgery, or chemotherapy, or radiation therapy involving the hypothalamus at least 6 months before Screening, OR

– Documented injury to the hypothalamus at least 6 months before Screening for which surgery/radiation is not indicated.

2. Aged 4 years and older at time of enrolment

3. Documented weight gain associated with the hypothalamic injury either before therapy or following therapy (surgery and/or following chemotherapy or radiotherapy), and a body mass index (BMI) of ≥ 30 kg/m2 for patients ≥18 years of age, or BMI ≥95th percentile for age and sex for patients 4 to <18 years of age based on the US Centers for Disease Control and Prevention criteria.

4. Patients must meet the contraception requirements

5. Ability to communicate well with the Investigator, understand and comply with the requirements of the trial, and understand and sign the written informed consent and/or assent for patients aged <18 years, a parent/legal guardian that can sign.

6. If receiving hormone replacement therapy (i.e., thyroid hormones, glucocorticoids, growth hormone, or other medications known to affect metabolism or weight/body composition), the dose of such therapy has remained stable for at least 2 months prior to Screening. Changes in dose of ≤25% may be permissible, with the Sponsor's approval. If results of free thyroxine (FT4) warrant changes in

therapy >50% or the addition of new medication the patient is screen failed and can be reassessed after 2 months. This does not apply to patients experiencing adrenal crisis.

Exclusion criteria :

1. Diagnosis of Prader-Willi syndrome (PWS) or Rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, neuroendocrine tumor syndrome (ROHHADNET).

2. Weight loss >2% in the previous 3 months for patients aged ≥18 years or >2% reduction in BMI for patients aged 4 to <18 years.

NOTE: Dietary and/or exercise regimens, with or without the use of medications, supplements or herbal treatments associated with weight loss (e.g., orlistat, lorcaserin, phentermine, topiramate, naltrexone, bupropion, glucagon-like peptide-1 [GLP-1] receptor agonists, etc) are allowed if:

– the regimen and/or dose has been stable for at least 3 months prior to randomization

– the patient has not experienced weight loss >2% (for patients ≥18 years) or >2% BMI (for patients aged 4 to <18 years) during the previous 3 months, and

– the patient intends to keep the regimen and/or dose stable throughout the course of the trial.

Note: This exclusion criterion applies only to initial study screening and is not applicable at the time of the inclusion/exclusion review for the LTE (or Bridging).

3. Bariatric surgery or procedure (e.g., gastric bypass/band/sleeve, duodenal switch, gastric balloon, intestinal barrier, etc) within the last 2 years. All patients with a history of bariatric surgery or procedures must be discussed with and receive approval from the Sponsor prior to enrolment.

4. Diagnosis of severe psychiatric disorders (e.g., schizophrenia, bipolar disorder, personality disorder), or Major Depressive Disorder (MDD) within the previous 2 years, or Screening Patient Health Questionnaire (PHQ)-9/PHQ-A score ≥15, or any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS), or a Children's Depression Inventory-2 (CDI-2) T-score ≥70 during Screening, or lifetime history of suicide attempts, or any suicidal behavior in the last month.

5. Glycated hemoglobin (HbA1c) >11.0% at Screening.

6. Current, clinically significant pulmonary, cardiac, metabolic, or oncologic disease considered severe enough to interfere with the trial and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor or contract research organization (CRO) monitor to determine eligibility.

7. End stage renal disease (GFR <15 mL min/1.73 m2) in any age or glomerular filtration rate (GFR) <30 mL/min/1.73 m2 during Screening in patients <12 years of age (GFR calculated using the Bedside Schwartz Formula for patients <18 years of age).

8. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a comprehensive skin evaluation performed by the Investigator during Screening. Any concerning lesions identified during Screening

will be biopsied and results known to be benign prior to enrolment. If the pre-treatment biopsy results are of significant concern, the patient is not eligible for trial participation.

9. History or close family history (parents or siblings) of skin cancer or melanoma (not including non-invasive, infiltrative basal or squamous cell lesion), or patient history of ocular-cutaneous albinism.

10. Participation in any clinical trial with an investigational drug/device within 3 months or 5 half-lives, whichever is longer, prior to the first trial dose.

11. Previously enrolled in a clinical trial involving setmelanotide or any previous exposure to setmelanotide.

12. Inability to comply with once daily (QD) injection regimen.

13. Pregnant and/or breastfeeding or desiring to become pregnant during this trial.

14. Patients with obesity attributable to other genetic or syndromic conditions (eg, PPL [POMC, PCSK1, LEPR, collectively], BBS) prior to the hypothalamic injury.

15. Cognitive impairment that, in the Investigator's opinion, precludes participation in the trial and completion of trial procedures or questionnaires.

16. Patient is, in the Investigator's opinion, otherwise not suitable to participate in the trial.

17. Legally protected persons per local regulations (eg, those that fall under the L1121-6 article of the Public Health Code in France).

18. The patient or a relative of the patient is the Investigator or a sub-investigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the trial.

19. Hypersensitivity to setmelanotide and/or any excipients contained in the investigational drug.

Study or treatment discontinuation

Patients had the right to withdraw their consent to participate in the study at any time for any reason, without prejudice to their medical care. The Investigator also had the right to withdraw patients from the study, after discussion with the Sponsor, for any of the following reasons:

· Adverse events (AEs), which justify treatment or study withdrawal.

· Non-adherence to study drug regimen or protocol requirements.

· Non-compliance with instructions or failure to return for follow-up.

Permitted/ Prohibited Prior and Concomitant Therapy

Medication that was considered necessary for the patient's safety and wellbeing could be given during the study at the discretion of the treating physician after discussion with the Medical Monitor.

All concomitant medications were to be kept at a stable dose throughout the course of the study unless a dose change was necessary due to a change in the patient's condition.

As GLP-1 treatments may cause nausea and vomiting, they were not to be started simultaneously with study treatment. However, study treatment could be started in patients who were on stable doses of GLP-1 treatments for at least 3 months prior to randomization.

Medications that are approved to treat obesity (e.g., orlistat, phentermine-topiramate, naltrexone bupropion, GLP-1 receptor agonists, etc), as well as the use of dietary and/or exercise regimens and weight loss supplements or herbal treatments associated with weight loss were permitted if the patient had <2% weight loss in the previous 3 months, the dose/regimen had been stable for at least 3 months prior to randomization, and the patient intended to continue the same dose/regimen throughout the study.

Treatments

Investigational product

Setmelanotide, 10 mg/mL in a sterile solution for injection.

Mode of administration

SC injection

Dosage administered QD:

Patients <6 years of age: all patients initiated study treatment at 0.5 mg and were dose escalated to 1.0 mg within 1 week. Patients weighing <30 kg, dose escalated in 0.5 mg increments and patients weighing ≥30 kg dose escalated in increments of 1 mg approximately weekly until the maximum tolerated therapeutic regimen was reached. The maximum dose was 1.5 mg for patients <20 kg, 2.0 mg for patients 20 to <25 kg, 2.5 mg for patients 25 to <30 kg, and 3.0 mg for patients ≥30 kg.

Patients ≥6 years of age: all patients initiated study treatment at 0.5 mg and were escalated to 1.0 mg within 1 week. After escalating to 1.0 mg QD, patients were escalated every 1 week (minimum) in increments of 1 mg up to a maximum dose of 3.0 mg. Doses could be escalated in 0.5 mg increments when warranted for safety or tolerability.

Table 5 Setmelanotide QD Dosing Scheme

Starting Dose			Dose Escalation Based on Tolerability				
			Escalation Steps				Maximum Dose
Age (years)	Weight (kg)	Dose	Dose (+1 week)	Dose (+1 week)	Dose (+1 week)	Dose (+1 week)	
<6	<20	0.5 mg	1.0 mg	1.5 mg (max)			1.5 mg
<6	20 to <25	0.5 mg	1.0 mg	1.5 mg	2.0 mg (max)		2.0 mg
<6	25 to <30	0.5 mg	1.0 mg	1.5 mg	2.0 mg	2.5 mg (max)	2.5 mg
<6	≥30	0.5 mg	1.0 mg	2.0 mg	3.0 mg (max)		3.0 mg

Starting Dose			Dose Escalation Based on Tolerability				
			Escalation Steps				Maximum Dose
Age (years)	Weight (kg)	Dose	Dose (+1 week)	Dose (+1 week)	Dose (+1 week)	Dose (+1 week)	
≥6	≥30	0.5 mg	1.0 mg	2.0 mg	3.0 mg (max)		3.0 mg

Patients could reach their therapeutic regimen in as little as 2 weeks for patients <20 kg, with most patients reaching their maximally tolerated therapeutic regimen between 4 and a maximum of 8 weeks. Each weekly dose escalation could be extended over 2 weeks as needed based on tolerability.

If a patient's weight decreased to below 15 kg during the study, the Investigator and Sponsor were to discuss the patient's status and determine if the patient should continue the current dose, decrease the dose, or discontinue treatment with setmelanotide temporarily or permanently. A dose reduction to 0.25 mg QD could be considered in such scenarios or in case of safety or tolerability concerns.

Dosing Recommendations in Special Populations- Renal Impairment

The use of setmelanotide in patients <12 years of age with severe renal impairment or in any patient with end stage renal disease was not permitted in this study.

In patients ≥12 years of age with severe renal impairment, the starting dose of setmelanotide (0.5 mg) was injected SC QD for 2 weeks. The dose could subsequently be increased by 0.5 mg QD every 2 weeks, if tolerated, to a maximum of 1.5 mg QD.

Duration of treatment

The duration of treatment in this study was up to 60 weeks and included a dose titration phase of up to 8 weeks plus 52 weeks of treatment with a therapeutic regimen. The total study duration was up to 70 weeks and included a screening period of up to 8 weeks, a treatment period of up to 60 weeks, and a SFV approximately 2 weeks after treatment.

Objectives

Primary objective

To evaluate the efficacy of setmelanotide on change in body mass index (BMI)

Key secondary objectives

To evaluate the efficacy of setmelanotide on proportion of patients with ≥5% reduction in BMI or ≥0.2-point reduction in BMI Z-score

To evaluate the efficacy of setmelanotide on the proportion of patients with ≥5% reduction in BMI

To evaluate changes in hunger in response to setmelanotide

Secondary objectives

Other secondary objectives included evaluation of changes in: hunger and symptoms of hyperphagia, additional parameters of body weight, quality of life, waist circumference, and cardiometabolic parameters following treatment with setmelanotide.

Safety Secondary objectives

To evaluate the safety and tolerability of setmelanotide compared to placebo

To evaluate the effect of setmelanotide on blood pressure (BP)

Outcomes/endpoints

Primary Endpoint

· Mean % change in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

Key Secondary Endpoints (in hierarchical order)

· The proportion of patients with ≥5% reduction in BMI in adult patients (≥18 years of age), or BMI z-score reduction of ≥0.2 points in paediatric patients (<18 years of age) from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

· The proportion of all patients with ≥5% reduction in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

· Mean change in the weekly average of the daily most hunger score in patients ≥12 years old from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to Placebo

Secondary Endpoints

• The proportion of patients with a ≥2-point reduction in the weekly average of the daily most hunger score from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

• Mean change in the weekly average of the Symptoms of Hyperphagia composite score from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

• The proportion of patients with a ≥10% reduction in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

• The proportion of patients with a ≥10% reduction in weight from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

• Mean percent change in weight in patients ≥18 years from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

• Mean BMI Z-score and BMI percentile reduction in patients <18 years of age from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

• The proportion of patients aged ≥4 to <18 years with ≥0.2-point reduction of BMI Z-score from

• Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

• The proportion of patients with BMI <30 kg/m2 (patients aged ≥18 years) or <95th percentile (patients aged <18 years) from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

• Mean change in physical functioning score and total score for the Impact of Weight on Quality of Life-Lite (IWQOL) (IWQOL-Lite-CT in patients ≥18 years and IWQOL-Kids in patients 11 to <18 years), from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

• Change in waist circumference from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

• The difference in change in cardiometabolic parameters including BP, lipid profile, glycated haemoglobin (HbA1c), liver function, and C-reactive protein from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

Safety Endpoints

• Safety and tolerability assessed by the frequency and severity of adverse events (AEs), AEs of special interest (AESIs), vital signs, and laboratory evaluations from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

• Change in ambulatory BP and heart rate (HR) from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo (in patients ≥12 years)

Sample size

Number of patients (planned and analyzed):

Planned: Approximately 120 patients (approximately 80 in the setmelanotide group and approximately 40 in the placebo group) were planned, including at least 12 patients from Japan.

Enrolled: All Patients: A total of 143 patients (95 in the setmelanotide group and 48 in the placebo group) were enrolled, including 12 patients from Japan.

Pivotal Patients: Of the 143 enrolled patients, 120 either completed the EOT visit or discontinued treatment prematurely and are included in the analyses.

Randomisation

Following screening (for up to 8 weeks), eligible patients were randomized in a blinded manner on Day 1 in a 2:1 ratio, stratified by age group (≥18 years old, ≥12 and <18 years old, <12 years old) and

subpopulation (Japanese vs non-Japanese), to receive either setmelanotide (2) or placebo (1) for up to 60 weeks.. The randomization schedule was generated by the Sponsor or its designee, and trial personnel used a web-based interactive response technology (IRT) system to obtain the patient number for each eligible patient.

Blinding (masking)

Blinded randomization occurred via an IRT system. At the initiation of the study, study site personnel were instructed on the method for breaking the blind. To conduct the primary analysis, the Sponsor was unblinded when 120 patients had completed the study. To ensure the integrity of the study at the site level, investigators and patients remained blinded after the unblinding of the Sponsor. Emergency unblinding for AEs prevued to be performed through the IRT system. The IRT system was programmed with blind-breaking instructions. For any unexpected serious adverse event (SAE) that was treatment-related (eg, possible or probable), the blind was to be lifted by the Sponsor only for that specific patient. The blind was Treatments to be maintained for persons responsible for the ongoing conduct of the study (such as the monitors, investigators, etc) and those responsible for data analysis and interpretation of results at the conclusion of the study (such as biometrics personnel). Unblinded information was only accessible to those who needed to be involved in the safety reporting to Health Authorities, the IEC, and/or IRB. Investigators received only blinded information unless unblinded information was judged necessary for safety reasons.

Statistical methods

Analysis populations

The following analysis populations were planned:

• Screening Analysis Set: defined as all patients who signed the informed consent form.

• Safety Analysis Set (SA): defined as all patients who received at least 1 dose of study treatment (placebo or setmelanotide). Analyses performed on the safety set were based on patients according to the treatment received.

• Full Analysis Set (FAS): defined as all randomized patients. Analyses performed on the FAS were based on treatment as randomized.

• Modified Intention-to-Treat Analysis Set (mITT): defined as all randomized patients who were exposed to at least 1 dose of study treatment. Analyses performed on the mITT were based on treatment as randomized.

• Per-Protocol Set (PP): defined as all patients in the mITT without any important protocol violations that warrant exclusion as determined by Sponsor (prior to database lock).

The mITT was the primary population for the analysis of efficacy data. The PP was to be used for sensitivity analyses only if the number of excluded patients in PP population was at least 10% of the overall mITT set. As this criterion was not met, per protocol analyses were not performed.

The SA was the primary population for the analysis of safety endpoints.

In addition, subgroup analyses were performed for age (<12 years old, 12 to <18, ≥18 years old), sex (male, female), race (white, black, other), ethnicity (Hispanic/Latino, non-Hispanic non-Latino), and region (North America, Europe, and Japan).

Disposition

Patient disposition was tabulated for the Pivotal and All Patient cohorts by randomized group and included the number screened, the number randomized, the number treated in total, the number dosed with setmelanotide, the number dosed with placebo, the number in each patient population for analysis, and the number who withdrew prior to completing the treatment and reason(s) for withdrawal.

Demographic and Baseline Characteristics

Demographic and Baseline characteristics were summarized by treatment group and overall using the mITT for the Pivotal and All Patient cohorts. Age, height, weight, waist circumference, BMI, the observed BMI percentage compared to the 95th percentile given the patient age and sex (P95), and BMI z-score at Baseline were summarized using descriptive statistics, as applicable.

The number and percentage of patients in each age group (<12 years old, ≥12 to <18 years old, ≥18 years old), sex, ethnicity, race, and subpopulation (Japanese vs non-Japanese), and skin type (as measured by the Fitzpatrick Classification Scale) was also presented.

Adjustment for Covariates

For efficacy analyses where an ANCOVA model with an unequal variance to account for possible unequal residual variances was used and multiple age groups and subpopulation (Japanese vs. non-Japanese) were considered, adjustments were made for the relevant age groups and subpopulation for that given analysis.

Handling of Dropouts or Missing Data

Missing data were imputed for height and body weight and, by extension, their derivatives (BMI, BMI z-score, BMI P95), as well as for daily hunger scores and AE dates. Imputation of other missing questionnaire data was applied for the derivation of summary scores, dependent on the questionnaire and imputation rules of the questionnaire. Unless otherwise specified, all other study data were summarized as reported (missing data were not imputed).

As height was only measured at Screening for patients 21 years, BMI was calculated using the last available height measurement prior to weight collection (LOCF). This approach was used for all patients regardless of age.

For weight, a retrieved dropout (RD) approach was planned. However, due to insufficient RD to provide a reliable multiple imputation model, a wash-out imputation method was utilized.

For wash-out imputation, placebo patients were first imputed assuming missing-at-random (MAR) regressing on baseline weight, Visit 2 weight, Visit 4 weight, Visit 7 weight, Visit 9 weight, Visit 11

weight, and primary timepoint weight. This accounted for planned on-site visits as well as a combined primary timepoint.

Once the placebo patients were imputed under MAR as directed above, the observed placebo patients were combined with the setmelanotide patients needing imputation of the primary timepoint. The setmelanotide patients were then imputed assuming missing-not-at-random (MNAR) using placebo-based imputation (jump to reference method) regressing only on baseline value and primary timepoint value.

Patients who died were considered as a treatment failure and the effective change and percent change from baseline was set to 0 once the imputation was complete.

One hundred imputed datasets were generated. Each of the imputed datasets was then analyzed according to the relevant statistical test outlined in the sections below.

Resulting estimates were combined using Rubin's rule to produce inferential results.

For analyses of the daily hunger score questionnaire in patients ≥12 years of age, MI was used to model missing measurements at the primary timepoint. The methods outlined above for weight were utilized for the daily hunger score questionnaire. The multiple imputation functioned at the weekly average of daily hunger score level and not at the daily level scores.

Primary efficacy analysis

The primary efficacy endpoint of this study was the mean percent change from Baseline in BMI after 52 weeks of treatment with the therapeutic regimen of either setmelanotide or placebo.

The statistical hypothesis for the primary efficacy endpoint was:

H0: $\mu t - \mu p \geq 0$ vs H1: $\mu t - \mu p < 0$

where μt is the mean percent change in BMI from Baseline after approximately 52 weeks on a therapeutic regimen in the setmelanotide group, and μp is the mean percent change in BMI from Baseline after approximately 52 weeks in the placebo group.

The primary endpoint analysis was conducted on the mITT utilizing BMI values resulting from the multiple imputation process. The difference between setmelanotide and placebo after 52 weeks on a therapeutic regimen was estimated using an analysis of covariance (ANCOVA) model with unequal variance to account for possible unequal residual variances.

The model was adjusted with stratification factors of age group (≥18 years old, ≥12 and <18 years old, and <12 years old) and subpopulation (Japanese and non-Japanese) as appropriate.

This difference was estimated for each of the 100 imputed datasets. The outcomes from the 100 imputed datasets were combined using Rubin's Rule to provide an overall estimate of least squares (LS) mean difference with corresponding 95% confidence intervals (CI) and p-value. The success criterion for the primary hypothesis required the rejection of the null hypothesis at the 2-sided 0.05 significance level.

Sensitivity and Supplementary Analyses for the Primary Efficacy Endpoint

The following sensitivity analysis was performed for the primary efficacy endpoint:

- Two-Dimensional Tipping Point Analysis: The two-dimensional tipping point analysis was conducted for the Pivotal and All Patient cohorts using the mITT with varying assumptions about the missing outcomes on the 2 treatment groups independently, including scenarios in which dropouts in the setmelanotide group had worse outcomes than dropouts on placebo. A penalty for the setmelanotide group and improvement on the placebo group changed by increments of 0.1 to 1, until the statistical significance was lost, i.e., until the p-value became >0.05.

The following supplementary analyses were performed for the primary efficacy endpoint:

- As-Observed Analysis: The primary analysis was repeated for the mITT population for both the Pivotal and All Patient cohorts based on observed data only.
- Last-Observation Carried Forward Analysis: A last-observation-carried-forward (LOCF) analysis was conducted for the Pivotal and All Patient cohorts using the mITT. For any patients missing the primary timepoint BMI value, the last available BMI value occurring at an on-site visit was carried forward and used as the primary timepoint value for analysis purposes.

Key Secondary efficacy analysis

Statistical testing was performed on the key secondary endpoints according to the pre-specified hierarchical order:

• The proportion of patients with ≥5% reduction in BMI in adult patients (≥18 years of age), or BMI z-score reduction of ≥0.2 points in paediatric patients (<18 years of age) from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

• The proportion of all patients with ≥5% reduction in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

• Mean change in the weekly average of the daily most hunger score in patients ≥12 years old from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

Formal inference of efficacy tests was based on the pivotal patients and was to stop once a result showed no statistical significance in favor of setmelanotide at the 2-sided alpha level of 0.05.

The key secondary endpoints relied upon the imputed values utilized for the primary efficacy endpoint or upon newly imputed values following same methodology as the primary efficacy endpoint.

Proportion of BMI/BMI z-score Percent Change from Baseline

The first key secondary endpoint was the proportion of patients with ≥5% reduction in BMI in adult patients (≥18 years of age) or BMI z-score reduction of ≥0.2 points in paediatric patients (<18 years of age) from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo.

The BMI z-score was calculated for patients aged 4 to <18 years of age using the World Health Organization's (WHO) 2007 BMI SAS Macro Package. If weight was collected but a corresponding height was not, the last available height record for that patient was used in the calculation of BMI.

The analysis was conducted using the following steps:

1. Binomial proportions were calculated for each treatment arm for each of the 100 imputed datasets. Analysis between arms were conducted for each of the 100 imputed datasets with a Cochran-Mantel-Haenszel (CMH) test with adjustment of stratification factors of age group and subpopulation (Japanese and non-Japanese), as appropriate. For each multiple imputation (MI) dataset, the COMMONRISKDIFF option in PROC FREQ calculated the adjusted estimate of the risk difference of success (setmelanotide minus placebo) over all strata with its 95% CI.

2. The estimates of the risk difference and their standard errors for all the MI datasets were input to PROC MIANALYZE.

3. PROC MIANALYZE outputted an overall estimate of the risk difference, its 95% CI, and a combined p-value as well as overall estimates of the proportions of responders in each treatment arm, along with 95% CIs.

This analysis was repeated for the PP population for pivotal patients only.

Proportion of Patients with ≥5% Reduction in BMI from Baseline

The second key secondary endpoint was the proportion of patients with a ≥5% reduction in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo and was analyzed as described above for "Proportion of BMI/BMI z-score Percent Change from Baseline".

Daily Hunger Questionnaire Change from Baseline

The third key secondary endpoint was the mean change from Baseline in the weekly average of the daily most hunger scores for pivotal patients ≥12 years old in the mITT after 52 weeks on a therapeutic regimen of setmelanotide compared to placebo.

The endpoint was analyzed using an ANCOVA model similar to that described for primary efficacy analysis. Prior to analysis, daily hunger scores for each of the hunger assessments were averaged separately for the 7 days immediately preceding the visit. For a week of hunger scores to be considered evaluable, scores need to be recorded and available for analysis on at least 1 of 7 days to provide sufficient data to determine mean values.

Other Secondary Efficacy Endpoints

Briefly, analyses for the other secondary efficacy endpoints based on binomial proportions (eg, the proportion of patients with a ≥10% reduction in BMI) were conducted as described above for "Proportion of BMI/BMI z-score Percent Change from Baseline", while endpoints using change from Baseline (eg, mean change in the weekly average of the Symptoms of Hyperphagia composite score) were analyzed with an ANCOVA model similar to that described for primary efficacy analysis.

Analysis of the other secondary endpoints relied upon imputed values utilized for the primary and key secondary efficacy endpoints where applicable (BMI/BMI z-score/BMI P95/Weight/weekly average in daily hunger). Endpoints relating to domains that had not previously relied on multiply imputed values were analyzed as observed.

