EU Risk Management Plan for IMCIVREE (setmelanotide)

RMP version to be assessed as part of this application:

RMP Version number:	3.2
Data lock point for this RMP:	26 March 2025
Date of final sign-off:	18 February 2026
Rationale for submitting an updated RMP:	Indication extension (for the treatment of obesity and the control of hunger in adults and children 4 years of age and above with acquired hypothalamic obesity (aHO) due to hypothalamic injury or impairment)
Summary of significant changes in this RMP:	RMP Parts I, II SI, II SIII, II SIV.2, II SV, II SVII.3, V and VI are updated to include data on the proposed indication of treatment of obesity and the control of hunger in adults and children 4 years of age and above with acquired hypothalamic obesity (aHO) due to hypothalamic injury or impairment, and to reflect the available clinical trial exposure and post authorisation exposure.
Other RMP versions under evaluation:	Not applicable
RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
RMP Version number:	2.3
Approved with procedure:	EMEA/H/C/005089/II/0018
Date of approval (opinion date):	27 June 2024
QPPV name:	Sergio Escriva

[redacted]

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List of Abbreviations

Abbreviation	Definition
aHO	acquired hypothalamic obesity
ACTH	adrenocorticotropic hormone
AESI	adverse event of special interest
AS	Alström syndrome
AUC	area under the curve
BBS	Bardet-Biedl syndrome
BMI	body mass index
BP	blood pressure
CNS	central nervous system
CV	cardiovascular
CVD	cardiovascular disease
DLP	data lock point
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EPAR	European Public Assessment Report
ESI	events of special interest
EU	European Union
GLP	good laboratory practice
hERG	human ether-à-go-go related gene
HO	hypothalamic obesity
HR	heart rate
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LEPR	leptin receptor
MC	melanocortin
MC1R	melanocortin 1 receptor
MC4R	melanocortin 4 receptor
mPEG-DSPE	methoxyl poly (ethylene glycol) conjugated with 1,2-distearoyl-sn-glycero-3-phosphoethanolamine

PCSK1	Proprotein Convertase Subtilisin/Kexin Type 1
PDE-V	phosphodiesterase-V
PK	pharmacokinetic
PL	package leaflet
PPL	POMC, PCSK1, and LEPR-deficiency obesity collectively
POMC	pro-opiomelanocortin
RMP	risk management plan
SC	subcutaneous
SD	standard deviation
SmPC	summary of product characteristics
TEAE	treatment emergent adverse event
Tg.rasH2	transgenic rasH2
US	United States
WT rasH2	wild-type rasH2

Part I: Product Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Setmelanotide
Pharmacotherapeutic group(s) (ATC Code)	Anti-obesity preparations, excl. diet products, centrally acting anti-obesity products (ATC code: A08AA12)
Marketing Authorisation Holder (in the European Economic Area [EEA])	Rhythm Pharmaceuticals Netherlands B.V.
Medicinal products to which this RMP refers	One - IMCIVREE 10 mg/mL solution for injection
Invented name(s) in the EEA	IMCIVREE
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Setmelanotide is a synthetic octapeptide melanocortin 4 receptor (MC4R) agonist
	Summary of mode of action: Setmelanotide is a selective MC4R agonist with less activity at the melanocortin 1 receptor (MC1R). MC4Rs in the brain are involved in regulation of hunger, satiety, and energy expenditure. In MC4R pathway diseases 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. The MC1R is expressed on melanocytes, and activation of this receptor leads to accumulation of melanin and increased skin pigmentation independently of ultraviolet light.
	Important information about its composition: Setmelanotide is an 8 amino acid cyclic peptide with a molecular formula of $C_{49}H_{68}N_{18}O_9S_2$ (anhydrous free base). Excipients in the formulation with known effect include benzyl alcohol.
Hyperlink to the Product Information	**Product Information**
Indication(s) in the EEA	Current: Treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS), 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 2 years of age and above. Proposed: Treatment of obesity and the control of hunger in adults and children 4 years of age and above with acquired hypothalamic obesity (aHO)

	due to hypothalamic injury or impairment. Treatment of obesity and the control of hunger associated with genetically confirmed BBS in adults and children 2 years of age and above. Treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency (PPL) in adults and children 2 years of age and above.
Dosage in the EEA	Current: **POMC, including PCSK1, deficiency and LEPR deficiency** *Adult population and children more than 12 years of age* For adults and children 12 to 17 years of age, the starting dose is a 1 mg once daily subcutaneous (SC) injection for 2 weeks. After 2 weeks, if setmelanotide is well tolerated, the dose can be increased to a 2 mg once daily SC injection. If dose escalation is not tolerated, patients may maintain administration of the 1 mg once daily dose. If additional weight loss is desired in adult patients, the dose can be increased to a 2.5 mg once daily SC injection. If the 2.5 mg once daily dose is well tolerated, the dose can be increased to 3 mg once daily. In patients aged 12 to 17 years, if weight remains above the 90th percentile with the 2 mg once daily SC injection and additional weight loss is desired, the dose may be increased to 2.5 mg with a maximum dose of 3 mg once daily. *Paediatric population (children aged 6 to <12 years)* For patients aged 6 to <12 years, the starting dose is a 0.5 mg once daily SC injection for 2 weeks. If tolerated after 2 weeks, the dose can be increased to 1 mg once daily. If dose escalation is not tolerated, paediatric patients may maintain administration of the 0.5 mg once daily dose. If the 1 mg dose is tolerated after 2 weeks, the dose can be increased to 2 mg once daily. If weight remains above the 90th percentile with the 2 mg once daily SC injection and additional weight loss is desired, the dose may be increased to 2.5 mg once daily. *Paediatric population (children aged 2 to <6 years)* For patients aged 2 to <6 years, the starting dose is a 0.5 mg once daily SC injection for 2 weeks. If the 0.5 mg starting dose is not tolerated, reduce to 0.25 mg (0.025 ml) once daily. If the 0.25 mg once daily dose is tolerated, the dose can be increased to 0.5 mg once daily for patients <20 kg. For patients 20 to <30 kg, the dose can be increased to 0.5 mg once daily for 2 weeks. If the 0.5 mg dose is well tolerated after 2 weeks, the dose can be increased to 1 mg once daily. For patients 30 to <40 kg, the dose can be increased to 0.5 mg once daily for 2 weeks. If 0.5 mg dose is well tolerated after 2 weeks, the dose can be increased to 1 mg once daily. If the 1 mg dose is well tolerated after 2 weeks, the dose can be increased to 1.5 mg once daily. For patients ≥40 kg, the dose can be increased to 0.5 mg once daily for 2 weeks. If 0.5 mg dose is well tolerated after 2 weeks, the dose can be increased to 1 mg once daily. If the 1 mg dose is well tolerated after 2 weeks, the dose can be increased to 1.5 mg once daily. If the 1.5 mg dose is well tolerated after 2 weeks, the dose can be increased to 2 mg once daily. If the 2 mg dose is well tolerated, the dose can be increased to 2.5 mg once daily. **Bardet-Biedl Syndrome** *Adult population and children more than 16 years of age* For adults and children 16 to 17 years of age, the starting dose is a

	2 mg (0.2 ml) once daily SC injection for 2 weeks. If the starting dose is not tolerated, reduce to 1 mg (0.1 ml) once daily. If the 1 mg once daily dose is tolerated, increase the dose to 2 mg once daily. If the 2 mg daily dose is well tolerated for 2 weeks, increase the dose to 3 mg (0.3 ml) once daily. If the 3 mg once daily dose is not tolerated, reduce to 2 mg once daily. *Paediatric population (children aged 6 to <16 years)* For patients aged 6 to <16 years, the starting dose is a 1 mg (0.1 ml) once daily SC injection for 2 weeks. If the starting dose is not tolerated, reduce to 0.5 mg (0.05 ml) once daily. If the 0.5 mg once daily dose is well tolerated, increase the dose to 1 mg once daily. If the 1 mg daily dose is well tolerated, increase the dose to 2 mg (0.2 ml) once daily. If the 2 mg once daily dose is not tolerated, reduce to 1 mg once daily. If the 2 mg once daily dose is tolerated, the dose should be increased to 3 mg (0.3 ml) once daily. If the 3 mg once daily dose is not tolerated, reduce to 2 mg once daily. *Paediatric population (children aged 2 to <6 years)* For patients aged 2 to <6 years, the starting dose is a 0.5 mg once daily SC injection for 2 weeks. If the 0.5 mg starting dose is not tolerated, reduce to 0.25 mg (0.025 ml) once daily. If the 0.25 mg once daily dose is tolerated, the dose can be increased to 0.5 mg once daily for patients <20 kg. For patients 20 to <30 kg, the dose can be increased to 0.5 mg once daily for 2 weeks. If the 0.5 mg dose is well tolerated after 2 weeks, the dose can be increased to 1 mg once daily. For patients 30 to <40 kg, the dose can be increased to 0.5 mg once daily for 2 weeks. If 0.5 mg dose is well tolerated after 2 weeks, the dose can be increased to 1 mg once daily. If the 1 mg dose is well tolerated after 2 weeks, the dose can be increased to 1.5 mg once daily. For patients ≥40 kg, the dose can be increased to 0.5 mg once daily for 2 weeks. If 0.5 mg dose is well tolerated after 2 weeks, the dose can be increased to 1 mg once daily. If the 1 mg dose is well tolerated after 2 weeks, the dose can be increased to 1.5 mg once daily. If the 1.5 mg dose is well tolerated after 2 weeks, the dose can be increased to 2 mg once daily. If the 2 mg dose is well tolerated, the dose can be increased to 2.5 mg once daily. <u>Proposed:</u> **Acquired hypothalamic obesity** *Adults and children 6 years of age and above* The starting dose is 0.5 mg once daily for 1 week. If setmelanotide is tolerated for a week, the dose can be increased to 1 mg in Week 2. If 1 mg dose is tolerated, the dose can be increased to 2 mg in Week 3. If clinical response is insufficient and if 2 mg dose is tolerated, the dose can be increased to 3 mg in Week 4 and onward. Dose titration may be performed both upward and downward based on individual tolerability and clinical response. Dose can be reduced to 0.25 mg if needed. *Children from 4 to less than 6 years of age* The starting dose is 0.5 mg once daily for 1 week. If clinical response is insufficient and if setmelanotide is tolerated, the dose can be increased weekly in increments of 0.5 mg. The maximum daily dose is 1.5 mg for children with weight <20 kg, 2 mg for children with weight 20 to <25 kg, and 2.5 mg for children with weight 25 to <30 kg. For children with weight ≥30 kg, following starting dose of 0.5 mg, if clinical response is insufficient and if setmelanotide is tolerated, the following weekly dose increments are 1 mg, 2 mg and 3 mg.

	Dose titration may be performed both upward and downward based on individual tolerability. Dose can be reduced to 0.25 mg if needed. **POMC, including PCSK1, deficiency and LEPR deficiency** *Adults and children 12 years of age and above* For adults and children 12 years of age and above, the starting dose is 1 mg once daily for 2 weeks. After 2 weeks, if setmelanotide is well tolerated, the dose can be increased to 2 mg once daily. If dose escalation is not tolerated, patients may maintain administration of the 1 mg once daily dose. If additional weight loss is desired in adult patients, the dose can be increased to 2.5 mg once daily. If the 2.5 mg once daily dose is well tolerated, the dose can be increased to 3 mg once daily. In patients from 12 to less than 18 years of age, if weight remains above the 90th percentile with the 2 mg once daily dose and additional weight loss is desired, the dose may be increased to 2.5 mg with a maximum dose of 3 mg once daily. *Children from 6 to less than 12 years of age* For paediatric patients from 6 to less than 12 years of age, the starting dose is 0.5 mg once daily for 2 weeks. If tolerated after 2 weeks, the dose can be increased to 1 mg once daily. If dose escalation is not tolerated, paediatric patients may maintain administration of the 0.5 mg once daily dose. If the 1 mg dose is tolerated after 2 weeks, the dose can be increased to 2 mg once daily. If weight remains above the 90th percentile with the 2 mg once daily dose and additional weight loss is desired, the dose may be increased to 2.5 mg once daily. *Children from 2 to less than 6 years of age* For paediatric patients from 2 to less than 6 years of age, the starting dose is 0.5 mg once daily for 2 weeks. If the 0.5 mg starting dose is not tolerated, the dose should be reduced to 0.25 mg (0.025 ml) once daily. If the 0.25 mg once daily dose is tolerated, the dose can be increased to 0.5 mg once daily for patients <20 kg. For patients 20 to <30 kg, the dose can be increased to 0.5 mg once daily for 2 weeks. If the 0.5 mg dose is well tolerated for 2 weeks and if clinical response is insufficient, the dose can be increased to 1 mg once daily from Week 3 and onward. For patients 30 to <40 kg, the dose can be increased to 0.5 mg once daily for 2 weeks. If 0.5 mg dose is well tolerated and if clinical response is insufficient, the dose can be increased to 1 mg once daily after 2 weeks. If the 1 mg dose is well tolerated after 2 weeks and if clinical response is insufficient, the dose can be increased to 1.5 mg once daily. For patients ≥40 kg, the dose can be increased to 0.5 mg once daily for 2 weeks. If 0.5 mg dose is well tolerated after 2 weeks, the dose can be increased to 1 mg once daily. If the 1 mg dose is well tolerated and if clinical response is insufficient, the dose can be increased to 1.5 mg once daily after 2 weeks. If the 1.5 mg dose is well tolerated after 2 weeks and if clinical response is insufficient, the dose can be increased to 2 mg once daily. If the 2 mg dose is well tolerated and if clinical response is insufficient, the dose can be increased to 2.5 mg once daily. **Bardet-Biedl Syndrome** *Adults and children 16 years of age and above* For adults and children 16 years of age and above, the starting dose is 2 mg (0.2 ml) once daily for 2 weeks. If the 2 mg starting dose is not tolerated, the dose should be reduced to 1 mg (0.1 ml) once daily. If the 1 mg once daily dose is tolerated, dose titration should be continued.

