21 July 2022
EMA/677091/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

IMCIVREE

International non-proprietary name: setmelanotide

Procedure No. EMEA/H/C/005089/II/0002/G

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

ADA	Anti-Drug Antibody
AE	Adverse Event
AG	Active Growth Analysis Set
AS	Alström Syndrome
ATB	Active Treatment Baseline
AUC	Area Under the Concentration-Time Curve
BBS	Bardet-Biedl Syndrome
BMI	Body Mass Index
BP	Blood Pressure
CDC	Centres For Disease Control and Prevention
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human use
CI	Confidence Interval
Cmax	Maximum Observed Concentration
CRIBBS	Clinical Registry Investigating Bardet-Biedl Syndrome
CS	Completers Set
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DCM	Dilated Cardiomyopathy
Diff	Difference
DUS	Designated Use Set
ECG	Electrocardiogram
EMA	European Medicines Agency
EOPx	End OF Period X
ERG	Electroretinography
ESI	Event Of Special Interest
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practices
GFR	Glomerular Filtration Rate
GLP-1	Glucagon-Like Peptide-1

H0	Null-Hypothesis
HbA1c	Haemoglobin A1c
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
HR	Heart Rate
ISI	Integrated Summary of Immunogenicity
ISR	Injection Site Reaction
ISS	Integrated Safety Summary
KSE	Key Secondary Endpoint
LEPR	Leptin Receptor
MA	Marketing authorisation
MAH	Marketing Authorisation Holder
Max	Maximum
MC	Melanocortin
MC1R	Melanocortin Receptor 1
MC4R	Melanocortin Receptor Type 4
MCR	Melanocortin Receptors
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
Min	Minimum
MSH	Melanocyte Stimulating Hormone
NA	Not applicable
NAFLD	Non- Alcoholic Fatty Liver Disease
OGTT	Oral Glucose Tolerance Test
PASS	Post-Auhtorisation Safety Study
PCP	Placebo-Controlled Period
PCPB	Placebo-Controlled Period Baseline
PCS	Placebo-Controlled Analysis Set
PCSK1	Proprotein Convertase Subtilisin/Kexin Type 1
PD	Pharmacodynamics
PE	Primary Endpoint
PECsw	Predicted Environmental Concentration in surface water
PHQ-9	Patient Health Questionnaire-9
PIP	Paediatric Investigation Plan

PIV	Pivotal
PK	Pharmacokinetics
Plac/PB/Pbo	Placebo
POMC	Pro-Opiomelanocortin
POP PK	Population Pharmacokinetics
PP	Per-Protocol
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
PVN	Paraventricular Nucleus
QD	Quaque Die (Once Per Day)
RGDO	Rare Genetic Disorders of Obesity
RMP	Risk Management Plan
SA	Safety Analysis
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SC	Subcutaneous
SCS	Summary of Clinical Safety
SD	Standard Deviation
SE	Secondary Endpoint
Set	setmelanotide
SH	Stable Height Analysis Set
SmPC	Summary of Product Characteristics
Supp	Supplemental
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment-Emergent Adverse Event
Tmax	Time To Observed Maximum Concentration
US	United States
Wx	Week X (Timepoint)
xW	X Weeks (Duration)
yo	Years Old

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Rhythm Pharmaceuticals Netherlands B.V., submitted to the European Medicines Agency on 13 October 2021 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Group of variations consisting of:

C.I.6.a - To add the new therapeutic indication for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC and sections 1, 3 and 4 of the PL are updated accordingly. The updated RMP version 1.0 has also been submitted.

C.I.6.a - To add the new therapeutic indication for the treatment of obesity and the control of hunger associated with genetically confirmed Alström syndrome (AS). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC and sections 1, 3 and 4 of the PL are updated accordingly. The updated RMP version 1.0 has also been submitted.

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

On 22 April 2022, on the basis that additional data were required and these were considered still provisional, the MAH withdrew the following variation:

C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

C.I.6.a - To add the new therapeutic indication for the treatment of obesity and the control of hunger associated with genetically confirmed Alström syndrome (AS). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC and sections 1, 3 and 4 of the PL are updated accordingly. The updated RMP version 1.0 has also been submitted.

Information relating to orphan designation

IMCIVREE was designated as an orphan medicinal product:

- EU/3/19/2192 on 21 August 2019 in the following indication: Treatment of Bardet-Biedl syndrome

- EU/3/19/2245 on 9 January 2020 in the following indication: Treatment of Alström syndrome

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0215/2021) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0215/2021) is not yet completed as some measures were deferred.

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 12 November 2020 (EMA/CHMP/SAWP/585846/2020). The Protocol assistance pertained to clinical aspects and in relation to paediatric development of the dossier.

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

Timetable	Actual dates
Submission date	13 October 2021
Start of procedure:	30 October 2021
CHMP Rapporteur Assessment Report	20 December 2021
PRAC Rapporteur Assessment Report	3 January 2022
PRAC Outcome	13 January 2022
CHMP members comments	14 January 2022
Updated CHMP Rapporteur Assessment Report	20 January 2022
Request for supplementary information (RSI)	27 January 2022
CHMP Rapporteur Assessment Report	22 March 2022
PRAC Rapporteur Assessment Report	25 March 2022
Updated PRAC Rapporteur Assessment Report	1 April 2022
PRAC Outcome	7 April 2022
CHMP members comments	11 April 2022

Timetable	Actual dates
Updated CHMP Rapporteur Assessment Report	14 April 2022
Request for supplementary information (RSI)	22 April 2022
MAH withdrawal letter submitted to CHMP	22 April 2022
CHMP Rapporteur Assessment Report	17 June 2022
PRAC Rapporteur Assessment Report	21 June 2022
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	7 July 2022
CHMP members comments	11 July 2022
Updated CHMP Rapporteur Assessment Report	n/a
Opinion	21 July 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Bardet-Biedl syndrome (BBS) is a rare pleiotropic autosomal recessive disorder caused by mutations in more than 20 different genes, all of which participate in cilia functioning and is therefore considered a primary ciliopathy. Extensive research suggests the obesity phenotype in BBS is caused by impaired transport of the leptin receptor (LEPR) to the ciliary membrane of pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus. Under normal conditions, leptin, a hormone predominantly made by adipose cells, stimulates firing and gene expression in POMC neurons, promoting the secretion of alpha-melanocyte stimulating hormone (α-MSH). Alpha-MSH stimulates the MC4R located in the second order neurons in the paraventricular nucleus (PVN) of the hypothalamus and results in decreased hunger and weight and increased energy expenditure. Impaired or absent LEPR signaling in POMC neurons would be expected to reduce MC4R stimulation in second order neurons, resulting in an increase in appetite, reduced metabolic rate, and increased weight.

Alström syndrome (AS), like BBS, is a ciliopathy characterized by a syndromic phenotype that includes progressive cone-rod dystrophy leading to blindness, sensorineural hearing loss, congestive heart failure, and marked childhood obesity associated with hyperinsulinemia and type 2 diabetes mellitus. It is caused by bi-allelic recessive mutations in a single gene, ALMS1. AS is considerably rarer than BBS. While the dominant phenotype in BBS is typically developmental defects, in AS it is metabolic function. Beginning in infancy, patients with AS have progressive multiorgan pathology that typically leads to truncal obesity, insulin resistance, hyperinsulinemia, hyperleptinemia, and hyperlipidaemia by 5 years of age and progresses to T2DM; excessive weight gain typically begins within the first year of life. The incidence of T2DM is one of the distinguishing features between AS and BBS. In patients with AS the

incidence of T2DM is ~50% to 75% compared with <25% in patients with BBS.

State the claimed therapeutic indication

Treatment of obesity and the control of hunger associated with genetically confirmed **BBS** and **AS** in adults and children 6 years of age and above. On 22 April 2022, on the basis that additional data were required, and these were considered still provisional, the MAH withdrew the variation application of the grouping related to AS in adults and children 6 years of age and above.

Epidemiology

BBS is a rare pleiotropic autosomal recessive disorder characterized by a syndromic phenotype with an overall prevalence of 1 in 125,000–160,000 in people of European descent, while AS is considerably rarer than BBS, with ~950 cases estimated worldwide.

Clinical presentation, diagnosis

BBS is characterized by marked obesity and hyperphagia as well as several other disease features (rod cone dystrophy, postaxial polydactyly, cognitive impairment, hearing loss, speech deficit, hepatic fibrosis, genitourinary malformations, renal abnormalities, diabetes mellitus, hypertension, and congenital heart disease that do not likely arise from hypothalamic impairment.

AS is characterized by a syndromic phenotype that includes progressive cone-rod dystrophy leading to blindness, sensorineural hearing loss, congestive heart failure, and marked childhood obesity associated with hyperinsulinemia and type 2 diabetes mellitus. It is caused by bi-allelic recessive mutations in a single gene, ALMS1. AS is considerably rarer than BBS. While the dominant phenotype in BBS is typically developmental defects, in AS it is metabolic function. Beginning in infancy, patients with AS have progressive multiorgan pathology that typically leads to truncal obesity, insulin resistance, hyperinsulinemia, hyperleptinemia, and hyperlipidaemia by 5 years of age and progresses to type 2 Diabetes Mellitus (T2DM); excessive weight gain typically begins within the first year of life.

Management

There are no approved therapies or products in development specifically for treatment of obesity and reduction of hyperphagia in patients with BBS or AS, and there is no evidence that alternative potential (unapproved) therapies might be useful. The only pharmacologic treatments available are products for general obesity/weight management; however, there is limited experience with these therapies in patients with MCR pathway associated obesity such as BBS and AS. In general, these therapies have not been successful in early-onset extreme genetic obesity as these therapies fail to address the MC4R pathway signalling defect that leads to obesity and hyperphagia in these patients.

The absence of drug therapy and unsuitability of surgical intervention leaves only lifestyle modification (i.e., diet and exercise) as available therapeutic interventions for patients with severe obesity. These, however, are rarely successful over the short-term and almost never effective in the long-term due to the intense drive to eat caused by the absence of satiety signals.

2.1.2. About the product

Setmelanotide is a synthetic octapeptide melanocortin 4 receptor (MC4R) agonist with 2-3-fold less activity at the melanocortin 3 receptor (MC3R) and melanocortin 1 receptor (MC1R). MC4Rs in the brain are involved in regulation of hunger, satiety, and energy expenditure. In genetic forms of obesity associated with insufficient activation of the MC4R, setmelanotide is believed to re-establish MC4R pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure. Nonclinical evidence shows that MC4Rs are important for setmelanotide-regulated appetite and weight loss. The MC1R is expressed on melanocytes, and activation of this receptor leads to accumulation of melanin and increased skin pigmentation independently of ultraviolet light.

IMCIVREE is currently indicated for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

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

The Applicant requested and received a Protocol Assistance (EMA/CHMP/SAWP/585846/2020) in November 2020 touching upon aspects of trial design, endpoint choice, population choice and evaluation methods. The Applicant decided not to follow the advice on several (key) issues in the final submission. See section 2.4.

2.1.4. General comments on compliance with GCP

All trials were conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline and trails carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC.

2.2. Non-clinical aspects

No new non-clinical data on pharmacology, pharmacokinetics and toxicology have been submitted in this application, which is considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The combined Predicted Environmental Concentration in surface water (PECsw) for setmelanotide from the use of IMCIVREE 10 mg/ mL solution for injection for all indications, including the two new indications, has been calculated to be 0.0000615 µg/L. This is 162.6 times lower than the Phase I action limit of 0.01 µg/L. The non-clinical data reveal no special hazards for the environment. In conclusion, IMCIVREE 10 mg/ mL solution for injection represents a negligible risk to the environment from use in treatment of obesity and the control of hunger associated with genetically confirmed Bardet Biedl syndrome (BBS) loss-of function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

2.2.2. Discussion on non-clinical aspects

The absence of pharmacology, pharmacokinetics, toxicology studies are considered acceptable, based on the available clinical data. However, the link between the MC4R receptor and the upstream genetic deficiency of Bardet-Biedl syndrome (BBS) and Alström syndrome (AS) was requested to be further justified during the procedure. Relevant information has been provided by the applicant and is summarised in sections 2.3.3 and 2.4.

2.2.3. 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.

2.3. Clinical aspects

2.3.1. 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

Type of Study	Study Identifier	Objectives	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	No. of Sub-jects	Diagnosis of patients	Duration of Treatment	Study status; Type of Report
Phase 3	RM-493-023	**Primary** • Assess the effect of setmelanotide on the proportion of patients >12 years of age at baseline treated with setmelanotide for -52 weeks who achieve a clinically meaningful reduction from baseline (i.e., >10%) in body weight. **Key Secondary** • Assess the effect of setmelanotide on mean percent change from baseline in body weight (in patients >12 years of age at baseline) after -52 weeks of treatment with setmelanotide. • Assess the effect of setmelanotide on the mean percent change from baseline in the weekly average of the daily hunger score (in patients > 12 years of age at baseline) after -52 weeks of treatment with setmelanotide.	Randomized Double-blind Placebo-controlled followed by an open-label treatment period.	Setmelanotide or placebo QD via SC injection for the first 14 weeks. Starting dose 2 mg with increase to 3 mg for patients >16 years Starting dose 1 mg with increase to 2 mg for patients <16 years of age). After the 14-week double-blind treatment period, all patients received open label setmelanotide QD via SC injection for 38 weeks. SC injection	52	Bardet-Biedl Syndrome and Alstrom syndrome	66 weeks	Complete; CSR

Type of Study	Study Identifier	Objectives	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	No. of Sub-jects	Diagnosis of patients	Duration of Treatment	Study status; Type of Report
		• Evaluation of long-term weight loss (over 1 to 2 years) • Global Hunger Scores (11-point scale (0 to 10)) • Changes of skin and nevi color • Psychological development during treatment period						
Phase 2	RM-493-014	**Primary** • Demonstrate statistically significant and clinically meaningful effects of setmelanotide, after 3 months of treatment, on percent body weight change in each type of the rare genetic disorders of obesity included in this study. **Secondary** To assess the effects of 3 months of setmelanotide treatment on: • Safety and tolerability • Hunger	Open label; No control	setmelanotide; Up to 12-week dose titration to therapeutic dose level (maximum of 3 mg) followed by 10 weeks at therapeutic dose followed by 32 weeks continued treatment at therapeutic dose; SC injection	210	POMC, LEPR or PCSK.1-heterozygous deficiency obesity POMC epigenetic deficiency obesity Bardet-Biedl Syndrome Alstrom Syndrome Smith-Magenis Syndrome Carboxypeptidase E Syndrome SH2B1 Haplo-insufficiency Leptin Deficiency Obesity	52 weeks	Ongoing; Summary of results (no interim CSR)

Type of Study	Study Identifier	Objectives	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	No. of Sub-jects	Diagnosis of patients	Duration of Treatment	Study status; Type of Report
		• Percent change in body fat mass • Glucose parameters: fasting glucose, fasting insulin, glycated hemoglobin (HbAlc), oral glucose tolerate test (OGTT) with focus on parameters of insulin sensitivity. (OGTT was not conducted in patients with established type 1 or type 2 diabetes.) • Waist circumference						
Extension Study	RM-493-022	**Primary** • To characterize safety and tolerability of setmelanotide in patients who have completed a previous trial on treatment of setmelanotide for obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway**.**	Open label; No control	Setmelanotide; Setmelanotide QD at the same dose administered towards the end of the index study;SC injection	137	Obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway	2 years	Ongoing; Interim CSR

2.3.2. Pharmacokinetics

The pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of setmelanotide have been studied in human volunteers and patients in a total of 15 clinical studies, of which the new Phase 3 Study RM-493-023 supporting the present application. Two other studies (Study RM-493-029, RM-493-026) were also submitted in this application and the CHMP assessment on these data had already concluded in the scope of the authorised indications (EMEA/H/C/005089/II/03) and thus not presented in this report.

Study RM-493-023

One of the exploratory objectives of study RM-493-023 was to determine the pharmacokinetics of setmelanotide in patients with BBS or AS. Trough concentration data were obtained after either multiple doses of 2.0 mg QD or 3.0 mg QD setmelanotide. Trough setmelanotide concentrations were available from patients in the pivotal and supplemental cohorts and included:10 children (<12 years; N = 1 to 10 per visit),16 adolescents (12 to 18 years; N = 4 to 14 per visit), and 23 adults (>18 years; N = 4 to 21 per visit).

For adults, mean trough setmelanotide concentrations after 2.0 mg setmelanotide were 3.35 ± 1.44 ng/mL (N = 8), 2.90 ng/mL (N = 2, individual values: 0.00 and 5.79 ng/mL), and 3.86 ± 2.31 ng/mL (N = 21) for Visits 3, 6, and 7 (Weeks 3, 15, and 17), respectively. Mean trough setmelanotide concentrations after 3.0 mg setmelanotide ranged from 2.95 ng/mL (N = 2, individual values 0.00 and 5.89 ng/mL; Visit 3 [Week 3]) to 10.5 ± 12.3 ng/mL (N = 4, Visit 10 [Week 35]).

For adolescents, mean trough setmelanotide concentrations after a dose of 2.0 mg setmelanotide were 5.56 ± 4.51 ng/mL (N = 8) and 5.11 ± 3.92 ng/mL (N = 12) for Visits 3 and 7 (Weeks 3 and 17), respectively. Mean trough setmelanotide concentrations after a 3.0 mg setmelanotide ranged from 2.22 ng/mL (N = 1, Visit 7 [Week 17]) to 17.5 ± 18.6 ng/mL (N = 12, Visit 13 [Week 53]).

For children, mean trough setmelanotide concentrations after 2.0 mg setmelanotide were 3.12 ± 2.83 ng/mL (N = 4), 4.06 (N = 1), 7.94 ± 7.22 ng/mL (N = 8), and 5.22 ng/mL (N = 1) for Visits 3, 6, 7, and 15 (Weeks 3, 15, 17, and 66), respectively. Mean trough setmelanotide concentrations after 3.0 mg setmelanotide ranged from 4.35 ± 2.46 ng/mL (N = 3, Visit 13 [Week 53]) to 33.0 ng/mL (N = 1, Visit 7 [Week 17]).

High (>30.0 ng/mL) trough setmelanotide concentrations, up to 68.4 ng/mL, were observed in this study in children (5 patients) and adolescents (3 patients). With the exception of one adolescent patient, all of the patients with trough concentrations >30 ng/mL had baseline body weights <100 kg. None of these patients had renal impairment, none had any temporally associated AE that could reflect systemic intolerance to setmelanotide, and none were prematurely discontinued.

PK profiles

Eight-hour PK profiles were available for 6 patients from the pivotal cohort on Visit 6 (Week 15) and Visit 7 (Week 17), and for 4 patients on Visit 9 (Week 29). See Figure 1, Figure 2, Figure 3 noting that the y-axis scale on the linear plots differs across these figures. The patients who participated in the 8-hour PK sampling were: 1 child with BBS (<12 years), 3 adolescents with BBS (12 to 18 years), and 2 adults with BBS (>18 years).

Maximum observed concentration (Cmax) and area under the concentration-time curve from time zero to time of last measurable concentration (AUClast) were highest for the child (N = 1) at all 3 visits

compared with the adolescents and adults. The high exposure for the child could be due to the high dose per kg (resulting from lower body weight, <100 kg, and the fixed dose levels of 2.0 to 3.0 mg).

In general, maximum Cmax was observed at or near the end of the 8-hour PK sampling interval; the median time to Cmax (Tmax) ranged from 5.00 to 7.90 hours across age groups, dose levels, and visits.

The exposure for one adult patient was much lower than expected; the reason is unknown. For this patient, consistently lower exposure, relative to other patients, was observed in the trough concentrations throughout the study, and in 0- to 8-hour PK samples from Visits 6 and 8 (Weeks 15 to 23). Despite low concentrations and PK exposure, this patient had clinically significant weight loss that began after switching to active treatment (setmelanotide 3.0 mg QD) following the end of the placebo period. See

Figure **1**, Figure 2 and Figure 3.

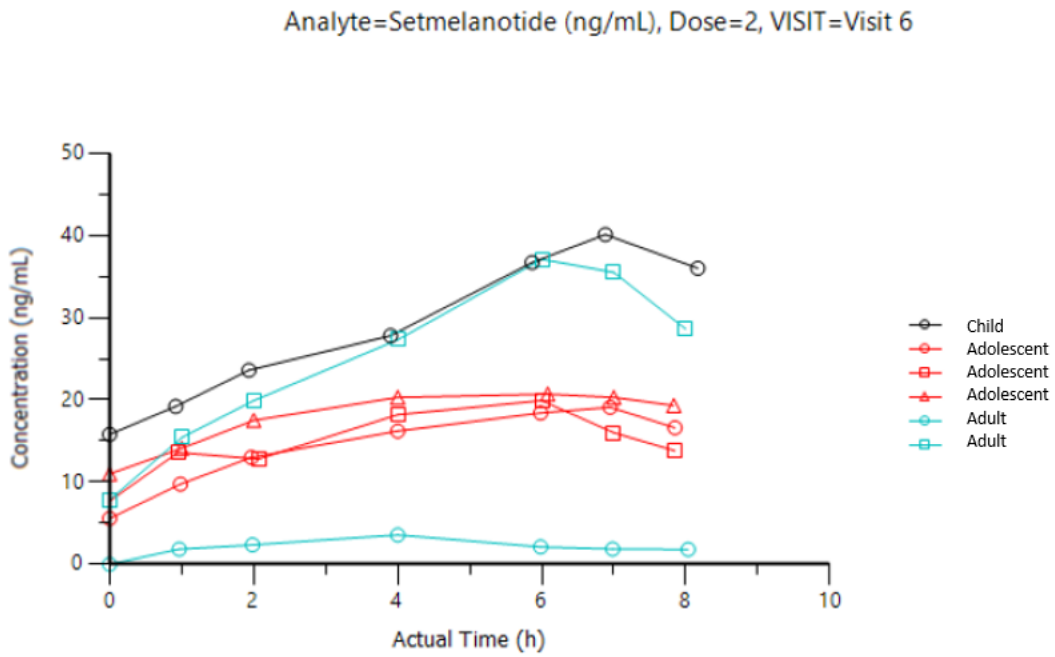


Figure 1 Setmelanotide Plasma Concentration-Time Profiles on Visit 6 (Week 15) on Linear and Semi-Logarithmic Scales

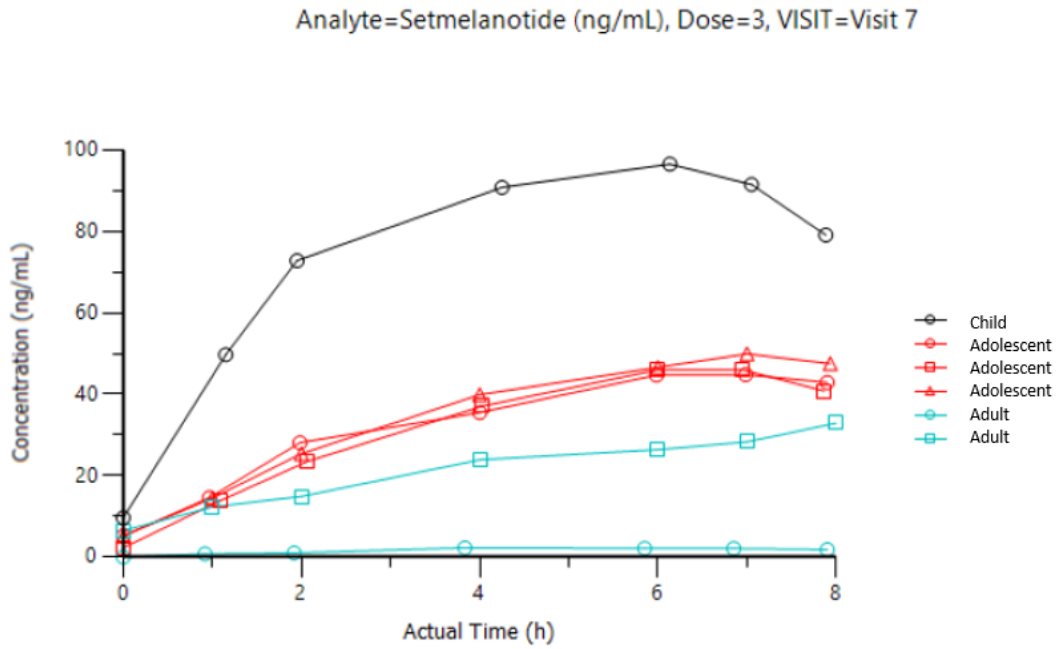


Figure 2 Setmelanotide Plasma Concentration-Time Profiles on Visit 7 (Week 17) on Linear and Semi-Logarithmic Scales

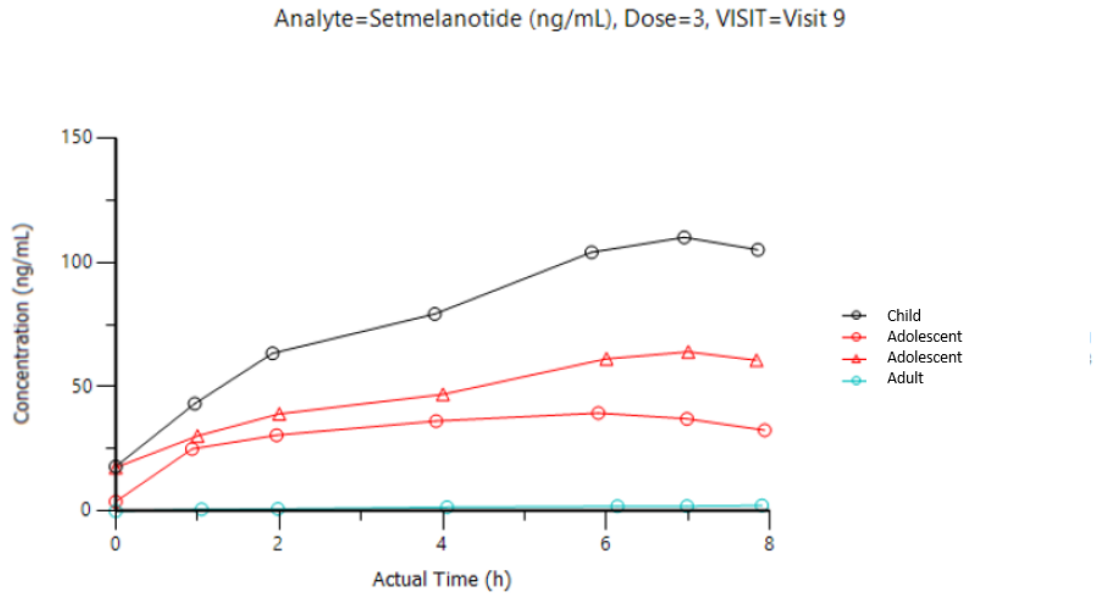


Figure 3 Setmelanotide Plasma Concentration-Time Profiles on Visit 9 (Week 29) on Linear and Semi-Logarithmic Scales

2.3.3. Pharmacodynamics

Mechanism of action

Primary cilia are evolutionarily conserved organelles whose dysfunction led to human disorders now defined as ciliopathies.

Bardet-Biedl Syndrome (BBS) is a rare and uncurable pleiotropic autosomal recessive ciliopathy characterized by a syndromic phenotype with an overall prevalence of 1 in 125,000–160,000 in people of European descent. The clinical presentation of BBS includes marked obesity and hyperphagia in addition to several other disease features that likely do not rise from hypothalamic impairment. The latter features include rod-cone dystrophy, postaxial polydactyly, cognitive impairment, hearing loss, speech deficit, hepatic fibrosis, genitourinary malformations, renal abnormalities, diabetes mellitus, hypertension, and congenital heart disease.

While birth weight in affected patients is usually normal, significant weight gain due to increased food intake and decreased energy expenditure begins in the first year and is a lifelong issue for most (72-92%). Relative to healthy subjects with comparable body mass index (BMI), patients with BBS tend to have higher adiposity, significantly more abdominal visceral fat, and less lean mass.

BBS is caused by mutations in more than 20 different genes, all of which participate in cilia functioning, and is therefore considered a primary ciliopathy. Eight of the most conserved BBS proteins (BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9 and BBS18) form a core complex, known as the BBSome, that associates with the ciliary membrane and functions as a unit to sort and direct trafficking of receptors and other proteins to the ciliary membrane. The BBS3 protein appears critical for recruitment of the BBSome complex onto the ciliary membrane, while BBS6, BBS10 and BBS12 form a complex that facilitates assembly of the BBSome. While the function of the remaining BBS proteins is less well characterized, the existence of these functional connections among the BBS proteins helps explain the phenotypic similarities among patients carrying mutations in such varied BBS genes.

Extensive research suggests the obesity phenotype in BBS is caused by impaired transport of the leptin receptor to the ciliary membrane of pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus. Under normal conditions, leptin, a hormone predominantly made by adipose cells, stimulates firing and gene expression in POMC neurons, promoting the secretion of alpha-melanocyte stimulating hormone (α-MSH). This stimulates the MC4R located in the second order neurons in the paraventricular nucleus (PVN) of the hypothalamus to decrease hunger and weight and increase energy expenditure (Figure 4). Impaired or absent leptin receptor signalling in POMC neurons would be expected to reduce MC4R stimulation in second order neurons, resulting in an increase in appetite, reduced metabolic rate, and increased weight.