Multiple Comparisons

No multiplicity adjustments were required for the primary analysis as this study had only 1 primary endpoint. This controls the overall alpha at 0.05, 2-sided. As there were 3 key secondary efficacy endpoints, the following order was used for sequential testing purposes:

1. The proportion of patients with ≥5% reduction in BMI in adult patients (≥18 years of age), or BMI z-score reduction of ≥0.2 points in paediatric patients from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide treatment compared to placebo.

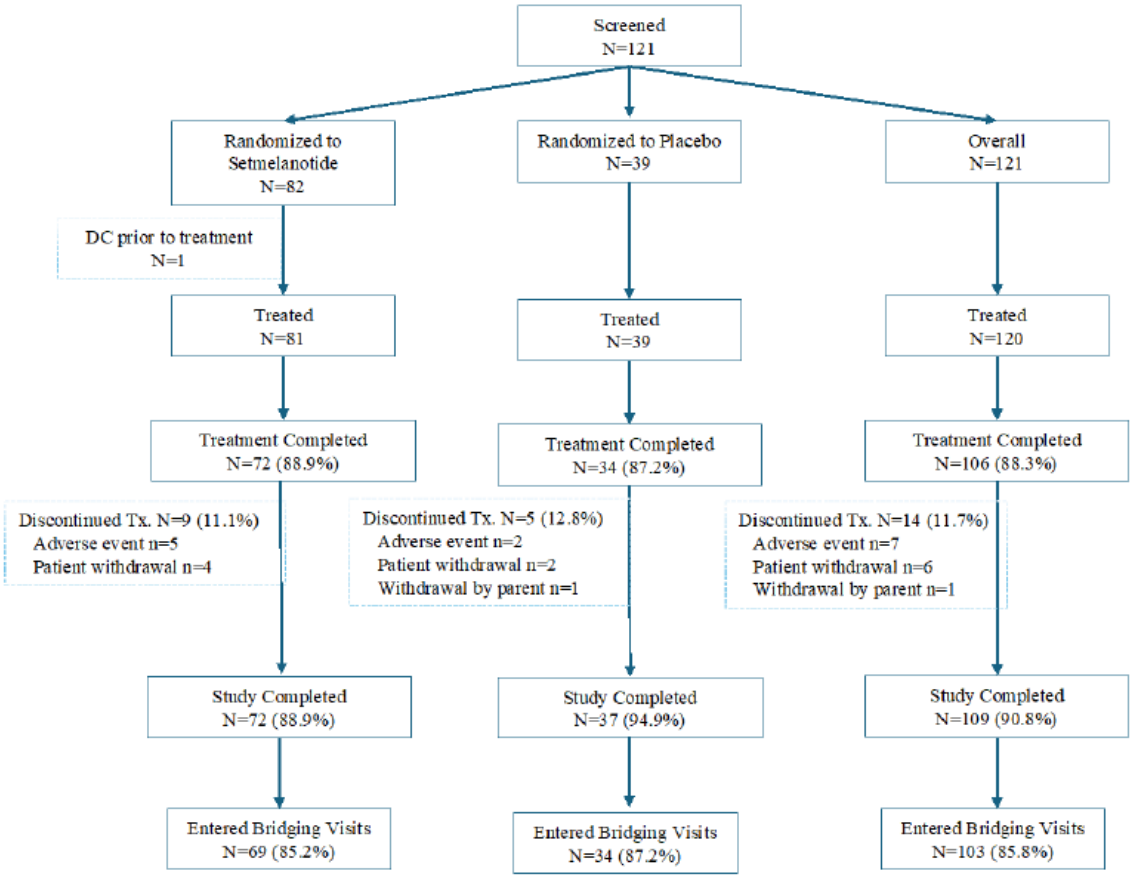
2. The proportion of all patients with ≥5% reduction in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo.

3. Mean change in the weekly average of the daily most hunger score in patients ≥12 years old from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide treatment compared to placebo.

Results

Participant flow

Patient Disposition for the Pivotal Cohort (Screening Analysis Set)



Abbreviations: DC = discontinued; Tx = treatment.

Recruitment

In the All Patient cohort, 161 patients were screened, 143 were randomized (95 setmelanotide and 48 placebo), and 142 were treated, (94 setmelanotide and 48 placebo). Seventy-two (76.6%) setmelanotide and 35 (72.9%) placebo-treated patients completed treatment. Primary reasons for treatment discontinuation in the setmelanotide group included AEs in 5 (5.3%) patients and patient withdrawal in 4 (4.3%) patients. Primary reasons for treatment discontinuation in the placebo group included AEs in 2 (4.2%) patients, patient withdrawal in 2 (4.2%) patients, and withdrawal by parent/guardian in 1 (2.1) patients. Most (73.2.%) of the patients who completed the study decided to continue or begin (for placebo patients) receiving open-label treatment with setmelanotide via Bridging visits.

Conduct of the study

Protocol Deviations

A total of 35 (37.2%) patients in the setmelanotide group and 17 (35.4%) in the placebo group had at least 1 important (major) protocol deviation. In the setmelanotide group, the most common categories of important deviations were "informed consent," which mostly consisted of deviations related to reconsent; "study procedures-dosing," which included dosing compliance deviations; and "study procedures-other," which included assessment completion/compliance deviations (eg, missed our out of window assessments). In the placebo group, the most common categories of important deviations were "study procedures-dosing," which included dosing compliance deviations and "study procedures-other," which included assessment completion/compliance deviations (eg, missed our out of window assessments).

Baseline data

Patients in the Phase 3 Study were an average of 19.9 years of age at enrolment and ranged from 4 to ≥60 years in both arms; 59.2% were <18 and 40.8% were ≥18 years of age. Patients were male (40.0%) or female (60.0%) and most (83.3%) were White. Consistent with their underlying diagnosis of acquired HO and the entry criteria requiring patients to have a mean BMI ≥30 kg/m2 (those ≥18 years) or a BMI ≥95th percentile (those <18 years), the mean BMI for all patients regardless of age was 36.07 and the mean BMI z-score and percent of the BMI 95th percentile in patients <18 years of age were 3.61 and 131.14, respectively. The 2 treatment groups were well-balanced across all of these parameters.

Table 6 Patient Demographics and Baseline Characteristics in Study RM-493-040 (Pivotal Cohort, mITT Analysis Set)

	Setmelanotide N=81	Placebo N=39	Overall N=120
Age (years) at Enrollment			
n	81	39	120
Mean (SD)	19.2 (12.98)	21.4 (15.50)	19.9 (13.82)
Median	16.0	15.0	16.0
Min,Max	4, 65	4, 66	4, 66
Age Category, n (%)			
<12 years	20 (24.7)	11 (28.2)	31 (25.8)
≥12 years and <18 years	28 (34.6)	12 (30.8)	40 (33.3)
≥18 years	33 (40.7)	16 (41.0)	49 (40.8)
Sex, n (%)			
Male	36 (44.4)	12 (30.8)	48 (40.0)
Female	45 (55.6)	27 (69.2)	72 (60.0)
Ethnicity, n (%)			
Hispanic or Latino	7 (8.6)	7 (17.9)	14 (11.7)
Not Hispanic or Latino	73 (90.1)	32 (82.1)	105 (87.5)
Unknown	1 (1.2)	0	1 (0.8)
Race, n (%)			
Asian	3 (3.7)	0	3 (2.5)
Black or African American	6 (7.4)	0	6 (5.0)
White	66 (81.5)	34 (87.2)	100 (83.3)
Other	6 (7.4)	5 (12.8)	11 (9.2)
Patients Enrolled by Country, n (%)			
Canada	4 (4.9)	3 (7.7)	7 (5.8)
Germany	8 (9.9)	4 (10.3)	12 (10.0)
Netherlands	7 (8.6)	4 (10.3)	11 (9.2)
United Kingdom	8 (9.9)	1 (2.6)	9 (7.5)
United States	54 (66.7)	27 (69.2)	81 (67.5)

	Setmelanotide N=81	Placebo N=39	Overall N=120
BMI (kg/m^2) [a]			
n	81	39	120
Mean (SD)	35.73 (9.173)	36.78 (9.332)	36.07 (9.199)
Median	33.27	37.35	34.09
Min, Max	21.3, 69.2	21.3, 70.0	21.3, 70.0
BMI z-score [b] (patients <18 years)			
n	48	23	71
Mean (SD)	3.72 (1.810)	3.37 (1.294)	3.61 (1.659)
Median	3.06	3.18	3.11
Min, Max	2.0, 10.4	1.9, 7.5	1.9, 10.4
BMI P95 [c] (patients <18 years)			
n	48	23	71
Mean (SD)	132.33 (28.872)	128.64 (22.682)	131.14 (26.915)
Median	124.12	127.84	124.93
Min, Max	98.0, 209.6	97.2, 189.9	97.2, 209.6
Waist Circumference (cm)			
n	81	39	120
Mean (SD)	106.57 (21.712)	108.64 (18.771)	107.24 (20.745)
Median	104.90	111.80	106.00
Min, Max	48.3, 187.0	66.5, 150.5	48.3, 187.0

Abbreviations: BMI = body mass index; CDC = Centers for Disease Control and Prevention; Max = maximum; Min = minimum; mITT = modified intention-to-treat; N = number of Patients; QD = once daily; P95 = BMI Percent of 95th percentile; SAS = Statistical Analysis Software; SD = Standard deviation; WHO = World Health Organization.

[a] BMI is calculated as weight (kg) / height (m)^2.

[b] BMI z-score calculated for patients <18 years old only is a measure of relative weight adjusted by child's age, sex and height at the time of data collection. The z-scores were calculated using the World Health Organization's WHO 2007 BMI SAS Macro Package.

[c] BMI Percent of 95th percentile for Patients <18 years old, was generated using the Center for Disease Control's (CDC) 2000 CDC Growth Chart Provided Source Code and Datasets, with patient's age (at date of data collection), sex, height, and weight as input variables.

Medical and Surgical History

The patients in this study were highly medically complex at study entry, with a notable preponderance of endocrine abnormalities related to their underlying hypothalamic tumors and/or surgery/chemotherapy/radiation therapy to treat the tumors. Importantly, the rates of the numerous

conditions present were, in general, highly similar between the 2 treatment groups. Of the 120 patients in the Pivotal cohort, 93 had a history of hypothalamic craniopharyngioma, 6 had a history of germinoma, 7 had a history of glioma, 6 had a history of astrocytoma, 2 had hamartomas, and 6 had a history of other documented injury to the hypothalamus that qualified them for enrolment in the study. Other common (occurring in ≥30% of patients) pre-existing diagnoses included diabetes insipidus, central hypothyroidism, growth hormone deficiency, hypopituitarism, secondary hypogonadism, obesity, and headache.

Table 7 ***Medical History Events Occurring in ≥5% of Patients (Pivotal Cohort, Safety Analysis Set)***

System organ class Preferred term	Setmelanotide N=81	Placebo N=39	Overall N=120
Patients with at Least One Medical History Event	**81 (100.0)**	**39 (100.0)**	**120 (100.0)**
Endocrine disorders	**81 (100.0)**	**38 (97.4)**	**119 (99.2)**
Diabetes insipidus	67 (82.7)	30 (76.9)	97 (80.8)
Central hypothyroidism	55 (67.9)	25 (64.1)	80 (66.7)
Growth hormone deficiency	55 (67.9)	22 (56.4)	77 (64.2)
Hypopituitarism	40 (49.4)	18 (46.2)	58 (48.3)
Secondary hypogonadism	32 (39.5)	13 (33.3)	45 (37.5)
Adrenal insufficiency	22 (27.2)	8 (20.5)	30 (25.0)
Secondary adrenocortical insufficiency	18 (22.2)	9 (23.1)	27 (22.5)
Adrenocorticotropic hormone deficiency	17 (21.0)	6 (15.4)	23 (19.2)
Hypothyroidism	13 (16.0)	5 (12.8)	18 (15.0)
Precocious puberty	5 (6.2)	6 (15.4)	11 (9.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**73 (90.1)**	**35 (89.7)**	**108 (90.0)**
Craniopharyngioma	57 (70.4)	28 (71.8)	85 (70.8)
Optic glioma	3 (3.7)	3 (7.7)	6 (5.0)

System organ class Preferred term	Setmelanotide N=81	Placebo N=39	Overall N=120
Metabolism and nutrition disorders	**53 (65.4)**	**29 (74.4)**	**82 (68.3)**
Obesity	36 (44.4)	18 (46.2)	54 (45.0)
Vitamin D deficiency	12 (14.8)	8 (20.5)	20 (16.7)
Type 2 diabetes mellitus	6 (7.4)	5 (12.8)	11 (9.2)
Hyperphagia	8 (9.9)	2 (5.1)	10 (8.3)
Hypertriglyceridaemia	7 (8.6)	3 (7.7)	10 (8.3)
Hyperlipidaemia	5 (6.2)	4 (10.3)	9 (7.5)
Glucose tolerance impaired	7 (8.6)	1 (2.6)	8 (6.7)
Hypercholesterolaemia	5 (6.2)	2 (5.1)	7 (5.8)
Dyslipidaemia	3 (3.7)	3 (7.7)	6 (5.0)
Insulin resistance	4 (4.9)	2 (5.1)	6 (5.0)
Nervous system disorders	**51 (63.0)**	**29 (74.4)**	**80 (66.7)**
Headache	24 (29.6)	16 (41.0)	40 (33.3)
Hydrocephalus	11 (13.6)	8 (20.5)	19 (15.8)
Seizure	8 (9.9)	6 (15.4)	14 (11.7)
Migraine	6 (7.4)	3 (7.7)	9 (7.5)
Narcolepsy	6 (7.4)	2 (5.1)	8 (6.7)
Hemiparesis	6 (7.4)	0	6 (5.0)
Hypersomnia	5 (6.2)	1 (2.6)	6 (5.0)
Psychiatric disorders	**40 (49.4)**	**25 (64.1)**	**65 (54.2)**
Depression	15 (18.5)	9 (23.1)	24 (20.0)
Anxiety	12 (14.8)	10 (25.6)	22 (18.3)
Attention deficit hyperactivity disorder	8 (9.9)	5 (12.8)	13 (10.8)
Insomnia	5 (6.2)	5 (12.8)	10 (8.3)
Sleep disorder	6 (7.4)	3 (7.7)	9 (7.5)
Surgical and medical procedures	**42 (51.9)**	**22 (56.4)**	**64 (53.3)**
Ventriculo-peritoneal shunt	11 (13.6)	6 (15.4)	17 (14.2)
Cerebrospinal fluid reservoir placement	7 (8.6)	1 (2.6)	8 (6.7)
Tumour excision	6 (7.4)	2 (5.1)	8 (6.7)
Adenotonsillectomy	5 (6.2)	2 (5.1)	7 (5.8)
Tonsillectomy	3 (3.7)	3 (7.7)	6 (5.0)

System organ class Preferred term	Setmelanotide N=81	Placebo N=39	Overall N=120
Eye disorders	**32 (39.5)**	**17 (43.6)**	**49 (40.8)**
Visual impairment	7 (8.6)	3 (7.7)	10 (8.3)
Blindness	6 (7.4)	2 (5.1)	8 (6.7)
Optic atrophy	4 (4.9)	4 (10.3)	8 (6.7)
Strabismus	6 (7.4)	2 (5.1)	8 (6.7)
Visual field defect	4 (4.9)	3 (7.7)	7 (5.8)
Blindness unilateral	5 (6.2)	1 (2.6)	6 (5.0)
Gastrointestinal disorders	**26 (32.1)**	**14 (35.9)**	**40 (33.3)**
Gastrooesophageal reflux disease	10 (12.3)	7 (17.9)	17 (14.2)
Constipation	9 (11.1)	5 (12.8)	14 (11.7)
Nausea	4 (4.9)	3 (7.7)	7 (5.8)
Respiratory, thoracic and mediastinal disorders	**30 (37.0)**	**9 (23.1)**	**39 (32.5)**
Obstructive sleep apnoea syndrome	16 (19.8)	2 (5.1)	18 (15.0)
Sleep apnoea syndrome	3 (3.7)	4 (10.3)	7 (5.8)
Immune system disorders	**22 (27.2)**	**8 (20.5)**	**30 (25.0)**
Seasonal allergy	11 (13.6)	7 (17.9)	18 (15.0)
Skin and subcutaneous tissue disorders	**18 (22.2)**	**11 (28.2)**	**29 (24.2)**
Acanthosis nigricans	7 (8.6)	1 (2.6)	8 (6.7)
General disorders and administration site conditions	**17 (21.0)**	**8 (20.5)**	**25 (20.8)**
Fatigue	7 (8.6)	3 (7.7)	10 (8.3)
Hepatobiliary disorders	**14 (17.3)**	**7 (17.9)**	**21 (17.5)**
Metabolic dysfunction-associated liver disease	7 (8.6)	2 (5.1)	9 (7.5)
Hepatic steatosis	3 (3.7)	3 (7.7)	6 (5.0)
Vascular disorders	**13 (16.0)**	**7 (17.9)**	**20 (16.7)**
Hypertension	6 (7.4)	5 (12.8)	11 (9.2)
Deep vein thrombosis	5 (6.2)	1 (2.6)	6 (5.0)

System organ class Preferred term	Setmelanotide N=81	Placebo N=39	Overall N=120
Reproductive system and breast disorders	**9 (11.1)**	**4 (10.3)**	**13 (10.8)**
Amenorrhoea	5 (6.2)	2 (5.1)	7 (5.8)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of Patients; QD = once daily.
Note: Not all diagnostic tumors were recorded in patients' medical histories. A full accounting of diagnostic tumor history is provided in Listing 16.2.4.4.
Note: Medical history findings are coded using MedDRA version 25.1 or later.
Note: In case of multiple events, a patient is counted only once per system organ class and once per preferred term.

Per protocol, all patients also had to have a history of the following to enter the study:

• Diagnosis of craniopharyngioma or other brain lesion affecting the hypothalamic region and has undergone surgery, or chemotherapy, or radiation therapy involving the hypothalamus at least 6 months before Screening, OR

• Documented injury to the hypothalamus at least 6 months before Screening for which surgery/radiation is not indicated.

The tumor types qualifying Pivotal patients for inclusion in this study are summarized below.

Table 8 Diagnostic Tumor History (Pivotal Cohort, Safety Analysis Set)

Tumor Type	Setmelanotide N=81 n(%)	Placebo N=39 n(%)
Craniopharyngioma	63 (77.78)	30 (76.92)
Germinoma	5 (6.17)	1 (2.56)
Glioma	4 (4.94)	3 (7.69)
Astrocytoma	3 (3.70)	3 (7.69)
Hamartoma	1 (1.23)	1 (2.56)
Other	5 (6.17)	1 (2.56)
Arachnoid cyst	1 (1.23)	-
Heterogeneous mass in the suprasellar region involving the hypothalamus and optic chiasm	1 (1.23)	-
Mature teratoma	1 (1.23)	-
Cavernous haemangioma	1 (1.23)	-
Either craniopharyngioma or astrocytoma.	1 (1.23)	-
Hypothalamic glioma pilocytic astrocytoma	-	1 (2.56)

Numbers analysed

Efficacy analyses were performed for the Pivotal Cohort, defined as the first 120 patients dosed in any region who had completed the study and any patients who discontinued after receiving their first dose of study drug. Unless otherwise specified, efficacy analyses were performed using the modified intent-to-treat set (mITT), defined as all randomized patients who were exposed to at least 1 dose of study treatment.

Treatment Compliance

Patients in the setmelanotide and placebo groups (Pivotal cohort) were compliant with administration of study drug 84.41% and 87.00% of the time on study, respectively (with consistent results in the All Patient cohort).

Table 9 Patient Compliance, Pivotal and All Patient Cohorts (Safety Analysis Set)

Pivotal Cohort			
Value	**Statistic**	**Setmelanotide QD N=81 n(%)**	**Placebo QD N=39 n(%)**
Dosing Compliance (%) (Prior to Start of Bridging visits)[b]	n	81	39
	Mean (SD)	84.41 (14.024)	87.00 (14.234)
	Median	87.32	92.25
	Min, Max	42.3, 100.0	44.3, 100.0

All Patient Cohort			
Value	**Statistic**	**Setmelanotide QD N=94 n(%)**	**Placebo QD N=48 n(%)**
Dosing Compliance (%) (Prior to Start of Bridging visits)[b]	n	94	48
	Mean (SD)	84.43 (14.309)	87.09 (13.992)
	Median	88.46	92.37
	Min, Max	42.3, 100.0	44.3, 100.0

Abbreviations: QD = once daily.
Note: The final trial treatment/ End of Treatment is planned to occur after 52 weeks on a therapeutic regimen. Patients who complete assessments through the EOT visit may be eligible to enter an open-label long-term extension (LTE) trial or attend Bridging visits with open-label setmelanotide.
[a] Treatment Duration (weeks) = (date of last dose – date of first dose + 1) / 7.
[b] Dosing Compliance (%) = (Number of Doses Administered (Prior to First Bridging visit) / Duration of Treatment in Days [Prior to First Bridging visit]) * 100.

Outcomes and estimation

Primary Efficacy Endpoint

Mean Percent Change From Baseline in BMI

Treatment with a therapeutic regimen of setmelanotide for 52 weeks in Phase 3 Study RM-493- 040 resulted in a statistically significant ($p<0.0001$) and clinically meaningful reduction in BMI compared to placebo-treated patients; thus, the primary efficacy endpoint for this pivotal study was met.

At baseline, patients in both treatment groups had a mean BMI >35 kg/m2 consistent with Class 2 obesity. After 52 weeks of treatment on a therapeutic regimen of setmelanotide, the LSM BMI decreased by -16.51%. In contrast, treatment with placebo resulted in a 3.32% increase in the LSM BMI for a placebo-corrected treatment effect (LSM difference) of -19.83%. Moreover, after 52 weeks at a therapeutic dose, the actual mean BMI for setmelanotide-treated patients was 29.58, which falls within the BMI classification of overweight, while the mean BMI for placebo-treated patients was 38.08, consistent with Class 2 obesity.

Table 10 ***BMI Mean Percent Change from Baseline After 52 Weeks on Therapeutic Regimen (Pivotal Cohort, mITT Analysis Set)***

Visit	Value	Statistic	Setmelanotide (N=81)	Placebo (N=39)
Baseline	Actual	n	81	39
		Mean (SD)	35.73 (9.173)	36.78 (9.332)
		Median	33.27	37.35
		Min, Max	21.3, 69.2	21.3, 70.0
		95% CI	(33.70, 37.76)	(33.75, 39.80)
Primary Timepoint	Actual	n	81	39
		Mean (SD)	29.58 (8.069)	38.08 (9.996)
		Median	29.14	38.82
		Min, Max	15.9, 59.4	18.9, 70.2
		95% CI	(27.82, 31.35)	(34.94, 41.22)
	Change	n	81	39
		Mean (SD)	-6.15 (5.861)	1.30 (2.185)
		Median	-4.79	1.45
		Min, Max	-22.6, 4.9	-5.0, 6.6
		95% CI	(-7.43, -4.86)	(0.60, 2.00)
	Percent Change	n	81	39
		Mean (SD)	-16.46 (14.028)	3.29 (6.821)
		Median	-15.74	3.91
		Min, Max	-40.1, 15.2	-17.7, 17.9
		95% CI	(-19.56, -13.37)	(1.11, 5.47)
		n	81	39
		ANCOVA LSM (SE)	-16.51 (1.401)	3.32 (1.984)
		95% CI for the LSM	(-19.26, -13.76)	(-0.57, 7.20)
		LSM Difference (SE)	-19.83 (2.411)	
		95% CI of LSM Difference	-24.55, -15.10	
		p-value	<0.0001	

Abbreviations: ANCOVA = analysis of covariance; BMI = body mass index; CI = confidence interval; LSM = least squared mean; Max = maximum; Min = minimum; mITT = modified intention-to-treat; N = number of patients in

As shown in Figure , setmelanotide's effects on BMI occurred rapidly, being evident within 4 weeks of initiating treatment (earliest timepoint assessed), and increased over time.