	Following the starting dose, if a subsequent dose is not tolerated, the dose should be reduced to the previous dose level. If the reduced dose is tolerated, dose titration should be continued. *Children from 6 to less than 16 years of age* For paediatric patients from 6 to less than 16 years of age, the starting dose is 1 mg (0.1 ml) once daily for 2 weeks. If the 1 mg daily dose is well tolerated, the dose should be increased to 2 mg (0.2 ml) once daily. If the 2 mg once daily dose is well tolerated, the dose should be increased to 3 mg (0.3 ml) once daily. If the 1 mg starting dose is not tolerated, the dose should be reduced to 0.5 mg (0.05 ml) once daily. If the 0.5 mg once daily dose is well tolerated, the dose should be increased to 1 mg once daily and dose titration should be continued. Following the starting dose, if a subsequent dose is not tolerated, the dose should be reduced to the previous dose level. If reduced dose is tolerated, dose titration should be continued. *Children from 2 to less than 6 years of age* For paediatric patients from 2 to less than 6 years of age, the starting dose is 0.5 mg once daily for 2 weeks. If the 0.5 mg starting dose is not tolerated, the dose should be reduced to 0.25 mg (0.025 ml) once daily. If the 0.25 mg once daily dose is tolerated, the dose can be increased to 0.5 mg once daily for patients <20 kg. For patients 20 to <30 kg, the dose can be increased to 0.5 mg once daily for 2 weeks. If the 0.5 mg dose is well tolerated and if clinical response is insufficient after 2 weeks, the dose can be increased to 1 mg once daily. For patients 30 to <40 kg, the dose can be increased to 0.5 mg once daily for 2 weeks. If 0.5 mg dose is well tolerated and if clinical response is insufficient after 2 weeks, the dose can be increased to 1 mg once daily. If the 1 mg dose is well tolerated and if clinical response is insufficient after 2 weeks, the dose can be increased to 1.5 mg once daily. For patients ≥40 kg, the dose can be increased to 0.5 mg once daily for 2 weeks. If 0.5 mg dose is well tolerated and if clinical response is insufficient after 2 weeks, the dose can be increased to 1 mg once daily. If the 1 mg dose is well tolerated and if clinical response is insufficient after 2 weeks, the dose can be increased to 1.5 mg once daily. If the 1.5 mg dose is well tolerated and if clinical response is insufficient after 2 weeks, the dose can be increased to 2 mg once daily. If the 2 mg dose is well tolerated and if clinical response is insufficient after 2 weeks, the dose can be increased to 2.5 mg once daily.
Pharmaceutical form(s) and strengths	Current (if applicable): Pharmaceutical form: Solution for injection Strength: 10 mg/mL concentration Clear to slightly opalescent, colourless to slightly coloured solution. Multiple Dose Vial: 10 mg/1 mL Proposed (if applicable): Not applicable
Is the product subject to additional monitoring in the EU?	Yes

Part II: Safety specification
Part II: Module SI - Epidemiology of the indications and target populations

Treatment of obesity and the control of hunger associated with genetically confirmed BBS in adults and children 2 years of age and above

Treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 2 years of age and above.

Human genetic studies have identified several diseases that are the result of genetic defects affecting the MC4R pathway (a highly conserved hypothalamic pathway critical for regulation of appetite, energy expenditure, and body weight) including, but not limited to:

- POMC deficiency obesity due to mutations in the *POMC* gene,
- PCSK1 deficiency due to mutations in the *PCSK1* gene, leading to a hormone processing defect that also causes POMC deficiency obesity,
- LEPR deficiency obesity due to mutations in the *LEPR* gene, and
- BBS

These MC4R pathway mutations can cause rare genetic disorders of obesity that progress over time and can become life-threatening in severity.

Incidence: There are no available data on incidence of obesity due to BBS, POMC deficiency or LEPR deficiency. BBS, POMC and LEPR deficiencies can be confirmed only following genetic testing. The overall incidence of BBS is ~1:160,000 (Forsythe 2013).

Prevalence: On the basis of the very small number of cases recorded in worldwide literature, it is estimated that fewer than 50 affected individuals with POMC deficiency (Challis & Millington, 2013), fewer than 90 individuals with LEPR deficiency (Kleinendorst et al 2020), and fewer than 50 PCKS1 deficiency cases have been reported thus far (Stijnen et al 2016; Argente et al 2019). These numbers are supported by the *orpha.net* POMC prevalence of <0.1/10,000 and the LEPR prevalence of approximately 0.1/10,000 (Orpha.net).

Demographics of the population in the proposed indications: Individuals with POMC deficiency obesity or LEPR deficiency obesity exhibit an onset very early in life, often beginning in infancy.

As patients grow and develop, paediatric weight curves demonstrate progressive and severe weight gain, tracking >3 standard deviations (SD) above normal weights for age and leading ultimately to adult BMI values >40 kg/m^2. Patients with POMC deficiency obesity often weigh over 100 kg by age 6 to 8 years (Challis & Millington, 2013).

In a systematic literature search performed by Kleinendorst et al 2020 the authors calculated 998 predicted patients with LEPR deficiency in Europe, corresponding to a prevalence of 1.34 per 1 million people. Consanguinity was reported in 74% LEPR cases of this analysis (Kleinendorst et al 2020).

The Marketing Authorisation Holder (MAH) commissioned a literature review, which identified a total of 150 cases of rare genetic disorders of obesity, including 31 of POMC, 76 of LEPR, and 43 of PCSK1 deficiency obesity. Key findings in each population from the Rhythm-commissioned literature review (Argente et al 2019) were as follows:

POMC: Among the population of patients with POMC deficiency obesity, 39% were from Turkey, North Africa, Middle East, or Southwest Asia, and 39% were from the European Union (EU) and North America; no country of origin was documented for the remaining 23% of patients. With regards to ethnicity, 48% were Turkish, Arabic, or Southwest Asian; 29% were Caucasian, and 6% were Hispanic. Twenty-six percent of patients were known to be from consanguineous families. A total of 74% of patients had been diagnosed by age 10 years. Sixty-eight percent of patients were noted to have hyperphagia, described as severe in some cases. Common laboratory findings included low adrenocorticotropic hormone (ACTH), hypocortisolism, hypoglycaemia, and hypothyroidism. Cognitive impairment was uncommon (3 patients). No specific findings were noted that were specific to the EU region.

LEPR: Among the population of patients with LEPR deficiency obesity, 51% were from Turkey, North Africa, Middle East, or Southwest Asia. With regard to ethnicity, 64% were Turkish, Arabic, or Southwest Asian. Seventy percent of patients were known or suspected to be from consanguineous families. Ninety-seven percent of patients had documentation of early-onset obesity, with 100% having hyperphagia, in some cases severe or marked. Among patients who were old enough for assessment, ~40% had delayed puberty. Common laboratory abnormalities included elevated leptin and hyperinsulinemia. Cognitive delay was not common (4 patients). No specific findings were noted that were specific to the EU region.

Overall, early-onset obesity and hyperphagia were prevalent in the patient populations identified, with the populations largely being consanguineous.

BBS: BBS, one of the ciliopathies, 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 (Forsythe 2013). 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. These 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 (Bardet 1995, Biedl 1995, Beales 1999, Forsythe 2013, Forsythe 2015).

The main existing treatment options:

POMC, including PCSK1 deficiency and LEPR deficiency

There are no approved therapies other than setmelanotide specifically for the treatment of obesity and hyperphagia associated with POMC or LEPR deficiencies. Furthermore, there is limited evidence of any efficacious treatment for children or adolescents with these genetic disorders. Although bariatric surgery has been attempted in a significant number of these patients, it is uniformly unsuccessful in the control of hunger and obesity. Bariatric surgery cannot address the underlying issue of the lack of a satiety signal in these patients. There are also no management guidelines in Europe for the treatment or management of POMC or LEPR deficiencies.

Commonly, patients with POMC deficiency require life-long glucocorticosteroid treatment using replacement doses. Mineralocorticoid replacement is not required. Hypothyroidism should be monitored and treated if present. Early onset obesity can be very difficult to treat beyond standard dietary and lifestyle measures, but the hyperphagic component is especially challenging (Çetinkaya et al 2008).

The outcome in the absence of treatment may result in hyperphagia, somatic conditions frequently associated with severe obesity; heart disease, obstructive sleep apnoea, hypertension, dyslipidaemia and type 2 diabetes mellitus which may result in significant and well-documented cardiac, renal, and/or ophthalmic complications for children and young adults, and which may lead to premature death.

Potential surgical approaches, such as gastric or intestinal bypass operations, are considered contraindicated because such patients maintain an extreme appetite and overeat even after such surgical restrictions, often leading to anatomical complications as a result.

In the cases of both POMC and LEPR deficiency obesity, severe hunger and early-onset obesity are a direct result of the genetic defect and are unresponsive to behavioural modification, surgery, drug intervention, or environmental changes. It is these characteristics that distinguish these patients from those with general severe obesity, and results in an intractable form of obesity with serious consequences starting in early childhood, with manifestations of the disease often apparent in the first year of life.

BBS

There are no approved therapies other than setmelanotide specifically for the 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; however, there is limited experience with these therapies in patients with MC receptor pathway associated obesity such as BBS. In general, these therapies have not been successful in early-onset extreme genetic obesity ([redacted], and [redacted] personal communications). This is not surprising since 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.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

POMC, including PCSK1 deficiency and LEPR deficiency

Obesity is well known to adversely impact quality of life, with more significant impairment and higher percentages of individuals affected as BMI increases with higher degrees of obesity (Hassan et al 2003, Mayo Clinic 2015). Associated features of obesity include depression, disability, sexual problems, shame and guilt, social isolation and lower work achievement. Obesity, in particular, is attributed as the cause of death in >300,000 persons annually in the United States (US) and in 2.8 million persons worldwide, making it the 5th leading global risk for death, and shortens life-span by ~7 years in women and 6 years in men.

Notably, obesity is also a significant risk factor for cardiovascular disease (CVD), with obese persons being 2 to 3 x more likely to develop CVD than those who are of normal weight (Stein & Colditz, 2004). Overall, 20 to 30% of CVD mortality is estimated to be attributable to overweight (Stein & Colditz, 2004). No EU specific data have been reported.

Individuals with POMC and LEPR deficiencies exhibit an unrelenting hunger and food-seeking behaviours (hyperphagia) very early in life, often beginning in infancy, and severe obesity follows shortly thereafter. As patients grow and develop, paediatric weight curves demonstrate progressive and severe weight gain, tracking >3 SD above normal weight-for-age and leading ultimately to adult BMI values >40 kg/m^2 (Challis & Millington, 2013).

When considering the POMC and LEPR deficiency obesity populations, the patients are not in a continuum that increases from overweight to obese through "severe" or "extreme" obesity (i.e., the worst obesity). Instead, consistent morbid obesity (e.g., extreme obesity) is characteristic of these genetically defined diseases and is the hallmark of every patient who has one of these diseases. The obesity in these populations begins very early in life, much earlier than in even the most severe patients with general obesity, so the exposure to the negative effects of extreme obesity plays a great role throughout the

paediatric period from earliest childhood. Patients with such POMC or LEPR gene mutations exhibit an onset very early in life, often beginning in infancy, with rapid weight gain that is associated with a voracious, overactive appetite and pronounced hyperphagic feeding behaviours. Remarkable weight increases over 3 SD from the normal weight growth curves are typical in these patients. Unlike in patients with general obesity, these patients continue to gain weight across their lifetime, with an average weight gain of 7-10 kg/year, for every year of life (primarily analysed in the paediatric and adolescent populations that have these diseases). Childhood weight gain is severe and rapidly progressive, ultimately leading to adult BMI values typically >40 kg/m^2. The effect of extreme obesity in childhood and adolescence is multi-faceted, affecting individuals from childhood through adolescence and adulthood. Extreme obesity shows substantial tracking into adulthood and entails elevated mortality and high rates of co-morbid disorders (Freedman et al 2001). Similarly, children and especially adolescents with extreme obesity experience increased mortality and morbidity, including cardiovascular (CV), metabolic, respiratory and orthopaedic complications (Norris et al 2011, Schwimmer et al 2003, Amin and Daniels 2002, Karlson et al 2003) and global impairments in daily functioning (Zeller et al 2006).

Although not directly life-threatening, intractable hunger is a second hallmark of these diseases. Hunger dominates the lives of these patients and their families as well as their quality of life and social development. Parents relate that children do not sleep well (hunger at night leading to night eating); cannot socialise well with other children (cannot control their urge to eat everything available no matter the social setting); and often suffer in school (distracted by the mental impact of intractable hunger that persists at all times).

Prominent features of the POMC and LEPR deficiency include:

- POMC deficiency obesity: ACTH deficiency and secondary cortisol deficiency. Clinical features of affected patients may include red hair and pale skin (Argente et al 2019)
- LEPR deficiency obesity: Hypothyroidism and/or growth hormone deficiency, delayed puberty, alterations in immune function, and hyperinsulinemia (Argente et al 2019; Kleinendorst et al 2020)

In patients with POMC deficiency red hair and skin paleness can develop due to the lack of melanocyte stimulating hormone effect on MC1R within the skin, but this phenotypic feature is variable, in part depending on ethnic background. The lack of ACTH production by the pituitary gland and consequential activation of melanocortin 2 receptors in the adrenal glands may result in secondary adrenal deficiency. Patients are often diagnosed soon after birth due to adrenal insufficiency. If the diagnosis is missed in early infancy, patients can die from adrenal glucocorticoid insufficiency (many POMC defect patients have had siblings with unexplained early deaths). However, if patients are identified and begun on life-sustaining glucocorticoid replacement or if patients have residual expression of ACTH from the pituitary, voracious infant feeding and weight gain is noted, and obesity develops rapidly during early infancy.

Other endocrine abnormalities observed include central hypothyroidism due to thyroid stimulating hormone deficiency, adult-onset growth hormone deficiency, and adolescent-onset hypogonadotropic hypogonadism due to lack of luteinising hormone or follicle stimulating hormone.

BBS

The most recognized and prevalent of the ciliopathies, BBS is a genetically heterogeneous disease with mutations in as many as 21 different genes all of which participate in cilia functioning (Supistin et al 2016). The clinical presentation includes congenital post-axial polydactyly (extra fingers or toes), marked obesity and hyperphagia beginning early in life, retinal dystrophy with visual impairment symptoms beginning most often in the first decade of life and progressing to blindness by the second or

third decade, developmental delay; and/or cystic renal abnormalities (Forsythe & Beales 2013). Of all these manifestations, obesity and hunger may be the most disturbing (Grace et al 2003). While birth weight in affected patients is usually normal, significant weight gain due to increased food intake and decreased energy expenditure (Forsythe et al 2015) begins in the first year and is a lifelong issue for most (72-92%) patients (Forsythe & Beales 2013). Relative to healthy subjects with a comparable BMI, patients with BBS tend to have higher adiposity (Grace et al 2003), significantly more abdominal visceral fat (Feuillan et al 2011), and less lean mass (Locke et al 2009).

Important co-morbidities: Individuals with BBS, POMC and LEPR deficiency obesities show extensive evidence of effects of their severe obesity to a level that is obvious and serious to their health. These effects generally are in the categories: respiratory, CV, hepatic/metabolic, and orthopaedic. Frequent comorbidities include lipid abnormalities, sleep apnoea, leg, hip, and knee fractures/malformation/arthritis, and delays in growth and pubertal development. Adrenal insufficiencies, other severe hormonal abnormalities, and risk of infections can add to the seriousness and potentially life-threatening nature of POMC and LEPR deficiency obesities.

Medications associated with the co-morbidities may include (Challis & Millington, 2013):

- Type-2 diabetes: Anti-diabetic medications that have additional actions to promote weight loss (such as glucagon-like peptide-1 analogues or sodium-glucose-linked transporter-2 inhibitors)
- Hypertension: Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers
- Anxiety and depression: Anti-depressants and anxiolytics
- Atherosclerosis: Anti-platelet medications to help prevent the build-up of plaque or help prevent clots. Statins may be prescribed to lower cholesterol. Angiotensin-converting enzyme inhibitors to help lower blood pressure (BP)
- Hormone deficiency: Hydrocortisone replacement for adrenal insufficiency, growth hormone for growth hormone deficiency, thyroid hormone for hypothyroidism, and/or sex hormone replacement for hypogonadotropic hypogonadism

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

Incidence and prevalence: Hypothalamic obesity (HO) is a severe, devastating disease that confers substantial morbidity and excess mortality (Roth & McCormack, 2024). The condition is characterized by rapid weight gain which is most dramatic in the first 6 to 12 months after disease onset (Rydin et al 2022, Shoemaker & Tamaroff, 2022, Roth & McCormack, 2024). Acquired HO affects approximately 5,000 to 10,000 patients in the US and is believed to have similar incidence and prevalence in the EU and rest of world (Teng et al 2021; Roth et al 2015). A German real-world database analysis (Witte et al 2024) estimated annual incidence of tumour/treatment-related aHO in Germany between 0.7 and 1.7 cases per 1,000,000 persons (2019 prevalence: n = 1262 patients). Most frequent aHO validated tumour diagnoses were benign sellar/suprasellar tumours (6.1/1,000,000 persons over 9 years), including tumours of the craniopharyngeal duct (1.3/1,000,000), neoplasms of the pituitary gland (4.1/1,000,000), and nonspecific brain tumours of endocrine glands (2.4/1,000,000).