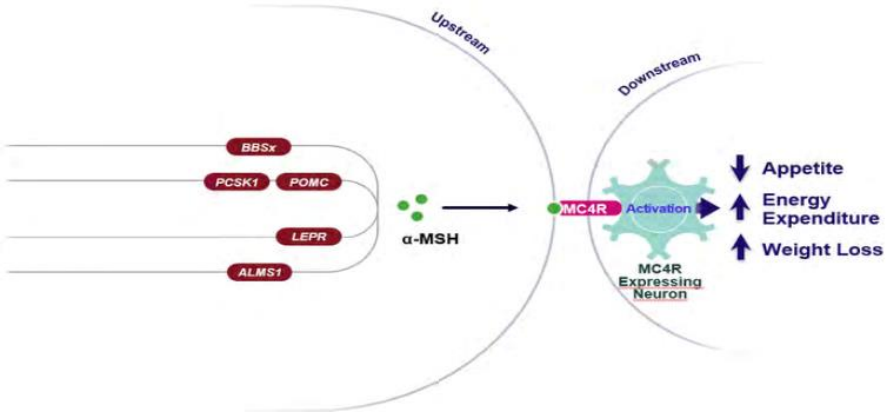


Figure 4 Leptin – Melanocortin Pathway

Alström Syndrome (AS), like BBS, is a ciliopathy characterized by a syndromic phenotype that includes progressive cone-rod dystrophy leading to blindness, sensorineural hearing loss, congestive heart failure, and marked childhood obesity associated with hyperinsulinemia and type 2 diabetes mellitus. However, it is caused by bi-allelic recessive mutations in a single gene, ALMS1. While the exact function of ALMS1 has not yet been elucidated, it is known to play a pivotal role in the function, formation, and maintenance of primary cilia and to be involved in energy balance and satiety regulation. AS is a considerably rarer condition than BBS, with ~ 950 cases estimated worldwide.

While AS shares many of the same clinical features as BBS, the disorders can usually be distinguished clinically and confirmed through genetics. While the dominant phenotype in BBS is typically developmental defects, in AS it is metabolic function. Beginning in infancy, patients with AS have progressive multiorgan pathology that typically leads to truncal obesity, insulin resistance, hyperinsulinemia, hyperleptinemia, and hyperlipidaemia by 5 years of age and progresses to type 2 diabetes mellitus (T2DM). The incidence of T2DM is one of distinguishing features between AS and BBS. In patients with AS the incidence of T2DM is ~50-75% compared with <25% in patients with BBS

Obesity is observed almost universally in patients with AS; excessive weight gain typically begins within the first year of life. Hyperphagia and obsession with food are also common in patients with AS. As with BBS, there is no cure for AS.

Setmelanotide is a MC4R agonist that retains the specificity and functionality of naturally occurring α-MSH, which is the natural ligand for the MC4R. Setmelanotide has the potential to restore lost activity in the MC4R pathway by bypassing the defects upstream of the MC4R and directly activating MC4R neurons in the hypothalamus below such defects (

Figure **5**). Thus, setmelanotide may serve as a "replacement" therapy to re-establish weight and appetite control in patients with disorders, such as BBS and AS, that are mediated by higher order defects.

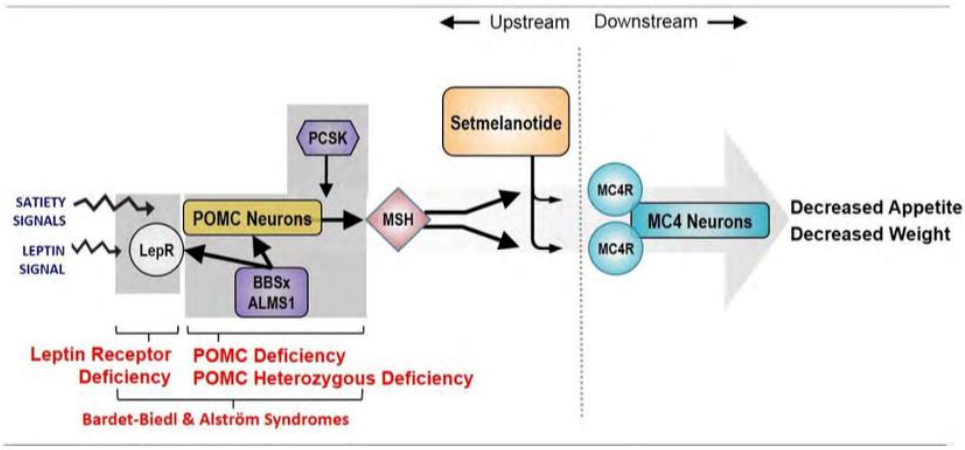


Figure 5 Schematic Diagram of the Hypothalamic MC4 Pathway Illustrating the Role of Setmelanotide Treatment to Replace Genetic Obesity Defects, including BBS and AS, that are Upstream of the MC4 Receptor

Study RM-493-023

Anti-drug Antibodies (ADA) assays

Immunogenicity samples were collected in the study RM-493-023 at the screening visit (V1), prior to the administration of study drug at V2 (week 1), V6 (week 15), V9 (week 29), V13 (week 53), V15 (week 66) and at the early termination visit. Sample collection for a potential antibody response to alpha-melanocyte-stimulating hormone (MSH) prior to and following setmelanotide treatment occurred at the same timepoints as the testing for antibodies to RM-493

A tiered approach was utilized for sample analysis. All samples that fall above the corresponding Assay Cut Point during screening or if the signal is 2 times that of the corresponding pre-dose sample for that subject, was considered potentially positive for the presence of anti-RM-493 antibodies. The potentially positive samples were then analyzed in a confirmatory assay. All samples confirmed to be positive for the presence of anti-RM-493 antibodies were titrated and a titer value was obtained.

A total of 169 samples from 48 patients were tested for ADAs. A negative result from the screening assay was reported for 70 samples. The remaining 94 samples were tested in the confirmatory assay. Of these, 1 sample from one patient (Visit 15) was confirmed positive for ADA with a very low titer. This patient achieved clinically meaningful reductions in body weight and BMI Z-scores during treatment with setmelanotide and did not experience any SAEs or any moderate or severe treatment related TEAEs. Samples from an additional 5 patients were flagged for re-analysis with the results to be reported in amendment to the Bioanalytical Report.

Based on the results at this time, there was 1 patient with confirmed anti-RM-493 antibodies with a low titer; there was no impact of ADA on safety or efficacy in this patient as reported by the MAH.

2.3.4. Discussion on clinical pharmacology

Pharmacokinetics

High (>30.0 ng/mL) trough setmelanotide concentrations were clearly observed in this study in children and adolescents. According to the applicant, patients with concentration values that are outliers have been observed throughout the program with no apparent negative clinical consequences. No robust

comparison of the PK parameters and profiles between BBS/AS population and POMC or LEPR deficient patients could be made based on the limited data available in children and the high variability observed in the studies. However, the CHMP agreed that in adults and adolescents the mean setmelanotide trough concentrations across studies based on dose were similar, with overlapping standard deviations.

Although the Population Pharmacokinetic (POPK) model has not been updated (due to insufficient data to allow reassessment of the model), it was also acknowledged that from the trough concentration values presented for studies RM-493-012 and RM-493-015, the concentration values for setmelanotide were overall consistent with repeat dosing across studies and disease population.

Given that there is no relationship between PK trough, dose and weight, the CHMP recommended the following update in section 5.2 of the SmPC based on the results of study RM-493-023: The PK of setmelanotide in patients with BBS was similar to that obtained in the population of patients with POMC, PCSK1, and LEPR deficiency, suggesting the disease state alone does not impact the PK of setmelanotide.

Pharmacodynamics

Two other studies (Study RM-493-029, RM-493-026) were submitted in this application and the CHMP assessment on these data had already concluded in the scope of the authorised indications (EMEA/H/C/005089/II/03). The posology recommendations resulting from these data are the same for the authorised indications and the BBS indication subject to the present assessment.

Only a very general high-level overview of the pathophysiology BBS and AS, including the effect on energy balance and satiety homeostasis have been presented in this application. On this basis, although the CHMP agreed that BBS and AS are both ciliopathies and that they are generally considered to excerpt a measure of influence on the energy homeostasis, more discussion on how the ALMS1 gene excerpts influence on this process should be provided. To better understand the purported method of action of the α-MSH analogue setmelanotide within context of these syndromes, discussion on how exactly disruption of the BBS- and AS-related genes leads to direct or indirect disruption of the MC4 pathway needed to be provided**.**

As reported by the MAH, there is a paucity in the current knowledge on how exactly the ciliopathic nature of BBS leads to a disruption of the MCH4 pathway, however animal studies have shown that BBS gene defects lead to heightened leptin concentrations while at the same time exhibiting hyperphagia, and also fail to respond to leptin-injections. This evidence leads to the expectation that BBS gene defects likely disrupt the normal function of the leptin receptor, culminating in a lowered production of α-MSH.Whether or not there may be a pathophysiological difference between AS and BBS syndromes in regard to the effect on the MC4R pathway is no longer considered relevant given the fact that the Applicant withdrew the variation application of the grouping related to AS.

One patient was confirmed positive to anti-setmelanotide antibodies. Sample analysis is still ongoing, as there was a change in the laboratory performing the assessment. An updated Integrated Summary of Immunogenicity (ISI) including this information is expected by the end of Q1 2022. To date, 2.3% of samples tested (32 of 1379 samples across multiple studies) confirmed positive for antibodies to alpha-MSH and have a reportable result in the titration assay. Confirmatory and titer results for the RM-493-023 study are pending analysis.

2.3.5. Conclusions on clinical pharmacology

Overall, the pharmacological profile of setmelanotide in human studies has been adequately documented and meets the requirements to support this application.

In the context of the obligation of the MAHs to take due account of technical and scientific progress,

the CHMP reminded the applicant of the following points for investigation from the initial marketing authorisation evaluation:

- To provide data from sample analysis in pending clinical and validation (e.g. long-term stability) studies as per EMA guidelines;

- To improve the reliability of the setmelanotide confirmatory ADA assay for the detection of the ADA in the patient samples in presence of clinically relevant drug levels;

- To provide updated integrated analysis of the clinical significance of immunogenicity of setmelanotide as data become available.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response studies were undertaken by the Applicant and all dosing decisions in the pivotal trial RM-493-023 were based upon observations made in the investigator led study RM-0493-011 and supportive study RM-493-014.

2.4.2. Main study

The main study, **RM-493-023** is a Phase 3, 3-period study designed to confirm the long-term efficacy and safety of setmelanotide in male and female patients ≥6 years of age with BBS or AS with moderate to severe obesity.

Methods

Study RM-493-023 consisted of three distinct treatment periods, including an initial 14-week double-blind placebo-controlled period, followed by two open-label treatment periods taking 38 weeks and 14 weeks respectively.

BBS and AS patients that satisfied the in- and exclusion criteria first entered a 14-week, randomized, double-blind, placebo-controlled treatment period (Period 1) that was followed by a 38-week open-label treatment period (Period 2) in which all patients received setmelanotide. Primary analysis was to be performed after Period 2. To maintain the blind through Period 2, dose escalation to the fixed maximal dose of 3.0 mg was performed during the first 2 weeks in both the double-blind (Period 1) and 38-week open-label (Period 2) treatment periods.

Patients were randomized in a 1:1 ratio, stratified by age group (≥12 years or <12 years) and disease (BBS or AS), to receive either setmelanotide QD or placebo QD via SC injection for the first 14 weeks. Patients ≥16 years of age were started on setmelanotide 2.0 mg or matching placebo during the 2-week dose escalation and increased to 3.0 mg or matching placebo at the beginning of Week 3. Patients <16 years of age started on setmelanotide 1.0 mg or matching placebo during Week 1, increased to 2.0 mg or matching placebo at the beginning of Week 2, and increased to 3.0 mg or matching placebo at the beginning of Week 3. During the 14-week double-blind treatment period, patients were evaluated at the beginning of Weeks 2 (telephone call only, patients <16 years old), 3, 7, 11, and 15.

After the initial 14-week double-blind treatment period (Period 1), all patients immediately transitioned to open-label setmelanotide QD via SC injection for 38 weeks (Period 2). To preserve the blind, all

patients were re-escalated to the 3.0-mg clinical dose. Thus, beginning at Week 15, patients ≥16 years of age received open-label setmelanotide 2.0 mg for 2 weeks, followed by a dose increase to 3.0 mg beginning at Week 17, and patients <16 years of age received open-label setmelanotide 1.0 mg during Week 15, 2.0 mg during Week 16, and 3.0 mg beginning at Week 17. Patients were evaluated at the beginning of Week 16 (telephone call only, patients <16 years old) and Week 17 and then every 6 weeks thereafter during this Period 2. In Period 3, patients were evaluated every 7 weeks.

The overall design is presented in **Figure *6***.

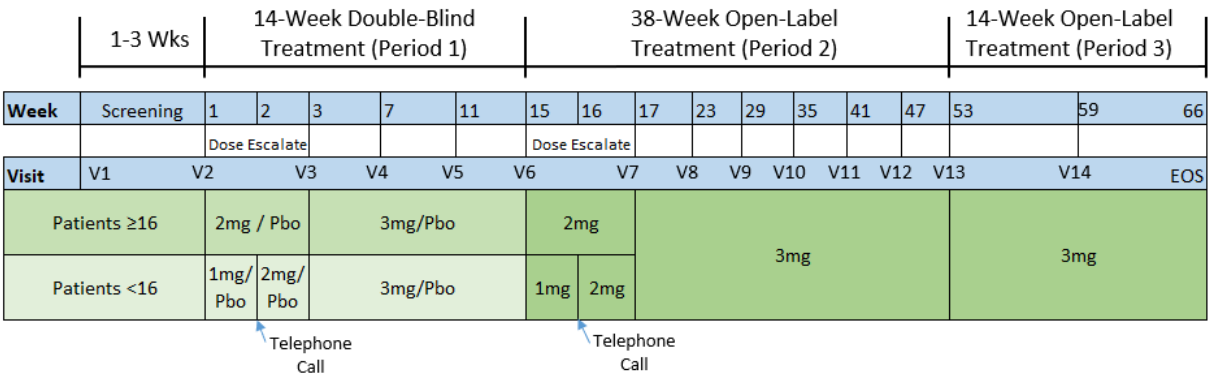


Figure 6 Study Design

Study participants

The study consisted of the following main criteria (non-exhaustive list, most pertinent listed):

Inclusion

1. BBS clinical diagnosis as per Beales, 1999 (with either 4 primary features or 3 primary and 2 secondary features from Table 1 or AS diagnosis as per Marshall, 2007 (using major and minor age adjusted criteria in the
2.
3. Table **2**.

Table 1: BBS clinical diagnosis as per Beales, 1999

Bardet-Biedl Syndrome	
Primary Diagnostic Criteria	
• Rod cone dystrophy	• Learning disabilities
• Polydactyly	• Hypogonadism in males
• Obesity	• Renal anomalies
Secondary Diagnostic Criteria	
• Speech disorder/delay	• Mild spasticity (especially lower limbs)
• Strabismus/cataracts/astigmatism	• Diabetes mellitus
• Brachydactyly/syndactyly	• Dental crowding/hypodontia/small roots/high arched palate
• Developmental delay	• Left ventricular hypertrophy/congenital heart disease
• Polyuria/polydipsia (nephrogenic diabetes insipidus)	• Hepatic fibrosis
• Ataxia/poor coordination	
Source: Beales 1999	

Table 2: AS diagnosis as per Marshall, 2007

Alström Syndrome		
Diagnostic Criteria		
Major	**Minor**	**Minimum Required**
For patients 6 to ≤14 years of age		
• Mutation of *ALMS1* and/or family history of AS • Vision (nystagmus, photophobia, diminished acuity, if old enough for testing: cone dystrophy by ERG)	• Obesity and/or insulin resistance and/or T2DM • History of DCM/CHF • Hearing loss • Hepatic dysfunction • Renal failure • Advanced bone age	2 major criteria ***or*** 1 major and 3 minor criteria
For patients ≥15 years of age		
• Mutation of *ALMS1* and/or family history of AS • Vision (history of nystagmus in infancy/childhood, legal blindness, cone and rod dystrophy by ERG)	• Obesity and/or insulin resistance and/or T2DM • History of DCM/CHF • Hearing loss • Hepatic dysfunction • Renal failure • Short stature • Males: hypogonadism • Females: irregular menses and/or hyperandrogenism	2 major and 2 minor criteria ***or*** 1 major and 4 minor criteria
Source: Marshall 2007		

Abbreviations: CHF = congestive heart failure; DCM = dilated cardiomyopathy; ERG = electroretinography;
T2DM = Type 2 diabetes mellitus
Note: at least 90% of patients with BBS and 100% of patients with AS must have genetically confirmed diagnosis at the time of enrollment

- A genetically confirmed diagnosis of BBS is defined as a homozygous or compound heterozygous loss-of-function mutation in BBS genes; patients without a genetically confirmed BBS diagnosis must be reviewed with the Sponsor's medical monitor prior to enrollment.
- A genetically confirmed diagnosis of AS is defined as a homozygous or compound heterozygous loss-of-function mutation in the ALMS1 gene.

Once 10% of patients without a confirmed BBS diagnosis have been enrolled in the study, sites will be notified that only genetically confirmed BBS patients may be enrolled.

4. ≥6 years of age at the time of randomization (first dose of setmelanotide).
5. Obese, defined as BMI ≥30 kg/m2 for patients ≥16 years of age or weight >97th percentile for age and sex on growth chart assessment for patients 6 to 15 years of age.

6. Female participants of child-bearing potential (must be confirmed non-pregnant) or male participants with female partners of child-bearing potential had to agree to use contraception as outlined in the protocol.

Exclusion

1. Recent intensive (within 2 months) diet and/or exercise regimen with or without the use of weight loss agents including herbal medications that has resulted in >2% weight loss. These patients may be reconsidered approximately 1 month after cessation of such intensive regimens.
2. Use of any medication that is approved to treat obesity within three months of randomization (e.g., orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion). Note: GLP-1 receptor agonists may be used up to the dose approved for the treatment of diabetes mellitus (e.g. liraglutide up to a daily dose of 1.8 mg) under special conditions as specified in the protocol.
3. Prior gastric bypass surgery resulting in >10% weight loss durably maintained from the baseline pre-operative weight with no evidence of weight regain.
4. Current, clinically significant pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study and/or confound the results.
5. Haemoglobin A1c > 9.0% at Screening.
6. History of significant liver disease or liver injury, or a current liver assessment due to abnormal liver tests for an aetiology other than non- alcoholic fatty liver disease (NAFLD).
7. Moderate to severe renal dysfunction defined as a glomerular filtration rate (GFR) <30 mL/min.
8. History or close family history (parents or siblings) of skin cancer or melanoma (excluding non-invasive basal or squamous cell lesion), or patient history of ocular- cutaneous albinism.
9. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions, determined as part of comprehensive skin evaluation performed by a qualified dermatologist.

Treatments

A dose 2-week escalation period was employed at the start of the 14-week DB period and the start of the open-label phase, according to the schedule shown in Table 3.

Table 3: Dose Escalation Schedule

Study Week	Patients ≥16 years of age (Dose in mg)	Patients <16 years of age Dose (mg)
1	2.0 or placebo	1.0 or placebo
2	2.0 or placebo	2.0 or placebo
3-14	3.0 or placebo	3.0 or placebo
15	2.0	1.0
16	2.0	2.0
17-66	3.0	3.0

Doses ranging from 0.12 to 9.12 mg total daily dose have been used in previous setmelanotide clinical studies, with meaningful and progressive weight loss seen with QD doses of 1.0 mg and above. In addition, there was no evidence of increased sensitivity or any new safety issues arising in patients treated at these latter dose levels. These data as collected from other studies served as guidance for the above simplified dosing regimen.

Although higher starting doses were justified for this study, dose escalation was maintained to improve tolerability; nausea and vomiting have been reported with administration of MC4R agents, including setmelanotide, occurring most commonly during the start of treatment and generally resolving with continued treatment. Based on historical data indicating that most patients at least 16 years of age had minimal, if any, additional growth in height, a starting dose of 2.0 mg was selected for both adolescents and adults (patients ≥16 years of age at enrolment) with a planned dose escalation to a clinical dose of 3.0 mg after 2 weeks. As a measure of added caution for the younger patient population, where the smallest patient weight would be at least 29 kg (based on the Centers for Disease Control and Prevention [CDC] >97th percentile weight for age and sex on growth chart for a 6-year-old), a starting dose of 1.0 mg was selected for patients <16 years of age at enrolment. Upward dose escalation in these patients was done in 2 steps: at the end of Week 1, the dose was increased to 2.0 mg and at the end of Week 2, the dose was increased to 3.0 mg.

Objectives

Primary Objective

- The primary objective of this study was to assess the effect of setmelanotide on the proportion of patients ≥12 years of age at baseline treated with setmelanotide for ~52 weeks who achieve a clinically meaningful reduction from baseline (i.e., ≥10%) in body weight.

Key Secondary Objectives

- Assess the effect of setmelanotide on mean percent change from baseline in body weight (in patients ≥12 years of age at baseline) after ~52 weeks of treatment.
- Assess the effect of setmelanotide on the mean percent change from baseline in the weekly average of the daily hunger score (in patients ≥12 years of age at baseline) after ~52 weeks of treatment with setmelanotide.
- Assess the effect of setmelanotide on the proportion of patients who achieve a ≥25% improvement (reduction in the score, indicated less hunger) in the weekly average of the daily hunger score (in patients ≥12 years of age at baseline) after ~52 weeks of treatment with setmelanotide.

Other Secondary Objectives

- Assess the effect of setmelanotide on the mean percent change from baseline in body weight (in patients ≥12 years of age at baseline) at the Week 14 visit compared with placebo.
- Assess the effect of setmelanotide on the mean percent change from baseline in the weekly average of the daily hunger score (in patients ≥12 years of age at baseline) at the Week 14 visit compared with placebo.

Exploratory Objectives

- Assess the effect of setmelanotide on the proportion of all patients who achieve a ≥10% reduction from baseline in body weight after ~52 weeks of treatment with setmelanotide.

- Assess the effect of setmelanotide on the proportion of patients who achieve a ≥25% improvement in the weekly average of the daily hunger score (in patients ≥12 years of age at baseline) at the Week 14 visit compared with placebo.
- Assess the composite response rate of patients who achieve either a ≥10% reduction in body weight or a ≥25% improvement in the weekly average of the daily hunger score after 52 weeks of treatment. Assess the effect of setmelanotide on:
    - Measures of weight loss (including weight, body mass index [BMI], BMI Z-score, waist circumference, and total body mass).
    - Measures of hunger.
    - Measures of health status (including measures of insulin sensitivity/resistance) and quality of life.
    - Biomarker measurements of hormonal, neuroendocrine, metabolic, and anti- inflammatory activity.
    - Biomarker measurements of renal inflammation and function.
    - Measures of neurocognitive function.
    - Measures of sleep.
    - Measures of pubertal development in patients who have yet to reach Tanner Stage V.
- Determine the pharmacokinetics (PK) of setmelanotide in patients with BBS or AS.
- Evaluate the safety and tolerability of setmelanotide administered once daily (QD) via subcutaneous (SC) injection in patients with BBS and AS.

Outcomes/endpoints

Primary endpoint

- The primary efficacy endpoint was the proportion of patients ≥12 years of age who achieved a ≥10% reduction in body weight from baseline after ~52 weeks of treatment compared to a historical untreated proportion of 10%.
    - Exploratory subgroup analyses, as the analyses were not adequately powered for subgroups, of this endpoint were also planned:
        - By disease type (BBS and AS)
        - Paediatric population by age-category (<17yo and <12yo), which would include all available paediatric pivotal and supplemental patients at time of analysis

Key secondary endpoints

- Mean percent change from baseline in body weight after ~52 weeks of treatment for patients in the ≥12yo FAS population
- Mean percent change from baseline in the weekly average of the daily hunger scores after ~52 weeks of treatment for patients in the ≥12yo FAS population

- The proportion of ≥12yo patients in the FAS population who achieve a ≥25% improvement from baseline in the weekly average of the daily hunger score, versus an historical untreated proportion of 10%.
    - Exploratory subgroup analyses, as the analyses were not adequately powered for subgroups, of these endpoints were also planned:
        - By disease type (BBS and AS)
        - Paediatric population by age-category (<17yo and <12yo), which would include all available paediatric pivotal and supplemental patients at time of analysis

Secondary endpoints

- Body weight percent change from baseline at 14 weeks comparison between placebo- and setmelanotide-treated patients (≥12 years old).
- Weekly average daily hunger score percent change from baseline at 14 weeks comparison between placebo- and setmelanotide-treated patients (≥12 years old).
    - Exploratory subgroup analyses, as the analyses were not adequately powered for subgroups, of these endpoints were also planned:
        - By disease type (BBS and AS)
        - Paediatric population by age-category (<17yo and <12yo), which would include all available paediatric pivotal and supplemental patients at time of analysis

Sample size

The sample size estimation was mainly driven by the primary hypothesis, although the rarity of the population was also taken into consideration.

The primary statistical hypothesis was that the proportion of patients (≥12 years of age) treated for ~52 weeks who achieve ≥10% reduction from baseline in body weight would be greater than a historical control rate of 10% in the Full Analysis Set (FAS). The null hypothesis (H0) tested was that the proportion of patients treated for ~52 weeks who achieve ≥10% reduction in body weight from baseline would be less than or equal to a historical control rate of 10%.

Note that there are 2 different uses of "10%" in the primary hypothesis:

- The use of "10%" in the endpoint definition is the response criterion for an individual patient. If a patient achieves a ≥10% reduction from baseline in body weight, the patient will be categorized as a responder in this analysis. Otherwise, the patient will be categorized as a non-responder.
- The use of "10%" as the historical control rate is the historical reference/control rate to be statistically compared to the observed response rate in patients treated with setmelanotide (i.e., the percentage of patients with BBS who lose at least 10% of body weight with no intervention). The observed response rate of setmelanotide will be calculated with the number of responders (using the above 10% endpoint definition) divided by the number of total patients.

For the primary hypothesis a sample size of 7 patients would provide ~91% power at 1-sided alpha of 0.025 to yield a statistically significant difference, assuming a 66% anticipated response rate in patients who are treated with setmelanotide (based on a preliminary review of data from the then ongoing Phase 2 study, RM-493-014) compared to a 10% historical control rate (based on data from the CRIBBS registry).

Although these data suggest that powering the study for the primary endpoint would require a minimal number of patients (N <10), the size of the trial was also a function of the rarity of BBS and AS and a desire to better understand the effect of setmelanotide in these patient populations. Hence, approximately 30 patients (including 6 AS patients) were planned for enrolment in the study. This number was deemed suitable for a single pivotal trial to support the indications in BBS and AS and to provide robust information for both the between-group analysis of the placebo-controlled, double-blinded period (Period 1) and the one-sample comparison to the historical control response rate after the last patient has completed the planned 38-week open- label treatment period.

Randomisation

Patients who qualified for the study were assigned a unique randomization number based on a randomization code generated prior to the start of the study. The randomization number codes the patient's initial treatment assignment (for the double-blind period) to either setmelanotide or placebo. The randomization scheme randomized patients in a 1:1 ratio, stratified by age group (≥12 years or <12 years) and disease (BBS or AS), to receive either setmelanotide or placebo during the first 14 weeks of the study. Randomization numbers were not to be re-used once assigned.

Blinding (masking)

This study was open label, with the exception of the 14-week double-blind placebo-controlled period. Placebo and setmelanotide were identical in appearance and were supplied in identical packaging. Each package and vial contained a code that identified the contents as either placebo or setmelanotide. At each site visit during the double-blind period, the study pharmacist selected the correct study drug based on the package code and provided the blinded study medication to the patient or the patient's caregiver.

The Investigator, study site staff, clinical research organization staff providing site management, and the Medical Monitor did not have access to the actual treatment assignment administered during the 14-week double-blind, placebo-controlled treatment period (Period 1). The blind was maintained through the end of the 38-week, open-label treatment period (Period 2) (i.e., until the database snapshot prior to completing the primary statistical analysis). To maintain the blind through Period 2, upward dose escalation to a fixed dose of 3.0 mg was performed during the first 2 weeks of both the double-blind (Period 1) and 38-week open-label (Period 2) treatment periods.

Breaking of the blind for an individual patient was only done in the event of a medical emergency where the identity of study drug was necessary to appropriately treat the patient. The reason for breaking the blind, as well as when and how the blind was broken were documented.

Statistical methods

Analysis populations

The following populations were defined:

- **Screening Analysis Set**: All patients who signed the informed consent form.
- **Safety Analysis (SA) Set**: All patients who received at least 1 dose of placebo or setmelanotide. The SA Set is the primary population for the analysis of safety endpoints.

- **Full Analysis Set (FAS)**: All patients (irrespective of age) who received at least 1 dose of setmelanotide and had baseline data. The FAS population is the primary population for the analysis of efficacy endpoints.
- **Designated Use Set (DUS)**: All patients in the FAS who demonstrated weight loss of at least 5 kg (or at least 5% if baseline body weight was <100 kg) over the first 14 weeks of active setmelanotide treatment, regardless of later disposition. The DUS population was used for sensitivity analyses of efficacy endpoints, as appropriate.

  Based on the definition the DUS subgroup hence included:

  - Those patients initially randomized into the setmelanotide group in the double-blinded, randomized, placebo-controlled period who achieved weight loss of at least 5 kg (or at least 5% if baseline body weight was <100 kg) from baseline at the Week 15 visit.
  - Those patients who were initially randomized in the placebo group in the double-blinded, randomized, placebo-controlled period, and achieved weight loss of at least 5 kg (or at least 5% if baseline body weight was <100 kg) from Week 15 (i.e., just prior to their first active dose of setmelanotide at Week 15) through Week 29 (i.e., after 14 weeks of active treatment with setmelanotide).
- **Placebo-controlled analysis Set (PCS)**: All randomized patients who received at least 1 dose of placebo or setmelanotide and had baseline data. This population was specifically defined for the 14-week placebo-controlled, double-blind period (Period 1). Analysis performed on PCS were based on patients as randomized.
- **Per-Protocol Set at End of Period 1 (PP at EOP1)**: All patients in PCS without any major protocol violations that would result in exclusion of the patients from the analysis.
- **Per-Protocol Set at End of Period 2 (PP at EOP2)**: All patients in FAS without any major protocol violations that would result in exclusion of the patients from the analysis.
- **Completers Set (CS)**: All patients in the PP at EOP1 population who continued on active treatment or placebo and completed a full 14-week placebo-controlled double-blinded period (Period 1).
- **Stable Height Analysis Set (SH)**, exploratory analysis only: All patients in the FAS who grew ≤2 cm in height from baseline to the primary endpoint timepoint (i.e., ~Week 53 visit for patients randomized to setmelanotide or ~Week 66 visit for patients randomized to placebo) or to the last available timepoint if it occurred prior to the primary endpoint.
- **Active Growth Analysis Set (AG)**, exploratory analysis only: All patients in the FAS who grew >2 cm in height from baseline to the primary endpoint timepoint (i.e., ~Week 53 visit for patients randomized to setmelanotide or ~Week 66 visit for patients randomized to placebo) or to the last available timepoint if it occurred prior to the primary endpoint.