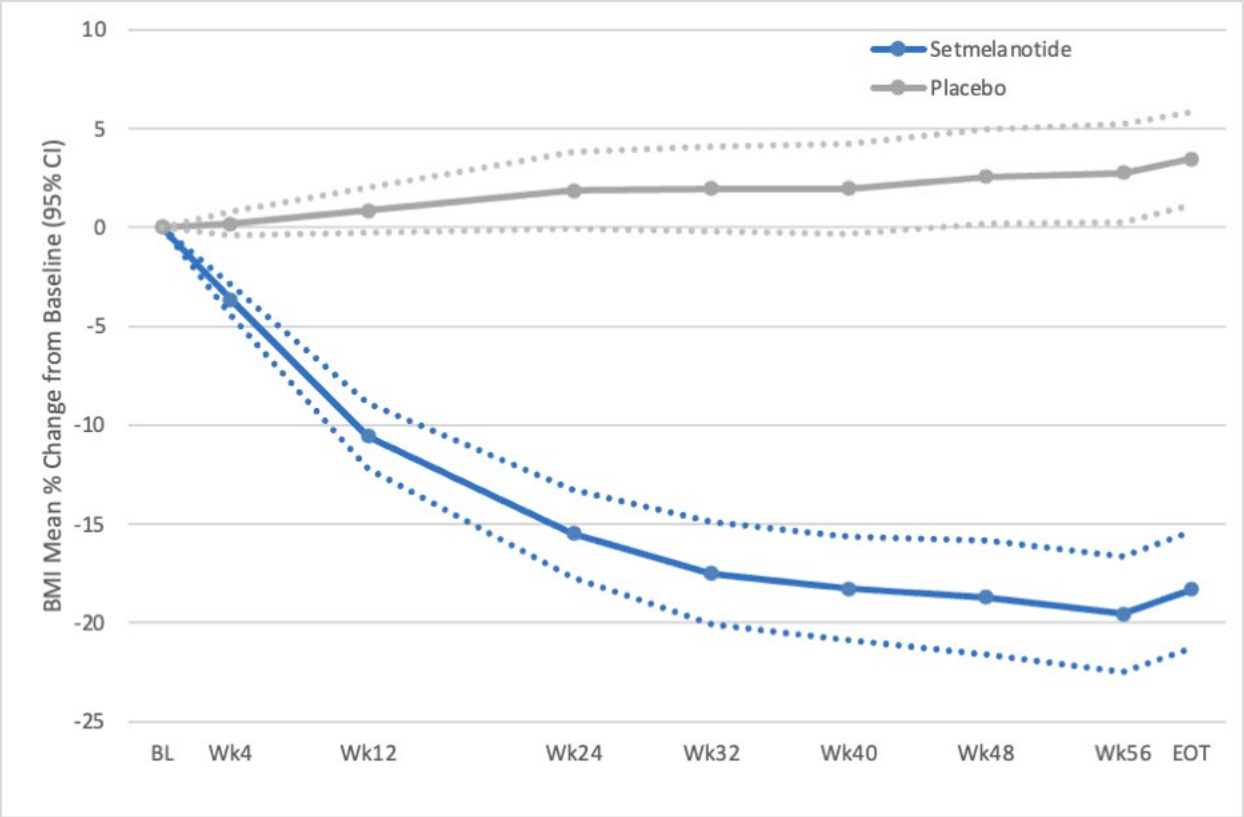


Figure 5 ***Mean Percent Change from Baseline in BMI by Visit As Observed Values (RM-493-040, mITT Analysis Set, Pivotal Cohort)***

Abbreviations: BMI = body mass index; CI = confidence interval; EOT = end of treatment; mITT = modified intention-to-treat; Wk = week.

Key Secondary Efficacy Endpoints

Proportion of Patients with a ≥5% Reduction in BMI (Patients ≥18 Years) or a ≥0.2-Point Reduction in BMI Z-Scores (Patients <18 Years) From Baseline

The first key secondary efficacy endpoint in study RM-493-040 was the proportion of patients with a clinically meaningful ≥5% reduction from baseline in BMI (patients ≥18 years) or a ≥0.2-point reduction from baseline in BMI z-score (patients <18 years of age). Consistent with its profound effect on the percent change in BMI, treatment with a therapeutic regimen of setmelanotide for 52 weeks also resulted in a statistically significant ($p<0.0001$) increase in the proportion of patients who met this endpoint (82.73%) compared to treatment with placebo (20.9%).

When this endpoint was re-analysed post hoc using more stringent cutoffs for clinically meaningfulness, i.e., a mean percent reduction from baseline in BMI of ≥10% (for patients ≥18 years)

or a mean reduction from baseline in BMI z-score of 0.5 points (for patients <18 years), the statistically significant difference between the 2 treatment groups was maintained (p<0.0001) with 69.32% of setmelanotide vs 10.41% of placebo-treated patients hitting this Endpoint.

Proportion of Patients with a ≥5% Reduction in BMI From Baseline

The next key secondary endpoint in RM-493-040 was the proportion of patients with a clinically meaningful ≥5% reduction from baseline in BMI. Treatment with a therapeutic regimen of setmelanotide for 52 weeks resulted in a statistically significant (p<0.0001) increase (79.53%) in the proportion of patients who met this endpoint compared to treatment with placebo (10.41%).

Importantly, the striking effect of setmelanotide on the proportion of patients achieving a clinically meaningful reduction in BMI were maintained when more stringent cutoffs of 10% (prespecified analysis), 15% (post hoc analysis), and 20% (post hoc analysis) were used. As shown in Figure , 63% of setmelanotide-treated patients achieved a ≥10% reduction in BMI compared to just 5.18% placebo patients (p<0.0001). Similarly, 50.64% of setmelanotide-treated patients achieved a ≥15% reduction in BMI compared to just 2.59% placebo patients (p<0.0001), and 43.21% of setmelanotide-treated patients achieved a ≥20% reduction in BMI compared to 0% of placebo patients (p<0.0001).

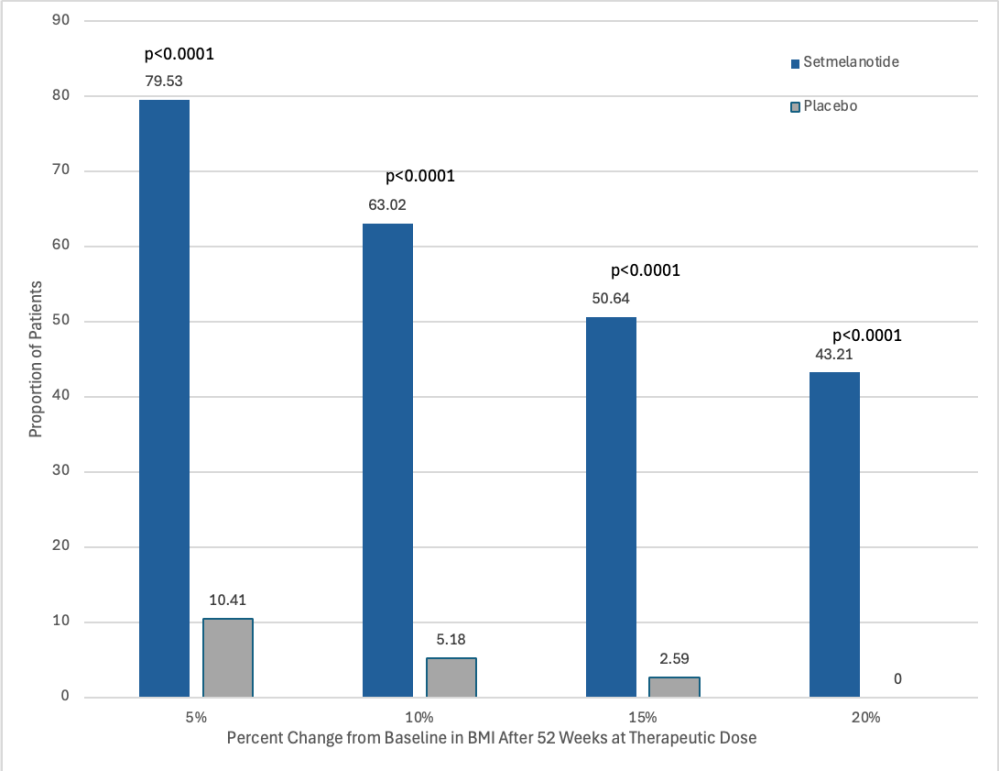


Figure 6 ***Proportion of Patients with ≥5%, ≥10%, ≥15%, or ≥20% Reductions in BMI From Baseline After 52 Weeks on a Therapeutic Regimen (RM-493-040, Pivotal Cohort, mITT Analysis Set)***

Abbreviations: BMI = body mass index; mITT = modified intention-to-treat.

Mean Change From Baseline in Most Hunger

The third key secondary endpoint in RM-493-040 was the mean change from baseline in the weekly average of the most daily hunger scores for patients ≥12 years of age. As shown in Figure , the weekly average of the most daily hunger scores was significantly (p=0.0086) reduced in the setmelanotide group (LSM of -2.73) compared to treatment with placebo (-1.45).

Average hunger scores were also significantly (p=0.0016) reduced in the setmelanotide-treated patients (LSM of -2.85) compared with placebo (-1.40). A 1- to 2-point reduction on these items (for patients ≥12 years of age) has been estimated as the clinically meaningful within-patient change threshold for patients with rare MC4R pathway diseases.

Note that directionally consistent results were obtained in patients 6 to <12 years of age that were administered the Hunger Questions for Patients 6 to <12 Years of Age© (Version 1.0).

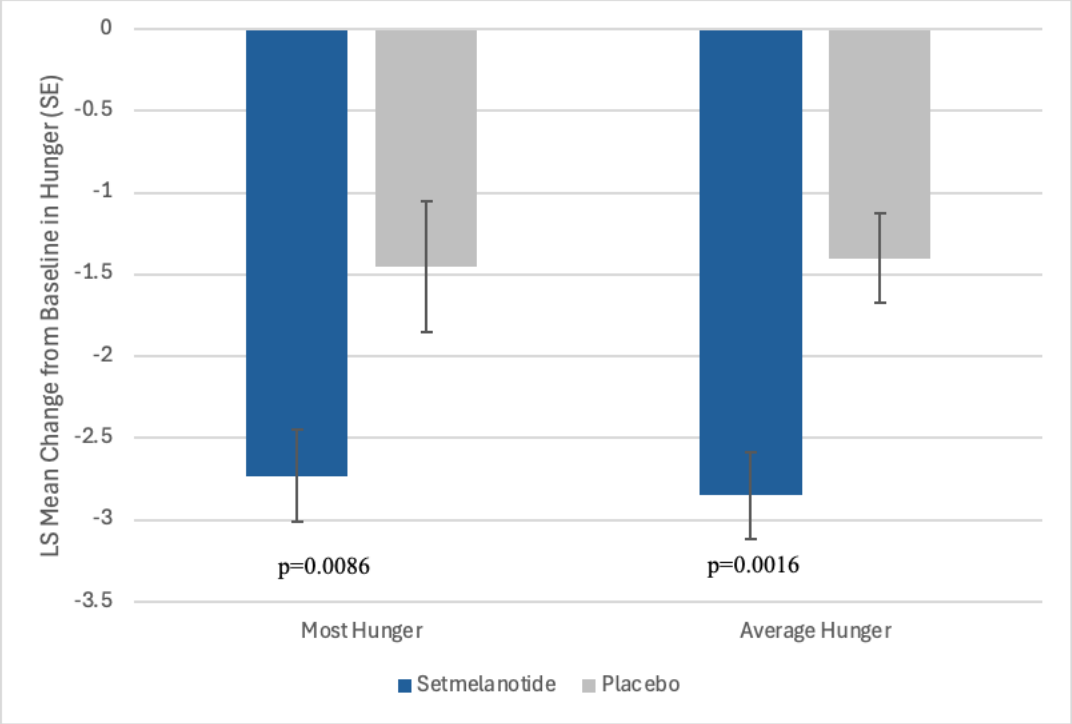


Figure 7 ***Weekly Average Daily Hunger Score Mean Change From Baseline After 52 Weeks on Therapeutic Regimen – Patients ≥12 Years Old (RM-493-040, Pivotal Cohort, mITT Analysis Set)***

Abbreviations: mITT = modified intention-to-treat

Other Secondary Efficacy Endpoints

Mean Change from Baseline in BMI Z-Scores in Patients <18 Years

Consistent with its positive effects on BMI in all patients, treatment with a therapeutic regimen of setmelanotide for 52 weeks in Study RM-493-040 resulted in a statistically significant (p<0.0001) reduction in LSM BMI z-score (-1.47) in patients <18 years of age compared to placebo-treated patients (-0.012). Of note, changes in BMI z-scores of ≥0.2 are considered clinically meaningful. Setmelanotide's effects on BMI z-scores occurred rapidly, being evident within 4 weeks of initiating treatment (earliest timepoint assessed), and increased over time.

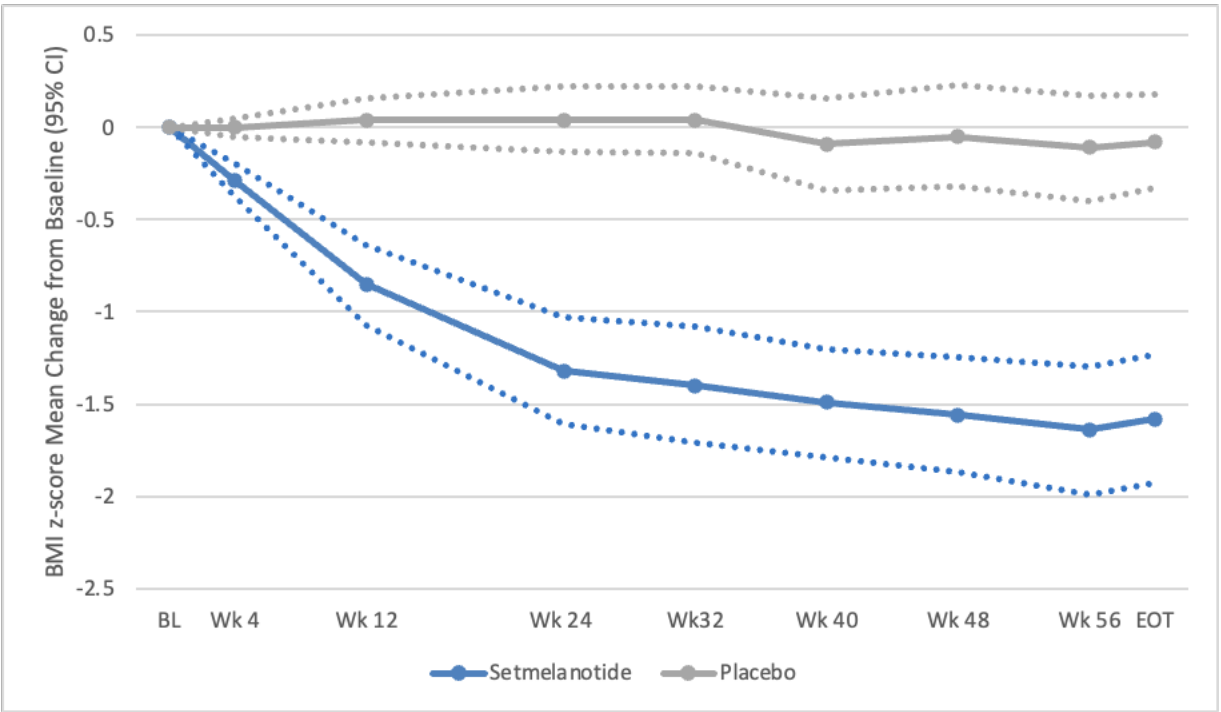


Figure 8 ***BMI Z-Score Mean Change From Baseline by Visit As Observed Values - <18 Years Old (RM-493-040, mITT Analysis Set, Pivotal Cohort)***

Abbreviations: BL = baseline; BMI = body mass index; CI = confidence interval; EOT = end of treatment; mITT = modified intention-to-treat; Wk = week.

Mean Change from Baseline in Waist Circumference

Treatment with a therapeutic regimen of setmelanotide for 52 weeks resulted in a statistically significant (p<0.0001) LSM reduction in waist circumference of -11.58 cm compared to an increase of 3.85 cm in patients treated with placebo. The positive effect of setmelanotide on waist circumference over time is displayed in Figure .

The National Institutes of Health (NIH) has stated that a sustained reduction of 4 cm may be clinically relevant (NIH 2000). More recently it has been suggested that similar to body weight and BMI, a reduction in waist circumference of >5% may be considered a clinically relevant change (Stevens 2006; Ross 2020). Of note, patients in the setmelanotide group had an observed mean waist circumference of 106.57 and 94.1 cm at baseline and the primary timepoint, respectively, consistent with an ~11.7% reduction in waist circumference.

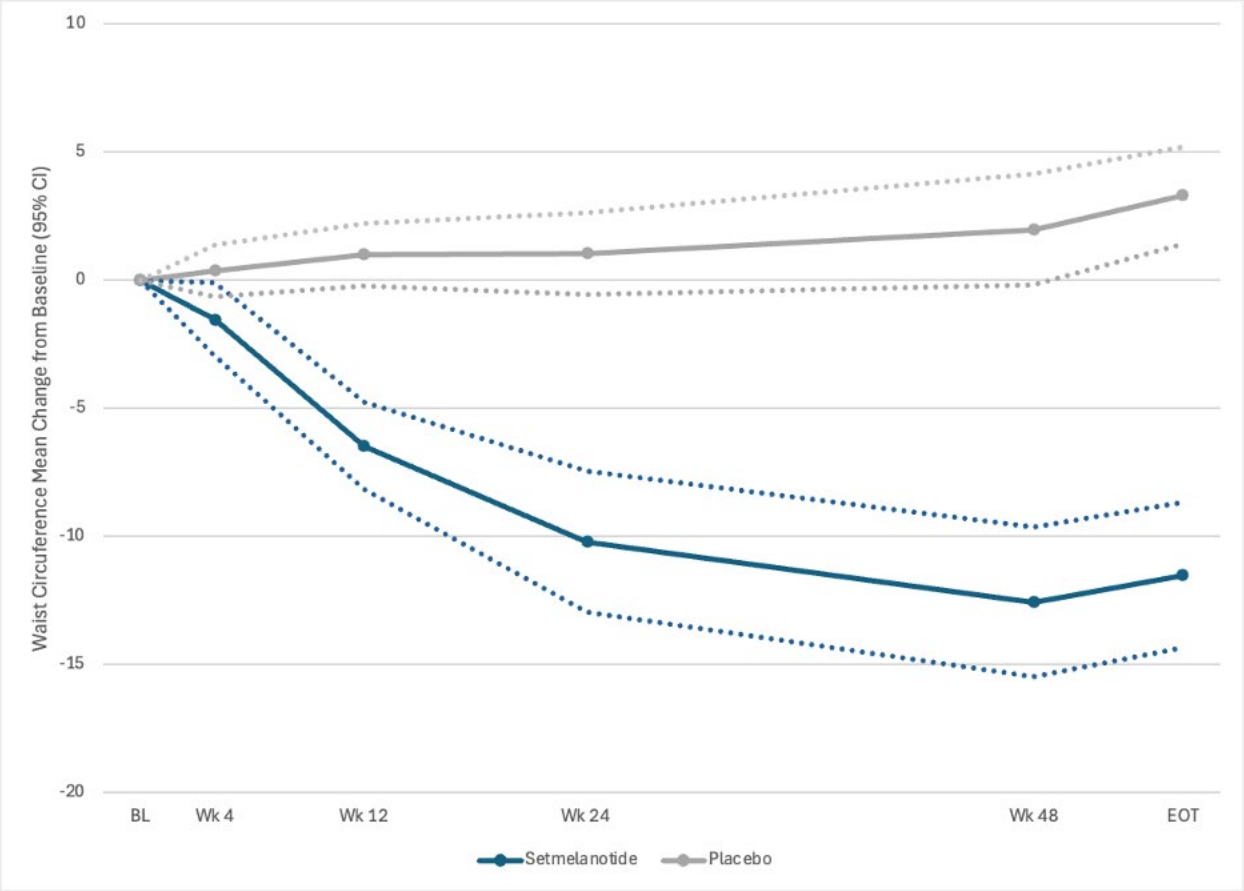


Figure 9 ***Mean Change From Baseline in Waist Circumference (cm) by Visit As Observed Values (Pivotal Cohort, RM-493-040, mITT Analysis Set)***

Abbreviations: CI = confidence interval; mITT = modified intention-to-treat; Wk = week.

Mean Change From Baseline in the Weekly Average of the Symptoms of Hyperphagia Composite Score

Consistent with its positive effects on hunger, treatment with a therapeutic regimen of setmelanotide for 52 weeks produced statistically significant reductions in hyperphagia as measured by the Symptoms of Hyperphagia scale compared to placebo. Note that scores on this scale range from 0 to 2 with higher scores indicating more hyperphagia. The LSM change from baseline on this scale in patients ≥12 years of age was -0.30 vs -0.14 in the setmelanotide and placebo-treated groups, respectively (p=0.0028). The LSM change from baseline on this scale in patients unable to self-report (caregiver assessment) was -0.65 vs -0.24 in the setmelanotide and placebo-treated groups, respectively (p=0.0004).

Mean Change from Baseline in Cardiometabolic Parameters

As shown in Figure , treatment with a therapeutic regimen of setmelanotide for 52 weeks resulted in statistically significant reductions in systolic and diastolic blood pressure compared to placebo. These results are directionally consistent with those obtained with 24-hour ambulatory blood pressure assessment.

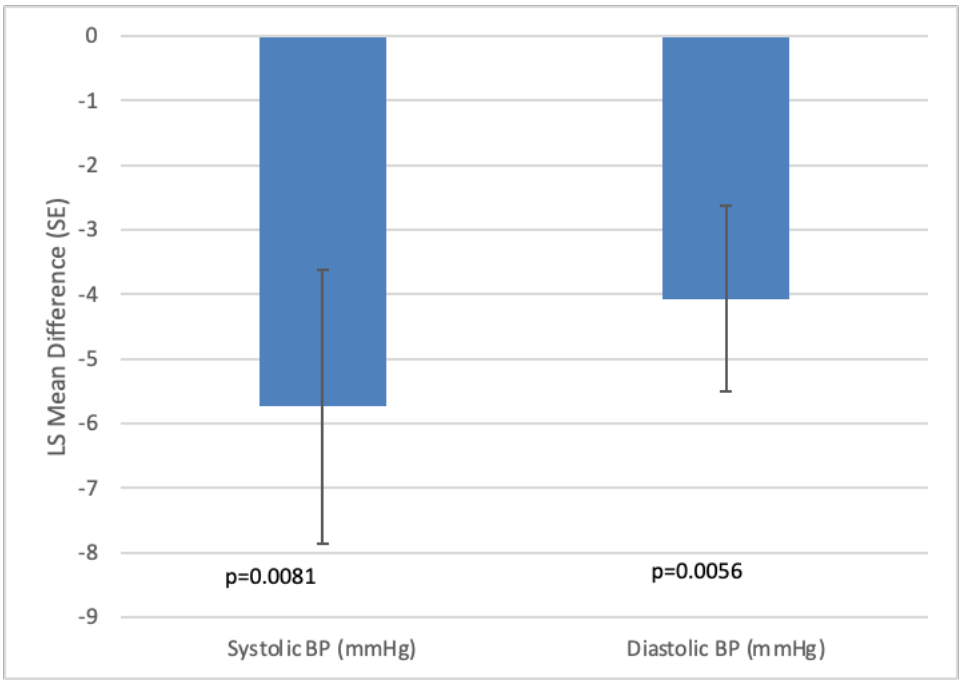


Figure 10 ***Placebo-Corrected Treatment Effect for Blood Pressure After 52 Weeks on a Therapeutic Regimen (RM-493-040, Pivotal Cohort mITT Analysis)***

Abbreviations: BP = blood pressure; LS = least squares; mITT = modified intention-to-treat; SE = standard error.

Statistically significant improvements in lipid and A1C levels as well in aspartate aminotransferase (AST; LSM difference = -7.46, p=0.0107) and alanine aminotransferase (ALT; LSM difference = -14.87, p=0.0051) levels were also observed.