Demographics of the population in the proposed indications: Craniopharyngiomas currently represent one of the most common tumours associated with the development of aHO and account for 5% to 15% of paediatric intracranial tumours, and occur with 2 peaks of incidence, one during childhood (10 to 19 years of age [29%]) and the second in adulthood (30 to 49 years of age [25%]) (Muller et al

2022). Similar results were observed from German database analysis which identified two tumour/ treatment-related aHO incidence peaks: in children and young adults aged 10 to 24 years and adults aged 40 to 44 years (Witte et al 2024).

Main existing treatment options: There is currently no approved or established standard of care therapies for the treatment of aHO.

Natural history of the indicated condition in the untreated population, including mortality and morbidity: Acquired HO develops after injury to the hypothalamus, most often as a result of a tumour (eg, craniopharyngiomas, gliomas, pituitary adenomas, hamartomas), and/or the surgery or radiation therapy used to treat the tumour (Hochberg & Hochberg, 2010). Other rarer causes of injury may include inflammatory conditions involving the hypothalamus such as sarcoidosis or traumatic brain injury. In other disorders which may involve the hypothalamus, a subset of patients develop obesity which is hypothesized to be due to developmental abnormalities of the hypothalamus. These disorders include septo-optic dysplasia, optic nerve hypoplasia, childhood-onset combined pituitary hormone deficiency (also called multiple pituitary hormone deficiency) and pituitary stalk interruption syndrome. Patients with these disorders often have a variable degree of endocrinopathies due to pituitary and or hypothalamic developmental abnormalities that may significantly impact growth, development, and survival (Hietamaki et al 2022, Cerbone et al 2020).

Regardless of the underlying cause, patients with aHO develop an aggressive form of obesity characterized by a high degree of sudden, severe, and sustained weight gain that has generally been unresponsive to lifestyle or medical intervention (Muller et al 2022).

The weight gain in patients with aHO is most dramatic in the first 6 to 12 months after injury and then continues for the next 8 to 12 years before plateauing (Sterkenburg et al 2015). Hyperphagia may occur in approximately 50% to 70% of patients along with lethargy due to decreased energy expenditure, and psychosocial disorders spanning from depression to aggressive behaviour are common (Muller 2011, Kayadjanian et al 2023).

Important co-morbidities: Acquired HO is one of the most refractory types of obesity and leads to severe atherosclerotic disease, type 2 diabetes mellitus, metabolic syndrome, and early mortality in some patients (Muller 2011, Olsson et al 2015, Sterkenburg et al 2015). As noted above, craniopharyngioma and its treatment are common causes of aHO. Although treatment of craniopharyngioma is associated with excellent overall survival, patients with aHO due to a craniopharyngioma have increased mortality compared to craniopharyngioma patients with no aHO (Haliloglu et al 2016, Rosenfeld et al 2014). Treated patients who develop aHO exhibit a marked increase in both CV and overall mortality compared to the general population (Bülow et al 1998).

In one study, an increase in BMI SD of samples after 6 months of therapy was observed to be a risk factor for mortality caused by aHO. In addition, diagnosis in patients aged less than 6 years and a maximum BMI SD of samples ≥ 3 were associated with a higher mortality rate (Haliloglu et al 2016). One study of patients with paediatric onset craniopharyngioma had an overall mortality rate of 16.6% which increased to 36.4% in obese patients (BMI > 97th percentile), and only obese patients (n=4) died during follow-up (Rosenfeld et al 2014).

Part II: Module SII - Non-clinical part of the safety specification

The non-clinical studies summarised below provide a comprehensive assessment of pharmacology, pharmacokinetics (PK), and toxicology of setmelanotide in its proposed commercial formulation, which contains the primary excipient mPEG-DSPE (N-[carbonyl-methoxypolyethylene glycol 2000]-1,2-distearoyl-glycero-3-phosphoethanolamine) and is referred to as setmelanotide/mPEG-DSPE. The toxicological profile of SC administered setmelanotide has been well characterised in repeat-dose general toxicity studies in adult rats and monkeys, reproductive and developmental toxicity studies in rats and rabbits, juvenile toxicity studies in rats, in vitro and in vivo genotoxicity studies, dose-ranging studies in wild-type rasH2 (WT rasH2) mice, and three 26-week SC injection carcinogenicity studies of setmelanotide/mPEG-DSPE in transgenic rasH2 (Tg.rasH2) mice. In vitro genotoxicity studies were conducted with setmelanotide in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance genotoxicity testing and data interpretation for pharmaceuticals intended for human use (ICH S2, Revision 1). All pivotal toxicology studies of setmelanotide were conducted in compliance with Organisation for Economic Co-operation and Development Good Laboratory Practice (GLP) standards.

Various GLP safety pharmacology studies were performed, which included respiratory safety, central nervous system (CNS) safety, in vitro human ether-à-go-go related gene (hERG) channel current safety and in vivo CV safety studies.

Table SII-1: Overview of non-clinical studies with setmelanotide

Key Safety Findings (from Non-clinical studies)	**Relevance to Human Usage**
Toxicity	
Setmelanotide in mPEG-DSPE or saline (the latter included to achieve higher doses and systemic exposure compared to setmelanotide/mPEG-DSPE) was well tolerated in repeat-dose SC injection toxicity studies when administered for up to 6 months in rats and 9 months in monkeys. Inflammatory injection site reactions were reported and have been attributed primarily to the mPEG-DSPE vehicle, with possible involvement of setmelanotide at high doses. No systemic adverse effects were observed in chronic toxicity studies at setmelanotide exposure levels up to 49- and 38- times the human exposure from a 3 mg clinical dose based on plasma AUC, or at mPEG-DSPE doses up to 60- and 20- times the human mPEG-DSPE dose (30 mg from a 3 mg dose of setmelanotide/mPEG-DSPE) on a mg/kg/day basis in rats and monkeys, respectively. Minimal, non-adverse cytoplasmic vacuolation related to the presence of mPEG-DSPE was observed in the choroid plexus of rats (epithelial cells) and monkeys (macrophages) following chronic administration of setmelanotide/mPEG-DSPE or the mPEG-DSPE vehicle alone. There was no distortion of brain tissue in any animal, and no evidence of any other microscopic changes in the brains of rats or monkeys suggestive of a toxic response, including no degeneration, inflammation, or necrosis. Furthermore, no functional changes in the brain were noted based on clinical observations. With the exception of the injection sites, vacuolation was not seen in any other organ or tissue at the end of the dosing period.	During clinical trials, injection site reactions, e.g., erythema, pruritus and other reactions, occurred in most patients. These reactions were typically mild, localised, of short duration and did not progress or lead to discontinuation of therapy. Cytoplasmic vacuolation observed following PEG administration is considered to be an adaptive response related to PEG clearance rather than a toxic response to PEG (Rudmann et al 2013). The PEG-related cytoplasmic vacuolation is considered non-adverse if 1) there is no distortion of normal tissue architecture, 2) there is no evidence of histopathological changes such as degeneration, inflammation, or necrosis, and 3) there is no evidence of functional impairment (Ivens et al 2015). These criteria for non-adversity were clearly met in both the 26-week rat and 39-week monkey studies with regard to the findings in the choroid plexus, and no similar histopathological changes were noted in other tissues with the exception of the injection

Key Safety Findings (from Non-clinical studies)	Relevance to Human Usage
Hyperpigmentation of skin on the muzzle and periorbital region that correlated microscopically with increased epidermal pigment consistent with melanin has been observed in all setmelanotide studies conducted in cynomolgus monkeys at all doses tested. The hyperpigmentation presented after approximately 1 week of dosing and had improved or resolved by the conclusion of the recovery periods, indicating reversibility. Increased pigmentation was noted clinically in the conjunctiva following high doses administered to monkeys by continuous SC infusion, but clear differences between control and treated animals were not apparent histologically due to a high degree of pigmentation at this site in control animals. Hyperpigmentation was not observed in other pigmented tissues, including retina. Microscopic examination of hyperpigmented skin indicated that facial hyperpigmentation in monkeys treated with setmelanotide was not due to cellular proliferation or differentiation of melanocytes. Genetic Toxicology Studies A battery of studies was conducted to assess the genotoxic potential of setmelanotide. Setmelanotide was negative for genotoxicity, with no evidence of mutagenic or clastogenic activity in any study at concentrations and doses up to the ICH S2(Revision 1) limits for each assay. These included: • bacterial reverse mutation, • in vitro chromosome aberration, • in vivo rat bone marrow micronucleus assays.	sites. In a recent study, PEG-related vacuolation in choroid plexus epithelial cells was considered non-adverse at PEG doses up to 120 mg/kg/week (7,200 mg/week for a 60 kg subject) (Fletcher et al 2019). The weekly dose of mPEG-DSPE at the maximum recommended setmelanotide clinical dose of 3 mg/day (30 mg/day mPEG-DSPE) is 210 mg/week (34-fold less than the highest non-adverse dose in monkeys). Therefore, findings of vacuolation from chronic toxicity studies in rats and monkeys are not considered to be a safety risk in humans. Skin darkening was observed in a majority of patients treated with setmelanotide. This generally occurred within 2 weeks of starting therapy and continued for the duration of treatment. This darkening of skin is mechanism based, resulting from stimulation of the MC1R. There is no evidence that this change in pigmentation is detrimental to the patient, and no cases of melanoma have been reported; however, based on limited clinical data is considered an important potential risk. The data from non-clinical studies suggest that setmelanotide is unlikely to cause other systemic adverse effects to humans at the recommended doses based on large safety margins from chronic toxicity studies. The data from these studies indicate that setmelanotide is non-genotoxic.
Carcinogenicity	
The carcinogenic potential of setmelanotide/mPEG- DSPE was evaluated in three 26-week SC injection study in Tg.rasH2 mice. Doses for these studies were selected based on the results from a 28-day dose range-finding study in WT rasH2 mice in accordance with ICH guidelines. In the first study, hemizygous Tg.rasH2 and WT mice were inadvertently randomised into the main study groups (mean number of Tg.rasH2 mice/sex/group = 15; range = 11 to 20 mice/sex/group). There was no evidence of increased mortality or tumorigenicity in mice, confirmed to be transgenic by polymerase chain reaction. Two additional 26-week SC injection carcinogenicity studies of setmelanotide/mPEG-DSPE in Tg.rasH2 mice only (no WT) were also performed to confirm the results from the first study.	Overall, based on the validity of the Tg.rasH2 mouse model to evaluate the carcinogenic potential of setmelanotide, the data from the three carcinogenicity studies in mice, and the toxicity studies in rats and monkeys, the weight-of-evidence indicates that setmelanotide does not pose a carcinogenic risk to humans.

Key Safety Findings (from Non-clinical studies)	Relevance to Human Usage
There was no evidence of carcinogenic potential or anti-setmelanotide antibodies in Tg.rasH2 mice following daily SC injection of setmelanotide in mPEG/DSPE at doses up to 10 mg/kg/day in any study. In addition to the results from the three 26-week carcinogenicity studies, setmelanotide has exhibited no genotoxic activity in bacterial reverse mutation, in vitro chromosome aberration, or in vivo micronucleus assays. Setmelanotide and the mPEG-DSPE vehicle have not been associated with increased hypertrophic, hyperplastic, or preneoplastic (proliferative) tissue changes in toxicity studies of up to 26-weeks in rats and 39-weeks in monkeys, or in juvenile rats treated from Days 7 to 55 postpartum at 9-, 26- and 7-times, respectively, for setmelanotide based on AUC and 9.5-, 6.5- and 9.5-times, respectively, for mPEG-DSPE on a mg/m2/day basis, the clinical dose of 3 mg setmelanotide/30 mg mPEG-DSPE. In conclusion, the available carcinogenicity data in Tg.rasH2 mice indicate that setmelanotide/mPEG-DSPE does not pose a carcinogenic risk to patients, with a safety margin of 17 for setmelanotide based on AUC and a dose margin of 16 for mPEG-DSPE on a mg/m^2/day basis, at the clinical dose of 3 mg setmelanotide/30 mg mPEG-DSPE. Due to the lack of pro-carcinogenic concern from the available non-clinical and clinical data on setmelanotide, a 2-year carcinogenicity study in rats has not been performed.	
Reproductive and Developmental Studies	
There was no evidence of setmelanotide-related effects on male or female fertility in rats, and no teratogenic or other adverse reproductive effects were observed in rats at setmelanotide exposure levels up to 34- and 11-times human exposures from a 3 mg clinical dose based on plasma Cmax and AUC, respectively, and mPEG-DSPE doses up to 100- times the human mPEG-DSPE dose on a mg/kg/day basis. In rabbits, increased embryo-foetal resorptions and post-implantation loss observed at exposure levels greater than approximately 0.4-times human AUC were likely attributable to very low levels of food consumption during the treatment period, indicating extreme sensitivity of rabbits to the primary pharmacodynamic activity of setmelanotide. No teratogenic effects were observed in rabbits at any dose. In rats, no maternal toxicity or adverse effects on F1 offspring were observed in a pre- and postnatal development study at setmelanotide exposure levels up to 20- and 7-times the estimated human Cmax and AUC, respectively, from the maximum proposed clinical dose of 3 mg/day. This study demonstrated that setmelanotide is excreted in milk in nursing rats. No quantifiable setmelanotide concentrations were detected in plasma from nursing pups.	Setmelanotide did not elicit adverse effects on fertility, embryo-foetal viability and development, or pre- and post-natal development in rats at large multiples of the human exposure from the maximum recommended clinical dose. Embryo-foetal resorptions and post-implantation loss in rabbits at low exposure multiples was attributed to extreme sensitivity to the pharmacological activity of setmelanotide on food consumption rather than a direct toxicological effect. As a precautionary measure, IMCIVREE should not be started during pregnancy or while attempting to get pregnant as weight loss during pregnancy may result in foetal harm. It is unknown whether setmelanotide is excreted in human milk. Setmelanotide was excreted in the milk of nursing rats however no quantifiable setmelanotide concentrations were detected in plasma from nursing. A risk to the newborns/infants cannot be excluded.

