20 May 2021
EMA/CHMP/319064/2021
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## IMCIVREE

International non-proprietary name: setmelanotide

Procedure No. EMEA/H/C/005089/0000

## Note

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

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# List of abbreviations

| | |
|---|---|
| Ab | Antibody |
| ABPM | Ambulatory Blood Pressure Monitoring |
| ACTH | Adrenocorticotrophic hormone |
| ADA | Anti-drug Antibody |
| ADME | Absorption, Distribution, Metabolism, Excretion |
| AE | Adverse Event |
| AGRP | Agouti-related Peptide |
| AUC | Area under the concentration-time curve |
| AUC 0-24 | Area Under the Curve from time 0 to 24 hours |
| AUClast | Area Under the Curve from time 0 to the last measurable timepoint |
| AUCss | Area Under the Curve at Steady State |
| AUCtau | Area Under the Curve during a time Interval |
| BCRP | Breast Cancer Resistance Protein |
| BDNF | Brain Derived Neurotrophic Factor |
| BET | Bacterial endotoxins |
| BMI | Body mass index |
| BP | Blood pressure |
| $C_{24}$ | Plasma concentration after 24 hours |
| cAMP | cyclic adenosine monophosphate |
| CAPAs | Corrective and preventative action |
| CFU | Colony forming units |
| CGIS | Clinical Global Impression Score |
| CHMP | Committee for Medicinal Products for Human use |
| CI | Confidence interval |
| CLss/F | Clearance |
| $C_{max}$ | Maximum plasma concentration |
| Cmax,ss | Maximum Plasma Concentration at Steady State |
| CMC | Carboxymethylcellulose sodium (croscarmellose sodium) |
| CNS | Central nervous system |
| CoeffV | Coefficient of Variation |
| CQA | Critical quality attribute |
| CS | Completers set |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| Ctrough | Lowest Concentration Reached by a Drug Before the Next Dose is Administered |
| CV | Cardiovascular |
| CYP | Cytochrome P450 |
| DDI | Drug Drug Interaction |
| DIO | Diet-induced obesity |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| DUS | Designated use set (analysis population) |
| EC | European Commission |
| EC50 | Concentration for half-maximal effect |
| ECG | Electrocardiogram |
| ELISA | Enzyme-linked immunosorbent assay |
| ESI | Event of Special Interest |
| EU | European Union |

| | |
|---|---|
| FAS | Full analysis set (analyses population) |
| FOB | Functional observation battery |
| GABA | Gamma-Aminobutyric Acid |
| GC | Gas chromatography |
| GC-MS | Gas chromatography - mass spectrometry |
| GCP | Good Clinical Practices |
| GHR | Ghrelin Receptor |
| GLP | Good laboratory practices |
| h | human |
| HbA1c | Glycated Haemoglobin |
| HDPE | High density polyethylene |
| HEK | Human Embryonic Kidney |
| hERG | Human ether-a-go-go related gene |
| HLM | human liver microsomes |
| HOPO | 2-Hydroxypyridine-*N*-oxide |
| HPLC | High performance liquid chromatography |
| HR | Heart rate |
| IBD | International Birth Date |
| IC | Ion chromatography |
| IC50 | Concentration for half-maximal inhibition |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICP-MS | Inductively coupled plasma mass spectrometry |
| IPC | In-process control |
| IR | Infrared |
| ISR | Insulin receptor |
| ISRs | Injection Site Reactions |
| IV | Intravenous |
| KF | Karl Fischer titration |
| Ki | Inhibitory Constant |
| LC-MS/MS | Liquid-chromatography-tandem mass spectrometry |
| LE | Long Evans |
| LEPR | Leptin receptor |
| LME | Linear Mixed Effect |
| LOCF | Last Observation Carried Forward |
| LogD | Distribution Coefficient |
| LS | Least squares (in the context of mean values) |
| MAD | Multiple Ascending Dose |
| MATE1 | Efflux Transporter MATE1 |
| MATE2K | Efflux Transporter MATE2K |
| Max | Maximum |
| MC1R | Melanocortin 1 receptor |
| MC2R | Melanocortin 2 receptor |
| MC3R | Melanocortin 3 receptor |
| MC4R | Melanocortin 4 receptor |
| MC5R | Melanocortin 5 receptor |
| MCR | Melanocortin Receptors |
| MDCK | Madin-Darby Canine Kidney |
| MDR1 | Multidrug Resistance Protein 1 |

| | |
|---|---|
| MedDRA | Medical Dictionary for Regulatory Activities Terminology |
| Min | Minimum |
| mPEG-2000-DSPE | *N*-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine sodium salt |
| mPEG-DSPE | N-[carbonyl-methoxypolyethylene glycol 2000]-1,2-distearoyl- glycero-3-phosphoethanolamine |
| MS | Mass spectrometry |
| MSH | Melanocyte stimulating hormone |
| MW | Molecular Weight |
| NA | Not Available |
| NAb | Neutralising Antibody |
| NAFLD | Non-Alcoholic Fatty Liver Disease |
| NFAT | Nuclear Factor of Activated T cells |
| NHP | Non Human Primate |
| NMR | Nuclear magnetic resonance |
| NMT | Not more than |
| NOAEL | No Observed Adverse Effect Level |
| NPY | Neuropeptide Y |
| OAT1 | Organic Anion Transporter 1 |
| OAT3 | Organic Anion Transporter 3 |
| OATP1B1 | Organic Anion Transporting Polypeptides 1B1 |
| OATP1B3 | Organic Anion Transporting Polypeptides 1B3 |
| OCT2 | Organic Cation Transporter 2 |
| OGTT | Oral Glucose Tolerance Test |
| PASS | Post-Authorisation Safety Study |
| PBT | Persistence BioAccumulation Toxicity |
| PC1 | Pro-hormone Convertase 1 (PCSK1) |
| PC2 | Pro-hormone Convertase 2 (PCSK2) |
| PCSK1 | Proprotein convertase subtilisin/kexin Type 1 |
| PD | Pharmacodynamics |
| PECsw | Predicted Environmental Concentration in surface water |
| PEG | Polyethylene glycol |
| PET | Preservative efficacy test |
| P-gp | P-glycoprotein |
| Ph. Eur. | European Pharmacopoeia |
| PHQ-9 | Patient Health Questionnaire-9 |
| PIP | Paediatric Investigation Plan |
| PK | Pharmacokinetics |
| pKa | Negative log of the acid dissociation constant Ka |
| PL | Placebo |
| POMC | Pro-opiomelanocortin |
| POPPK | Population Pharmacokinetic |
| PP | Per Protocol |
| PROM | Patient Reported Outcome Measures |
| PVDF | Polyvinylidene fluoride |
| PWS | Prader Willi Syndrome |
| Q | Quartile |
| QD | Once Daily |

| | |
|---|---|
| QoL | Quality of Life |
| QTcB | QT correction based on Bazett's formula |
| QTcF | QT correction based on Fridericia's formula |
| QTPP | Quality target product profile |
| QW | Once Weekly |
| Rac | Systemic Accumulation ratio |
| REE | Resting Energy Expenditure |
| REE-H | Resting Energy Expenditure by Bedside Hood Calorimeter |
| RGDO | Rare Genetic Disorders of Obesity |
| RH | Relative Humidity |
| RM-493 | Setmelanotide |
| RMP | Risk Management Plan |
| ROI | Region of Interest for Measured Radioactivity |
| RRT | Relative retention time |
| SAD | Single Ascending Dose |
| SAE | Serious adverse event |
| SAS | Safety Analysis Set |
| SAWP | Scientific Advice Working Party |
| SC | Subcutaneous |
| SD | Standard Deviation |
| SmPC | Summary of Product Characteristics |
| SOC | System Organ Class |
| T1/2 | Half Life |
| TD | Therapeutic Dosing |
| TEAE | Treatment-emergent adverse event |
| TEE-C | Total Energy |
| TK | Toxicokinetic |
| TLC | Thin layer chromatography |
| Tmax | Time to Maximum Plasma Concentration |
| UHPLC | Ultra-high performance liquid chromatography |
| USP | United States Pharmacopoeia |
| UV | Ultraviolet |
| Vz/F | Volume of distribution |
| WFI | Water for injections |
| WT | Wild type |
| α-MSH | α-Melanocyte stimulating Hormone |
| β -MSH | β -Melanocyte stimulating Hormone |
| β-MSH | β-Melanocyte Stimulating Hormone |
| γ-MSH | γ- Melanocyte stimulating Hormone |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Rhythm Pharmaceuticals Limited submitted on 26 June 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Imcivree, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 31 May 2018.

Imcivree was designated as an orphan medicinal product:

- EU/3/6/1703 on 14 July 2016 in the following condition: Treatment of pro-opiomelanocortin deficiency

- EU/3/18/2101 on 19 November 2018 in the following condition: Treatment of leptin receptor deficiency

Imcivree was granted eligibility to PRIME on 28 June 2018 in the following indication: Treatment of obesity and the control of hunger associated with deficiency disorders of the MC4R receptor pathway.

Eligibility to PRIME was granted at the time in view of the following:

- There is an unmet medical need for the treatment of morbid obesity in the targeted genetic conditions given the lack of effective treatment options; morbid obesity in these conditions is associated with increased long-term morbidity and mortality, e.g. development of type 2 diabetes, dyslipidaemia, cardiovascular morbidity and mortality, impaired mobility, social/psychological impact adding to other primary symptoms of the genetic syndromes.
- The presented preliminary evidence from 11 patients with POMC deficiency, LEPR deficiency, Bardet-Biedl syndrome and Alstroem syndrome provides clinical proof of concept in genetic obesity syndromes affecting signalling upstream MC4Rs.
- Weight reduction and hunger score reduction of highly clinically relevant effect size have been demonstrated, sustained for treatment durations of up to 118 weeks with evidence of dose-response upon dose reduction or treatment cessation/re-initiation; Insulin levels, OGTT profiles, lipid profiles were improved suggesting a potential to lower risk for long-term cardiovascular morbidity and mortality.

The applicant initially applied for the following indication:

Imcivree is indicated for the treatment of obesity and the control of hunger associated with biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency obesity or leptin receptor (LEPR) deficiency obesity in adults and children 6 years of age and above.

The final applied indication was as follows:

Imcivree is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature

substituting/supporting certain test(s) or study(ies).

## *Information on Paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0164/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the agreed PIP (P/0164/2018) was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Imcivree as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/imcivree

## Similarity

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

## *Applicant's request(s) for consideration*

## New active substance status

The applicant requested the active substance setmelanotide contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

## *PRIME support*

Upon granting of eligibility to PRIME, Bart Van der Schueren was appointed by the CHMP as rapporteur and later replaced by Karin Janssen van Doorn.

A kick-off meeting was held on 12 November 2018. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

Accuracy of drug delivery to adult and paediatric patient populations, comparability of once weekly formulations in vials versus pre-filled syringes produced at different manufacturing sites, use of patient registries for long-term follow-up of patients, and pathway driven development

## *Protocol assistance*

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

- 

| Date | Reference |
|---|---|
| 23 March 2017 | EMEA/H/SA/3498/1/2017/PA/SME/III |
| 25 July 2019 | EMEA/H/SA/3498/2/2019/PA/SME/PR/I |

***Scientific Advice***

The applicant received Scientific Advice on two occasions as mentioned in the table above for the development of Setmelanotide for treatment of obesity and hyperphagia associated with POMC and LepR deficiency. The Scientific Advice pertained to the following Quality, Non-Clinical and Clinical aspects:

- Evidence to support the safety of mPEG-2000-DSPE formulations and control of amount of mPEG-2000-DSPE during the manufacturing process
- Starting material for drug substance manufacture, drug substance specifications, characterisation of drug substance stability, process validation via continuous process verification, comparability testing for alternative drug substance manufacturer
- Drug product process validation via continuous process verification, plans for extractables testing on drug product batches
- Plans to support post-approval manufacturing changes: batch size increase and changed method for the addition of mPEG-2000-DSPE, introduction of a second vial-filling line and extension of drug product production time
- Non-clinical evidence generation strategy: safety pharmacology, PK, toxicology, juvenile animal study and carcinogenicity study plans
- Clinical evidence generation strategy in in rare genetic syndromes of obesity
- Clinical pharmacology programme
- Pivotal clinical trial plans: patient population definition, individualised dose titration, 12-week futility analysis, primary efficacy endpoint, randomised-withdrawal design, safety database

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Karin Janssen van Doorn Co-Rapporteur: Kirstine Moll Harboe

| | |
|---|---|
| The application was received by the EMA on | 26 June 2020 |
| Accelerated Assessment procedure was agreed-upon by CHMP on | 30 April 2020 |
| The procedure started on | 16 July 2020 |
| The Rapporteur's first Assessment Report was circulated to all CHMP members on | 14 September 2020 |

| | |
|---|---|
| The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on | 18 September 2020 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on | 22 September 2020 |
| In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days | |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 1 October 2020 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 13 October 2020 |
| The applicant submitted the responses to the CHMP List of Questions on | 22 January 2021 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on | 3 March 2021 |
| The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on | 25 March 2021 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 20 April 2021 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 6 May 2021 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Imcivree on | 20 May 2021 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

The indication initially applied for is: "Treatment of obesity and the control of hunger associated with biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency obesity or leptin receptor (LEPR) deficiency obesity in adults and children 6 years of age and above."

The final applied indication was as follows:

"Imcivree is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above."

Genetic obesity disorders caused by defects in melanocortin 4 receptor (MC4R) pathway, including POMC and LEPR deficiency obesity, are unified by their shared pathogenesis arising from specific gene defects along a common hypothalamic neuroendocrine pathway.

Throughout the report, the terminology "POMC, LEPR patients or populations" are used to define the population with deficiencies affecting these genes.

### 2.1.2. Epidemiology

There are no available data on incidence of obesity due to POMC deficiency or LEPR deficiency. POMC and LEPR deficiencies can be confirmed only following genetic testing. Nonetheless, 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).

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 greater than 3 standard deviations (SD) above normal weights for age and leading ultimately to adult body mass index (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 (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).

According to a literature review commissioned by the applicant (Argente et al., 2019) the population key findings can be summarised as follows:

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.

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.

The published literature for LEPR deficiency includes a few small series of patients from key academic medicine centers. The existence of these series suggested that LEPR deficiency may be slightly more frequent than POMC deficiency. The prevalence of LEPR deficiency in the United States based on genetic epidemiology is ~3500 patients, with an assumed similar number of patients in Europe. But it is worth noting that these patients are generally "hidden" in the extremely large number of early-onset, severe obesity patients in the global population. Until diagnostic genotyping becomes an established procedure in the evaluation of early-onset obesity, the actual number of diagnosed LEPR deficiency patients is likely to remain very small.

### 2.1.3. Biologic features, aetiology and pathogenesis

The physiology of hypothalamic control of appetite is the basis of disorders arising from genetic defects upstream in the MC4R pathway. The hypothalamus serves as the key integrative region of the brain for energy metabolism, hunger and satiety. It includes both stimulatory and inhibitory pathways / regions that coordinate and regulate appetite, caloric intake and energy expenditure.

In the hypothalamus, the melanocortin system is set up to defend against starvation by promoting hunger and food seeking behaviour; MC4R acts as a natural brake. Activation of MC4R suppresses food intake (reduces appetite); inhibition of MC4R (removal of the brake) causes increased food intake. The activation of MC4R is controlled by 2 distinct populations of neurons, which lie immediately upstream and synapse with neurons that express MC4R on their surface. See Figure 1.

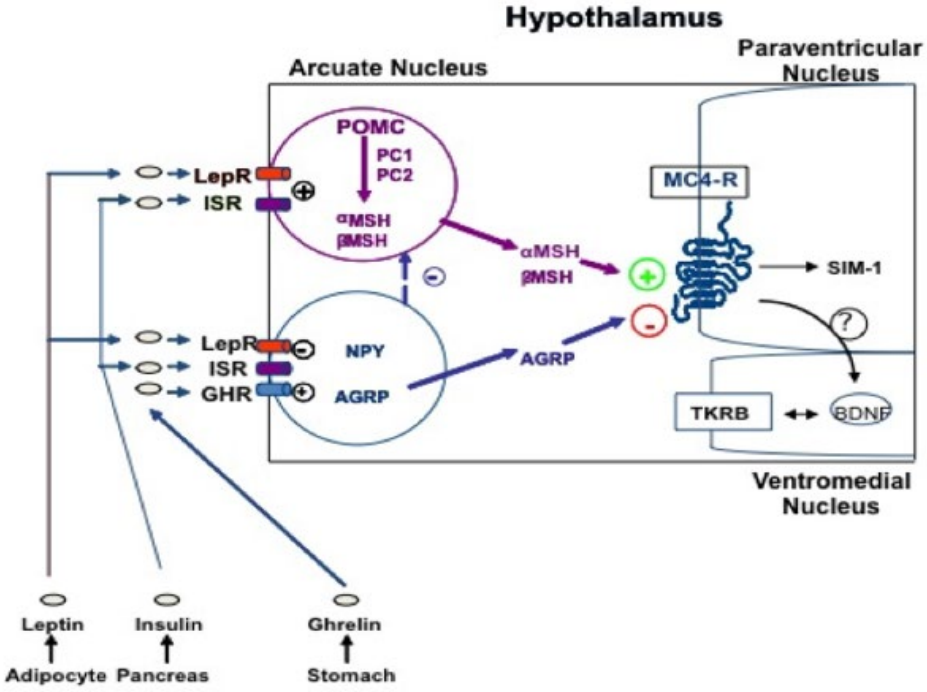



**Figure 1 : Schematic of the Hypothalamic MC4R Pathway**

| | |
|---|---|
| LepR = leptin receptor | β-MSH = β-melanocyte stimulating hormone |
| ISR = insulin receptor | NPY = Neuropeptide Y |
| GHR = ghrelin receptor | AGRP = agouti-related peptide |
| POMC = pro-opiomelanocortin | MC4R = melanocortin receptor type 4 |
| PC1 = pro-hormone convertase 1 (PCSK1) | SIM-1 = Single minded homolog 1 |
| PC2 = pro-hormone convertase 2 (PCSK2) | TKRB = tropomyosin receptor kinase B |
| α-MSH = α-melanocyte stimulating hormone | BDNF = brain derived neurotrophic factor |

One population of upstream neurons releases POMC-derived melanocortin peptides from their nerve terminals, which act as endogenous agonists at MC4R; the primary function of this population is to suppress appetite. The second population of neurons releases a different neuropeptide, AGRP (agouti-related peptide), which is a competitive antagonist at MC4R; the primary function of this population is to stimulate food intake. These are not on/off signals – the relative amount of pro-opiomelanocortin (POMC) or AGRP released in a particular setting determines the degree of activation of MC4R or melanocortin tone, which in turn modulates food intake. These 2 neuronal populations express the leptin receptor (LEPR) and as such respond to the peripheral hormone leptin, which is the major signal of nutritional state.

In healthy subjects, in the fasted state, low levels of leptin stimulate AGRP neurons while at the same time inhibiting POMC neurons. The cumulative effect is more antagonist than agonist, reduced MC4R signal (the brake), increased food intake – the physiological response to seek more food to restore energy homeostasis. In the fed state, increased leptin levels stimulate POMC neurons, while at the same time inhibiting AGRP neurons. The cumulative effect is more agonist than antagonist, increased MC4R signal, reduced food intake.

Consistent with its sensory role, POMC neurons express both LEPR and insulin receptors (ISR). Importantly, however, in contrast to LEPR, ISR signalling within the MC4R- pathway does not influence appetite or body weight.

The melanocortins are a family of peptide hormones (including ACTH, α-MSH, β-MSH, and γ-MSH) that are all derived from the common precursor, POMC. The melanocortins regulate energy homeostasis and body weight. The MC4R has been identified as the dominant melanocortin receptor involved in body weight, hunger, and energy homeostasis regulation. Under normal conditions, the natural ligands for the MC4R (different forms of melanocyte stimulating hormone; MSH) in the hypothalamus derive from POMC neurons, are cleaved by the specific proprotein convertase subtilisin / kexin type 1 (PCSK1) cleavage enzyme, and activate the MC4R resulting in decreased hunger, weight, and resting energy expenditure. In turn, POMC neurons can be activated by the anorexigenic, fat-derived hormone, leptin and by other brain signals. In addition, a second inhibitory pathway also converges on the MC4R in which the peripheral hormone ghrelin stimulates hypothalamic Neuropeptide Y and Agouti- Related Peptide producing neurons, which each increase appetite and reduce metabolic rate. These powerful orexigenic (appetite-stimulating) signals can be countered by melanocortin agonists through activation of the MC4R.