A cohort of supplemental patients was added into the protocol in the midcourse of the study. The pivotal cohort includes all the enrolled BBS/AS patients at the time of the planned sixth AS patient enrolment, and hence compromised a total of 38 patients (the first 32 BBS patients and 6 AS patients). All analyses for the RM-493-023 were performed and the conclusions based on the data from the pivotal cohort of patients only unless explicitly stated otherwise. The purpose of the supplemental cohort was to gain more treatment experience.

Analyses Timing and Definition of baseline data

The primary analysis will occur approximately at the time that the last enrolled patient in the Pivotal cohort has completed Period 2. If the last patient is randomized into the setmelanotide arm, this

means the patient will have ~52 weeks (~12 months) of setmelanotide treatment by the time of the data cut for NDA submission at the end of Period 2. However, if the last patient is randomized into the placebo arm, this means the patient will have ~9 months of setmelanotide treatment by the time of the data cut for the NDA submission and that the patient's ~12 month data will be missing (not yet occurred).

Consequently, by nature of the study design, a small percentage of patients who are randomized into the placebo arm may have less than ~52 weeks of setmelanotide treatment by the timing of the primary analysis (end of Period 2); hence, a Multiple Imputation approach will be used to impute their measurements after ~52 weeks of setmelanotide treatment for the primary analysis.

Two efficacy baseline definitions were used.

- Placebo-controlled period baseline (PCPB): is defined as the last available measurement prior to the first dose of setmelanotide or placebo. PCPB will be used for efficacy analysis based upon 14 weeks of treatment with either setmelanotide or placebo.
- Active treatment baseline (ATB): is defined as the last available measurement prior to the first dose of active setmelanotide. ATB will be used for efficacy analyses based upon ~52 weeks of treatment.

Analyses – Primary

Weight was measured in triplicate and mean weight calculated at the study visit was utilized for analysis purposes.

Binomial proportions were calculated 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 against the H0 with corresponding confidence intervals (CIs) and p-value. The 1-sided 0.025 significance level was chosen based on the small sample size due to the rarity of the disease. The success criterion for the primary hypothesis requires the rejection of the H0 at the 1-sided 0.025 significance level. The statistical criterion corresponds to the 2-sided 95% CI for setmelanotide of the response rate excluding 10% (i.e., lower bound of the CI >0.10).

This analysis was repeated on the DUS, PP at EOP2, SH and AG populations.

Descriptive statistics for the change and percent change from baseline in body weight (kg) were presented for the FAS population by active treatment visit.

Analyses – Key Secondary

Statistical testing used the hierarchical order as shown under the Objectives and Endpoints sections. The secondary endpoint was compared against the H0 for each of the 100 imputed datasets. The outcomes from the 100 imputed datasets were combined using Rubin's Rule to provide a p-value and corresponding CI as appropriate. Evaluations were done at a 1-sided, 0.025 significance level.

- Mean percent change from baseline in body weight after ~52 weeks of treatment for patients in the FAS population was analyzed. Analyses were based on a one-sample t-test for each of the 100 imputed datasets and assuming a mean percent change from baseline in body weight of zero.

  Sensitivity analysis based on the DUS population was also performed.

  Descriptive statistics for the change and percent change from baseline in body weight (kg) were presented for the FAS population by active treatment visit.

- Mean percent change from baseline in the weekly average of the daily hunger scores after ~52 weeks of treatment for patients in FAS population was analyzed. Note that Daily hunger scores were not collected in patients who were cognitively impaired.

  Prior to analysis, daily hunger scores for each of the 3 hunger assessments (worst/most, morning, and average) were averaged separately by week. Given that peak (most/worst) hunger does not require patients to do a mathematical computation (as does average hunger) and peak hunger is inherently meaningful and conceptually equivalent to standard assessment of other symptoms (e.g., pain, itching), it is considered the most appropriate among the 3 daily hunger scores.

  For a week of hunger scores to be considered evaluable, scores had to be recorded and available for analysis on at least 1 of 7 days to provide sufficient data to determine mean values. This was based on prior experience in other conditions.

  Sensitivity analysis based on the DUS population was also performed.

  Descriptive statistics for the change and percent change from baseline in weekly average of daily hunger scores were presented for the FAS population by active treatment visit.

- The proportion of patients in the FAS population who achieve a ≥25% improvement from baseline in the weekly average of the daily hunger score after ~52 weeks of treatment was analyzed similarly to the primary efficacy endpoint.

  Descriptive statistics for the change and percent change from baseline in weekly average of daily hunger scores were presented based on the FAS population. Due to the suitability of using the hunger score tool in younger patients, this was conducted in patients ≥12 years of age at baseline.

Analyses - Secondary

These analyses were performed on patients in the PCS population with the secondary endpoints being compared against the null hypothesis for each of the 100 imputed datasets. The outcomes from the 100 imputed datasets were combined using Rubin's Rule to provide a p-value. All analyses his were evaluated at a 1-sided, 0.025 significance level.

- Body weight percent change from baseline at 14 Weeks was a between-group comparison to investigate if setmelanotide-treated patients (≥12 years old) exhibited a greater decrease in percent change in body weight from baseline following ~14 weeks of therapy, as compared with placebo-treated patients.

  Sensitivity analyses based on PP at EOP1 and CS were performed.

  Descriptive statistics for the change and percent change from baseline in body weight (kg) were presented for the PCS population by visit by randomized treatment.

- Daily hunger score percent change from baseline at 14 Weeks was a between-group comparison to investigate if setmelanotide-treated patients exhibited a greater improvement from baseline following ~14 weeks of therapy in weekly average of daily hunger scores, as compared with placebo-treated patients.

  Prior to analysis, daily hunger scores for each of the 3 hunger assessments were averaged separately by week, as outlined above. Sensitivity analyses based on PP at EOP1 and CS were performed.

  Descriptive statistics for the change and percent change from baseline in weekly average of daily hunger scores were presented based on the PCS population by visit by randomized treatment. Due

to the suitability of using the hunger score tool in younger patients, this was conducted in patients ≥12 years of age at baseline.

Analyses - Missing Data

For the primary analysis and key secondary analyses, the multiple imputation (MI) imputed 52-week values were utilized for patients who had missing 52-week weight data due to nature of study design, but patients who had missing 52-week data for any other reason were considered treatment failures (including change and percent change from baseline set to 0).

The MI 52-weeks value data were mainly generated for patients initially assigned to placebo, as these subjects only reached 52 weeks of setmelanotide treatment at their Week 66 visit and some of the placebo patients had not reached their Week 66 visit by the time of the primary analysis.

For analyses outside of the primary and key secondary analyses, handling differed based upon the analysis specified. Endpoints/analyses requiring imputations that were closely related to the primary or key secondary analyses utilized the same handling as the primary and key secondary endpoints (baseline replacement). Other analyses utilizing imputation that were not closely related to the primary or key secondary analyses utilized the values generated via MI and were not replaced with baseline values.

Missing values in the 14-Week placebo-controlled period analyses were imputed with a similar MI approach as defined in the primary imputation approach.

Analyses – Sensitivity

Four sensitivity analyses were performed to assess the impact of missing data on weight (non replacement, active treatment completers), hunger score and data on comparisons between setmelanotide-treated patients and placebo patients after ~14 weeks of treatment (treatment failure).

All sensitivity analyses generated 100 imputed datasets as appropriate and the outcomes from the 100 imputed datasets were combined using Rubin's Rule to provide a p-value and corresponding CIs.

- *Non replacement analysis*

Same data handling as the primary and key secondary analyses.

- *Active Treatment-Completer's Analysis*

Same data handling as the primary and key secondary analyses. However, placebo patients who did not complete 52 weeks of setmelanotide treatment due to the administrative data cut (i.e., those who had not completed the relevant visits yet) were excluded.

- *Daily Hunger analysis*

Analysis for daily hunger scores was repeated for patients with at least 3 of 7 days of data present. No imputations were made for missing data.

- *Treatment Failure analysis*

For the non-key secondary endpoints, patients who had missing 14-week data were considered treatment failures. As for the secondary analyses, this sensitivity analysis was based on a two-sample t-test for each of the 100 imputed datasets.

Analyses – Exploratory

- *Daily Hunger Score Reduction (25%) from Baseline at 14 Weeks:*

The between-group comparison to investigate if a greater proportion of setmelanotide-treated patients achieved a ≥25% improvement from baseline in the weekly average of the daily hunger score at the Week 14 visit as compared to placebo-treated patients will be conducted for each of the 100 imputed datasets utilizing difference of proportions. The outcomes from each of the 100 imputed datasets will be combined using Rubin's rule to provide a p-value and corresponding confidence intervals. Values as imputed by multiple imputation methods will be used and no baseline replacement values will be utilized for this analysis.

The analysis will be based on PCS population.

- *Body Weight*

The proportion of patients ≥12 years of age who meet categorical thresholds of 5%, 15%, 20%, 25%, 30%, 35% and 40% weight loss from baseline after ~52 weeks of treatment will be summarized for the FAS population. Handling similar to the primary analysis will be used for this endpoint.

- *Body Weight and BMI*

The proportion of patients ≥12 years of age at baseline who achieve a ≥10% reduction from baseline in body weight or ≥15% reduction in BMI after ~52 weeks of treatment will be summarized based on FAS population.

Descriptive statistics for the change and percent change from baseline in BMI after ~52 weeks of treatment will be presented for FAS population.

- *BMI Z-score*

Change and percentage change of BMI Z-score from baseline after ~52 weeks of treatment in paediatric subjects (6-11 years old and/or 6-16 years old) will be summarized based on the FAS population, by the specified age group.

- *Body Composition*

Descriptive statistics for the change and percent change from baseline in total body mass, including body fat, non-bone lean mass, and bone density, after ~52 weeks of treatment will be presented for the FAS population

- *Insulin*

Descriptive statistics for the change and percent change from baseline in measures of insulin sensitivity/resistance after ~52 weeks of treatment will be presented for the FAS population.

- *Lipids*

Descriptive statistics for the change and percent change from baseline in fasting lipids (total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol and triglycerides) after ~52 weeks of treatment will be presented for the FAS population.

Results

The presentation of the results may contain data for cohorts other than the FAS pivotal cohort, though efficacy is mainly evaluated based on the latter. Data of importance for the efficacy discussion are therefore highlighted in yellow, while other colours will be used if additional attention to specific data from pivotal or other cohorts would be needed.

Participant flow

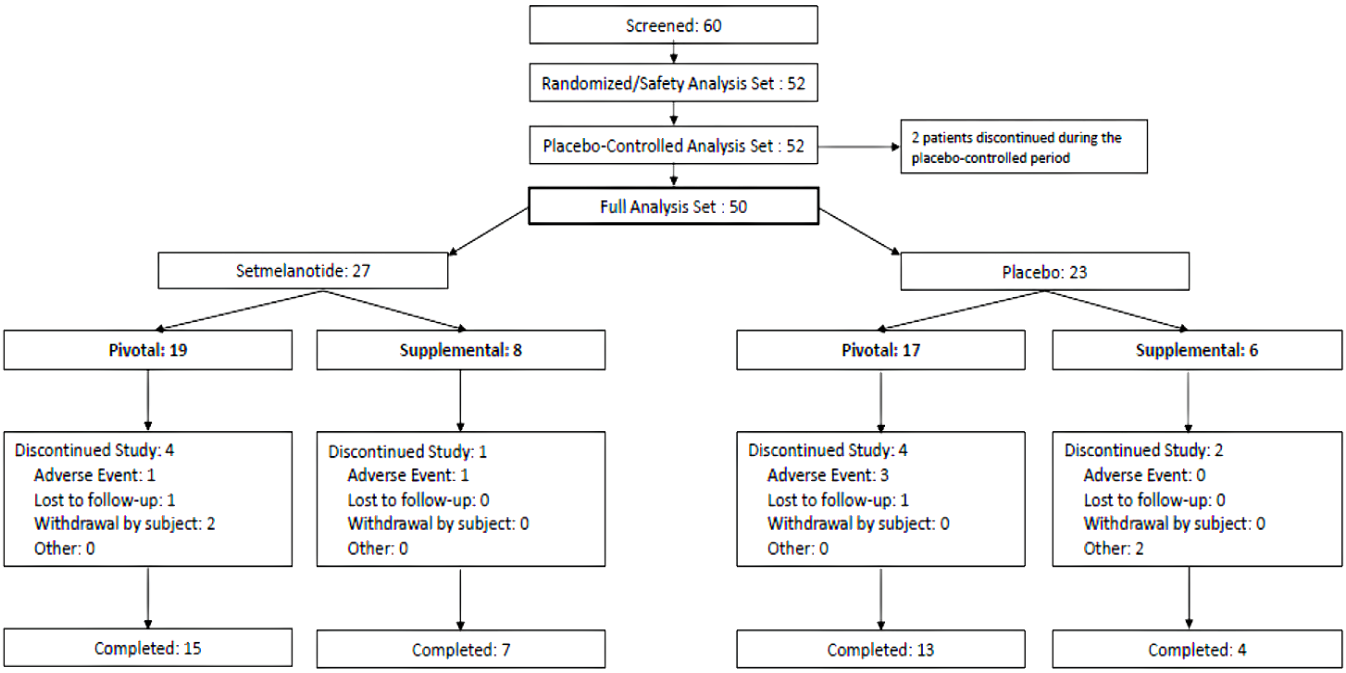


Figure 7: Summary of Patient Disposition in the ~52-Week Treatment Period – FAS

Abbreviations: ATB = active treatment baseline; FAS = full analysis set.
Note: Pivotal patients who completed Week 66 were considered to have completed the study. Under Version 3.0 of the protocol, supplemental patients were permitted to enrol in a separate long-term extension study (RM-493- 022) upon completion of the Week 24 (Visit 8) visit at the earliest, thus, supplemental patients who completed Week 24 (or later) were considered to have completed the study.

Recruitment

Date first patient enrolled: 23 November 2018

Date last patient completed: 08 March 2021

Conduct of the study

Of the 52 enrolled patients 32 had a total of 61 major protocol violations. Most (75%) of these violations were related to missed assessments at scheduled visits due to COVID-19-related shortening or remote visit procedures. Other violations included failure to timely procure Informed Consent (8 violations) or quality issues with investigational product (5 violations). A total of two violations were related to a failure to properly apply exclusion criteria 7-9. None of the violations led to exclusion from the PP.

AS patients only represented 10% of the pivotal FAS ≥12yo cohort.

Baseline data

Baseline and demographic data by cohort are presented in

Table **4** with the pivotal FAS ≥12yo data, which is the cohort intended for the key analyses, highlighted in yellow.

Table 4: Demographic and Baseline Characteristics

Parameter	Statistic	Safety Analysis Set N = 52		Full Analysis Set Patients ≥12 N = 39	
		Pivotal N = 38	Supplemental N = 14	Pivotal N = 31	Supplemental N = 8
Age at PCPB (years)	N	38	14	31	8
	Mean (SD)	19.8 (10.20)	18.6 (13.21)	21.6 (10.32)	27.3 (11.17)
Age Group					
<12 years old	n (%)	5 (13.2)	6 (42.9)	-	-
<17 years old	n (%)	19 (50.0)	7 (50.0)	14 (45.2)	1 (12.5)
Sex					
Female	n (%)	23 (60.5)	8 (57.1)	17 (54.8)	4 (50.0)
Male	n (%)	15 (39.5)	6 (42.9)	14 (45.2)	4 (50.0)
Race					
Asian	n (%)	1 (2.6)	1 (7.1)	0	0
Black or African American	n (%)	3 (7.9)	1 (7.1)	2 (6.5)	0
Other	n (%)	3 (7.9)	5 (35.7)	3 (9.7)	5 (62.5)
White	n (%)	31 (81.6)	7 (50.0)	26 (83.9)	3 (37.5)
Ethnicity					
Hispanic or Latino	n (%)	1 (2.6)	0	1 (3.2)	0
Not Hispanic or Latino	n (%)	37 (97.4)	7 (50.0)	30 (96.8)	1 (12.5)
Not Reported	n (%)	0	4 (28.6)	0	4 (50.0)
Unknown	n (%)	0	3 (21.4)	0	3 (37.5)
Clinically Defined Subgroup					
AS	n (%)	6 (15.8)	2 (14.3)	3 (9.7)	1 (12.5)
BBS	n (%)	32 (84.2)	12 (85.7)	28 (90.3)	7 (87.5)
Cognitively Impaired					
No	n (%)	19 (50.0)	11 (78.6)	16 (51.6)	6 (75.0)
Yes	n (%)	19 (50.0)	3 (21.4)	15 (48.4)	2 (25.0)
Height (cm)					
PCPB	N	38	14	31	8
	Mean (SD)	162.31 (10.785)	151.40 (19.048)	164.52 (9.609)	164.87 (11.870)
ATB	N	36	14	31	8
	Mean (SD)	162.63 (10.885)	151.90 (18.606)	164.71 (9.446)	164.93 (11.890)
Weight (kg)					
PCPB	N	38	14	31	8
	Mean (SD)	111.67 (30.413)	97.25 (43.540)	117.20 (29.206)	127.23 (32.303)
	Min, Max	49.3, 191.8	46.4, 168.4	68.1, 191.8	72.5, 168.4
ATB	N	36	14	31	8
	Mean (SD)	112.00 (30.997)	97.86 (42.896)	117.03 (29.363)	127.14 (32.222)
	Min, Max	49.3, 191.8	46.4, 168.4	68.1, 191.8	72.5, 168.4
BMI (kg/m^2) [1]					
PCPB	N	38	14	31	8
	Mean (SD)	42.25 (11.028)	40.51 (11.670)	43.46 (11.428)	46.67 (11.165)
	Min, Max	24.4, 83.0	24.6, 66.1	24.4, 83.0	31.8, 66.1
ATB	N	36	14	31	8
	Mean (SD)	42.18 (11.144)	40.61 (11.584)	43.28 (11.434)	46.60 (11.107)
	Min, Max	24.4, 83.0	25.0, 65.8	24.4, 83.0	31.8, 65.8

Numbers analysed

A total of 52 patients were enrolled, including 38 patients in the pivotal cohort and 14 in the supplemental cohort. Two patients in the pivotal cohort discontinued the study during the randomized placebo-controlled period and prior to completing their ATB assessments. Therefore these 2 patients were included in the PCS (N = 52) for the 14-week placebo-controlled analyses but not the FAS (N = 50) for the 52-week analyses.

With respect to clinical diagnoses, 44 of the 52 randomised patients had BBS and 8 had AS.

The number of patients in each of the study populations used to evaluate the efficacy and safety of setmelanotide in patients with BBS and AS are listed for patients in the pivotal and supplemental cohorts by the treatment to which each patient was originally randomized (setmelanotide or placebo).

Two patients in the pivotal cohort that were originally randomized to placebo discontinued the study prior to the open-label treatment period and are not included in the FAS.

Table 5: Study Populations – Screening Analysis Set

Study Populations	Statistic	Setmelanotide		Placebo	
		Pivotal N = 19	Supplemental N = 8	Pivotal N = 19	Supplemental N = 6
Screening Analysis Set [1]	n (%)	19 (100.0)	8 (100.0)	19 (100.0)	6 (100.0)
Safety Analysis Set [2]		19 (100.0)	8 (100.0)	19 (100.0)	6 (100.0)
Full Analysis Set [3]	n (%)	19 (100.0)	8 (100.0)	17 (89.5)	6 (100.0)
Designated Use Set [4]	n (%)	4 (21.1)	3 (37.5)	7 (36.8)	1 (16.7)
Placebo-controlled Analysis Set [5]	n (%)	19 (100.0)	8 (100.0)	19 (100.0)	6 (100.0)
Per-Protocol Set at End of Period 1 (Randomized Placebo Controlled) [6]	n (%)	19 (100.0)	8 (100.0)	19 (100.0)	6 (100.0)
Per-Protocol Set at End of Period 2 (Open Label Setmelanotide) [7]	n (%)	19 (100.0)	8 (100.0)	17 (89.5)	6 (100.0)
Completers Set [8]	n (%)	18 (94.7)	8 (100.0)	18 (94.7)	6 (100.0)
Stable Height Analysis Set [9]	n (%)	10 (52.6)	5 (62.5)	12 (63.2)	4 (66.7)
Active Growth Analysis Set [10]	n (%)	9 (47.4)	3 (37.5)	5 (26.3)	2 (33.3)

Note: Percentages are based on the number of patients randomized.

[1] Screening Analysis Set defined as patients who signed the informed consent form.

[2] Safety Analysis Set defined as patients who received at least 1 dose of study drug (placebo or setmelanotide).

[3] Full Analysis Set defined as randomized patients who received at least 1 dose of study drug and have ATB data.

[4] Designated Use Set defined as patients in the Full Analysis Set who demonstrate at least 5-kg weight loss (or at least 5% if baseline body weight <100 kg) over the first 14 weeks of active setmelanotide treatment, regardless of later disposition.

[5] Placebo-controlled Analysis Set defined as randomized patients who received at least 1 dose of placebo or setmelanotide and have PCB data.

[6] Per-Protocol Set at End of Period 1 defined as patients in the Placebo-controlled Analysis Set without major protocol violations that result in exclusion of the patients from the analysis.

[7] Per-Protocol Set at End of Period 2 defined as patients in the Full Analysis Set without any major protocol violations that will result in exclusion of the patient from analysis.

[8] Completers Set defined as patients in the Per-Protocol at End of Period 1 who continue on active treatment or placebo to complete a full 14-week placebo-controlled double blind period (Period 1).

[9] Stable Height Analysis Set defined as patients in the Full Analysis Set who grow ≤2 cm in height from study baseline to the primary endpoint timepoint or to the last available timepoint if it occurs prior to the primary endpoint.

[10] Active Growth Analysis Set defined as patients in the Full Analysis Set who grow >2 cm in height from study baseline to the primary endpoint timepoint or to the last available timepoint if it occurs prior to the primary endpoint.

Outcomes and estimation

Primary efficacy and sensitivity analyses

Primary efficacy and sensitivity analyses are presented in Table 6 and Table 7.

Table 6: Proportion of Pivotal Patients ≥12 Years Old who Achieve ≥10% Reduction in Body Weight from the ATB After 52 Weeks of Setmelanotide - FAS

Group	Statistic [1]	Result [2]
Pivotal (N = 31)	Estimated %	32.3
	(95% CI)	(16.7, 51.4)
	p-value	0.0006

Abbreviations: ATB = active treatment baseline; CI = confidence interval; FAS = full analysis set.
Note: If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation
model is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52 weeks due to any other reason, the patient is considered a failure.

[1] Estimated %, 95% CI and p-value are based on Rubin's Rule. P-value is one-sided and compared with alpha = 0.025.

[2] Six (6) patients (19.35%) had missing measurements at 52 weeks due to study discontinuation and were considered a failure.

Table 7: Proportion of Patients ≥12 Years Old who Achieve ≥10% Reduction in Body Weight from the ATB After 52 Weeks of Setmelanotide: Sensitivity Analyses

Group	Statistic [1]	Result
Per-Protocol Set at End of Period 2 [2]	Estimated %	32.3
	(95% CI)	(16.7, 51.4)
	p-value	0.0006
Nonreplacement Analysis [3]	Estimated %	36.9
	(95% CI)	(19.2, 54.7)
	p-value	0.0015
Completers Analysis [4]	Estimated %	32.3
	(95% CI)	(16.7, 51.4)
	p-value	0.0006
Reanalysis of Data Using the PCPB [5]	Estimated %	32.3
	(95% CI)	(16.7, 51.4)
	p-value	0.0006

Abbreviations: ATB= active treatment baseline; CI = confidence interval; PCPB=placebo-controlled period baseline.

[1] Estimated %, 95% CI and p-value are based on Rubin's Rule. P-value is one-sided.

[2] If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation model is
used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52 weeks due to any other reason, the patient is considered a failure.

[3] If missing measurements after ~52 weeks, a multiple imputation model is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment.

[4] If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation model is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52 weeks due to any other reason, the patient is considered a failure. If patient started with Placebo and does not have qualifying 52 week measurement, patient is excluded from this analysis.

[5] For this analysis baseline is defined as the last available measurement prior to the first dose of setmelanotide or placebo; 6 patients (19.35%) had missing measurements at 52 weeks due to study discontinuation and were considered a failure.

Key secondary efficacy and sensitivity analyses

Key secondary efficacy and sensitivity analyses are presented in Table 8, Table 9, Table 10, Table 11, Table 12 and Table 13.

Table 8: Body Weight (kg) Change and Percent Change from ATB After 52 Weeks of Active Treatment Among Pivotal Patients ≥12 Years Old - FAS

Group/Parameter	Statistic [1]	Result [2]
Pivotal		
Change After 52 weeks	N	31
	Mean (SD)	-5.90 (9.293)
	Median	-4.37
	Min, Max	-27.0, 13.8
	95% CI	-9.31, -2.49
	p-value	0.0007
Percent Change After 52 weeks	N	31
	Mean (SD)	-5.21 (7.895)
	Median	-3.57
	Min, Max	-20.5, 13.9
	95% CI	-8.10, -2.31
	p-value	0.0005

Abbreviations: ATB = active treatment baseline; CI = confidence interval; FAS = full analysis set; max = maximum; min = minimum; SD = standard deviation.
Note: If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation model is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52 weeks due to any other reason, the patient is considered a failure.

[1] 95% CI and p-value are based on Rubin's Rule. p-value is one-sided and compared with alpha = 0.025

[2] Six (6) patients (19.35%) had missing measurements at 52 weeks due to study discontinuation and were considered as percent change = 0.

Table 9: Body Weight (kg) Change and Percent Change from ATB After 52 Weeks of Setmelanotide: Sensitivity Analyses

Group/Parameter	Statistic [1]	Result
Designated Use Set [2]		
Change After 52 weeks	N	11
	Mean (SD)	-11.57 (8.383)
	p-value	0.0005
Percent Change After 52 weeks	N	11
	Mean (SD)	-10.53 (6.964)
	p-value	0.0003
Nonreplacement Analysis [3]		
Change After 52 weeks	N	31
	Mean (SD)	-7.04 (9.703)
	p-value	0.0001
Percent Change After 52 weeks	N	31
	Mean (SD)	-6.13 (8.258)
	p-value	0.0001
Completers Analysis [4]		
Change After 52 weeks	N	31
	Mean (SD)	-5.90 (9.293)
	p-value	0.0007
Percent Change After 52 weeks	N	31
	Mean (SD)	-5.21 (7.895)
	p-value	0.0005
Reanalysis of Data Using the PCPB [5]		
Change After 52 weeks	N	31
	Mean (SD)	-6.09 (9.922)
	p-value	0.0009
Percent Change After 52 weeks	N	31
	Mean (SD)	-5.33 (8.428)
	p-value	0.0007

Abbreviations: ATB = active treatment baseline; SD = standard deviation.

[1] p-value based on Rubin's Rule. p-value is one-sided.

[2] If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation model is
used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52 weeks due to any other reason, the patient is considered a failure.

[3] If missing measurements after ~52 weeks, a multiple imputation model is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment.

[4] If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation model is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52 weeks due to any other reason, the patient is considered a failure. If patient started with Placebo and does not have qualifying 52 week measurement, patient is excluded from this analysis.

[5] For this analysis baseline is defined as the last available measurement prior to the first dose of setmelanotide or placebo; 6 patients (19.35%) had missing measurements at 52 weeks due to study discontinuation and were considered as percent change = 0.

Table 10: Daily Hunger Score Weekly Average Change/Percent Change from ATB After 52 Weeks of Active Treatment Among Pivotal Patients ≥12 Years Old - FAS

Group/Parameter	Statistic [1]	Average Hunger over 24 Hours	Most/Worst Hunger over 24 Hours	Morning Hunger
Pivotal				
Weekly Average Change	N	16	16	16
	Mean (SD)	-2.17 (2.060)	-2.26 (1.955)	-2.36 (2.433)
	Median	-2.00	-1.90	-1.83
	Min, Max	-6.7, 0.0	-6.7, 0.0	-7.3, 0.8
	95% CI	-3.27, -1.08	-3.30, -1.22	-3.66, -1.06
	p-value	0.0004	0.0002	0.0007
Weekly Average Percent Change [2]	N	16	16	16
	Mean (SD)	-32.58 (27.539)	-30.91 (24.733)	-36.69 (36.888)
	Median	-33.90	-27.50	-32.97
	Min, Max	-77.0, 0.0	-77.0, 0.0	-100.0, 33.3
	95% CI	-47.26, -17.91	-44.09, -17.73	-56.35, -17.04
	p-value	0.0001	<0.0001	0.0006

Abbreviations: ATB= active treatment baseline; CI = confidence interval; FAS = full analysis set; max = maximum; min = minimum; SD = standard deviation.
Note: Based on qualifying patients within FAS, i.e., patients ≥12 years with no cognitive impairment. Note: If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation model is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52 weeks due to any other reason, the patient is considered a failure.

[1] 95% CI and p-value are based on Rubin's Rule. p-value is one-sided and compared with alpha=0.025.

[2] Three (3) patients (18.75%) had missing measurements at 52 weeks due to study discontinuation and were
considered as percent change = 0.