Key Safety Findings (from Non-clinical studies)	Relevance to Human Usage
Juvenile Toxicology Studies	
Setmelanotide was well tolerated when administered by SC injection to juvenile rats from the age of 7 to 55 days postpartum at doses up to 3 mg/kg/day in mPEG-DSPE, and at 15 mg/kg/day in saline, the highest doses tested. There were no setmelanotide-related adverse clinical signs, no systemic organ effects, and no effects on growth parameters, sexual maturation, behaviour, learning and memory, or reproductive performance at setmelanotide exposure levels up to 94- and 33-times the human exposure from a 3 mg dose based on plasma C_{max} and AUC, and mPEG-DSPE doses up to 60 times the human mPEG-DSPE dose on a mg/kg/day basis. Inflammatory injection site reactions were similarto those observed in adult rats (see Toxicity). Notably, there was no evidence of PEG-related vacuolation in juvenile rats in any tissue or organ system, including no vacuolation in the choroid plexus.	The toxicity profile in juvenile rats was similar to that of adult animals. The data from this study suggest that setmelanotide is unlikely to cause systemic adverse effects to paediatric subjects at the recommended doses based on large safety margins in juvenile rats.
Safety Pharmacology	
Setmelanotide was evaluated in a standard battery of GLP-compliant safety pharmacology studies, including an *in vitro* hERG assay and *in vivo* CV, respiratory, and CNS studies. No safety concerns were noted. These studies, as well as several other CV safety studies, as summarised below.	Safety pharmacology studies have not identified any safety concerns.
Other Toxicity-Related Information or Data	
Cardiovascular	
In a GLP CV telemetry study in cynomolgus monkey, there were no biologically significant setmelanotide-related effects on haemodynamic or ECG parameters following a 3-day SC continuous infusion at doses up to 25 mg/kg/day. A critical part of the preclinical programme was to evaluate the CV safety of setmelanotide in light of reported increase in HR and BP induced by a comparator MC4R agonist LY2112688 in an earlier human clinical study (Greenfield et al, 2009). Non-human primates were a major focus on these evaluations. The lack of HR and BP effects associated with setmelanotide in the GLP CV study were confirmed in obese rhesus monkeys, where animals were treated for one week in a crossover study comparing setmelanotide to LY2112688 at the same dose level (Kievit et al, 2013). In this model, SC infusion of LY2112688 for one week (0.5 mg/kg/day) caused increases in both HR and BP similar to that seen in the clinic, with the effect on HR being statistically significant. When the same group of animals were crossed-over to treatment with setmelanotide at the same dose level (0.5 mg/kg/day; a dose that was shown to be very efficacious in a weight loss study), no increases in HR or BP were noted during one week of setmelanotide treatment. In addition, no increases in HR or BP were observed in obsess rhesus monkeys treated with setmelanotide by SC infusion at 0.50 mg/kg/day for 8 weeks. Since MC4R agonists have been shown to induce increases	Obesity is a significant risk factor for CVD, with obese persons being 2 to 3x more likely to develop CVD than those who are of normal weight (Stein & Colditz, 2004). No clinically significant changes in HR or BP were seen in non-clinical studies in monkeys with continuous SC infusion. There were also no concerning signals for adverse changes in HR or BP in the Phase 1 clinical studies employing careful CV evaluations at doses ~10-fold higher than pharmacodynamically active doses. In completed longer term clinical studies of setmelanotide in obese patients, there has been no evidence of clinically significant changes in HR or BP. As no adverse CV effects were observed in human clinical trials with setmelanotide, or in monkeys treated with 10-times the maximum recommended human dose on a mg/kg/day basis (assuming 60 kg human), it appears that results in

Key Safety Findings (from Non-clinical studies)	Relevance to Human Usage
in BP and HR in rats (Nordheim et al, 2006), the CV effects of acute and sub-chronic setmelanotide administered by SC injection and SC infusion were studied in rats at doses from 0.01 to 3.0 mg/kg, and in minipigs at 0.5 mg/kg. Variable CV effects were observed, including increased HR and BP. In the rat model, HR and BP effects were linked to an increase in sympathetic tone and they were found to diminish progressively upon repeated daily dosing. It is unclear why CV effects were observed in rats and minipigs, but not in monkeys. Setmelanotide inhibited hERG current by approximately 1.6% at 10 µM and 9.2% at 300 µM, the highest concentration tested.	monkeys were predictive of humans, whereas the CV effects noted in rats and minipigs were not. The results from the hERG channel current safety studies suggest a low risk for hERG-related QT prolongation with setmelanotide at clinical doses. Human Cmax for unbound setmelanotide in plasma following SC injection of a 3 mg clinical dose is estimated to be approximately 0.02 µM, or 500-and 17,500-times less than the 10 and 300 µM concentrations of setmelanotide that had negligible and minimal effects on hERG activity, respectively. ECGs have been evaluated across the clinical trials and have shown no evidence of QTc prolongation.
Respiratory and CNS Safety	
In an ICH-compliant battery of GLP safety pharmacology studies, there were no setmelanotide-related effects on any of the qualitative or quantitative functional observation battery parameters nor any effect on motor activity at doses up to 120 mg/kg in a neurobehavioral safety pharmacology study in male rats by continuous SC infusion, nor any treatment-related effects in rats on respiratory rate, tidal volume and minute volume at doses up to 120 mg/kg. These no-effect doses are 2,400- times the maximum recommended human dose on a mg/kg basis (assuming 60 kg subject).	No adverse effects of setmelanotide were observed on respiratory or CNS safety pharmacology parameters at very large multiples of the maximum recommended human dose on a mg/kg basis.

Abbreviations: AUC = area under the curve; BP = blood pressure; Cmax = maximum observed concentration; CNS = central nervous system; CV = cardiovascular; CVD = cardiovascular disease; ECG = electrocardiogram; GLP = good laboratory practice; hERG = human ether-à-go-go related gene; HR = heart rate; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; MC1R = melanocortin 1 receptor; MC4R = melanocortin 4 receptor; mPEG-DSPE = methoxyl poly(ethylene glycol) conjugated with 1,2-distearoyl-sn-glycero-3- phosphoethanolamine; PEG = polyethylene glycol; SC = subcutaneous; Tg.rasH2 = transgenic rasH2; WT = wild-type

No safety concerns for IMCIVREE were identified from the non-clinical studies.

Part II: Module SIII - Clinical trial exposure

Safety data are presented through a data cut-off date of 26 March 2025 for all patients studied in the setmelanotide clinical development programme including healthy volunteers and otherwise healthy subjects with obesity, including patients 2 years and older with POMC, PCSK1, and LEPR-deficiency obesity (PPL) or BBS and patients 4 years and older with aHO.

As of 26 March 2025, a total of 24 clinical studies contribute to the overall exposure to setmelanotide in the clinical development programme and are described in the below table.

Table SIII-1: Tabular Listing of Completed and Ongoing Studies with QD Setmelanotide

Study number	Study Title	Study Population	Status
RM-493-001	A Phase 1, Randomized, Double-blind, Placebo Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of RM-493 Administered to Healthy Obese Non-Diabetic Volunteers	Otherwise healthy subjects with obesity	Complete
RM-493-002	A Phase 1, Randomized, Double-blind, Placebo Controlled, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of RM-493 Administered to Healthy Obese Non-Diabetic Volunteers	Otherwise healthy subjects with obesity	Complete
RM-493-003	A Phase 2, Randomized, Double-blind, Placebo Controlled Study to Evaluate the Safety and Efficacy of RM-493, a Melanocortin 4 Receptor (MC4R) Agonist in Obese Patients	Otherwise healthy subjects with obesity	Complete
RM-493-006	A Phase 1b, Randomized, Double-blind, Placebo Controlled, Multiple Dose, 2-Period Crossover Study to Evaluate the Effect of RM-493 on Energy Expenditure in Obese Subjects	Otherwise healthy subjects with obesity	Complete
RM-493-008	A Phase 1, Open-Label, 3-Period Single Dose Crossover Study to Evaluate the Pharmacokinetics of New Once-Daily Injectable Formulations of RM-493 in Obese Subjects	Otherwise healthy subjects with obesity	Complete
RM-493-009	A Staged, Phase 1b/Phase 2a, Randomized, Double Blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of RM-493, a Melanocortin 4 Receptor (MC4R) Agonist in Obese Patients using a Once or Twice Daily Subcutaneous Injection Formulation	Otherwise healthy subjects with obesity	Complete
RM-493-010	A Phase 2, Randomized, Double-Blind, Placebo Controlled Pilot Study to Assess the Effects of RM-493, a Melanocortin 4 Receptor (MC4R) Agonist, in Obese Subjects with Prader-Willi Syndrome (PWS) on Safety, Weight Reduction, and Food-Related Behaviors	Prader-Willi Syndrome	Complete

Study number	Study Title	Study Population	Status
RM-493-011	Setmelanotide (RM-493) Treatment Trial in Patients with Rare Genetic Disorders of Obesity	POMC-homozygous, heterozygous and epigenetic deficiency, LEPR deficiency, MC4R	Complete
RM-493-012 (pivotal study in patients with POMC/PCSK1 mutations)	An Open-Label, 1-Year Trial, Including a Double-Blind Placebo-Controlled Withdrawal Period, of Setmelanotide (RM-493), a Melanocortin 4 Receptor (MC4R) Agonist, in Early Onset POMC Deficiency Obesity Due to Biallelic Loss-of-Function POMC or PCSK1 Genetic Mutation	POMC deficiency obesity due to biallelic, loss-of-function POMC or PCSK1 gene mutations	Complete
RM-493-014	Setmelanotide (RM-493) Phase 2 Treatment Trial in Patients with Rare Genetic Disorders of Obesity	Various genetic diseases including: BBS/AS SMS MC4R, rescuable, non-rescuable, hyper-responders PPL bi-allelic, N221D bi-allelic, PPL heterozygous SH2B1 SRC1 16Pl1.2	Complete
RM-493-015 (pivotal study in patients with LEPR mutations)	An Open-Label, 1-Year Trial, Including a Double-Blind Placebo- Controlled Withdrawal Period, of Setmelanotide (RM-493), a Melanocortin 4 Receptor (MC4R) Agonist, in Leptin Receptor (LEPR) Deficiency Obesity Due to Biallelic Loss-of-Function LEPR Genetic Mutation	Biallelic, homozygous or compound heterozygous (a different gene mutation on each allele) genetic status for either the LEPR genes, with the loss-of-function variant for each allele conferring a severe obesity phenotype	Complete
RM-493-019	Expanded-Access for the use of Setmelanotide in a Single Patient with Partial Lipodystrophy (LD) Associated with Leptin Deficiency and Multiple Autoimmune Diseases	Partial Lipodystrophy Associated with Leptin Deficiency and Multiple Autoimmune Diseases	Complete
RM-493-022	Long-term Extension Trial of Setmelanotide (RM-493) for Patients Who Have Completed a Trial of Setmelanotide for the Treatment of Obesity Associated with Genetic Defects Upstream of the MC4 Receptor in the Leptin-Melanocortin Pathway	Obesity associated with genetic defects upstream of the MC4R in the leptin MC pathway	Complete
RM-493-023 (pivotal study in patients with BBS and AS)	A Phase 3 Trial of Setmelanotide (RM-493), a Melanocortin 4 Receptor (MC4R) Agonist, in Bardet-Biedl syndrome (BBS) and Alström Syndrome (AS) Patients with Moderate to Severe Obesity	BBS and AS	Complete

Study number	Study Title	Study Population	Status
RM-493-026[a]	A Phase 1b Study to Evaluate the Effect of Once-Daily and Once-Weekly Formulations of Setmelanotide on Weight Loss and Pharmacokinetics in Healthy Obese Subjects	Otherwise healthy subjects with obesity	Complete
RM-493-029	A Phase 1, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of Setmelanotide in Subjects with Varying Degrees of Renal Impairment	Subjects with renal impairment and healthy subjects with normal renal function	Complete
RM-493-030	A Phase 2, Open-Label 20-Week Study to Evaluate the Safety and Efficacy of Setmelanotide in Subjects with Hypothalamic Obesity	Patients with HO aged 6 to 40 years-40 years.	Complete
RM-493-032	A Randomized, Double-Blind, 3-arm, Parallel Group, Placebo- and Positive-controlled Study to Investigate the Effects of Setmelanotide on QTc Interval in Healthy Subjects	Healthy subjects aged 18 to 50 years	Complete
RM-493-033 (pivotal study in patients with PPL and BBS)	A Phase 3 Multicenter, One-Year, Open-Label study of Setmelanotide in Pediatric Patients Aged 2 to <6 years of age with Rare Genetic Causes of Obesity	POMC/PCSK1, LEPR, and BBS patients aged 2 to <6 years of age	Complete
RM-493-034	A 2-Stage (Open-Label Run-in followed by Randomized Withdrawal), Double-Blind, Placebo-Controlled, Phase 2 Study of Setmelanotide in Patients with Specific Gene Defects in the Melanocortin-4 Receptor Pathway	Patients with specific gene defects in the MC4R pathway aged 6 to 65 years	Complete
RM-493-035	A Phase 3 Randomized Double-Blind Placebo Controlled Trial: Multiple Independent Sub-studies of Setmelanotide in Patients with POMC/PCSK1, LEPR, NCOA1 (SRC1) or SH2B1 Gene Variants in the Melanocortin-4 Receptor Pathway	Patients with POMC/PCSK1, LEPR, NCOA1 (SRC1) or SH2B1 Gene Variants in the MC4R Pathway	Ongoing
RM-493-037[a]	A Phase 3, Randomized, Double-Blind Trial of Two Formulations of Setmelanotide (Daily and Weekly) with a Crossover to Open-Label Once Weekly Setmelanotide in Patients with Specific Gene Defects in the Melanocortin-4 Receptor Pathway Who Are Currently on a Stable Dose of the Once Daily Formulation	Patients with specific gene defects in the MC4R pathway who were on a stable dose of the once daily formulation	Complete
RM-493-040	A Phase 3, Double Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Setmelanotide in Patients with Acquired Hypothalamic Obesity	Patients with aHO aged ≥4 years	Ongoing (pivotal patients complete)
RM-493-042	Open-Label Extension Study of Setmelanotide in Patients with a Rare	Patients with a rare genetic, syndromic or acquired	Ongoing

Study number	Study Title	Study Population	Status
	Genetic, Syndromic or Acquired Disease of the MC4R Pathway	disease of the MC4R Pathway	

Abbreviations: aHO = acquired hypothalamic obesity; AS = Alström Syndrome; BBS = Bardet-Biedl syndrome; HO = hypothalamic obesity; LEPR = leptin receptor; MC = melanocortin; MC4 = melanocortin-4; MC4R = melanocortin-4 receptor; NCOA1 = nuclear receptor coactivator 1; PCSK1 = proprotein convertase subtilisin/kexin Type 1; POMC = pro-opiomelanocortin; PPL = POMC, PCSK1, and LEPR-deficiency obesity, collectively; QD = once daily; QTc = corrected QT interval; SMS = Smith-Magenis syndrome; SRC1 = steroid receptor coactivator-1.

[a] Only data from patients who received QD setmelanotide are included to support the safety of QD setmelanotide

Overall, as of 26 March 2025, from these studies, a total of 982 subjects have been exposed to at least 1 dose of setmelanotide, 209 subjects received only placebo and treatment assignment remains blinded for 166 subjects (in Study RM-493-035 or Study RM-493-040). The duration of exposure is provided in Table SIII-2.

Overall, the mean time on treatment was 366 days (range, 1 to 2781 days [~91.4 months]) in the 982 setmelanotide-treated patients. The median duration of all participants treated with setmelanotide (107 days) was shorter due to limited exposure in the Phase 1 studies.