The vital importance of this pathway in hunger and weight reduction is supported by strong clinical genetic validation. Genetic defects for all the steps in the stimulatory MC4R pathway (both in humans and in rodents) have resulted in the expected phenotype: early-onset extreme obesity and hyperphagia. POMC deficiency obesity is caused by bi-allelic (either homozygous or compound heterozygous) loss of the POMC gene function and/or bi-allelic loss of PCSK1 gene function impairing cleavage of the POMC precursor peptide.

Complete POMC deficiency (biallelic mutations) results in loss of endogenous MC4R agonist. As the endogenous antagonist (Agouti-related peptide or AGRP) is not affected, this results in markedly reduced melanocortin tone, which manifests as hyperphagia, driving severe obesity.

LEPR deficiency obesity is caused by bi-allelic (either homozygous or compound heterozygous) loss of the LEPR.In LEPR deficiency, patients lose the ability to regulate both POMC and AGRP neurons, likely resulting in basal low levels of melanocortin tone. In addition, LEPR is expressed on other (non-melanocortin) neuronal populations both within the hypothalamus and in other areas involved in food reward such as the striatum and ventral tegmental area. As such the hyperphagia and obesity in LEPR deficient patients is usually more severe than seen in POMC deficiency (many patients do not survive) and is mediated by both melanocortin (setmelanotide-responsive) and melanocortin-independent (setmelanotide-unresponsive) pathways.

*POMC deficiency obesity*

Neuropeptides synthesized and processed from the POMC gene are absent or deficient in patients with POMC deficiency obesity due to defects in 2 genes, both of which are upstream of MC4R. These defects are loss of function mutations in the POMC gene itself; and loss of function mutations in the PCSK1 gene, which encodes proprotein convertase subtilisin/kexin type 1. The PCSK1 protein processes the POMC peptide into derivative MSH neuropeptides that bind to MC4R in target hypothalamic neurons.

These 2 specific monogenic disorders result in clinical POMC deficiency due to missing derivative (MSH) neuropeptide synthesis and/or processing, with subsequent absence or reduction in signalling through the hypothalamic MC4R pathway mediating central nervous system (CNS) control of appetite and weight regulation. POMC deficiency is the most proximal genetic defect in the MC4R pathway obesity disorders. Accordingly, affected patients demonstrate extreme early- onset obesity and hyperphagia as core clinical features.

*LEPR deficiency obesity*

Congenital LEPR deficiency is caused by bi-allelic mutations in the LEPR gene. As with POMC deficiency, it also results in absent or insufficient signalling through the MC4R pathway to activate MC4R.

### 2.1.4. Clinical presentation, diagnosis

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.

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, dominatingly affecting the quality of daily life. 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 (MC2R) 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.

LEPR deficiency patients may show additional phenotypic features specific to this genetic disorder besides the core clinical features of early onset severe obesity and hyperphagia. Frequent respiratory infections resulting from obesity and reduced immune function have been reported in children with LEPR deficiency, sometimes resulting in childhood mortality. Insulin resistance and type 2 diabetes mellitus are also often reported as complications of extreme obesity in those patients who survive childhood. Finally, early mortality associated with acute upper respiratory infections was reported in 2 of 10 LEPR deficiency patients, suggesting a reduced lifespan because of this congenital genetic disorder.

Next to the direct negative effects experienced due to the morbid obesity and insatiable hunger experienced by these patients, they also must contend with several serious and potentially life-threating co-morbidities in the respiratory, CV, hepatic/metabolic, and orthopaedic areas. Frequent comorbidities include heart disease, hypertension, lipid abnormalities and type 2 diabetes mellitus, obstructive 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. Given the high risk of cardiac, renal, and/or ophthalmic complications for children and young adults, which may lead to premature death, most of these patients are often heavily medicated to treat these co-morbidities.

### 2.1.5. Management

There are currently no approved therapies nor products in development specifically for the 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. As a result, 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 addition, there is no evidence that drugs approved for general obesity (including Orlistat, Saxenda, and Mysimba) can reduce weight in MC4R pathway disorder patients. This lack of efficacy is not surprising because these general obesity medicines do not address the underlying MC4R pathway signalling defects that lead to obesity and hyperphagia. Tremendous efforts in lifestyle modification, including exercise and diet, have also proven unsuccessful in most cases. 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.

There are currently no clinical 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).

### *About the product*

Setmelanotide is an 8-amino acid cyclic peptide analogue of naturally occurring alpha-melanocyte stimulating hormone ($\alpha$-MSH) that functions as a potent melanocortin-4 receptor (MC4R) agonist.

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

The product is presented as 10 mg/ml solution for subcutaneous injection and is intended to be administered once daily.

### *Type of Application and aspects on development*

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the fact that the therapeutic indication for which an accelerated assessment was requested is a confirmed ultra-rare disease of potentially life-threatening nature and imposing a significant burden on the patient's quality of life. Given that no adequate treatments for the condition currently exist there is a high unmet medical need for an effective treatment.

However, during the procedure, the applicant decided to revert to standard timetable to address the CHMP questions.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as a solution for injection containing 10 mg/mL of setmelanotide as active substance. The product contains the acetate salt and contains between 2 and 4 molecules of acetate per molecule of setmelanotide.

Other ingredients are: *N*-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl- glycero-3-phosphoethanolamine sodium salt (mPEG-2000-DSPE), carmellose sodium (CMC), mannitol, phenol, benzyl alcohol, sodium edetate and water for injections.

The product is available in clear glass type I vials with bromobutyl stoppers and aluminium caps as described in section 6.5 of the SmPC.

## 2.2.2. Active Substance

***General information***

The chemical name of setmelanotide is acetyl-*L*-arginyl-*L*-cysteinyl-*D*-alanyl-*L*-histidinyl-*D*-phenylalanyl-*L*-arginyl-*L*-tryptophanyl-*L*-cysteinamide cyclic (2→8)-disulfide corresponding to the molecular formula $C_{49}H_{68}N_{18}O_9S_2$. The free base has a relative molecular mass of 1117.3 g/mol and the following structure:

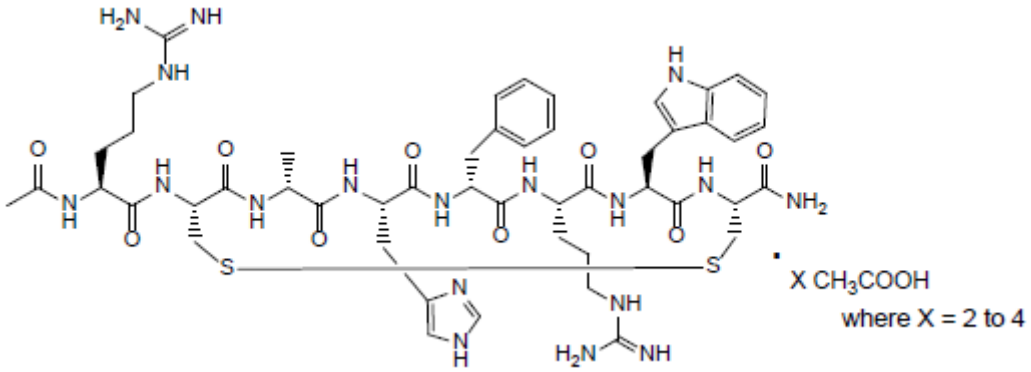



**Figure 2: active substance structure**

The chemical structure of setmelanotide is inferred from the sequential amino acid coupling process and was confirmed by NMR spectroscopy, mass spectrometry (MS), IR spectroscopy and UV spectroscopy. Amino acid sequence was confirmed by MS/MS and the stereochemistry of each component amino acid was determined by chiral GC-MS.

The solid-state properties were investigated by thermogravimetric analysis, differential scanning calorimetry and dynamic vapour sorption. Setmelanotide is a white to off-white powder.

Setmelanotide contains 8 chiral centres. Enantiomeric purity of the individual amino acids is controlled in the starting material specifications.

***Manufacture, characterisation and process controls***

Setmelanotide is synthesized in multiple steps followed by preparative chromatographic purification using well-defined starting materials with acceptable specifications. The starting materials were redefined to protected amino acid monomers and dimers during the procedure as a result of a CHMP major objection, in line with earlier scientific advice.

There are multiple manufacturers for specific stages of the manufacturing process. The process consists of a series of peptide coupling reactions followed by cyclisation to form the disulfide bridge. Impurities are removed by several chromatographic purifications. The purification steps can be repeated as described in the dossier to ensure adequate purity of intermediates and the active substance. The cyclisation and purification steps are considered critical for both preventing formation of impurities and purging them. The optimisation of these processes has been discussed at length including impurity spike and purge studies and elution profiles for key impurities. The manufacturing processes conducted at the different sites are slightly different to accommodate the different equipment. However, it has been shown that the active substance produced is of comparable and suitable quality, irrespective of the site at which it is produced.

An additional manufacturing site was added to the dossier to ensure a robust supply of active substance considering the extensive cycle time for manufacture. In the initial submission, there was limited information available including batch data on the process as conducted at this site. Given the

re-definition of starting materials and introduction of an intermediate manufacturer, some outstanding activities need to be carried out post-approval but prior to commercialisation. Active substance lots manufactured using RSM-1 and RSM-2 will only be commercialized after the process is validated at the commercial batch size and using the validation approach laid down in the dossier. In addition, the first batch of active substance made with RSM-1 and RSM-2 will be placed on stability.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Some intermediate specifications do not contain limits on unspecified impurities and limits for several impurities are considered rather broad. Therefore, the applicant should review the current impurity limits for intermediates RSM-1, RSM-2, crude 1-8L, purified 1-8L and crude 1-8C once additional lots are produced at commercial scale and revise the acceptance limits accordingly.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in high-density polyethylene (HDPE) bottles closed with poly-propylene screw caps. The bottles are placed in heat-sealed aluminium pouches. The primary packaging complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

***Specification***

The active substance specification includes tests for appearance, identity, colour and clarity of solution (Ph. Eur.), assay , peptide related impurities , non-peptide related impurities , acetate content , water content (KF), residual solvents (GC, HPLC), elemental impurities (ICP-MS), microbial limits (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The initially proposed specification was considered deficient in multiple aspects resulting in a major objection from CHMP. In response, the applicant updated the specification by tightening limits for various impurities, adding tests for colour and clarity of solution, and updating the overall control strategy to ensure that the process routinely delivers active substance of suitable quality, irrespective of the manufacturing site. The revised specification is considered to be acceptable. However, the proposed limits for colour and clarity of the solution should be properly justified based on results from at least 3 consecutive commercial scale active substance batches when available, as well as results at the end of the re-test period for stability batches.

Limits for peptide related impurities are set in line with Ph. Eur. 2034 (substances for pharmaceutical use) and the demonstrated capability of the manufacturing process. The potentially genotoxic impurity is controlled in line with ICH M7 with a limit in the active substance specification. Residual solvents are controlled according to ICH Q3C.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 3 production scale batches of the active substance from each manufacturer are provided. Initially, limited data from the second manufacturing site was submitted resulting in a major objection. In response, the applicant provided satisfactory data from additional batches. The results are within the specifications and consistent from batch to batch, irrespective of the active substance manufacturer.

***Stability***

Stability studies were conducted with production scale batches of active substance from both manufacturers packaged in a container closure system that is representative of the proposed commercial container closure system. The following parameters were tested: appearance, assay, impurities, acetate content, water content and microbial limits. The analytical methods used were the same as for release and are stability indicating.

At the first manufacturing site, primary stability studies have been conducted using batches of active substance manufactured according to the registered process stored at -20°C, 5°C for up to 36 months (both long-term conditions) and 25°C/60% RH for up to 6 months(accelerated conditions). Supportive data was provided on further batches manufactured using an earlier process stored at -25°C, 5°C for up to 36 months and 25°C/60% RH for up to 6 months (accelerated). No significant trends were observed to any of the measured attributes and all parameters met the specification limits in place at the time of testing.

One active substance batch was subjected to forced degradation studies under stressed conditions including acidic, alkaline, oxidative, thermal and ICH Q1B photolytic conditions. The active substance has been shown to be unstable under most stressed conditions and is photosensitive. The chosen primary packaging provides sufficient protection from light.

Based on a linear regression analysis for the different measured parameters, all properties are stable up to the end of the stability study and a re-test period of 36 months is proposed for active substance manufactured at the first manufacturing site when stored at -20 ± 5°C in the proposed container closure system.

The manufacturing processes used at the two sites are slightly different, resulting in slightly different impurity profiles based on the limited batch data available. Therefore, assigning a re-test period for the second site batches required standalone stability data. At the second site, stability studies results are presented on one batch stored up to 12 months at -20°C and 5°C (both long term conditions) and up to 6 months at 25°C/60% RH (accelerated conditions). Stability studies are further presented for two more batches, up to the 5-month time point under all conditions. Samples were tested according to the same protocol used at both sites. Given the limited data available, regression analysis doesn't provide meaningful results. Therefore, no extrapolation of stability data is possible. The results to date nonetheless indicate that active substance manufactured at the second site has an equivalent stability profile to that manufactured at the first site. Based on assessment of the currently available stability data, a retest period of 6 months is proposed for the active substance manufactured at the second site when stored at -20° ± 5°C in the proposed container closure system.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed re-test period for the first site of 36 months at -20° ± 5°C in the proposed container closure system. For active substance manufactured at the second site, a re-test of 6 months at -20° ± 5°C in the proposed container closure system is applied.

## 2.2.3. Finished Medicinal Product

***Description of the product and Pharmaceutical development***

Imcivree is a sterile, preserved, clear to slightly opalescent and colourless to slightly coloured solution for once a day subcutaneous (SC) injection presented in a multi-dose vial.

The Applicant has established a quality target product profile (QTPP) which was a preserved aqueous, relatively low-viscous, solution of the setmelanotide with one or more ion pairing agents (each with known safety profile) that is suitable for once-a-day SC injection and exhibits acceptable stability.

CMC has a history of use as viscolyzer in parenteral and SC preparations and mPEG-2000-DSPE is approved for use in other controlled release products marketed in the EU. Pre-clinical PK studies demonstrated that formulations containing combinations of the excipients mPEG-2000-DSPE and CMC resulted in the desired setmelanotide PK profile following SC injection.

The final quantitative composition in mPEG-2000-DSPE was set on the basis of the pre-clinical PK studies. The concentrations of the antimicrobial preservatives phenol and benzyl alcohol have been optimised based on the effective levels seen in preservative efficacy test (PET) studies and are acceptable from safety point of view also for children aged ≥6 years.

All excipients, except mPEG-2000-DSPE, are controlled in accordance with the respective current Ph. Eur. monographs and some additional limits for microbial limits and bacterial endotoxins (BET) are included. Since the mPEG-2000-DSPE has already been approved for parenteral use in the EU, it is considered a non-compendial, non-novel excipient. Suitable information has been provided in the dossier for mPEG-2000-DSPE including details of the manufacturing process, characterization, impurities, specifications, analytical methods, validation of analytical methods, container closure system, reference standards and stability data. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

In accordance with the quality EU scientific advice, the applicant generated a set of development data to demonstrate that the assay values of mPEG-2000-DSPE as well as the molecular weight distribution of both ion pairing agents do not significantly change upon finished product storage.

In the initial submission, it was unclear how the applied control strategy would ensure consistent prolonged release behaviour of the active substance, resulting in a major objection. In response, the applicant explained how the applied control strategy ensures the desired PK properties without the need for a bespoke release test. The controls consist of a test for setmelanotide assay, an excess of mPEG-2000-DSPE controlled by the amount charged and an assay test in the finished product, ensuring pH remains within the defined range as determined by both an IPC and a release test, and fixed charges of CMC, phenol and benzyl alcohol. Batches manufactured within these parameters (and slightly wider ranges in some cases) were investigated *in vivo* and found to exhibit consistent PK profiles, indicating that the control strategy is effective in ensuring the prolonged release properties.

The container closure system consists of a type 1 glass vial with bromobutyl grey stopper and an aluminium cap. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. There is an overfill of 0.1 mL in order to achieve the nominal fill volume of 1 mL and a nitrogen head space. Injection volumes of 0.05 to 0.3 mL (based on the posology as proposed by the Applicant) are withdrawn using a commercially available 1 mL plastic syringe and 28G or 29G needle (which are not co-packed with the product). Dose accuracy studies according to ISO 7886-1 'Sterile hypodermic syringes for single use – Part 1 Syringes for manual use' demonstrate that these syringes fitted with 28G x ½ inch needle are suitable for the administration of Imcivree solution for injection.

The chosen multi-dose presentation is not ideal given the daily dosing, long term use and potential for self-administration (adult patients). It is to be noted, however, that the applicant has initiated the development of a once-a-week injectable formulation presented in single-dose pre-filled syringes. Given the unmet medical need and PRIME status, the multi-dose vial presentation is considered appropriate until a longer acting formulation is developed.

The manufacturing process consists of compounding followed by sterile filtration and aseptic filling. The choice of sterilisation method is imposed by the nature of the active substance and excipients. Risk assessments were performed to evaluate the impact of the different manufacturing steps on the finished product critical quality attributes (CQAs). The dissolution of the mPEG-2000-DSPE, the sterilizing filtration and the aseptic filling are deemed critical process steps. The dispersion method for mPEG-2000-DSPE was optimised to ensure full dissolution and homogeneity without causing excessive foaming. A pre-filtration step is performed prior to the sterilizing filtration to mitigate the risk of clogging of the sterilising filter due to the insoluble stearic acid impurity of the mPEG-2000-DSPE material. The link between the manufacturing process risk assessment and the final control strategy consisting of critical process parameters and controls has been explained and is considered acceptable.

The influence of the source of active substance on the finished product quality was verified. Finished product batches were shown to be of consistent quality compared to the development batches, irrespective of the source of active substance.

***Manufacture of the product and process controls***

The manufacturing process and in process controls consists of 4 main steps: sequential addition of excipients and the active substance to water for injections (WFI) to generate a solution; sterile filtration; aseptic filling; stoppering and crimping. The process is considered to be a non-standard manufacturing process. The manufacturing site, process, process parameters, scale, equipment and controls for commercial manufacture are overall the same as for the manufacture of the pivotal clinical finished product batches and primary stability batches.

The critical process parameters and critical in-process controls together with their acceptance criteria are provided and are generally acceptable. The microbiological control of the finished product manufacturing process is appropriately addressed. Bioburden of the bulk solution is determined before sterilizing filtration. Both of the sterilizing filters are tested for integrity before use and at least one of them is tested and must comply after the sterilizing filtration. Satisfactory media fill validation has been confirmed. The sterilization and depyrogenation of the primary packaging components are satisfactorily described. Filter validation results and extractables/leachables data for the sterilizing filters are presented.

The applicant originally proposed a concurrent validation approach given the PRIME status and unmet medical need. Although this approach was endorsed, the associated validation protocol was not adequate and no actual validation data was submitted, resulting in a major objection. In response, the applicant provided a detailed process validation scheme foreseeing extended analytical testing throughout the different manufacturing steps. In addition, satisfactory data was presented on three process validation batches according to this protocol. The data submitted is considered sufficient to support the proposed hold time limit from compounding to completion of bioburden reduction filtration. For one of the validation batches, the process was challenged by holding the batch during the filtration step. This had no impact on the assay of any components or impurity levels but did result in a slight discolouration of the bulk which wasn't subsequently reflected in the colour of the filled vials. In order to avoid this slight discolouration, the applicant is recommended to clearly define in the dossier the volume of solution to be discarded from the prefilter after a prolonged solution filling stop. This will be further checked during manufacture of a 4$^{th}$ process validation batch.

***Product specification***

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, colour and clarity of solution (Ph. Eur.), identification, identification of carmellose sodium (USP), identification and assay of mPEG-2000-DSPE , assay of setmelanotide , peptide related impurities, phenol identity and assay, benzyl alcohol identity and assay, pH (Ph. Eur.),

extractable volume (Ph. Eur.), osmolality (Ph. Eur.), particulate matter (Ph. Eur.), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

During the procedure, the applicant was asked to introduce an *in vitro* release test to ensure the prolonged release characteristics of the formulation. This is in line with provided scientific advice and was raised as a major objection. In response, the applicant was able to demonstrate that the overall control strategy ensures a consistent *in vivo* release profile as evidenced by PK data in multiple patients from multiple batches of finished product used throughout clinical development. The control strategy consists of:

- Correct setmelanotide content to ensure the ion-pair is formed consistently is controlled by assay in the release specifications;
- Identity and content of mPEG-2000-DSPE to ensure the setmelanotide ion-pair is formed consistently. This is ensured by charging a large molar excess of mPEG-2000-DSPE and by identity and assay tests in the release specifications.;
- Correct pH to ensure ion pair formation consistency across the narrow pH range which setmelanotide naturally buffers. This is ensured by an IPC and a release test for pH;
- Presence of CMC is controlled through the release specifications and the amount charged is part of the process description;
- Correct phenol and benzyl alcohol content which ensures homogeneity and hence PK properties. Phenol and benzyl alcohol assay are controlled in the release specifications.