Table 11: Daily Hunger Score Weekly Average Change/Percent Change from ATB After 52 Weeks of Active Treatment: Sensitivity Analyses

Group/Parameter	Statistic [1]	Average Hunger over 24 Hours	Most/Worst Hunger over 24 Hours	Morning Hunger
Designated Use Set (BBS subgroup) [2]				
Weekly Average Change	N	5	5	5
	Mean (SD)	-2.89 (1.745)	-2.70 (1.652)	-2.43 (1.714)
	p-value	0.0104	0.0108	0.0170
Weekly Average Percent Change	N	5	5	5
	Mean (SD)	-47.70 (21.160)	-44.42 (22.211)	-43.66 (23.758)
	p-value	0.0036	0.0055	0.0074
Patients with ≥3 of 7 Days of Data [3]				
Weekly Average Change	N	13	13	13
	Mean (SD)	-2.68 (1.963)	-2.78 (1.790)	-2.91 (2.384)
	p-value	0.0002	<0.0001	0.0004
Weekly Average Percent Change	N	13	13	13
	Mean (SD)	-40.10 (24.927)	-38.04 (21.696)	-45.16 (35.870)
	p-value	<0.0001	<0.0001	0.0003
Nonreplacement Analysis [4]				
Weekly Average Change	N	16	16	16
	Mean (SD)	-2.48 (1.891)	-2.60 (1.756)	-2.77 (2.261)
	p-value	<0.0001	<0.0001	<0.0001
Weekly Average Percent Change	N	16	16	16
	Mean (SD)	-36.57 (24.743)	-35.03 (21.879)	-42.33 (34.305)
	p-value	<0.0001	<0.0001	<0.0001
Completers Analysis [5]				
Weekly Average Change	N	16	16	16
	Mean (SD)	-2.17 (2.060)	-2.26 (1.955)	-2.36 (2.433)
	p-value	0.0004	0.0002	0.0007
Weekly Average Percent Change	N	16	16	16
	Mean (SD)	-32.58 (27.539)	-30.91 (24.733)	-36.69 (36.888)
	p-value	0.0001	0.0001	0.0006
Reanalysis of Data Using the PCPB [6]				
Weekly Average Change	N	16	16	16
	Mean (SD)	-2.09 (2.053)	-2.71 (2.202)	-2.52 (2.380)
	p-value	0.0005	<0.0001	0.0004
Weekly Average Percent Change	N	16	16	16
	Mean (SD)	-31.64 (27.316)	-34.54 (26.439)	-38.65 (37.089)
	p-value	0.0002	<0.0001	0.0004

Abbreviations: ATB= active treatment baseline; FAS = full analysis set; SD = standard deviation. Note: Based on qualifying patients within FAS, i.e., patients ≥12 years with no cognitive impairment.

[1] p-value is based on Rubin's Rule; p-value is one-sided.

[2] If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation model is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52 weeks due to any other reason, the patient is considered a failure.

[3] P-value based on t-test.

[4] If missing measurements after ~52 weeks, a multiple imputation model is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment.

[5] If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation model is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52

weeks due to any other reason, the patient is considered a failure. If patient started with Placebo and does not have qualifying 52 week measurement, patient is excluded from this analysis.

[6] For this analysis baseline is defined as the last available measurement prior to the first dose of setmelanotide or placebo; 3 patients (18.75%) had missing measurements at 52 weeks due to study discontinuation and were considered as percent change = 0.

Table 12: Proportion of Pivotal Patients ≥12 Years of Age Who Achieve ≥25% Improvement in Daily Hunger Score Weekly Average from ATB After 52 Weeks of Active Treatment - FAS

Group	Statistic [1]	Average Hunger over 24 Hours	Most/Worst Hunger over 24 Hours	Morning Hunger
Pivotal [2]				
	Estimated %	62.5	62.5	62.5
	(95% CI)	(35.4, 84.8)	(35.4, 84.8)	(35.4, 84.8)
	p-value	<0.0001	<0.0001	<0.0001

Abbreviations: ATB = active treatment baseline; CI =. Confidence interval; FAS = full analysis set.
Note: Based on qualifying patients within FAS, i.e., patients ≥12 years with no cognitive impairment. Note: If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation model is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52 weeks due to any other reason, the patient is considered a failure.

[1] Estimated %, 95% CI and p-value are based on Rubin's Rule; p-value is one-sided and compared with alpha = 0.025.

[2] Three (3) patients (18.75%) had missing measurements at 52 weeks due to study discontinuation and were considered a failure.

Table 13: Proportion of Patients ≥12 Years of Age Who Achieve ≥25% Improvement in Daily Hunger Score Weekly Average from ATB After 52 Weeks of Active Treatment: Sensitivity Analyses

Group	Statistic [1]	Average Hunger over 24 Hours	Most/Worst Hunger over 24 Hours	Morning Hunger
Patients with ≥3 of 7 Days of Data [2]				
	Estimated %	76.9	76.9	76.9
	(95% CI)	(46.2, 95.0)	(46.2, 95.0)	(46.2, 95.0)
	p-value	<0.0001	<0.0001	<0.0001
Nonreplacement Analysis [3]				
	Estimated %	71.6	71.6	75.2
	(95% CI)	(48.2, 95.0)	(48.0, 95.1)	(52.6, 97.8)
	p-value	<0.0001	<0.0001	<0.0001
Completers Analysis [4]				
	Estimated %	62.5	62.5	62.5
	(95% CI)	(35.4, 84.8)	(35.4, 84.8)	(35.4, 84.8)
	p-value	<0.0001	<0.0001	<0.0001
Reanalysis of Data Using the PCPB [5]				
	Estimated %	56.3	62.5	68.8
	(95% CI)	(29.9, 80.2)	(35.4, 84.8)	(41.3, 89.0)
	p-value	<0.0001	<0.0001	<0.0001

Abbreviations: ATB = active treatment baseline; CI = confidence interval; PCPB = placebo-controlled period baseline.

[1] Estimated %, 95% confidence interval and p-value are based on Rubin's Rule; p-value is one-sided.

[2] P-value is based on 1-sided exact binomial test.

[3] If missing measurements after ~52 weeks, a multiple imputation model is used to impute the measurements for
patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment.

[4] If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation model is
used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52 weeks

due to any other reason, the patient is considered a failure. If patient started with Placebo and does not have qualifying 52 week measurement, patient is excluded from this analysis.

[5] For this analysis baseline is defined as the last available measurement prior to the first dose of setmelanotide or placebo; 3 patients (18.75%) had missing measurements at 52 weeks due to study discontinuation and were considered a failure.

Secondary efficacy analyses

Secondary efficacy and sensitivity analyses are presented in Table 14, Table 15, Table 16, Table 17, Table 18, Table 19 and Figure 8.

Table 14: Body Weight (kg) Change/Percent Change from PCPB After 14 Weeks of Treatment Among Pivotal Patients ≥12 Years Old - PCS

Group/Parameter	Statistic [1]	Setmelanotide (N = 16)	Placebo (N = 17)
Pivotal [2]			
Change after 14 Weeks	N	16	17
	Mean (SD)	-3.06 (5.617)	-0.29 (2.768)
	Difference	-2.77	
	95% CI of Difference	-5.77, 0.24	
	p-value	0.0355	
Percent Change after 14 Weeks	N	16	17
	Mean (SD)	-2.41 (4.752)	-0.32 (2.253)
	Difference	-2.10	
	95% CI of Difference	-4.62, 0.42	
	p-value	0.0516	

Abbreviations: CI = confidence interval; PCS = placebo-controlled analysis set; PCPB = placebo-controlled period baseline; SD = standard deviation.

[1] Difference, 95% CI of difference, and p-value are based on Rubin's Rule and difference calculated as Setmelanotide – Placebo

[2] If missing measurements after ~14 weeks, a multiple imputation model is used to impute the measurements for patients with less than ~14 weeks of setmelanotide or placebo treatment to a timepoint that approximates 14 weeks of setmelanotide or placebo treatment.

Table 15: Body Weight (kg) Change/Percent Change from PCPB After 14 Weeks of Treatment Among Pivotal Patients ≥12 Years Old: Sensitivity Analyses

Group/Parameter	Statistic [1]	Setmelanotide (N = 16)	Placebo (N = 17)
Per Protocol Set at End of Period 1 [2]			
Change after 14 Weeks	N	16	17
	Mean (SD)	-3.06 (5.617)	-0.29 (2.768)
	p-value	0.0355	
Percent Change after 14 Weeks	N	16	17
	Mean (SD)	-2.41 (4.752)	-0.32 (2.253)
	p-value	0.0516	
Completers Set [2]			
Change after 14 Weeks	N	16	16
	Mean (SD)	-3.06 (5.617)	-0.24 (2.794)
	p-value	0.0409	
Percent Change after 14 Weeks	N	16	16
	Mean (SD)	-2.41 (4.752)	-0.28 (2.275)
	p-value	0.0574	
Treatment Failures Analysis [3]			
Change after 14 Weeks	N	16	17
	Mean (SD)	-3.06 (5.617)	-0.22 (2.706)
	p-value	0.0357	
Percent Change after 14 Weeks	N	16	17
	Mean (SD)	-2.41 (4.752)	-0.26 (2.204)
	p-value	0.0507	

Abbreviations: PCPB = placebo-controlled period baseline; SD = standard deviation.

[1] p-value is based on Rubin's Rule and difference calculated as Setmelanotide – Placebo

[2] If missing measurements after ~14 weeks, a multiple imputation model is used to impute the measurements for patients with less than ~14 weeks of setmelanotide or placebo treatment to a timepoint that approximates 14 weeks of setmelanotide or placebo treatment.

[3] If missing measurements after ~14 weeks, the patient is considered a failure.

Table 16: Body Weight (kg) Change/Percent Change from PCPB After 14 Weeks of Treatment Among All Patients ≥12 Years Old - PCS

Group/Parameter	Statistic [1]	Setmelanotide (N = 21)	Placebo (N = 21)
Pivotal [2, 3]			
Change after 14 Weeks	N	21	20
	Mean (SD)	-3.48 (5.445)	-0.28 (2.536)
	Difference	-3.20	
	95% CI of Difference	-5.84, -0.57	
	p-value	0.0085	
Percent Change after 14 Weeks	N	21	20
	Mean (SD)	-2.78 (4.494)	-0.29 (2.064)
	Difference	-2.49	
	95% CI of Difference	-4.66, -0.33	
	p-value	0.0121	

Table 17: Daily Hunger Score Weekly Mean Percent Change from PCPB After 14 Weeks of Treatment Among All Patients ⩾12 Years Old - PCS

Group/Parameter	Statistic [1]	Average Hunger over 24 Hours		Most/Worst Hunger over 24 Hours		Morning Hunger	
		Setmelanotide (N = 21)	Placebo (N = 20)	Setmelanotide (N = 21)	Placebo (N = 20)	Setmelanotide (N = 21)	Placebo (N = 20)
Weekly Average Percent Change	N	9	13	9	13	9	13
	Mean (SD)	-30.86 (17.590)	4.37 (43.838)	-26.65 (19.029)	-14.83 (14.576)	-34.10 (32.555)	-9.30 (17.092)
	Median	-33.33	-1.90	-25.00	-10.79	-32.61	-9.75
	Min, Max	-53.6, -7.9	-40.0, 141.8	-52.4, 0.0	-36.7, 3.4	-100.0, 18.5	-40.0, 23.1
	95% CI	-44.38, -17.34	-19.56, 28.30	-41.28, -12.03	-22.95, -6.70	-59.12, -9.08	-18.78, 0.18
	Difference	-35.23		-11.83		-24.80	
	95% CI of Difference	-65.68, -4.78		-25.97, 2.31		-45.69, -3.91	
	p-value	0.0117		0.0506		0.0100	

Table 18: Daily Hunger Score Weekly Average at PCPB and Mean Change/Percent Change from PCPB After 14 Weeks of Treatment Among Pivotal Patients ≥12 Years Old - PCS

Group/Parameter	Statistic [1]	Average Hunger over 24 Hours		Most/Worst Hunger over 24 Hours		Morning Hunger	
		Setmelanotide (N = 16)	Placebo (N = 17)	Setmelanotide (N = 16)	Placebo (N = 17)	Setmelanotide (N = 16)	Placebo (N = 17)
Pivotal [2]							
Weekly Average at PCPB	N	7	10	7	10	7	10
	Mean (SD)	6.82 (1.163)	6.39 (2.103)	7.84 (1.455)	7.98 (1.457)	5.87 (2.110)	6.50 (1.875)
	Median	6.71	6.04	8.00	8.50	6.43	5.87
	Min, Max	5.4, 8.6	2.6, 9.9	5.3, 9.7	6.0, 10.0	2.3, 8.3	4.3, 9.4
Weekly Average Change	N	7	10	7	10	7	10
	Mean (SD)	-2.34 (1.133)	0.16 (1.538)	-2.52 (1.029)	-0.94 (1.207)	-2.35 (1.834)	-0.39 (1.006)
	Median	-2.86	-0.09	-2.75	-0.43	-2.14	-0.34
	Min, Max	-3.1, -0.4	-2.0, 3.7	-3.9, -1.1	-3.2, 0.5	-4.7, 0.4	-2.0, 1.3
	95% CI	-3.39, -1.29	-0.81, 1.14	-3.47, -1.57	-1.72, -0.16	-4.04, -0.65	-1.05, 0.27
	Difference	-2.50		-1.58		-1.96	
	95% CI of Difference	-3.86, -1.14		-2.70, -0.46		-3.33, -0.59	
	p-value	0.0002		0.0029		0.0025	
Weekly Average Percent Change	N	7	10	7	10	7	10
	Mean (SD)	-34.71 (18.081)	9.54 (49.267)	-33.38 (15.564)	-13.11 (15.918)	-37.32 (36.687)	-6.08 (18.838)
	Median	-40.43	-1.10	-34.38	-5.80	-37.78	-4.31
	Min, Max	-53.6, -7.9	-40.0, 141.8	-52.4, -14.3	-36.7, 5.2	-100.0, 18.5	-40.0, 23.5
	95% CI	-51.43, -17.98	-21.17, 40.24	-47.77, -18.98	-23.28, -2.93	-71.25, -3.39	-18.10, 5.93
	Difference	-44.24		-20.27		-31.24	
	95% CI of Difference	-82.86, -5.63		-35.72, -4.82		-57.87, -4.61	
	p-value	0.0124		0.0051		0.0107	

Abbreviations: CI = confidence interval; Max = maximum; Min = minimum; PCS = placebo-controlled analysis set; PCPB = placebo-controlled period baseline; Abbreviations: CI = confidence : SD = standard deviation.
Note: Based on qualifying patients within PCS (12 years or older and no cognitive impairment)
1 95% CI of mean is based on Rubin's Rule. If no imputation is needed for given treatment, then 95% CI of mean reflects observed CI; Difference, 95% CI of difference, and p-value are based on Rubin's Rule and difference calculated as Setmelanotide – Placebo; p-value is one-sided.
2 If missing measurements after ~14 weeks, a multiple imputation model is used to impute the measurements for patients with less than ~14 weeks of setmelanotide or placebo treatment to a timepoint that approximates 14 weeks of setmelanotide or placebo treatment.

Table 19: Daily Hunger Score Weekly Average Percent Change from PCPB After 14 Weeks of Treatment Among Pivotal Patients ≥12 Years Old –Sensitivity Analyses

Group/Parameter	Statistic [1]	Average Hunger over 24 Hours		Most/Worst Hunger over 24 Hours		Morning Hunger	
		Setmelanotide (N = 16)	Placebo (N = 17)	Setmelanotide (N = 16)	Placebo (N = 17)	Setmelanotide (N = 16)	Placebo (N = 17)
Per Protocol Set [2]							
Weekly Average Change	N	7	10	7	10	7	10
	Mean (SD)	-2.34 (1.133)	0.16 (1.538)	-2.52 (1.029)	-0.94 (1.207)	-2.35 (1.834)	-0.39 (1.006)
	p-value	0.0002		0.0029		0.0025	
Weekly Average % Change	N	7	10	7	10	7	10
	Mean (SD)	-34.71 (18.081)	9.54 (49.267)	-33.38 (15.564)	-13.11 (15.918)	-37.32 (36.687)	-6.08 (18.838)
	p-value	0.0124		0.0051		0.0107	
Completer Set [2]							
Weekly Average Change	N	7	9	7	9	7	9
	Mean (SD)	-2.34 (1.133)	0.05 (1.552)	-2.52 (1.029)	-1.04 (1.192)	-2.35 (1.834)	-0.47 (0.979)
	p-value	0.0021		0.0102		0.0096	
Weekly Average % Change	N	7	9	7	9	7	9
	Mean (SD)	-34.71 (18.081)	8.63 (51.885)	-33.38 (15.564)	-14.48 (15.776)	-37.32 (36.687)	-7.26 (19.050)
	p-value	0.0272		0.0157		0.0257	
Patients with ≥ 3/7 Days of Data Present							
Weekly Average Change	N	7	9	7	9	7	9
	Mean (SD)	-2.34 (1.133)	0.05 (1.552)	-2.52 (1.029)	-1.04 (1.192)	-2.35 (1.834)	-0.47 (0.979)
	p-value	0.0021		0.0102		0.0096	
Weekly Average % Change	N	7	9	7	9	7	9
	Mean (SD)	-34.71 (18.081)	8.63 (51.885)	-33.38 (15.564)	-14.48 (15.776)	-37.32 (36.687)	-7.26 (19.050)
	p-value	0.0272		0.0157		0.0257	
Treatment Failure [3]							
Weekly Average Change	N	7	10	7	10	7	10
	Mean (SD	-2.34 (1.133)	0.05 (1.463)	-2.52 (1.029)	-0.93 (1.171)	-2.35 (1.834)	-0.42 (0.935)
	p-value	0.0013		0.0057		0.0060	
Weekly Average % Change	N	7	10	7	10	7	10
	Mean (SD)	-34.71 (18.081)	7.77 (48.994)	-33.38 (15.564)	-13.04 (15.563)	-37.32 (36.687)	-6.54 (18.107)
	p-value	0.0230		0.0091		0.0180	

Abbreviations: PCS = placebo-controlled analysis set; PCPB = placebo-controlled period baseline; SD = standard deviation.
Note: Based on qualifying patients within PCS (12 years or older and no cognitive impairment).

[1] p-values are based on Rubin's Rule and difference calculated as Setmelanotide – Placebo; p-value is one-sided.

[2] If missing measurements after ~14 weeks, a multiple imputation model is used to impute the measurements for patients with less than ~14 weeks of
setmelanotide or placebo treatment to a timepoint that approximates 14 weeks of setmelanotide or placebo treatment.

[3] If missing measurements after ~14 weeks, the patient is considered a failure

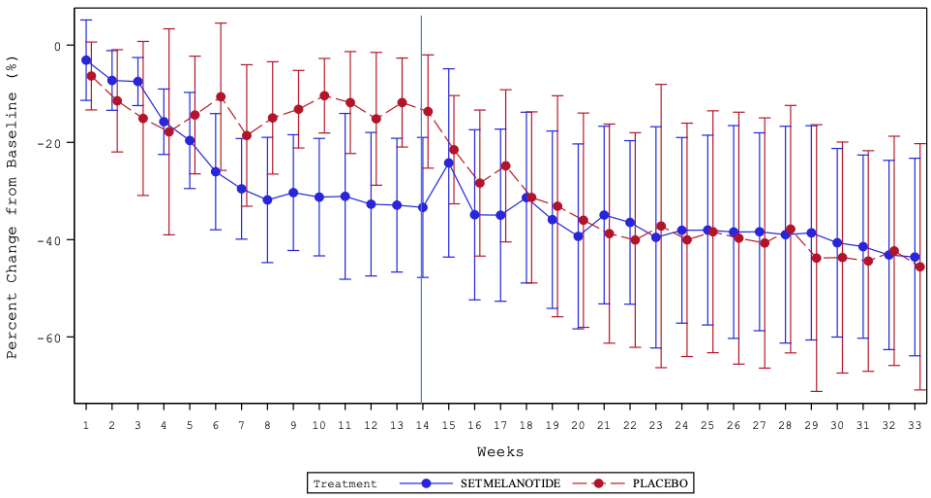


Figure 8: Percent Change from the PCPB in the Weekly Average of the Daily Hunger Questionnaire's Most/Worst Score Among Pivotal Patients ≥12 Years Old - PCS

Abbreviations: PCS = placebo-controlled analysis set; PCPB = placebo-controlled period baseline.
Note: Line at Week 14 represents the end of the 14-week placebo-controlled period and the initiation of setmelanotide for patients randomized to placebo.

Ancillary analyses

Exploratory analyses

Data are presented in Table 20, Table 21, Table 22, Table 23, Table 24.

Table 20: Proportion of Pivotal Patients who Achieve ≥10% Reduction in Body Weight Among Patients ≥12 Years Old or 15% Reduction in BMI Among Patients <12 Years Old from ATB After 52 Weeks of Setmelanotide - FAS

Parameter	Statistic [1]	Total (N = 36)
≥10% Reduction in Body Weight or 15% Reduction in BMI from ATB After 52 weeks of Active Treatment	n (%)	10 (27.8)
	(95% CI)	(14.2, 45.2)
	p-value	0.0022

Abbreviations: ATB = Active treatment baseline; BMI = body mass index; CI = confidence interval; FAS = full analysis set.

[1] Two-sided 95% CI calculated using the exact Clopper-Pearson method; p-value is based on 1-sided exact binomial test.

Table 21: Proportion of Pivotal Patients ≥12 Years Old who Achieve Reductions in Body Weight from ATB After 52 Weeks of Setmelanotide - FAS

Reduction in Body Weight from the ATB	Statistic [1]	Total (N = 31)
≥5%	Estimated %, (95% CI)	45.2 (27.3, 64.0)
≥15%	Estimated %, (95% CI)	12.9 (3.6, 29.8)
≥20%	Estimated %, (95% CI)	3.2 (0.1, 16.7)
≥25%	Estimated %, (95% CI)	0.0 (0.0, 11.2)
≥30%	Estimated %, (95% CI)	0.0 (0.0, 11.2)
≥35%	Estimated %, (95% CI)	0.0 (0.0, 11.2)
≥40%	Estimated %, (95% CI)	0.0 (0.0, 11.2)

Abbreviations: ATB = Active treatment baseline; CI = confidence interval; FAS = full analysis set.
Note: If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation model
is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52 weeks due to any other reason, the patient is considered a failure.

[1] Estimated % and 95% CI are based on Rubin's Rule

Table 22: Body Composition Among Pivotal Patients: Actual Value, Change, and Percent Change from ATB After 52 Weeks of Setmelanotide - FAS

Parameter/Timepoint	Actual/ Change from ATB/ Percent Change from ATB	Statistic	Total (N = 36)
Body Fat Measurement (g)			
ATB	Actual	N	33
		Mean (SD)	51885.10 (20987.022)
After 52 weeks Setmelanotide	Actual	N	20
		Mean (SD)	43325.97 (16174.413)
	Change from ATB	N	19
		Mean (SD)	-4464.35 (11950.267)
	% Change from ATB	N	19
		Mean (SD)	-8.929 (26.0590)
Total Body Bone Mineral Density (g)			
ATB	Actual	N	7
		Mean (SD)	2758.99 (673.447)
After 52 weeks Setmelanotide	Actual	N	5
		Mean (SD)	3057.00 (804.049)
	Change from ATB	N	5
		Mean (SD)	177.40 (86.913)
	Percent Change from ATB	N	5
		Mean (SD)	6.117 (2.6061)
Total Body Mass (g)			
ATB	Actual	N	33
		Mean (SD)	112350.76 (30790.212)
After 52 weeks Setmelanotide	Actual	N	20
		Mean (SD)	100934.62 (18170.138)
	Change from ATB	N	19
		Mean (SD)	-7010.28 (10703.518)
	Percent Change from ATB	N	19
		Mean (SD)	-5.707 (9.6154)

Table 23: Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) Among Pivotal Patients: Actual Value, Change, and Percent Change from ATB After 52 Weeks of Setmelanotide - FAS

Parameter/Timepoint	Actual/ Change from ATB/ Percent Change from ATB	Statistic	Total (N = 36)
HOMA-IR			
ATB	Actual	N	20
		Mean (SD)	0.0115 (0.01057)
After 52 weeks Setmelanotide	Actual	N	25
		Mean (SD)	0.0109 (0.02391)
	Change from ATB	N	13
		Mean (SD)	-0.0005 (0.01284)
	% Change from ATB	N	13
		Mean (SD)	-12.7718 (80.59238)

Abbreviations: ATB = Active treatment baseline; FAS = full analysis set; HOMA-IR = Homeostasis Model Assessment of Insulin Resistance; SD = standard deviation.
HOMA-IR was computed as follows: HOMA-IR= (glucose in mmol/L x insulin in mIU/mL)/22.5.

Table 24: Lipids Among Pivotal Patients: Actual Value, Change, and Percent Change from ATB After 52 Weeks of Setmelanotide - FAS

Parameter/Timepoint	Actual/ Change from ATB/ Percent Change from ATB	Statistic	Total (N = 36)
Total Cholesterol (mmol/L)			
ATB	Actual	N	36
		Mean (SD)	4.38 (1.028)
After 52 weeks Setmelanotide	Actual	N	26
		Mean (SD)	3.88 (0.913)
	Change from ATB	N	26
		Mean (SD)	-0.30 (0.420)
	% Change from ATB	N	26
		Mean (SD)	-6.96 (10.236)
High Density Lipoprotein Cholesterol (mmol/L)			
ATB	Actual	N	36
		Mean (SD)	1.07 (0.193)
After 52 weeks Setmelanotide	Actual	N	26
		Mean (SD)	1.12 (0.233)
	Change from ATB	N	26
		Mean (SD)	0.05 (0.136)
	Percent Change from ATB	N	26
		Mean (SD)	4.31 (11.611)
Low Density Lipoprotein Cholesterol (mmol/L)			
ATB	Actual	N	36
		Mean (SD)	2.95 (0.950)
After 52 weeks Setmelanotide	Actual	N	26
		Mean (SD)	2.56 (0.908)
	Change from ATB	N	26
		Mean (SD)	-0.23 (0.418)
	Percent Change from ATB	N	26
		Mean (SD)	-8.77 (16.152)
Triglycerides (mmol/L)			
ATB	Actual	N	36
		Mean (SD)	2.02 (1.447)
After 52 weeks Setmelanotide	Actual	N	26
		Mean (SD)	1.40 (0.772)
	Change from ATB	N	26
		Mean (SD)	-0.24 (0.596)
	Percent Change from ATB	N	26
		Mean (SD)	-10.69 (31.950)

Abbreviations: ATB = Active treatment baseline; FAS = full analysis set; SD = standard deviation.

Subgroup analyses

- *Patients ≥6 and <12 years of age*

Data are presented in Table 25 and Table 26.

Table 25 By Patient Summary of Weight Related Outcomes at ATB and Last Assessment for Patients ≥6 and <12 Years

Cohort	Treatment Assignment/ Age at Study Entry	Weeks on Study at Last Visit[1]	Height (cm) at ATB / Last Visit	Weight (kg) at ATB / Last Visit (% Change)	BMI (kg/m^2) at ATB / Last Visit (Diff)	BMI Z-Score at ATB / Last Visit (Diff)	BMI 95% at ATB / Last Visit (Diff)
BBS							
Piv	Set/ 7	66	131.1/139.0	49.3/51.2 (3.85)	28.7/26.5 (-2.2)	3.83/2.88 (-0.95)	137.7/119.0 (-18.7)
Piv	Set/ 10	65	153.5/155	95.8/98.6 (2.92)	40.7/41.1 (0.4)	4.37/4.07 (-0.3)	163.7/156.9 (-6.8)
Piv	Plac/10	66 (52)	158.1/162.5	109.1/102.9 (-5.68)	43.1/39 (-4.1)	5.51/4.31 (-1.2)	183.8/159.5 (-24.3)
Supp	Set/ 6	40	129.9/132.4	46.4/45.6 (-1.72)	27.5/26.0 (-1.5)	4.1/3.33 (-0.77)	138.9/126.5 (-12..4)
Supp	Set / 7	22	141.2/142.6	67.8/67.0 (-1.18)	34.0/33 (-1.0)	5.88/5.2 (-0.68)	164.3/156.1 (-8.2)
Supp	Plac /6	41 (27)	122.5/128.2	49.0/47.8 (-2.45)	31.6/29.1 (-2.5)	5.03/4.07 (-0.96)	157.4/141.5 (-15.9)
Supp	Plac /8	28 (14)	145.2/147.6	54.3/47.6 (-12.34)	25.0/21.8 (-3.2)	2.89/2.1 (-0.79)	114.4/98.4 (-16.0)
Supp	Plac /6	28 (14)	129.9/134.0	76.2/74.4 (-2.36)	43.6/41.4 (-2.2)	9.07/7.97 (-1.1)	224.0/209.3 (-14.7)
AS							
Piv	Set / 10	4	157.0/158.5	76.8/76.2 (-0.8)	31.2/30.3 (-0.9)	3.25/3.1 (-0.15)	131.4/127.5 (-3.9)
Piv	Plac /10	66 (52)	146.8/150.7	72.8/69.7 (-4.3)	33.2/30.7 (-2.5)	3.15/2.66 (-0.49)	130.9/116.2 (-14.7)
Supp	Set / 10	54	132.0/139.5	59.3/54.9 (-7.4)	34.0/28.2 (-5.8)	3.57/2.51 (-1.06)	140.7/111.1 (-29.6)

Abbreviations: ATB = active treatment baseline, defined the last assessment prior to initiation of setmelanotide; BMI = body mass index; Diff = difference; PIV = pivotal patients; Plac = placebo; Set = setmelanotide; Supp = supplemental patients.[1] For patients randomized to 14 weeks of placebo before setmelanotide, weeks on setmelanotide at last visit, calculated by subtracting 14 weeks from the total weeks on study, is provided in parentheses.