Table SIII-2: Overall Extent of Exposure in the QD Setmelanotide Clinical Development Programme through 26 March 2025

Parameter Statistic	All Patients with aHO		BBS patients(N=58)	PPL patients (N=42)	All Patients with RDO	All Participants
	Setmelanotide (N=147)	Placebo (N=48)			Setmelanotide (N=694)	Setmelanotide (N=982)
Time on Treatment (days)						
n	147	48	58	42	694	982
Mean (SD)	412.4 (306.9)	365.6 (108.8)	978.0 (537.8)	1304.5 (784.2)	502.3 (565.4)	365.7 (520.8)
Median	429.0	413.0	988.5	1288.0	253.5	107.0
Min, Max	1, 1327	23.0, 452.0	106.0, 2131.0	50.0, 2781.0	1, 2781	1, 2781
Duration of Exposure, n (%)						
<1 month	10 (6.8)	1 (2.1)	0	0	80 (11.5)	264 (26.9)
1 to <3 months	15 (10.2)	1 (2.1)	0	2 (4.8)	109 (15.7)	190 (19.3)
3 to <6 months	18 (12.2)	3 (6.3)	5 (8.6)	2 (4.8)	135 (19.5)	158 (16.1)
6 to <12 months	13 (8.8)	4 (8.3)	3 (5.2)	2 (4.8)	45 (6.5)	45 (4.6)
12 to <18 months	53 (36.1)	39 (81.3)	8 (13.8)	3 (7.1)	96 (13.8)	96 (9.8)
≥18 months	38 (25.9)	0	42 (72.4)	33 (78.6)	229 (33.0)	229 (23.3)

Abbreviations: aHO = acquired hypothalamic obesity; BBS = Bardet-Biedl syndrome; LEPR = leptin receptor; Max = maximum; Min = minimum; PCSK1 = proprotein convertase subtilisin/kexin type 1; POMC = pro-opiomelanocortin; PPL = POMC, PCSK1, and LEPR-deficiency obesity; RDO = rare diseases of obesity; QD = once daily; SD = standard deviation.
Note: Placebo data are only shown for patients with aHO, because placebo data are limited for the other populations.

The setmelanotide dosage regimen for each clinical study is presented in Table SIII-3.

Table SIII-3: Setmelanotide dosage regimen per clinical study

Study number	**Dosage regimen**
RM-493-001	SC infusion: Single dose of 0.0025, 0.01, 0.02, 0.025, 0.05 or 0.1 mg/kg/24 hours SC injection; 0.01 mg/kg
RM-493-002	SC infusion: repeat doses of 0.0025, 0.01 or 0.015 mg/kg/24 hours for 14 or 28 days SC injection: 0.0075 mg/kg/Q12hr for 14 days
RM-493-003	Repeat doses of 1.0 mg/24 hour for 90 days
RM-493-006	Repeat doses of 1.0 mg/24 hour for 3 days
RM-493-008	Part A: Both formulations of setmelanotide at a fixed dose of 1.5 mg. Part B: Repeat doses of 1.5 mg QD for 4 days or 1.0 mg QD for 2 days followed by 2.0 mg QD for 2 days
RM-493-009	Stage A: 1.5 mg/day or 0.75 mg twice daily both increased to 2 mg/day at 4 weeks for a total of 12 weeks Stage B: 1.5 mg/day increased to 2 mg/day at 4 weeks for a total of 12 weeks Stage C: 2 mg/day for a total of 12 weeks
RM-493-010	10-week cross-over design of 0.5 to 2.5 mg QD setmelanotide/mPEG-DSPE with randomised discontinuation and concluding active treatment period (at 1.5 mg QD);
RM-493-011	2 to 12-week dose titration to therapeutic dose level (maximum of 3.0 mg) followed by 13 weeks at therapeutic dose followed by long term treatment at therapeutic dose
RM-493-012	Up to 12-week dose titration to therapeutic dose level (maximum of 3.0 mg) followed by 10 weeks at therapeutic dose followed by 8-week double blind placebo withdrawal and 32 weeks continued treatment at therapeutic dose
RM-493-014	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
RM-493-015	Up to 10- or 12-week dose titration to therapeutic dose level (maximum of 3.0 mg) followed by 10 weeks at therapeutic dose followed by 8-week double blind placebo withdrawal and 32 weeks continued treatment at therapeutic dose
RM-493-019	Up to 10 weeks dose titration to therapeutic dose level (maximum of 3 mg) followed by 10 weeks at therapeutic dose followed by 1-year continued treatment at therapeutic dose
RM-493-022	Setmelanotide QD at the same dose administered towards the end of the index study
RM-493-023	Setmelanotide or placebo QD via SC injection for the first 14 weeks. Starting dose 2 mg with increase to 3 mg for subjects ≥16 years Starting dose 1 mg with increase to 2 mg for subjects <16 years of age). After the 14-week double-blind treatment period, all subjects receive open label setmelanotide QD via SC injection for 38 weeks

Study number	Dosage regimen
RM-493-026	2 mg daily during Week 1 3 mg daily Weeks 2-12
RM-493-029	Subjects in Cohorts A, B, and D received a single dose of 2 mg setmelanotide. The dose administered for subjects in Cohort C (severe impairment) was decreased to 1.0 mg and further to 0.5 mg
RM-493-030	Setmelanotide by SC injection, 1.0, 2.0, 3.0 mg QD for subjects 6 to <16 years of age, and 2.0 to 3.0 mg QD for subjects ≥16 years of age
RM-493-032	Group 1: SC setmelanotide QD x 16 days (2 mg × 7 days, 3 mg × 3 days, 5 mg × 3 days, 7 mg × 3 days) + oral placebo on Days 10 and 16 Group 2: SC placebo QD x 16 days + oral moxifloxacin on Day 10 and oral placebo on Day 16 Group 3: SC placebo QD x 16 days + oral placebo on Day 10 and oral moxifloxacin on Day 16
RM-493-033	All patients will begin treatment at a dose of 0.5 mg of setmelanotide per day. Patients will then increase their dose by 0.5 mg increments, every 2 weeks. The highest dose in this study for patients who weigh <20 kg, 20 to <30 kg, 30 to <40 kg and ≥40 kg will be 0.5 mg, 1.0 mg, 1.5 mg and 2.0 mg per day.
RM-493-034	Setmelanotide by SC injection QD. In patients 12 years of age and older, setmelanotide 2 mg QD will be administered for approximately the first 14 days, then increased to setmelanotide 3 mg QD for the remainder of the study. In patients aged 6 to <12 years old, setmelanotide 1 mg QD will be administered for approximately the first 7 days, then increased to setmelanotide 2 mg for approximately 7 days, then increased to 3 mg QD for the remainder of the study.
RM-493-035	Patients 6 to <12 years old will start at a dose of 1.0 mg/day for 1 week, escalate to 2.0 mg/day for 1 week, and then to 3.0 mg/day for the remaining 50 weeks of treatment. Patients ≥12 years old will start at a dose of 2.0 mg/day for 2 weeks and then escalate to 3.0 mg/day for the remaining 50 weeks of treatment.
RM-493-037	The setmelanotide QW formulation (in FluidCrystal-vehicle) is provided as a sterile solution at a concentration of 30 mg/mL for administration of dose levels of 20, 25, and 30 mg by SC injection.
RM-493-040	Setmelanotide 0.5 mg QD or placebo equivalent will be administered as the starting dose for all patients. After the initial dose of 0.5 mg, patients will be escalated each week in increments of either 0.5 or 1.0 mg to achieve the individual patient's therapeutic regimen. Patients could reach their therapeutic regimen in as little as 2 weeks for patients <20 kg, with most patients reaching their maximally tolerated therapeutic dose between 4 and a maximum of 8 weeks. Each weekly dose escalation may be extended over 2 weeks as needed based on tolerability.

Study number	Dosage regimen
RM-493-042	The lowest dose is 0.5 mg and the highest dose is 3 mg in patients ≥6 years and 2.5 mg in patients <6 years.

Abbreviations: mPEG-DSPE = methoxyl poly(ethylene glycol) conjugated with 1,2-distearoyl-sn-glycero-3-phosphoethanolamine; QD = once daily; SC = subcutaneous.

Demographics and baseline characteristics among all setmelanotide-treated patients are summarised in Table SIII-4.

Table SIII-4: Demographics and Baseline Characteristics of Patients in the Setmelanotide QD Clinical Development Programme through 26 March 2025

Demographic or Characteristic	All Patients with aHO		BBS (N = 58)	PPL (N = 42)	All RDO Patients (N = 694)	All Participants
	Setmelanotide (N=147)	Placebo (N=48)				Setmelanotide (N=982)
Sex, n (%)						
Male	62 (42.2)	17 (35.4)	26 (44.8)	22 (52.4)	256 (36.9)	396 (40.3)
Female	85 (57.8)	31 (64.6)	32 (55.2)	20 (47.6)	438 (63.1)	586 (59.7)
Age, n (%)						
2 to <6 years[a]	3 (2.0)	2 (4.2)	5 (8.6)	7 (16.7)	15 (2.2)	15 (1.5)
6 to <12 years	31 (21.1)	10 (20.8)	8 (13.8)	6 (14.3)	98 (14.1)	98 (10.0)
12 to <18 years	48 (32.7)	15 (31.3)	20 (34.5)	10 (23.8)	178 (25.6)	178 (18.1)
2 to <18 years	82 (55.8)	27 (56.3)	33 (56.9)	23 (54.8)	291 (41.9)	291 (29.6)
≥18 years	65 (44.2)	21 (43.8)	25 (43.1)	19 (45.2)	403 (58.1)	691 (70.4)
Race, n (%)						
American Indian or Alaska Native	0	0	0	0	3 (0.4)	5 (0.5)
Asian	11 (7.5)	5 (10.4)	2 (3.4)	0	23 (3.3)	24 (2.4)
Black or African American	9 (6.1)	1 (2.1)	3 (5.2)	1 (2.4)	67 (9.7)	189 (19.2)
Native Hawaiian or Other Pacific Islander	1 (0.7)	0	0	0	1 (0.1)	2 (0.2)
White	115 (78.2)	36 (75.0)	46 (79.3)	27 (64.3)	530 (76.4)	681 (69.3)
Other	11 (7.5)	6 (12.5)	7 (12.1)	12 (28.6)	54 (7.8)	65 (6.6)
Not Reported	0	0	0	2 (4.8)	9 (1.3)	9 (0.9)
Missing	0	0	0	0	7 (1.0)	7 (0.7)

Demographic or Characteristic	All Patients with aHO		BBS (N = 58)	PPL (N = 42)	All RDO Patients (N = 694)	All Participants
	Setmelanotide (N=147)	Placebo (N=48)				Setmelanotide (N=982)
Ethnicity, n (%)						
Hispanic or Latino	18 (12.2)	8 (16.7)	2 (3.4)	3 (7.1)	87 (12.5)	149 (15.2)
Not Hispanic or Latino	128 (87.1)	40 (83.3)	49 (84.5)	33 (78.6)	574 (82.7)	800 (81.5)
Not reported	0	0	3 (5.2)	2 (4.8)	13 (1.9)	13 (1.3)
Missing/Unknown	1 (0.7)	0	4 (6.9)	4 (9.5)	20 (2.9)	20 (2.0)
BMI (kg/m^2)						
n	147	48	58	42	693	981
Mean (SD)	36.5 (8.9)	36.4 (8.8)	40.6 (10.3)	42.7 (11.2)	42.5 (10.9)	40.2 (10.5)
Median (Min, Max)	34.6 (21, 70)	34.6 (21, 70)	42.0 (19, 66)	41.7 (26, 70)	41.5 (19,91)	39.1 (19, 91)

Abbreviations: aHO = acquired hypothalamic obesity; BBS = Bardet-Biedl syndrome; BMI = Body Mass Index; LEPR = leptin receptor; Max = maximum; Min = minimum; PCSK1 = proprotein convertase subtilisin/kexin type 1; POMC = pro-opiomelanocortin; PPL = POMC, PCSK1, and LEPR-deficiency obesity; RDO = rare diseases of obesity; QD = once daily; SD = standard deviation.

[a] Patients with aHO are 4 to <6 years of age

Note: Placebo data are only shown for patients with aHO, because placebo data are limited for the other populations.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The main exclusion criteria for the Phase 3 clinical trials are detailed below.

Clinically significant pulmonary, cardiac, or oncologic disease

Reason for exclusion: Patients with clinically significant pulmonary, cardiac, or oncologic disease were excluded from the pivotal clinical trials to ensure that they did not confound the safety and/or efficacy evaluation of setmelanotide.

Is it considered to be included as missing information? No

Rationale: There is no reason to expect any issues with this population.

Suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale

Reason for exclusion: The population under study had a significant background rate of depression and suicidality. To perform a thorough evaluation of the significance of these events in the setmelanotide-treated population and obtain a full understanding of the benefit-risk balance of setmelanotide without confounding factors, this population was excluded.

Is it considered to be included as missing information? No

Rationale: Some drugs that target the CNS have been associated with depression or suicidal ideation. Appropriate language regarding depression and suicidal ideation is in the summary of product characteristics (SmPC) and depression (including suicidal ideation) is considered an important potential risk for setmelanotide.

Severe renal impairment as defined by a glomerular filtration rate <30 mL/min

Reason for exclusion: The pathological features of CVD, which are altered in subjects with severe renal dysfunction may have confound the data, thus impacting the evaluation of the safety and/or efficacy of setmelanotide. Additionally, population PK analysis suggests decreased clearance in patients with renal impairment.

Is it considered to be included as missing information? Yes

Rationale: Not applicable

History of significant liver disease or liver injury, or a current liver assessment due to abnormal liver tests

Reason for exclusion: As there was limited experience with use in patients with pre-existing liver disease, this patient population was excluded from the pivotal clinical trials to ensure that they did not confound the safety and efficacy data.

Is it considered to be included as missing information? Yes

Rationale: Not applicable.

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

Reason for exclusion: Skin hyperpigmentation is a known effect of MC1R agonism. To perform a thorough evaluation of the significance of skin hyperpigmentation events in the setmelanotide-treated population and to obtain a full understanding of the benefit-risk balance of setmelanotide without confounding factors, these patients were excluded from the pivotal clinical studies.

Is it considered to be included as missing information? No

Rationale: Melanoma is considered an important potential risk for setmelanotide.

Significant hypersensitivity to any excipient of the study drug

Reason for exclusion: Patients who were hypersensitive to any component of the product were excluded from study participation on grounds of safety.

Is it considered to be included as missing information? No

Rationale: Hypersensitivity is listed as a Contraindication in the SmPC.

Use in children less than 2 years

Reason for exclusion: The EU paediatric investigation plan (PIP) for setmelanotide in the condition "treatment of appetite and nutrition disorders" waives the need for data in patients less than 2 years of age.

Is it considered to be missing information? No

Rationale: The EU PIP waiver applies on the grounds that the product does not represent a significant therapeutic benefit over existing treatments.

Use in pregnant/breastfeeding women

Reason for exclusion: Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. However, administration of setmelanotide to pregnant rabbits resulted in decreased maternal food consumption leading to embryo-foetal effects. Additionally, a non-clinical study showed that setmelanotide is excreted in the milk of nursing rats. As no experience in pregnant or breastfeeding women exists, patients who were pregnant/breastfeeding were excluded on grounds of safety.

Is it considered to be missing information? Yes

Rationale: Not applicable.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as those associated with prolonged or cumulative exposure (> 4 years).