This justification was accepted by CHMP.

Overall, the finished product release and shelf-life specifications are acceptable. The applicant should nonetheless envisage the use of the Ph. Eur. 2.2.2 instrumental method (method III) as described in Ph. Eur. volume 10.3, implemented from 1st January 2021, for colour evaluation instead of the currently used visual check.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data from 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that no specific elemental impurity controls are needed.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product was provided following a major objection from CHMP. All known suspected and actual root causes were considered in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Results from extractables/leachables studies were presented. Given the nature of the finished product and the proposed container closure system, which is commonly used for aqueous parenteral products, the provided extractables/leachables studies are considered sufficient. Based on these studies, it is concluded that there is no need for routine control of any leachables.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 8 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

***Stability of the product***

Stability data from 4 production scale batches of finished product stored for up to 24 months under long term conditions (5°C) and for up to 12 months under accelerated conditions (25°C / 60% RH) according to the ICH guidelines were provided. 3 Batches were manufactured with active substance from both manufacturing sites. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, colour and clarity of solution, pH, assay, peptide related impurities, phenol potency and benzyl alcohol potency at every timepoint and osmolality, particulate matter, sterility, extractable volume and bacterial endotoxin at less frequent intervals. The analytical procedures used are stability indicating.

Under refrigerated conditions, no significant trends were observed to any of the measured parameters which all remained within specification. Under accelerated conditions, there were out of specification (OOS) results for colour and clarity of solution at 9 and 12 months. In addition, there was a within-specification reduction in assay and increase in 1 impurity.

In addition, material was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is photosensitive but the cardboard carton was shown to provide sufficient protection from light.

Data from a simulated in-use study with 2 primary stability batches, of which one was 19 months old, and a satisfactory PET study support a 1 month in-use shelf-life at 5°C and room temperature, even in absence of light protection. In use conditions are included in section 6.3 of the SmPC as follows: "*chemical and physical in use stability has been demonstrated for 28 days at 2 – 30°C. From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 2 - 30°C. Other in use storage times and conditions are the responsibility of the user*."

Based on available stability data, the proposed shelf-life of 2 years stored "in a refrigerator (2°C to 8°C) - do not freeze - store in the original carton in order to protect from light" as stated in the SmPC (sections 6.3 and 6.4) is acceptable. The same shelf-life applies irrespective of the source of active substance used to manufacture the finished product.

***Adventitious agents***

No excipients derived from animal or human origin have been used.

## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

6 Major objections were raised during the evaluation procedure concerning the choice of starting materials, inadequate active substance release specifications, insufficient batch data to support the second site as an active substance manufacturer, missing finished product process validation data and inadequate validation protocol, lack of a release test to ensure consistent prolonged release characteristics and the missing nitrosamines risk evaluation. These were resolved by redefining the starting materials, amending the specifications, providing additional data from the second site batches, providing validation data on 3 finished product batches and an updated process validation scheme and providing an adequate nitrosamines risk evaluation. The applicant demonstrated that the overall control strategy ensures the prolonged release characteristics of the finished product and supported this with consistent PK data and therefore, no bespoke release test is deemed necessary.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. These include justifying the limits for colour and clarity of solution tests in the active substance specification, revising the limits for impurities in active substance intermediates, validation of the active substance manufacturing process at the commercial scale at one manufacturer, defining the volume of solution to discard from the pre-filter after a prolonged filling stop and updating the method used to measure colour and clarity of solution in the finished product in line with the European Pharmacopoeia. These points are put forward and agreed as recommendations for future quality development.

## 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

## 2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- Active substance lots manufactured using RSM-1 and RSM-2 should only be commercialized after the process is validated at the commercial batch size and using the validation approach laid down in the dossier. In addition, the first batch of active substance made with RSM-1 and RSM-2 should be placed on stability.
- The applicant should review the current limits for specified and unspecified impurities for intermediates RSM-1, RSM-2, crude 1-8L, purified 1-8L and crude 1-8C once additional lots are produced at commercial scale and revise the acceptance limits accordingly.
- The proposed limits for colour and clarity of the solution in the active substance specification should be properly justified based on results from at least 3 consecutive commercial scale active substance batches when available, as well as results at the end of the re-test period for stability batches.
- The applicant is should clearly define in the dossier the volume of solution to be discarded from the pre-filter after a prolonged solution filling stop in the finished product manufacturing process. This should be further checked during manufacture of a 4$^{th}$ process validation batch.
- The applicant should envisage the use of the Ph. Eur. 2.2.2 instrumental method (method III) as described in Ph. Eur. volume 10.3, which is implemented from 1$^{st}$ January 2021, for colour evaluation of the finished product.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

Both in vitro and in vivo non-clinical studies were performed to characterise the primary pharmacodynamics of setmelanotide. Furthermore, the potential for off target effects of setmelanotide was investigated in vitro and additional observations were reported in the primary pharmacology study conducted in obese rhesus monkeys. These included potential effects of the activations of MC4R pathways such as increased stretching, yawning, muscular stiffness, and penile erection (Argiolas et al., 2000; Martin and MacIntyre, 2004); skin hyper-pigmentation induced by setmelatonide; and adverse effects that could result in confounding factors in regard to food intake e.g headaches, asthenia, nausea, vomiting, and diarrhea. Several efficacy and cardiovascular pharmacodynamic studies were conducted in parallel with a comparator MC4R agonist i.e. LY2112688.

GLP-compliant safety pharmacology studies were conducted to evaluate potential adverse effects of setmelanotide on the respiratory and central nervous systems after a single 24h SC infusion in male Sprague-Dawley rats. The potential adverse effects of setmelanotide on the cardiovascular (CV) system included a GLP-compliant in vitro assay on cloned hERG potassium channel. A GLP in vivo cardiovascular safety study was also conducted in telemetered male and female cynomolgus monkey. Additional safety pharmacology data derived from informative CV studies in rhesus monkeys, rats and minipigs.

Studies have also been performed to characterize the pharmacokinetics (PK), toxicokinetics (TK), absorption, distribution, metabolism and excretion (ADME) of setmelanotide. Setmelanotide was dosed by single or multiple dose administration via intravenous (IV) injection, subcutaneous (SC) injection or SC infusion to mice, rats, rabbits and monkeys.

Repeat-dose toxicity studies were performed up to 13-week in both rats and monkeys with continuous SC infusion of setmelanotide in saline, as well as up to 6 months in rats and 9 months in monkeys with SC injection of setmelanotide in mPEG-DSPE or in saline. The standard battery of genotoxicity tests was done. 26 week carcinogenicity data (rat, mice) and fertility and embryo-fetal development studies, local tolerance data were also submitted.

### 2.3.2. Pharmacology

#### *Primary pharmacodynamic studies*

In vitro, Setmelanotide binds to several human melanocortin receptors (hMCRs), and preferentially recognizes human melanocortin 4 receptor (hMC4R), with a Ki of 2.1 nM and an EC50 of 0.27 nM in the Gαs/adenylyl cyclase signalling mediated cAMP accumulation assay. It is about 20-fold less potent in activating the human melanocortin (MC) receptors-1 and -3 (EC50: 5.8nM and 5.3nM, respectively). At the melanocortin 5 receptor (MC5R) it has an EC50 of >1 μM and displays no activity at the human melanocortin 2 receptor (MC2R). Setmelanotide induced accumulation of cAMP through MC4R-coupled Gαs-protein is fully blocked by an MC4R antagonist.

To allow cross-species comparison, the in vitro efficacy of setmelanotide at all the five melanocortin receptors (MCRs) from various species used in the nonclinical studies was further evaluated. Specifically, the ability of setmelanotide to induce cAMP accumulation was evaluated in transiently transfected HEK293 cells with MCRs from mouse, rat, cynomolgus monkey, rhesus macaque, dog and human. The EC50s of setmelanotide at MC4Rs of the 6 species were within a comparable range (0.21

to 3.05 nM). Similarly, the EC50s at MC3Rs was also comparable (range: 0.39 to 1.31 nM). With MC1Rs of the 6 species, the EC50s ranged 0.83 to 26.6 nM. No stimulation of transiently expressed MC5Rs of human, mouse and rat was observed, while dog, cynomolgus, and rhesus MC5R were stimulated by setmelanotide with EC50 of 2.5, 7.9, and 29.25 nM, respectively. Setmelanotide did not stimulate MC2R (ACTH receptor) of all these 6 species assayed. A recent in vitro potency study using transiently expressed receptors suggested that setmelanotide could be marginally more efficacious at the cynomolgus MC1R (EC50=7.20 nM) than the rhesus MC1R (EC50=26.6 nM. Under similar assay conditions, the EC50 of setmelanotide at human MC1R was 1.73 nM.

A study was performed to evaluate if in-vitro pharmacology of setmelanotide differs from two comparator agents the natural ligand alpha-MSH and LY2112688 (another MC4R compound that showed acute increases in heart rate (HR) and blood pressure (BP) in humans) in activating the Gαs (cAMP accumulation) or the phospholipase C (NFAT reporter assay) pathways using cell transfected with the hMC4R. For the Gαs signalling, setmelanotide was about 5-fold more potent than α-MSH or LY2112688. Setmelanotide was about 50- to 100-fold more potent in the NFAT signalling assay compared to α-MSH or LY2112688. In addition, the setmelanotide induced NFAT activation could not be blocked by the antagonist Agouti-related peptide (AGRP), whereas both α-MSH and LY2112688 effects were completely blocked. The clinical relevance of this, or the implication with respect to cardiovascular safety in the clinical setting remains unclear.

In vivo, the primary pharmacology studies were performed in lean and diet-induced obese (DIO) rodent (rat and mouse) and Rhesus monkey models to establish the effects of setmelanotide on food intake and body weight. Metabolic parameters, such as improvement of glucose tolerance and insulin sensitivity were also investigated. The efficacy of setmelanotide was also studied in the dog as well as in two genetic models of obesity in rodents. These includes the leptin-receptor deficient Zucker fa/fa rats (a rodent model of genetic obesity impacting the MC4R pathway) and the Magel2-null mice (a mouse model for Prader-Willi syndrome, or PWS). Different dosing schedules were tested (SC once daily morning or evening, up to 3 times daily) in rats. SC infusion was used in 7 primary pharmacology studies with the saline formulation of setmelanotide.

In lean and DIO mice administered setmelanotide by SC infusion, a dose-related decrease in body weight gain relative to vehicle control was seen across all dose groups (0.22 to 2.00 mg/kg/day) throughout the 14-day treatment period whereas in lean mice, the effect on body weight was transient, occurring over the first 4 days with partial recovery by Day 14.

The setmelanotide-mediated decrease in body weight was even more pronounced in DIO Sprague-Dawley rats (0.08 to 1.34 mg/kg/day; SC infusion for 14 days) and persisted after cessation of dosing for at least 7 days. A dose-related decrease in food intake relative to vehicle was also seen in lean and obese rats, the effect being more pronounced in obese animals.

MC4R+/+ mice treated with setmelanotide (1.34 mg/kg/day) elicited weight loss, while MC4R-/- mice treated under the same conditions gained comparable amount of weight to their vehicle-treated controls.

Support for the use of setmelanotide was also shown in genetic obesity models. In the Zucker rat model of leptin-receptor mutation SC infusion of setmelanotide was highly effective at decreasing the rate of body weight gain and suppressing appetite at both doses tested (0.06 or 0.56 mg/kg/day; for 7 days). Similarly, in the Magel2-null mouse, acute intraperitoneal administration of setmelanotide (0.04 to 1 mg/kg) was found to be significantly efficacious in appetite suppression at all the doses investigated when compared with the Wild-type (WT) mouse.

In normal beagle dog, SC injection of setmelanotide at doses of 150 to 4500 nmol/kg/day (0.17 to 5.0 mg/kg/day) for 3 consecutive days resulted in a progressive dose-dependent decrease in body weight

which correlated with dose-related decreases in food consumption. At the end of a 4- or 5- day washout period, total or partial recovery was noted.

In rhesus monkeys, SC infusion of setmelanotide at 0.5 mg/kg/day gave rise to decreased food consumption in lean animals, and this dose was used in DIO animals. In those obese monkeys, a -13.5% loss in total body weight was noted over the 8-week treatment period. This finding was contributed by increased energy expenditure since early drop in food intake was seen reversing back to baseline during weeks 4 through 7 and even showed a modest increase from baseline during week 8. After cessation of treatment, there was a slow return of body weight to baseline by 10-12 weeks post-dose. Decreases in triglycerides, cholesterol, free fatty acids and fat mass and improving glucose homeostasis, insulin sensitivity, and leptin levels were also noted. The effects of setmelanotide on food intake were significantly greater than those seen with the comparator MC4R agonist, LY2112688, at the same dose level.

Independent of its effects on body weight gain and food intake, setmelanotide acts as an insulin sensitizer, with setmelanotide treatment resulting in increased glucose tolerance and insulin sensitivity in both Sprague-Dawley rats and non-human primates, even in the absence of weight loss. These effects were not apparent in MC4R knockout mice treated with setmelanotide, providing evidence that the effects of setmelanotide on insulin and glucose are due to its action on the MC4R. In DIO mice, concurrent with inhibiting feeding, decreasing body weight and fat mass, setmelanotide improved glucose clearance, and enhances both hepatic and peripheral insulin sensitivity.

Overall, in diet-induced obese rodent and Rhesus monkey models the decreases in food intake, body weight, and fat mass, were seen shortly after initiation of chronic setmelanotide treatment. The effects were marked and persisted after cessation of treatment. In addition, the weight loss effects were also associated with decreased adiposity, increased energy expenditure and improved glucose homeostasis and increased insulin sensitivity.

In lean animals the pharmacological effects of setmelanotide in reducing body weight was noted but lower when compared with obese animals. Both the prolonged stability of setmelanotide and the 5-fold higher potency than the endogenous ligand alpha-MSH in an efficacy assay, are anticipated to translate into its superior efficacy over alpha-MSH in animal models where endogenous alpha-MSH is expected to be expressed.

## *Secondary pharmacodynamic studies*

Towards a panel of 71 receptors and 16 enzymes at a concentration of 1 µM, ligand binding was inhibited by 20-50% at 5 receptors (muscarinic, neurokinin-2, sigma, thyrotropin-releasing hormone, and GABA transporter), and by 59% at opioid receptors. As the clinical Cmax for unbound setmelanotide (approximately 38 ng/mL or 0.034 µM) is around 55-fold less, the relevance of the off-target binding observed is considered limited.

In the rhesus monkey study, no behaviour signs linked to MC4R pathway activation, like yawning, stretching, muscular stiffness and penile erection were identified. Likewise, there was no skin tanning or coat colour changes.

## *Safety pharmacology programme*

In those studies, there were no test article-related effects on any functional observation battery (FOB) or respiratory parameters at doses up to 120 mg/kg, resulting in ~ 290-fold higher exposure levels as compared to the Cmax and AUC (37.9 ng/mL and 576 ng•hr/mL) values in the clinic at the maximum recommended daily dose of 3 mg. The doses tested in the respiratory and CNS safety pharmacology

studies were 50- to 250-fold higher than those used in the weight loss studies in normal and DIO rodents.

In an in vitro assay on cloned hERG potassium channel, the IC50 was estimated to be greater than 0.3 mg/mL (~ 0.3 mM). Knowing that the free concentration of setmelanotide in the clinic for the therapeutic dose of 3 mg is ~290 fold lower than the 10 µM concentration of setmelanotide that had a negligible effect on hERG, the risk for QTc prolongation in humans is considered very low.

In the GLP in vivo cardiovascular safety study conducted in telemetered male and female cynomolgus monkey administered setmelanotide by continuous SC infusion for three days at doses up to 25 mg/kg/day, there were no biologically or toxicologically significant test item-related effects on hemodynamic or ECG parameters. This dose resulted in a 187- and 259-fold safety margin as compared to the human Cmax and AUC at the maximum recommended dose of 3 mg/day. Such a dose also corresponded to 50-fold the dose that produced marked weight loss in the 8-week obese Rhesus monkey efficacy study without producing any effects on HR or PB neither acutely nor chronically.

Likewise, in an informative non-GLP study, no cardiovascular findings were noted in obese Rhesus monkeys in a one-week crossover study comparing setmelanotide to LY2112688 (both at 0.5 mg/kg due to comparable molecular weight). Unlike setmelanotide, LY2112688 was shown to increase HR and BP in this model. The lack of cardiovascular finding in obese Rhesus monkey was also confirmed when setmelanotide was continuously SC infused for 8-weeks.

In contrast to the primates, an increase in HR and mean BP was observed in the rat following single or repeated SC bolus administration of setmelanotide, which were of similar magnitude to the changes observed with the comparator LY2112688. Moreover, it appeared that the increase observed in HR and BP in the rat given setmelanotide were linked to an increase in sympathetic tone since the pharmacological inhibition of a and b receptors was able to antagonise the cardiovascular effect of the drug.

In a minipig study, increased HR (approximately 23.4%) was also observed following SC doses of 0.5 mg/kg either by bolus injection or by infusion.

### *Pharmacodynamic drug interactions*

In a published study (Clemmensen et al., 2015), the co-administration of liraglutide (a GLP-1 receptor agonist) and setmelanotide treatment in DIO mice showed improvement in body weight loss and enhanced glycaemic control and cholesterol metabolism beyond what can be achieved with either mono-therapy. The superior metabolic efficacy is attributed to the anorectic and glycaemic actions of both drugs, along with the ability of setmelanotide to increase energy expenditure.

## 2.3.3. Pharmacokinetics

During development, the setmelanotide formulation and delivery methods were changed. Initially, setmelanotide was administered by a SC 24-h continuous infusion, formulated in saline. Revised formulations and mode of administration included saline, mPEG-DSPE, and mPEG-DSPE for SC bolus injection, as well as mPEG-DSPE with a preservative for SC bolus injection. At no point in development was setmelanotide conjugated to mPEG-DSPE, rather mPEG-DSPE was a component of the formulation. The final formulation used for the pivotal clinical studies is the mPEG-DSPE for SC bolus injection, with and without preservative. Thus, the conclusions on the PK of setmelanotide in the non-clinical species described in this section primarily focus on studies using the mPEG-DSPE formulation or studies supporting its use.

In addition, to further characterise the PK profile of the component mPEG-DSPE used in the final formulation, a dedicated ADME study using radio-labelled mPEG-DSPE was performed in the rat.

**Absorption and plasma pharmacokinetics**

The absolute SC bioavailability of setmelanotide was high (76 - 85%), as determined in a radiolabelled PK study comparing IV and SC administration to rats at a dose of 2 mg/kg.

The PK/TK parameters of setmelanotide as mPEG-DSPE formulation have been investigated in GLP-compliant toxicity studies following single and multiple daily SC injection at dose up to 3 mg/kg for 26 weeks in the Sprague Dawley rat and at dose up to 1 mg/kg/day for the 39 weeks in the Cynomolgus monkey. In both species, the volume of distribution and plasma clearance were high, with a relatively short half-life.

In the 26-week rat toxicity, the clearance (CLss/F) ranged from 0.338 to 0.512 L/h/kg for males and from 0.742 to 1.54 L/h/kg for females. The volume of distribution (Vz/F) values ranged from 5.06 to 14.7 L/kg for males and from 3.22 to 9.44 L/kg for females. Half-life ranged from 7.20 to 19.9 h for males and from 1.55 to 5.69 h for females.

In the 39-week monkey study, mean CLss/F ranged from 0.0842 to 0.216 L/h/kg, Vz/F ranged from 0.563 to 1.19 L/kg, and t½ ranged from 2.49 h to 17.6 h.

To support the mouse carcinogenicity study, the TK parameters of setmelanotide were also determined in the WT rasH2 mouse following daily SC injection of setmelanotide as mPEG-DSPE formulation at doses up to 20 mg/kg/day for 28 days.

Following repeated SC injection of setmelanotide in mPEG-DSPE in mice, rats and monkeys, systemic exposure was generally close to dose proportional, although variable the Cmax increased in a less than dose proportional manner whereas AUC increased mainly in a dose proportional manner with the increase in dose.

Though not considered significant, in the mouse and rat repeat-dose toxicity studies, the exposure levels of setmelanotide (Cmax and AUC) were overall higher in males as compared to females, following SC injection of setmelanotide independently of the formulation of the test item investigated (mPEG-DSPE or saline). No such a gender effect was noted in the cynomolgus monkey. Likewise, in human no clinically significant differences in the pharmacokinetics of setmelanotide were observed based on sex.