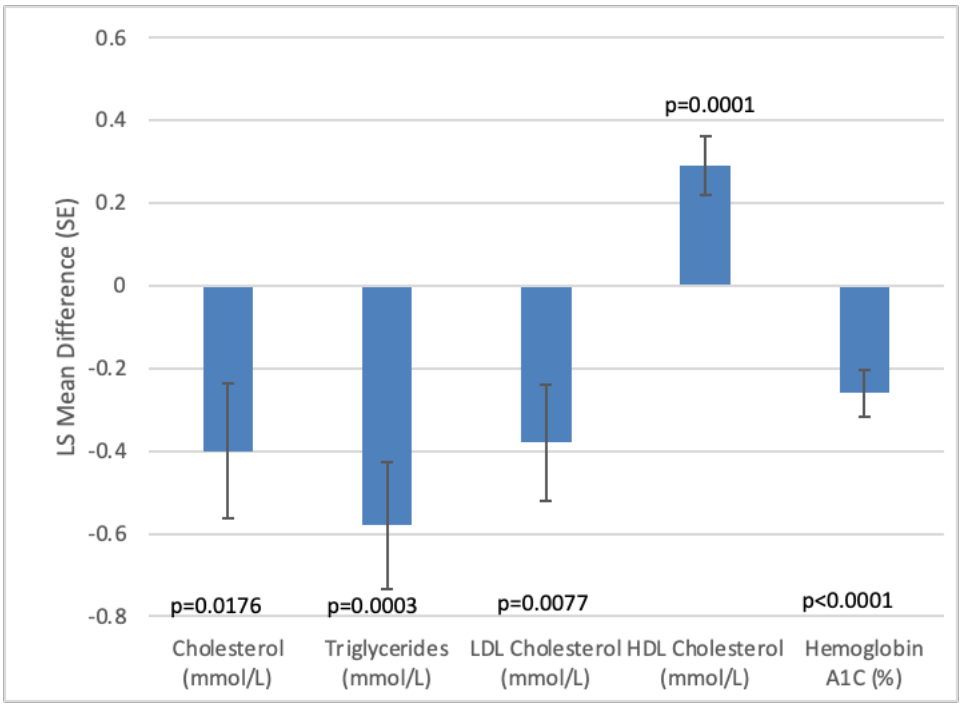


Figure 11 ***Placebo-Corrected Treatment Effect for Lipid and Hemoglobin A1C Parameters After 52 Weeks on a Therapeutic Regimen (RM-493-040, Pivotal Cohort, mITT Analysis)***

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein; LS = least squares; mITT = modified intention-to-treat; SE = standard error.

Mean Change From Baseline in Total and Physical Functioning Score for the Impact of Weight on Quality of Life-Lite

The Impact of Weight on Quality of Life for Clinical Trials (IWQOL-Lite-CT) was used to evaluate the specific impact of obesity on quality of life in adults ≥18 years of age while the Impact of Weight on Quality of Life (IWQOL-Kids) was used for patients between the ages of 11 and <18. On both measures, scores range from 0 to 100 with higher scores reflecting higher quality of life.

After 52 weeks on a therapeutic regimen of setmelanotide, adult patients showed large, statistically significant (p<0.0001) improvements relative to placebo-treated patients in both IWQOL-Lite Total and Physical Function scores (Table). Of note, an improvement of 16.6 points on IWQOL-Lite-CT Total Score is considered meaningful (Kolotkin 2021).

Similar to adults, setmelanotide-treated paediatric patients experienced a large, statistically significant (p=0.0027) improvement in the impact of weight on their quality of life as measured by IWQOL-Kids Total scores (Table). Note that on this scale, a change ≥4.8 is considered clinically meaningful (Modi 2010).

Table 11 ***Mean Change in IWQOL Scores in Adult (≥18 Years) and Paediatric (11 to <18 Years) Patients After 52 Weeks on Therapeutic Regimen (RM-493-040, mITT Analysis Set, Pivotal Cohort)***

Adult Patients ≥18 Years (IWQOL-Lite-CT)			
Mean Change in Total Scores After 52 weeks on Therapeutic Regimen - ≥18 years olds	Statistic	Setmelanotide N=33	Placebo N=16
	N ANCOVA LSM (SE) a 95% CI	25 32.04 (3.059) (25.83, 38.25)	13 3.00 (4.249) (-5.62, 11.63)
	LSM Difference (SE) 95% CI p-value	29.04 (5.248) 18.38, 39.69 <0.0001	
Mean Change in Physical Function Scores After 52 weeks on Therapeutic Regimen - ≥18 years olds	N ANCOVA LSM (SE) a 95% CI	25 31.32 (3.702) (23.80, 38.84)	13 -4.46 (5.145) (-14.91, 5.98)
	LSM Difference (SE) 95% CI p-value	35.78 (6.357) 22.88, 48.69 <0.0001	
Paediatric Patients 11 to <18 Years (IWQOL-Kids)			
Mean Change in Reported Total Scores After 52 weeks on Therapeutic Regimen – 11 to <18 years olds	Statistic	Setmelanotide N=48	Placebo N=23
	N ANCOVA LSM (SE) b 95% CI	17 22.05 (4.708) (12.34, 31.77)	11 7.92 (4.001) (-0.34, 16.18)
	LSM Difference (SE) 95% CI p-value	14.13 (4.222) 5.42, 22.85 0.0027	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; IWQOL = Impact of Weight on Quality of Life; LSM = least squared mean; mITT = modified intention-to-treat; N = number of patients in the treatment group; SE = standard error.

[a] ANCOVA model with unequal variance to account for possible unequal residual variances was used to estimate the difference between treatment groups. The model was adjusted with the baseline

measurements, and subpopulation (Japanese and non-Japanese). Resulting overall estimates of LS means, differences in LS means, corresponding CI and p-value are presented.

[b] ANCOVA model with unequal variance to account for possible unequal residual variances was used to estimate the difference between treatment groups. The model was adjusted with the baseline measurements, stratification factors of age group (≥12 and <18 years, and <12 years) and subpopulation (Japanese and non-Japanese). Resulting overall estimates of LS means, differences in LS means, corresponding CI and p-value are presented.

Qualitative Exit Interviews

At participating US sites, patients ≥12 years old and caregivers of patients who could not self-report were invited to participate in a qualitative interview study which was conducted outside of the main study protocol. The interviews were approximately 75 minutes in duration and were conducted via Zoom by 2 experienced qualitative researchers from RTI-HS using a semi-structured interview guide, with each interview beginning with a series of questions about experiences or observations (for patients and caregivers, respectively) related to hunger, eating behaviors, energy levels, and physical activity after damage to the hypothalamus. Patients were then asked to describe any changes they experienced (for patients) or observed (for caregivers) in hunger, eating behaviors, energy levels, and physical activity after initiating treatment with the study drug (setmelanotide or placebo), as well as the perceived meaningfulness of these changes.

In total, 30 interviews were completed with consenting participants from US sites: 16 interview participants were caregivers, 10 were adult patients, and 4 were adolescent patients. The mean age of adult patients was 28.2 years (range, 19-49 years) and the mean age of adolescent patients was 15.0 years (range, 13-17 years). The mean age of patients for whom caregivers provided care was 13.4 years (range, 4-24 years); 8 were caregivers of patients aged ≤11 years at the time of interview, and 8 were caregivers of patients aged ≥12 years. The majority of interview participants were female (n=24).

Consistent with the clinical trial results, interview participants on setmelanotide were more likely to report improvements in weight and hunger, with a total of 23 (n=22 on setmelanotide; n=1 on placebo) of the 30 participants experiencing or observing reductions in both weight and hunger during the clinical study. Additionally, 19 of these 23 participants reported an increase in physical activity (n=18 on setmelanotide; n=1 on placebo), and 14 reported an increase in energy (n=14 on setmelanotide). Specifically, the 23 individuals who reported a reduction in hunger and weight consistently described positive impacts including physical changes (i.e., reductions in pain and improvements in energy) that corresponded with improvements in their ability and desire to engage in physical activities. Reductions in hunger were also described as having far-reaching benefits, with positive impacts reported on self-esteem, social and family activities and relationships, and concentration/focus. All study participants who reported a reduction in hunger and weight reported that this change was incredibly meaningful and allowed them or their child (and family) to live a more "normal" life.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12 ***Summary of Efficacy for trial RM-493-040***

Title: A PHASE 3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF SETMELANOTIDE IN PATIENTS WITH ACQUIRED HYPOTHALAMIC OBESITY		
Study identifier	Protocol number: RM-493-040 EudraCT number: 2022-503116-16-00	
Design	This was a Phase 3, double-blind, multi-center, placebo-controlled, randomized 2:1 (active to placebo), registrational study designed to assess the efficacy and safety of setmelanotide in patients ≥4 years of age with acquired hypothalamic obesity (HO). Following screening (for up to 8 weeks), eligible patients were randomized 2:1 to receive either setmelanotide or placebo for up to 60 weeks. Setmelanotide 0.5 mg once daily (QD) or the placebo equivalent was administered as the starting dose for all patients. After the initial 0.5 mg dose, patients dose escalated each week in increments of either 0.5 or 1.0 mg to achieve the individual patient's therapeutic regimen. The target therapeutic regimen varied by age (and weight for patients <6 years of age) and ranged from a maximum of 1.5 mg to 3.0 mg QD. The end-of-treatment (EOT) visit occurred after 52 weeks on a therapeutic regimen, which was the final planned week of dosing with study treatment. At the EOT visit, patients who completed 52 weeks on a therapeutic regimen and completed assessments through the EOT visit could be eligible to enter an open-label long-term extension (LTE) study or attend Bridging visits with open-label setmelanotide if the LTE was not yet available. For patients who did not receive setmelanotide following the EOT visit, a safety follow-up visit (SFV) was conducted ~2 weeks after the last dose of study treatment. During the treatment period efficacy and safety assessments were performed approximately every 4 weeks via either in-clinic visits or at-home telehealth visits.	
	Duration of main phase:	60 weeks
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable

Hypothesis	Superiority	
Treatments groups	Setmelanotide QD	Setmelanotide. 60 weeks, 82 patients randomised.
	Placebo QD	Placebo. 60 weeks, 39 patients randomised.
Endpoints and definitions	Primary endpoint (P)	Mean % change in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
	Key Secondary endpoint 1 (KS1)	The proportion of patients with ≥5% reduction in BMI in adult patients (≥18 years of age), or BMI z-score reduction of ≥0.2 points in paediatric patients (<18 years of age) from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
	Key Secondary endpoint 2 (KS2)	The proportion of all patients with ≥5% reduction in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
	Key Secondary endpoint 3 (KS3)	Mean change in the weekly average of the daily most hunger score in patients ≥12 years old from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
Data Cut-off Date	26 MARCH 2025	
Results and Analysis		
Analysis description	**Primary Analysis (P)**	
Analysis population and time point description	Modified intent to treat, defined as all randomized patients who were exposed to at least 1 dose of study treatment. Analyses performed on the mITT were based on treatment as randomized.	

Descriptive statistics and estimate variability	Visit	Value	Statistic	Setmelanotide N=81	Placebo N=39
	Baseline	Actual	n	81	39
			Mean (SD)	35.73 (9.173)	36.78 (9.332)
			Median	33.27	37.35
			Min, Max	21.3, 69.2	21.3, 70.0
			95% CI	(33.70, 37.76)	(33.75, 39.80)
	Primary Timepoint	Actual	n	81	39
			Mean (SD)	29.58 (8.069)	38.08 (9.996)
			Median	29.14	38.82
			Min, Max	15.9, 59.4	18.9, 70.2
			95% CI	(27.82, 31.35)	(34.94, 41.22)
		Change	n	81	39
			Mean (SD)	-6.15 (5.861)	1.30 (2.185)
			Median	-4.79	1.45
			Min, Max	-22.6, 4.9	-5.0, 6.6
			95% CI	(-7.43, -4.86)	(0.60, 2.00)
		Percent Change	n	81	39
			Mean (SD)	-16.46 (14.028)	3.29 (6.821)
			Median	-15.74	3.91
			Min, Max	-40.1, 15.2	-17.7, 17.9
			95% CI	(-19.56, -13.37)	(1.11, 5.47)
			n	81	39
			ANCOVA LSM (SE)	-16.51 (1.401)	3.32 (1.984)
			95% CI for the LSM	(-19.26, -13.76)	(-0.57, 7.20)
			LSM Difference (SE)	-19.83 (2.411)	
			95% CI of LSM Difference	-24.55, -15.10	
			p-value	<0.0001	
	Abbreviations: ANCOVA = analysis of covariance; BMI = body mass index; CI = confidence interval; LSM = least squared mean; Max = maximum; Min = minimum; mITT = modified intention-to-treat; N = number of patients in the treatment group; n = number of patients with non-missing values; SD = standard deviation; SE = standard error. Note: BMI is calculated as weight (kg) / height (m)^2. ANCOVA model with unequal variance to account for possible unequal residual variances was used to estimate the difference between treatment groups. The model was adjusted with the stratification factors of age group (≥18 years, ≥12 and <18 years, and <12 years) and subpopulation (Japanese and non-Japanese). Rubin's Rule was used to provide the overall estimates of differences in LS means, corresponding CI, and p-value.				
Analysis description	**Secondary analysis (KS1)**				

<table>
<tr><td>Analysis population and time point description</td><td>Modified intent to treat, defined as all randomized patients who were exposed to at least 1 dose of study treatment. Analyses performed on the mITT were based on treatment as randomized.</td></tr>
<tr><td>Descriptive statistics and estimate variability</td><td>
<table>
<tr><td rowspan="3">Adult Patients with ≥5% Reduction in BMI or Paediatric Patients with ≥0.2 BMI ZScore Reduction</td><td>Statistic</td><td>Setmelanotide N=81</td><td>Placebo N=39</td></tr>
<tr><td>Estimated %
95% CI</td><td>82.73
74.13, 91.33</td><td>20.90
8.01, 33.78</td></tr>
<tr><td>Risk Difference (SE) [a]
Risk Difference 95% CI [a]
p-value [a]</td><td colspan="2">62.53 (7.393)
48.04, 77.02
<0.0001</td></tr>
</table>
Abbreviations: BMI = body mass index; CI = confidence interval; MI = multiple imputation; mITT = modified intention-to-treat; N = number of patients in the treatment group; SE = standard error.

[a] The Binomial proportions for MI was analyzed using Cochran-Mantel-Haenszel test with adjustment of stratification factors of age group and subpopulation (Japanese and non-Japanese). For each MI dataset, the COMMONRISKDIFF option in PROC FREQ calculated the adjusted estimate of the risk difference of success (setmelanotide minus placebo) over all stratification factors with its 95% CI. Rubin’s Rule (PROC MIANALYZE) was used to provide the overall estimates of risk differences, corresponding CI, and p-value.
</td></tr>
<tr><td>Analysis description</td><td>Secondary analysis (KS2)</td></tr>
<tr><td>Analysis population and time point description</td><td>Modified intent to treat, defined as all randomized patients who were exposed to at least 1 dose of study treatment. Analyses performed on the mITT were based on treatment as randomized.</td></tr>
<tr><td>Descriptive statistics and estimate variability</td><td>
<table>
<tr><td rowspan="3">Patients with ≥5% Reduction in BMI from Baseline After 52 weeks on Therapeutic Regimen</td><td>Statistic</td><td>Setmelanotide N=81</td><td>Placebo N=39</td></tr>
<tr><td>Estimated %
95% CI</td><td>79.53
70.60, 88.47</td><td>10.41
0.75, 20.07</td></tr>
<tr><td>Risk Difference (SE) [a]
Risk Difference 95% CI [a]
p-value [a]</td><td colspan="2">69.07 (6.695)
55.95, 82.19
<0.0001</td></tr>
</table>
Abbreviations: BMI = body mass index; CI = confidence interval; MI = multiple imputation; mITT = modified intention-to-treat; N = number of patients in the treatment group; SE = standard error.

[a] The Binomial proportions for MI was analyzed using Cochran-Mantel-Haenszel test with adjustment of stratification factors of age group and subpopulation (Japanese and non-Japanese). For each MI dataset, the COMMONRISKDIFF option in PROC FREQ calculated the adjusted estimate of the risk difference of success (setmelanotide minus placebo) over all stratification factors with its 95% CI. Rubin’s Rule (PROC MIANALYZE) was used to provide the overall estimates of risk differences, corresponding CI, and p-value
</td></tr>
<tr><td>Analysis description</td><td>Secondary analysis (KS3)</td></tr>
<tr><td>Analysis population and time point description</td><td>Modified intent to treat, defined as all randomized patients who were exposed to at least 1 dose of study treatment. Analyses performed on the mITT were based on treatment as randomized.</td></tr>
</table>

Descriptive statistics and estimate variability	Visit	Value	Statistic	Setmelanotide N=61	Placebo N=28
	MOST HUNGER				
	Baseline	Actual	n	57	24
			Mean (SD)	6.77 (2.322)	7.23 (2.114)
			Median	7.43	7.93
			Min, Max	0.0, 10.0	1.1, 10.0
			95% CI	(6.15, 7.38)	(6.34, 8.13)
	Primary Timepoint	Actual	n	57	24
			Mean (SD)	4.08 (2.339)	5.64 (2.223)
			Median	3.97	5.95
			Min, Max	0.0, 8.8	0.0, 9.0
			95% CI	(3.43, 4.73)	(4.74, 6.54)
		Change	n	57	24
			Mean (SD)	-2.69 (2.265)	-1.59 (1.705)
			Median	-2.45	-1.23
			Min, Max	-7.8, 2.1	-5.0, 1.3
			95% CI	(-3.32, -2.06)	(-2.29, -0.90)
			n	57	24
			ANCOVA LSM (SE)	-2.73 (0.279)	-1.45 (0.399)
			95% CI for the LSM	(-3.28, -2.18)	(-2.23, -0.67)
			LSM Difference (SE)	-1.28 (0.486)	
			95% CI of LSM Difference	-2.23, -0.33	
			p-value	0.0086	

Visit	Value	Statistic	Setmelanotide N=61	Placebo N=28
AVERAGE HUNGER				
Baseline	Actual	n	57	24
		Mean (SD)	5.56 (2.160)	6.39 (2.195)
		Median	5.80	7.00
		Min, Max	0.0, 9.3	0.7, 10.0
		95% CI	(4.99, 6.13)	(5.46, 7.31)
Primary Timepoint	Actual	n	57	24
		Mean (SD)	2.89 (1.827)	4.66 (2.348)
		Median	2.72	4.79
		Min, Max	0.0, 7.7	0.0, 9.0
		95% CI	(2.36, 3.41)	(3.71, 5.61)
	Change	n	57	24
		Mean (SD)	-2.67 (2.269)	-1.73 (1.861)
		Median	-2.75	-1.28
		Min, Max	-8.2, 2.1	-6.0, 1.7
		95% CI	(-3.30, -2.04)	(-2.49, -0.97)
		n	57	24
		ANCOVA LSM (SE)	-2.85 (0.263)	-1.40 (0.374)
		95% CI	(-3.37, -2.34)	(-2.13, -0.67)
		LSM Difference (SE)	-1.45 (0.461)	
		95% CI	-2.36, -0.55	
		p-value	0.0016	

Abbreviations: ANCOVA = analysis of covariance; BMI = body mass index; CI = confidence interval; LSM = least squared mean; Max = maximum; Min = minimum; mITT = modified intention-to-treat; N = number of patients in the treatment group; n = number of patients with non-missing values; SD = standard deviation; SE = standard error.

ANCOVA model with unequal variance to account for possible unequal residual variances was used to estimate the difference between treatment groups. The model was adjusted with the Baseline weekly average hunger score, stratification factors of age group (≥18 years, and ≥12 and <18 years) and subpopulation (Japanese and non-Japanese). Rubin's Rule was used to provide the overall estimates of differences in LSMs, corresponding CI and p value.

2.3.2. Supportive studies

Study RM-493-030

Additional confirmatory/supportive efficacy and safety data derive from a completed Phase 2, multicenter, open-label study of setmelanotide in patients 6 to 40 years of age with acquired HO (Study RM 493-030).

Study design

Study RM 493-030 was a Phase 2, multicenter, open-label study designed to assess the effect of setmelanotide in patients with acquired HO. The study consisted of an 8 week screening period followed by a 16 week treatment period during which all patients received setmelanotide. After 16 weeks in the study, patients who met the study's primary endpoint could be eligible to enroll in a separate LTE study, RM 493-022; those who did not meet the primary endpoint or who elected not to continue setmelanotide had a final study visit for review of safety at Week 20.

To be eligible for this study, patients aged 6 to 40 years (inclusive) had to have documented evidence of acquired HO, including recent (within the previous 8 months) evidence of hypothalamic injury on magnetic resonance imaging (MRI), a diagnosis of craniopharyngioma or other non-malignant brain tumor affecting the hypothalamic region, and have undergone surgery, chemotherapy, or radiation ≥6 months and ≤15 years before Screening. Patients were also required to have either unilateral (at least 6 patients) or bilateral (at least 7 patients) hypothalamic lesions as assessed by MRI.

Patients from ≥6 to <16 years of age received 1 mg setmelanotide QD during Weeks 1 2, 2 mg QD during Weeks 3 4, and 3 mg QD through Week 16 while those >16 years received 2 mg QD during Weeks 1 2 followed by and 3 mg QD through Week 16.

Efficacy Endpoints and Analyses Methods

The endpoints (and analysis methods) for RM 493-030 that correspond to key endpoints assessed in pivotal Study RM 493-040 are summarized below.

Table 13 Select Efficacy Endpoints for Phase 2 Study RM-493-030

Endpoint	Analysis Methods 1
Mean percent change from baseline in BMI after 16 weeks of treatment with setmelanotide	Analyzed in the FAS. LOCF used. Analyzed using an exact binomial test at a 1-sided 0.05 significance level, compared to the null hypothesis proportion of 0.05 (which comes from a historical control rate of 5%) test, at a one-sided 2.5% significance level. The number of and the binomial proportion of patients who achieved at least 5% BMI reduction from baseline at 16 weeks, the corresponding 2-sided 90% confidence interval (CI), and one-sided binomial test p-value were presented. The Clopper-Pearson method was used to calculate the CI.

Endpoint	Analysis Methods 1
The proportion of patients with a ≥5% reduction in BMI (patients ≥18 years) or a ≥0.2-point reduction in BMI z-score (patients <18 years) from baseline after 16 weeks of treatment with setmelanotide	Same as above.
The proportion of patients with a ≥5% reduction in BMI from baseline after 16 weeks of treatment with setmelanotide	Same as above.
Mean change from baseline in the weekly average of the daily most hunger score in patients ≥12 years old after 16 weeks of treatment with setmelanotide	Descriptive statistics using data as observed.
Mean change from baseline in BMI z-scores in patients <18 years of age after 16 weeks of treatment with setmelanotide	Descriptive statistics using data as observed.
Mean change from baseline in waist circumference (cm) after 16 weeks of treatment with setmelanotide	Descriptive statistics using data as observed.

Abbreviations: BMI = body mass index; FAS = Full Analysis Set; LOCF = last observation carried forward.

[1]FAS population includes all patients who received at least 1 dose of setmelanotide and had baseline weight data.

Patient Baseline Characteristics

Patients in Study RM 493-030 were primarily White (77.8%) and male (61.1%) and were between the ages of 6 and 24 years with 13 patients below the age of 18 and 5 patients ≥18 years of age. Like the patients in RM 493-040, the patients in this study were medically complex at study entry. Of the 18 patients enrolled, 14 had a history of craniopharyngioma, 3 patients had a history of hypothalamic hamartoma, and 1 patient had a history of juvenile pilocytic astrocytoma in the hypothalamus. Other common (occurring in ≥30% of patients) pre-existing diagnoses included obesity, hypothyroidism, diabetes insipidus, growth hormone deficiency, adrenal insufficiency, hypopituitarism, secondary hypogonadism, hyperphagia, headache, and anxiety

Results

Mean Percent Change From Baseline in BMI

In the Phase 2 study, RM-493-030, treatment with setmelanotide for 16 weeks reduced mean BMI by -14.906% and the 90% CI (-18.9586, -10.8526) did not contain 0 indicating a statistically significant change from baseline.

Proportion of Patients with a ≥5% Reduction in BMI (Patients ≥18 Years) or a ≥0.2-Point Reduction in BMI ZScores (Patients <18 Years) From Baseline

In the Phase 2 study (RM-493-030), treatment with setmelanotide for 16 weeks in Study RM-493-030 resulted in a statistically significant (p<0.0001) 88.9% of patients meeting the endpoint of the proportion of patients with a clinically meaningful ≥5% reduction from baseline in BMI (patients ≥18 years) or a ≥0.2-point reduction from baseline in BMI z-score (patients <18 years of age).

Proportion of Patients with a ≥5% Reduction in BMI From Baseline

In the Phase 2 study (RM-493-030), treatment with setmelanotide for 16 weeks resulted in a statistically significant (p<0.0001) 88.9% and 72.2% of patients achieving reductions in BMI of ≥5% and ≥10%, respectively.

Mean Change From Baseline in Most Hunger

Treatment with setmelanotide for 16 weeks in Study RM-493-030 resulted in a mean reduction of most hunger of -2.922 and the 90% CI (-4.1708, -1.6733) did not contain 0 indicating the statistical significance of this finding

Mean Change from Baseline in BMI Z-Scores in Patients <18 Years

Treatment with setmelanotide for 16 weeks in Study RM-493-030 resulted in a mean reduction in BMI z-score of -1.280 and the 90% CI (-1.7918, -0.7684) did not contain 0 indicating the statistical significance of this finding

Mean Change from Baseline in Waist Circumference

Treatment with setmelanotide for 16 weeks in Study RM-493-030 resulted in a mean reduction in waist circumference of -11.996 cm and the 90% CI (-14.5431, -9.4486) did not contain 0 indicating the statistical significance of this finding.