Table 26: Body Mass Index Z-Score Change/Percent Change from PCPB After 14 Weeks of Treatment for All Patients 6-11 Years of Age (PCS)

Parameter	Statistic [1]	Setmelanotide (N = 6)		Placebo (N = 5)
Mean Body Mass Index Z-Score at PCPB	N	6		5
	Mean (SD)	4.17 (0.926)		5.15 (2.496)
	Median	3.97		5.23
	Min, Max	3.3, 5.9		2.9, 9.0
Mean Body Mass Index Z-Score After 14 Weeks of Treatment	N	5		5
	Mean (SD)	3.81 (0.961)		5.13 (2.481)
	Median	3.28		5.03
	Min, Max	3.2, 5.4		2.9, 9.1
Mean Body Mass Index Z-Score Change from PCPB After 14 Weeks of Treatment	N	5		5
	Mean (SD)	-0.54 (0.188)		-0.02 (0.126)
	Median	-0.47		0.00
	Min, Max	-0.8, -0.4		-0.2, 0.1
	95% CI	-0.78, -0.31		-0.17, 0.14
	Difference		-0.53	
	95% CI of Difference		-0.76, -0.29	
	p-value		0.0004	
Mean Body Mass Index Z-Score Percent Change from PCPB After 14 Weeks of Treatment	N	5		5
	Mean (SD)	-12.98 (5.308)		0.04 (3.066)
	Median	-11.48		0.00
	Min, Max	-20.0, -8.0		-3.8, 4.7
	95% CI	-19.57, -6.39		-3.77, 3.85
	Difference		-13.02	
	95% CI of Difference		-19.34, -6.70	
	p-value		0.0007	

Abbreviations: CI = confidence interval; PCPB = placebo-controlled period baseline; PCS = placebo-controlled set; SD = standard deviation.
Note: PCPB is the placebo-controlled period baseline, defined as the last available measurement prior to the first dose of setmelanotide or placebo.
[1] Difference, 95% CI of Difference, and p-value based on two-sample t-test; p-value is one-sided.

Patients ≥18 years of age

When setmelanotide's effect on body weight was examined in an ad hoc analysis of the data from pivotal BBS patients who were ≥18 years of age, its impact was even greater than that observed in the population of patients ≥12 years of age, with ~47% and 60% of patients ≥18 years of age achieving ≥10% and ≥5% weight loss at ~Week 52, respectively.

None of the 3 AS patients in this study who were ≥18 years of age achieved ≥5% weight loss at ~Week 52.

Subgroup – Diagnosis – BBS (≥12yo)

Data are presented in Table 27,Table 28,Table 29, Table 30, Table 31 and Table 32.

Table 27: Proportion of Pivotal BBS Patients ≥12 Years Old who Achieve ≥10% Reduction in Body Weight from the ATB After 52 Weeks of Setmelanotide - FAS

Group	Statistic [1]	Result [2]
Pivotal	Estimated %	35.7
	(95% CI)	(18.6, 55.9)
	p-value	0.0002

Abbreviations: ATB = active treatment baseline; CI = confidence interval; FAS = full analysis set.
Note: If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation model is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52 weeks due to any other reason, the patient is considered a failure.
[1] Estimated %, 95% CI and p-value are based on Rubin's Rule. P-value is one-sided and compared with alpha = 0.025.

Table 28: Body Weight (kg) Change and Percent Change from ATB After 52 Weeks of Active Treatment Among Pivotal BBS Patients ≥12 Years Old - FAS

Group/Parameter	Statistic [1]	Result
Pivotal		
Change After 52 weeks	N	28
	Mean (SD)	-7.42 (8.208)
	Median	-5.23
	Min, Max	-27.0, 7.5
	95% CI	-10.60, -4.24
	p-value	<0.0001
Percent Change After 52 weeks	N	28
	Mean (SD)	-6.47 (6.970)
	Median	-4.58
	Min, Max	-20.5, 4.5
	95% CI	-9.17, -3.77
	p-value	<0.0001

Abbreviations: ATB = active treatment baseline; CI = confidence interval; FAS = full analysis set; max = maximum; min = minimum; SD = standard deviation.
Note: If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation model is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52 weeks due to any other reason, the patient is considered a failure.
[1] 95% CI and p-value are based on Rubin's Rule. p-value is one-sided and compared with alpha = 0.025

Table 29: Daily Hunger Score Weekly Average Change/Percent Change from ATB After 52 Weeks of Active Treatment Among Pivotal BBS Patients ≥12 Years Old – FAS

Group/Parameter	Statistic [1]	Average Hunger Over 24 Hours	Most/Worst Hunger Over 24 Hours	Morning Hunger
Pivotal				
Weekly Average Change	N	14	14	14
	Mean (SD)	-2.06 (2.176)	-2.12 (2.051)	-1.85 (2.075)
	Median	-1.50	-1.69	-1.29
	Min, Max	-6.7, 0.0	-6.7, 0.0	-6.7, 0.8
	95% CI	-3.32, -0.81	-3.31, -0.94	-3.05, -0.65
	p-value	0.0018	0.0010	0.0027
Weekly Average Percent Change	N	14	14	14
	Mean (SD)	-31.80 (29.458)	-30.45 (26.485)	-28.51 (31.429)
	Median	-29.17	-25.00	-32.60
	Min, Max	-77.0, 0.0	-77.0, 0.0	-77.0, 33.3
	95% CI	-48.81, -14.79	-45.74, -15.16	-46.66, -10.37
	p-value	0.0007	0.0004	0.0024

Abbreviations: ATB = active treatment baseline; CI = confidence interval; FAS = full analysis set; max = maximum; min = minimum; SD = standard deviation.
Note: Based on qualifying patients within FAS, i.e., patients ≥12 years with no cognitive impairment. Note: If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation model is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52 weeks due to any other reason, the patient is considered a failure.
[1] 95% CI and p-value are based on Rubin's Rule. p-value is one-sided and compared with alpha = 0.025.

Table 30: Proportion of Pivotal BBS Patients ≥12 Years of Age Who Achieved ≥25% Improvement in Daily Hunger Score Weekly Average from ATB After 52 Weeks of Active Treatment - FAS

Group	Statistic [1]	Average Hunger Over 24 Hours	Most/Worst Hunger Over 24 Hours	Morning Hunger
Pivotal				
	Estimated %	57.1	57.1	57.1
	(95% CI)	(28.9, 82.3)	(28.9, 82.3)	(28.9, 82.3)
	p-value	<0.0001	<0.0001	<0.0001

Abbreviations: ATB = active treatment baseline; CI = Confidence interval; FAS = full analysis set
Note: Based on qualifying patients within FAS, i.e., patients ≥12 years with no cognitive impairment. Note: If missing measurements after ~52 weeks due to the nature of the study design, a multiple imputation model is used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. If missing measurement after ~52 weeks due to any other reason, the patient is considered a failure.
[1] Estimated %, 95% CI and p-value are based on Rubin's Rule; p-value is one-sided and compared with alpha = 0.025.

Table 31: Body Weight (kg) Change/Percent Change from PCPB After 14 Weeks of Treatment Among Pivotal BBS Patients ≥12 Years Old – PCS

Group/Parameter	Statistic [1]	Setmelanotide	Placebo
Pivotal [2]			
Change after 14 Weeks	N	14	15
	Mean (SD)	-4.02 (5.312)	-0.21 (2.890)
	Difference	-3.81	
	95% CI of Difference	-7.03, -0.58	
	p-value	0.0113	
Percent Change after 14 Weeks	N	14	15
	Mean (SD)	-3.21 (4.474)	-0.25 (2.353)
	Difference	-2.96	
	95% CI of Difference	-5.65, -0.26	
	p-value	0.0164	

Abbreviations: BBS = Bardet-Biedl syndrome; CI = confidence interval; CSR = clinical study report; PCS = placebo-controlled analysis set; PCPB = placebo-controlled period baseline; SD = standard deviation.
[1] Difference, 95% CI of difference, and p-value are based on Rubin's Rule and difference calculated as Setmelanotide – Placebo.
[2] If missing measurements after ~14 weeks, a multiple imputation model is used to impute the measurements for patients with less than ~14 weeks of setmelanotide or placebo treatment to a timepoint that approximates 14 weeks of setmelanotide or placebo treatment.

Table 32: Daily Hunger Score Weekly Average at PCPB and Mean Change/Percent Change from PCPB After 14 Weeks of Treatment Among Pivotal BBS Patients ≥12 Years Old - PCS

Group/Parameter	Statistic [1]	Average Hunger over 24 Hours		Most/Worst Hunger over 24 Hours		Morning Hunger	
		Setmelanotide (N = 14)	Placebo (N = 15)	Setmelanotide (N = 14)	Placebo (N = 15)	Setmelanotide (N = 14)	Placebo (N = 15)
Pivotal [2]							
Weekly Average at PCPB	N	5	9	5	9	5	9
	Mean (SD)	6.49 (1.061)	6.38 (2.230)	7.20 (1.165)	7.91 (1.525)	5.65 (2.177)	6.40 (1.964)
	Median	6.14	5.57	7.43	8.33	6.43	5.17
	Min, Max	5.4, 8.0	2.6, 9.9	5.3, 8.2	6.0, 10.0	2.3, 8.0	4.3, 9.4
Weekly Average Change	N	5	9	5	9	5	9
	Mean (SD)	-2.16 (1.335)	0.05 (1.552)	-2.41 (1.214)	-1.04 (1.192)	-1.43 (1.165)	-0.47 (0.979)
	Median	-3.08	-0.14	-2.75	-0.33	-2.00	-0.43
	Min, Max	-3.1, -0.4	-2.0, 3.7	-3.9, -1.1	-3.2, 0.1	-2.4, 0.4	-2.0, 1.1
	95% CI	-3.82, -0.50	-1.14, 1.25	-3.92, -0.90	-1.95, -0.12	-2.88, 0.02	-1.22, 0.28
	Difference	-2.21		-1.38		-0.96	
	95% CI of Difference	-4.01, -0.41		-2.83, 0.08		-2.23, 0.31	
	p-value	0.0101		0.0311		0.0622	
Weekly Average Percent Change	N	5	9	5	9	5	9
	Mean (SD)	-33.84 (21.927)	8.63 (51.885)	-34.85 (18.517)	-14.48 (15.776)	-20.87 (24.552)	-7.26 (19.050)
	Median	-44.00	-1.61	-44.00	-4.55	-32.61	-4.55
	Min, Max	-53.6, -7.9	-40.0, 141.8	-52.4, -14.3	-36.7, 1.5	-40.0, 18.5	-40.0, 22.9
	95% CI	-61.06, -6.61	-31.25, 48.51	-57.84, -11.86	-26.61, -2.36	-51.36, 9.61	-21.91, 7.38
	Difference	-42.47		-20.37		-13.61	
	95% CI of Difference	-96.20, 11.27		-40.71, -0.03		-39.18, 11.97	
	p-value	0.0554		0.0249		0.1344	

Abbreviations: BBS = Bardet-Biedl syndrome; CI = confidence interval; Max = maximum; Min = minimum; PCS = placebo-controlled analysis set; PCPB = placebo-controlled period baseline; SD = standard deviation.
Note: Based on qualifying patients within PCS (12 years or older and no cognitive impairment)

[1] 95% CI of mean is based on Rubin's Rule. If no imputation is needed for given treatment, then 95% CI of mean reflects observed CI; Difference, 95% CI of
difference, and p-value are based on Rubin's Rule and difference calculated as Setmelanotide – Placebo; p-value is one-sided.

[2] If missing measurements after ~14 weeks, a multiple imputation model is used to impute the measurements for patients with less than ~14 weeks of
setmelanotide or placebo treatment to a timepoint that approximates 14 weeks of setmelanotide or placebo treatment.

Subgroup – Diagnosis – AS (age-independent)

Data are presented in Table 27.

Table 33: By Patient Summary of Weight Related Outcomes in AS Patients at ATB and Last Assessment

Treat. Assign./ Age at Study Entry	Weeks on Study at Last Visit[1]	Height (cm) at ATB/ Last Visit	Weight (kg) at ATB/ Last Visit	Weight (% Change)	BMI at ATB/ Last Visit	BMI (Diff)	BMI Z-Score at ATB / Last Visit	BMI Z-Score (Diff)	BMI 95% at ATB/ Last Visit (Diff)	Most/Worst Hunger at ATB/ Last Visit[3]	Most/ Worst Hunger (Diff)
Set/ 12	64	155.5/161.3	98.7/113.6	15.1	40.8/43.6	2.8	3.89/4.12	0.23	154.7/155.8 (1.1)	9.7/4	-5.7
Set/ 10	4	157.0/158.5	76.8/76.2	-0.8	31.2/30.3	-0.9	3.25/3.1	-0.15	131.4/127.5 (-3.9)	NA	NA
Set/39	51	152.0/159.0[2]	191.8/202.8	5.7	82.8/80.2	-2.6[2]	NA	NA	NA	9.1/6.5	-2.6
Plac/10	66 (52)	146.8/150.7	72.8/69.7	-4.3	33.2/30.7	-2.5	3.15/2.66	-0.49	130.9/116.2 (-14.7)	NA	NA
Plac /17	2 (0)	156.2/156.2	NA	NA	NA	NA	NA	NA	NA	NA	NA
Plac /19	56 (42)	158.0/159.2	91.4/93.4	2.2	36.1/36.9	0.8	NA	NA	NA	NA	NA
Set /10	54	132.0/139.5	59.3/54.9	-7.4	34.0/28.2	-5.8	3.57/2.51	-1.06	140.7/111.1 (-29.6)	NA	NA
Set /18	18	176.0/176.0	123/125.3	1.9	39.7/40.4	0.7	3.71/3.85	0.14	NA	8/8	0

Abbreviations: AS = Alström Syndrome; ATB = active treatment baseline, defined as last assessment before initiation of setmelanotide; BMI = body mass index; Diff = difference; PIV = pivotal patients; Plac = placebo; Set = setmelanotide; Supp = supplemental patients.

[1] For patients randomized to 14 weeks of placebo before setmelanotide, weeks on setmelanotide at last visit, calculated by subtracting 14 weeks from the total weeks on study, is provided in parentheses.

[2] This patient's height was 152 cm at all visits with a record of height except for the last visit. Based on this and the fact that the patient was 39 years old, the measurement of 159 cm at the last visit is likely an error. The patient's BMI at the last visit

is likely also in error given that BMI is calculated based on height and weight.

[3] Not administered to patients <12 or to patients assessed as cognitively impaired by the Investigator.

Post-hoc analysis

At the CHMP request, the MAH submitted primary and secondary endpoint analyses using only non-imputed 52-week active treatment data for pivotal Bardet-Biedl syndrome (BBS) patients.

Data using the ATB are presented in Table 34,Table 35, Table 36, Table 37 and Table 38 . ATB is defined as the last available measurement prior to randomization for subjects initially randomized into the Setmelanotide group and is defined as the last available measurement prior to the first dose of open-label Setmelanotide treatment for subjects initially randomized into the placebo group.

Table 34. Proportion of Observed Pivotal BBS Subjects who Achieve >= 10% Reduction in Body Weight from Active Treatment Baseline After 52 Weeks of Active Treatment Among Subjects >= 12 Years Old (Full Analysis Set)

Parameter	Statistic	Total (N=23)
>=10% Reduction in Body Weight from ATB After 52 Weeks of Active Treatment	n(%)	10 (43.5)
	(95% CI)	(23.2, 65.5)
	p-value	<0.0001

Note: The null hypothesis (H0) to be tested is that the proportion of patients treated for ~52 weeks who achieve >= 10% reduction in body weight from baseline is less than or equal to a historical control rate of 10%. The alternative hypothesis (H1) is that the proportion is greater than a historical control rate of 10%: H0: pt >= 10% vs H1: pt > 10% 95% Confidence interval and p-value is based on 1-sided exact binomial test. p-value is one sided and compared with alpha=0.025 Source: Listing 16.2.6.1

Table 35 Proportion of Observed Pivotal BBS Subjects who Achieve >= 10% Reduction in Body Weight from Active Treatment Baseline After 52 Weeks of Active Treatment Among Subjects >= 12 Years Old (Full Analysis Set)

Parameter	Statistic	Total (N=23)
>=10% Reduction in Body Weight from Baseline After 52 Weeks of Active Treatment	n(%)	10 (43.5)
	(95% CI)	(23.2, 65.5)
	p-value	<0.0001

Table 36 Observed Body Weight (kg) Change and Percent Change from Active Treatment Baseline After 52 Weeks of Active Treatment Among Pivotal BBS Subjects >= 12 Years Old (Full Analysis Set)

Parameter	Statistic	Total (N=23)
Body Weight at ATB	N	23
	Mean (SD)	116.16 (28.171)
	Median	115.60
	Min, Max	68.1, 173.8
Body Weight After 52 Weeks of Active Treatment	N	23
	Mean (SD)	107.13 (28.382)
	Median	104.80
	Min, Max	54.3, 174.8
Body Weight Change from ATB After 52 Weeks of Active Treatment	N	23
	Mean (SD)	-9.03 (8.213)
	Median	-8.10
	Min, Max	-27.0, 7.5
	95% CI	-12.58, -5.48
	p-value	<0.0001
Body Weight Percent Change from ATB After 52 Weeks of Active Treatment	N	23
	Mean (SD)	-7.87 (6.932)
	Median	-6.16
	Min, Max	-20.5, 4.5
	95% CI	-10.87, -4.88
	p-value	<0.0001

Table 37 Observed Daily Hunger Score Weekly Average Change and Percent Change from Active Treatment Baseline After 52 Weeks of Active Treatment Among Pivotal BBS Subjects >= 12 Years Old (Full Analysis Set)

		Total (N=11)		
Parameter	Statistic	Average Hunger over 24 Hours	Most/Worst Hunger over 24 Hours	Morning Hunger
Daily Hunger Score Weekly Average at ATB	N	11	11	11
	Mean (SD)	6.16 (1.598)	6.80 (1.766)	5.54 (1.849)
	Median	6.14	7.14	6.14
	Min, Max	3.0, 8.7	4.0, 9.7	2.3, 8.7
Daily Hunger Score Weekly Average After 52 Weeks of Active Treatment	N	11	11	11
	Mean (SD)	3.53 (1.767)	4.10 (1.936)	3.19 (1.340)
	Median	3.00	3.67	3.00
	Min, Max	2.0, 6.7	2.0, 7.7	2.0, 6.0
Daily Hunger Score Weekly Average Change from ATB After 52 Weeks of Active Treatment	N	11	11	11
	Mean (SD)	-2.63 (2.128)	-2.70 (1.936)	-2.36 (2.072)
	Median	-2.00	-2.00	-2.10
	Min, Max	-6.7, 0.0	-6.7, -0.3	-6.7, 0.8
	95% CI	-4.06, -1.20	-4.00, -1.40	-3.75, -0.96
	p-value	0.0011	0.0005	0.0018
Daily Hunger Score Weekly Average Percent Change from ATB After 52 Weeks of Active Treatment	N	11	11	11
	Mean (SD)	-40.47 (27.241)	-38.75 (23.618)	-36.29 (31.204)
	Median	-40.00	-30.16	-33.33
	Min, Max	-77.0, 0.0	-77.0, -4.8	-77.0, 33.3
	95% CI	-58.77, -22.17	-54.62, -22.89	-57.25, -15.33
	p-value	0.0003	0.0001	0.0016

Table 38 Proportion of Observed Pivotal Subjects who Achieve >= 25% Improvement in Daily Hunger Score Weekly Average from Active Treatment Baseline After 52 Weeks of Active Treatment Among BBS Subjects >= 12 Years Old (Full Analysis Set)

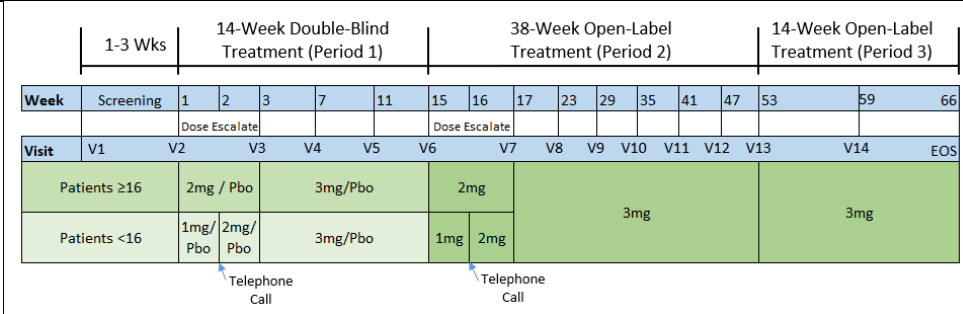
		Total (N=11)		
			Most/Worst	
Parameter	Statistic	Average Hunger over 24 Hours	Hunger over 24 Hours	Morning Hunger
>=25% Improvement in Daily Hunger Score Weekly Average from ATB After 52 Weeks of Treatment	n(%)	8 (72.7)	8 (72.7)	8 (72.7)
	(95% CI)	(39.0, 94.0)	(39.0, 94.0)	(39.0, 94.0)
	p-value	<0.0001	<0.0001	<0.0001

Similar results are obtained using data from PCPB, when baseline was considered the last assessment prior to initiation of either setmelanotide or placebo and are not further described here.

Summary of main study

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 1. Summary of Efficacy for RM-493-023

Title: A PHASE 3 TRIAL OF SETMELANOTIDE (RM-493), A MELANOCORTIN-4 RECEPTOR (MC4R) AGONIST, IN BARDET-BIEDL SYNDROME (BBS) AND ALSTRØM SYNDROME (AS) PATIENTS WITH MODERATE TO SEVERE OBESITY		
Study identifier	RM-493-023	
Design		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 Weeks (14 Weeks DB + 38 Weeks Open-label) 1-3 Weeks 14 Weeks
Hypothesis	Superiority	
Treatments groups	Placebo-controlled Analysis Set (PCAS) – Placebo, pivotal	Placebo, 14 weeks, N=19
	Placebo-controlled Analysis Set (PCAS) – Placebo, supplemental	*Placebo, 14 weeks, N=6*
	Placebo-controlled Analysis Set (PCAS) – Setmelanotide, pivotal	Setmelanotide 3mg QD, 14 Weeks, N=19
	Placebo-controlled Analysis Set (PCAS) – Setmelanotide, supplemental	*Setmelanotide 3mg QD, 14 Weeks, N=8*
	Full Analysis Set (FAS) – Setmelanotide, pivotal	Setmelanotide 3mg QD, up to 66 Weeks, N=36

	Full Analysis Set (FAS) – Setmelanotide, supplemental		*Setmelanotide 3mg QD, up to 66 Weeks, N=14*
Endpoints and definitions	Primary endpoint	PE	Proportion of pivotal FAS patients ≥12 years of age who achieved a ≥10% reduction in body weight from baseline after ~52 weeks of treatment compared to a historical untreated proportion of 10%.
	1st Key Secondary endpoint	KSE 1	Mean percent change from active treatment baseline in body weight after ~52 weeks of treatment for patients in the ≥12yo pivotal FAS population
	2nd Key Secondary endpoint	KSE 2	Mean percent change from active treatment baseline in the weekly average of the daily hunger scores after ~52 weeks of treatment for patients in the not cognitively impaired ≥12yo pivotal FAS population
	3rd Key Secondary endpoint	KSE 3	Proportion of not cognitively impaired ≥12yo patients in the pivotal FAS population who achieve a ≥25% improvement from active treatment baseline in the weekly average of the daily hunger score, versus an historical untreated proportion of 10%.
	Secondary endpoint	SE 1	Body weight percent change from baseline at 14 weeks comparison between placebo- and setmelanotide-treated patients in the pivotal ≥12yo PCAS population
	Secondary endpoint	SE 2	Weekly average daily hunger score percent change from baseline at 14 weeks comparison between placebo- and setmelanotide-treated patients in the not cognitively impaired pivotal ≥12 years old PCAS population.
Database lock	16 April 2021		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Pivotal ≥12-year-old Full Analysis Set, after last enrolled patient in the Pivotal cohort has completed Period 2 (W52)		
Descriptive statistics and estimate variability	Endpoint	Statistic	≥12yo FAS, pivotal (N = 31)
	PE	Estimated %	32.3
		(95% CI)	(16.7, 51.4)
		p-value (one-sided)	0.0006
	KSE 1	Mean (SD)	-5,21 (7.895)
		(95% CI)	(-9.31, -2.49)
		p-value (one-sided)	0.0007
	Endpoint	Statistic	≥12yo FAS, pivotal, not cognitively impaired (N = 16)
	KSE 2	Mean (SD)	-30.91 (24.733)
		(95% CI)	(-44.09, -17.73)
		p-value (one-sided)	<0.0001
	KSE 3	Estimated %	62.5
		(95% CI)	(35.4, 84.8)
		p-value (one-sided)	<0.0001
Analysis description	**Secondary analysis**		
Analysis population and time point description	Pivotal ≥12-year-old Placebo Controlled Analysis Set (not cognitively impaired for hunger-bases SE 2), after last patient completes the 14 Week Double Blind Placebo Controlled period (W14)		
	Endpoint	Statistic	Setmelanotide	Placebo

Descriptive statistics and estimate variability	SE 1	N	16	17
		Mean (SD)	-2.41 (4.752)	-0.32 (2.253)
		Difference	-2.10	
		95% CI	-4.62, 0.42	
		p-value (one-sided)	0.0516	
	Endpoint	Statistic	Setmelanotide	Placebo
	SE 2	N	7	10
		Mean (SD)	-33.38 (15.564)	-13.11 (15.918)
		Difference	-20,27	
		95% CI of difference	-35.72, -4.82	
		p-value (one-sided)	0.0051	

Analysis performed across trials

An analysis across the pivotal trial RM-493-023 and another trial RM-493-014 have been submitted.

BBS population

Data are presented in Table 39, Table 40, Table 41, Table 42, Table 43, Table 44 and Table 45.

Table 39: Enrolment and Disposition in RM-493-022 for BBS and AS Patients who Participated in Study RM-493-023 and Supportive Study RM-493-014

Disposition	Statistic	BBS (N = 42)	AS (N = 5)
Study Status			
Enrolled in Extension Study	n (%)	42 (100.0)	5 (100.0)
Treated in Extension Study	n (%)	42 (100.0)	5 (100.0)
Total Time Followed (days) from Start of Index Study [1]	N	42	5
	Mean (SD)	681.8 (381.70)	789.8 (435.12)
	95% CI	562.9, 800.8	249.5, 1330.1
	Median	602.0	550.0
	Min, Max	168, 1489	393, 1310
Total Time Followed (days) from Start of Extension Study [2]	N	42	5
	Mean (SD)	248.1 (301.84)	322.0 (403.50)
	95% CI	154.1, 342.2	-179.0, 823.0
	Median	113.0	81.0
	Min, Max	4, 970	1, 792
Discontinued Treatment	n (%)	2 (4.8)	1 (20.0)
Primary Reason for Early Treatment Discontinuation			
Adverse Event	n (%)	1 (2.4)	0
Withdrawal by Patient	n (%)	1 (2.4)	0
Other	n (%)	0	1 (20.0)
Discontinued Study	n (%)	2 (4.8)	1 (20.0)
Primary Reason for Early Study Discontinuation			
Adverse Event	n (%)	1 (2.4)	0
Physician Decision	n (%)	0	1 (20.0)
Withdrawal by Patient	n (%)	1 (2.4)	0
Other	n (%)	0	0

Note: Percentages are based on the number of BBS or AS patients enrolled in Study RM-493-022.[1] Defined as last date of follow-up – date of enrolment index study +1.[2] Defined as last date of follow-up – date of enrolment in extension study +1.

Table 40: Demographic and Baseline Characteristics in BBS and AS Patients Enrolled and Treated in Study RM-493-022

Parameter	Statistic	BBS (N = 42)	AS (N = 5)
Age at Enrollment (years)	N	42	5
	Mean (SD)	20.5 (12.80)	11.8 (2.05)
	95% CI	16.5, 24.5	9.3, 14.3
	Median	16.0	12.0
	Min, Max	6, 61	10, 15
Investigational Site Country			
Canada	n (%)	4 (9.5)	0
France	n (%)	4 (9.5)	0
Spain	n (%)	3 (7.1)	0
United States	n (%)	2 (4.8)	5 (100.0)
United Kingdom	n (%)	29 (69.0)	0
Sex			
Male	n (%)	15 (35.7)	1 (20.0)
Female	n (%)	27 (64.3)	4 (80.0)
Race			
American Indian or Alaska Native	n (%)	0	0
Asian	n (%)	1 (2.4)	0
Black or African American	n (%)	3 (7.1)	1 (20.0)
Native Hawaiian or Other Pacific Islander	n (%)	0	0
White	n (%)	36 (85.7)	4 (80.0)
Other	n (%)	2 (4.8)	0
Ethnicity			
Hispanic or Latino	n (%)	2 (4.8)	0
Not Hispanic or Latino	n (%)	37 (88.1)	5 (100.0)
Not Reported	n (%)	0	0
Unknown	n (%)	3 (7.1)	0
BMI (kg/m^2) at Extension Baseline [1]	N	42	5
	Mean (SD)	38.10 (10.278)	31.04 (7.967)
	95% CI	34.90, 41.31	21.15, 40.93
	Median	37.55	30.70
	Min, Max	20.4, 60.8	21.8, 43.7
BMI Z-Score at Extension Baseline [2]	N	22	5
	Mean (SD)	3.41 (1.854)	2.58 (1.126)
	95% CI	2.59, 4.24	1.18, 3.98
	Median	2.97	2.58
	Min, Max	0.4, 8.3	1.1, 4.2

[1] BMI calculated as weight (kg)/[height(m)]^2.
[2] BMI Z-score is calculated only for patients <18 years old.

Table 41: Proportion of BBS Patients ≥12 Years of Age who Achieved ≥10% Reduction in Body Weight from Baseline After ~52 Weeks – Studies RM-493-023 and RM-493-014

Study	Statistic [1]	Total
RM-493-023 Pivotal Patients ≥12 Years of Age	Estimated %	35.7
	(95% CI)	(18.6, 55.9)
	p-value	0.0002
RM-493-014 Patients ≥12 Years of Age	n (%)	7 (70.0)
	(95% CI)	(34.8, 93.3)
	p-value	NC

Abbreviations: BBS = Bardet-Biedl syndrome; CI = confidence interval; NC = not calculated. Note: Baseline is the last assessment prior to initiation of setmelanotide in both studies.
[1] Estimated%, 95% CI and p-value are based on Rubin's Rule; p-values are one-sided.