In the mouse administered SC injection of setmelanotide in mPEG-DSPE no significant increase in exposure was noted following repeated dosing as compared to day 1. In the chronic rat study, the systemic accumulation ratio (Rac) was variable and ranged from 1.10 to 3.85. Similarly, in the 39-week toxicity study conducted in the cynomolgus monkey the Rac values ranged from 0.276 to 3.81. Overall these data indicated no or limited accumulation after repeated SC injection of setmelanotide in mPEG-DSPE in the mouse, rat and monkey for both males and females.

In the repeat-dose toxicity studies conducted in the mouse, rat and monkey following SC injection of setmelanotide in mPEG-DSPE, there was no evidence of potential neutralising anti-drug antibodies (ADA), except for two samples from the 6- month Tg.rasH2 mouse carcinogenicity study.

A single-dose crossover study in cynomolgus monkeys was performed to assess the PK of setmelanotide formulated in mPEG-DSPE with and without the preservatives i.e. benzyl alcohol (10 mg/mL), phenol (5 mg/mL) and disodium edetate (1 mg/mL) when administered by SC injection at a dose of 5 mg/kg. The results demonstrated that the preservatives did not impact the PK of setmelanotide.

**Distribution**

No in vitro data comparing the distribution profile of setmelanotide in blood cells vs plasma from animal species and human are available. In vivo, the blood:plasma ratios calculated from AUClast were 0.89 and 0.81 in male and female Sprague Dawley rats, respectively after a SC injection of radiolabelled setmelanotide at 2 mg/kg.

Using the equilibrium dialysis method, the plasma protein binding of setmelanotide appeared to be comparable across human and the different animal species investigated (mouse, rat, rabbit, and monkey) ranging from 76.3 to 82.4%.

The tissue distribution and tissue PK of [$^{14}$C]-setmelanotide-derived radioactivity following a single SC (bolus) dose were investigated in male and female Sprague Dawley rats and male Long Evans (LE) rats for 168h and 504h respectively, using quantitative whole-body autoradiography methods.

In the Sprague Dawley rat, the highest exposure was noted in the kidney that is consistent with the urine primary path of excretion, followed by moderately high concentrations and exposures comparable to the plasma and whole blood in the liver and lung of males and females, as well as in the uterus and ovaries. The lowest radioactivity and exposure were observed in the brain and eye. The tissue:plasma ratios for kidney were as high as 37, confirming that [$^{14}$C]-setmelanotide and/or its metabolites are highly concentrated in the kidney. All other tissue:plasma ratios demonstrated limited affinity for remaining tissue types. There were no substantial differences in plasma or whole blood concentrations over the first 168 hours post-dose for the LE rat as compared to the non-pigmented Sprague Dawley rat. In LE rats, [14C]- setmelanotide was detected in the lens and uveal tract up to 504 hours post-dose, indicating that the compound has an affinity for pigmented tissue. The measured concentrations in uveal tract during 168 to 504 hours ranged 63-71 ng/g tissue which was slightly above the 59.1 ng/g limit of quantitation, and the concentration in the lens during the same period was 64-103 ng/g tissue. These concentrations were comparable as the whole blood range of 51-73 ng/g tissue during the same period. No toxicological concern was identified regarding accumulation in eye, as repeat dose toxicity studies in monkeys and rats did not reveal any ophthalmic findings.

As part of a pre/postnatal development toxicity study, setmelanotide was found to be excreted in the milk of lactating rats that received repeated SC injection of setmelanotide in mPEG-DSPE at 0.5, 3 or 5 mg/kg starting on gestation day 6. This observation was adequately reported under section 4.6 of the SmPC of Imcivree.

Placental transfer has not been investigated for setmelanotide. Since this compound is extensively distributed to tissues in both albino and pigmented rats, there is a high likelihood of placental transfer and embryo-foetal exposure in utero. In the SmPC it has been reflected that setmelanotide should not be used during pregnancy, as a precautionary matter, based on the results of the embryofoetal development toxicity study conducted in the rabbit.

**Metabolism**

Setmelanotide was found to be stable in human, rat and monkey liver and kidney microsomes as well as in human, rat and monkey hepatocytes. Moreover, setmelanotide was not degraded by Hs68, a cell line of human skin fibroblasts.

In the rat administered [$^{14}$C]-setmelanotide, analysis of the plasma samples indicated that parent compound accounted for 76% to 95% of the measured radioactivity. The primary metabolite of setmelanotide in plasma was M19 (3 to 12%) of measured radioactivity (ROI). Two additional metabolites not present in urine were M16 (0.4 to 7% ROI) and M17 (0.1 to 6% ROI).

Nineteen metabolites of setmelanotide plus parent drug were identified in various rat excreta extracts, primarily the urine. Four metabolites present at > 5% of dose in the urine, were M7 (0 to 14% of

dose), M10 (1 to 11% of dose), M12 (2 to 11% of dose), and M19 (14 to 59% of dose). Parent setmelanotide was present at 4 to 29% of dose.

The metabolite M19 was identified as setmelanotide that had undergone hydrolysis at the C-terminal amide to a free carboxylic acid. M12 resulted from further hydrolysis of M19, cleavage of the peptide chain, and acetylation. M7 resulted from further hydrolysis of M19, cleavage of the peptide chain, and loss of tryptophan. M10 was from further hydrolysis of M19 with the loss of the side chain of histidine. M14 (1 to 4% of dose) and M15 (1 to 3% of dose) can both arise from cleavage of the peptide chain via hydrolysis at different locations within the chain.

Of the above rat metabolites, only M19, was found to have activity on human MC1R, MC3R, and MC4R in vitro. Compared to setmelanotide it was about 10-fold less potent at both MC4R and MC3R while being 3-fold less potent at MC1R. The other metabolites were inactive on MC4R and MC3R and 10- to 600-fold less potent than setmelanotide on MC1R.

**Excretion**

Greater than 90% of the dose administered was recovered in urine, feces, and cage rinse from male and female rats over 168 hours following a single SC or IV dose of [$^{14}$C]-setmelanotide at 2 mg/kg. The majority of the excreted [14C]-setmelanotide was recovered in the urine, and < 10% was recovered in the faeces regardless of dose route. In the Bile-duct cannulated animals given a SC dose, urine was the major route of excretion (82.7%), as compared to faeces (4.3%) and bile (1.9%) over 48 h post-dose.

## 2.3.4. Toxicology

### *Single dose toxicity*

No single dose toxicology studies were conducted which was considered acceptable by the CHMP.

### *Repeat dose toxicity*

Several changes in formulations were introduced during the toxicological testing programme in rats and monkeys due to convenience of treatment regimen and subsequent local intolerability observed at the infusion/injection site in test animals. In human, setmelanotide is intended to be administered with mPEG-DSPE formulation by SC injection, and therefore the repeat-dose toxicity studies with SC injection of Setmelanotide in mPEG-DSPE are the most relevant studies. The applicant is currently working on a second-generation formulation which would permit an even longer dose interval (e.g. possibly weekly), with the possibility to avoid the use of mPEG-DSPE.

In both rats and monkeys, no systemic toxicities were identified in repeat-dose toxicity studies at any dose of setmelanotide in saline or setmelanotide in mPEG-DSPE.

In the repeat-dose toxicity studies in rats and monkeys, local injection site inflammatory reactions were observed with administration of setmelanotide formulated in mPEG-DSPE and in saline, as well as in the vehicle mPEG-DSPE control group. The increased incidence and/or severity of injection sites reactions were related to increased mPEG-DSPE volume and increased setmelanotide concentrations. These effects were therefore considered related primarily to mPEG-DSPE with some involvement of setmelanotide at high doses. The injection site reactions were generally mild and partially reversible (except fibrosis and thickening), and the macroscopic observations were generally correlated to microscopic changes. The injection site reactions were considered non-adverse at doses up to up to 3

mg/kg in rats and at 3/1 mg/kg/day in monkeys, which corresponds to exposure margins of 9 and 26 in rats and monkeys, respectively, based on AUC for setmelanotide and to dose margins of 9.5 and 6.5, respectively, based on mg/m$^2$/day for mPEG-DSPE. In the clinical studies, injection site reactions were also observed at high frequency and were typically mild in severity, short of duration and tolerated by the patients.

In the repeat dose studies, setmelanotide related decreases in body weight, food consumption or body weight gain was not consistently observed across sex, dosing groups and species. Some effects on body weight gain was observed, even statistically significantly in some treated groups. Therefore, the expected effects on body weight and food intake in the toxicity studies (conducted in normal (lean) animals), were of minor magnitude in spite of higher doses used in the toxicity setting, compared to both diet-induced and genetic obesity models used in PD studies.

Potential vacuolisation in the brain of adult rats and monkeys were investigated after 6 and 9 months repeat dosing, respectively, using the diluted formulation of mPEG-DSPE. This was in accordance with the CHMP advice. In the 26-week study in rats, minimal vacuolation related to the mPEG-DSPE vehicle was observed in the epithelial cells of the choroid plexus with sporadic incidence (9/117 animals) in all mPEG-DSPE groups +/- setmelanotide with no mPEG-DSPE dose-volume dependency. In the 39-week study in monkeys, vacuolated (foamy) macrophages aggregates of minimal severity were observed in the choroid plexus of all animals treated with formulations containing mPEG-DSPE. In contrast to rats, no vacuolation was observed in the epithelial cells in the brain. After a period of 4-week recovery, the vacuolation findings were still observed in female rats and in all monkeys. In both rats and monkeys, no distortion of brain tissue, no evidence of any other microscopic changes in the brains and no evidence of functional changes in the brain were observed. The pathology peer-review confirmed that no treatment-related vacuolation were observed in other tissues in adult rats and monkeys, except at injection sites. The additional immunohistochemical staining with an anti-PEG antibody showed that no staining for PEG was observed in the choroid plexus of either species, but the presence of pegylated material in these vacuoles cannot be ruled out since potential limitations of the immunostaining procedure and the location in the choroid plexus. The evaluation of the absorption, distribution, metabolism and elimination of mPEG-DSPE in rat using 14C-mPEG-DSPE (labelled on mPEG only) showed that the concentration in the choroid plexus was below the quantitation limit at 24 hours, 2 weeks, 7 weeks and 14 weeks after the 7th dose for the majority of the animals. No sign of vacuolation in the choroid plexus was observed in juvenile rats during 7 weeks of dosing of mPEG-DSPE up to 3 mg/kg/day, corresponding to a dose margin for mPEG-DSPE of 14 times on mg/m$^2$/day basis assuming 40 kg body weight in paediatric patients, at the clinical dose of 2 mg.

Hyperpigmentation (darkening) 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. Increased pigmentation was also observed in the conjunctiva with continuous SC infusion of Setmelanotide, 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. After recovery period, the facial hyperpigmentation was improved but not totally reversible.

In the 26-week study in rats, skeletal muscle myofiber degeneration/regeneration was observed and considered treatment-related. This adverse effect was considered related to be an extension of local injection site irritation, was minimal in severity and reversible. The skeletal muscle myofiber degeneration/regeneration was observed with very low incidence at doses up to 3 mg/kg, but with higher incidence (10 of 29 rats) at 15 mg/kg with setmelanotide in saline (exposure margin of 49 based on AUC at the clinical dose of 3 mg/day). The other neuromuscular changes observed in other studies were not considered related to study treatment. In the clinical studies, mild muscle soreness

and moderate cramping were observed in one heterozygous POMC patient but were transient and both AEs recovered/resolved. The available non-clinical and clinical data suggest that neuromuscular toxicity is not a major concern in the indicated patient population.

## *Genotoxicity*

The data from the standard battery of genotoxicity assessments, in line with ICH S2(R1), indicated that Setmelanotide does not present a genotoxic hazard to humans.

## *Carcinogenicity*

The carcinogenic potential of setmelanotide/mPEG-DSPE was investigated in hemizygous Tg.rasH2 mice following SC administration during 26 weeks in three independent studies, due to technical issues in the first (erroneous randomisation) and second (malfunction of the water supply system) studies. However, these issues did not impact the outcome or conclusions of the study.

In the three 26-week carcinogenicity studies, there were no increase in mortality and no neoplastic changes attributed to the daily subcutaneous administration of setmelanotide in mPEG/DSPE at doses up to 10 mg/kg/day for up to 6 months. In addition, setmelanotide has exhibited no genotoxic activity and has not been associated with increased hypertrophic, hyperplastic, or preneoplastic tissue changes in the repeat-dose toxicity studies in both rats and monkeys. The non-neoplastic changes at the injection sites observed in these studies were also observed in the repeat-dose toxicity studies and are related to mPEG and/or Setmelanotide.

In the first 26-week carcinogenicity study in Tg.rasH2 mice, black staining on fur was observed starting from day 156 at ≥ 1 mg/kg/day Setmelanotide with dose-dependency and with generalized appearance at 10 mg/kg/day. The observed black staining on fur is likely related to the off-target effect at MC1 receptors, as observed in monkeys and human. In the third carcinogenicity study (RM-493-TOX-045), black staining on fur was observed but only on day 77 in 4/25 female. In the second carcinogenicity study (RM-493-TOX-044), black staining on fur/skin was also observed but a summary table should be provided. In addition, the difference between the three carcinogenicity studies for the occurrence of black staining on fur/skin should be discussed.

## *Reproduction Toxicity*

The fertility and embryo-fetal developmental studies in rats showed no evidence of setmelanotide-related effects on male or female fertility, maternal toxicity and teratogenic effects. The safety margins based on AUC for setmelanotide in mPEG-DSPE are at least 9 for fertility and 7 for the risk of teratogenicity, at the clinical dose of 3 mg. The dose margin for the mPEG-DSPE vehicle is at least 9.5-fold on a mg/$m^2$/day basis.

In the embryo-fetal developmental study, the rabbits were extremely sensitive to the primary pharmacodynamic effect of setmelanotide which lead to severe reductions in food consumption during the treatment period. By consequence, increased embryo-fetal resorptions and post-implantation loss were observed at setmelanotide exposure level of approximately 0.4-times human AUC and mPEG-DSPE dose margin of 0.15 on a mg/$m^2$/day basis. The maternal toxicity effects observed in rabbits may not be relevant to humans. No teratogenic effect was observed in rabbits at doses up to 0.2 mg/kg/day, which corresponds to safety margin of 1.5 based on AUC and a dose margin for mPEG-DSPE of 0.6-fold on a mg/$m^2$/day basis.

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 7-times human AUC and mPEG-DSPE dose margin of 16 on a mg/m$^2$/day basis.

### *Toxicokinetic data*

Toxicokinetic data were collected from pharmacokinetics or toxicology studies and the data are presented in the previous sections.

### *Local Tolerance*

In all repeat-dose studies in monkeys and rats treated with setmelanotide, local intolerability was observed with differing severity depending on the tested type of formulation, where setmelanotide formulated in undiluted mPEG-DSPE caused the most severe reactions locally at the injection site. Local effects such as edema, swelling and thickened skin as well as clinical pathological signs of inflammation have been observed at the injection site in all studies, regardless of vehicle formulation used.

### *Other toxicity studies*

Two separate studies on local reactions were performed for different formulations containing setmelanotide. The studies confirmed the findings in the general toxicological studies that mPEG-DSPE formulations generally induce more severe local reactions than saline formulations and that setmelanotide seems to have a contributory effect on local reactions at high concentrations. In the two studies, the mPEG-DSPE vehicle was deemed the vehicle to be best tolerated, despite also giving rise to local injection site reactions. other formulations were also investigated, which lead to more severe local reactions compared to saline.

Setmelanotide consists of a number of impurities, which have been included the drug substance specification, such as peptide related impurities as well as residual solvents and elemental impurities. Most impurities are below the qualification limit according to ICH Q3A and are controlled during manufacturing.

## 2.3.5. Ecotoxicity/environmental risk assessment

**Table 1 : Summary of main study results**

| **Substance (INN/Invented Name): Setmelanotide** | | | |
|---|---|---|---|
| **CAS-number (if available): 920014-72-8** | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | Shake-flask | pH 5.5 < -3.32<br>pH 7.4 < -0.8/-0.2 | Potential PBT (N) |
| ***Phase I*** | | | |
| **Calculation** | **Value** | **Unit** | **Conclusion** |
| PEC $_{surfacewater}$, default or refined (e.g. prevalence, | 0.00003 µg/L | µg/L | > 0.01 threshold (N) |

| | | | |
|---|---|---|---|
| literature) | | | |
| Other concerns: PEC surfacewater of excipient mPEG-2000-DSPE | 0.0003 µg/l | µg/L | > 0.01 threshold (N) |

## 2.3.6. Discussion on non-clinical aspects

Setmelanotide, an analogue of α-MSH, is a MC4R agonist indicated for the treatment of obesity and the control of hunger associated with biallelic pro-opiomelanocortin (POMC) or leptin receptor (LEPR) deficiency.

Setmelanotide binds to several human hMCRs, and preferentially recognizes human melanocortin type 4 receptor (hMC4R), It is about 20-fold less potent in activating MC1R and MC3R.

In vitro, similar binding affinity and/or EC50s were observed for human, rodent (rat and mouse), dog, and non-human primates (rhesus and cynomolgus) MC4R. Among those species the EC50 values for the MC1R and MC3R were comparable. For the MC5R of human, mouse and rat setmelanotide showed no agonist activity whereas a >10-fold lower activity as compared to the target MC4R was noted for the MC5R of the dog and the non-human primates. All together, these data showed that the rat and the non-human primates (NHP) but also the mouse and the dog are all pharmacologically relevant animal species for the safety assessment of setmelanotide.

No specific rationale for choosing the cynomolgus monkey was provided. The rhesus monkey in the toxicology studies, was presented but it may have been more logical to have used the same NHP in both pharmacology and toxicity studies. Also, in view of the in vitro efficacy data and consistent with the 3R principle, the dog should have been preferred as the non-rodent species rather than the cynomolgus monkey for the pivotal repeat-dose toxicity studies.

In vivo, the non-clinical efficacy studies in diet-induced obese rodent and Rhesus monkey models as well as in genetic models of obesity, including leptin-receptor deficient Zucker fa/fa rats confirmed the MC4R-mediated pharmacological effect of setmelanotide in decreasing body weight and food intake. In those obese models (diet induced or genetic models), it was furthermore demonstrated that setmelanotide had beneficial effects with respect to improved insulin and glucose parameters. In a MC4R knock-out mouse model, it was shown that MC4R+/+ mice treated with setmelanotide exhibited weight loss, while MC4R-/- mice did not show similar effects, but rather were similar compared to vehicle treated animals with respect to body weight gain. In the primary pharmacology studies, only the saline formulation of setmelanotide was used, and no studies were performed with the mPEG-DSPE formulation. As the final formulation is rarely finished at the time of nonclinical proof of concept this is not considered to be an issue, and the safety of the excipient has been established in the toxicology studies.

In vitro screening for potential off-target effect showed that setmelanotide inhibited ligand binding by 20%-50% at 5 receptors (muscarinic, neurokinin-2, sigma, thyrotropin-releasing hormone, and GABA transporter), and by ~60% at opioid receptors.

In addition, the inhibitory effect occurred at higher (50-fold) concentration as compared to the exposure level achieved in the clinic for the planned therapeutic dose.

In the rhesus monkey study, no behaviour signs linked to MC4R pathway activation were identified. Likewise, there was no skin tanning or coat colour changes. This is in contrast with the skin findings observed in all the toxicity studies in cynomolgus monkey where facial hyperpigmentation associated microscopically with increased epidermal pigment consistent with melanin, was noted following SC

infusion or SC injection. This occurred with all the dose levels of setmelanotide tested and with both the saline and the mPEG-DSPE formulations. The effect of setmelanotide on skin pigmentation is considered related to the off-target effect on the closely related melanocortin 1 receptor (MC1R). Since the primary pharmacodynamic study in the Rhesus monkey was not GLP compliant but only involved limited cage-side observation a definitive statement about the presence or absence of the hyperpigmentation cannot be confirmed. Skin hyperpigmentation has been observed in the clinical setting. In addition, skin hyperpigmentation is an identified risk in the RMP and is included in the SmPC as a very common adverse reaction (see 2.6.1).

In line with the ICHS7 guideline, GLP-compliant safety pharmacology studies with setmelanotide included assessment of the respiratory and CNS functions in the rat, in vitro hERG channel, and in vivo cardiovascular safety study in the cynomolgus monkey. Those studies did not raise safety concern. Adverse cardiovascular effects on HR and mean BP were however, observed in several rat studies following single or repeated SC bolus administration of setmelanotide, but they were counteracted by pre-treatment with propranolol and terazosin (β and α1 blocker respectively). In a minipig study, increased in HR was also observed following SC injection or infusion of setmelanotide. Since the safety pharmacology studies performed in rats and non-rodents (monkeys and minipig), does not produce a clear picture of the effects of setmelanotide on HR and BP, the cardiovascular effects observed in other species besides the cynomolgus, was recommended to be describe briefly in the 5.3 section of SmPC.