Additional confirmatory/supportive efficacy and safety data derive from a completed Phase 2, multicenter, open-label study of setmelanotide in patients 6 to 40 years of age with acquired HO (Study RM 493-030).

Study design

Study RM 493-030 was a Phase 2, multicenter, open-label study designed to assess the effect of setmelanotide in patients with acquired HO. The study consisted of an 8 week screening period followed by a 16 week treatment period during which all patients received setmelanotide. After 16 weeks in the study, patients who met the study's primary endpoint could be eligible to enroll in a separate LTE study, RM 493-022; those who did not meet the primary endpoint or who elected not to continue setmelanotide had a final study visit for review of safety at Week 20.

To be eligible for this study, patients aged 6 to 40 years (inclusive) had to have documented evidence of acquired HO, including recent (within the previous 8 months) evidence of hypothalamic injury on magnetic resonance imaging (MRI), a diagnosis of craniopharyngioma or other non-malignant brain tumor affecting the hypothalamic region, and have undergone surgery, chemotherapy, or radiation ≥6

months and ≤15 years before Screening. Patients were also required to have either unilateral (at least 6 patients) or bilateral (at least 7 patients) hypothalamic lesions as assessed by MRI.

Patients from ≥6 to <16 years of age received 1 mg setmelanotide QD during Weeks 1 2, 2 mg QD during Weeks 3 4, and 3 mg QD through Week 16 while those >16 years received 2 mg QD during Weeks 1 2 followed by and 3 mg QD through Week 16.

Efficacy Endpoints and Analyses Methods

The endpoints (and analysis methods) for RM 493-030 that correspond to key endpoints assessed in pivotal Study RM 493-040 are summarized below.

Table 14 Select Efficacy Endpoints for Phase 2 Study RM-493-030

Endpoint	Analysis Methods 1
Mean percent change from baseline in BMI after 16 weeks of treatment with setmelanotide	Analyzed in the FAS. LOCF used. Analyzed using an exact binomial test at a 1-sided 0.05 significance level, compared to the null hypothesis proportion of 0.05 (which comes from a historical control rate of 5%) test, at a one-sided 2.5% significance level. The number of and the binomial proportion of patients who achieved at least 5% BMI reduction from baseline at 16 weeks, the corresponding 2-sided 90% confidence interval (CI), and one-sided binomial test p-value were presented. The Clopper-Pearson method was used to calculate the CI.
The proportion of patients with a ≥5% reduction in BMI (patients ≥18 years) or a ≥0.2-point reduction in BMI z-score (patients <18 years) from baseline after 16 weeks of treatment with setmelanotide	Same as above.
The proportion of patients with a ≥5% reduction in BMI from baseline after 16 weeks of treatment with setmelanotide	Same as above.
Mean change from baseline in the weekly average of the daily most hunger score in patients ≥12 years old after 16 weeks of treatment with setmelanotide	Descriptive statistics using data as observed.

Endpoint	Analysis Methods 1
Mean change from baseline in BMI z-scores in patients <18 years of age after 16 weeks of treatment with setmelanotide	Descriptive statistics using data as observed.
Mean change from baseline in waist circumference (cm) after 16 weeks of treatment with setmelanotide	Descriptive statistics using data as observed.

Abbreviations: BMI = body mass index; FAS = Full Analysis Set; LOCF = last observation carried forward.

[1]FAS population includes all patients who received at least 1 dose of setmelanotide and had baseline weight data.

Patient Baseline Characteristics

Patients in Study RM 493-030 were primarily White (77.8%) and male (61.1%) and were between the ages of 6 and 24 years with 13 patients below the age of 18 and 5 patients ≥18 years of age. Like the patients in RM 493-040, the patients in this study were medically complex at study entry. Of the 18 patients enrolled, 14 had a history of craniopharyngioma, 3 patients had a history of hypothalamic hamartoma, and 1 patient had a history of juvenile pilocytic astrocytoma in the hypothalamus. Other common (occurring in ≥30% of patients) pre-existing diagnoses included obesity, hypothyroidism, diabetes insipidus, growth hormone deficiency, adrenal insufficiency, hypopituitarism, secondary hypogonadism, hyperphagia, headache, and anxiety

Results

Mean Percent Change From Baseline in BMI

In the Phase 2 study, RM-493-030, treatment with setmelanotide for 16 weeks reduced mean BMI by -14.906% and the 90% CI (-18.9586, -10.8526) did not contain 0 indicating a statistically significant change from baseline.

Proportion of Patients with a ≥5% Reduction in BMI (Patients ≥18 Years) or a ≥0.2-Point Reduction in BMI ZScores (Patients <18 Years) From Baseline

In the Phase 2 study (RM-493-030), treatment with setmelanotide for 16 weeks in Study RM-493-030 resulted in a statistically significant (p<0.0001) 88.9% of patients meeting the endpoint of the proportion of patients with a clinically meaningful ≥5% reduction from baseline in BMI (patients ≥18 years) or a ≥0.2-point reduction from baseline in BMI z-score (patients <18 years of age).

Proportion of Patients with a ≥5% Reduction in BMI From Baseline

In the Phase 2 study (RM-493-030), treatment with setmelanotide for 16 weeks resulted in a statistically significant (p<0.0001) 88.9% and 72.2% of patients achieving reductions in BMI of ≥5% and ≥10%, respectively.

Mean Change From Baseline in Most Hunger

Treatment with setmelanotide for 16 weeks in Study RM-493-030 resulted in a mean reduction of most hunger of -2.922 and the 90% CI (-4.1708, -1.6733) did not contain 0 indicating the statistical significance of this finding

Mean Change from Baseline in BMI Z-Scores in Patients <18 Years

Treatment with setmelanotide for 16 weeks in Study RM-493-030 resulted in a mean reduction in BMI z-score of -1.280 and the 90% CI (-1.7918, -0.7684) did not contain 0 indicating the statistical significance of this finding

Mean Change from Baseline in Waist Circumference

Treatment with setmelanotide for 16 weeks in Study RM-493-030 resulted in a mean reduction in waist circumference of -11.996 cm and the 90% CI (-14.5431, -9.4486) did not contain 0 indicating the statistical significance of this finding.

Studies RM-493-022 and RM-493-042

Evidence of setmelanotide's long-term efficacy derives from patients with acquired HO who participated in the Phase 2 study (RM 493-030) and then sequentially enrolled in the open-label long-term extension (LTE) Studies RM 493-022 (now closed) and RM 493-042 (ongoing) receiving setmelanotide for ≥2.5 years.

Study Design

Both RM 493-022 and RM 493-042 are long-term studies for patients who received treatment (setmelanotide or placebo) in a prior Rhythm setmelanotide study including patients with acquired HO treated in RM 493-030. In both studies, patients begin on the same dose of setmelanotide they were taking when they completed their prior study (unless tolerability or safety reasons justify a dose decrease) and are assessed quarterly for safety and tolerability; weight and height data are also collected. The lowest dose in both studies is 0.5 mg. In RM 493-022, patients ≥18 years who tolerated the 3 mg QD dose level for at least 6 months could receive a higher dose of setmelanotide (up to 5 mg QD in patients >60 kg and up to 4 mg in patients >50 to <60 kg). In Study RM 493-042, the highest dose is 3 mg in patients ≥6 years and 2.5 mg in patients <6 years.

Efficacy Endpoints and Analyses Methods

To evaluate the long-term efficacy of setmelanotide, BMI and BMI z scores (in patients <18 years) for patients with acquired HO who were treated in the Phase 2 Study RM 493-030, enrolled in LTE RM 493-022, and then enrolled in LTE RM 493-042 were descriptively summarized and plotted from baseline of RM 493-030 through a cutoff date of 26 March 2025.

Baseline Characteristics

Fourteen of the 18 patients in Study RM 493-030 enrolled in the LTE RM 493-022 upon completion of the Phase 2 study and 11 of the 14 in RM 493-022 enrolled in the LTE RM 493-042 when the former study closed. The 14 patients who enrolled in RM 493-022 were primarily White (78.6%) and male (71.4%) and were between the ages of 6 and 24 years with 12 patients below the age of 18 and 2 patients ≥18 years of age.

Results

The long-term efficacy of setmelanotide for the treatment of HO is supported by the striking positive results across the majority of endpoints assessed in Phase 3 Study RM 493-040 after 52 weeks on a therapeutic regimen, which was actually ~60 weeks of treatment for most patients as it included an ~8 week dose titration period.

The long-term efficacy of setmelanotide is further supported by results in patients from the Phase 2 study, RM 493-030, most of whom (14/18, 77.8%) enrolled in the LTE Study RM 493-022 and then transitioned (n=11) to another LTE study, RM 493-042, when RM 493-022 was closed. Marked reductions from RM 493-030 baseline in BMI and BMI z scores (in patients <18 years) persisted for up to 144 weeks (≥2.5 years). Of note, 12 of the 14 patients with acquired HO who enrolled in RM 493-022 were <18 years of age.

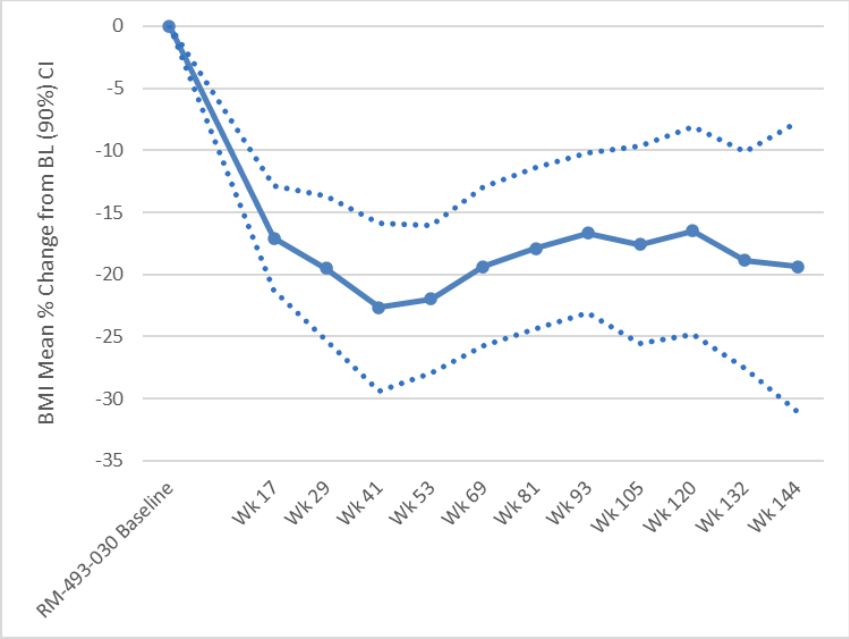


Figure 12 Mean Percent Change from RM-493-030 Baseline in BMI Over Time

Abbreviations: BL = baseline; BMI = body mass index; CI = confidence interval; Wk = week. Note: At each timepoint shown, data were available for ≥5 patients

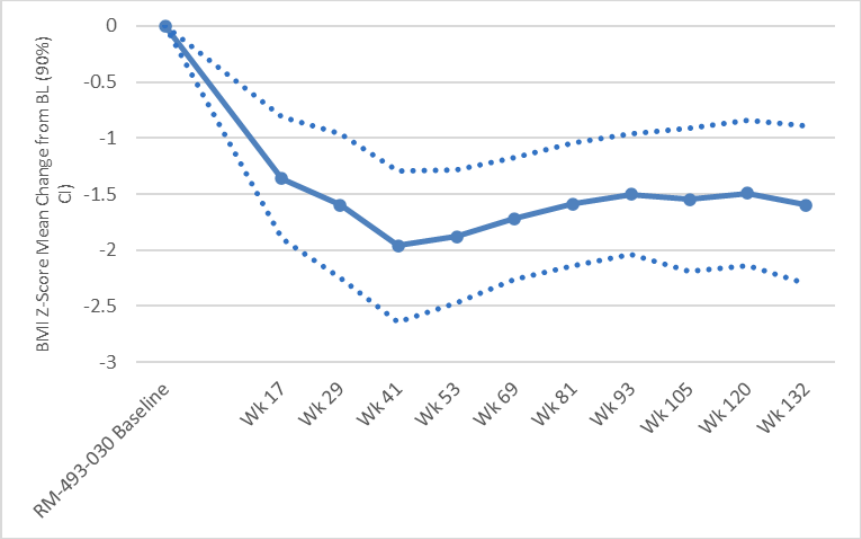


Figure 13 Mean Change from RM-493-030 Baseline in BMI Z-Score Over Time in Patients <18 Years of Age

Abbreviations: BL = baseline; BMI = body mass index; CI = confidence interval; Wk = week. Note: At each timepoint shown, data were available for ≥5 patients

Ancillary Analyses

Efficacy Data from Setmelanotide-Treated Patients in Studies RM-493-040 and RM-493-030 were compare with those from an External Placebo Control group.

Study Design

Results from setmelanotide-treated patients from Studies RM 493-040 (Phase 3) and RM 493-030 (Phase 2) were compared with those from external patients with acquired HO who received placebo in the ECHO (The Energy Balance and Weight Loss in Craniopharyngioma-related or Other Hypothalamic Tumours in Hypothalamic Obesity) trial (Roth 2021). The ECHO trial was a randomized, multicenter, double-blind, placebo-controlled trial conducted in 10- to 25-year-olds with hypothalamic injury following intracranial tumor and HO in which patients received QD subcutaneous (SC) injections of the glucagon-like peptide receptor 1 agonist (GLP 1), exenatide, or placebo for 36 weeks. Study eligibility included: age- and sex-adjusted BMI ≥95 percentile or BMI ≥32 kg/m2 if aged 18 years or older; evidence of hypothalamic injury by MRI confirmed by 1 central neuroradiologist; 6 months or longer postsurgical or radiation treatment; weight stable or increasing over 3 months; and stable hormone replacement for at least 3 months.

Efficacy Endpoints and Analyses Methods

The efficacy endpoints and analyses methods for the ECHO trial are provided in Roth 2021.

Demographic data from placebo-treated patients in RM 493-040 and the ECHO trial were summarized using descriptive statistics.

The difference between setmelanotide treated patients in RM 493-040, RM 493-030, and RM 493-040 + RM 493-030 combined and placebo-treated patients in the ECHO trial in the change from baseline to

36 weeks (the primary efficacy timepoint for the ECHO trial) and 52 weeks (the primary timepoint for the Phase 3 setmelanotide study) for BMI (the primary efficacy endpoint for the Phase 3 study) and waist circumference (a validated surrogate marker for body composition) were analyzed using an ANCOVA model with unequal variance to account for possible unequal residual variances. The model was adjusted with stratification factors of age group (≥18 years, ≥12 and <18 years, and <12 years). Resulting overall estimates of LSM, differences in LSM, corresponding CI and p value are presented. Missing data was imputed using last observation carried forward (LOCF).

Baseline Characteristics

Table 15 Demographic and Baseline Characteristics in Placebo-Treated Patients from Study RM-493-040 and the ECHO Trial

Characteristic	RM-493-040 Placebo (N=39)	ECHO Placebo (N=18)
Sex		
Male	12 (30.8)	7 (38.9)
Female	27 (69.2)	11 (61.1)
Ethnicity		
Hispanic or Latino	7 (17.9)	0
Not Hispanic or Latino	32 (82.1)	18 (100.0)
Race		
Asian	0	1 (5.6)
Black or African American	0	1 (5.6)
White	34 (87.2)	15 (83.3)
Other	5 (12.8)	1 (5.6)
Age (years) at Enrollment		
N	39	18
Mean (SD)	21.36 (15.50)	16.82 (4.75)
Median	15.00	16.22
Min, Max	4.0, 66.0	10.5, 25.4
95% CI	16.33, 26.38	14.45, 19.18
Age Category		
< 12 Years	11 (28.2)	4 (22.2)

≥12 years and < 18 Years	12 (30.8)	8 (44.4)
≥ 18 Years	16 (41.0)	6 (33.3)
Tumor Type		
Astrocytoma	3 (7.7)	0
Craniopharyngioma	30 (76.9)	15 (83.3)
Germinoma	1 (2.6)	0
Glioma	3 (7.7)	0
Hamartoma	1 (2.6)	0
Mixed Germ Cell Tumor	0	1 (5.6)
Other	1 (2.6)	0
Suprasellar Ganglioglioma	0	1 (5.6)
Suprasellar Germinoma	0	1 (5.6)

Patients in both groups were primarily female, White, and not Hispanic or Latino. Patients in RM 493-040 were slightly older than those in the ECHO trial with a mean age of 21.36 years (vs 16.82 in the ECHO trial); however, the distribution of patients within the 3 age brackets (<12, ≥12 to <18, and ≥ 18) was very similar between the 2 studies. Also similar was the type of hypothalamic tumor, with a majority of patients in both studies presenting with craniopharyngioma.

Results

When compared to the external control group, treatment with setmelanotide resulted in statistically significant and clinically meaningful (≥5%) reductions from baseline in BMI substantiating that the outcomes observed in the Phase 3 control group are valid and representative of what would be expected in the absence of the intervention (i.e., setmelanotide).

Table 16 BMI Mean Percent Change from Baseline in Setmelanotide-Treated Patients vs An External Placebo Control Group

Visit	Statistic	030 Setmelanotide (N=18)	040 Setmelanotide (N=81)	Pooled Setmelanotide (N=99)	ECHO Placebo (N=18)
	n	18	81	99	18

Visit	Statistic	030 Setmelanotide (N=18)	040 Setmelanotide (N=81)	Pooled Setmelanotide (N=99)	ECHO Placebo (N=18)
Baseline Actual	Mean (SD)	38.04 (6.487)	35.73 (9.173)	36.15 (8.763)	39.22 (7.295)
	Median	39.26	33.27	34.38	38.26
	Min, Max	22.9, 50.3	21.3, 69.2	21.3, 69.2	29.8, 58.7
	95% CI	34.81, 41.26	33.70, 37.76	34.40, 37.90	35.60, 42.85
Percent Change from Baseline at Week 36	n	18	81	99	18
	Mean (SD)	-17.39 (14.531)	-16.76 (11.389)	-16.87 (11.941)	3.46 (4.312)
	Median	-18.31	-16.58	-17.41	3.19
	Min, Max	-41.8, 14.4	-36.7, 6.6	-41.8, 14.4	-4.7, 10.9
	95% CI	-24.61, -10.16	-19.27, -14.24	-19.25, -14.49	1.32, 5.61
	ANCOVA LSM (SE)	-17.37 (2.713)	-17.08 (1.287)	-17.14 (1.163)	3.25 (2.716)
	95% CI for the LSM	(-22.72, -12.02)	(-19.62, -14.55)	(-19.43, -14.84)	(-2.10, 8.61)
	LSM Difference (SE)	-20.62 (3.829)	-20.34 (2.997)	-20.39 (2.945)	
	95% CI of LSM Difference (SET-Placebo)	(-28.17, -13.07)	(-26.24, -14.43)	(-26.19, -14.58)	
	p-value	<0.0001	<0.0001	<0.0001	
Percent Change from Baseline at Week 52	n	18	81	99	18
	Mean (SD)	-16.57 (15.742)	-17.38 (12.838)	-17.23 (13.328)	3.46 (4.312)
	Median	-15.07	-16.30	-15.73	3.19
	Min, Max	-42.4, 14.4	-40.1, 9.7	-42.4, 14.4	-4.7, 10.9

Visit	Statistic	030 Setmelanotide (N=18)	040 Setmelanotide (N=81)	Pooled Setmelanotide (N=99)	ECHO Placebo (N=18)
	95% CI	-24.40, -8.74	-20.21, -14.54	-19.89, -14.57	1.32, 5.61
	ANCOVA LSM (SE)	-16.60 (3.047)	-17.58 (1.445)	-17.40 (1.307)	3.29 (3.050)
	95% CI for the LSM	(-22.61, -10.60)	(-20.42, -14.73)	(-19.97, -14.82)	(-2.72, 9.30)
	LSM Difference (SE)	-19.89 (4.301)	-20.87 (3.366)	-20.69 (3.308)	
	95% CI of LSM Difference (SET-Placebo)	(-28.37, -11.42)	(-27.50, -14.23)	(-27.21, -14.17)	
	p-value	<0.0001	<0.0001	<0.0001	

Abbreviations: ANCOVA = analysis of covariance; BMI = body mass index; CI = confidence interval; LSM = least squares mean; Max = maximum; Min = minimum; N = number of patients in the treatment group; n = number of patients with non-missing values; SD = standard deviation; SE = standard error.

ANCOVA model with unequal variance to account for possible unequal residual variances was used to estimate the difference between treatment groups. The model was adjusted with stratification factors of age group (≥18 years, ≥12 and <18 years, and <12 years). Resulting overall estimates of LS means, differences in LS means, corresponding CI and p-value are presented. Missing data imputed with last observation carried forward.

Treatment with setmelanotide in the Phase 2, Phase 3, and Phase 2 + 3 studies combined resulted in statistically significant reductions from baseline in waist circumference compared to placebo-treated patients from an external control group supporting the validity of the Rhythm studies and the generalizability of the results from these studies.

Table 17 Waist Circumference (cm) Mean Percent Change from Baseline in Setmelanotide-Treated Patients vs An External Placebo Control Group

Visit	Statistic	030 Setmelanotide (N=18)	040 Setmelanotide (N=81)	Pooled Setmelanotide (N=99)	ECHO Placebo (N=18)
Baseline Actual	n	18	81	99	18
	Mean (SD)	114.07 (16.354)	106.57 (21.712)	107.93 (20.969)	119.70 (16.222)
	Median	119.80	104.90	106.00	118.13
	Min, Max	76.2, 142.6	48.3, 187.0	48.3, 187.0	95.0, 144.5
	95% CI	105.94, 122.20	101.77, 111.37	103.75, 112.11	111.63, 127.76
Percent Change from Baseline at Week 36	n	18	81	99	18
	Mean (SD)	-9.79 (6.908)	-9.23 (14.287)	-9.33 (13.227)	3.02 (3.949)
	Median	-10.70	-8.91	-9.35	3.75
	Min, Max	-19.4, 3.8	-67.2, 70.6	-67.2, 70.6	-3.9, 13.1
	95% CI	-13.22, -6.35	-12.39, -6.07	-11.97, -6.70	1.05, 4.98
	ANCOVA LSM (SE)	-9.47 (3.010)	-9.08 (1.428)	-9.15 (1.291)	3.42 (3.014)
	95% CI for the LSM	(-15.40, -3.53)	(-11.89, -6.26)	(-11.69, -6.60)	(-2.52, 9.36)
	LSM Difference (SE)	-12.89 (4.250)	-12.50 (3.326)	-12.57 (3.269)	
	95% CI of LSM Difference (SET-Placebo)	(-21.26, -4.51)	(-19.05, -5.94)	(-19.01, -6.13)	
	p-value	0.0027	0.0002	0.0002	
Percent Change from Baseline	n	18	81	99	18
	Mean (SD)	-10.82 (8.413)	-9.34 (13.115)	-9.61 (12.370)	3.02 (3.949)

Visit	Statistic	030 Setmelanotide (N=18)	040 Setmelanotide (N=81)	Pooled Setmelanotide (N=99)	ECHO Placebo (N=18)
at Week 52	Median	-8.12	-9.91	-8.78	3.75
	Min, Max	-25.7, 0.3	-29.4, 72.3	-29.4, 72.3	-3.9, 13.1
	95% CI	-15.01, -6.64	-12.24, -6.44	-12.08, -7.14	1.05, 4.98
	ANCOVA LSM (SE)	-10.59 (2.817)	-9.12 (1.336)	-9.38 (1.208)	3.38 (2.820)
	95% CI for the LSM	(-16.15, -5.04)	(-11.75, -6.48)	(-11.77, -7.00)	(-2.18, 8.94)
	LSM Difference (SE)	-13.98 (3.976)	-12.50 (3.112)	-12.77 (3.058)	
	95% CI of LSM Difference (SET-Placebo)	(-21.82, -6.14)	(-18.63, -6.36)	(-18.80, -6.74)	
	p-value	0.0005	<0.0001	<0.0001	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LSM = least squares mean; Max = maximum; Min = minimum; N = number of patients in the treatment group; n = number of patients with non-missing values; SD = standard deviation; SE = standard error.

ANCOVA model with unequal variance to account for possible unequal residual variances was used to estimate the difference between treatment groups. The model was adjusted with stratification factors of age group (≥18 years, ≥12 and <18 years, and <12 years). Resulting overall estimates of LS means, differences in LS means, corresponding CI and p-value are presented. Missing data imputed with last observation carried forward.