Table 42: Effect of Setmelanotide on Body Weight (kg) Over ~52 Weeks in Patients with BBS - Studies RM-493-023 and RM-493-014

Timepoint	Statistic	RM-493-023 Pivotal ≥12	RM-493-014 All
Baseline	N	28	10
	Mean (SD)	115.93 (26.700)	128.05 (28.629)
	Median	114.53	121.85
	Min, Max	68.1, 173.8	88.5, 171.5
Week 52	N	28	10
	Mean (SD)	108.51 (27.048)	116.77 (37.051)
	Median	106.65	114.70
	Min, Max	54.3, 174.8	73.3, 181.3
Change at Week 52	N	28	10
	Mean (SD)	-7.42 (8.208)	-11.28 (13.234)
	Median	-5.23	-14.60
	Min, Max	-27.0, 7.5	-27.0, 9.8
	95% CI [1]	-10.60, -4.24	-20.75, -1.81
	p-value [1]	<0.0001	NC
% Change at Week 52	N	28	10
	Mean (SD)	-6.47 (6.970)	-10.19 (10.665)
	Median	-4.58	-12.41
	Min, Max	-20.5, 4.5	-23.5, 5.7
	95% CI [1]	-9.17, -3.77	-17.82, -2.56
	p-value [1]	<0.0001	NC

Abbreviations: BBS = Bardet-Biedl syndrome; CI = confidence interval; NC = not calculated; SD = standard deviation.
Note: Baseline is the last assessment prior to initiation of setmelanotide in both studies.
[1] Estimated%, 95% CI and p-value are based on Rubin's Rule; p-value is one-sided.

Table 43: Effect of Setmelanotide on BMI 95th Percentile Score Over ~52 Weeks in BBS Patients <18 Years of Age - Studies RM-493-023 and RM-493-014

Timepoint	Statistic	RM-493-023 <17 years	RM-493-014 <18 years
Baseline	N	22	6
	Mean (SD)	147.12 (36.011)	160.399 (28.4932)
	Median	139.84	149.308
	Min, Max	94.9, 239.8	133.15, 202.49
Week 52	N	14	6
	Mean (SD)	126.82 (37.059)	142.758 (46.0239)
	Median	120.24	123.665
	Min, Max	74.2, 216.7	103.49, 211.59
Change at Week 52	N	14	6
	Mean (SD)	-17.30 (7.674)	-17.641 (18.3850)
	Median	-19.45	-36.935, 1.653
	Min, Max	-28.7, -6.4	-22.858
	95% CI	-21.73, -12.87	-35.49, 9.10

Abbreviations: BBS = Bardet-Biedl syndrome; CI = confidence interval; Max = maximum; Min = minimum; SD = standard deviation.
Note: Baseline is the last assessment prior to initiation of setmelanotide in both studies.

Table 44: Effect of Setmelanotide on BMI Z-Score Over ~52 Weeks in BBS Patients <18 Years of Age- Studies RM-493-023 and RM-493-014

Timepoint	Statistic	RM-493-023 <17 years	RM-493-014 <18 years
Baseline	N	22	6
	Mean (SD)	4.08 (1.696)	4.35 (0.953)
	Median	3.71	4.02
	Min, Max	1.8, 9.1	3.2, 5.8
Week 52	N	14	6
	Mean (SD)	2.98 (1.545)	3.70 (1.584)
	Median	2.85	3.11
	Min, Max	0.2, 6.3	2.2, 6.1
Change at Week 52	N	14	6
	Mean (SD)	-0.75 (0.458)	-0.66 (0.689)
	Median	-0.77	-0.79
	Min, Max	-1.9, -0.2	-1.4, 0.3
	95% CI	-1.02, -0.49	-1.38, 0.07

Abbreviations: BBS = Bardet-Biedl syndrome; BMI = body mass index; CI = confidence interval; Max = maximum; Min = minimum; SD = standard deviation.
Note: Baseline is the last assessment prior to initiation of setmelanotide in both studies.

Table 45: Effect of Setmelanotide on the Daily Hunger Questionnaire Most/Worst Score Over ~52 Weeks in Patients ≥ 12 Years of Age with BBS - Studies RM- 493-023 and RM-493-014

Timepoint	Statistic	RM-493-023 Pivotal	RM-493-014
Baseline	N	18	6
	Mean (SD)	6.84 (1.758)	7.50 (1.407)
	Median	6.57	7.49
	Min, Max	4.0, 10.0	6.0, 9.1
Week 52	N	19	6
	Mean (SD)	4.70 (2.335)	3.04 (2.076)
	Median	4.29	2.63
	Min, Max	1.6, 10.0	1.0, 6.0
Change at Week 52	N	18	5
	Mean (SD)	-2.06 (2.027)	-5.35 (1.119)
	Median	-1.70	-5.14
	Min, Max	-6.7, 0.7	-6.9, -3.9
	95% CI [1]	-3.03, -1.09	-6.73, -3.96
	p-value [1]	<0.0001	NC
% Change at Week 52	N	18	5
	Mean (SD)	-29.99 (27.504)	-70.16 (17.243)
	Median	-25.38	-75.39
	Min, Max	-80.9, 11.9	-85.4, -43.5
	95% CI [1]	-43.38, -16.59	-91.57, -48.75
	p-value [1]	<0.0001	NC

Abbreviations: BBS = Bardet-Biedl syndrome; CI = confidence interval; Max = maximum; Min = minimum; NC = not calculated; SD = standard deviation.
Note: Baseline is the last assessment prior to initiation of setmelanotide in both studies.
Note: The Daily Hunger Questionnaire is not administered to patients <12 years or to patients with cognitive impairment as assessed by the Investigator.
[1] 95%CI and p-value are based on Rubin's Rule; p-value is one-sided.

AS population

Data are presented in Table 46.

Table 46 Change from Baseline to Last Visit in Body Weight, BMI, BMI Z-Scores and Hunger Scores in Patients with AS – Studies RM-493-023 and RM-493-014

Treatment / Age at Informed Consent	Weeks on Study at Last Visit [1]	Weight (kg) at ATB/ Last Visit	Weight % Change (kg)	BMI (kg/m^2) at ATB/ Last Visit	BMI Difference	BMI Z-Score at ATB/ Last Visit)	BMI Z-Score Difference	Most/Worst Hunger at BL/Last Visit	Most/Worst Hunger Difference
RM-493-023									
Set/ 10	4	76.8/76.2	-0.8	31.2/30.3	-0.9	3.25/3.1	-0.15	NA	NA
Plac/10	66(52)	72.8/69.7	-4.3	33.2/30.7	-2.5	3.15/2.66	-0.49	NA	NA
Set /10	54	59.3/54.9	-7.4	34.0/28.2	-5.8	3.57/2.51	-1.06	NA	NA
Set/ 12	64	98.7/113.6	15.1	40.8/43.6	2.8	3.89/4.12	0.23	9.7/4	-5.7
Plac /17	2(0)	NA	NA	NA	NA	NA	NA	NA	NA
Set /18	18	123/125.3	1.9	39.7/40.4	0.7	NA	NA	8/8	0
Plac /19	56(42)	91.4/93.4	2.2	36.1/36.9	0.8	NA	NA	NA	NA
Set/39	51	191.8/202.8	5.7	82.8/80.2	-2.6	NA	NA	9.1/6.5	-2.6
RM-493-014									
Set /12	71	78.6/61.9	-21.2	27.85/21.80	-6.05	2.65/1.06	-1.59	5/3	-2
Set /15	72	70.7/69.5	-1.7	31.85/30.85	-1.0	2.49/2.25	-0.24	7/1	-6
Set /16	79	91.6/89.7	-2.1	35.34/33.55	-1.79	2.89/2.64	-0.25	5/5	0
Set /21	15.4	108.1/107	-1.0	47.41/46.93	-0.48	NA	NA	8/9	1

Abbreviations: AS = Alström syndrome; ATB = active treatment baseline, defined as the last assessment before initiation of setmelanotide; BMI = body mass
index; NA = not applicable; ND = not done; Plac = placebo; Set = setmelanotide.
Notes: In this table, baseline is defined as the last assessment prior to initiation of setmelanotide; BMI Z-scores were not calculated/presented for patients ≥18 years of age; hunger was not assessed in patients <12 years of age or patients who are assessed as cognitively impaired.
[1] For patients in RM-493-023 randomized to 14 weeks of placebo before setmelanotide, weeks on setmelanotide at last visit, calculated by subtracting 14 weeks from the total weeks on study, is provided in parentheses.
[2] The patient received their last dose of setmelanotide on Day 3.
[3] The patient received their last dose of setmelanotide on Day 8.
[4] This patient's height was 52 cm at all visits except for the last visit. Based on this and the fact that the patient was 39 years old, the measurement of 159.0 cm at the last visit is likely an error; therefore, this patient's BMI at the last visit is likely also in error given that BMI is calculated based on height and weight.

Supportive study(ies)

BBS population

A total of 42 BBS patients from studies RM-493-023 and RM-493-014 enrolled in the ongoing extension study, RM-493-022. At the time of data cut-off (08 March 2021), they had received QD setmelanotide for a median of 86 weeks, 70 of which were during the index study and the remainder in the extension study.

The clinically meaningful and statistically significant (assessed only in Study RM-493-023) effects of setmelanotide on body weight, BMI, and BMI Z-scores observed in BBS patients during the index studies were sustained during the extension study.

AS population

A total of 5 AS patients from Studies RM-493-023 (3) and RM-493-014 (2) enrolled in the ongoing extension study, RM-493-022; however only the 2 patients from supportive Study RM-493-014 had any data beyond the extension study's baseline visit.

At the time of data cutoff for this submission, the AS patients in this study had received QD setmelanotide for a mean of 112.8 weeks, 66.8 of which were during the index study and the remainder (46 weeks) in the extension study.

Maintenance of the effect of setmelanotide on body weight, and BMI Z-scores was observed in these 2 AS patients, although high fluctuations in these parameters could be seen in one patient.

2.4.3. Discussion on clinical efficacy

To support this grouped application (BBS and AS indications), the clinical efficacy package consisted of the clinical trial report of a pivotal Phase 3 partially blinded study, RM-493-023, in addition to short summaries of two supportive studies, RM-493-014 (Phase 2, open-label, uncontrolled basket) and RM-493-022 (observational long-term extension). At the time of this evaluation, RM-493-014 (part of the PIP) was still ongoing and no BBS or AS patients <12 years old were included. Study RM-493-014 enrolled 28 patients who were aged <12 years at the time of enrollment; of these 28 patients, 22 completed the study and 6 withdrew.

On 22 April 2022, on the basis that additional data were required and these were considered still provisional, the MAH withdrew the variation related to AS indication.

To support the pharmacological effect of setmelanotide in the BBS population, the MAH claimed that in general the exact mechanism of how this ciliopathy is interacting with the MC4R pathway is currently unknown, but based on animal model observations and limited human data it is strongly believed that in BBS, it is the leptin receptor which loses some degree of functionality, ultimately believed to culminate in deficient α-MSH signalling further downstream. Predicated on this assumption it is therefore believed that setmelanotide can function as a replacement α-MSH analogue to take over or at least aid in this deficient signalling step.

Design and conduct of clinical studies

The pivotal efficacy trial, RM-493-023, was a blinded phase 3 study with a rather peculiar design supposedly informed by the design of RM-493-014. However, as no report or protocol for the study RM-493-014 is available**,** it is difficult to draw any informative comparison at this point in time. RM-493-023 consisted of three distinct study phases following a 1-to-3-week screening. The first phase consisted of a 14-week double-blind randomized placebo-controlled period, followed by a 38-week open label treatment, which was in turn followed by a further 14-Week open-label phase. The choice of a 14 Week placebo period versus a full 52 Week placebo design was discussed at the time of the CHMP Scientific Advice and also during this procedure. Overall, the CHMP still considered that the 52 week design would have been more appropriate. Nevertheless, the rationale for limiting to 14-week placebo design (retention issues of placebo patients, even with techniques such as rescue-medication-and-counting-as-non-responder) is acknowledged. Furthermore, whereas the most valuable efficacy data would in principle be collected during the 14-week double-blind period, as this would be the most unbiased

comparison between treatment and placebo, the CHMP noted that the MAH chose to deviate from the CHMP Scientific Advice and maintained the week 14 analysis as a non-key secondary endpoint, in particular because this period was considered too short to show the true potential impact on weight outcomes. This further supported the CHMP earlier view on a longer placebo design.

The choice of dosing levels in the various age groups was not well understood. No dose finding trials were undertaken and the dosing in the pivotal trial was based on observations from studies RM-493-014 and RM-493-011. No clinical study reports are yet available for these studies, but a clarification on how these studies informed the dosing choices for the pivotal trial was submitted and considered acceptable by the CHMP. Doses ranging from 0.12 to 9.12 mg total daily dose have been used in previous setmelanotide clinical studies, in both healthy volunteers and in various patient populations, including patients with BBS. Dose titration in clinical study RM-493-011 resulted in minimal initial weight loss at doses of 0.25 to 0.5 mg QD, yet produced meaningful and progressive weight loss with QD doses of 1.0 mg and above. In addition, there was no evidence of increased sensitivity or any new safety issues arising in patients treated with doses of 1.0 mg and above. In Study RM-493-014, the setmelanotide dose was individualized, starting at 0.5 or 1.0 mg QD and was escalated by 0.5 mg every 2 weeks up to a maximum dose of 3.0 mg. The tolerability profile of setmelanotide from this study and additional data from other studies supported a simplified dosing regimen and higher starting dose. Study RM-493-014 did not include any BBS or AS patients aged <12yo, therefore dosing experiences in other indications and safety precautions were used to guide the dosing schedule in this young group. This was considered acceptable by the CHMP.

During the first phase patients randomized to active setmelanotide treatment were up-titrated to the final 3 mg QD dose level, and when the double-blind period was finished both phase 1 placebo patients as well as setmelanotide patients would be (re)titrated from the base level to the final 3 mg QD level. This was supposedly done in order to not break the phase 1 blind while the trial was ongoing. However, whether this approach would have really succeeded in this goal was questioned as presumably prior placebo patients would likely quickly notice a difference in their appetite compared to the previous phase (assuming the treatment works and there was no appreciable placebo effect) while prior setmelanotide randomized patients could potentially notice an increase in their appetite while they were re-titrated. However, based on the results presented there is no immediate indication that aberrant unblinding happened or influenced results.

The trial aimed to enrol 30 patients (with at least 20 BBS and 6 AS subjects), and the first 30 to enrol would form the pivotal cohort on which all confirmative analyses would be done. Any other patients enrolling after these 30 would form a supplemental cohort and could transition to the RM-493-022 extension study prior to the Week 66 endpoint of the pivotal trial. Hence any data from these supplemental patients can only be considered explorative at best. The CHMP further noted that the supplemental patients could end participation in the pivotal trial prior to finishing the 38 week open-label period (Period 2) and considered that it severely weakens the supportive data provided by these patients outside of the initial 14-week DB period.

Analysis of the primary (PE) and key secondary endpoints (KSE) would occur when the last pivotal patient had finished his/her Week 52 visit. Analysis of the PE and KSE would make use of the active treatment baseline (ATB), and the timing of this ATB differed between phase 1 placebo and setmelanotide treated patients as it coincided with the first dose of active treatment. This could lead to the issue that some of the initially placebo-treated patients would not have 52 weeks of treatment data available at time of analysis, and hence their data would be imputed. Here a major concern over the study design becomes apparent, as BBS and AS are very to ultra-rare conditions, limiting the amount of patients available. Mixing two patient groups together already implies an inherent level of

heterogeneity, and then having different analysis baselines and imputation methods additionally factored in this uncertainty and heterogeneity.

Primary and key secondary endpoints as used in RM-493-023 study resemble to the endpoints used for the POMC/LEPR deficiency studies. However there are some differences, hunger was only analysed in not cognitively impaired patients and an historical comparator was used for the proportional endpoints and based on data from the CRIBBS registry. Additionally, data from the CRIBBS was also used in the sample size calculations. The CHMP noted that the CRIBBS registry was specifically aimed at BBS patients and hence questioned to which extent these data could be used for calculations of a mixed BBS/AS patient group. Nevertheless, with the withdrawal of the variation related to AS, this design issue was not further discussed.

All PE, KSE and SE analyses were to be done in mixed condition pivotal patients ≥12yo, with results per age-group (<12yo, 12yo≤ & <17yo, and ≥18yo), condition (AS or BBS) and functional cognitive level (impaired versus non-impaired) to be analysed in subanalyses. In order to minimise Type I error risks the KSE were evaluated in a hierarchical fashion. However the CHMP noted the choice of the MAH to select weight to be the most pertinent endpoint as opposed to the CHMP Scientific Advice recommendation to include the hunger endpoint first in the hierarchical order. This was explained by the importance of the effect on weight, i.e. a failure on weight therein would have led to the validity of the trial being questioned even if positive effects on hunger outcomes were achieved.

Efficacy data and additional analyses

Overall compliance with study drug, defined as the number of doses administered as recorded in an electronic diary divided by the duration of treatment × 100, was sufficiently similar between placebo and setmelanotide groups in the pivotal FAS ≥12yo cohort during the 14 week placebo controlled period (89.50%, [79.93, 99.08] 95% CI versus 94,53%, [91.57, 97.48] 95%CI).

Primary endpoint, Key secondary endpoints- primary analysis

Overall, in the pivotal ≥12yo FAS, being the key analysis population, all PE and KSE were met. The study reached the primary endpoint as 32.3% of pivotal patients ≥12 years of age who achieved a ≥10% reduction in body weight from the ATB was statistically significant (p = 0.0006) compared to a historical control rate of 10%. This outcome was confirmed in sensitivity testing using a per protocol analysis, a completers analysis, a non-replacement analysis, and a post hoc reanalysis of the data using the placebo-controlled period baseline (PCPB) for all patients (as opposed to the ATB).The mean percent change from the ATB in body weight in pivotal patients ≥12 years of age after ~52 weeks of treatment resulted in a significantly greater reduction in both the mean percent change and the mean change from the ATB in body weight as compared to a reference value of 0% reduction from ATB. A sensitivity analysis was also conducted using the designated use set as well as a non-replacement analysis, a completers analysis, and a post hoc reanalysis of the data using the PCPB. All of these confirmed the significant result outcome of the first KSE. The hierarchically second key secondary efficacy endpoint is the mean percent change from the ATB in the weekly average of the daily hunger score in pivotal patients ≥12 years of age who were not cognitively impaired after ~52 weeks of treatment, which was represented by the change in "Most/Worst Hunger over 24 Hours". This endpoint was met, and analyses using different hunger contexts confirmed the findings. Sensitivity analyses conducted using patients with at least 3 of 7 days of weekly data and the BBS subgroup in the designated use set, as well as the results of a non-replacement analysis, a completers analysis, and a post hoc reanalysis of the data using the PCPB instead of the ATB all confirmed the second KSE outcome results.

Additional analysis

Following the CHMP major concern over the use of the active treatment baseline (ATB) and imputation techniques to adjust for the chosen design (using different ATB sampling points as described earlier), an ad-hoc sensitivity analysis was perform on the primary (PE) and key secondary endpoints (KSE), using the true Week 52 data, instead of imputed ones, of all pivotal BBS patients in order to minimize the inherent uncertainty of the data. Considering the high variability of the results seen in AS patients, the CHMP requested to exclude AS patients to further reduce heterogeneity. Without the AS patients and with true Week 52 (W52) BBS data, the results of the study RM-493-023 improved and confirmed the validity of the positive effects in the BBS-only patient cohort, that were considered of clinically relevant magnitude: Forty-three percent (43%) of these patients met the conservative primary endpoint of >10% weight loss, and mean/median losses in bodyweight versus baseline were improved to -9/-8 kg (equivalent to mean/median 7.9/6.2% change versus baseline). The CHMP concluded that the AS patients were exerting a relatively strong dampening effect on the overall primary and KSE outcomes.

Given the withdrawal of the variation related to AS patients, no further discussion in this specific patient population was necessary.

Non Key secondary endpoints – secondary analysis

Secondary analysis in the pivotal ≥12yo PCS population was also underwhelming, as the weight-based SE was missed yet the hunger-based SE was met. In contrast, the same analysis for all ≥12yo PCS subjects, including supplemental patients, both SE results were reversed (Table 14, Table 15, Table 16, Table 17, Table 18, Table 19 and Figure 8). These mixed results may be due to the overall design of the trial using a 14 week placebo period instead of 52 weeks. Nevertheless all the pivotal BBS patients reached the primary and key secondary endpoints, indicating that the effects seen at W14 were not predictive or representative of the efficacy potential of the treatment.

Subgroup analyses

Subgroup analysis by age group was most pertinent for the 6-<12yo patients, given their very limited numbers. Overall, changes in BMI-Z scores versus active treatment baseline were clinically relevant for all patients, including the supplemental and thus exploratory subjects, some of which were only treated for a limited time. The placebo-controlled period outcomes comparison did also indicate a significantly beneficial effect of setmelanotide on the BMI-Z scores.

Subgroup analysis by condition showed that the clinical outcomes in the pivotal ≥12yo BBS patients appeared to mirror or even outperform the pivotal ≥12yo FAS. In contrast, the outcomes in the AS population ≥12yo (n=5, 4 pivotal and 1 supplemental patient) were negative, with all subjects gaining weight or increasing their BMI-Z score despite treatment and this for both pivotal and supplemental patients. All three <12yo AS patients (n=3, 2 pivotal and 1 supplemental) achieved clinically meaningful reductions in BMI-Z scores. Nonetheless, given the extremely limited numbers, the very disparate results and the fact that possible extrapolation of results from the BBS patients has not been established, it is deemed impossible to consider the treatment effective in AS patients, or a subgroup thereof, at this point in time. Hence, even though a medical need in these patients is certainly acknowledged, the inclusion of AS patients as a new indication cannot be supported at the present time. Subsequently, the variation related to AS was withdrawn and not further discussed.

Exploratory analyses

An exploratory cross-trial comparison of outcomes in the RM-493-023 and RM-493-014 trials was performed. Though only exploratory and cross-trial it seems that the outcomes for AS and BBS

patients in study RM-493-023 were generally better than in study RM-493-014. However, given the limitations inherent to this comparison no conclusions can be drawn.

RM-493-014 also provided some additional clinical data in a limited number of AS patients, however the results in these subjects were generally underwhelming and did not provide any additional reason to reconsider the disparate and inconclusive results seen in the RM-493-023 pivotal trial in the AS population.

In the ongoing study RM-493-022, 42 BBS patients had transitioned from trials RM-493-023 and -014 with a median of 86 weeks QD setmelanotide treatment at the time of the database lock. Overall, the trends seen indicate that the weight loss achieved in the index studies was maintained during the extension follow-up. No trend on hunger outcomes were submitted. Only a total of 5 AS patients from the aforementioned studies had transitioned at DB lock time, and only 2 of those (both from study RM-493-014) had data beyond the RM-493-022 baseline visit. Both continued to show a clinically meaningful reduction of BMI-Z scores. This result however is not considered to address the major concern noted with the results of the AS patients in the pivotal trial. Subsequently, the variation related to AS was withdrawn and not further discussed.

Assessment of the paediatric data on clinical efficacy

Regarding BBS/AS patients aged ≥6yo and <12yo, only 11 subjects of this age category were part of the FAS used for the primary, key secondary and secondary analyses as well as the sub-group analyses. Of these 11 subjects only 5 were pivotal cohort patients (3 BBS and 2 AS patients) and of these, one AS subject discontinued after 4 weeks on setmelanotide in the PCP. Hence clinical experience in this age group is extremely limited. Narratives of a total of 6 supplemental patients in this age category provided further supportive data, with the majority achieving meaningful BMI-Z and hunger score reductions. Based on the totality of evidence available there does not seem to be any indication that efficacy or safety in this group (6-11 years) differs essentially from the other age groups and hence treatment in these young patients with setmelanotide in the BBS population can be considered supported. The overall weak results seen in AS patients was not further discussed following the withdrawal of the related variation. See further discussion on safety under 2.5.1.

2.4.4. Conclusions on the clinical efficacy

In general, positive results are seen in BBS patients, with the clinical relevance further confirmed by way of an ad-hoc BBS-only analysis using the true W52 data, but the clinical outcomes in AS patients were extremely disparate. Subsequently, the MAH decided to withdraw the variation related to the AS indication in the present grouping of variations. The clinical outcomes in 6 to <12yo BBS patients are generally positive and further supported by the clinical outcomes in the equivalent supplemental group.

2.5. Clinical safety

Introduction

Setmelanotide is already authorised for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above. In the currently approved indication, the most frequent adverse reactions were hyperpigmentation (51%), injection site reaction (39%), nausea (33%), and headache (26%).

The safety profile based on the limited data seemed to be reassuring, but caution was warranted due to experience from other centrally acting anti-obesity products and important potential risks of melanoma, prolonged penile erections and depression/suicidal thoughts were to be further monitored long-term in the proposed PASS. Since approval, there has only been very limited post-marketing exposure.

The clinical safety dataset for BBS and AS patients (safety data lock point: 8 March 2021) is based on the following studies:

- the **pivotal** Phase 3 study **RM-493-023** with 44 BBS and 8 AS patients and only 50 out of 52 exposed to setmelanotide

- the ongoing supportive study, an open-label Phase 2 study **RM-493-014** (which also included patients with other RGDOs) with 10 BBS and 4 AS patients

- and the other ongoing supportive study, RM-**493-022** (42 BBS and 5 AS), an open-label study including patients after completing their index studies RM-493-023 and -014.

Overall, 64 patients in the BBS/AS population were included in the setmelanotide clinical program. During the procedure, the variation related to AS indication was withdrawn by the applicant. Assessing safety was an exploratory objective for the pivotal study RM-493-023, a secondary objective for study RM-493-014 and a primary objective for study RM-493-022.

No interim study reports have been provided for the ongoing studies, only a specific document with tables, listings and figures. For study RM-493-022, a Summary of Clinical Safety (SCS) has been submitted. For study RM-493-014, data have just been included in the tables on combined BBS/AS population.

During the procedure, the variation related to AS has been withdrawn, however since the safety analyses have been performed for the combined BBS/AS populations, the combined data (with only 11 AS patients who have been treated with setmelanotide in total) will be further discussed below in the context of the BBS indication, remaining variation applied for.

Patient exposure

Data are presented in Table 47.

Table 47 Overall Extent of Exposure in the Setmelanotide Clinical Development Program

Parameter / Statistic	Setmelanotide-Treated Patients					Placebo (N=112)
	All (N=561)	RGDO (N=308)	BBS or AS (N=64)	BBS (N=53)	AS (N=11)	
Time on Treatment (days)						
n	561	308	64	53	11	112
Mean	183.8	304.0	495.3	507.6	435.9	67.4
SD	312.67	380.87	366.39	361.17	403.41	32.79
Median	66.0	133.0	463.0	481.0	365.0	84.0
Min, Max	1, 2249	1, 2249	8, 1450	8, 1450	8, 1289	2, 105
Duration of Exposure, n (%)						
<1 month	220 (39.2)	68 (22.1)	3 (4.7)	2 (3.8)	1 (9.1)	29 (25.9)
1 to <3 months	143 (25.5)	58 (18.8)	3 (4.7)	2 (3.8)	1 (9.1)	55 (49.1)
3 to <6 months	66 (11.8)	50 (16.2)	9 (14.1)	8 (15.1)	1 (9.1)	28 (25.0)
6 to <12 months	38 (6.8)	38 (12.3)	10 (15.6)	7 (13.2)	3 (27.3)	0
12 to <18 months	34 (6.1)	34 (11.0)	18 (28.1)	15 (28.3)	3 (27.3)	0
≥18 months	60 (10.7)	60 (19.5)	21 (32.8)	19 (35.8)	2 (18.2)	0

AS = Alström syndrome; BBS = Bardet-Biedl syndrome; Max = maximum; Min = minimum; RGDO = rare genetic disorders of obesity; SD = standard deviation.

Source: ISS Table 3.1, ISS Table 3.2, ISS Table 3.3, ISS Table 3.4, ISS Table 3.5, and Adhoc Table 3.

Of the 561 exposed subjects in all studies, 132 have been treated for at least 6 months, 94 have been treated for at least 1 year and 60 for at least 18 months. Of the BBS/AS population, 49 patients have been treated for at least 6 months, 39 have been treated for at least 1 year and 21 for at least 18 months which is a larger sample size than for POMC/LEPR deficiency patients used to support the initial approval. The BBS patients in the long-term extension study RM-493-022 had received setmelanotide for a median of 86 weeks (70 during the index study and 16 weeks in the extension study) while the AS patients had received setmelanotide for a mean of 112.8 weeks (66.8 during the index study and 46 weeks in the extension study).

Adverse events

All BBS and AS patients (100%) in the setmelanotide group reported at least 1 TEAE (n=64) while 92.3% of placebo-patients reported at least 1 TEAE (n=26).

Data on for the pivotal study RM-493-023 are presented in Table 48 and Table 49.