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Children < 2 years of age	Not included in the clinical development programme
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with CV impairment • Immunocompromised patients	Patients with significant liver disease, significant pulmonary, cardiac, or oncologic disease were not included in the clinical development programme. Setmelanotide has been studied in a small number (8) of patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) in one Phase 1 study. No patients with eGFR <15 mL/min/1.73 m^2 were included in the clinical development programme.
Population with relevant different ethnic origin	There were no inclusion/exclusion criteria for patients based on ethnic origin.
Subpopulations carrying relevant genetic polymorphisms	Not applicable. Population studies included genetic deficiencies.

Abbreviations: CV = cardiovascular; eGFR = estimated glomerular filtration rate

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The estimated number of treated patients is derived from sales figures based on shipments of product sent through the Specialty Pharmacy in US. For Canada, the number of treated patients is provided from the patient support programme. Outside the US, the local regional managers maintain exposure data and provide patients on treatment by indication.

SV.1.2 Exposure

As of 26 March 2025, setmelanotide has received authorisation in the US (25 November 2020), in the EEA (16 July 2021), in United Kingdom (15 September 2021), in Israel (29 December 2022) and in Canada (05 May 2023). As of 26 March 2025, setmelanotide has been commercially launched in the US, Germany, United Kingdom, Italy, Netherlands, Spain, and Canada. Since first approval, cumulative post-authorisation exposure through 26 March 2025 is [redacted] patients receiving IMCIVREE through specialty pharmacy (including patients in [redacted] and [redacted]) plus [redacted] patients receiving IMCIVREE through other therapeutic programmes.

The cumulative exposure to setmelanotide is provided in Table SV.1 below.

Table SV.1: Cumulative patient numbers by category and country - per data cut 26 Mar 2025

Countries	On-label	Off-label	Total
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: US = United States

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is no information to indicate that setmelanotide would have the potential to be misused for illegal purposes.

Part II: Module SVII - Identified and potential risks

The focus of the safety data presentation is for a total of 982 setmelanotide-treated patients, which include healthy volunteers, otherwise healthy subjects with obesity, and all patients with aHO treated in either single-arm or comparative studies up to 26 March 2025.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

1. Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

The following are not classified as important risks based on the nature of the adverse reactions observed in clinical trials, and are expected to be easily managed during the use of setmelanotide:

- Injection site reactions (Includes injection-site-associated events of erythema, pruritus, oedema, pain, induration, bruising, reaction, swelling, haemorrhage, hypersensitivity, haematoma, nodule, discoloration, erosion, inflammation, irritation, warmth, atrophy, dryness, hypertrophy, rash, scab, scar, urticaria)
- Pruritis, rash (rash, rash papular, rash erythematous, rash pustular, urticaria)
- Dry skin
- Erythema
- Hyperhidrosis
- Dermal cyst
- Dermatitis
- Nail disorder
- Fatigue
- Asthenia
- Pain
- Chills
- Chest pain
- Temperature intolerance
- Appetite disorders
- Gastrointestinal disorders (nausea, vomiting, polydipsia, diarrhoea, abdominal pain, abdominal pain upper, abdominal pain lower, dry mouth, dyspepsia, constipation, flatulence, abdominal discomfort, Gingival discoloration, abdominal distention, salivary hypersecretion)
- Headache and sinus headache
- Dizziness
- Somnolence
- Dysgeusia
- Migraine
- Parosmia
- Insomnia

- Sleep disorder
- Back pain
- Myalgia
- Muscle spasms, Pain in extremity
- Arthralgia, Musculoskeletal chest pain
- Yawning
- Cough
- Rhinorrhoea
- Scleral discolouration
- Hot flush
- Eosinophilia
- Vertigo

These adverse reactions are included in the SmPC.

2. Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

None

3. Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

Systemic hypersensitivity reactions

Whilst anaphylactic reactions have not been observed in the patients receiving setmelanotide within clinical development programme, it is recognised that life-threatening anaphylactic reactions may occur with some medications. Setmelanotide is contraindicated in individuals with a known hypersensitivity to the active substance or any excipients.

4. Known risks that do not impact the risk-benefit profile

Skin hyperpigmentation

Skin darkening was observed in 56% of patients treated with setmelanotide. This generally occurred within 2 to 3 weeks of starting therapy, continued for the duration of treatment, and resolved upon discontinuation of treatment. There is no evidence that this change in pigmentation is detrimental to the patients.

Transient penile erections/sexual arousal

Spontaneous penile erections, an effect associated with MC4R agonism, were reported in 44 of 226 male setmelanotide-treated subjects. These were mild or moderate in nature and resolved quickly without need for medical intervention. There were no cases of prolonged erections (> 4 hours).

Based on the effects of setmelanotide on penile erections/sexual arousal, it is recognised that there is potential for misuse and off-label use, but not due to drug dependency. The frequency of penile

erections/sexual arousal with setmelanotide in the setmelanotide clinical development programme was low and unpredictable such that the desired effect by a potential misuser would be inconsistent. In contrast, drugs that are indicated for erectile dysfunction, such as phosphodiesterase (PDE)-V inhibitors, have a consistent effect. In addition, one of the leading causes for PDE-V inhibitors misuse is the availability of the drug at low cost through internet pharmacies. [redacted]

5. Other reasons for considering the risks not important:

Hypertension

Individuals with early-onset extreme obesity frequently suffer CV complications, and hypertension has been seen in the drug class in certain species of animal. Safety assessments have included ambulatory BP measurement evaluations in several studies in order to thoroughly evaluate this possible mechanistic effect, which was evident with the less selective oral MC4R agonists previously studied. Setmelanotide has demonstrated no evidence of increasing BP in human and monkey studies. In completed longer term clinical studies of setmelanotide in obese patients, there has been no evidence of clinically significant changes in BP. In fact, some patients demonstrated improvements.

Other CV events

Cardiovascular events other than hypertension have been seen in the drug class and background disease. Overall, 20 to 30% of CVD mortality is estimated to be attributable to being overweight (Stein & Colditz, 2004). Setmelanotide has demonstrated no evidence of increasing heart rate (HR) in human and monkey studies. In completed longer term clinical studies of setmelanotide in obese patients, there has been no evidence of clinically significant changes in HR. In fact, some patients demonstrated improvements in CV parameters.

Off-label use

- Other obesities

  The possibility exists that setmelanotide may be used off-label in other obese populations not related to POMC/PCSK1 and LEPR deficiencies or BBS. However, clinical data from setmelanotide use in healthy subjects with obesity has shown minimal decrease in weight and no difference in the safety profile. In addition, treatment with setmelanotide will be supervised by a physician with expertise in genetic obesity. A confirmed genetic diagnosis by laboratory testing may be required to obtain the drug. Each vial will contain 10 mg of setmelanotide, approximately 5 doses, less than a week of therapy. Finally, another deterrent to the abuse of setmelanotide for weight loss is the requirement for daily injections, and the fact that [redacted]; therefore, off label use in this population is considered unlikely and is not expected to have a different safety profile.

- Erectile dysfunction

  Given the low, transient and unpredictable frequency of penile erections/ sexual arousal with setmelanotide as well as the low duration of the effect, in contrast to drugs that are indicated for erectile dysfunction, such as PDE-V inhibitors, and which have a consistent effect, it is considered unlikely for setmelanotide to be used off-label for erectile dysfunction. [redacted] Overall, the applicant assesses the risk of abuse of setmelanotide for off-label uses to be extremely low.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

No important identified risks have been established for setmelanotide.

Three important potential risks have been established for setmelanotide.

Important Potential Risk 1: Melanoma

Risk-benefit impact: More than half (57% [322/561]) of setmelanotide-treated patients experienced a hyperpigmentation disorder, most commonly skin hyperpigmentation (49% [277/561]). Other hyperpigmentation disorder events were less commonly reported, including melanocytic naevus (9% [52/561]) and skin discoloration (6% [35/561]). All other hyperpigmentation disorders were reported in <1% of setmelanotide-treated patients. These events were expected due to the melanocyte stimulating hormone like effect of MC4R agonists on the MC1R.

For most patients who experienced hyperpigmentation disorders, the event was assessed by the Investigator as mild to moderate in intensity, with 5 (1%) patients experiencing a severe hyperpigmentation disorder (skin hyperpigmentation in all cases). There were no setmelanotide-related serious hyperpigmentation disorders; one case of melanocytic naevus was considered serious, but unrelated to setmelanotide. Setmelanotide interruption due to a hyperpigmentation disorder was uncommon (2 subjects; <1%). Seventeen (3%) patients discontinued setmelanotide due to a hyperpigmentation disorder.

Additionally, there is little likelihood for an activation of melanocyte or skin cell proliferation, as this skin pigmentation effect is likely mediated by stimulation of the MC1R in skin to augment melanin production. However, given the natural incidence of melanoma and other skin pigmentary lesions in the general population, there is a likelihood that reports of melanoma or other skin pigmentary lesions coincident with setmelanotide administration could be reported in the post-marketing setting. Although there is no evidence to indicate that skin hyperpigmentation caused by MC1R agonism results in melanoma, given the limited clinical data in the setmelanotide-treated population, melanoma is considered an important potential risk for setmelanotide.

Important Potential Risk 2: Prolonged Penile Erections

Risk-benefit impact: While spontaneous penile erections and increased erections have been reported with the use of setmelanotide, there have been no prolonged penile erections requiring medical intervention. There was no signal of prolonged penile erections in pre-clinical or clinical setmelanotide studies, or published in the wider drug class; however, rare case reports of priapism have been reported with other MC receptor agonists (Devlin et al 2013; Dreyer et al 2019).

Prolonged penile erections can cause serious complications and are considered an acute medical emergency, without which, permanent injury is possible. Given the clinical significance of priapism, prolonged penile erections will be monitored as an important potential risk.

Important Potential Risk 3: Depression (including suicidal ideation)

Risk-benefit impact: In clinical trials with setmelanotide, subjects were monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour; there were no treatment related events of depression or suicidal ideation. However, medications that target the CNS have been associated with depression and suicidal ideation. In addition, patients with severe obesity are known to have both depression and suicidal ideation and behaviours (Amiri and Behnezhad 2019).

Severe depression may require hospitalisation and become life-threatening should suicidal ideation develop. Based on the clinical significance of depression and the potential for development of suicidal ideation, depression (including suicidal ideation) is considered an important potential risk for

setmelanotide.

Missing information 1: Use in pregnant/breastfeeding women

Risk-benefit impact: There are no clinical data on the use of setmelanotide in pregnancy or breastfeeding. Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. However, administration of setmelanotide to pregnant rabbits resulted in decreased maternal food consumption leading to embryo-foetal effects. There are no data on foetal outcomes from the use of setmelanotide in pregnant women. Additionally, it is unknown whether setmelanotide is excreted in human milk. A non-clinical study showed that setmelanotide is excreted in the milk of nursing rats. No quantifiable setmelanotide concentrations were detected in plasma from nursing pups. The SmPC notes that setmelanotide should not be started during pregnancy, as it has not been studied in pregnant women. Weight loss during pregnancy can harm the baby. The SmPC also advises to request advice from the doctor before taking setmelanotide when breastfeeding. It is unknown whether setmelanotide is excreted in human milk. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from IMCIVREE therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the mother; therefore, the potential for setmelanotide to be administered to pregnant and/or breastfeeding women is rare; however, given the data from non-clinical studies, use in pregnant/breastfeeding women is considered missing information.

Missing information 2: Use in hepatic impairment

Risk-benefit impact: Setmelanotide is stable in human, rat, and monkey hepatocytes; therefore, a study in hepatically impaired subjects was not conducted. There are no clinical data in hepatically impaired subjects and thus the clinical consequences of use in this patient population are unknown.

Missing information 3: Use in severe renal impairment

Risk-benefit impact: The vast majority of subjects in clinical studies had normal renal function. Pharmacokinetic analysis showed a 12%, 26%, and 49% lower clearance (CL/F) of setmelanotide in patients with mild, moderate, and severe renal impairment, respectively, as compared to patients with normal renal function.

No dose adjustments for patients with mild (estimated glomerular filtration rate [eGFR] of 60-89 mL/min/1.73 m^2) or moderate renal impairment (eGFR of 30-59 mL/min/1.73 m^2) are needed. Dose adjustments are recommended for patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2). There are no clinical data in patients with eGFR <15 mL/min/1.73 m^2.

Missing information 4: Long-term use

Risk-benefit impact: There are limited long-term data in the setmelanotide clinical studies, however, in the ongoing extension studies, setmelanotide continued to be well tolerated and without clinical signals of concern and no new safety signals. Further evaluation is required to determine whether there are risks associated with cumulative or long-term exposure.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Important Potential Risk: Benzyl alcohol accumulation in young children

Risk-benefit impact: In mammals, benzyl alcohol is metabolised into benzoic acid, and afterwards, is primarily metabolised to its glycine conjugate, hippuric acid, which is readily excreted via the renal organic anion transport system. The main concern associated with the use of benzyl alcohol is the risk of accumulation in newborn babies (pre-and full-term) due to metabolic immaturity. Benzyl alcohol

administered intravenously in the range of 100 to 200 mg/kg/day has been linked to the gasping syndrome in several pre-term newborns with metabolic acidosis that resulted in deterioration of the neurological status, cardio-vascular failure, and haematological anomalies (Brown et al 1982, Gershanik et al 1982). Young children (<3 years old) may not be sufficiently mature to metabolise and eliminate benzyl alcohol as efficiently as adults.

There are no clinical data of benzyl alcohol accumulation in children <3 years. The minimum amount of benzyl alcohol at which toxicity may occur is not known.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

No important identified risks have been established for setmelanotide.

Important Potential Risks: The cut-off periods for safety data are based on latest aggregate report with data lock point (DLP) of 24 November 2024 and clinical module with DLP of 26 March 2025.

Important Potential Risk 1: Melanoma

Potential mechanisms:
Setmelanotide is a selective MC4R agonist with 2-3-fold less activity at melanocortin 3 receptor and MC1R. The MC1R is expressed on melanocytes, and activation of this receptor leads to accumulation of melanin and increased skin pigmentation independently of ultraviolet light. There is little likelihood for an activation of melanocyte or skin cell proliferation, as the reversible skin pigmentation effect is mediated by stimulation of the MC1R in skin to augment melanin production rather than through sensitisation to sun exposure.

Evidence source(s) and strength of evidence:
There is no evidence from non-clinical data, clinical data or the drug class for the development of melanoma, however given the limited exposure in the clinical development programme, melanoma is considered an important potential risk.

Facial hyperpigmentation correlating microscopically with increased epidermal pigment was observed at all setmelanotide doses tested in studies in cynomolgus monkeys. This effect was reversible off drug. This skin darkening was not associated with differentiation or proliferation of melanocytes and is considered to be a pharmacological effect of setmelanotide activity at the MC1R.

Characterisation of the risk:
Studies of setmelanotide in cynomolgus monkeys have shown that transient facial hyperpigmentation was correlated with increased epidermal pigment (i.e., melanin) on the muzzle and periorbital region at all doses. Based on immunohistochemistry analysis of muzzle skin, there was no difference in the number of epidermal melanocytes in monkeys treated with setmelanotide compared with control animals, suggesting that hyperpigmentation was not due to proliferation of melanocytes.