2.3.3. Early Access Use of Setmelanotide in Patients With Acquired HO in Italy and France

Real world data on the efficacy of setmelanotide in HO derives from ongoing studies of patients receiving treatment with setmelanotide through early access programs in Italy and France. Data from 2 patients treated in Italy were summarized in an abstract by Favero et al (Favero 2025) while data from 35 patients treated in France were summarized in a presentation by Faucher et al (Faucher 2025).

Early access use of setmelanotide by patients with HO in Italy and France demonstrated marked reductions in body weight.

In Italy, one adult patient who received treatment with setmelanotide for ≥16 weeks experienced reductions in body weight (from a baseline of 148.5 kg, BMI of 45.4 kg/m2) of 19.5 kg at Week 16 and 26.0 kg at Week 20, with a reduction in BMI of approximately 17.5%. In addition, another adult patient who received treatment with setmelanotide for 16 weeks experienced reductions in body weight and BMI (from a baseline of 122.8 kg, BMI of 42.5 kg/m2) of 15.1 kg and 12.2% at Week 16, respectively (Favero 2025).

In France, treatment of patients with acquired HO with setmelanotide for up to 9 months was overall associated with clinically meaningful reductions from baseline in BMI (reductions ≥5%) in adult patients, clinically meaningful reductions in BMI z scores (reductions ≥0.2) in paediatric patients, and consistent reductions in hunger in adult patients. Clinically meaningful reductions in BMI z scores in paediatric patients with congenital HO were also observed, and the 1 adult patient with congenital HO experienced a reduction in BMI from baseline (39.6 kg/m2) to Month 3 (35.5 kg/m2) and Month 6 (33.7 kg/m2), reflecting a reduction of 14.8% after 6 months of setmelanotide treatment.

2.3.4. Discussion on clinical efficacy

Design and conduct of clinical studies

The current variation aims to extend the currently approved indications for IMCIVREE, which is currently authorized for genetic forms of obesity (POMC, PCSK1, LEPR deficiency, and Bardet-Biedl syndrome). The rationale for including acquired HO is based on the shared pathophysiology : a deficit or absence of α-MSH signaling in the MC4R pathway. The mechanism of action of setmelanotide as an MC4R agonist is consistent across these conditions, providing a strong scientific basis for its use in acquired HO.

Changes from Baseline in BMI and BMI z-score were selected as key efficacy endpoints to evaluate weight-loss, and changes in the daily maximal hunger scores were selected as key endpoints to evaluate improvements in the hunger that may be associated with obesity due to acquired HO. These endpoints are consistent with the endpoints used in already approved indications for setmelanotide and reflect the core clinical manifestations of MC4R pathway dysfunction: excessive weight gain and hyperphagia.

The pivotal Phase 3 study RM-493-040 was a randomized, double-blind, placebo-controlled trial evaluating setmelanotide in patients aged ≥4 years with acquired hypothalamic obesity. The study enrolled 143 patients, with 120 included in the mITT analysis. Patients were stratified by age and subpopulation and treated for up to 60 weeks, including an 8-week dose titration phase. The treatment and placebo groups were well-balanced at baseline in terms of age, sex, BMI, and medical history. The population is medically complex, with high prevalence of endocrine disorders, which appears to reflect the real-world HO population.

The inclusion and exclusion criteria appear appropriate for the target population with acquired hypothalamic obesity and adequately supportive of the trial's investigational objectives. The inclusion criteria were limited to patients with acquired hypothalamic obesity.Patients with hypopituitarism were allowed if receiving stable hormone replacement therapy (e.g., thyroid hormones, glucocorticoids, growth hormone), with doses maintained for at least 2 months prior to screening. This approach is appropriate and ensures that metabolic effects observed during the trial are attributable to the investigational treatment rather than fluctuations in background therapy. The Daily Hunger Questionnaire, while validated in prior MC4R pathway disorders, was only administered to patients ≥12 years of age. Although directionally consistent results were observed in

younger children using an adapted tool, the measurement of hunger in children <12 years remains less standardized, which may limit interpretability of hunger-related efficacy results in this subgroup.

Overall, the design of the pivotal study was appropriate for the target population and allowed for robust assessment of efficacy and safety.

Supportive studies included the single-arm Phase 2 trial RM-493-030, long-term extension studies RM-493-022 and RM-493-042, and external comparative analyses with placebo-treated patients from the ECHO trial. These studies were methodologically aligned to assess similar endpoints and patient populations.

Dosing regimens

Efficacy results with significant reductions in BMI and hunger scores in acquired HO population were observed in RM-493-040 at the age- and weight-adjusted dosing regimen, starting at 0.5 mg QD with weekly escalation to a maximum of 3.0 mg QD. In the acquired HO indication, a weight-based dosing approach is applied for children aged 4 to <6 years. However, the posology differs from the SmPC-approved titration schedule for genetic indications, which typically starts at 1.0 mg and escalates every two weeks with lower maximum doses in younger children across all weight categories. Specifically, children weighing ≥ 30 kg may receive up to 3 mg once daily, which is the adult maximum dose.

The MAH submitted an updated popPK analysis to support the proposed dosing in adult and paediatric patients with HO aged ≥ 4 years. Though the maximum doses in patients <6 years and in renal impaired patients do not match with the RGDO reference range, the titrated dose escalation practice in patients who need additional clinical effect and have no prior tolerability issues, is considered acceptable from clinical perspective. See section 2.2.7.

Efficacy data and additional analyses

The pivotal Phase 3 trial RM-493-040 demonstrated that treatment with setmelanotide in patients with acquired hypothalamic obesity resulted in statistically significant and clinically meaningful reductions in key efficacy endpoints.

The primary endpoint (mean percent change in BMI from baseline after 52 weeks) was met with a −16.51% reduction in the setmelanotide group versus a +3.32% increase in the placebo group, showing a placebo-corrected treatment effect of −19.83% ($p<0.0001$). This effect was evident as early as Week 4 and increased over time.

Key secondary endpoints further supported efficacy. Thus, 82.73% of patients achieved a ≥5% BMI reduction or ≥0.2-point BMI Z-score reduction ($p<0.0001$) and 79.53% achieved a ≥5% BMI reduction overall. Furthermore, significant reductions in hunger scores were observed in patients ≥12 years (LSM −2.68 vs −1.24, $p=0.003$).

Additional endpoints (e.g., waist circumference, hyperphagia symptoms, cardiometabolic parameters, quality of life) consistently favoured setmelanotide over placebo. Improvements in waist circumference (−11.58 cm), BMI Z-score (−1.47), and quality of life scores (IWQOL) were also statistically significant.

These results reinforce the positive findings observed in the primary and key secondary endpoint analyses, and support the broader therapeutic potential of setmelanotide in patients with acquired HO.

There are no direct measurements or endpoints related to energy expenditure reported in the trial RM-493-040.

There are indirect qualitative observations from exit interviews suggesting that 14 participants reported an increase in energy and 18 participants reported an increase in physical activity. These findings were based on self-reported or caregiver-observed changes and are subjective, not quantitatively measured. Therefore, while these observations may suggest improved energy levels or activity, they do not constitute formal evidence of increased energy expenditure.

In the pivotal trial, after 52 weeks at a therapeutic dose, the actual mean BMI for setmelanotide-treated patients was 29.58, transitioning to the overweight range, indicating a clinically meaningful shift in weight status. While the mean BMI for placebo-treated patients was 38.08, consistent with Class 2 obesity.

Supportive data from the Phase 2 study RM-493-030 confirmed consistent improvements in the same endpoints over a shorter 16-week period. Although single-arm and open-label, the study used predefined comparisons to historical benchmarks and demonstrated early onset of efficacy, with 88.9% of patients achieving a ≥5% BMI reduction or ≥0.2-point BMI Z-score reduction ($p<0.0001$). The magnitude and direction of effects observed over 16 weeks in RM-493-030 closely align with those seen in the randomized, placebo-controlled Phase 3 trial RM-493-040, which strengthens the overall evidence on efficacy of setmelanotide in this population . The Phase 2 study also supports the early onset of action of setmelanotide, with significant changes evident within a shorter treatment duration.

Long-term data on the durability of setmelanotide effects in patients with acquired HO were provided from LTE studies. Sustained reductions in BMI and BMI Z-scores over ≥2.5 years support the persistence of treatment benefits beyond the 52-week duration of RM-493-040. The data from these LTE studies are relevant to both adult and paediatric age groups, but the majority of the supportive data (especially sustained BMI and BMI Z-score reductions) come from paediatric patients.

In long-term extension studies, higher doses (up to 5 mg QD) were permitted in adults under close monitoring. Although RM-493-042 includes dosing tiers for patients <6 years (e.g., 2.5 mg QD), these do not apply to the acquired HO population, as no patients <6 years were enrolled in the Phase 2 trial.

Cross-trial comparisons with placebo-treated patients from the ECHO trial provide external validation of the Phase 3 results. Statistically significant differences in BMI and waist circumference between setmelanotide-treated patients and external controls support the efficacy findings of RM-493-040. The consistent placebo outcomes across trials reinforce validity of the observed treatment effect.

Real-world data from early access programs in Italy and France offer additional supportive evidence of setmelanotide's effectiveness in routine clinical settings. Clinically meaningful reductions in BMI and hunger were observed in both acquired and congenital HO patients. Although uncontrolled, these findings complement clinical trial data and demonstrate the drug's potential impact in broader practice. They are considered supplementary and non-confirmatory, but relevant for supporting efficacy in real-world use.

Clinical Efficacy in subpopulations

Subgroup analyses showed that the efficacy of setmelanotide was generally maintained across age, sex, race, and region for all primary and key secondary endpoints. However, no meaningful change in the most hunger score was observed in the Hispanic/Latino subgroup, potentially due to the small sample size.

Duration of treatment

The pivotal Phase 3 study, treatment with setmelanotide for 52 weeks resulted in a statistically significant increase in the proportion of patients who shifted from obese to overweight or below—defined as BMI <30

kg/m² in adults or BMI <95th percentile in paediatric patients—compared to placebo (39.95% vs. 12.82%, p=0.0004). Weight loss and hunger control associated with setmelanotide appear to be maintained during uninterrupted treatment. According to the MAH, treatment should not be discontinued solely because a target clinical parameter (e.g. BMI) has normalised since setmelanotide is a replacement therapy addressing deficient α-MSH signalling and such recommendation would also be in line with other endocrine replacement therapies (e.g., vasopressin for diabetes insipidus). The MAH claimed that continuous setmelanotide treatment is required to achieve and maintain weight loss and hunger control, as there is no intrinsic means of repairing the MC4R pathway. In this regard it is the MAH's experience that once a weight nadir has been achieved, withdrawal of therapy or change in dose will lead to rebound weight gain and re-emergence of feelings and symptoms of hyperphagia. Thus, there is no fixed recommendation to systematically reduce or stop treatment upon achieving normal BMI; rather, dosing decisions should be guided by clinical judgement. Patients who reach a normal BMI may continue treatment, with dose adjustments based on individual tolerability and clinical response. Therefore, the MAH proposed to update section 4.2 of the SmPC to explicitly state that dose titration may be performed both upward and downward based on individual tolerability and clinical response. The overall argumentation and subsequent update of the SmPC to further emphasise that treatment management is based on tolerability and clinical response, rather than BMI normalisation, were considered acceptable by the CHMP.

Maintenance of the effect

While long-term efficacy was demonstrated in extension studies for up to 2.5 years, these data were derived from a small number of patients (n=11) from the Phase 2 study who entered LTE trials. The limited sample size and absence of a control group reduce the strength of conclusions regarding long-term effects. Moreover, variations in dosing regimens in the LTE studies (RM-493-022 and RM-493-042), which differed from those used in the pivotal Phase 3 trial, complicate direct comparisons and introduce uncertainty regarding the consistency of long-term efficacy across different dose levels and patient subgroups. The MAH further noted that patients in the pivotal Phase 3 study RM-493-040 continued treatment beyond the 1-year placebo-controlled period. While continued treatment beyond the 1-year placebo-controlled period in the pivotal study RM-493-040 is acknowledged as supportive of longer-term efficacy, the absence of quantitative long-term efficacy outcomes under the pivotal trial conditions limits substantiation of durability. The CHMP therefore recommended that once available, quantitative long-term efficacy outcomes from continued treatment beyond the placebo-controlled period, collected under the pivotal trial conditions, should be submitted in an appropriate regulatory procedure to further support durability of effect.

Assessment of paediatric data on clinical efficacy

Paediatric patients constituted a substantial proportion of the study population in both pivotal and supportive trials. In RM-493-040, 59.2% of patients were <18 years of age. Improvements in BMI Z-score (−1.47) and hunger scores were statistically significant and clinically meaningful in this subgroup.

Supportive data from RM-493-030 and long-term extension studies RM-493-022 and RM-493-042 included predominantly paediatric patients, with sustained efficacy observed over ≥2.5 years.

Due to the acute onset and progressive nature of HO, early intervention is clinically justified. Although the Phase 3 and Phase 2 trials included paediatric patients starting from 4 and 6 years respectively, very limited clinical experience is available in children <6 years. Only two patients in this age group with normal renal function treated with setmelanotide and 1 placebo patient who transitioned to setmelanotide after completing

the placebo-controlled study were included in the pivotal Phase 3 trial. Although the available efficacy and safety data in this age group are very limited, no new or dose-related safety concerns were identified and reported adverse events were consistent with the known safety profile of setmelanotide; together with favourable efficacy outcomes and individual dose titration based on tolerability and clinical response, treatment is considered acceptable in this age group despite the limited evidence base (see section 2.2.7).

2.3.5. Conclusions on the clinical efficacy

In the pivotal Phase 3 trial, clinically meaningful reductions in both body weight and hunger were consistently demonstrated for both adult and pediatric age groups. These findings were supported by an appropriate randomized, placebo-controlled design and statistical methodology.

Overall, the efficacy outcomes observed in trial RM-493-040 and supportive data from Phase 2, long-term extension studies, external placebo comparisons, and real-world use indicate a positive effect of setmelanotide in patients with acquired hypothalamic obesity. The totality of evidence supports the efficacy of setmelanotide in acquired HO, with early onset, sustained effect, and applicability across paediatric and adult patients.

However, the initial proposed wording of the new therapeutic indication was questioned by the CHMP as it should generally only describe the condition and the applicable age range. During the assessment, the CHMP acknowledged that inclusion of "control of hunger" across age groups may be considered acceptable, given the shared MC4R-mediated mechanism of action of setmelanotide, the established experience of hunger-related effects across paediatric age groups in other approved IMCIVREE indications (as evaluated in patients aged 2 years and above), and the supportive qualitative evidence from study RM493040 (self and observer-reported assessments and qualitative interviews for patients aged 6 to <12 years; caregiver-reported hunger observations in children aged <6 years (n=2)). This despite the limitations in the data across all age groups, as validated quantitative hunger endpoints were only collected in patients aged ≥12 years, while assessments in younger children were limited or exploratory in nature.

As a result, the final recommended wording by the CHMP was as follows:

IMCIVREE is indicated for the treatment of obesity and the control of hunger in adults and children 4 years of age and above with acquired hypothalamic obesity (aHO) due to hypothalamic injury or impairment.

In addition, the CHMP recommended to further support the maintenance of the effect by providing further quantitative long term efficacy outcomes from continued treatment beyond the placebo-controlled period, collected under the pivotal trial conditions, when available.

2.4. Clinical safety

Introduction

The most frequent adverse reactions identified before were hyperpigmentation disorders (66%), injection site reactions (45%), nausea (36%), and headache (19%).

Patient exposure

HO

The exposure data for all patients with HO in the QD clinical development program through 26 March 2025 are summarized by study below.

Across the studies of patients with HO, exposure to study drug was consistent with the study's planned duration; the mean duration of exposure to study drug during the double-blind treatment period was 52 weeks in both treatment arms in Study RM 493-040 and was 16 weeks in Study RM 493-030. Open-label treatment with setmelanotide via Bridging Visits in Study RM 493-040 ranged from <1 to 40 weeks, and open-label treatment with setmelanotide in the Long-Term Extension ranged from 106 to 190 weeks.

Table 18 Extent of Exposure in Patients with HO by Clinical Study Through 26 March 2025

	Study RM-493-040			Patients from Study RM-493-030	
	Double-Blind Treatment Period			Study RM-493-030	LTE
Parameter	Setmelanotide (N=94)	Placebo (N=48)	BVs (N=104)	Setmelanotide (N=18)	Setmelanotide (N=14)
Treatment Duration (Weeks)					
n	94	48	104	18	14
Mean (SD)	52.48 (15.303)	52.23 (15.535)	13.9 (11.25)	15.93 (2.732)	159.2 (22.26)
Median	59.00	59.00	11.1	16.14	163.9
Min, Max	4.7, 62.1	3.3, 64.6	<1, 40.3	7.4, 22.6	106.1, 189.6

Abbreviations: BVs = bridging visits; HO = hypothalamic obesity; LTE = long-term extension; Max = maximum; Min = minimum; SD = standard deviation.
Note: Data from Study RM-493-040 double-blind treatment period are for all patients in the safety analysis set prior to the start of bridging visits; data from the BVs are for all patients with BV data in Study RM-493-040 through 26-Mar-2025; data from Study RM-493-030 are for all patients in the safety analysis set; and data from the LTE Studies RM-493-022 (N=14) and RM-493-042 (N=11) are for patients with HO from Index Study RM-493-030 with LTE data through 26-Mar-2025.
Source: RM-493-040 CSR Table 14.1.4.1 (double-blind), ISS Table 3.3.1 (BV), RM-493-030 CSR Table 14.3.5.6 (Study RM 493-030), ISS Table 3.4.1 (LTE)

HO and RGDO

The overall extent of exposure for all participants treated with QD setmelanotide in the clinical development program through 26 March 2025 is shown below.

While the median duration of exposure to setmelanotide was longer for patients with HO (429.0 days) compared to all patients with RGDO (253.5 days), the mean exposure was shorter for patients with HO (412.4 days) compared to all patients with RGDO (502.3 days). The median (107.0 days) and mean (365.7 days) durations of all participants treated with setmelanotide was shorter due to limited exposure in the Phase 1 studies.

Table 19 Overall Extent of Exposure in the QD Clinical Development Program Through 26 March 2025

Parameter Statistic	All Patients with HO		All Patients with RDO	All Participants
	Setmelanotide (N=147)	Placebo (N=48)	Setmelanotide (N=694)	Setmelanotide (N=982)
Time on Treatment (days)				
n	147	48	694	982
Mean (SD)	412.4 (306.94)	365.63 (108.75)	502.3 (565.43)	365.7 (520.84)
Median	429.0	413.00	253.5	107.0
Min, Max	1, 1327	23.0, 452.0	1, 2781	1, 2781
Duration of Exposure, n (%)				
<1 month	10 (6.8)	1 (2.1)	80 (11.5)	264 (26.9)
1 to <3 months	15 (10.2)	1 (2.1)	109 (15.7)	190 (19.3)
3 to <6 months	18 (12.2)	3 (6.3)	135 (19.5)	158 (16.1)
6 to <12 months	13 (8.8)	4 (8.3)	45 (6.5)	45 (4.6)
12 to <18 months	53 (36.1)	39 (81.3)	96 (13.8)	96 (9.8)
≥18 months	38 (25.9)	0	229 (33.0)	229 (23.3)

Abbreviations: HO = hypothalamic obesity; Max = maximum; Min = minimum; QD = once daily; RDO = rare diseases of obesity; SD = standard deviation.
Note: Placebo data are only shown for patients with HO, because placebo data are limited for the other populations.
Source: ISS Table 3.3.1 (all setmelanotide patients with HO), ISS Adhoc Table 5 (all placebo patients with HO), ISS Table 3.2.1 (all patients with RDO), ISS Table 3.1.1 (all participants)

Table 20 Demographics and Baseline Characteristics in the QD Clinical Development Program Through 26 March 2025

Demographic or Characteristic	All Patients with HO		All Patients with RDO	All Participants
	Setmelanotide (N=147)	Placebo (N=48)	Setmelanotide (N=694)	Setmelanotide (N=982)
Sex, n (%)				
Male	62 (42.2)	17 (35.4)	256 (36.9)	396 (40.3)
Female	85 (57.8)	31 (64.6)	438 (63.1)	586 (59.7)
Age, n (%)				
2 to <6 years[a]	3 (2.0)	2 (4.2)	15 (2.2)	15 (1.5)
6 to <12 years	31 (21.1)	10 (20.8)	98 (14.1)	98 (10.0)
12 to <18 years	48 (32.7)	15 (31.3)	178 (25.6)	178 (18.1)
2 to <18 years	82 (55.8)	27 (56.3)	291 (41.9)	291 (29.6)
≥18 years	65 (44.2)	21 (43.8)	403 (58.1)	691 (70.4)
Race, n (%)				
American Indian or Alaska Native	0	0	3 (0.4)	5 (0.5)
Asian	11 (7.5)	5 (10.4)	23 (3.3)	24 (2.4)
Black or African American	9 (6.1)	1 (2.1)	67 (9.7)	189 (19.2)
Native Hawaiian or Other Pacific Islander	1 (0.7)	0	1 (0.1)	2 (0.2)
White	115 (78.2)	36 (75.0)	530 (76.4)	681 (69.3)
Other	11 (7.5)	6 (12.5)	54 (7.8)	65 (6.6)
Not Reported	0	0	9 (1.3)	9 (0.9)
Missing	0	0	7 (1.0)	7 (0.7)

Adverse events

Common TEAEs in Patients with HO

TEAEs occurring in ≥15% of patients (in any treatment group) are presented by study in Table 7. Importantly, these events were largely consistent with the most common events reported among all participants treated with setmelanotide (Table 8) and with the most common adverse reactions reported in the setmelanotide labelling. In general, these events were consistent across the setmelanotide treatment arm of the double-blind treatment period in Study RM 493-040 and the RM 493-030 and LTE studies, despite the variable treatment durations and sample sizes. While no individual preferred term (PT) occurred with at least 15% incidence during BVs in Study RM 493-040, this may be due to the lower exposure to setmelanotide (median=11.1 weeks) in this treatment group compared with the other groups.

Importantly, the pivotal clinical study in patients with HO (RM 493-040) was a double-blind, placebo-controlled study with a treatment period of up to 60 weeks. This is the first clinical study of setmelanotide with a placebo-controlled arm of this duration. It is notable that the incidence of diarrhoea, abdominal pain, local reactions at the injection site (e.g., ISR, injection site erythema, injection site pruritus, injection site induration, injection site pain), and fatigue were similar in both the setmelanotide and placebo treatment arms during the double-blind treatment period. Events that occurred with a higher incidence in the setmelanotide treatment arm compared to placebo during the double-blind treatment period included events that are known effects of setmelanotide including: nausea, vomiting, skin hyperpigmentation, and melanocytic naevus.