Table 48 Overview of Treatment-emergent Adverse Events Overall by Treatment Group (SAS Population; N = 52)

Patients with at least 1:	Double-Blind Placebo-Controlled Period			Full Study		
	Setmelanotide (N = 27) n (%)	Placebo (N = 25) n (%)	Total (N = 52) n (%)	Setmelanotide → Setmelanotide (N = 27) n (%)	Placebo → Setmelanotide (N = 25) n (%)	Total (N = 52) n (%)
TEAE	26 (96.3)	24 (96.0)	50 (96.2)	27 (100.0)	25 (100.0)	52 (100.0)
Treatment-Emergent Related Adverse Event[1]	24 (88.9)	22 (88.0)	46 (88.5)	27 (100.0)	24 (96.0)	51 (98.1)
Serious TEAE	1 (3.7)	2 (8.0)	3 (5.8)	1 (3.7)	2 (8.0)	3 (5.8)
Serious Related TEAE	0	1 (4.0)	1 (1.9)	0	1 (4.0)	1 (1.9)
TEAE Leading to Death	0	0	0	0	0	0
TEAE Leading to Study Drug Withdrawal[2]	2 (7.4)	3 (12.0)	5 (9.6)	2 (7.4)	4 (16.0)	6 (11.5)
Related TEAE Leading to Study Drug Withdrawal	–	–	–	2 (7.4)	3 (12.0)	5 (9.6)
Severe TEAE	–	–	–	1 (3.7)	2 (8.0)	3 (5.8)

Abbreviations: SAS = Safety Analysis Set; TEAE = treatment-emergent adverse event.
Note: Full Study includes data from the double-blind, placebo-controlled period.
[1] Related indicates the adverse event was noted as possibly or probably related to the study drug.
[2] Study drug permanently withdrawn.
Source: Table 14.3.1.1.1, Table 14.3.1.1.2, Table 14.3.1.5.5 ad hoc, and Listing 16.2.7.6

Table 49 Treatment-Emergent Adverse Events Occurring in >2 Patients with BBS or AS who Received Setmelanotide during the 14-week Placebo-controlled Period in Study RM-493-023, by MedDRA Preferred Term

System Organ Class/ Preferred Term	Setmelanotide (N = 27) n (%)	Placebo (N = 25) n (%)
Skin hyperpigmentation	17 (63.0)	0
Injection site erythema	12 (44.4)	11 (44.0)
Injection site pruritus	8 (29.6)	9 (36.0)
Nausea	7 (25.9)	6 (24.0)
Vomiting	7 (25.9)	0
Injection site bruising	6 (22.2)	9 (36.0)
Injection site induration	6 (22.2)	4 (16.0)
High density lipoprotein decreased	4 (14.8)	0
Injection site pain	3 (11.1)	8 (32.0)
Injection site haemorrhage	3 (11.1)	2 (8.0)
Nasal congestion	3 (11.1)	0
Injection site oedema	2 (7.4)	1 (4.0)
Diarrhoea	2 (7.4)	1 (4.0)
Nasopharyngitis	2 (7.4)	1 (4.0)

Abbreviations: AS = Alström syndrome; BBS = Bardet-Biedl syndrome; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Source: Table 53 RM-493-023 CSR.

Overall, the most common TEAEs among BBS and AS setmelanotide-treated patients, with the corresponding incidence among placebo-treated patients, were: skin hyperpigmentation: 70% (45/64) versus 0%; Injection site erythema: 38% (24/64) versus 39% (10/26); Injection site pruritus: 36% (23/64) versus 31% (8/26); Nausea: 33% (21/64) versus 15% (4/26) and Vomiting: 28% (18/64) versus 0%.

The most common type of TEAE was skin and subcutaneous tissue disorders, most commonly skin hyperpigmentation. Other common types of TEAEs were general disorders and administration site conditions, primarily local reactions at the injection site (i.e., erythema, pruritus, induration, bruising, pain, and oedema) and gastrointestinal disorders, most commonly nausea and vomiting.

In study RM-493-023 (full period), a total of 51 (98.1%) patients experienced at least 1 TEAE in the full study that was considered by the Investigator to be study drug-related. As was the case for TEAEs overall, the most common study drug-related TEAEs were reactions at the injection site, including injection site erythema (25 patients; 48.1%), injection site pruritus (18 patients; 34.6%), injection site bruising (17 patients; 32.7%), injection site pain (14 patients; 26.9%), and injection site induration (13 patients; 25.0%), as well as skin hyperpigmentation (33 patients; 63.5%), nausea (13 patients; 25.0%), and vomiting (8 patients; 15.4%). During the placebo controlled period, the most common type of TEAEs were skin hyperpigmentation, injection site reactions, and nausea and vomiting. Nasal congestion (3 patients) and high-density lipoprotein increased (4 patients) also occurred in ≥2 patients who received setmelanotide during the double-blind treatment period. A total of 51 (98.1%) patients experienced at least 1 TEAE in the full study that was considered by the Investigator to be study drug-related. As was the case for TEAEs overall, the most common study drug-related TEAEs were reactions at the injection site, including injection site erythema (25 patients; 48.1%), injection site pruritus (18 patients; 34.6%), injection site bruising (17 patients; 32.7%), injection site pain (14 patients; 26.9%), and injection site induration (13 patients; 25.0%), as well as skin hyperpigmentation (33 patients; 63.5%), nausea (13 patients; 25.0%), and vomiting (8 patients; 15.4%).

Serious adverse event/deaths/other significant events

No death was reported in patients with BBS or AS.

Serious adverse events (SAE) are presented in Table 50.

Table 50 Serious Adverse Events in Patients with BBS or AS through 08 March 2021, by MedDRA System Organ Class and Preferred Term

System Organ Class/ Preferred Term	Setmelanotide (N=64) n (%)	Placebo (N=26) n (%)
Patients with at least 1 SAE	7 (10.9)	2 (7.7)
Gastrointestinal disorders	**2 (3.1)**	**0**
Abdominal pain	1 (1.6)	0
Pancreatitis	1 (1.6)	0
Infections and infestations	**2 (3.1)**	**0**
COVID-19 pneumonia	1 (1.6)	0
Rotavirus infection	1 (1.6)	0
Psychiatric disorders	**2 (3.1)**	**0**
Suicidal ideation	1 (1.6)	0
Hallucination, auditory	1 (1.6)	0

System Organ Class/ Preferred Term	Setmelanotide (N=64) n (%)	Placebo (N=26) n (%)
Blood and lymphatic system disorders	**1 (1.6)**	**0**
Anaemia	1 (1.6)	0
Eye disorders	**0**	**1 (3.8)**
Blindness	0	1 (3.8)
Immune system disorders	**0**	**1 (3.8)**
Anaphylactic reaction	0	1 (3.8)
Metabolism and nutritional disorders	**1 (1.6)**	**0**
Diabetic ketoacidosis	1 (1.6)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1.6)**	**0**
Renal neoplasm	1 (1.6)	0

Source: Module 2.7.4 Table 6.5.1

In study RM-493-023 (full period), 3 (5.8%) patients experienced a total of 5 SAEs. After the double-blind treatment period, 1 patient (who experienced complete vision loss [blindness] during the double-blind period) had 2 events of suicidal ideation (verbalized suicidal thought). The patient had no previous history of depression, and the events were judged by the Investigator to be unlikely related to study medication and attributable to concomitant disease. During the double-blind study period, 3 (5.8%) patients experienced SAEs, 2 of whom were receiving placebo. One SAE was considered by the Investigator to be related to study drug (anaphylactic reaction in a placebo patient). One SAE (anaemia) was reported in a patient receiving setmelanotide as being due to gynaecological bleeding and was judged by the Investigator to be most likely due to initiation of oral contraceptives. No SAEs were reported in >1 patient.

In all BBS and AS patients, most TEAEs were mild or moderate in intensity. Severe TEAEs were reported in 7 (11%) setmelanotide-treated patients with BBS or AS. Severe TEAEs in this patient population included anaemia (2 subjects; 3%), abdominal pain, pancreatitis, urinary tract infection, COVID-19, COVID-19 pneumonia, rotavirus infection, hypoxia, diabetes mellitus, diabetic ketoacidosis, hypertriglyceridemia, renal neoplasm, auditory hallucination, suicidal ideation, and blood phosphorus decreased (each 1 subject; 2%). Both severe cases of anaemia resolved and were considered by the investigator as not related to setmelanotide.

Events of special interest (ESIs)

ESIs were defined as those either related to TEAEs commonly occurring during treatment with setmelanotide (hyperpigmentation disorders, disturbances in sexual arousal, nausea, vomiting, and injection site reactions) or potential MC4 pathway mechanistic-related events such as hypertension, or other events associated with background disease such as depression and suicidal ideation. TEAE verbatim and preferred terms were reviewed by Sponsor medical personnel to identify those TEAEs that represented ESIs in each category.

Hyperpigmentation Disorders

Data are presented in Table 51.

Table 51 Summary of Hyperpigmentation Disorders Occurring in >1% of Setmelanotide-treated Patients Overall, by Patient Population

ESI Category / MedDRA Preferred Term	Setmelanotide-Treated Patients, n (%)				
	All (N=561)	RGDO (N=308)	BBS and AS (N=64)	BBS (N=53)	AS (N=11)
Hyperpigmentation disorders	**322 (57.4)**	**210 (68.2)**	**48 (75.0)**	**38 (71.7)**	**10 (90.9)**
Skin hyperpigmentation	277 (49.4)	191 (62.0)	45 (70.3)	35 (66.0)	10 (90.9)
Melanocytic naevus	52 (9.3)	45 (14.6)	8 (12.5)	8 (15.1)	0
Skin discolouration	35 (6.2)	7 (2.3)	1 (1.6)	1 (1.9)	0

AS = Alström syndrome; BBS = Bardet-Biedl syndrome; ESI = event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; RGDO = rare genetic disorders of obesity.
Source: ISS Table 13.1, ISS Table 13.2, ISS Table 13.3, ISS Table 13.4, and ISS Table 13.5.

In the BBS/AS population, 70% (45/64) and 0% (0/26) of setmelanotide- and placebo-treated patients, respectively, experienced at least 1 TEAE representative of a skin hyperpigmentation and 1 patient discontinued due to skin hyperpigmentation.

In study RM-493-023, TEAEs of skin hyperpigmentation occurred in 63.0% of patients in the setmelanotide treatment group and 0% of patients in the placebo group during the double-blind placebo-controlled period.

Sexual Events

Data are presented in Table 52.

Table 52 Summary of Disturbances in Sexual Arousal Occurring in >1% of Setmelanotide-treated Patients Overall, by Patient Population

ESI Category / MedDRA Preferred Term	Setmelanotide-Treated Patients, n (%)				
	All (N=561)	RGDO (N=308)	BBS and AS (N=64)	BBS (N=53)	AS (N=11)
Disturbances in sexual arousal	**86 (15.3)**	**40 (13.0)**	**8 (12.5)**	**8 (15.1)**	**0**
Spontaneous penile erection	44 (7.8)	18 (5.8)	8 (12.5)	8 (15.1)	0
Erection increased	17 (3.0)	10 (3.2)	0	0	0
Disturbance in sexual arousal	11 (2.0)	1 (0.3)	1 (1.6)	1 (1.9)	0
Libido increased	6 (1.1)	6 (1.9)	1 (1.6)	1 (1.9)	0

AS = Alström syndrome; BBS = Bardet-Biedl syndrome; ESI = event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; RGDO = rare genetic disorders of obesity.
Source: ISS Table 13.1, ISS Table 13.2, ISS Table 13.3, ISS Table 13.4, and ISS Table 13.5.

In the BBS/AS population, 13% (8/64) experienced at least 1 TEAE representative of a sexual event. In study RM-493-023, no females experienced sexual events of interest during the double-blind study period. Four male patients experienced sexual events of interest during the study. Changes included change in frequency of erections (N = 3) and change in sex drive, change in ability to achieve erection, and groin discomfort (N = 1 each). There were no occurrences of prolonged or painful erections that required intervention.

Hypertension

In study RM-493-023, there were no TEAEs of hypertension or blood pressure increased that started while a patient was on setmelanotide, except for 2 patients.

One patient had a history of hypertension. Exacerbation of hypertension was reported as a mild TEAE. The patient completed the study. For the other patient, although not in the medical history, hypertension was diagnosed on Day -7 of screening, no treatment was initiated, and the event was reported as resolved by Day 42. A TEAE of moderate hypertension was subsequently reported on Day 99, no treatment was initiated, and the event was reported as resolved by Day 156.

Depression/suicidal ideation

Data are presented in Table 53.

Table 53 Summary of Depression Events Occurring in Setmelanotide-treated Patients Overall, by Patient Population

ESI Category / MedDRA Preferred Term	Setmelanotide-Treated Patients, n (%)				
	All (N=561)	RGDO (N=308)	BBS and AS (N=64)	BBS (N=53)	AS (N=11)
Depression	**22 (3.9)**	**18 (5.8)**	**2 (3.1)**	**2 (3.8)**	**0**
Depression	15 (2.7)	11 (3.6)	1 (1.6)	1 (1.9)	0
Depressed mood	9 (1.6)	9 (2.9)	1 (1.6)	1 (1.9)	0

AS = Alström syndrome; BBS = Bardet-Biedl syndrome; ESI = event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; RGDO = rare genetic disorders of obesity.
Source: ISS Table 13.1, ISS Table 13.2, ISS Table 13.3, ISS Table 13.4, and ISS Table 13.5.

In the BBS/AS population, 3% (2/64) experienced at least 1 TEAE representative of a depression. There was 1 patient with suicidal ideation, however no apparent drug-related increase in suicidality or depression as measured by the C-SSRS and the PHQ-9 were reported.

Nausea and vomiting

Data are presented in Table 54.

Table 54 Summary of Nausea and Vomiting Events Among Setmelanotide-treated Patients, by Patient Population

MedDRA Preferred Term	Setmelanotide-Treated Patients, n (%)				
	All (N=561)	RGDO (N=308)	BBS and AS (N=64)	BBS (N=53)	AS (N=11)
Nausea	198 (35.3)	105 (34.1)	21 (32.8)	17 (32.1)	4 (36.4)
Vomiting	86 (15.3)	49 (15.9)	18 (28.1)	17 (32.1)	1 (9.1)

AS = Alström syndrome; BBS = Bardet-Biedl syndrome; MedDRA = Medical Dictionary for Regulatory Activities; RGDO = rare genetic disorders of obesity.
Source: ISS Table 13.1, ISS Table 13.2, ISS Table 13.3, ISS Table 13.4, and ISS Table 13.5.

In study RM-493-023, the majority of patients who experienced events of nausea or vomiting, experienced mild events and no event of nausea or vomiting was severe. Review of the time of onset of nausea and vomiting events among setmelanotide-treated patients with BBS or AS in Study RM-493-023 showed that during the randomized controlled period, the onset was most common in the first month of setmelanotide treatment and was much less common over the subsequent months of

treatment. A similar pattern was observed in patients who were randomized to placebo but switched to setmelanotide during the open-label period.

Injection Site Reactions (ISRs)

Data are presented in Table 55.

Table 55 Summary of Injection Site Reactions Occurring in >1% of Setmelanotide-treated Patients Overall, by Patient Population

ESI Category / MedDRA Preferred Term	Setmelanotide-Treated Patients, n (%)				
	All (N=561)	RGDO (N=308)	BBS and AS (N=64)	BBS (N=53)	AS (N=11)
Injection site reactions	**260 (46.3)**	**204 (66.2)**	**41 (64.1)**	**34 (64.2)**	**7 (63.6)**
Injection site erythema	161 (28.7)	132 (42.9)	24 (37.5)	21 (39.6)	3 (27.3)
Injection site pruritus	120 (21.4)	101 (32.8)	23 (35.9)	19 (35.8)	4 (36.4)
Injection site induration	73 (13.0)	69 (22.4)	17 (26.6)	15 (28.3)	2 (18.2)
Injection site pain	71 (12.7)	58 (18.8)	12 (18.8)	11 (20.8)	1 (9.1)
Injection site bruising	64 (11.4)	62 (20.1)	13 (20.3)	13 (24.5)	0
Injection site oedema	53 (9.4)	51 (16.6)	12 (18.8)	12 (22.6)	0
Injection site reaction	22 (3.9)	22 (7.1)	1 (1.6)	0	1 (9.1)
Injection site swelling	13 (2.3)	9 (2.9)	2 (3.1)	2 (3.8)	0
Injection site haemorrhage	11 (2.0)	10 (3.2)	5 (7.8)	5 (9.4)	0
Injection site haematoma	11 (2.0)	10 (3.2)	1 (1.6)	1 (1.9)	0
Injection site discolouration	9 (1.6)	8 (2.6)	0	0	0

AS = Alström syndrome; BBS = Bardet-Biedl syndrome; ESI = event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; RGDO = rare genetic disorders of obesity.
Source: ISS Table 13.1, ISS Table 13.2, ISS Table 13.3, ISS Table 13.4, and ISS Table 13.5.

In the BBS/AS population, 64.1% (41/64) and 76.9% (20/26) of setmelanotide- and placebo-treated patients, respectively, experienced at least 1 TEAE representative of an ISR.

In study RM-493-023 (double-blind period), placebo-controlled treatment period, events occurred at similar incidence in patients who received setmelanotide as in those who received placebo, indicating that injection site reactions are not due to setmelanotide, but are related to the injection and/or excipients.-

Laboratory findings

In patients with BBS or AS, there were no clinically significant changes from baseline and no discernable pattern of shift from baseline to abnormal in hematology and clinical chemistry parameters. In Study RM-493-023, for hematologic and clinical chemistry parameters, there were no clinically significant findings, beyond results reported as TEAEs, no clinically significant changes from baseline and no clinically significant shifts from baseline. Also in urinalysis and in coagulation parameters, no significant abnormalities or changes from baseline were seen.

Vital signs, physical findings and other safety observations

In Study RM 493-023, there was no apparent effect of setmelanotide on BP, HR, or other vital signs in patients with BBS or AS. One patient, randomized to setmelanotide, had a clinically significantly abnormal ECG finding at Week 15 (Visit 6), which was reported as a moderate TEAE of bradycardia and the event was considered by the Investigator as related to study drug.

Immunological events

In study RM-493-023, a total of 169 samples from 48 patients were tested for ADAs. Of these, 1 sample from 1 paediatric BBS patient was confirmed positive for ADA with a very low titer. Importantly, this patient achieved clinically meaningful reductions in body weight and BMI Z-scores during treatment with setmelanotide and did not experience any SAEs or any moderate or severe treatment related TEAEs. Samples from an additional 5 patients were flagged for re-analysis with the results to be reported in amendment to the Bioanalytical Report. Based on the results at this time, it is concluded that there was 1 patient with confirmed antiRM-493 antibodies with a low titer; there was no impact of ADA on safety or efficacy in this patient.

Safety in special populations

No elderly patients were included in the pivotal or supportive RM-493-023, RM-493-014 and RMP-493-022 studies.

Of the BBS patients 6-<12 years old, 2 were treated with setmelanotide for 3-6 months, 3 for 6-12 months, 1 for 12-18 months and 2 for more than 18 months so only 3 of these patients were treated for more than 1 year. Of the AS patients 6-<12 years old, 1 was treated with setmelanotide for less than 1 month and 2 for 6-12 months so none of these patients were treated for more than 1 year.

There were 5 pivotal paediatric patients (aged 6-<12 years) with BBS or AS, included in Study RM-493-023, and 6 supplemental paediatric patients (aged 6-<12 years) with BBS or AS. No unexpected safety issues were identified for these paediatric BBS/AS patients. For the 20 pivotal paediatric patients (aged 6 -<18 years) in study RM-493-023 (16 BBS/4 AS), 4 discontinued early: 2 due to AEs (1 BBS/1 AS), 1 due to the dislike of the injections (AS) and 1 was lost to follow-up i.e., a 12-year old BBS patient who was withdrawn early by his parents due to previously recorded headache, leg pain and belligerent behaviour.

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

Data are presented in Table 56.

Table 56 Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by MedDRA System Organ Class and Preferred Term – All BBS and AS Patients (Safety Population)

System Organ Class/ Preferred Term	Statistic	Setmelanotide (N=64)	Placebo (N=26)	Total (N=66)
Number of Subjects With at Least 1 TEAE Leading to Study Drug Discontinuation	n (%)	6 (9.4)	1 (3.8)	7 (10.6)
Gastrointestinal disorders	n (%)	3 (4.7)	0	3 (4.5)
Nausea	n (%)	3 (4.7)	0	3 (4.5)
Vomiting	n (%)	3 (4.7)	0	3 (4.5)
Abdominal pain	n (%)	1 (1.6)	0	1 (1.5)
Skin and subcutaneous tissue disorders	n (%)	2 (3.1)	0	2 (3.0)
Acne	n (%)	1 (1.6)	0	1 (1.5)
Hidradenitis	n (%)	1 (1.6)	0	1 (1.5)
Skin hyperpigmentation	n (%)	1 (1.6)	0	1 (1.5)
Eye disorders	n (%)	1 (1.6)	0	1 (1.5)
Ocular hyperaemia	n (%)	1 (1.6)	0	1 (1.5)
General disorders and administration site conditions	n (%)	1 (1.6)	0	1 (1.5)
Face oedema	n (%)	1 (1.6)	0	1 (1.5)
Immune system disorders	n (%)	0	1 (3.8)	1 (1.5)
Anaphylactic reaction	n (%)	0	1 (3.8)	1 (1.5)
Nervous system disorders	n (%)	1 (1.6)	0	1 (1.5)
Headache	n (%)	1 (1.6)	0	1 (1.5)
Psychiatric disorders	n (%)	1 (1.6)	0	1 (1.5)
Hallucination, auditory	n (%)	1 (1.6)	0	1 (1.5)
Vascular disorders	n (%)	1 (1.6)	0	1 (1.5)
Hot flush	n (%)	1 (1.6)	0	1 (1.5)

TEAE = Treatment-Emergent Adverse Event; SOC = System Organ Class; PT = Preferred Term.
Note: If a subject experienced more than 1 event in a given SOC, that subject is counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT.
Note: For All BBS and AS Patients population, subjects are counted in more than one column if they switched from one treatment to another during the reporting period. The TEAE is counted in the column associated with the treatment at the initiation of the adverse event.
Source Listing(s): 7

In all BBS and AS patients, discontinuation of setmelanotide due to TEAEs occurred in 6 (9%) of 64 BBS/AS patients. Most TEAEs leading to study drug discontinuation were reported in 1 patient each (multiple events in 1 patient): abdominal pain, acne, hidradenitis, skin hyperpigmentation, ocular hyperaemia, face oedema, headache, auditory hallucination, hot flush. The only TEAEs leading to setmelanotide discontinuation in >1 patient were nausea and vomiting, which occurred in 3 (5%) patients.

In study RM-493-023, the most common reasons for stopping study drug prematurely were nausea and vomiting (each occurring in 5.8% of patients overall). During the double-blind period), a few patients prematurely stopped study drug due to a TEAE, The incidence of patients who discontinued during the double-blind period due to nausea was similar in both treatment groups (3.7% vs 4.0%) and 1 patient (3.7%) in the setmelanotide treatment group discontinued due to vomiting.

Post marketing experience

Post-marketing data are available in the United States (US). In a total of 15 patients, 29 cases were reported with 82 events of which one was serious but unrelated (staphylococcal infection). No new safety signals or potentially serious drug interactions have been identified in the post-marketing setting. The most commonly reported events are non-serious injection site reactions and non-serious skin discolorations.

2.5.1. Discussion on clinical safety

Overall, safety data from 64 BBS/AS patients treated with setmelanotide have been presented which is limited but inherent to orphan diseases, and these data were completed by an updated safety "all population" analysis using data from other setmelanotide studies in healthy volunteers with obesity, in other RGDOs, in other indications and in subjects with renal impairment, including a total, 673 patients (561 treated with setmelanotide and 112 received placebo).

Still, long-term data are limited in the setmelanotide clinical studies. Of the BBS/AS population, 49 patients have been treated for at least 6 months, 39 have been treated for at least 1 year and 21 for at least 18 months which is a larger sample size than for POMC/LEPR deficiency patients used to support the initial approval. The CHMP therefore recommended to extend the observational Registry (PASS, RM-IMC-901) in the POMC/LEPR deficiency populations to include BSS patients noting the withdrawal of the variation related to AS.

All BBS and AS patients (100%) in the setmelanotide group reported at least 1 TEAE (n=64) while 92.3% of placebo-patients reported at least 1 TEAE (n=26). The most common type of TEAE in BBS and AS patients was skin and subcutaneous tissue disorders, most commonly skin hyperpigmentation. Other common types of TEAEs were general disorders and administration site conditions, primarily local reactions at the injection site (i.e., erythema, pruritus, induration, bruising, pain, and oedema) and gastrointestinal disorders, most commonly nausea and vomiting. The frequencies of some of the most common TEAEs were much higher in the BBS and AS population than in the "all population" original and updated analyses but were lower than or similar than the ones observed in the POMC/LEPR deficiency patients original safety analysis (SCS January 2021): skin hyperpigmentation (70% vs 51%/49%/86%), injection site erythema (38% vs 24%/29%/69%), injection site pruritis (36% vs 17%/21%/49%), and vomiting (28% vs 12%/15%/29%). Four out of 27 setmelanotide-treated patients (14.8%) reported high density lipoprotein decreased in the 14-week placebo-controlled period in study RM-493-023 while none of the 25 placebo-treated patients reported this. However, these all occurred on the day of randomisation and do not raise any particular concerns at the present time.

No death was reported in patients with BBS or AS.

SAEs were reported in 7 setmelanotide-treated BBS/AS patients were not considered treatment-related, although one SAE was abdominal pain and is listed adverse drug reaction (ADR).

In all BBS and AS patients, most TEAEs were mild or moderate in intensity. Severe TEAEs were reported in 7 (11%) setmelanotide-treated patients with BBS or AS. Severe TEAEs in this patient population included anaemia (2 subjects; 3%) and abdominal pain, pancreatitis, urinary tract infection, COVID-19, COVID-19 pneumonia, rotavirus infection, hypoxia, diabetes mellitus, diabetic ketoacidosis, hypertriglyceridemia, renal neoplasm, auditory hallucination, suicidal ideation, and blood phosphorus decreased (each 1 subject; 2%). Both severe cases of anaemia resolved and were considered by the investigator as not related to setmelanotide.

During the procedure, the CHMP raised concerns over the presentation and discussion of the safety data, which were subsequently addressed by the applicant within the responses to supplementary information. Overall, the CHMP considered that the updated "all population" safety analysis and the new data for the BBS/AS population did not change the overall safety profile of setmelanotide. However information on elderly and paediatric populations have been updated in the SmPC and is further discussed below. In addition, frequencies of some existing ADRs have been updated in the SmPC and new ADRs have also been added based on these new data.

The frequencies of the hyperpigmentation disorders-related TEAEs in the BBS and AS population (75% [48/64] were higher than in the "all population" original (51% [244/476]) and updated (58% [322/561])

analyses but lower than in the POMC and LEPR deficiency population (86% [30/35]). All except one of the AS patients (91% [10/11]) reported hyperpigmentation disorders. The impact of hyperpigmentation disorders remains limited as most reports of hyperpigmentation disorders in BBS and AS patients were mild to moderate, there were no serious related hyperpigmentation disorders, and these only led to setmelanotide interruption in 2 subjects (N= 561, <1%, none in BBS/AS patients) and although it led to 17 discontinuations in the all-patients population (N= 561, 3%), this only occurred in 1 BBS/AS patient (N=64, 1.6%). No melanoma (important potential risk of setmelanotide) was reported in the BBS/AS population or in the updated "all population" analysis that was submitted in this procedure.

In BBS and AS patients, 13% (8/64) experienced at least 1 TEAE representative of a sexual event, which appeared consistent with the "all-population" original (15% [72/476] and updated (15% [86/561]) analyses and to POMC/LEPR deficiency patient population (17% [6/35]). In BBS and AS patients the most commonly reported sexual event was spontaneous penile erection (13% [8/64]). No prolonged penile erections (important potential risk of setmelanotide)–were reported.

In the BBS/AS population, 3% (2/64) experienced at least 1 TEAE representative of a depression. There was 1 patient with suicidal ideation, however no apparent drug-related increase in suicidality or depression as measured by the C-SSRS and the PHQ-9 were reported.

In the "all population" updated analysis, depression (important potential risk of setmelanotide) was reported in a total of 22 setmelanotide-treated patients (4%). Suicidal ideation was reported in a total of 5 (1%) setmelanotide-treated patients. In 4 patients, the suicidal ideation during treatment occurred in conjunction with depression, and for 2 patients it was considered serious but non-treatment-related by the investigator. The current SmPC includes a warning to monitor each medical visit for any depressive symptoms and consider discontinuing treatment if patients experience suicidal thoughts or behaviours. This is considered sufficient to manage this important potential risk of setmelanotide.

ISRs were reported more frequently in BBS and AS patients (64% [41/64]) than in the "all population" original (l 39% [184/476] and updated (46% [260/561]) analyses but much less frequently than in POMC and LEPR deficiency populations (89% [31/35]). These ISR appeared to be related to the injection and/or excipients rather than to setmelanotide as more placebo-treated patients (77% [20/26]) reported ISRs than setmelanotide-treated patients in the BBS and AS population. The safety profile for ISRs remain consistent with the one observed during the initial marketing evaluation.

Hypertension and blood pressure increased were reported more frequently in BBS and AS patients (8% [5/64]) than in the "all population" original (1% [6/476]), updated (2% [12/561]) analyses and than in POMC and LEPR deficiency populations (3% [1/35]). For the 5 patients, 3 with hypertension and 2 with BP increased, the event was assessed by the Investigator as setmelanotide-related. Nevertheless, in the BBS/AS population as compared to placebo over 14 weeks there was no evidence of a difference between placebo or active therapy for both systolic and diastolic BP and thus the addition of hypertension as an ADR is not warranted at the present time.

In BBS and AS patients, the incidence of nausea (33% [21/64]) was consistent with the "all-population" original (33% [157/476]), updated (35% [198/561]) analyses and was much lower than in POMC/LEPR deficiency patients (57% [20/35]). The incidence of vomiting (28% [18/64]) was however much higher than in "all- population" original (12% [59/476]), updated (15% [86/561]) analyses but similar to the one observed in the POMC/LEPR deficiency population (29% [10/35]). Given the initial doses in the pivotal study for BBS and AS patients were twice as high as those in the pivotal study for POMC/LEPR deficiency patients, these observations do not raise a particular concern, nausea and vomiting are listed ADRs in the current SmPC of setmelanotide.