Cumulatively, there have been two cases of melanoma. One case reported serious event of Malignant melanoma (Grade 3) originating from clinical trials, and the other reported serious event of Superficial spreading melanoma stage I, originating from post-marketing sources. Both events were considered unrelated to setmelanotide.

Consistent with the overall patient population, the most common hyperpigmentation disorders in patients 2 to <6 years of age were skin hyperpigmentation (67%) and melanocytic naevus (40%). None of the hyperpigmentation disorders were serious, severe, or led to treatment interruption or

discontinuation in these patients.

Clinical trial data:

More than half (70.4% [692/982]) of setmelanotide-treated patients experienced a hyperpigmentation disorder, most commonly skin hyperpigmentation (61% [595/982]) and ephelides (2.4% [24/982]).

For most patients, the event was assessed by the Investigator as mild to moderate, with 5 (<1%) patients experiencing a severe hyperpigmentation disorder (skin hyperpigmentation in all cases). All events were non-serious. Setmelanotide interruption due to a hyperpigmentation disorder was uncommon (<1%). The most common hyperpigmentation disorder resulting in setmelanotide discontinuation was skin hyperpigmentation occurring in 41 (4%) patients. Hyperpigmentation disorders were the most common events of special interest (ESI) category in participants who received setmelanotide.

Hyperpigmentation disorders are summarised in Table SVII.1.

Table SVII.1 Events of Special Interest of Hyperpigmentation Disorders Occurring in ≥2% of any Setmelanotide-Treatment Group in QD Clinical Development Programme through 26 March 2025 (N=982)

ESI Category **Preferred Term**	**All Participants** **Setmelanotide (N=982) n (%)**
Hyperpigmentation Disorders	
Skin Hyperpigmentation	595 (60.6)
Ephelides	24 (2.4)
Skin Discolouration	21 (2.1)
Nail Pigmentation	20 (2.0)
Macule	17 (1.7)
Tongue Pigmentation	15 (1.5)

Abbreviations: ESI = Events of special interest; N = number of patients; QD = once daily

Throughout the setmelanotide development programme (n=982), 6 treatment emergent adverse events (TEAEs) within the System Organ Class 'Neoplasms benign, malignant and unspecified (incl cysts and polyps) led to study drug discontinuation. The most common TEAEs were 5 events of melanocytic naevus.

Risk factors and risk groups:

Risk factors for developing melanoma include ultraviolet light exposure, moles, fair skin, freckling and light hair, family or personal history of melanoma, having a weakened immune system, being older, being male, and xeroderma pigmentosum (American Cancer Society resource page [www.cancer.org]).

Preventability:

Patients can decrease the risks of developing melanoma through the following measures:

- avoiding the sun during the middle of the day
- wearing sunscreen year-round
- wearing protective clothing
- avoiding tanning lamps and beds

- performing regular skin exams for new skin growths or changes in existing moles, freckles, bumps and birthmarks (American Cancer Society resource page [www.cancer.org])

Full body skin examinations should be conducted to monitor pre-existing and new skin pigmentary lesions.

Impact on the risk-benefit balance of the product:
Two cases of melanoma (both considered unrelated to setmelanotide) have been reported to date. Regular monitoring through full body skin examinations is currently mandated in all setmelanotide clinical trial protocols and the IMCIVREE SmPC contains language that mandates yearly skin examinations to monitor both pre-existing and new lesions. These measures are considered adequate as these should aid in the identification of pre-existing and new skin pigmentary lesions, their timely evaluation and appropriate follow-up. Importantly, the use of an MC1R agonist such as setmelanotide, in the setting of regular and careful dermatologic follow up may facilitate the earlier diagnosis of a pre-existing melanoma. Informing patients and healthcare professionals of this possibility should increase their awareness and encourage patients to notify their healthcare professionals should any suspicious lesions develop.

Public health impact:
Not yet established as estimated exposure to setmelanotide in the post-marketing setting is limited.

Important Potential Risk 2: Prolonged Penile Erections

Potential mechanisms:
Spontaneous penile erections, an effect associated with MC4R agonism, have been reported in setmelanotide-treated subjects.

Evidence source(s) and strength of evidence:
Pro-erectile effects of MC compounds are well-described (King et al 2007). Rare case reports of prolonged penile erection have been described in the literature with other MC receptor agonists (Devlin et al 2013; Dreyer et al 2019).

Spontaneous penile erections been reported in setmelanotide-treated subjects. Occurrence of these events did not appear to correlate with dose or duration of dosing, as the number of events did not increase with dose or duration of dosing.

Characterisation of the risk:

Clinical trial data:

No serious events of prolonged erections have been reported in clinical trials with setmelanotide.

The characterisation of the risk includes all events under the broad term sexual disorder. Overall, 190 (19%) of 982 setmelanotide-treated patients experienced a sexual disorder, most commonly spontaneous penile erection (57 [14%] of 396 males), erection increased (53 [13%] of 396 males), libido increased (31 [3%]), disturbance in sexual arousal (23 [2%]), and genital pain (4 [<1%]). ESIs of disturbance in sexual arousal occurring in ≥2% of any setmelanotide treatment group in the clinical development programme are summarised in Table SVII.2. Of note, the incidence in the male population is provided since "spontaneous penile erection" and "erection increased" only apply to males. All sexual events were non-serious, mild or moderate. The incidence of disturbances in sexual arousal overall was generally consistent across patient populations. There were no cases of prolonged erections >4 hours or cases requiring medical intervention.

As expected, the incidence of disturbances in sexual arousal was lower in the younger paediatric patient population, with 3 patients (20%) 2 to <6 years of age experiencing these events (spontaneous penile erection and erection increased). These events were non-serious and did not result in treatment interruption or discontinuation.

Table SVII.2 Events of Special Interest of disturbance in sexual arousal by MedDRA Preferred Terms in ≥2% of any Setmelanotide Treatment Group in the Clinical Development Programme through 26 March 2025

ESI Category **Preferred Term**	**All Participants** **Setmelanotide (N=982) n (%)**
Disturbance in sexual arousal	
Spontaneous Penile Erection	57 (5.8)[a]
Erection Increased	53 (5.4)[b]
Libido Increased	31 (3.2)
Disturbance In Sexual Arousal	23 (2.3)
Genital Pain	4 (0.4)

Abbreviations: ESI = Events of Special Interest; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients
a Using the denominator of N=396 for males, the percentage of setmelanotide-treated patients with spontaneous penile erection is 14.4%.
b Using the denominator of N=396 for males, the percentage of setmelanotide-treated patients with erection increased is 13.4%.

Post-marketing data:

Cumulatively, 74 non-serious events (Spontaneous penile erection [58], Priapism [8], Erection increased [7], and Excessive masturbation [1]) in 68 cases have been received from the post-authorisation sources. For the non-serious events of spontaneous penile erection, lack of sufficient information prevented confirmation of the duration of the event and therefore the classification of prolonged penile erections was not confirmed.

Risk factors and risk groups:
No risk factors or risk groups have been identified to date in setmelanotide-treated patients.
Patients with sickle cell anaemia or trait, thrombocythemia, polycythaemia or multiple myeloma or who are prone to venous thrombosis or who have a hyperviscosity syndrome may be at increased risk of priapism.

Preventability:
Unknown.

Impact on the risk-benefit balance of the product:
Prolonged penile erections can cause serious complications and are considered an acute medical emergency, without which a permanent injury is possible. Informing patients and healthcare professionals of this risk should increase their awareness and encourage patients to notify their healthcare professional so that they can obtain appropriate treatment.

Public health impact:
Not yet established as estimated exposure to setmelanotide in the post-authorisation setting is limited.

Important Potential Risk 3: Depression (including suicidal ideation)

Potential mechanisms:

Some drugs that target the CNS have been associated with depression or suicidal ideation; however, the exact mechanism is not known.

Evidence source(s) and strength of evidence:

Patients with severe obesity are known to have both depression and suicidal ideation behaviours (Amiri and Behnezhad, 2019), therefore the background rate of depression and suicidal ideation in these studies is not unexpected.

However, given that drugs which target the CNS are associated with depression/suicidal ideation, depression (including suicidal ideation) is considered an important potential risk for setmelanotide.

Characterisation of the risk:

Clinical trial data:

In clinical trials with setmelanotide, subjects were monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

A total of 17 SAEs (Suicidal ideation [12], Depression [4], Major depression [1]) have been received from clinical trials. The 12 SAEs of Suicidal ideation occurred in a total of 4 subjects, none of which were considered related to setmelanotide administration, and one occurred prior to starting study drug. Of the 5 SAEs consistent with depression (Depression [4], Major depression [1]) presented in 5 subjects, 2 were considered possibly/probably related by either Investigator or Rhythm.

No patient 2 to <6 years of age experienced a TEAE of this risk category.

Depression

Depression ESI among any setmelanotide treatment group in the clinical development programme are summarised in Table SVII.3. Overall, 6% (58/982) of patients experienced a depression event, including depression (3% [33/982]), depressed mood (2% [17/982]), and depressive symptom (1% [8/982]). The depression events were severe for 7 patients, and serious for 3 patients. One (<1%) patient required a setmelanotide dose interruption and 6 (1%) patients discontinued setmelanotide due to depression.

Table SVII.3 Events of Special Interest of depression by MedDRA Preferred Terms in ≥2% of any Setmelanotide Treatment Group in the Clinical Development Programme through 26 March 2025

ESI Category **Preferred Term**	**All Participants** **Setmelanotide (N=982) n (%)**
Depression	
Depression	33 (3.4)
Depressed Mood	17 (1.7)
Depressive Symptom	8 (0.8)

Abbreviations: ESI = Events of Special Interest; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients

Suicidal Ideation

In clinical trials, a total of 12 setmelanotide-treated patients experienced suicidal ideation during setmelanotide treatment. Three patients experienced serious TEAEs of suicidal ideation. No patients experiencing suicidal ideation required study drug interruption and 1 patient discontinued setmelanotide due to suicidal ideation.

There were no TEAEs of suicidal ideation in paediatric patients 2 to <6 years of age.

Post-marketing data:

From post-authorisation sources, a total of 113 events (Depression [61], Depressed mood [32], Suicidal ideation [10], Intentional self-injury [3], Discouragement [2], Suicide attempt [1], Intentional overdose [1], Anhedonia [1], Major depression [1], Self-injurious ideation [1]) in 104 cases have been received. Seventeen (17) events (Suicidal ideation [10], Intentional self-injury [3], Suicide attempt [1], Major depression [1], Self-injurious ideation [1], Depression [1]) were considered serious; all others were non-serious.

Risk factors and risk groups:
Patients with severe obesity are known to have both depression and suicidal ideation behaviours (Amiri and Behnezhad, 2019).

In the general population, other risk factors for depression include the following:

- Personal or family history of depression
- Major life changes, trauma, or stress
- Female gender
- Serious illness or mental illness
- Substance abuse
- Other medications known to cause depression

Preventability:
Effective measures to successfully prevent depression and suicidal ideation are not known. However, in order to minimise the risk, patients with depression should be monitored. Consideration should be given to discontinuing setmelanotide if suicidal thoughts or behaviours develop.

Impact on the risk-benefit balance of the product:
Patients with severe depression may develop suicidal ideation and/or require hospitalisation. Through monitoring of subjects with depression, the risk for severe depression can be reduced and treatment re-evaluated should suicidal thoughts or behaviours develop. Informing patients and healthcare professionals of this risk should increase their awareness and encourage patients to notify their healthcare professional so that they can obtain appropriate treatment before their depression becomes severe.

Public health impact:
Not yet established as estimated exposure to setmelanotide in the post-authorisation setting is limited.

Important Potential Risk 4: Benzyl alcohol accumulation in young children

Potential mechanisms:
The use of benzyl alcohol in children <3 years old was associated with respiratory, CV, and neurological impairment. Also, the risk of hyperbilirubinemia and metabolic acidosis was observed. As for benzoic

acid, there was a predominance of reports of bronchoconstriction in asthmatic patients. Most of the restrictions on the excipients use were due to adverse reactions targeted at neonates and children under three years of age. In this sense, the child's age group played a decisive role in the development of adverse reactions (Cabral et al 2021).

Evidence source(s) and strength of evidence:
Reports on fatal benzyl alcohol poisoning in premature neonates implied that the toxicity may be due to larger doses per kilogram than for adults. It has been postulated that the load of benzoic acid (metabolite of benzyl alcohol) may exceed the capacity of the immature liver or kidney for detoxification through glycine conjugation to form hippuric acid (LeBel et al 1988).

Characterisation of the risk:
There were no adverse events observed from clinical and post-authorisation sources that would imply benzyl alcohol accumulation in young children.

One additional case (reported Preferred Terms: Gasping Syndrome, Somnolence), involved neonatal gasping syndrome in a child. The patient was sent to the emergency room for an episode of gasping syndrome three weeks after starting treatment. Gasping syndrome is typically seen in neonates and very low birth weight infants exposed to benzyl alcohol preservatives and presents with a metabolic acidosis progressing to respiratory distress/gasping respirations, and sometimes also CNS dysfunction. This subject's presentation with rash, injection site erythema and swelling, throat tightness, difficulty breathing and face/lips turning blue is thought to be more consistent with an allergic reaction. There is no evidence of progression to overt anaphylaxis; the limited information available does not indicate typical treatment for anaphylaxis such as steroids, epinephrine, or antihistamines. This event was most likely due to an allergic reaction, and temporal association suggests it is related to setmelanotide.

Risk factors and risk groups:
Patients from 2 years of age. No risk factors have been identified to date in setmelanotide-treated patients.

Preventability:
Effective measures to successfully prevent benzyl alcohol accumulation in young children are not known. Patients from 2 to <3 years of age should be monitored for any sign of metabolic acidosis while under treatment.

Impact on the risk-benefit balance of the product:
The accumulation of benzyl alcohol in children <3 years old can potentially lead to toxicity which was severe in some cases. Informing caregivers and healthcare professionals of this risk should increase their awareness and encourage close monitoring of the children in this age group to ensure any adverse effects related to benzyl alcohol exposure are detected.

Public health impact:
Not yet established as estimated exposure of children age <3 years to setmelanotide in the post-authorisation setting is limited.

Missing information #1: Use in pregnant/breastfeeding women

Evidence source:
Pregnancy was reported in 2 patients in the setmelanotide clinical programme during setmelanotide treatment. One of these resulted in an elective termination. Given that the pregnancy was terminated, any effect of setmelanotide on the foetus is unknown. The second pregnancy resulted in a healthy baby

at term (greater or equal to 37 weeks of gestation) following setmelanotide use during approximately the first month of pregnancy. There were no complications during pregnancy or birth. There are no data from the use of setmelanotide in women who are lactating.

Cumulatively, there have been 6 post-authorisation cases of possible pregnancy coincident with setmelanotide use; however, pregnancy was medically confirmed in one case only.

Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. However, administration of setmelanotide to pregnant rabbits resulted in decreased maternal food consumption leading to embryo-foetal effects.

A non-clinical study showed that setmelanotide is excreted in the milk of nursing rats. However, no quantifiable setmelanotide concentrations were detected in plasma from nursing pups.

Population in need of further characterisation:
As this patient population has not been studied, the safety of setmelanotide is unknown, therefore use in women who are pregnant or breastfeeding, is considered missing information.