Table 21 Most Common (i.e., Incidence ⩾15% in any Treatment group) TEAEs in Patients with HO by Clinical Study Through 26 March 2025

System Organ Class Preferred Term	Study RM-493-040			Patients from Study RM-493-030	
	Double-Blind Treatment Period			Study RM-493-030	LTE
	Setmelanotide (N=94) n (%)	Placebo (N=48) n (%)	BVs (N=104) n (%)	Setmelanotide (N=18) n (%)	Setmelanotide (N=14) n (%)
Number of patients with at least 1 TEAE	**94 (100.0)**	**44 (91.7)**	**39 (37.5)**	**18 (100)**	**14 (100)**
Gastrointestinal disorders	**69 (73.4)**	**28 (58.3)**	**23 (22.1)**	**14 (77.8)**	**9 (64.3)**
Nausea	50 (53.2)	13 (27.1)	10 (9.6)	11 (61.1)	1 (7.1)
Vomiting	36 (38.3)	9 (18.8)	11 (10.6)	6 (33.3)	6 (42.9)
Diarrhoea	19 (20.2)	10 (20.8)	7 (6.7)	4 (22.2)	1 (7.1)
Abdominal pain	12 (12.8)	6 (12.5)	2 (1.9)	3 (16.7)	2 (14.3)
General disorders and administration site conditions	**57 (60.6)**	**33 (68.8)**	**12 (11.5)**	**8 (44.4)**	**6 (42.9)**
Injection site reaction	21 (22.3)	11 (22.9)	0	0	0
Injection site pruritus	16 (17.0)	8 (16.7)	0	2 (11.1)	0
Injection site erythema	16 (17.0)	6 (12.5)	2 (1.9)	1 (5.6)	0
Fatigue	10 (10.6)	5 (10.4)	4 (3.8)	3 (16.7)	1 (7.1)
Injection site pain	10 (10.6)	7 (14.6)	0	3 (16.7)	1 (7.1)
Injection site induration	8 (8.5)	2 (4.2)	1 (1.0)	1 (5.6)	3 (21.4)
Skin and subcutaneous tissue disorders	**60 (63.8)**	**18 (37.5)**	**11 (10.6)**	**7 (38.9)**	**6 (42.9)**
Skin hyperpigmentation	52 (55.3)	4 (8.3)	10 (9.6)	6 (33.3)	4 (28.6)
Infections and infestations	**53 (56.4)**	**23 (47.9)**	**14 (13.5)**	**8 (44.4)**	**10 (71.4)**
Upper respiratory tract infection	15 (16.0)	7 (14.6)	1 (1.0)	2 (11.1)	6 (42.9)
COVID-19	11 (11.7)	5 (10.4)	1 (1.0)	4 (22.2)	3 (21.4)
Nervous system disorders	**48 (51.1)**	**20 (41.7)**	**11 (10.6)**	**5 (27.8)**	**6 (42.9)**
Headache	34 (36.2)	15 (31.3)	6 (5.8)	2 (11.1)	3 (21.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**17 (18.1)**	**5 (10.4)**	**2 (1.9)**	**0**	**2 (14.3)**
Melanocytic naevus	14 (14.9)	3 (6.3)	2 (1.9)	0	0
Reproductive system and breast disorders	**14 (14.9)**	**5 (10.4)**	**3 (2.9)**	**3 (16.7)**	**3 (21.4)**
Erection increased	4 (4.3)[a]	1 (2.1)[b]	3 (2.9)[c]	3 (16.7)[d]	3 (21.4)[e]
Musculoskeletal and Connective Tissue Disorders	**21 (22.3)**	**12 (25.0)**	**4 (3.8)**	**3 (16.7)**	**5 (35.7)**
Back pain	6 (6.4)	1 (2.1)	0	2 (11.1)	3 (21.4)

Abbreviations: BVs = bridging visits; HO = hypothalamic obesity; LTE = long-term extension; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

[a] Using the denominator of N=40 for males, the percentage of setmelanotide-treated patients with erection increased is 10.0%.

[b] Using the denominator of N=17 for males, the percentage of placebo-treated patients with erection increased is 5.9%.

[c] Using the denominator of N=41 for males, the percentage of setmelanotide-treated patients with erection increased is 7.3%.

[d] Using the denominator of N=11 for males, the percentage of setmelanotide-treated patients with erection increased is 27.3%.

[e] Using the denominator of N=10 for males, the percentage of setmelanotide-treated patients with erection increased is 30.0%.

Note: Data from Study RM-493-040 double-blind treatment period are for all patients in the safety analysis set prior to the start of bridging visits and were coded using MedDRA v25.1 or later; data from the BVs are for all patients with BV data in Study RM-493-040 through 26-Mar-2025 and were coded using MedDRA v25.1 or later; data from Study RM-493-030 are for all patients in the safety analysis set and were coded using MedDRA v24.0; and data from LTE Studies RM-493-022 (N=14) and RM-493-042 (N=11) are for patients with HO from Index Study RM-493-030 with LTE data through 26-Mar-2025 and were coded using MedDRA v25.1 or later

Source: RM-493-040 CSR Table 14.3.1.2A (double-blind), ISS Table 4.3.1 (BV), RM-493-030 CSR Table 14.3.1.2 (Study RM 493-030), ISS Table 4.4.1 (LTE)

Common TEAEs Among Participants in the QD Setmelanotide Clinical Development Program

The most common (i.e., incidence ≥5% in any setmelanotide treatment group) TEAEs occurring among participants in the QD setmelanotide clinical development program are summarized in Table 8.

The TEAE profile of setmelanotide in patients with HO is consistent with the known TEAE profile of setmelanotide, including that observed in all patients with RGDO and all participants. Importantly, events commonly associated with setmelanotide (e.g., skin hyperpigmentation, nausea, headache, melanocytic naevus, spontaneous penile erection, and erection increased) occurred at a similar or lower incidence in setmelanotide-treated patients with HO as in other setmelanotide treatment groups. The one exception is vomiting, which occurred in 36.1% of setmelanotide-treated patients with HO compared with 24.8% of all patients with RGDO and 22.5% of all participants treated with setmelanotide. It is important to note that patients with HO have a higher background incidence of gastrointestinal complaints given their complex medical history, which may contribute to the higher overall incidence of complaints in patients with HO. There was a 27.1% incidence of nausea and 18.8% incidence of vomiting in the HO placebo group.

As noted above, the HO development program included the longest double-blind, placebo-controlled treatment period (up to 60 weeks) of any clinical study with setmelanotide to date. Importantly, local reactions at the injection site (e.g., injection site erythema, injection site pruritus, injection site induration, injection site pain, injection site reaction) and fatigue occurred with a similar or higher incidence in patients who received placebo compared to those who received setmelanotide even when data from all patients with HO who received setmelanotide were pooled. This was also true for some gastrointestinal events (e.g., diarrhoea, abdominal pain, and constipation) as well as headache and, in males, spontaneous penile erection (but not for erection increased).

Table 22 Most Common (i.e., Incidence ⩾5% in Any Setmelanotide Treatment Group) TEAEs Through 26 March 2025: Participants in the QD Clinical Development Program

System Organ Class Preferred Term	All Patients with HO		All Patients with RDO	All Participants
	Setmelanotide (N=147) n (%)	Placebo (N=48) n (%)	Setmelanotide (N=694) n (%)	Setmelanotide (N=982) n (%)
Number of participants with at least 1 TEAE	**134 (91.2)**	**44 (91.7)**	**667 (96.1)**	**918 (93.5)**
Skin and Subcutaneous Tissue Disorders	**79 (53.7)**	**18 (37.5)**	**532 (76.7)**	**671 (68.3)**
Skin Hyperpigmentation	69 (46.9)	4 (8.3)	477 (68.7)	595 (60.6)
General Disorders and Administration Site Conditions	**78 (53.1)**	**33 (68.8)**	**444 (64.0)**	**564 (57.4)**
Injection Site Erythema	19 (12.9)	6 (12.5)	216 (31.1)	263 (26.8)
Injection Site Pruritus	18 (12.2)	8 (16.7)	171 (24.6)	198 (20.2)
Injection Site Pain	13 (8.8)	7 (14.6)	119 (17.1)	150 (15.3)
Injection Site Induration	13 (8.8)	2 (4.2)	139 (20.0)	147 (15.0)
Fatigue	18 (12.2)	5 (10.4)	113 (16.3)	135 (13.7)
Injection Site Bruising	4 (2.7)	2 (4.2)	87 (12.5)	91 (9.3)
Injection Site Oedema	7 (4.8)	4 (8.3)	85 (12.2)	87 (8.9)
Pyrexia	10 (6.8)	6 (12.5)	49 (7.1)	50 (5.1)
Injection Site Reaction	21 (14.3)	11 (22.9)	48 (6.9)	50 (5.1)
Gastrointestinal Disorders	**102 (69.4)**	**28 (58.3)**	**450 (64.8)**	**595 (60.6)**
Nausea	69 (46.9)	13 (27.1)	289 (41.6)	401 (40.8)
Vomiting	53 (36.1)	9 (18.8)	172 (24.8)	221 (22.5)
Diarrhoea	29 (19.7)	10 (20.8)	115 (16.6)	140 (14.3)
Abdominal Pain	18 (12.2)	6 (12.5)	77 (11.1)	89 (9.1)
Abdominal Pain Upper	8 (5.4)	6 (12.5)	58 (8.4)	61 (6.2)
Constipation	12 (8.2)	3 (6.3)	39 (5.6)	47 (4.8)

System Organ Class Preferred Term	All Patients with HO		All Patients with RDO	All Participants
	Setmelanotide (N=147) n (%)	Placebo (N=48) n (%)	Setmelanotide (N=694) n (%)	Setmelanotide (N=982) n (%)
Infections and Infestations	**71 (48.3)**	**23 (47.9)**	**341 (49.1)**	**371 (37.8)**
Upper Respiratory Tract Infection	21 (14.3)	7 (14.6)	76 (11.0)	83 (8.5)
COVID-19	18 (12.2)	5 (10.4)	102 (14.7)	102 (10.4)
Nasopharyngitis	9 (6.1)	7 (14.6)	86 (12.4)	88 (9.0)
Influenza	10 (6.8)	4 (8.3)	43 (6.2)	43 (4.4)
Gastroenteritis	11 (7.5)	1 (2.1)	35 (5.0)	39 (4.0)
Urinary Tract Infection	4 (2.7)	3 (6.3)	37 (5.3)	39 (4.0)
Nervous System Disorders	**66 (44.9)**	**20 (41.7)**	**293 (42.2)**	**379 (38.6)**
Headache	45 (30.6)	15 (31.3)	222 (32.0)	298 (30.3)
Dizziness	15 (10.2)	2 (4.2)	61 (8.8)	70 (7.1)
Musculoskeletal and Connective Tissue Disorders	**30 (20.4)**	**12 (25.0)**	**181 (26.1)**	**221 (22.5)**
Back Pain	10 (6.8)	1 (2.1)	57 (8.2)	73 (7.4)
Arthralgia	7 (4.8)	2 (4.2)	49 (7.1)	59 (6.0)
Pain in Extremity	6 (4.1)	4 (8.3)	35 (5.0)	44 (4.5)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**21 (14.3)**	**5 (10.4)**	**189 (27.2)**	**197 (20.1)**
Melanocytic Naevus	16 (10.9)	3 (6.3)	160 (23.1)	167 (17.0)
Reproductive System and Breast Disorders	**21 (14.3)**	**5 (10.4)**	**155 (22.3)**	**211 (21.5)**
Spontaneous Penile Erection	3 (2.0)[a]	1 (2.1)[b]	29 (4.2)[c]	57 (5.8)[d]
Erection Increased	11 (7.5)[e]	1 (2.1)[f]	41 (5.9)[g]	53 (5.4)[h]
Respiratory, Thoracic and Mediastinal Disorders	**32 (21.8)**	**13 (27.1)**	**145 (20.9)**	**169 (17.2)**
Cough	15 (10.2)	6 (12.5)	57 (8.2)	60 (6.1)
Oropharyngeal Pain	11 (7.5)	2 (4.2)	34 (4.9)	36 (3.7)
Metabolism and Nutrition Disorders	**28 (19.0)**	**7 (14.6)**	**125 (18.0)**	**167 (17.0)**
Decreased Appetite	10 (6.8)	1 (2.1)	33 (4.8)	75 (7.6)

Abbreviations: HO = hypothalamic obesity; QD = once daily; RDO = rare diseases of obesity; TEAE = treatment-emergent adverse event.
[a] Using the denominator of N=62 for males, the percentage of setmelanotide-treated patients with spontaneous penile erection is 4.8%.
[b] Using the denominator of N=17 for males, the percentage of placebo-treated patients with spontaneous penile erection is 5.9%.
[c] Using the denominator of N=256 for males, the percentage of setmelanotide-treated patients with spontaneous penile erection is 11.3%.
[d] Using the denominator of N=396 for males, the percentage of setmelanotide-treated patients with spontaneous penile erection is 14.4%.
[e] Using the denominator of N=62 for males, the percentage of setmelanotide-treated patients with erection increased is 17.7%.
[f] Using the denominator of N=17 for males, the percentage of setmelanotide-treated patients with erection increased is 5.9%.
[g] Using the denominator of N=256 for males, the percentage of setmelanotide-treated patients with erection increased is 16.0%.
[h] Using the denominator of N=396 for males, the percentage of setmelanotide-treated patients with erection increased is 13.4%.
Note: Placebo data are only shown for patients with HO, because placebo data are limited for the other populations.
Source: ISS Table 4.3.1 (all patients with HO), ISS Table 4.2.1 (all patients with RDO), ISS Table 4.1.1 (all participants)

Serious adverse event/deaths/other significant events

Across the setmelanotide clinical development program, 4 patients (2 of whom had HO) had TEAEs that resulted in death through the data cutoff date of 26 March 2025; none were considered to be related to study drug For the 2 paediatric patients with HO, it was related to underlying conditions.

Events of Special Interest

The overall incidence of events of special interest was similar among all treatment groups, including patients with HO who received placebo during the double-blind treatment period of Study RM 493-040. While hyperpigmentation disorders was the most common events of special interest category for both all patients with RGDO and all participants who received setmelanotide, the most common events of special interest category in patients with HO was GI disorders. This is consistent with a higher overall incidence of GI events associated with the underlying disease, as evidenced by the similar incidence of these events in the patients who received placebo during the double-blind treatment period.

Importantly, the incidence of events related to local reactions at the injection site, as well as events in the events of special interest categories of psychiatric disorders and depression were similar or lower in setmelanotide-treated patients with HO compared to patients with HO who received placebo. There was also no evidence that setmelanotide causes hypertension in any population.

Events that are typically associated with setmelanotide treatment, such as hyperpigmentation disorders, nausea, vomiting, and disturbances in sexual arousal (particularly erection increased), occurred with a higher incidence in setmelanotide-treated patients with HO compared to patients who received placebo. Notably, these events occurred at a similar or lower incidence in setmelanotide-treated patients with HO as in all patients with RGDO and all participants treated with setmelanotide.

Laboratory findings

As shown below, the incidence of patients with TEAEs related to abnormal clinical laboratory parameters was in general similar across studies in patients with HO as well as in patients who received setmelanotide and those who received placebo.

Overall, the majority of TEAEs related to abnormal clinical laboratory parameters occurred in only 1 patient each. While there appears to be a higher incidence of patients with TEAEs related to blood sodium abnormalities in the setmelanotide arm compared with the placebo arm during the double-blind treatment period, many of the setmelanotide patients experienced both hypernatraemia as well as hyponatraemia or blood sodium abnormal. Thus, the overall incidence of unique patients with TEAEs related to blood sodium abnormalities in the setmelanotide arm (7/94, 7.4%) is relatively similar compared with the placebo arm (3/48, 6.3%). Of note in RM 493-040, 82.7% of setmelanotide-treated had diabetes insipidus and 76.9% of placebo patients had diabetes insipidus, a disease in which sodium abnormalities are relatively common (RM 493-040). There were no TEAEs related to blood sodium abnormalities in the Phase 2 study, RM 493-030, and there was 1 patient (7.1%) with 1 event of blood sodium increased in the LTE.

Table 23 TEAEs Related to Abnormal Clinical Laboratory Parameters in Patients with HO by Clinical Study Through 26 March 2025

Preferred Term	Study RM-493-040 Double-blind Treatment Period		Study RM-493-030	LTE
	Setmelanotide (N=94) n (%)	Placebo (N=48) n (%)	Setmelanotide (N=18) n (%)	Setmelanotide (N=14) n (%)
Number of patients with a TEAE related to abnormal clinical laboratory parameters	**24 (25.5)**	**11 (22.9)**	**6 (33.3)**	5 (35.7)
Hyponatraemia	6 (6.4)	1 (2.1)	0	0
Hypernatraemia	5 (5.3)	1 (2.1)	0	0
Alanine aminotransferase increased	4 (4.3)	0	1 (5.6)	5 (35.7)
Blood creatine phosphokinase increased	2 (2.1)	4 (8.3)	1 (5.6)	1 (7.1)
Aspartate aminotransferase increased	2 (2.1)	0	0	2 (14.3)
Blood creatinine increased	1 (1.1)	1 (2.1)	0	0
Blood uric acid increased	1 (1.1)	1 (2.1)	1 (5.6)	0
C-reactive protein increased	1 (1.1)	1 (2.1)	0	0
Blood sodium increased	0	1 (2.1)	0	1 (7.1)
Blood sodium abnormal	1 (1.1)	0	0	0
Hepatic enzyme increased	1 (1.1)	0	1 (5.6)	0
Gamma-glutamyltransferase increased	1 (1.1)	0	0	0
Liver function test abnormal	1 (1.1)	0	0	0
Liver function test increased	0	0	0	1 (7.1)
Hypertransaminasaemia	0	0	2 (11.1)	0
Blood cholesterol increased	1 (1.1)	0	0	0
Hypercalcaemia	1 (1.1)	0	0	0

Preferred Term	Study RM-493-040 Double-blind Treatment Period		Study RM-493-030	LTE
	Setmelanotide (N=94) n (%)	Placebo (N=48) n (%)	Setmelanotide (N=18) n (%)	Setmelanotide (N=14) n (%)
Hypoglycaemia	1 (1.1)	0	0	0
Blood glucose decreased	1 (1.1)	0	0	0
Blood iron decreased	1 (1.1)	0	0	0
Blood lactate dehydrogenase increased	1 (1.1)	0	0	0
Blood glucose increased	0	1 (2.1)	0	0
Hyperchloraemia	0	1 (2.1)	0	0
Hypertriglyceridaemia	0	1 (2.1)	0	1 (7.1)
Blood triglycerides increased	0	1 (2.1)	0	0
Blood bicarbonate increased	0	1 (2.1)	0	0
Glycosylated haemoglobin increased	0	2 (4.2)	0	0
Anaemia	2 (2.1)	0	1 (5.6)	0
Haemoglobin decreased	2 (2.1)	0	0	0
White blood cell count increased	2 (2.1)	0	0	0
Haematocrit decreased	1 (1.1)	0	0	0
Lymphocyte count decreased	0	1 (2.1)	0	0

Abbreviations: HO = hypothalamic obesity; LTE = long-term extension; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Note: Data from Study RM-493-040 are for all patients in the safety analysis set prior to the start of bridging visits and were coded using MedDRA v25.1 or later; data from Study RM-493-030 are for all patients in the safety analysis set and were coded using MedDRA v24.0; and data from the LTE Studies RM-493-022 (N=14) and RM-493-042 (N=11) are for patients with HO from Index Study RM-493-030 with LTE data through 26-Mar-2025.
Source: RM-493-040 CSR Table 14.3.1.2A and Listing 16.2.7.1; RM-493-030 CSR Table 14.3.1.2 and Listing 16.2.7.1; ISS Table 4.4.1

Safety in special populations

Age

TEAEs were evaluated by age for the populations of all patients with RGDO and all participants treated with setmelanotide. The most common TEAE across all age groups in both populations was skin hyperpigmentation, which is consistent with the overall setmelanotide TEAE profile. Overall, the incidence of the most common TEAEs was similar across age groups among all participants treated with setmelanotide. The main exceptions included a higher incidence of vomiting, injection site bruising, pyrexia, and melanocytic naevus and a lower incidence of nausea in paediatric participants 2 to <6. The incidence of respiratory infections decreased with increasing age.

Renal Disease

No dose adjustments are necessary for patients with mild or moderate renal impairment. For patients with severe renal impairment, a modified dosing scheme is recommended as provided in the proposed Product Label.

Hepatic Disease

Setmelanotide, a cyclic octapeptide, is stable in human, rat, and monkey hepatocytes and therefore a study in hepatically impaired patients was not conducted. Furthermore, peptides are generally metabolized by endopeptidases, then further degraded to amino acids by exopeptidases. Due to the ubiquitous availability of proteases and peptidases throughout the body, proteolytic degradation of many peptides is rapid and not

limited to organs typically associated with drug elimination, such as the liver. Therefore, hepatic metabolism rarely plays a significant role in the clearance of peptides.

Other Subgroups

TEAE data are summarized by age, sex, race, and ethnicity for each of the populations (all patients with HO, all patients with RGDO, and all participants). Overall, the TEAE profile of setmelanotide was generally consistent regardless of race, ethnicity, or sex with the exception of events of disturbances in sexual arousal, which occurred more frequently in males than females.

Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies have been conducted, which is considered acceptable by the CHMP.

Discontinuation due to adverse events

In general, the incidence of patients treated with setmelanotide who had TEAEs leading to study drug interruptions were similar in Study RM 493-040 (23.4%), Study RM 493-030 (27.8%), and the LTE (21.4%) despite the variable treatment durations and sample sizes. The incidence of patients with study drug interruption while receiving setmelanotide during the BVs (7.7%) was similar to that of patients who received placebo (8.3%) during the double-blind treatment period of Study RM 493-040. Not unexpectedly, the TEAEs leading to study drug interruptions that occurred with the highest incidence across studies were nausea and vomiting.

The majority of TEAEs leading to study drug interruption occurred in only 1 patient. TEAEs leading to study drug interruption that occurred in ≥2 patients in any treatment group are summarized by study below.

Consistent with incidence of all TEAEs leading to study drug interruption, the incidence of patients treated with setmelanotide who had treatment-related TEAEs leading to study drug interruptions were similar in both Study RM 493-040 (9.6%) and Study RM 493-030 (11.1%) (RM 493-040 and RM 493-030). Treatment-related TEAEs leading to study drug interruptions that occurred with the highest incidence across studies were nausea and vomiting. The only other treatment-related TEAE leading to study drug interruption that occurred in ≥2 patients was hypernatraemia (n=2). These events all occurred in patients who received setmelanotide.

Table 24 TEAEs Leading to Treatment Interruption in ⩾2 Patients with HO by Clinical Study Through 26 March 2025

System Organ Class Preferred Term	Study RM-493-040			Patients from Study RM-493-030	
	Double-Blind Treatment Period			Study RM-493-030	LTE
	Setmelanotide (N=94) n (%)	Placebo (N=48) n (%)	BVs (N=104) n (%)	Setmelanotide (N=18) n (%)	Setmelanotide (N=14) n (%)
Number of patients with at least 1 TEAE leading to treatment interruption	**22 (23.4)**	**4 (8.3)**	**8 (7.7)**	**5 (27.8)**	**3 (21.4)**
Gastrointestinal disorders	**8 (8.5)**	**2 (4.2)**	**2 (1.9)**	**2 (11.1)**	**2 (14.3)**
Nausea	4 (4.3)	0	1 (1.0)	2 (11.1)	0
Vomiting	5 (5.4)	2 (4.2)	1 (1.0)	0	2 (14.3)
Abdominal pain	2 (2.1)	0	0	0	0
Endocrine disorders	**3 (3.2)**	**0**	**0**	**0**	**0**
Adrenocortical insufficiency acute	2 (2.1)	0	0	0	0
Metabolism and nutritional disorders	**3 (3.2)**	**0**	**1 (1.0)**	**1 (5.6)**	**0**
Hypernatraemia	2 (2.1)	0	1 (1.0)	0	0
Hyponatraemia	2 (2.1)	0	0	0	0
Infections and infestations	**7 (7.4)**	**1 (2.1)**	**2 (1.9)**	**2 (11.1)**	**1 (7.1)**
Influenza	2 (2.1)	0	0	0	1 (7.1)

Abbreviations: BVs = bridging visits; HO = hypothalamic obesity; LTE = long-term extension; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: Data from Study RM-493-040 double-blind treatment period are for all patients in the safety analysis set prior to the start of bridging visits and were coded using MedDRA v25.1 or later; data from the BVs are for all patients with BV data in Study RM-493-040 through 26-Mar-2025 and were coded using MedDRA v25.1 or later; data from Study RM-493-030 are for all patients in the safety analysis set and were coded using MedDRA v24.0; and data from LTE Studies RM-493-022 (N=14) and RM-493-042 (N=11) are for patients with HO from Index Study RM-493-030 with LTE data through 26-Mar-2025 and were coded using MedDRA v25.1 or later

Source: RM-493-040 CSR Listing 16.2.7.1 (double-blind), ISS Table 10.3.1 (BV), RM-493-030 CSR Listing 16.2.7.1 (Study RM 493-030), ISS Table 10.4.1 (LTE)

Post marketing experience

There is no postmarketing experience on the use of setmelanotide in acquired hypothalamic obesity (aHO).

Since marketing in the authorised indications, no signals were newly identified, and no significant new safety findings were identified which alter the characterization of the safety profile of setmelanotide.

2.4.1. Discussion on clinical safety

Safety data obtained to date show that setmelanotide is generally well-tolerated and there is no evidence for setmelanotide-induced medically serious safety events. Adverse events commonly associated with setmelanotide include skin hyperpigmentation. Less commonly, nausea and vomiting were reported, and rarely, disturbances in sexual arousal have been observed. Potential mechanistic-based events such as hypertension were assessed carefully throughout development but were not observed. Events associated with severe obesity such as depression and suicidal ideation occurred infrequently. The imbalance in SAEs may relate in part to the changes in BMI, decreased food and potentially water intake, which must be monitored in patients with complex medical conditions, specifically in those patients with the adipsic form of diabetes insipidus. The need for medication dosing adjustments and water guidance adjustments should be assessed as patients respond to the medication.