Several clinical chemistry TEAEs occurred in BBS/AS patients in the pivotal study (active treatment), some were serious and/or severe and/or led to study drug interruption or discontinuation: blood creatine phosphokinase increased (7 total, 1 BBS/AS pivotal cohort RM-493-023, 2 related, 1 severe, 1 leading to study drug interruption); alanine aminotransferase increased (5 total, 1 BBS/AS pivotal cohort RM-493-023, 2 related); hypoglycemia (4 total, 1 related, 2 serious, 2 severe, 1 leading to study drug discontinuation); blood uric acid increased (3 total, 1 BBS/AS pivotal cohort RM-493-023, 1 related); blood bilirubin increased (2 total, 2 related); eosinophil count decreased (2 total, 1 related); blood creatine increased (1 total, 1 BBS/AS pivotal cohort RM-493-023, 1 related). However, all these AEs were considered unrelated to setmelanotide since no causal relationship could be established.

One case of bradycardia was reported in a setmelanotide-treated patient in study RM-493-023 that was considered treatment-related by the Investigator. In the absence of any other concomitant symptoms and considering that these heart rates represent a mild bradycardia, which is a common and usually benign condition, this appears to be a benign event with a conservative classification of the AE based on observed findings rather than an actual clinical event. Previous comprehensive assessments of effects on heart rate (24-hour Holter) were included in the initial MAA without evidence of effects on heart rate.

No elderly patients were included in the pivotal or supportive RM-493-023, RM-493-014 and RMP-493-022 studies. However based on the "all population" updated analysis, additional new information was included in the SmPC. Available data in a small sample of elderly patients suggest no marked changes in setmelanotide exposure with increased age. However, these data are too limited to draw definite conclusions. Nineteen patients (in studies of unapproved indications) and healthy volunteers aged 65 years or older have been treated with Imcivree in clinical trials. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients."

Discontinuation of setmelanotide due to AEs occurred in 6 of the 64 BBS and AS patients treated with setmelanotide (9%), and in 60 of setmelanotide-treated patients (11%) and 6 placebo-treated patients (5%) in the "all population" updated analysis with nausea and vomiting as the most common reason. Most of these AEs leading to discontinuation in BBS and AS patients are already listed in SmPC section 4.8. and those that are not (acne, hidradenitis, ocular hyperaemia, face oedema) were not considered treatment-related by the investigator and there was only 1 case each. For the "all population" updated analysis, most of the AEs leading to discontinuation of setmelanotide in more than 1 patient, are already listed in SmPC section 4.8. except for ventricular tachycardia. This was reported in 2 patients, both healthy subjects with obesity, and was moderate and resolved in less than 1 minute after onset, In one of the cases, it was considered not treatment-emergent. Based on this information, ventricular tachycardia is not considered at the present time as a safety signal.

Assessment of the paediatric data on clinical safety

For the paediatric patients (aged 6-<12 years) with BBS or AS, no unexpected safety issues were identified and this was further supported by an analysis of "all population" aged -<12 years old regarding common, treatment-related, severe and serious TEAEs which concluded to a similar safety profile across these 2 populations in this age group. For the 20 pivotal paediatric patients (aged 6 -<18 years) in study RM-493-023 (16 BBS/4 AS), 4 discontinued early: 2 due to AEs (1 BBS/1 AS), 1 due to the dislike of the injections (AS) and 1 was lost to follow-up i.e., a 12-year old BBS patient who was withdrawn early by his parents due to previously recorded headache, leg pain and belligerent behaviour. The SmPC was updated to include information on BBS patients including the patient aged ≥ 12 years confirmed positive to setmelanotide anti-drug antibodies with a very low titre.

Safety in paediatric patients with POMC or LEPR deficiency and BBS is intended to be further followed-up in the PASS (observational Registry) noting the MAH has withdrawn the variation related to AS, Whereas many of the most common TEAEs (>10%) in the updated "all-patients population" analysis were reported much more frequently in the paediatric population (especially 6-< 12 years old) than in the adult population, some are expected to occur more frequently in general in children (e.g. cough, pharyngitis streptococcal, nasopharyngitis). Given data are collected from multiple studies with different study designs and in different patient populations including healthy volunteers, firm conclusions on observed differences between adult and paediatric population are difficult to draw due to the relatively small number of events. At the present time, the safety profile in the paediatric population is not considered to be different to that in adult patients.

2.5.2. Conclusions on clinical safety

The safety data from the Phase 3 clinical studies in BBS and AS patients, and the updated safety data from ongoing studies in other indications, demonstrate a safety profile of setmelanotide that is generally consistent with the overall safety profile in POMC and LEPR deficiency populations as established in the initial evaluation, and also in the paediatric population. Safety is intended to be further followed-up in the PASS (observational Registry) to be extended to BBS paediatric and adult patients.

No new important safety concerns have emerged so no new identified or important potential risks were recommended to be added to the RMP, beyond those already reflected in the currently approved RMP. The SmPC, patient leaflet and RMP have been revised to extend the indication by including BBS patients and to include the updated information on the safety profile.

2.5.3. 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.

2.6. Risk management plan

The MAH submitted/was requested to submit 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 2 is acceptable.

The CHMP endorsed the Risk Management Plan version 2 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	None

Summary of safety concerns	
Important potential risks	Melanoma Prolonged penile erections Depression (including suicidal ideation)
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				
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 with biallelic POMC/PCSK1 or LEPR deficiency obesity or BBS, according to the current local prescribing information. **Secondary objectives:** To document the incidence and characteristics of AESIs including the following: • Prolonged penile erection • Depression (including suicidal ideation)	Melanoma Prolonged penile erection Depression (including suicidal ideation) Patients with hepatic impairment Patients with severe renal impairment Use in	Start of data collection First annual progress report Second annual progress report Third annual progress report Fourth annual progress report Completion of enrolment	Q1 2023 Q1 2024 Q1 2025 Q1 2026 Q1 2027 Q1 2027

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	To document AESI and new adverse event occurrence in special populations, including: • Patients with hepatic impairment • Patients with severe renal impairment • Use in pregnancy and breastfeeding To evaluate the long-term effectiveness of setmelanotide when it is prescribed as part of routine practice To describe baseline characteristics and history of obesity in patients treated with setmelanotide **Exploratory objectives:** To document any cases of melanoma and their characteristics To document obesity-related hospitalisations and surgeries	pregnancy and breastfeeding Long term use	First annual interim analysis report Fifth annual progress report Second annual interim analysis report Sixth annual progress report Third annual 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	Q3 2027 Q1 2028 Q3 2028 Q1 2029 Q3 2029 Q1 2030 Q3 2030 Q1 2031 Q3 2031 Q1 2032 Q1 2032 Q3 2032

Risk minimisation measures

Safety concern	Risk minimisation measures
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
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 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
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

Safety concern	Risk minimisation measures
	No additional risk minimisation measures
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 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 woman. 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
Use in severe renal 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 recommend specific dose titration in patients with severe renal impairment

Safety concern	Risk minimisation measures
	Other routine risk minimisation measures beyond the Product Information: • Legal status: prescription only medication No additional risk minimisation measures
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

2.7. Update of the Product information

As a consequence of this new indication, sections 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet (PL) has been updated accordingly.

In addition section 4.6 of the SmPC was amended to include a cross reference to 4.4 in relation to a warning on potential risk from the excipient benzyl alcohol and section 3 of the PL was updated to include more information on the preparation of the syringe based on further data submitted during the procedure.

2.7.1. 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

At the time of the initial submission, the Applicant requested a group of extension of indications to add the treatment of obesity and uncontrolled hunger associated with Bardet-Biedl and Alström Syndromes (BBS and AS) in adults and children 6 years of age and above. On 22 April 2022, on the basis that additional data were required and these were considered still provisional, the MAH withdrew the variation related to the AS indication.

BBS is a primary ciliopathy which is believed to play a role in impaired transport of the leptin receptor (LEPR) to the ciliary membrane of pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus. Under normal conditions, leptin, a hormone predominantly made by adipose cells, stimulates firing and gene expression in POMC neurons, promoting the secretion of alpha-melanocyte stimulating hormone (α-MSH). Alpha-MSH stimulates the MC4R located in the second order neurons in the paraventricular nucleus (PVN) of the hypothalamus and results in decreased hunger and weight and increased energy expenditure. Impaired or absent LEPR signaling in POMC neurons would be expected to reduce MC4R stimulation in second order neurons, resulting in an increase in appetite, reduced metabolic rate, and increased weight.

3.1.2. Available therapies and unmet medical need

There are currently no approved therapies or products in development specifically for treatment of obesity and reduction of hyperphagia in patients with BBS and there is no evidence that alternative potential (unapproved) therapies might be useful.

The only pharmacologic treatments available are products for general obesity/weight management of which four products are currently authorised with obesity-related indications in the EU: Xenical, Saxenda, Mysimba, and Celevac. These general obesity medicines have mechanisms of action which do not address the underlying MC4R pathway signalling defects that lead to insatiable hunger and extreme obesity. Therefore, there is no indication that these drugs are therapeutically useful in patients with POMC or LEPR deficiency obesity.

The absence of drug therapy and unsuitability of surgical intervention leaves only lifestyle modification (i.e., diet and exercise) as available therapeutic interventions for patients with severe obesity. These, however, are rarely successful over the short-term and almost never effective in the long-term due to the intense drive to eat caused by the absence of satiety signals.

3.1.3. Main clinical studies

Results of a single phase 3 study, RM-493-023 were submitted to support this application. Study RM-493-023 consisted of three distinct treatment periods, including an initial 14 week double-blind placebo-controlled period, followed by two open-label treatment periods taking 38 weeks and 14 weeks respectively. During the double placebo-controlled period patients would be randomised to receive either placebo or setmelanotide. The treatment group used a dose titration schedule informed by clinical observations from trials RM-493-014 and -011. Two different cohorts were defined: the Pivotal cohort (the first 30 BBS and 6 AS subjects enrolled) and the Supplemental cohort (all patients enrolled after the pivotal cohort). All main confirmatory analyses would be performed using the Pivotal cohort and results from the Supplemental were only considered exploratory, given that the latter could exit the study to enrol in the RM-493-022 extension trial at any time after they completed the PCP.

After 14 Weeks of PCP participations patients would enrol in the open-label Period 2 and at this point former placebo-randomised patients would be uptitrated with active treatment according to the informed schedule while former setmelanotide-randomised patients would once again undergo a similar up titration starting from the initial PCP starting dose in order to preserve the PCP blind. Analysis of PCP data, a secondary endpoint, would use the PCPB (as measured at time of PCP enrolment) as baseline values, while the primary and key secondary endpoints would use the ATB (as measured when a subject first received setmelanotide) as baseline values. Analysis would take place when the last pivotal patient enrolled would complete his/her Period 2, which could lead to a situation

where some placebo patients have less than 52 Weeks of active treatment data available and hence their W52 values would be imputed.

Analysis according to age and condition were to be performed as exploratory subgroup analyses.

3.2. Favourable effects

The primary and key secondary endpoints were met in the pivotal ≥12yo FAS population, which was the main population to be used for H0 testing.

- A statistically significant proportion of 32.3% of these patients had a weight decrease of at least 10% versus active treatment baseline compared to a 10% historic control of untreated patients.
- A statistically significant mean -5.2% difference in bodyweight was achieved in this population versus active treatment baseline.
- A statistically significant mean -30.91% difference in weekly average worst daily hunger was achieved in this population versus active treatment baseline.
- A statistically significant proportion of 62.5% of these patients had a weight decrease of at least 25% versus active treatment baseline compared to a 10% historic control of untreated patients.

An ad-hoc analysis of the pivotal ≥12yo BBS-only cohort using true W52 data for all subjects confirmed the clinical relevance of the prespecified primary and key secondary outcomes in in the pivotal ≥12yo FAS population:

- A statistically significant proportion of 43.5% of these patients had a weight decrease of at least 10% versus active treatment baseline compared to a 10% historic control of untreated patients.
- A statistically significant mean -7.78% difference in bodyweight was achieved in this population versus active treatment baseline.
- A statistically significant mean -38.75% difference in weekly average worst daily hunger was achieved in this population versus active treatment baseline.
- A statistically significant proportion of 72.7% of these patients had a weight decrease of at least 25% versus active treatment baseline compared to a 10% historic control of untreated patients.

In the 14 Week placebo-controlled period setmelanotide-treated patients showed a statistically significant difference of weekly average daily hunger score versus PCPB of -20,27% compared to the placebo-control cohort.

In the subgroup analysis in patients <12yo, though only exploratory, there was a clear trend towards clinically meaningful positive changes in BMI-Z scores.

Subgroup analysis in the pivotal ≥12yo FAS BBS patients revealed results that mirrored and even outperform the pivotal ≥12yo full FAS results in weight outcomes:

- A statistically significant proportion of 35,7% of BBS patients had a weight decrease of at least 10% versus active treatment baseline compared to a 10% historic control of untreated patients.
- A statistically significant mean -6.47% difference in bodyweight was achieved in the BBS population versus active treatment baseline.
- A statistically significant mean -30.45% difference in weekly average worst daily hunger was achieved in the BBS population versus active treatment baseline.

- A statistically significant proportion of 57.1% of BBS patients had a weight decrease of at least 25% versus active treatment baseline compared to a 10% historic control of untreated patients.

3.3. Uncertainties and limitations about favourable effects

Despite meeting the prespecified primary and key secondary objectives, the overall outcomes in the pivotal RM-493-023, only 32.3% of patients attained the primary endpoint with a mean weight loss of 5.9 kg versus baseline (median loss = 4.37 kg) at Week 52 and a mean weight loss of 3.06 kg, which was not statistically different from the placebo group.

Outcomes in AS patients were unconvincing, but as the AS population is no longer a claimed indication following the withdrawal of the related variation, this uncertainty is not further discussed.

Only very few pivotal patients (n=5) below the age of 12 were included in the trial, making statistically sound decision making difficult. The subgroup analyses by age were only exploratory. PE, KSE and secondary (SE) were not evaluated in patients younger than 12 years of age, though positive effects on BMI-Z scores were seen. In combination with the full clinical data for these patients, the totality of evidence supports use of setmelanotide in the 6 to 12 yo BBS patient population since there does not seem to be any indication that efficacy or safety in this group (6-11 years) differs essentially from the other age groups.

PCP outcomes were at times contradictory, indicating that a longer PCP may have been preferable to allow a more robust analysis. These findings are consistent with the MAH's observation that 14 weeks of follow-up is likely too short to detect appreciable weight changes but that the hunger outcomes, though not significantly different, are at least directionally similar.

Historical data used for sample size estimation and historical control was determined from the CRIBBS registry. This registry is however a BBS-exclusive registry, and it was not clear how the data thereof could therefore be used in statistically valid way for methodologic decisions on a population that mixes BBS and AS patients, being two distinct conditions. Nevertheless, with the withdrawal of the variation related to AS, this design issue was not further discussed.

Long-term efficacy in regard to maintenance of weight loss is currently lacking in AS patients, and likewise data on long term hunger control maintenance is currently lacking in BBS and AS patients. Note that AS is no longer part of the requested indication, and thus data for this condition are no longer considered pertinent for this variation.

No robust comparison of the PK parameters and profiles between BBS/AS population and POMC or LEPR deficient patients could be made based on the limited data available in children and the high variability observed in the studies. However the CHMP agreed that in adults and adolescents the mean setmelanotide trough concentrations across studies based on dose were similar, with overlapping standard deviations. In addition, the Population Pharmacokinetic (POPK) model has not been updated (due to insufficient data to allow reassessment of the model), although it was acknowledged that from the trough concentration values presented for studies RM-493-012 and RM-493-015, the concentration values for setmelanotide were overall consistent with repeat dosing across studies and disease population.

3.4. Unfavourable effects

During the procedure, the CHMP raised concerns over the presentation and discussion of the safety data, which were subsequently addressed by the applicant within the responses to supplementary information. Overall, the CHMP considered that the updated "all population" safety analysis and the

new data for the BBS/AS population did not change the overall safety profile of setmelanotide. However information on elderly and paediatric populations have been updated in the SmPC. In addition, frequencies of some existing ADRs have been updated in the SmPC and new ADRs have also been added based on these new data.

Some of the most common TEAEs (e.g. skin hyperpigmentation, injection site erythema, injection site pruritus, vomiting) are reported much more frequently in the BBS and AS population than in the "all-population" original and update analyses but these TEAEs are reported at a lower or similar frequency as observed in POMC/LEPR deficiency populations.

The frequencies of the hyperpigmentation disorders-related TEAEs in the BBS and AS population (75% [48/64] were higher than in the "all population" original (51% [244/476]) and updated (58% [322/561]) analyses but lower than in the POMC and LEPR deficiency population (86% [30/35]). All except one of the AS patients (91% [10/11]) reported hyperpigmentation disorders. The impact of hyperpigmentation disorders remains limited as most reports of hyperpigmentation disorders in BBS and AS patients were mild to moderate. No melanoma (important potential risk of setmelanotide) was reported in the BBS/AS population or in the updated "all population" analysis that was submitted in this procedure.

In BBS and AS patients, 13% (8/64) experienced at least 1 TEAE representative of a sexual event, which appeared consistent with the "all-population" original (15% [72/476] and updated (15% [86/561]) analyses and to POMC/LEPR deficiency patient population (17% [6/35]). In BBS and AS patients the most commonly reported sexual event was spontaneous penile erection (13% [8/64]). No prolonged penile erections (important potential risk of setmelanotide) were reported.

In the BBS/AS population, 3% (2/64) experienced at least 1 TEAE representative of a depression. There was 1 patient with suicidal ideation, however no apparent drug-related increase in suicidality or depression as measured by the C-SSRS and the PHQ-9 were reported. In the "all population" updated analyses, depression (important potential risk of setmelanotide) was reported in a total of 22 setmelanotide-treated patients (4%). Suicidal ideation was reported in a total of 5 (1%) setmelanotide-treated patients. In 4 patients, the suicidal ideation during treatment occurred in conjunction with depression, and for 2 patients it was considered serious but non-treatment-related by the investigator. The current SmPC includes a warning to monitor each medical visit for any depressive symptoms and consider discontinuing treatment if patients experience suicidal thoughts or behaviours. This is considered sufficient to manage this important potential risk of setmelanotide.

ISRs were reported more frequently in BBS and AS patients (64% [41/64]) than in the "all population" original (l 39% [184/476] and updated (46% [260/561]) analyses but much less frequently than in POMC and LEPR deficiency populations (89% [31/35]) and appeared to be related to the injection and/or excipients rather than to setmelanotide as more placebo-treated patients (77% [20/26]) reported ISRs than setmelanotide-treated patients in the BBS and AS population. The safety profile for ISRs remain consistent with the one observed during the initial marketing evaluation.

Hypertension and blood pressure increased were reported more frequently in BBS and AS patients (8% [5/64]) than in the "all population" original (1% [6/476]), updated (2% [12/561]) analyses and than in POMC and LEPR deficiency populations (3% [1/35]). For the 5 patients, 3 with hypertension and 2 with BP increased, the event was assessed by the Investigator as setmelanotide-related. Nevertheless, in the BBS/AS population as compared to placebo over 14 weeks there was no evidence of a difference between placebo or active therapy for both systolic and diastolic BP and thus the addition of hypertension as an ADR is not warranted at the present time.

In BBS and AS patients, the incidence of nausea (33% [21/64]) was consistent with the "all-population"original (33% [157/476]), updated (35% [198/561]) and was much lower than in

POMC/LEPR deficiency patients (57% [20/35]). The incidence of vomiting (28% [18/64]) was however much higher than in "all- population" original (12% [59/476]), updated (15% [86/561]) but similar to the one observed in the POMC/LEPR deficiency population (29% [10/35]). Given the initial doses in the pivotal study for BBS and AS patients were twice as high as those in the pivotal study for POMC/LEPR deficiency patients, these observations do not raise a particular concern, nausea and vomiting are listed ADRs in the current SmPC of setmelanotide .

Many of the most common TEAEs (>10%) in the updated "all-patients population" analysis were reported much more frequently in the paediatric population (especially 6-< 12 years old) than in the adult population, some however are expected to occur more frequently in general in children (e.g. cough, pharyngitis streptococcal, nasopharyngitis).

3.5. Uncertainties and limitations about unfavourable effects

Given data are collected from multiple studies with different study designs and in different patient populations including healthy volunteers, firm conclusions on observed differences between adult and paediatric population are difficult to draw due to the relatively small number of events. At the present time, the safety profile in the paediatric population is not considered to be different to that in adult patients.

The clinical safety data set is limited leading to a number of uncertainties: the number of patients treated in the intended indication is small so it is unlikely to detect rarer adverse reactions, and there is a need for longer-term data to detect adverse reactions associated with prolonged or cumulative exposure. In addition, the paediatric safety data was very limited especially in regard to children 6 11 years old.

The pivotal study had a short placebo controlled period, in a patient population with several comorbidities. This made it challenging to determine the causal relationship to the treatment.

Existing uncertainties from the initial evaluation remain i.e. effect of long-term or cumulative use of setmelanotide on hyperpigmentation is not known; the risk of prolonged penile erections (>4 hours) as up until now is not fully characterised, depression is a potential risk and the clinical impact of ADAs is unknown as more data are expected and the suitability of the assays is yet to be confirmed.

3.6. Effects Table

Effects Table for setmelanotide in the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) and Alström syndrome (AS)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Body Weight	***PE*** Proportion of patients who achieved a ≥10% reduction in body weight from ATB after ~52 weeks of treatment compared to a historical untreated proportion of 10%.	% (95% CI) p-value	***Setmelanotide*** 32.3 (16.7, 51.4) 0.0006	*N/A*	Imputation used for patients with missing W52 data. Only ≥12yo patients.	RM-493-023 ≥12yo Pivotal FAS N=31
Body Weight	***KSE*** Mean percent change from ATB in body weight after ~52 weeks of treatment	% (95% CI) p-value	***Setmelanotide*** -5.21 (-8.10, -2.31) 0.0005	*N/A*	Imputation used for patients with missing W52 data. Only ≥12yo patients. Indeterminate results in AS subgroup analyses.	RM-493-023 ≥12yo Pivotal FAS N=31
Hunger	***KSE*** Mean percent change from ATB in the weekly average of the daily hunger scores after ~52 weeks	% (95% CI) p-value	***Setmelanotide*** -30.91 (-44.09, -17.73) <0.0001	*N/A*	Imputation used for patients with missing W52 data. Only ≥12yo cognitively functional patients. Indeterminate results in AS subgroup analyses.	RM-493-023 ≥12yo Pivotal FAS, not cognitively impaired N=16
Hunger	***KSE*** The proportion of patients who achieve a ≥25% improvement from ATB in the weekly average of the daily hunger score, versus an historical untreated proportion of 10%.	% (95% CI) p-value	***Setmelanotide*** 62.5 (35.4, 84.8) <0.0001	*N/A*	Imputation used for patients with missing W52 data. Only ≥12yo cognitively functional patients.	RM-493-023 ≥12yo Pivotal FAS, not cognitively impaired N=16
Body Weight	***SE*** Body weight percent change from PCPB at 14 weeks	Mean %	***Setmelanotide N=16*** -2.41	***Placebo N=17*** -0.32	Becomes significant when supplemental patients are considered.	RM-493-023 ≥12yo Pivotal PCS
		Difference (95% CI) p-value	-2.10 (-4.62, 0.42) 0.0516			
Hunger	***SE*** Weekly average daily hunger score percent change from PCPB at 14 weeks	Mean %	***Setmelanotide N=7*** -33.38	***Placebo N=10*** -13.11	Becomes non-significant when supplemental patients are considered. Results in placebo patients may indicate existence of a placebo-effect.	RM-493-023 ≥12yo Pivotal PCS, not cognitively impaired
		Difference (95% CI) p-value	-20,27 (-35.72, -4,82) 0.0051			

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Unfavourable Effects						
		N (%)	**Setmelanotide (N=27)**	**Placebo (N=25)**	Limited number of patients and duration	
TEAE	Treatment-emergent		26 (96.3%)	24 (96.0%)		RM-493-023, placebo-controlled period
TEAE	Treatment-related		24 (88.9%)	22 (88.0%)		
SAE	Serious Treatment-emergent		1 (3.7%)	2 (8.0%)		
SAE	Serious Treatment-related		0	1 (4.0%)		
SAE	Leading to death		0	0		
TEAE	Leading to withdrawal		2 (7.4%)	3 (12.0%)		
TEAE	Related, Leading to withdrawal					
TEAE	Severe					
		N (%)	**Setmelanotide (N=27)**	**Placebo (N=25)**	Limited number of patients and duration	
TEAE	Treatment-emergent		27 (100.0%)	25 (100.0%)		RM-493-023, full study
TEAE	Treatment-related		27 (100.0%)	24 (96.0%)		
SAE	Serious Treatment-emergent		1 (3.7%)	2 (8.0%)		
SAE	Serious Treatment-related		0	1 (4.0%)		
SAE	Leading to death		0	0		
TEAE	Leading to withdrawal		2 (7.4%)	4 (16.0%)		
TEAE	Related, Leading to withdrawal		2 (7.4%)	3 (12.0%)		
TEAE	Severe		1 (3.7%)	2 (8.0%)		
		N (%)	**Setmelanotide (N=64)**	**Placebo (N=26)**	Limited number of patients and duration	
Most common TEAE	Skin hyperpigmentation		45 (70.0%)	0		All BBS + AS (RM-493-023 + -014 + -022)
	Injection site erythema		24 (38.0%)	10 (39.0%)		
	Injection site pruritus		23 (36.0%)	8 (31.0%)		
	Nausea		21 (33.0%)	4 (15.0%)		
	Vomiting		18 (28.0%)	0		
Important potential risks	Melanoma		0	0		
	Prolonged penile erections		0	0		
	Depression (+ depressed mood)		2 (3.1%)	0		
	Suicidal ideation		1 (1.6%)	1 (3.8%)		

Abbreviations: TEAE = Treatment-emergent adverse event, SAE = Serious adverse event, PE = Primary Endpoint, KSE = Key Secondary Endpoint, SE – Secondary Endpoint, PCPB = Placebo Period Baseline, ATB = Active treatment Baseline

Notes: as there are many-many common adverse events (due to the low number of included patients), only the most common ones have been listed in the effects table, as well as those considered to be Important potential risks in the RMP

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Setmelanotide is a MC4R agonist with the potential to restore lost activity in the MC4R pathway aiming at re-establishing weight and appetite control in patients with POMC and LEPR obesity. BBS is a primary ciliopathy which is believed to play a role in impaired transport of the leptin receptor (LEPR) to

the ciliary membrane of pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus. As reported by the MAH, the exact mechanism of how this ciliopathy is interacting with the MC4R pathway is currently unknown, the MAH however claimed that based on animal model observations and limited human data it is strongly believed that in BBS, it is the leptin receptor which loses some degree of functionality, ultimately believed to culminate in deficient α-MSH signalling further downstream and thus setmelanotide could function as a replacement α-MSH analogue to take over or at least aid in this deficient signalling step. There are no pharmacological treatment options for the patient populations and there is a substantial medical need.

Despite meeting the prespecified primary and key secondary objectives, the overall outcomes in the pivotal RM-493-023, only 32.3% of patients attained the primary endpoint with a mean weight loss of 5.9 kg versus baseline (median loss = 4.37 kg) at Week 52 and a mean weight loss of 3.06 kg, which was not statistically different from the placebo group, versus baseline at Week 14. Notably, the MAH opted for a pivotal trial design that differs entirely from the design as used in the POMC/LEPR/PCKS1-deficiency studies which formed the basis for the initial marketing authorisation. In addition, a number of deviations from the CHMP Scientific Advice were identified in the choice of design (population, duration of placebo controlled period, hierarchy of endpoints) as well as some other limitations in the chosen design (use of different ATB sampling points and adjustment through imputation techniques). These resulted in heterogeneity in the results and efficacy uncertainties in the trial population including mixed BBS/AS populations. To address these efficacy uncertainties, an ad-hoc sensitivity analysis was performed on the primary (PE) and key secondary endpoints (KSE), using the actual Week 52 data, instead of imputed ones, of all pivotal BBS patients and confirmed the clinical relevance of the magnitude of the effect in BBS patients. More patients (43%) met the conservative primary endpoint of >10% weight loss, and mean/median losses in bodyweight versus baseline were improved to -9/-8 kg (equivalent to mean/median 7.9/6.2% change versus baseline). Only very few pivotal patients below the age of 12 were included in the trial, nevertheless positive effects on BMI-Z scores were seen and there did not seem to be any indication that efficacy or safety in this group (6-11 years) differs essentially from the other age groups.

Forty-two (42) BBS patients had transitioned from trials RM-493-023 and -014 with a median of 86 weeks QD setmelanotide treatment at the time of the database lock. Overall, the trends seen indicate that the weight loss achieved in the index studies was maintained during the extension follow-up. However long term data are still limited. Of the BBS/AS population, 49 patients have been treated for at least 6 months, 39 have been treated for at least 1 year and 21 for at least 18 months which is a larger sample size than for POMC/LEPR deficiency patients used to support the initial approval.

Given the expected life-long nature of the treatment, the proposed pharmacovigilance plan to extend the follow-up to BBS patients in the planned registry (PASS) is agreed upon.

Based on the new safety data generated in BBS/AS populations and other populations, the overall safety profile of setmelanotide remain consistent, although frequencies of some existing ADRs have been updated in the SmPC and new ADRs have also been added. Existing uncertainties from the initial evaluation remain and the agreed PASS will thus be extended to BBS patients to monitor the long term safety and other important potential risks and missing information.

3.7.2. Balance of benefits and risks

Overall, the favourable outcomes, both in a statistical and clinically relevant sense, on body weight and hunger suppression in the ultra-rare condition of BBS are promising for a patient population that until now suffers from a high unmet medical need due to the absence of an effective durable treatment for their condition. Although the same potential risks are identified as those in POMC/PCSK1/LEPRS

deficiency obesity, these are not considered to outweigh the benefits of Setmelanotide in the proposed indication.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall B/R of Imcivree for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) in adults and children 6 years of age and above is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

C.I.6.a - To add the new therapeutic indication for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS). As a consequence, sections 4.1, 4.2, 4.6, 4.8, 5.1, 5.2 and 5.3 of the SmPC and sections 1, 3 and 4 of the PL are updated accordingly. The updated RMP version 1.0 has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP (P/0215/2021) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.