In the clinical setting, no adverse cardiovascular effects and no evidence of increased heart rate and blood pressure were identified in the limited number of patients administered setmelanotide at the proposed therapeutic daily dose of 3 mg. However, in view of the rat findings and the fact that MC4R agonists are linked to an increase in sympathetic tone, a pharmacodynamic effect on HR and BP can be anticipated. Hence recommendations to monitor heart rate and blood pressure in case of overdose have been further included in the section 4.9 of the SmPC, the clinical long-term safety and tolerability of setmelanotide being unknown and considered as missing information**.**

In the non-clinical pharmacokinetic studies, the species and strains reflect also those employed in the toxicological evaluation of setmelanotide, thus enabling assessment of the exposure levels of the parent compound in the toxicology studies to support the safe administration to humans.

The PK after both single and repeat dosing appear well described in all species and an approximately dose proportional relationship was observed with slight signs of accumulation. Some gender differences in setmelanotide exposure (AUC and Cmax) were observed following SC injection in the rat, the exposure levels being overall higher in males as compared to females; however, they were not considered significant. No such a gender effect was noted in the cynomolgus monkey. No ADA was found in rats, monkeys, mice or rabbits.

Distribution of setmelanotide was evaluated in adult Sprague Dawley and LE rats. There was no substantial difference in plasma or whole blood concentrations over the first 168 hours post-dose for the pigmented LE rat as compared to the non-pigmented Sprague Dawley rat. In addition, there appeared to be no difference in binding to pigmented or non-pigmented skin. However, in LE rats, [14C]- setmelanotide was detected in the lens and uveal tract up to 504 hours post-dose, indicating that the compound has an affinity for pigmented tissue. Setmelanotide being a peptide no potential for phototoxicity is anticipated.

Placental transfer was not investigated for setmelanotide. However, in view of the extensive distribution of the compound to tissues in both albino and pigmented rats, placental transfer and embryo-foetal exposure in utero are likely.

The ADME study for setmelanotide was performed in the rat as the rat was one of the species chosen for the pivotal toxicological studies. No data was available for the in vivo metabolic pathways and

excretion in monkeys. The absence of ADME study in this species was justified based on the chemical structure of setmelanotide as well as on the 3R principle. As setmelanotide is a cyclic peptide, the primary metabolites are expected to be proteolytic hydrolysis products and smaller peptides and amino acids, which due to their low molecular weight are expected to be cleared renally. In the rat, of the four main metabolites of setmelanotide identified in the urine, only the metabolites M19 and M17, were quantified in human urine samples. In vitro M19 was pharmacologically active on human MC4R, MC1R, and MC3R but it was less potent than the parent compound. The metabolites of setmelanotide identified to date in the rat support this mechanistic metabolism path.

Plasma was not assessed for determination of metabolites in human whereas only two metabolites, M19 and M17, were quantifiable in urine of few patients administered setmelanotide for 12 weeks. In none of the pivotal toxicity studies conducted with setmelanotide were the TK parameters of the systemic metabolites determined. In the absence of human exposure data for the circulating metabolites, it is not possible to draw conclusion on the non-clinical characterisation of metabolite toxicity. Nevertheless, unlike the classical small chemical drug, setmelanotide, as an octapeptide, is not expected to show metabolism that differs greatly from species to species. The main pharmacologically active compound is the parent drug, which has been comprehensively evaluated in the toxicology studies. In addition, the main metabolite in rats, M19, had a 10-fold lower activity on MC1R, MC3R and MC4R than setmelanotide, whereas the other metabolites were >1000-fold less active. Overall the available non-clinical data does not indicate potential issues linked to the metabolism of setmelanotide.

The toxicology package presented is in line with the requirements under the relevant guidelines (ICH M3 and S6) and with due consideration to the proposed posologyAn LC-MS/MS and ELISA methods were developed to measure setmelanotide and anti-setmelanotide antibody (ADA) in rat, mice, monkey and rat serum, respectively, in support of the GLP pivotal toxicological studies. The LC-MS/MS method were validated across the concentrations ranging from 5.0 to 2000 ng/mL. The accuracy and precision of within-run and between-run values was acceptable and in line with relevant guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2). Furthermore, dilution integrity as well as long-term stability and stability during freeze thaw cycles was sufficiently addressed. The method for detecting ADA in the different plasma samples was considered sufficiently validated. Incurred sample reanalysis was investigated in all toxicological species.

In the repeat-dose toxicity studies, no systemic toxicities were identified at any dose of setmelanotide. Local injection site inflammatory reactions were observed and were considered related primarily to mPEG-DSPE with some involvement of setmelanotide at high doses. Similar findings were observed in the clinical studies and are included in the SmPC. In the repeat dose studies conducted in normal (lean) animals, the expected effects of setmelanotide on body weight and food intake were of minor magnitude in spite of higher doses used, compared to both diet-induced and genetic obesity models used in pharmacology studies. 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 skin darkening is considered as an exaggerated pharmacological off-target effect of setmelanotide at the MC1 receptor and has also been observed in a very high proportion of patients in clinical studies. In the repeat-dose toxicity studies, adverse effects on the neuro-muscular system were observed in the 26-week rat study with higher incidence at exposure margin of 49 at the clinical dose of 3 mg/day, but no other neuromuscular changes related to study treatment were observed in the other toxicities studies.

Minimal vacuolation in the choroid plexus related to the mPEG-DSPE vehicle were observed in the epithelial cells with sporadic incidence in the 26-week study in rats and in the macrophages of all animals in the 39-week study in monkeys. The vacuolation findings were still observed in female rats

and in all monkeys after 4-week recovery period. Taking into account (i) the minimal severity of vacuolation observed sporadically in the brain of rats, (ii) the absence of vacuolation in the epithelial cells in the brain of monkeys, (iii) the absence of vacuolation in other tissues in adult animal species, (iv) the absence of accumulation of mPEG-DSPE in the brain observed in rat study using $^{14}$C-mPEG-DSPE, (v) the absence of adverse effects on brain function and (vi) the high clinical need in the targeted population, the potential risks of vacuolation in the brain of paediatric/adult subjects is low and considered acceptable. The vacuolation findings in the choroid plexus of rats and monkeys have been briefly described in section 5.3 of the SmPC.

The data from the standard battery of genotoxicity assessments, in line with ICH S2(R1), indicated that Setmelanotide does not present a genotoxic hazard to humans.

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/m2/day basis, at the clinical dose of 3 mg/day. Setmelanotide/mPEG-DSPE meets the criteria for a 2-year rat study waiver as set forth in ICH guideline S1 Regulatory notice on changes to core guideline on rodent carcinogenicity testing of pharmaceuticals (EMA/CHMP/ICH/536328/2013 Rev. 1) based on the following weight of evidence approach: (i) Setmelanotide/mPEG-DSPE is not genotoxic, (ii) no histopathological evidence of cellular hypertrophy, hyperplasia, dysplasia, preneoplastic changes, or neoplasia in any toxicity study, (iii) activation of MC1R protects melanocytes against the genotoxic effects of ultraviolet light and (v) no malignant melanomas or cutaneous malignancies were reported in clinical trials. Melanoma is specified in the risk management plan as an important potential risk and routine risk measures are included in SmPC sections 4.4 and 4.8 as well as in the Package Leaflet (full body skin examinations prior to initiating treatment and during treatment to monitor pre-existing and new skin pigmentary lesions).

Setmelanotide did not show effects on fertility or teratogenicity, nor was any systemic effects observed in the juvenile toxicity studies, specifically no effects related to vacuolisation of the choroid plexus.

Additional toxicity studies supported mPEG-DSPE formulation as best tolerated vehicle, despite giving rise to local injection site reactions. The applicant claimed that other formulations were also investigated, which led to more severe local reactions compared to saline formulation, however no data or comparison were made available to support this statement.

The available non-clinical data in toxicity studies revealed no evidence of antigenicity in mice, rats, monkeys or rabbits.The absence of immunotoxicity study is considered acceptable, as no evidence of immunotoxicity was observed in the repeat-dose toxicity studies in rats and monkeys.

The secondary in vitro pharmacodynamics studies showed that setmelanotide competitively inhibited ligand binding to the opioid receptor, at concentration of free setmelanotide 55-fold higher than the concentration reached in the clinical setting and at the therapeutic dose of 3 mg. In the repeat-dose toxicity studies in rats and monkeys, no signs of drug withdrawal were observed during post-treatment periods. In addition, setmelanotide is a large molecule and distribution studies shows limited penetration into the brain. Additional investigation is not deemed necessary and the absence of dependence studies is considered acceptable.

The absence of phototoxicity studies is considered acceptable in line with ICH S10. In the distribution study in LE rats, accumulation in the pigmented tissue in eyes were observed, however, no ophthalmic findings were observed in repeat dose toxicity studies in monkeys and rats. Hyperpigmentation of the muzzle was observed in all studies and dose-levels in monkeys; however, this was likely related to the pharmacological action of setmelanotide and not due to phototoxicity.

The estimation of the LogD of setmelanotide has been investigated at pH 5.5 and pH 7.4, but not at pH 9. In addition, the study on determination of the octanol water partition coefficient at pH5.5 had some

major lacks in quality. However, the LogD at pH9 is estimated to be in the same range taking into account that the pKa of setmelanotide is >13 and the probability for an exceedance of the logD trigger regarding the requirement of a bioaccumulation assessment is negligible low. No additional studies have been therefore requested. Setmelanotide and the excipient mPEG-DSPE-2000 are not expected to pose a risk to the environment.

Setmelanotide and the excipient mPEG-DSPE-2000 are not expected to pose a risk to the environment.

### *Assessment of paediatric data on non-clinical aspects*

In accordance with the nonclinical requirements of the paediatric investigation plan for setmelanotide, the applicant also conducted a study with the radiolabelled mPEG-DSPE (20 mg/kg/day) in order to determine the concentration of [$^{14}$C]-mPEG2000-DSPE equivalents in the blood, plasma, and choroid plexus in the rat after single and repeated SC bolus administration for up to 7 weeks.

In this study, the concentration in blood and plasma was generally below quantitation limit whereas in tissues the concentration of [$^{14}$C]-mPEG2000-DSPE-derived radioactivity was highest in the injection site after single dose administration, or last dose administration site with repeat dosing. The concentration in the choroid plexus was below the quantitation limit at 2 weeks and 7 weeks after the 7th dose for all animals except 1 female that had a high concentration that was inconsistent with all other measurements, including those at preceding time points. These data suggested limited uptake of [$^{14}$C]-mPEG2000-DSPE in the choroid plexus following 7 weeks of SC administration.

The design of the juvenile study in rats supports the administration of setmelanotide in paediatric population from 6 years to 17 years. The adverse findings observed in the 7-week juvenile study in rats were related to the pharmacological activity of setmelanotide (body weight, food consumption) and to injection site reactions, which were similar to those observed in adult rats. At the No Observed Adverse Effect Level (NOAEL) of 3 mg/kg/day for setmelanotide/mPEG-DSPE, based on the clinical exposure observed at 2 mg in paediatric patients, the safety margin for setmelanotide in mPEG-DSPE is 18 based on AUC and the dose margin for mPEG-DSPE is 14 on mg/m$^2$/day basis assuming 40 kg body weight.

## 2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical aspects of Imcivree have been adequately documented and meet the requirements to support this application.

## *2.4. Clinical aspects*

## 2.4.1. Introduction

### *GCP*

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

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

- Tabular overview of clinical studies

**Table 2 : Clinical studies supporting pharmacokinetics/pharmacodynamics and safety**

| Study #/ Phase | Description | Population | Formulation | Doses | Subjects Enrolled /Subjects with PK | PK and PD Objectives |
|---|---|---|---|---|---|---|
| Single Dose Studies | | | | | | |
| RM-493-001<br>Phase 1 USA | Randomized, double-blind, placebo-controlled, crossover, single, ascending-dose, safety and tolerability, PK and PD | Healthy obese subjects<br>Adults >18 years | Setmelanotide-Saline, (preservative free) | SC infusion<br>Parallel<br>0.01 mg/kg/24 h or PL (n=3)<br>0.0025 mg/kg/24 h or PL (n=3)<br>0.025 mg/kg/24 h or PL (n=3)<br>Crossover<br>0.01 mg/kg/24 h and PL (n=4)<br>0.05 mg/kg/24 h and PL (n=4)<br>0.02 mg/kg/24 h and PL (n=4)<br>0.1 mg/kg/24h and PL (n=4)<br>0.01 mg/kg and PL (n=4) | 36 / 31 | Characterize single-dose PK following 24-hour SC administration.<br>Asses urine PK<br>Assess Immunogenicity, Assess dose proportionality<br>Plasma insulin, hunger and satiety and REE |
| | | | | SC injection<br>0.01 mg/kg single dose (n=4) | 4 | Characterize single-dose PK following SC injection |
| RM-493-008<br>Part 1/<br>Phase 1 USA | Part 1<br>Open label, 2-period crossover, single dose PK | Adults >18 years | Setmelanotide-Saline and Setmelanotide/mPEG-DSPE (preservative free) | SC injection<br>1.5 mg single dose | 8 / 8 | Determine the PK of single doses administration of mPEG/DSPE formulation |
| Study #/ Phase | Description | Population | Formulation | Doses | Subjects Enrolled /Subjects with PK | PK and PD Objectives |

| | | | | | | |
|---|---|---|---|---|---|---|
| Multiple Doses Studies | | | | | | |
| RM-493-002<br>Phase<br>1 USA | Randomized, double-blind, placebo controlled, multiple, ascending-dose safety and tolerability, PK and PD | Healthy obese volunteers or heterozygous<br>Adults >18 years | Setmelanotide-Saline, (preservative free) | SC infusion<br>0.0025 mg/kg/24 h or PL for 14 days (cohort 2, n=8)<br>0.01 mg/kg/24 h or PL for 14 days (Cohort 1, n=6)<br>0.01 mg/kg/24 h or PL for 28 days (Cohort 3, n=6)<br>0.015 mg/kg/24 h 28 days (Cohort 4, n= 6<br>SC injection<br>0.015 mg/kg/day (0.0075 mg BID) for 14 days (Cohort 5, n=6) | 57 / 39 | Characterize the PK of multiple dose<br>Characterize the PK in urine<br>Assess immunogenicity<br>PD: Weight and waist circumference<br>Ambulatory blood pressure<br>Quantitative skin color assessment (heterozygotes) |
| | | | | SC infusion (MC4R Heterozygous)<br>0.01 mg/kg/24 h for 28 day (Cohort 6, n= 6) | | Single and multiple dose PK profiles |
| RM-493-008<br>Part 2<br>Phase<br>1 USA | Placebo controlled, double blind, randomized, dose titration | Healthy obese Adults >18 years | Setmelanotide/mPEG-DSPE (preservative-free) | SC injection<br>1.5 mg QD for 4 days<br>1.0 mg QD for 2 days followed by 2.0 mg QD for 2 days | 14 / 12 | Characterize safety, tolerability and PK of setmelanotide/mPEG-DSPE following multiple administration. |
| RM-493-003<br>Phase<br>2 USA | Randomized. Double blind, placebo controlled to evaluate safety and efficacy<br>Weight loss in obese | Healthy obese Adults >18 years | Setmelanotide-Saline, (preserved) | SC infusion<br>1.0 mg/24 h for 90 days | 74 / 37 | PK: Trough concentrations<br>Assess immunogenicity |

| | | | | | | |
|---|---|---|---|---|---|---|
| RM-493- 026<br>Phase 1ba | Randomized, placebo controlled | Obese adults<br>>18 years | Setmelanotide/mPEG-DSPE (preserved) | SC injection<br>QD formulation<br>2.0 mg QD or placebo Week 1 followed by 3 mg Weeks 2-12 (n=9)<br>QW formulation<br>10 mg or placebo QW for 12 weeks (n=4) | 50 / 9 | PK, safety and tolerability<br>Urine collection<br>Assess immunogenicity<br>(QD dosing) |
| Pharmacodynamic Studies | | | | | | |
| RM-493-006<br>Phase 1b<br>USA | Randomized, double blind, placebo-controlled, multiple dose, crossover Energy expenditure | Healthy obese Adults >18 years | Setmelanotide-Saline, (preserved) | SC infusion<br>1.0 mg/24 h for 3 days | 12 / 8 | Evaluation of exposure-REE, TEE-C, and REE-H |
| Study #/ Phase | Description | Population | Formulation | Doses | Subjects Enrolled /Subjects with PK | PK and PD Objectives |
| RM-493-009<br>Phase 1b, 2a<br>USA | Randomized, double-blind, placebo-controlled Safety and efficacy in healthy, obese subjects with once or twice | Healthy obese<br>Adults >18 years | Setmelanotide/mPEG-DSPE (preservative-free) | SC injection Part A:<br>0.75 mg BID for 4 weeks increased to 1 mg BID on Day 18 to 2 mg QD on Day 29 to Day 84<br>1.5 mg QD for 4 weeks increased to 2 mg QD on Day 18 to Day 84 | 99 / 59<br>19 | Stage A - Characterize the multiple dose PK Full PK profile on Day 8 and trough up to 84 days<br>Assess immunogenicity |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | Part B:<br>1.5 mg QD for 4 weeks increased to 2 mg QD on Day18 to Day 84 | 11 | Stage B- trough samples up to 84 days |
| | | | | Part C:<br>2 mg QD on Day18 to Day 84 | 29 | Stage C – Characterize the multiple dose PK Full PK profile on Day 8 and trough up to 12 weeks |
| Patient Studies | | | | | | |
| RM-493-010<br>Phase 2 USA | Randomized, double-blind, placebo controlled, crossover pilot study Safety and efficacy in PWS | Subjects with PWS<br>Adults > 18 years | Setmelanotide/mPEG-DSPE (preservative-free) | SC injection<br>Part 1 single-blind<br>placebo, 0.5, or 1.5 mg QD for 2 weeks | 20 / 18 | Characterize the PK of setmelanotide in patients. Develop a population PK model of setmelanotide in patients.<br>Assess immunogenicity |
| | | | | Part 2: double-blind<br>placebo, 1.5 mg, or 2.5 mg QD for 4 weeks | 20 | Characterize the PK of setmelanotide in patients. Develop a population PK model of setmelanotide in patients.<br>Assess immunogenicity |
| | | | | Part 3 Sub-Study: double-blind, placebo withdrawal<br>placebo same dose (2.5 mg QD 1.5 mg QD) for 2 weeks | 8 | Characterize the PK of setmelanotide in patients. Develop a population PK model of setmelanotide in patients.<br>Multiple dose PK during a 24-hour steady state interval (sub-study) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | Part 4 open label extension<br>0.5 mg and 1.5 mg for 2 weeks | 8 | |
| RM-493-011<br>Phase 2<br>Investigator initiated<br>Germany<br>5.3.5 | Open label, dose titration<br>Trial in rare genetic disorders | Heterozygous POMC deficiency, LEPR and Epigenetic deficiency and PCSK1<br>>12 years | Setmelanotide/mPEG-DSPE (preservative free and preserved) | <u>SC-injection</u><br>Part 1 – baseline (2 days)<br>Part 2 – dosage findings<br>(Weeks 2 - 4) dose titration from 0.5 mg to 1 mg, 1.5 mg and 2 mg<br>Part 3- outpatient (Weeks 4 - 11) to therapeutic dose level<br>Extension phase – up to years | 10 / 7<br>(2 – POMC;<br>3 – LEPR;<br>2 – Epigenetic) | PK collected on final visit of Part 3,<br>Assess safety and Immunogenicity |
| RM-493-012<br>Phase 3<br>Germany, UK, France, USA, Canada, Spain, Belgium | Open label, double-blind, placebo-controlled withdrawal period Safety and efficacy in POMC Patients | Early onset POMC Deficiency obesity due to bi-allelic, loss of function POMC or PCSK1 genetic mutation<br>>6 years | Setmelanotide/mPEG-DSPE (preservative free and preserved) | <u>SC injection</u><br>*Adults* - Initial dose 1.0mg titrated up to 3.0 mg QD<br>Dose titration with incremental increases of 0.5 mg every 2 weeks | 12 / 12<br>4 (2 – Both; 1 – Preservative Free; 1 - Preserved) | Characterize the PK in adults, adolescents and pediatrics patients<br>Develop a population PK model of setmelanotide in patients<br>All Patients ≥12 years at titration visit:<br>8-hour PK profile.<br>Subset (optional for ≥ 12 years adults): 24-hour PK profile<br>Trough samples all patients at all visits<br>Assess immunogenicity in patients |
| | | | | *Adolescents* - initial dose 0.5mg titrated up to-3 mg QD | 4 (1 - Preserved, 3 - Both) | |
| | | | | *Pediatric* – initial dose 0.5 mg titrated up to 2.5 mg<br>Followed by 10 - weeks open label and then 8 - weeks double blind withdrawal. | 4 (Preserved) | |