The incidence of ISRs was lower in setmelanotide-treated patients with HO (39.5% of patients) compared to the incidence in placebo-treated patients with HO (54.2%), which was similar to that observed in patients with RGDO (53.3%) and all participants (45.7%). The most common preferred terms within this category in patients with HO included ISR, injection site pruritus, and injection site erythema, all occurring in just over 10% of patients.

The incidence of GI disorders was slightly higher in setmelanotide-treated patients with HO (69.4% of patients) compared to the incidence in placebo-treated patients with HO (58.3%), and similar to that observed in patients with RGDO (64.8%) and all participants (60.6%). The most common preferred terms within this category in patients with HO included nausea and vomiting, occurring in 46.9% and 36.1% of patients, respectively.

The incidence of hyperpigmentation disorders was higher in setmelanotide-treated patients with HO (48.3% of patients) compared to the incidence in placebo-treated patients with HO (10.4%), but lower than that observed in patients with RGDO (72.0%) and all participants (63.7%). The most common preferred term within this category in patients with HO was skin hyperpigmentation, occurring in 46.9% of patients.

The incidence of disturbances in sexual arousal was higher in setmelanotide-treated patients with HO (13.6% of patients) compared to the incidence in placebo-treated patients with HO (4.2%), and slightly lower than that observed in patients with RGDO (19.5%) and all participants (19.5%). The most common preferred term within this category in patients with HO was erection increased, occurring in 7.5% of patients.

There have been concerns that MC4R agonism may increase BP as prior MC4R agonists, including LY2112688 (Eli Lilly and Company), have led to increased HR and BP. In the placebo-controlled Phase 3 study, RM 493-040, treatment with setmelanotide was associated with reductions in BP and HR and consistent results were observed in ABPM assessments. Moreover, the incidence of TEAEs of hypertension and BP increased were slightly higher in placebo-treated patients with HO (4.2%, 2.1%) compared with all 3 setmelanotide-treated populations (ie, patients HO [1.4, 0.7%%], those with RGDO [3.3%, 0.7%], and all participants who received setmelanotide [2.4%, 0.7%]).

The incidence of psychiatric disorders, in particular depression and depressive symptoms, was lower in setmelanotide-treated patients with HO (3.4% and 4.1% of patients) compared to the incidence in placebo-treated patients with HO (6.3% and 10.4%), and similar to that observed in patients with RGDO (4.2%) and 1.2% and all participants (3.4% and 0.8%). The most common preferred term within this category in patients with HO was depressive symptoms occurring in 4.1% of patients.

The observed safety profile in the new indication HO was in general similar to the safety profile in the already approved indications.

The MAH proposed two new warnings in section 4.4 about aHO-related conditions requiring replacement therapy i.e., for patient with central diabetes insipidus and patients with adrenal insufficiency to consider monitoring and adjustment of the doses for concomitant medications following weight loss due to setmelanotide therapy. These were considered acceptable by the CHMP.

2.4.2. Conclusions on clinical safety

From the safety database all the adverse reactions reported have been included or updated in the SmPC with their frequencies. The finding related to more serious adverse events (n=32, 21.8%) in the active treatment group compared to placebo-treated patients with HO (6.3%) versus (11.1%) in all setmelanotide treated patients with RGDO was adequately addressed with the further adapted dosing regimen for patients with aHO in section 4.2 of the SmPC. See section 2.2.7.

2.4.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.5. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.2 is acceptable.

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Melanoma Prolonged penile erections Depression (including suicidal ideation) Benzyl alcohol accumulation in young children
Missing information	Use in pregnant/breastfeeding women Use in hepatic impairment Use in severe renal impairment Long-term use

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide*	**Primary objective:** To assess the long-term safety of setmelanotide as prescribed in routine practice for patients from 2 years of age and older, with biallelic POMC/PCSK1 or LEPR deficiency obesity or BBS, according to the current local prescribing information. **Secondary objectives:** To document and characterise the following AESIs for all patients: • Prolonged penile erection • Depression (including suicidal ideation) To document and characterise AESIs and adverse events in the following special populations: • Patients with hepatic impairment • Patients with severe renal impairment • Pregnant/ breastfeeding women To evaluate the long-term effectiveness of setmelanotide when it is prescribed as	Melanoma Prolonged penile erection Depression (including suicidal ideation) Risk of benzyl alcohol accumulation in young children Patients with hepatic impairment Patients with severe renal impairment Use in pregnancy and breastfeeding Long term use	Start of data collection First annual progress report Second annual progress report Third annual progress report Fourth annual progress report Completion of enrolment First annual interim analysis report Fifth annual progress report Second annual interim analysis report Sixth annual progress report Third annual	Q1 2023 Q1 2024 Q1 2025 Q1 2026 Q1 2027 Q1 2027 Q3 2027 Q1 2028 Q3 2028 Q1 2029 Q3 2029 Q1 2030 Q3 2030

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	part of routine practice To describe baseline characteristics and history of obesity in patients treated with setmelanotide To assess young children who could be at potential risk for accumulation of benzyl alcohol for any signs or symptoms which could suggest metabolic acidosis. **Exploratory objectives:** To document any cases of melanoma and their characteristics To document obesity-related hospitalisations and surgeries		interim analysis report Seventh annual progress report Fourth annual interim analysis report Eighth annual progress report Last (fifth) annual interim analysis report Last (ninth) annual progress report End of data collection: +9 years Final study report: +6 months	Q1 2031 Q3 2031 Q1 2032 Q1 2032 Q3 2032

*Rhythm has agreed the expansion of the existing registry population to include adults and children 4 years of age and above with aHO.

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Melanoma	Routine risk minimisation measures: Routine risk communication: • SmPC sections 4.4 and 4.8 • PL section 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 recommends full body skin examinations be conducted before and during treatment with setmelanotide to monitor pre-existing and new skin pigmentary lesions. • PL section 2 recommends a skin examination be conducted prior and during treatment. Other routine risk minimisation measures beyond the Product Information: • Legal status: prescription only medication No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Prolonged penile erections	Routine risk minimisation measures: Routine risk communication: • SmPC section 4.4 • PL section 2 and 4 Routine risk minimization specific clinical measures to address the risk: • SmPC section 4.4 includes the statement that patients who have an erection lasting greater than 4 hours should seek emergency medical attention. • PL section 2 recommends	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	patients seek urgent medical care if they experience an erection lasting greater than 4 hours. Other routine risk minimisation measures beyond the Product Information: • Legal status: prescription only medication No additional risk minimisation measures	Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Depression (including suicidal ideation)	Routine risk minimisation measures: Routine risk communication: • SmPC section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 recommends subjects with depression be monitored if treated with IMCIVREE and notes consideration should be given to discontinuing IMCIVREE if patients experience suicidal thoughts or behaviours. Other routine risk minimisation measures beyond the Product Information: • Legal status: prescription only medication No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Benzyl alcohol accumulation in young children	Routine risk minimisation measures: Routine risk communication: • SmPC section 4.4 • PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	recommends patients aged 2 years to be monitored for any sign of metabolic acidosis while under treatment. • PL section 2 notes that in young children (less than 3 years old), there is an increased possibility that benzyl alcohol could build-up in their body. Children aged 2 years old should be monitored by their doctor for side effects of this build-up (called "metabolic acidosis"). Other routine risk minimisation measures beyond the Product Information: • Legal status: prescription only medication No additional risk minimisation measures	Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Use in pregnant/breastfeeding women	Routine risk minimisation measures: Routine risk communication: • SmPC section 4.6 • PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.6 notes that IMCIVREE should not be started during pregnancy or while attempting to get pregnant. If a patient who is taking setmelanotide has reached a stable weight and becomes pregnant, consideration should be given to maintaining setmelanotide. If a patient who is taking setmelanotide and is still losing weight becomes pregnant, setmelanotide should either be discontinued, or the dose reduced while monitoring the recommended weight gain during pregnancy. The treating	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	physician should carefully monitor weight during pregnancy in a patient taking setmelanotide. • SmPC section 4.6 notes that if breastfeeding, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from IMCIVREE therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the mother. Other routine risk minimisation measures beyond the Product Information: • Legal status: prescription only medication No additional risk minimisation measures	
Use in hepatic impairment	Routine risk minimisation measures: Routine risk communication: • SmPC sections 4.2 and 5.2 • PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC sections 4.2 and 5.2 note that setmelanotide should not be administered to patients with hepatic impairment. Other routine risk minimisation measures beyond the Product Information: • Legal status: prescription only medication No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Use in severe renal impairment	Routine risk minimisation measures: Routine risk communication:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• SmPC sections 4.2 and 5.2 • PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC sections 4.2 and 5.2 recommend specific dose titration in patients with severe renal impairment Other routine risk minimisation measures beyond the Product Information: • Legal status: prescription only medication No additional risk minimisation measures	detection: • None Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Long-term use	Routine risk minimisation measures: Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Legal status: prescription only medication No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032

*Rhythm has agreed to extend the existing registry population to include adults and children 4 years of age and above with aHO. For this purpose, protocol of the PASS study is currently under amendment.

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, new warnings with regard to aHO (ie related to central diabetes insipidus and adrenal insufficiency) have been added to the product information. Immunogenicity information has been updated and relocated to section 5.1 of the SmPC. The Package Leaflet has been updated accordingly.

2.6.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Hypothalamic obesity is a devastating disease in which patients experience rapid, severe, and intractable weight gain and hyperphagia associated with hypothalamic injury and/or dysfunction. Acquired HO affects approximately 5,000 to 10,000 patients in the US and is believed to have similar incidence and prevalence in the EU and rest of world.

Acquired HO develops after injury to the hypothalamus, most often as a result of a tumor (e.g., craniopharyngiomas, gliomas, pituitary adenomas, hamartomas), and/or the surgery or radiation therapy used to treat the tumor. Other rarer causes of injury may include inflammatory conditions involving the hypothalamus such as sarcoidosis or traumatic brain injury. Craniopharyngiomas currently represent the most common tumor associated with the development of acquired HO and account for 5% to 15% of paediatric intracranial tumors, and occur with 2 peaks of incidence, one during childhood (10 to 19 years of age [29%]) and the second in adulthood (30 to 49 years of age [25%]). In other disorders which may involve the hypothalamus, a subset of patients develop obesity which is hypothesized to be due to developmental abnormalities of the hypothalamus. These disorders include septo-optic dysplasia (SOD), optic nerve hypoplasia (ONH), childhood-onset combined pituitary hormone deficiency (CPHD) also called multiple pituitary hormone deficiency (MPHD) and pituitary stalk interruption syndrome (PSIS). Patients with these disorders often have a variable degree of endocrinopathies due to pituitary and or hypothalamic developmental abnormalities that may significantly impact growth, development, and survival.

Regardless of the underlying cause, patients with HO develop an aggressive form of obesity characterized by a high degree of sudden, severe, and sustained weight gain that has generally been unresponsive to lifestyle or medical intervention.

The weight gain in patients with HO is most dramatic in the first 6 to 12 months after injury and then continues for the next 8 to 12 years before plateauing. Hyperphagia may occur in approximately 50% to 70% of patients along with lethargy due to decreased energy expenditure, and psychosocial disorders spanning from depression to aggressive behavior are common. There is currently no approved effective treatment for HO.

3.1.2. Available therapies and unmet medical need

There are no approved therapies specifically for the treatment of HO. While recent studies suggest that GLP 1 receptor agonists and the triple monoamine reuptake inhibitor, tesofensine, may help reduce weight in some patients with HO, these studies have generally been small and of relatively short duration. Moreover, in the only 2 placebo-controlled trials of a GLP 1 (exenatide) in patients with HO, the primary endpoint was not met in either trial. In the first of these 2 studies, the 36 week mean percent change in BMI (primary endpoint) was a gain of 1.7% in the exenatide group and a gain of 3.5% in the placebo group (p=0.40). In the second study, the 26 week mean change in weight (primary endpoint) was a decrease of 3.8 kg (10.2%) in the exenatide group and a decrease of 1.6 kg (4.3%) in the placebo group (p=0.11).

3.1.3. Main clinical studies

The main evidence comes from the pivotal phase 3 study RM-493-040, a randomized, double-blind, placebo-controlled trial evaluating setmelanotide in patients aged ≥4 years with acquired hypothalamic obesity. In addition, data from 3 supportive studies were submitted in various study populations, a completed phase 2 trial RM-493-030, long-term extension studies RM-493-022 and RM-493-042. The latter is still ongoing.

3.2. Favourable effects

Setmelanotide demonstrated favourable effects in patients aged ≥4 years with acquired HO, addressing both core manifestations of the disease: excessive weight gain and hyperphagia. Due to the acute injury and progressive symptoms of HO, there is a strong rationale to treat patients earlier in life. The efficacy was observed across adult and paediatric age groups.

In the pivotal Phase 3 trial RM-493-040, treatment with setmelanotide for 52 weeks resulted in a statistically significant and clinically meaningful reduction in BMI of 16.51%, compared to a 3.32% increase in the placebo group, yielding a LSM difference of −19.83% (p<0.0001). Additionally, 82.73% of treated patients achieved either a ≥5% reduction in BMI (for adults) or a ≥0.2-point reduction in BMI z-score (for paediatric patients), compared to only 20.9% in the placebo group. Hunger was also significantly reduced, with patients aged ≥12 years reporting a mean decrease of 2.68 points in their weekly average of the most hunger score, versus a 1.24-point reduction in the placebo group (p=0.003). Among paediatric patients under 18 years, the mean reduction in BMI z-score was 1.47, compared to just 0.012 in the placebo group (p<0.0001). Furthermore, waist circumference decreased by an average of 11.58 cm in the setmelanotide group, while it increased by 3.85 cm in the placebo group (p<0.0001).

These effects were evident as early as Week 4 and sustained through 52 weeks of treatment.

Supportive evidence from the Phase 2 study RM-493-030, long-term extension studies (RM-493-022 and RM-493-042), external placebo comparisons (ECHO trial), and real-world data from early access programs in Italy and France further reinforce the favourable effects of setmelanotide. These data confirm the early onset and durability (up to 2.5 years) of treatment benefits across diverse patient populations and study designs.

3.3. Uncertainties and limitations about favourable effects

While the rationale for early treatment in HO is strong, clinical experience in children <6 years remains limited. Only two patients in this age group with normal renal function treated with setmelanotide and 1 placebo patient who transitioned to setmelanotide after completing the placebo-

controlled study were included in the pivotal Phase 3 trial. Although the available efficacy and safety data in this age group are very limited, no new or dose-related safety concerns were identified and reported adverse events were consistent with the known safety profile of setmelanotide; together with favourable efficacy outcomes and individual dose titration based on tolerability and clinical response, treatment is considered acceptable in this age group despite the limited data.

Although the pivotal Phase 3 trial RM-493-040 demonstrated significant reductions in BMI and hunger, not all patients achieved clinically meaningful thresholds, and predictive factors for response remain undefined. Current real-world experience did not identify which patients are most likely to benefit from treatment.

While long-term efficacy was demonstrated in extension studies for up to 2.5 years, these data were derived from a small number of patients (n=11) from the Phase 2 study who entered LTE trials. The limited sample size and absence of a control group reduce the strength of conclusions regarding long-term effects. Moreover, variations in dosing regimens in the LTE studies (RM-493-022 and RM-493-042), which differed from those used in the pivotal Phase 3 trial, complicate direct comparisons and introduce uncertainty regarding the consistency of long-term efficacy across different dose levels and patient subgroups. The CHMP recommended to further support the maintenance of the effect by providing further quantitative long term efficacy outcomes from continued treatment beyond the placebo-controlled period, collected under the pivotal trial conditions, when available.

3.4. Unfavourable effects

Adverse events commonly associated with setmelanotide include skin hyperpigmentation. Less commonly, nausea and vomiting were reported, and rarely, disturbances in sexual arousal have been observed. Potential mechanistic-based events such as hypertension were assessed carefully throughout development but were not observed. Events associated with severe obesity such as depression and suicidal ideation occurred infrequently.

3.5. Uncertainties and limitations about unfavourable effects

Although the final model estimated effect of HO on CL/F suggested similar PK between patients with RGDO and HO, simulations among adults with normal renal function, predicted slightly higher exposures in patients with HO compared to patients with RGDO when receiving the same fixed dose. This difference is attributed to differences in weight distributions: enrolled patients with HO generally weighed less than those with RGDO. More pronounced deviations from the adult RGDO reference range (i.e., higher exposure) were predicted in younger patients and those with concomitant renal impairment, in line with the known effect of body weight and renal impairment on clearance. Given the very limited clinical data in children <6 years (n=2) and in patients with renal impairment, the adequacy of the proposed posology was questioned. In addition, there were more Serious Adverse Events n=32 (21.8%) in the active treatment group compared to placebo-treated patients with HO (6.3%) versus (11.1%) in all setmelanotide treated patients with RGDO.

Following several analyses across the predefined age groups (4 to <6, 6 to <12, 12 to <18, ≥18) in study RM-493-40, no consistent relationship between Ctrough and the occurrence of SAEs was identified in any age group, noting that for the age group 4 to <6-year-old, no firm conclusions can be drawn due to limited number of patients. Nevertheless, the CHMP agreed that the proposed starting doses for each age group/renal impairment group are predicted to lie within the RGDO exposure reference range. Upward titration to doses that are predicted to largely exceed the reference range is only allowed in patients who show an insufficient clinical response and have no prior tolerability issues. With regard to the age group 4 to <6-year-old, the CHMP also agreed that

the dose may be individually adjusted based on both tolerability and efficacy for these patients and despite limited data. This information has been reflected in the SmPC to guide the individual dose titration based on tolerability and clinical response. Additionally, the adapted dosing regimen for severe RI patients has been extended to moderate RI patients with HO to further reduce risks.

Only 38 HO patients were treated for more than 18 months.

3.6. Effects Table

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
BMI change	***PE*** Mean % change in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo	%	Setmelanotide N=81 -16.51%	Placebo N=39 3.32%		RM-493-040 mITT Analysis Set, Pivotal Cohort
Hunger	***KSE3*** Mean change in the weekly average of the daily most hunger score in patients ≥12 years old from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo	points	Setmelanotide N=61 2.68	Placebo N=28 1.24		RM-493-040 patients aged ≥12 years

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Unfavourable Effects						
		N (%)	Setmelanotide (N=147)	Placebo (N=48)	Limited number of patients and duration	All patients with HO
Skin Hyperpigmentation			69 (46.9%)	4 (8.3%)		
Injection Site Reaction			21 (14.3%)	11 (22.9%)		
Nausea			69 (46.9%)	13 (27.1%)		
Headache			45 (30.6%)	15 (31.3%)		
Melanocytic Naevus			16 (10.9%)	3 (6.3%)		
Number of participants with at least 1 serious TEAE			32 (21.8%)	3 (6.3%)		

Abbreviations: TEAE treatment emergent adverse events

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

HO is characterized by rapid, intractable weight gain and hyperphagia following hypothalamic injury, often occurring in childhood, and leading to lifelong health complications. Conventional weight-loss interventions, including lifestyle modification and pharmacotherapy, have shown limited efficacy in this population. The observed reductions in BMI, BMI z-score, waist circumference, and hunger scores in both adult and paediatric patients reflect meaningful improvements in the core symptoms of the disease.

These effects were not only statistically significant but also clinically relevant, with early onset and sustained benefit over the 52-week treatment period. Thus, a ≥5% reduction in BMI in adults and a ≥0.2-point reduction in BMI z-score in children is recognized as clinically significant improvements in weight-related outcomes (*EMA's Guideline on Clinical Evaluation of Medicinal Products Used in Weight Control, 2014*). In RM-493-040, 82.73% of patients treated with setmelanotide met or exceeded these thresholds, compared to only 20.9% in the placebo group, confirming the clinical relevance of the observed effects. Moreover, the reduction in mean BMI to below the obesity threshold (29.58) highlights the clinical relevance of treatment, as patients transitioned from obesity to the overweight category, which is associated with reduced long-term health risks.

Similarly, the reduction in hunger scores (particularly the "most hunger") was evaluated using the Daily Hunger Questionnaire, which has been validated in prior MC4R pathway disorders. A 1–2 point reduction on this scale is considered a meaningful within-patient change. In RM-493-040, patients ≥12 years experienced a mean reduction of 2.68 points, exceeding this threshold and indicating a substantial improvement in hyperphagia.

The observed reductions in waist circumference (−11.58 cm) and improvements in quality of life scores (e.g., IWQOL-Lite and IWQOL-Kids) further support the clinical impact of treatment. Waist circumference is a recognized surrogate marker for cardiometabolic risk, and reductions >5% are considered clinically relevant (*Ross et al., Nat Rev Endocrinol, 2020*).

Finally, the impact on hunger and weight translated into improved quality of life, as reported in patient-reported outcomes and qualitative interviews.

In the context of a high unmet medical need, these favourable effects are of particular importance for the acquired HO population.

The safety profile of setmelanotide is consistent with prior experience in genetic MC4R pathway disorders. The most important common adverse events were skin hyperpigmentation, nausea, and vomiting. They were predictable and manageable. No new safety signals were identified in the HO population. However, the incidence of serious adverse events was higher in the setmelanotide group. Overall, these adverse events are acceptable in light of the benefit shown and in light of the severity of the disease.

3.7.2. Balance of benefits and risks

Setmelanotide has demonstrated a favourable benefit-risk profile in patients aged ≥4 years with acquired HO, a population with no approved therapeutic options and a high burden of disease. The pivotal Phase 3 trial RM-493-040 met the primary and secondary endpoints and showed that treatment with setmelanotide for 52 weeks resulted in a statistically significant and clinically meaningful reduction in BMI of 16.51%, compared to a 3.32% increase in the placebo group, with a LSM difference of −19.83% ($p<0.0001$). Furthermore, 82.73% of treated patients achieved either a ≥5% reduction in BMI or a ≥0.2-point reduction in BMI z-score, versus 20.9% in the placebo group.

In paediatric patients <18 years, the mean reduction in BMI z-score was −1.47, compared to −0.012 in the placebo group ($p<0.0001$). While the rationale for early treatment in HO is strong, clinical experience in children <6 years remains limited. Only two patients in this age group with normal renal function treated with setmelanotide and 1 placebo patient who transitioned to setmelanotide after completing the placebo-controlled study were included in the pivotal Phase 3 trial. Although the available efficacy and safety data in this age group are very limited, no new or dose-related safety concerns were identified and reported adverse events were consistent with the known safety profile of setmelanotide; together with favourable efficacy outcomes and individual dose titration based on tolerability and clinical response, treatment is considered acceptable in this age group despite the limited evidence base.

Setmelanotide also significantly reduced hunger, with a −2.68 point reduction in the weekly average of the most hunger score in patients ≥12 years, compared to −1.24 in the placebo group ($p=0.003$). Waist circumference decreased by an average of 11.58 cm in the setmelanotide group, while it increased by 3.85 cm in the placebo group ($p<0.0001$). These effects were observed early (from Week 4) and sustained throughout the treatment period.

The safety profile of setmelanotide is consistent with prior experience in genetic MC4R pathway disorders. The most common adverse events were predictable and manageable, including skin hyperpigmentation, nausea, and vomiting. No new safety signals were identified in the HO population. While the incidence of serious adverse events was higher in the setmelanotide group, further analyses nevertheless showed that there were no consistent relationship between Ctrough and the occurrence of SAEs in any age group. The section 4.2 of the SmPC has been reinforced regarding the recommendation on individual titration based on tolerability and clinical responses and further adaptation on dosing regimen for moderate RI patients with HO has been made to further reduce risks.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall benefit-risk of Imcivree is positive in the following indication:

IMCIVREE is indicated for the treatment of obesity and the control of hunger in adults and children 4 years of age and above with acquired hypothalamic obesity (aHO) due to hypothalamic injury or impairment.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I and IIIB

Extension of indication to include treatment of obesity and control of hunger in adults and children 4 years of age and above, above with acquired hypothalamic obesity (aHO) due to hypothalamic injury or impairment, based on results from study RM-493-040 as well as supportive study RM-493-030. RM-493-040 is a phase 3, double blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of setmelanotide in patients with acquired hypothalamic obesity, while RM-493-030 is a phase 2, open-label 20-week study to evaluate the safety and efficacy of setmelanotide in subjects with hypothalamic obesity. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated. The Package Leaflet is updated accordingly. The RMP version 3.2 has also been submitted. In addition, the MAH took the opportunity to introduce editorial and administrative changes to the PI.

The variation leads to amendments to the annexes I and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion EMA/VR/0000288021

Attachments

1. SmPC, Package Leaflet (changes highlighted) of Imcivree, 10 mg/ml, solution for injection, as adopted by the CHMP on 26 March 2026