Missing information #2: Use in hepatic impairment

Evidence source:
Setmelanotide has not been studied in patients with hepatic impairment. One event of use in hepatic impairment (Preferred Term: Liver injury) was received from the post-authorisation sources and setmelanotide was discontinued in response. It was likely that this patient with a history of liver disease, strong history of systemic reactions to food and other medications, developed an acute liver injury following administration of setmelanotide. The determination of which component of the formulation may have precipitated the reaction was unclear.

Population in need of further characterisation:
As this patient population has not been studied, the safety of setmelanotide is unknown, therefore use in patients with hepatic impairment is considered missing information.

Missing information #3: Use in severe renal impairment

Evidence source:
Setmelanotide has been studied in a small number (8) of patients with severe renal impairment as defined by a glomerular filtration rate <30 mL/min.

Study RM-493-029 showed that setmelanotide clearance decreased with worsening renal function. Maximum observed concentration was not statistically significantly different (i.e., $p > 0.05$) in subjects with mild, moderate, or severe renal impairment compared to subjects with normal renal function, and area under the curve (AUC) in mild impairment also was not different. In subjects with moderate or severe renal impairment, AUC was significantly higher, and clearance (CL/F) was significantly lower compared to subjects with normal renal function.

Overall, systemic exposure (i.e., setmelanotide dose-normalized AUC) was higher, clearance was lower, and half-life was longer with worsening renal function. A modified dosing regimen is warranted in patients with severe renal impairment. There are no clinical data in patients with eGFR <15 mL/min/1.73 m^2.

Population in need of further characterisation:
The safety data is limited, therefore use in patients with severe renal impairment is considered missing information.

Missing information #4: Long-term use

Evidence source:

Limited data are available for subjects treated with setmelanotide for > 4 years.

Population in need of further characterisation:

Long term use has not been extensively studied in setmelanotide clinical programme, therefore the long-term safety and tolerability of setmelanotide is unknown and considered missing information.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Rhythm does not propose to utilise event-specific follow-up questionnaires.

Other forms of routine pharmacovigilance activities:

Rhythm does not propose to utilise any other forms of routine pharmacovigilance activities.

III.2 Additional pharmacovigilance activities

The following post-authorisation safety study is ongoing:

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

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

Study short name and title:

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

Rationale and study objectives:

This observational registry will provide data to further characterise the long-term safety profile of setmelanotide under real-world conditions but also its long-term effectiveness in patients from 2 years of age and older. This Post-Authorisation Safety Study (PASS) will collect data from patients with biallelic homozygous POMC/PCSK1 or LEPR deficiency obesity, or BBS who are prescribed setmelanotide in routine clinical practice.

Primary objective:

- To assess the long-term safety of setmelanotide as prescribed in routine clinical practice for patients with bi-allelic POMC, PCSK1, LEPR deficiency obesity or BBS according to the current local prescribing information.

Secondary objectives:

- To document and characterise the following adverse events of special interest (AESI) for all patients:
    - Prolonged penile erection
    - Depression (including suicidal ideation)
- To document and characterise AESIs and adverse events in the following special populations:
    - Patients with hepatic impairment
    - Patients with severe renal impairment
    - Pregnant/breastfeeding women
- To evaluate the long-term effectiveness of setmelanotide when it is prescribed as part of routine

practice

- To describe baseline characteristics and history of obesity in patients treated with setmelanotide
- To assess young children who could be at potential risk for accumulation of benzyl alcohol for any signs or symptoms which could suggest metabolic acidosis

Exploratory objectives:

- To document any cases of melanoma and their characteristics
- To document obesity-related hospitalisations and surgeries

Study design:

This study is an observational, prospective, multi-country, longitudinal cohort study (a registry) of patients with POMC, PCSK1, LEPR deficiency obesities, or BBS treated with setmelanotide 10 mg/ml solution for injection, conducted at centres prescribing setmelanotide in routine practice in at least five European countries.

The study period will be nine years from the earliest setmelanotide market entry.

Study population:

The study population will be patients from 2 years of age or older diagnosed with POMC, PCSK1, LEPR deficiency obesity or BBS, and treated with setmelanotide as prescribed in routine clinical practice according to the product labelling. The subjects will be categorised as new users, current users (e.g., those continuing setmelanotide from an open-label or long-term follow-up extension trial or from an early access programme), or past users (e.g., those who resume treatment after setmelanotide discontinuation) during enrolment period.

Milestones:

- Start of data collection: Q1 2023
- First annual progress report: Q1 2024
- Second annual progress report: Q1 2025
- Third annual progress report: Q1 2026
- Fourth annual progress report: Q1 2027
- Completion of enrolment: Q1 2027
- First annual interim analysis report: Q3 2027
- Fifth annual progress report: Q1 2028
- Second annual interim analysis report: Q3 2028
- Sixth annual progress report: Q1 2029
- Third annual interim analysis report: Q3 2029
- Seventh annual progress report: Q1 2030
- Fourth annual interim analysis report: Q3 2030
- Eighth annual progress report: Q1 2031

- Last (fifth) annual interim analysis report: Q3 2031
- Last (ninth) annual progress report: Q1 2032
- End of data collection: +9 years: Q1 2032
- Final study report: +6 months: Q3 2032

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

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 from 2 years of age and older, with biallelic POMC/PCSK1 or LEPR deficiency obesity or BBS, according to the current local prescribing information. **Secondary objectives:** To document and characterise the following AESIs for all patients: • Prolonged penile erection • Depression (including suicidal ideation) To document and characterise AESIs and adverse events in the following special populations:	Melanoma Prolonged penile erection Depression (including suicidal ideation) Risk of benzyl alcohol accumulation in young children Patients with hepatic impairment Patients with severe renal impairment Use in pregnancy and breastfeeding	Start of data collection First annual progress report Second annual progress report Third annual progress report Fourth annual progress report Completion of enrolment First annual interim analysis report Fifth annual	Q1 2023 Q1 2024 Q1 2025 Q1 2026 Q1 2027 Q1 2027 Q3 2027 Q1 2028

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	• Patients with hepatic impairment • Patients with severe renal impairment • Pregnant/ breastfeeding women To evaluate the long-term effectiveness of setmelanotide when it is prescribed as part of routine practice To describe baseline characteristics and history of obesity in patients treated with setmelanotide To assess young children who could be at potential risk for accumulation of benzyl alcohol for any signs or symptoms which could suggest metabolic acidosis. **Exploratory objectives:** To document any cases of melanoma and their characteristics To document obesity-related hospitalisations and surgeries	Long term use	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 2028 Q1 2029 Q3 2029 Q1 2030 Q3 2030 Q1 2031 Q3 2031 Q1 2032 Q1 2032 Q3 2032

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

Part IV: Plans for post-authorisation efficacy studies

No planned and on-going post-authorisation efficacy studies have been imposed as a condition of the marketing authorisation or which are specific obligations in the context of a conditional marketing authorisation or marketing authorisation under exceptional circumstances.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important potential risks	
Melanoma	Routine risk communication SmPC sections 4.4 and 4.8 Package Leaflet (PL) sections 2 and 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 to monitor pre-existing and new skin pigmentary lesions. PL section 2 recommends a skin examination be conducted prior and during treatment with setmelanotide. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medication
Prolonged penile erections	Routine risk communication: SmPC section 4.4 and 4.8 PL section 2 and 4 Routine risk minimisation activities recommending 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
Depression (including suicidal ideation)	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 at each medical visit if treated with IMCIVREE and notes consideration should be given to discontinuing IMCIVREE if patients experience suicidal thoughts or behaviours.

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medication
Benzyl alcohol accumulation in young children	Routine risk communication: SmPC section 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4 recommends patients aged 2 years to be monitored for any sign of metabolic acidosis while under treatment. PL section 2 notes that in young children (less than 3 years old), there is an increased possibility that benzyl alcohol could build-up in their body. Children aged 2 years old should be monitored by their doctor for side effects of this build-up (called "metabolic acidosis"). Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medication
Missing information	
Use in pregnant/breastfeeding women	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 as weight loss during pregnancy may result in foetal harm. If a patient who is taking setmelanotide has reached a stable weight and becomes pregnant, consideration should be given to maintaining setmelanotide as there was no proof of teratogenicity in the non-clinical data. 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 mother. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medication
Use in hepatic impairment	Routine risk communication: SmPC section 4.2 and 5.2 PL section 2

Safety concern	Routine risk minimisation activities
	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
Use in severe renal impairment	Routine risk communication: SmPC section 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 setmelanotide dose titration in patients with severe renal impairment. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medication
Long-term use	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

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

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

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

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

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

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

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

Part VI: Summary of the risk management plan

Summary of risk management plan for IMCIVREE (setmelanotide)

This is a summary of the risk management plan (RMP) for IMCIVREE. The RMP details important risks of IMCIVREE, how these risks can be minimised, and how more information will be obtained about IMCIVREE's risks and uncertainties (missing information).

IMCIVREE's SmPC and its PL give essential information to healthcare professionals and patients on how IMCIVREE should be used.

This summary of the RMP for IMCIVREE should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of IMCIVREE's RMP.

I. The medicine and what it is used for

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

IMCIVREE is authorised for the treatment of obesity and the control of hunger associated with genetically confirmed BBS in adults and children 2 years of age and above.

IMCIVREE is authorised for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency (PPL collectively) in adults and children 2 years of age and above. It contains setmelanotide as the active substance and it is given by SC injection.

Further information about the evaluation of IMCIVREE's benefits can be found in IMCIVREE's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/imcivree.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of IMCIVREE, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimisation measures.

Information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute routine

pharmacovigilance activities.

If important information that may affect the safe use of IMCIVREE is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of IMCIVREE are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of IMCIVREE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected:

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

II.B Summary of important risks

Important identified risk: None	
Important potential risk: Melanoma	
Evidence for linking the risk to the medicine	There is no evidence from non-clinical data, clinical data or the drug class for the development of melanoma, however given the limited exposure in the clinical development programme, melanoma is considered an important potential risk. Facial hyperpigmentation correlating microscopically with increased epidermal pigment was observed at all setmelanotide doses tested in studies in cynomolgus monkeys. This effect was reversible off drug. This skin darkening was not associated with differentiation or proliferation of melanocytes and is considered to be a pharmacological effect of setmelanotide activity at the MC1R.
Risk factors and risk groups	Risk factors for the development of melanoma include ultraviolet light exposure, moles, fair skin, freckling and light hair, family or personal history of melanoma, having a weakened immune system, being older, being male, and xeroderma pigmentosum.

Risk minimisation measures	Routine risk minimisation measures • SmPC sections 4.4 and 4.8 • PL section 2 and 4 • 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 before and during treatment. • Legal status: prescription only medication Additional risk minimisation measures • None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Important potential risk: Prolonged penile erections	
Evidence for linking the risk to the medicine	Medicines that activate MC receptors are known to potentially cause erections in male patients. Rare cases of prolonged erections in male patients have been described in the literature with other medicines in the drug class. Spontaneous penile erections, an effect associated with MC4R agonism, have been reported in IMCIVREE-treated patients. Occurrence of these events did not appear to correlate with dose or duration of dosing, as the number of events did not increase with dose or duration of dosing.
Risk factors and risk groups	No risk factors or risk groups have been identified to date in IMCIVREE-treated patients. Patients with sickle cell anaemia or trait, thrombocythemia, polycythaemia or multiple myeloma or who are prone to venous thrombosis or who have a hyperviscosity syndrome may be at increased risk of priapism.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 • PL section 2 and 4 • 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. • Legal status: prescription only medication Additional risk minimisation measures: • None
Additional pharmacovigilance activities (See section II.C of this summary for	Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro

an overview of the post-authorisation development plan).	Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Important potential risk: Depression (including suicidal ideation)	
Evidence for linking the risk to the medicine	Some drugs that target the CNS have been associated with depression or suicidal ideation; however, the exact mechanism is not known.
Risk factors and risk groups	Patients with severe obesity are known to have both depression and suicidal ideation and behaviours. In the general population, other risk factors for depression include the following: • Personal or family history of depression • Major life changes, trauma, or stress • Serious illness or mental illness • Substance abuse • Female gender • Other medications known to cause depression
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4 • 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. • Legal status: prescription only medication Additional risk minimisation measures: • None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Important Potential Risk: Benzyl alcohol accumulation in young children	
Evidence for linking the risk to the medicine	Studies have found that benzyl alcohol poisoning can be harmful for premature babies. This is because they may receive higher doses of benzyl alcohol per kilogram of body weight compared to adults. It is believed that the immature liver or kidney of premature babies may struggle to process the byproduct of benzyl alcohol called benzoic acid. This can lead to a buildup of benzoic acid in the body.
Risk factors and risk groups	Patients 2 years of age. No risk factors have been identified to date in setmelanotide-treated patients.
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4 • SmPC section 4.4 recommends patients aged 2

	years to be monitored for any sign of metabolic acidosis while under treatment. • PL section 2 • PL section 2 notes that in young children (less than 3 years old), there is an increased possibility that benzyl alcohol could build-up in their body. Children aged 2 years old should be monitored by their doctor for side effects of this build-up (called "metabolic acidosis"). • Legal status: prescription only medication Additional risk minimisation measures: • None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Missing Information: Use in pregnant/breastfeeding women	
Risk minimisation measures	Routine risk minimisation measures • SmPC section 4.6 • PL section 2 • SmPC section 4.6 notes IMCIVREE should not be started during pregnancy or while attempting to get pregnant. • SmPC section 4.6 notes that if breastfeeding, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from IMCIVREE therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the mother. • Legal status: prescription only medication Additional risk minimisation measures • None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Missing Information: Use in hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures • SmPC sections 4.2 and 5.2 • PL section 2 • SmPC sections 4.2 and 5.2 note IMCIVREE should not be administered to patients with hepatic impairment • Legal status: prescription only medication

	Additional risk minimisation measures • None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Missing information: Use in severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures • SmPC sections 4.2 and 5.2 • PL section 2 • SmPC sections 4.2 and 5.2 recommend specific dose titration in patients with severe renal impairment • Legal status: prescription only medication Additional risk minimisation measures • None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Missing information: Long-term use	
Risk minimisation measures	Routine risk minimisation measures • Legal status: prescription only medication Additional risk minimisation measures • None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities*: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032

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

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of IMCIVREE.

II.C.2 Other studies in post-authorisation development plan

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

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

Purpose of the study:

This observational registry will provide data to further characterise the long-term safety profile of setmelanotide under real-world conditions but also its long-term effectiveness in patients aged 2 years and older, the PASS will collect data from patients with biallelic homozygous POMC/PCSK1 or LEPR deficiency obesity, or BBS who are prescribed setmelanotide in routine clinical practice.

Primary objective:

- To assess the long-term safety of setmelanotide as prescribed in routine practice for patients with bi-allelic POMC, PCSK1, LEPR deficiency obesity, or BBS according to the current local prescribing information.

Secondary objectives:

- To document and characterise the following AESIs for all patients:
    - Prolonged penile erection
    - Depression (including suicidal ideation)
- To document and characterise AESIs and new adverse events in the following special populations:
    - Patients with hepatic impairment
    - Patients with severe renal impairment
    - Use in pregnant/breastfeeding women
- 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
- To assess young children who could be at potential risk for accumulation of benzyl alcohol for any signs or symptoms which could suggest metabolic acidosis

Exploratory objectives:

- To document any cases of melanoma and their characteristics
- To document obesity-related hospitalisations and surgeries

Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

None

Annex 6 - Details of proposed additional risk minimisation activities

None