| Study #/ Phase | Description | Population | Formulation | Doses | Subjects Enrolled /Subjects with PK | PK and PD Objectives |
|---|---|---|---|---|---|---|
| RM-493-014<br>Phase 2 (ongoing)<br>USA<br>UK | Phase 2 safety study in rare genetic disorder's (Basket) | >12 years of age<br>Rare genetic disorders (i.e., LEPR mutation, heterozygous and epigenetic defects in POMC, Bardet-Biedl or Alström syndrome). | Setmelanotide/mPEG-DSPE (preservative-free and preserved) | SC injection<br>*Adults* - 1.0 to 3.0 mg QD, increments 0.5 mg every 2 weeks | 27 / 27<br>15 (5-Both; 7-Preserved; 3 – Preservative Free) | Characterize the PK adults in patients. Develop a population PK model of setmelanotide in patients<br>(24-hours PK profiles during titration phase)<br>Assess immunogenicity in patients |
| | | | | *Adolescents* - 0.5 to 3 mg QD increments 0.5 mg every 2 weeks | 12 (2 – Both; 7 – Preserved; 3 - Preservative Free) | Characterize the PK in adolescent patients. Develop a population PK model of setmelanotide in patients<br>(8-hour PK profiles during titration phase)<br>Assess immunogenicity in patients |
| | | | | *Pediatric* - 0.5 to 2.5 mg QD | 0 | Characterize the PK pediatrics in patients. Develop a population PK model of setmelanotide in patients.<br>(trough samples at clinic visits).<br>Assess immunogenicity in patients |
| RM-493-015<br>Phase 3<br>Germany, UK, France, Netherlands<br>USA | An Open Label Double-Blind Placebo-Controlled Withdrawal Period | > 6 years old, in LEPR deficiency. obesity due allelic, loss-of-function LEPR gene mutations. | Setmelanotide/mPEG-DSPE (preserved) | SC injection<br>*Adults* - Initial dose 1.0mg titrated up to 3.0 mg QD | 14 / 13<br>9 (9 - Preserved) | Characterize the PK in adult patients. Develop a population PK model of setmelanotide in patients<br>(All Patients ≥12 years at titration visit:<br>8-hour PK profile.<br>Subset (optional for ≥ 12 years adults): 24-hour PK profile.<br>Trough samples all patients at all visits).<br>Assess immunogenicity in patients. |

| Study #/ Phase | Description | Population | Formulation | Doses | Subjects Enrolled /Subjects with PK | PK and PD Objectives |
|---|---|---|---|---|---|---|
| | | | | *Adolescents* - initial dose 0.5mg titrated up to-3 mg QD | 4 (4 - Preserved) | Characterize the PK in adolescent patients. Patients 6 to 11 years - full PK profile at dose titration visit.<br>Assess immunogenicity in adolescents. |
| | | | | *Pediatrics* – initial dose 0.5 mg titrated up to 2.5 mg<br>Dose titration with incremental increases of 0.5 mg every 2 weeks | 0 | Characterize the PK in pediatric patients.<br>Assess immunogenicity in pediatrics |
| RM-493-022<br>Germany<br>(Ongoing) | Extension study | >6 years | Setmelanotide/mPEG-DSPE<br>(preserved) | SC injection<br>Same dose as index study. Dose adjustments (either increase or decrease were made in increments of 0.5 mg.<br>Max 3 mg – US Canada and UK<br>Max 2.5 mg – Germany and France | 16 / 10 | Characterize the PK of setmelanotide following long-term administration.<br>Assess immunogenicity. |

[a] PK data from once weekly (QW) dosing is not included in this submission.

Key: SC - subcutaneous; REE = resting energy expenditure; TEE-C = total energy; REE-H = resting energy expenditure by bedside hood calorimeter; LEPR- leptin receptors; PWS Prader-Willi Syndrome ; POMC – Pro-opiomelanocortin; PCSK1 – proprotein convertase subtilisin/Kexin Type 1; B – number of patients that used setmelanotide/mPEG-DSPE preserved and preservative free during the study; P – use setmelanotide/mPEG-DSPE with preservative; PF – use setmelanotide/mPEG-DSPE preservative free. QD – once a day; QW – once a week.

**Table 3 : Clinical studies supporting efficacy and safety**

| Study ID | No. of study centres / locations | Design | Study Posology | Study Objective | Subjs by arm entered/ compl. | Duration | Gender M/F Age distribution | Diagnosis Incl. criteria | Primary Endpoint |
|---|---|---|---|---|---|---|---|---|---|
| RM-493-012 (Pivotal, ongoing) | 7 | Phase 3 open-label with double-blind placebo-controlled withdrawal period | Dose titration from 0.5 up to 3 mg (2.5 mg for paediatric subjects) | Statistically significant & clinically meaningful effects on percent body weight change at end of 1-year TP | 14/9 (ongoing) | 52 Weeks | M: 57%<br>F: 43%<br>N < 12years: 4<br>N ≥ 12 years: 10 | Obese<br>>6 years<br>Bi-allelic, homozygous or compound heterozygous genetic deficiency status for either the POMC or PCSK1 genes | Proportion of patients who demonstrated at least 10% weight reduction at ~1 year compared to baseline |
| RM-493-015 (Pivotal, ongoing) | 5 | Phase 3 open-label with double-blind placebo-controlled withdrawal period | Dose titration from 0.5 up to 3 mg (2.5 mg for paediatric subjects) | Statistically significant & clinically meaningful effects on percent body weight change at end of 1-year TP | 13/9 (ongoing) | 52 Weeks | M: 38.5%<br>F: 61.5%<br>N < 12 years: 0<br>N ≥ 12 years: 13 | Obese<br>>6 years<br>Bi-allelic, homozygous or compound heterozygous genetic deficiency status for the LEPR gene | Proportion of patients who demonstrated at least 10% weight reduction at ~1 year compared to baseline |
| RM-493-022 (Long term extension, ongoing) | Not yet known | Phase 3 open-label observatory | Continued with last dosing level received at end of patient's participatory Index study | To characterize safety and tolerability of setmelanotide in patients who have completed treatment in a previous trial of setmelanotide for obesity | 16/-, 7 of which were POMC deficicent patients from study RM-493-012. No patients from study RM-493-015 enrolled yet. | Up to 104 Weeks | (POMC/PCSK1 deficiency patients only)<br>M: 57%<br>F: 43%<br>Median age: 17 years | Patients 6 years of age or older that completed participation on active drug and demonstrated adequate safety in a previous setmelanotide study for | The safety and tolerability of setmelanotide was assessed by the frequency and severity of adverse events (AEs) as well as changes in physical examinations, |

| Study ID | No. of study centres / locations | Design | Study Posology | Study Objective | Subjs by arm entered/ compl. | Duration | Gender M/F Age distribution | Diagnosis Incl. criteria | Primary Endpoint |
|---|---|---|---|---|---|---|---|---|---|
| | | | | associated with | | | | obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway. | electrocardiograms (ECGs), vital signs (including resting BP and HR), laboratory evaluations, and injection site reactions. |
| RM-493-011 (Supportive & investigator-led) | 1 | Phase 2 open-label, uncontrolled, non-randomized | Up to 2 mg for paediatric subjects, up to 3 mg for adults | Assess changes in body weight within each patient population with rare genetic disorders of obesity following 3 months of setmelanotide-treatment. | 7/7, 5 of which had confirmed POMC/LEPR deficiency | | M: 43%<br>F: 57%<br>Median age: 20 years<br>POMC and LEPR only:<br>M: 40%<br>F: 60%<br>Median LEPR deficiency patient age: 21 years<br>Median POMC/PCSK1 deficiency patient age: 23 years | Obesity due to rare genetic disease, ≥12 years, no other therapeutic option | Assess changes in body weight within each patient population with rare genetic disorders of obesity following 3 months of setmelanotide-treatment. |

## 2.4.2. Pharmacokinetics

The overall pharmacokinetic data to support this application for setmelanotide are relatively complex due to the fact that throughout the clinical studies three different formulations and two different administration routes with both body weight-adjusted and fixed dosing have been used.

During the clinical development program, setmelanotide was initially administered with body weight-adjusted (mg/kg) dosing, and subsequently on a fixed-dose basis (mg). Body weight-adjusted dosing was used in a total of 2 clinical studies (RM-493-001 and RM-493-002), administered as a SC infusion. Single and multiple doses ranging from 0.0025 mg/kg/24 hour to 0.1 mg/kg/24 hours were investigated (range 0.12 to 9.1 mg/day).

The change from body weight-adjusted dosing to fixed dosing of setmelanotide was made following Studies RM-493-001 and RM-493-002, in which the weights of the obese subjects were fairly uniform, averaging ~100 kg, so that the mean (range) of daily drug administration was 0.913 (0.72 – 1.2) mg/24 hours. To simplify the dosing regimen, fixed doses were used in all subsequent studies including 1 Phase 1 (RM-493-008), multiple Phase 2 studies (RM-493-009, RM-493-010, RM-493-011, RM-493-014), 2 Phase 3 studies (RM-493-012 and RM-493-015), and an open-label extension study (RM-493-022).

The first 4 clinical studies, (RM-493-001, RM-493-002, RM-493-003, and RM-493-006) used a setmelanotide sterile saline solution formulation, administered as a 24-hour subcutaneous (SC) infusion, and in 3 studies as an SC injection (RM-493-001, RM-493-002, RM-493-008). Subsequently, a sterile setmelanotide preparation for injection containing setmelanotide/mPEG-DSPE was developed, which allowed once daily (QD) treatment. Study RM-493-008 was conducted to investigate the PK, safety and tolerability of setmelanotide/mPEG-DSPE as well as study the relative PK comparability of SC injection of setmelanotide/mPEG-DSPE to setmelanotide-saline. This study showed that the PK properties of this early formulation were significantly different from those obtained with the mPEG-DSPE formulation. Therefore, these early studies with the saline-based formulation will not be discussed in the present report. However, they have been considered in the secondary pharmacology analyses. All clinical studies conducted thereafter, including the pivotal studies (RM-493-012, RM-493-015) as well as Phase 1b and Phase 2 studies (RM-493-009, RM-493-010, RM-493-011, RM-493-014, and RM-493-026) were conducted with setmelanotide/mPEG-DSPE formulation, which is the intended commercial material. Setmelanotide-saline formulation is no longer in use.

Early during the conduct of Studies RM-493-012 (Phase 3, POMC) and RM-493-014 (Phase 2, rare genetic obesity), a preservative-free mPEG-DSPE formulation was used. Further in the product development, preservatives were added to the mPEG/DSPE formulation to support multi-dose vials. Study RM-493-026 included an assessment of the steady-state safety, tolerability, and PK of setmelanotide/mPEG-DSPE preserved formulation administered by SC injection QD to healthy obese subjects. Some of the initial patients in Studies RM-493-012 and RM-493-014 were transferred from the preservative-free mPEG-DSPE formulation to the preserved mPEG-DSPE formulation.

In addition, a POPPK model was conducted using mixed effects modelling for repeated-measures endpoints. The dataset was comprised of 120 subjects in 8 studies (RM-493-008, -010, -011, -012, -014, -015, -026 and -022) in healthy obese patients or patients with RGDO; a total of 2711 quantifiable PK observations were included.

## *Absorption*

Setmelanotide is characterised by a very low permeability based on in vitro experiments performed in TC7 human intestinal epithelial cells and in MDCK cells. In vitro experiments in MDR1-MDCK, BCRP-MDCK, and MDCK cells showed that setmelanotide is not a substrate of P-gp and BCRP.

Concerning the different administration routes, the SC infusion route was used in the first 4 clinical studies. Plasma setmelanotide concentrations in subjects receiving SC infusions reached a plateau by 24 to 48 hours after starting the infusion, suggesting that steady state is achieved by 24 to 48 hours After completion of the 24-hour continuous SC infusion doses, setmelanotide exhibited two-compartmental pharmacokinetics. A lag time was observed after continuous SC infusions of setmelanotide. Excluding the data for the 0.0025 mg/kg dose, the mean lag times ranged from 0.74 to 6.0 hour. However, this administration route is less convenient in an outpatient setting in comparison with a SC injection administration and, limited data suggested that the SC infusion dose was slightly suboptimal. A SC injection of the saline solution of setmelanotide was further tested but found not appropriate for OD dosing. Therefore, a sterile preservative-free solution with a pegylated phospholipid ion-pairing agent 1,2-disteroyl-phosphotidylethanolamine-methyl-pluethylene glycol 2000 conjugate (setmelanotide/mPEG-DSPE) was developed. Study RM-493-008 showed that the PK properties of this new (mPEG-DSPE) formulation at a dose of 1.5 mg (SC injection) were significantly different from those obtained with saline solution, with a median Tmax increasing from 1h to 6h, and, as such, decreasing the average Cmax value from 37.6 ng/mL to 18.9 ng/mL, while the AUC0-24 values remained approximately similar.

A clear trend towards a more readily absorption of the preserved formulation was found in comparison with the non-preserved formulation, with approximately 20% higher Cmax and AUC values. Although not based on a direct comparison in a dedicated clinical study, this was confirmed in the POPPK analysis and falls within the intra-subject variability.

Overall, after SC injection of the preserved mPEG-DSPE formulation with setmelanotide, steady-state plasma concentrations of setmelanotide increased slowly, reaching maximum concentrations at a median tmax of 8.0h after dosing. The mean Cmax,ss and AUCtau for 3 mg QD was 37.9 ng/mL (%CoeffV 14.0) and 495 h*ng/mL (%CoeffV 16.8), respectively (Study RM-493-026 – healthy obese population). Mean setmelanotide trough concentration for 3.0 mg once daily was 6.77 ng/ml.

## *Distribution*

The results obtained with transfected HEK cell lines showed that setmelanotide is neither a substrate of OATP1B1, OATP1B3, OAT1, OAT3 nor OCT2. The protein binding was determined using two different techniques: using ultrafiltration, the bound fraction ranged from 45.5± 1.3 - 53.4±0.9% for the tested concentrations 1 – 100 µM; with equilibrium dialysis the bound fraction was 79.1% at a tested concentration of 5 µM.

The mean apparent volume of distribution after SC administration of setmelanotide 3.0 mg QD is approximately 63 L.

## *Elimination*

The effective elimination t1/2 of setmelanotide (mPEG-DSPE formulation with preservative) is approximately 11 hours (Study RM-493-026). The CL/F value is 4.86 L/h. Approximately 39% of the administered setmelanotide dose was excreted unchanged in urine during the 24-hour dosing interval following subcutaneous administration of 3 mg once daily.

In vitro experiments showed that setmelanotide is not a MATE1 substrate and a borderline MATE2K substrate.

Only trace amounts of two urine metabolites, M19 and M7 (found in rat urines) were observed in a small number of subjects in study 4006777.

## *Dose proportionality and time dependencies*

Despite a relatively high variability in PK parameters (due to the different formulations and administration routes used during the development), study RM-493-015 indicated dose proportionality following SC (mPEG-DSPE, preserved) injection at steady state in patients and it could be seen that setmelanotide generally exhibited close to dose proportionality across doses and studies.

Accumulation of setmelanotide in systemic circulation during QD dosing over 12 weeks was approximately 30% relative to the first dose (after dose-normalization). This degree of accumulation is consistent with a once-daily dosing regimen and an effective T1/2 of 11 h. An accumulation in AUC of 20% to 30%, is also consistent with a half-life observed through the clinical development of setmelanotide. The catabolic effects of weight loss have not impacted the PK.

Based on the POPPK model, the inter-subject variability is estimated to be 28.7% and the intrasubject variability 27.6% which is considered as moderate.

## *Special populations*

A specific phase I study in subjects with renal impairment is ongoing (RM-493-029). No dedicated study in hepatic impaired patients has been undertaken by the applicant. However, in view of the fact that setmelanotide is predominantly excreted by the kidneys, this is considered acceptable by the CHMP. Other data related to renal function, age, weight, gender was derived from population pharmacokinetic (POPPK) analyses. During the procedure, additional data were also provided to assess other factors such as race/ethnicity.

The effects of renal function on the PK of setmelanotide were modelled using estimates of creatinine clearance calculated from serum creatinine concentration together with age, sex, and body weight. In this model, subjects with mild renal impairment had a 0.852-fold (0.701, 1.04) lower CL/F as compared to those with normal renal function. Preliminary data from study RM-493-029 showed nearly 2-fold increased half-life of setmelanotide and around 20% decreased clearance for mild as well as nearly 30% decrease in clearance for moderate renal impairment.

The POPPK indicated that age was not a significant factor influencing clearance of setmelanotide but the strong relationship between age and weight impacts recommendations for paediatric dosing. In addition, mean Ctrough levels at all doses were significantly lower for females in comparison with males (percent ratio female/male of the geometric means was 61%), and were significantly below 5 ng/mL which was considered to be the target level related to efficacy. This is further discussed in section 2.4.4.

Additional data did not reveal any significant effects of race/ethnicity noting subjects were predominantly Caucasian (N=81) or black (N=27) in the clinical studies.

The population PK model indicated that age was not a significant factor influencing clearance of setmelanotide but a strong strong continuous correlation between weight and PK parameters, resulting in higher exposure for lower weight and younger age was observed. This is further discussed in section 2.4.4.

The pharmacokinetic profile setmelanotide in the elderly population has not been studied.

## *Pharmacokinetic interaction studies*

No specific drug-drug interaction studies have been performed.

## *Pharmacokinetics using human biomaterials*

In vitro data using human biomaterials suggested that the potential for setmelanotide to cause drug interactions may be considered as low.

*Direct CYP inhibition*

The inhibition potential of setmelanotide to inhibit cytochrome P450 (CYP) was evaluated in two studies. The first study used only one concentration of 1 mM setmelanotide showing greater IC50 values of CYP inhibition than 1 mM in four CYP isoforms CYP1A2, 2C9, 2C19 and 2D6. In the second study, only one concentration of setmelanotide (1.2 µM) has been tested to investigate the direct inhibitory potential of setmelanotide of CYP1A2, CYP2A6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4/5 enzymes. The 50 x the unbound Cmaxss is estimated to be approximately 0.357 µM for a therapeutic dose of 3 mg once daily, the concentration of 1.2 µM was thus deemed higher and not representative of the maximal concentrations expected in the liver. Although the methodology used is not optimal and a range of concentrations should also normally be tested for direct CYP inhibition, the results suggested a very low % of direct inhibition for the different isoenzymes at this higher concentration and only a weak inhibition of CYP3A at 1.2 µM is observed.

*Time-dependent inhibition*

The potential for time-dependent inhibition (TDI) of cytochrome P450 (CYP) (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A) in human liver microsomes (HLM) by setmelanotide was tested. The calculated IC50 values were greater than the cut-off concentration calculated for the hepatocytes (0.36 µM) thus suggesting that there is no time-dependent inhibition of any of the CYP enzymes by setmelanotide.

*Induction*

Setmelanotide did not increase either mRNA or activity of CYP1A2, CYP2B6, or CYP3A at any of the three tested concentrations (0.05, 0.2, and 0.5 µM) in any of the tested human hepatocyte donors. The examination of mRNA levels showed <2-fold vs. vehicle control. The activities in the three CYP isoforms were less than 20% of positive control and were not considered as positive for induction.

*Transporter inhibition*

The risk for drug-interactions through an inhibition mechanism at the level of investigated efflux transporters PgP and BCRP is unlikely at clinically relevant concentrations as no inhibitory effects of more than 50% have been shown in MDR1-MDCK and BCRP-MDCK cells using digoxin and cladribine as probe substrates for P-gp and BCRP, respectively. The ratio of unbound Cmax/IC50 is less than 0.02 for BCRP and PgP and suggest no significant inhibition of BCRP and PgP.

Investigations using cell lines with overexpression of the target genes did not reveal potential for clinically relevant inhibition of OATP1B1 and OATP1B3, OAT1, OAT3 and OCT2, MATE1 and MATE2K transporters.

## 2.4.3. Pharmacodynamics

### *Mechanism of action*

Setmelanotide retains the specificity and functionality of the naturally occurring POMC-derived neuropeptide, alpha-melanocyte stimulating hormone (αMSH), which is the natural ligand for MC4R. Therefore, setmelanotide has the potential to restore lost activity in the POMC-MC4R pathway by bypassing the defects upstream of MC4R and directly activating MC4R neurons in the hypothalamus, thus ameliorating the genetic defects in the critical signalling pathway that regulate energy homeostasis and food intake in humans.

Setmelanotide may serve as a form of "replacement" therapy to re-establish weight and appetite control in patients with these monogenic disorders and is considered a selective MC4 receptor agonist.

### *Primary and Secondary pharmacology*

No specific patient pharmacodynamic studies were performed. Pharmacodynamic endpoints (e.g. the effect of setmelanotide on the degree of hunger experienced by the patients, energy expenditure) were incorporated as secondary and tertiary endpoints in the pivotal efficacy and safety studies. This is considered acceptable by the CHMP given the ultra-rarity of the condition and thus lack of available subjects. The effect of Setmelanotide on resting energy expenditure was also evaluated in study RM-493-006. An increase in expenditure of 6.4% versus placebo was found and this study showed a higher trending total daily energy expenditure. Pharmacodynamic effects of setmelanotide on blood pressure, heart rate, ECG, skin pigmentation, administration sites, anti-drug antibodies, depression and suicidal ideation have been investigated.

No pharmacodynamics studies have been conducted in human subjects that are relevant to dose selection. The proposed regimen has been derived entirely from the efficacy and safety results of clinical trials.

**Blood Pressure and Heart Rate**

In Study RM-493-001, crossover cohorts allowed a within-subject comparison between setmelanotide and placebo. The average 24-hour mean values were analysed and supplementary data were derived from the comparisons at multiples of the anticipated clinical dose (e.g., at 5x and 10x the anticipated clinical dose), and also at the Tmax timepoints (i.e., 24-hours for the infusion and 3 hours for the injection). There were no clinically relevant or statistically significant changes from baseline for any of the comparisons.

24-hour ambulatory blood pressure monitoring (ABPM) was incorporated into Study RM-493-002 with 3 full days of monitoring for each cohort: on baseline day, halfway through treatment and on the last dosing day. The data were reassuring in 2 ways. First, the change from baseline in the actively treated group on the last day of dosing (Day 28) clusters around the zero change line, indicating that the setmelanotide group did not show a change in SBP with 28 days of treatment compared to baseline (i.e., within-subject assessment). Second, the data for the active-treatment group were generally similar to the placebo group showing that after setmelanotide treatment for 28 days there is no difference from placebo.

An ABPM sub-study, which included 20 full days of monitoring, was also conducted at a subset of sites in Study RM-493-003. The data revealed little if any differences in heart rate and blood pressure between the setmelanotide and placebo groups (analyses of both the entire 24-hour interval and the night interval).

Study RM-493-009 again included ABPM obtained twice, once at baseline and once on Day 8-9. Analysis of change from baseline in systolic BP, diastolic BP and HR for all subjects with both pre- and post-dose measurements showed no differences from placebo.

**ECG**

In Study RM-493-001 there were no clinically relevant or statistically significant differences between setmelanotide and placebo with regard to the change from baseline in QTcB or QTcF. One placebo subject recorded a QTcB increase of >30 ms, ≤60 ms.

Cardiac telemetry revealed no clinically relevant abnormalities after drug infusions had started.

Similar analyses in Study RM-493-002 also showed no clinically relevant or statistically significant differences between setmelanotide and placebo with regard to the change from baseline in QTcB or QTcF. One subject administered setmelanotide and 1 subject administered placebo in the 14-day infusion treatment group had a >30 ms change from baseline of the QTcB interval. One subject in the heterozygous treatment group administered setmelanotide had a QTcB interval >450 ms following setmelanotide administration. There was a single abnormal finding identified during cardiac telemetry: one subject administered setmelanotide had a non-sustained, asymptomatic, episode of ventricular tachycardia. This finding was reported as an adverse event of moderate intensity and considered unlikely to be related to study medication. A subsequent cardiologist evaluation determined the brief arrhythmia was of no clinical significance and the subject was cleared for continued participation in the study.

In Study RM-493-009 there were again no clinically relevant mean changes in QTcB or QTcF in either actively treated or placebo-treated subjects. Statistical comparisons between the groups were not performed for this study.

Increases in QTcB from baseline of between 30 and 60 ms were recorded for 7 of 59 (11.9%) of setmelanotide subjects compared to 5 of 40 (12.5%) placebo subjects; the equivalent proportions for QTcF were 3 of 59 (5.1%) for setmelanotide and 3 of 40 (7.5%) for placebo. No subject, regardless of treatment, recorded an increase of >60 ms or an absolute value >500 ms for either QT correction.

**Skin Pigmentation**

In Study RM-493-001 quantitative skin colour measurements were performed with the Mexameter-18 device. The amount of melanin in the skin was measured on the cheek, on the forehead and on the buttock.

Overall, small numerical trends on change from baseline to Day 3 were reported and approximately dose related. However, no significant changes were seen for change from baseline to Day 1 or Day 7. Overall, few if any of the changes reached statistical significance.

Identical measurements were made in Study RM-493-002. Generally, the data suggest a trend towards an effect of setmelanotide on quantitative skin colour darkening, especially on the cheek and forehead, and to a somewhat lesser degree on the hip. Overall, clinical examination findings support conclusions based on Mexameter assessment.

Quantitative skin colour assessment was again repeated in Study RM-493-003 and in this study it showed a statistically significant increase in pigmentation for setmelanotide compared to placebo at all three sites.

In addition, as part of the same study protocol, patients had 3 representative pigmented skin lesions (prospectively identified by the site dermatologist prior to study start) which were randomised to protocol-mandated biopsy at one of three times: before dosing, at the end of the 3-month study, and approximately 90 days after the final dose of setmelanotide. The pathological diagnoses were

performed by the central clinical dermatopathologist. The majority of the lesions biopsied carried pathological diagnoses of nevi, lentigo and seborrheic keratosis, as would be expected for these pigmented lesions. Of these biopsies, only 4 (from lesions in 3 patients [one patient had a non-protocol mandated biopsy taken at the same time as the protocol mandated biopsy]) showed any evidence of atypia, the first potential evidence of any dysplastic changes. All these lesions were nevi and all had low levels of atypia. Two of these patients' biopsies were pre-dose (i.e., before any exposure to setmelanotide), and one was at the end of the 3-month treatment period.

**Administration sites**

Administration site reactions were systematically assessed in studies RM-493-001 and RM-493-002.For each evaluation there were 5 possible reactions assessed (oedema, erythema, induration, itching, pain or tenderness).

In Study RM-493-001 injection site reactions were noted in both the active and placebo groups, but all were mild (with the exception of 3 moderate reactions that were all in the placebo group). Most of the site reactions were mild erythema at the site of the indwelling continuous infusion catheter. Many were transient, not presenting consistently at consecutive or most of the timepoints for a given subject. None were considered clinically relevant.

In Study RM-493-002 Infusion/injection site reactions were noted in both the active and placebo groups, and the majority were mild (3 moderate reactions: 2 pain or tenderness and 1 erythema). The majority of the reactions were mild erythema, and approximately a third of these erythema reactions were in subjects administered placebo. The majority were transient, and none were considered clinically relevant.

**Anti-drug Antibodies (ADA)**

Of the 48 patients in Study RM-493-002 tested with pre-dose and 2 post-dose timepoints and of the 6 patients tested with pre-dose and 1 post-dose timepoint, none had a post-dose titre that exceeded the pre-dose titre. Therefore, no samples were considered reactive, and no samples were positive for setmelanotide antibodies.

Eighty-three patients had samples collected in Study RM-493-009 for the presence of antibodies to setmelanotide. No samples were positive.

**Depression and Suicidal Ideation**

Subjects in Study RM-493-009 were assessed for depression and suicidal ideation using the Patient Health Questionnaire-9 (PHQ9) and Columbia-Suicide Severity Rating Scale (C-SSRS) instruments, respectively. Generally, there were no significant differences in the overall depression /suicidality assessments scores measured during the study in those subjects receiving RM-493 versus placebo. No subject, regardless of treatment group, was identified by C-SSRS as having any suicidal ideation at any point in the study.

## 2.4.4. Discussion on clinical pharmacology

Three different formulations have been used throughout the clinical development: a non-preserved saline solution of setmelanotide for SC infusion and SC injection, a non-preserved mPEG-DSPE/CMC formulation and a preserved mPEG-DSPE formulation for SC injection. The latter (preserved mPEG-DSPE) is the proposed commercial formulation. These formulations have been administered to different populations (mostly healthy obese volunteers) in 13 studies investigating the clinical pharmacology of setmelanotide.

Concentrations of setmelatonide were measured in plasma and urine using LC-MS/MS methods. To address the requirement for sample reanalysis as per EMA guidelines, the CHMP recommended to provide data from sample analysis in pending clinical and validation (e.g. long-term stability) studies.

Setmelanotide is characterized by a very low permeability and it is *in vitro* not a substrate of P-gp and BCRP.

After the SC injection of the to-be-marketed preserved mPEG-DSPE formulation, steady-state plasma concentrations of setmelanotide increased slowly, reaching maximum concentrations at a median tmax of 8.0h after dosing. In several clinical studies, patient numbers were (very) low, and, in addition, the conclusions were hampered due to aberrantly high or low concentrations, probably due to a limited compliance and consistency in the outpatient setting (see also section 2.5 Clinical efficacy). No IV formulation has been developed for use in humans, therefore the absolute bioavailability in humans is unknown. However, a bioavailability of less than 100% is expected as, following subcutaneous administration, the drug passes through the lymphatic system, which usually results in pre-systemic elimination.

Given the uncertainties on the rate and extent of absorption in function of the injection site and given that that the clinical studies for setmelanotide used the injection in the abdomen only, the CHMP recommended to limit the injection to the abdominal region. This has been reflected in section 4.2 of the SmPC.

The results obtained with transfected HEK cell lines showed that it is neither a substrate of OATP1B1, OATP1B3, OAT1, OAT3 nor OCT2.

Different results in the protein binding were reported due to the use of different methodologies. The ultrafiltration method is often used at the early discovery stage of the program because it is a faster technique than the equilibrium dialysis method but is often seen as less reliable and suffers from non-specific binding of drug to the apparatus. Equilibrium dialysis is still regarded as the reference technique to use in investigating the binding characteristics of a new drug to serum. Therefore, the actual protein binding is set to 79.1%. Given that the lower percentages in protein binding estimated by ultrafiltration are considered to be more conservative since a higher free fraction of drug is present, the findings related to the studies on transporters were considered valid.

The mean apparent volume of distribution after SC administration of setmelanotide 3.0 mg QD is approximately 63 L, which is consistent with the value estimated from the POPPK model, 48.7 L.

The effective elimination t1/2 of setmelanotide (mPEG-DSPE formulation with preservative) is approximately 11 hours. The CL/F value is 4.86 L/h. In vitro experiments showed that setmelanotide is not a MATE1 substrate and a borderline MATE2K substrate. Setmelanotide is excreted in urine, with ~39% excreted unchanged.

No in vivo Drug Drug Interaction (DDI) study with a MATE2K inhibitor was considered necessary. Mass-balance studies are not useful for determining the excretion pattern of therapeutic proteins. Setmelanotide did not appear to be metabolized by human hepatic microsomes and hepatocytes. Despite the routes of elimination of setmelanotide in humans have not been explained in detail, it can be expected that small proteins of Molecular Weight (MW)<50000 Da (MW of setmelanotide = 1117.3 Da) are eliminated through renal filtration followed by tubular re-absorption and subsequent metabolic catabolism.

Based on the study 4006777, only trace amounts of two urine metabolites, M19 and M7 (found in rat urines) were observed in a small number of subjects.

Setmelanotide generally exhibited close to dose proportionality across doses and studies. Accumulation of setmelanotide in systemic circulation during QD dosing over 12 weeks was approximately 30%

relative to the first dose (after dose-normalization) which is consistent with a half-life of 7 to 10 hours observed through the clinical development of setmelanotide. The catabolic effects of weight loss have not impacted the PK.

Based on the population PK model, the inter-subject variability is estimated to be 28.7% and the intrasubject variability 27.6% which is considered as moderate. It has been demonstrated in the exposure-response analyse that variability in treatment responses may not be due to PK covariates. Setmelanotide being well tolerated and being titrated to effect, this variability was considered acceptable.

In the POPPK analyses, gender differences were observed. Lower Ctrough levels in females were reported than in males at all doses, the CHMP however accepted that such differences could be due to other factors such as body weight and renal function. Given that the proposed posology is based on dose titration to the response, rather than correlated with body weight, no dose adjustment in females was considered necessary.

Additional data did not reveal any significant effects of race/ethnicity noting subjects were predominantly Caucasian (N=81) or black (N=27) in the clinical studies.

Given the patient populations for POMC and LEPR deficiency obesity are predominantly young, the PK of setmelanotide in the elderly have not been studied.

No specific drug interaction studies in human subjects have been performed.

*In vitro* studies showed that setmelanotide has low potential for pharmacokinetic interactions related to cytochrome P450 (CYP), transporters and plasma protein binding.

No specific patient pharmacodynamic studies were performed. Pharmacodynamic endpoints (e.g. the effect of setmelanotide on the degree of hunger experienced by the patients, energy expenditure) were incorporated as secondary and tertiary endpoints in the pivotal efficacy and safety studies. No pharmacodynamics studies have been conducted in human subjects that are relevant to dose selection. The proposed regimen has been derived entirely from the efficacy and safety results of clinical trials. This was considered acceptable by the CHMP given the ultra-rarity of the condition and thus lack of available subjects.

Pharmacodynamic effects of setmelanotide on blood pressure, heart rate, ECG, skin pigmentation, administration sites, anti-drug antibodies, depression and suicidal ideation have been investigated. These data did not reveal any trends or clinically meaningful changes. However, due to the limited number of patients included in the trials, these events (in particular skin pigmentation, hypertension) are further discussed in the clinical safety section of this report (see section 2.6). In addition, further updated data are expected to be available on the effect of setmelanotide on ADA and the CHMP recommended to submit them as post authorisation commitment (see further below and section 2.6.1 Clinical Safety).

No pharmacodynamics studies have been conducted in human subjects that are relevant to dose selection. The proposed regimen has been derived entirely from the efficacy and safety results of clinical trials.

**Additional PK/PD analyses**

POPPK simulations were used to identify a relevant starting dose for children from 6 years of age based on historical growth data over the desired age range. While the use of model-based approach was supported in principle, scarce data were available in the lower age/bodyweight ranges and no clinical data were available for validation. Initially, the applicant proposed an age-based flat dosing while the

final population PK model shows a strong continuous correlation between weight and PK parameters, resulting in higher exposure for lower weight and younger age. The appropriateness of the proposed fixed dose regimen, especially as patients are supposed to lose weight during the treatment and the possible risk of children getting overexposed by the fixed dose regimen was questioned. In addition, the lowest age in the model building dataset was 10 years old with only 4 patients aged 10-12 years. Yet the model was used to extrapolate the dose for children down to 6 years old.

To address these concerns, data from studies RM-493-012 and RM-493-015 were used to generate a plot of the titrated dose (mg) associated with effective weight-loss versus age, which showed no correlation between effective dose and age. See Figure 2.

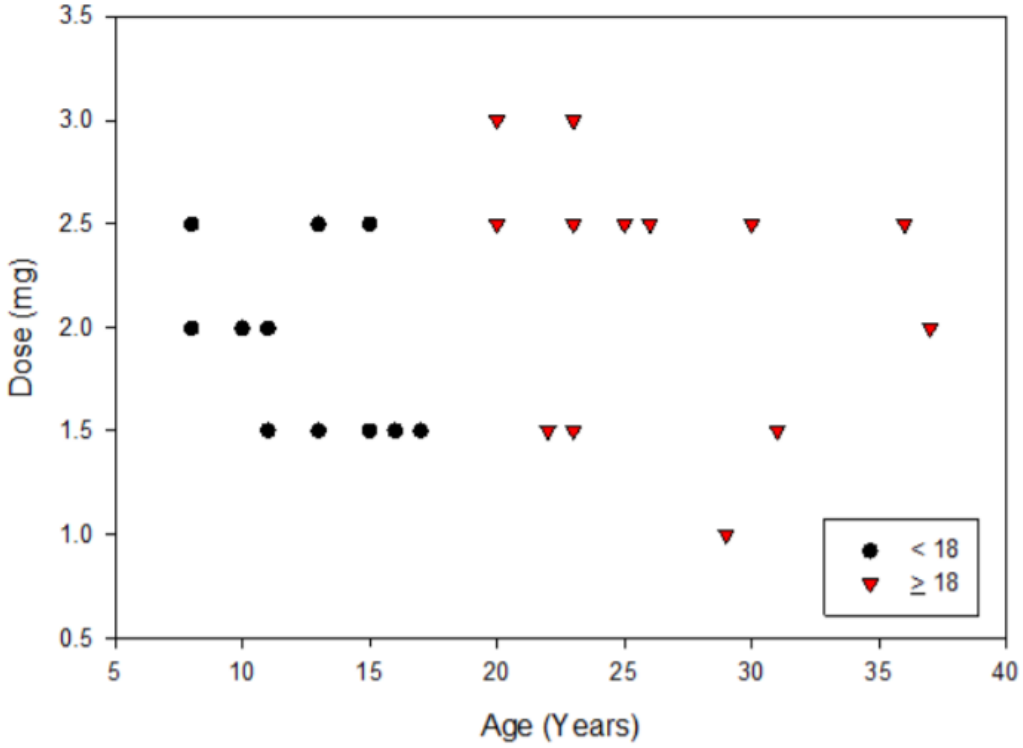



**Figure 3: Titrated dose (mg) as a function of age (years)**

Another plot displaying effect in terms of change in bodyweight as a function of bodyweight-adjusted dose. Here it is apparent that 5 children (<18 years) received higher weight-based doses than given to adults. One child (<18y) experienced very high doses up to 0.056 mg/kg which is more than twice the maximum dose of 0.022 mg/kg given to adults and 3.7-fold higher than the maximum dose of the multiple ascending dose (MAD) study. The maximum single ascending dose (SAD) dose was 0.05 mg/kg. It is also apparent that 4 adults and 2 children never achieved any weight loss. The applicant clarified that the dose was chosen based on clinical response and tolerance. All 5 children who received higher weight-based doses than given to adults experienced adverse events (AEs) and 2 patients experienced serious AEs (SAEs). None of the three reported SAEs were considered related to the study treatment and resolved within 7 days. See Figure 3.

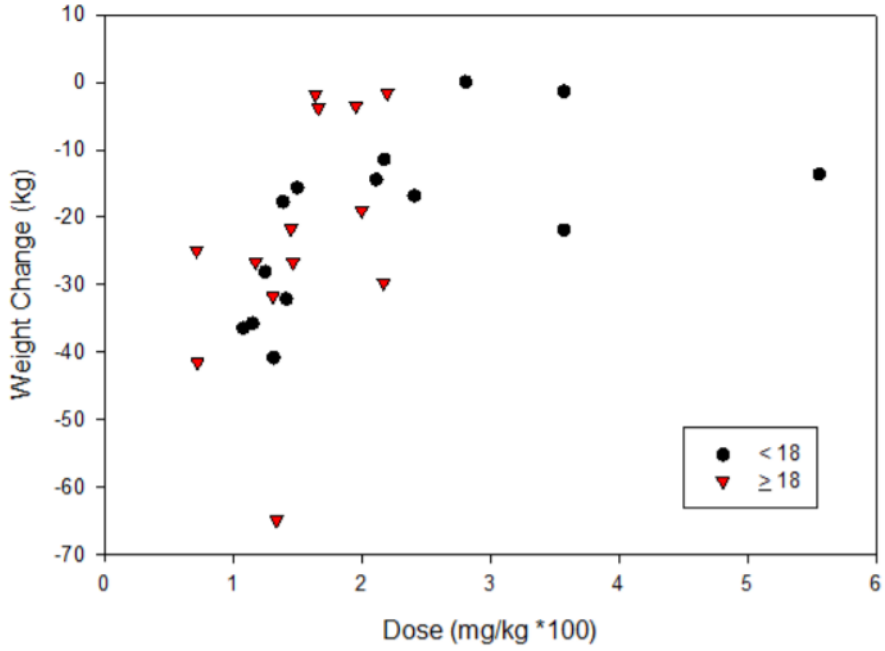



**Figure 4: Weight change (kg) as a function of body weight adjusted dose (mg/kg*100)**

Overall, the above data did not allow to support a dosing regimen either based on age in the paediatric population. After further analyses of the quantitative data, the added-value of bodyweight adjustment was also not apparent based on efficacy based titration. See Figure 4 and Figure 5.

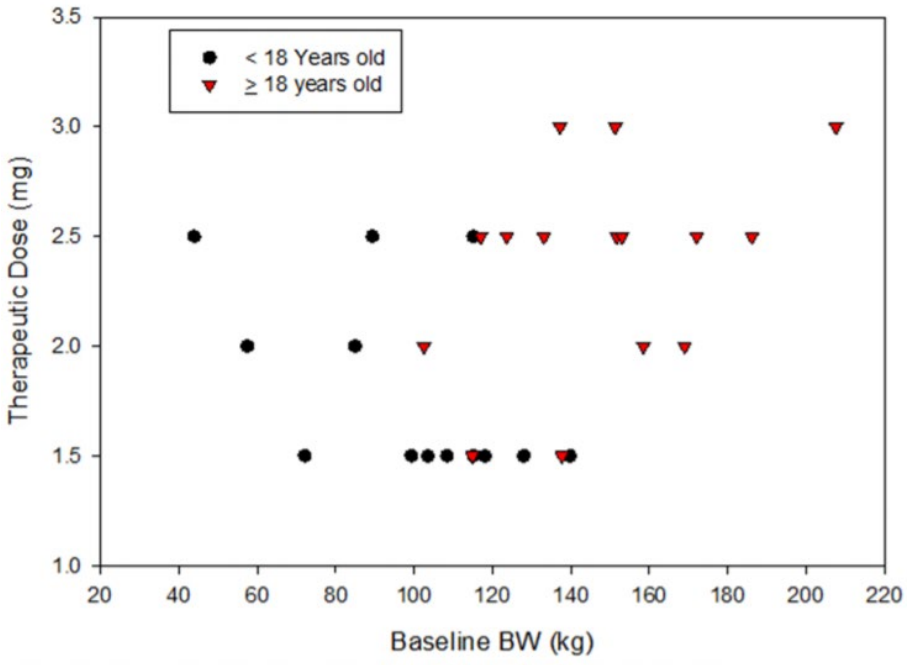



**Figure 5: Therapeutic dose (mg) as a function of baseline bodyweight (kg)**

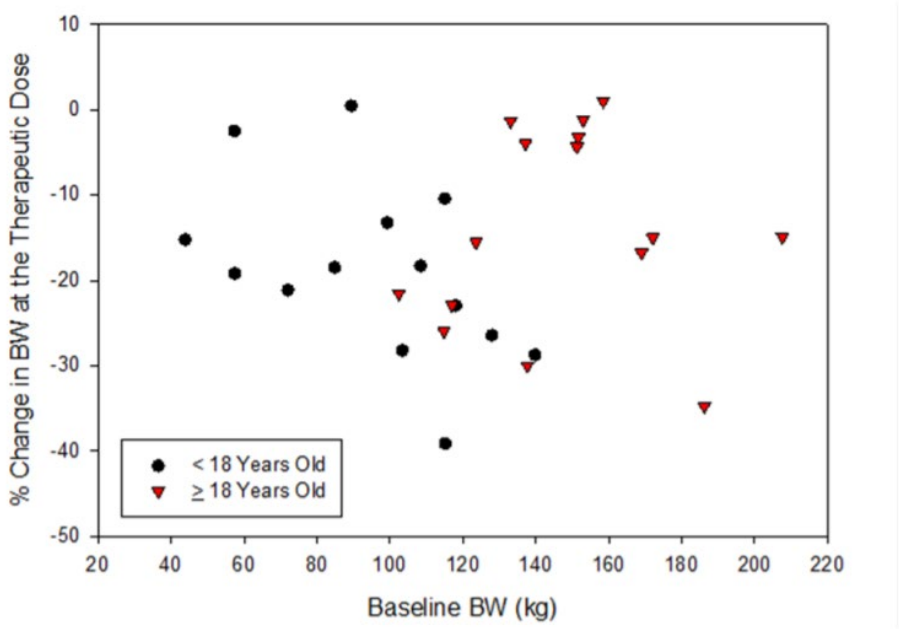



**Figure 6: % change in bodyweight at the therapeutic dose as a function of baseline bodyweight (kg)**

To improve the POPPK model, the CHMP recommended to re-fit the population data to a 2-compartment model since:

- Concentration-time profiles in studies 001, 002 and 008 indicated setmelanotide exhibits two-compartmental pharmacokinetics;

- In saline formulation, the second compartment with a slower elimination is apparent about 8 hours post-dose and delayed to 24 hours post-dose when given in the commercial DSPE formulation.

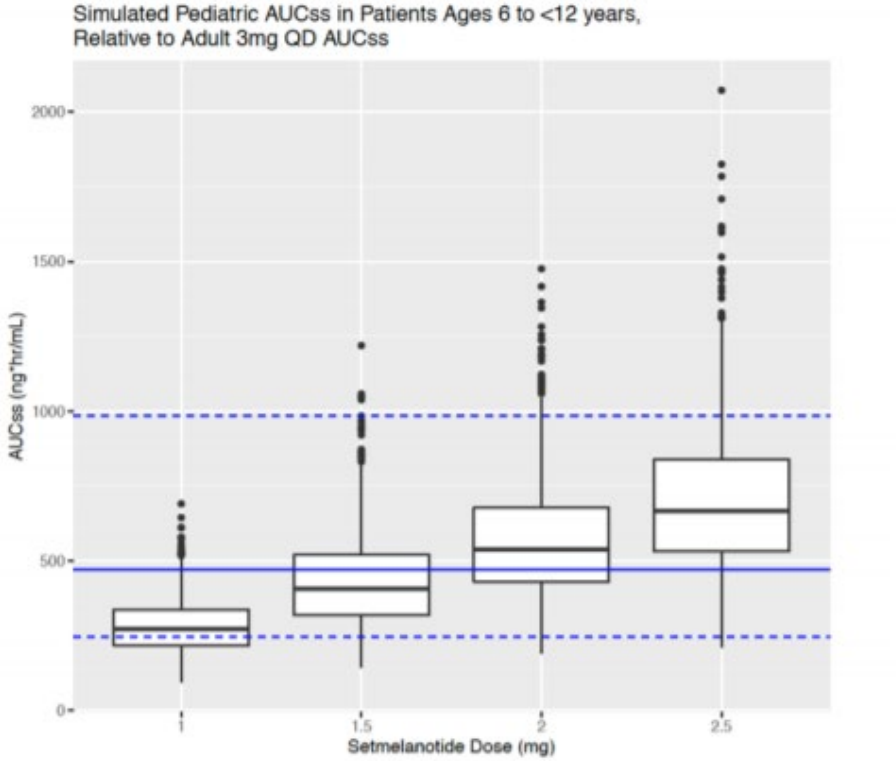
- Patient PK is not well described beyond 24 hours post dose; and

- Population PK of setmelanotide was described by a 1-compartment model.

However, it was clarified by the applicant that this approach was not feasible. The saline formulation, both infusion and subcutaneous bolus administration, was the original formulation used to assess the potential for RM-493 as a drug. The saline data showed that setmelanotide exhibits 2-compartment disposition kinetics. However, these data were not included in the POPPK model. The POPPK model was also based on data with the intended commercial formulation in which Tmax is delayed to 6-8 hours and the 2$^{nd}$ elimination delayed to 24 hours post-dose. Setmelanotide was given once daily. No samples were taken beyond 24 hours post-dose.

Upon CHMP request, additional simulations were also conducted for paediatric patients and exposures for the different doses proposed be compared to the target adult reference range, accounting for age related weight for obesity and available EMA guidance (Modelling and Simulation Working Party Q&A) on modelling and simulation for the paediatric population. However, the original Pop-PK mode was used since no model improvement could be made, as explained above. Based on these additional analyses, exposure matching between adults and children was not achieved neither for Cmax nor for AUC: the levels simulated were lower for the lowest dose groups and higher for the upper dose groups. See Figure 6 and Figure 7.

In the absence of an adequate PK/PD model, the actual impact of the observed discrepancy is unknown. It could thus not be claimed that the age-based dosing recommendation is informed by exposure matching using the POPPK model.

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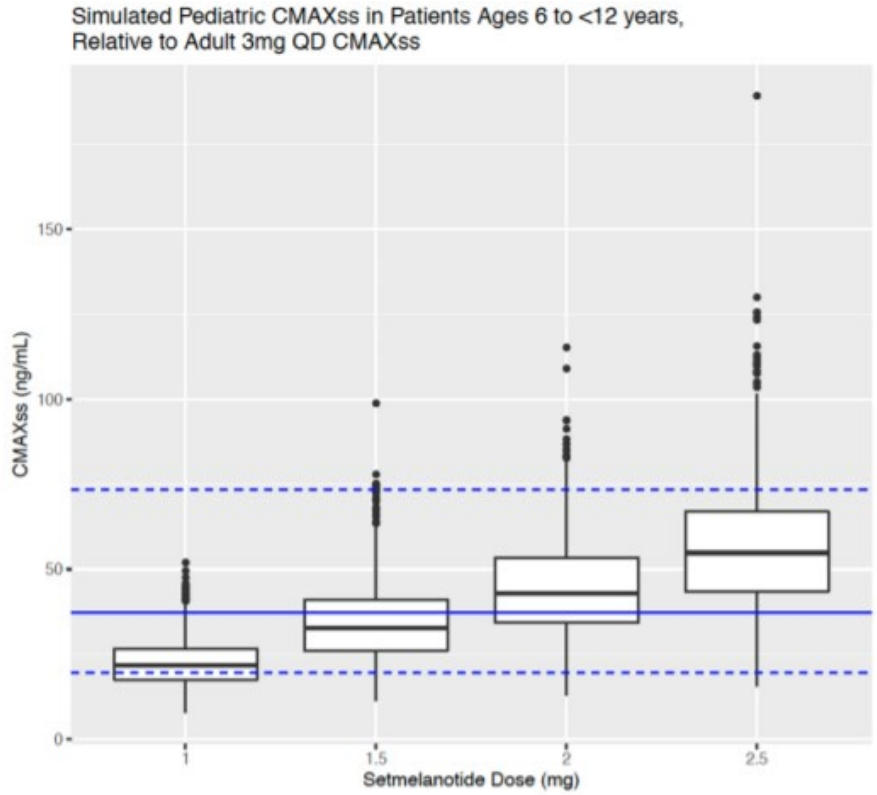
$AUC_{ss}$ = area under the plasma-concentration time curve at steady-state.
A boxplot matrix is shown for simulated pediatric exposures for patients 6 to <12 years of age following 1, 1.5, 2, and 2.5 mg doses. Boxes depict the 25th, 50th, and 75th percentiles of the data. Vertical lines extending from the boxes show the 25th percentile -1.5 x interquartile range (IQR) and the 75th percentile +1.5 x IQR, where IQR is the distance between the 25th and 75th percentiles. Outliers are marked outside of the vertical whisker lines by black circles. Blue reference lines represent the median and 95% confidence interval (CI) of the adult reference range.

**Figure 7 Simulation of Paediatric AUCss in patients aged 6 to below 12 years old relative to an adult administered 3 mg QD**

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$C_{MAXss}$ = maximum concentration at steady-state.
A boxplot matrix is shown for simulated pediatric exposures for patients 6 to <12 years of age following 1.0, 1.5, 2.0, and 2.5 mg doses. Boxes depict the 25th, 50th, and 75th percentiles of the data. Vertical lines extending from the boxes show the 25th percentile - 1.5 x interquartile range (IQR) and the 75th percentile + 1.5 x IQR, where IQR is the distance between the 25th and 75th percentiles. Outliers are marked outside of the vertical whisker lines by black circles. Blue reference lines represent the median and 95% confidence interval (CI) of the adult reference range.

**Figure 8 Simulation of Paediatric Cmax, ss in patients aged 6 to below 12 years old relative to an adult administered 3 mg QD**

Given the limitations and given the fact that the data do not support any model improvement, the presented POPPK modelling could not be followed. Dosing regimen only based on modelling and simulations is thus not considered appropriate.

Overall, the POPPK modelling is considered not appropriate for extrapolation towards the youngest children and the dosing recommendation. A proposed dosing scheme based on up-titration to effect and acceptable tolerance is thus recommended based on clinical observations in trials. This is further discussed in section 2.5.3.

Only preliminary data are available in renal impairment patients (ongoing study RM-493-029). These data indicate that setmelanotide showed nearly 2-fold increased half-life and around 20% decreased clearance for mild as well as nearly 30% decrease in clearance for moderate renal impairment. Based on these findings, the applicant suggested a reduction in initial starting dose by 2-fold for the moderate renal impairment group would be a conservative approach. However, the CHMP considered that the use of setmelanotide is not to be recommended in this population until the final results of study RM-493-029 are reported. This has been reflected in section 4.2 of the SmPC.

In subjects with mild renal impairment, the applicant proposed to initiate dosing with a dose of 0.5 mg versus the 1.0-mg starting dose given to subjects with normal renal function and thereafter dose escalation as indicated for subjects with normal renal function, taking into account both the achievement of desired weight loss and safety/tolerability as doses are titrated upwards. This was considered acceptable. In adults, the maximum daily dose remains 3mg. However, in children aged 6-12 years, the maximum daily dose is to be reduced from 2.5mg down to 2mg. This has been reflected in section 4.2 of the SmPC and is to be reviewed when final results of study RM-493-029 are reported.

**Immunogenicity assay**

A tiered strategy for analysis and reporting of samples for ADA to setmelanotide was utilized and applied to studies RM-493-011, -012, -014, -015, -022, and -026. A similar strategy using an original version of the setmelanotide ADA assay was applied to the earlier studies (RM-493-001 through -010), although the revalidated assay is considered to be more robust and was used for the pivotal studies, RM-493-012 and RM-493-015. The original assay, using a qualitative enzyme linked immunosorbent assay (ELISA) technique has been refined on several occasions, first to compensate for the functional affinity loss in the PC antibodies and to meet the updated ADA Guidelines, and second to improve the sensitivity of the assay for the three tested populations: normal adult, obese adult and paediatric obese subjects.

Samples with signals above the screening cut point or post-dose sample that was less than the screening cut-point but at least 2-fold higher than the treatment-naïve screening sample were considered positive and were tested in the confirmatory assay. Antibody (Ab) titer was determined in confirmed positive. Furthermore, confirmed positive samples were tested to determine neutralising (N) Ab using a cell-based assay. All subject samples tested in the setmelanotide ADA assay were also tested in a validated anti-α-MSH antibody assay using the same format than the setmelanotide ADA assay. To mitigate the risk of false positive results, i.e. the confirmatory results should be based on 3 independent analysis of each samples. A sample should be considered positive only if 2 of 3 are found positive in the confirmatory assay. However, a high intra-assay variability has been observed for the % inhibition results of study samples. Moreover, the impact of the presence of the drug in the patient sample is unknown for the confirmatory ADA assay. Some uncertainties regarding a potential prozone effect are also remaining. Therefore, the suitability of the confirmatory ADA assay to exclude potential false-positive results obtained from the ADA screening assay sample is to be confirmed. For this reason, the CHMP recommended the inclusion in section 4.8 of the SmPC of only the results of screened anti-setmelanotide ADA positive patients instead of the presentation of the confirmatory results for setmelanotide ADA screened positive patients.

Currently, only subjects showing an increase in the signal in the screening ADA assay after drug treatment relative to the pre-treatment sample were considered as potentially positive in screening. But the post-treatment samples in the anti-setmelanotide ADA assay that are above the screening cut point and below the screening result of their respective pre-treatment-naïve sample should also be considered positive and be further tested in the confirmatory assay. This analysis is still pending and is recommended to be submitted as a post-authorization commitment. The same strategy is applied for the analysis of screening sample results in the anti-α-MSH antibody assay.

Overall, further data are expected on the effect of setmelanotide on ADA and the CHMP recommended to submit an update including the results of all immunogenicity samples collected in pivotal clinical studies RM-493-012 and RM-493-015, once available. At the same time, an updated integrated analysis of the clinical significance of immunogenicity of setmelanotide is expected. Due to the transfer of the immunogenicity assays to a new CRO, the CHMP also recommended to provide revalidation data as well as in-study performance data, including the applied assay cut points, to demonstrate that all

immunogenicity assays used are suitable for their intended purpose. The final bioanalytical reports are also expected in this submission.

A number of approaches have been tested for the detection of antibodies to mPEG-DPSE in human serum. But all attempts to provide a sensitive assay to detect anti mPEG-DSPE antibodies failed. As mPEG-DPSE is an excipient, it is not expected that anti-mPEG-DSPE antibodies would impact the efficacy of setmelanotide. Furthermore, no safety concerns that may be related to antibodies to setmelanotide or to mPEG-DSPE have been observed by the applicant up to now. Therefore, the strategy of not planning any further development work on an assay to detect anti-mPEG-DSPE antibodies in clinical samples is considered acceptable by the CHMP at the present time, noting development of anti-mPEG-DSPE antibodies may need further consideration in the future, in case of hypersensitivity reactions are reported later on.

### 2.4.5. Conclusions on clinical pharmacology

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

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

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

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

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

## *2.5. Clinical efficacy*

The clinical development program comprises the following clinical studies:

- a phase III, one year, multicentre, global, open label, non-randomised study **(RM-493-012)** including a 2-12 week initial dose titration and a double-blind placebo controlled 8-week withdrawal period in which patients would randomly be administered placebo for a duration of four week to assess efficacy of setmelanotide in POMC deficiency obesity.

- a phase III, one year, multicentre, global, open label, non-randomised study **(RM-493-015)** including a 2-12 week initial dose titration and a double-blind placebo controlled 8-week withdrawal period in which patients would randomly be administered placebo for a duration of four week to assess efficacy of setmelanotide in LEPR deficiency obesity.

- a phase II, investigator-led, ongoing, 12 week, open-label, uncontrolled, setmelanotide treatment study (**RM-493-011)** with an additional one-year extension in patients with POM homozygous, heterozygous, epigenetic deficiency, LEPR deficiency to assess long term efficacy and safety.

- a phase III ongoing extension study (**RM-493-022**) in all 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 (including but not limited to the patients enrolled in the RM-493-012 and -015 pivotal studies in POMC/PCSK1/LEPR deficiency obesity) to assess long term safety.

## 2.5.1. Dose response study(ies)

No dose response studies were conducted and the choice of the dosing regimens in the pivotal trials RM-493-012 and RM-493-011 was based on clinical findings from the investigator-led RM-493-011 study, as well as the RM-493-002 Phase 1b multiple ascending dose study in healthy obese subjects.

## 2.5.2. Main study(ies)

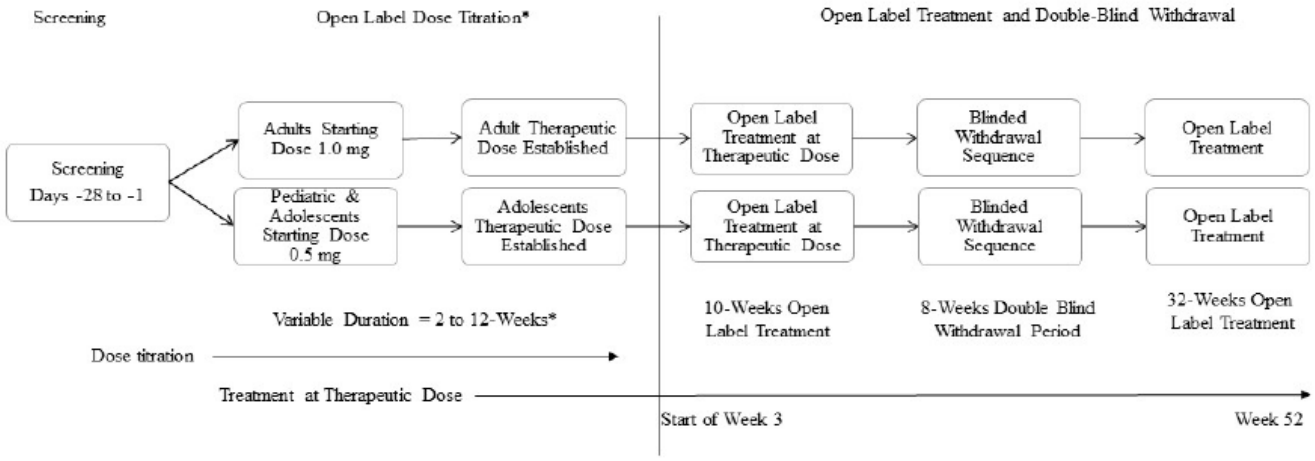
As both pivotal studies RM-493-012 and RM-493-015 had a near identical setup and protocol, all modalities other than results will be presented for both studies under common sections in this report. The only difference is that both studies differ in the genetic deficiency causing a similar outcome, lack of endogenous alpha-MSH signal peptide release at POMC-neuron axons, with the former recruiting POMC/PCSK1 deficiency obesity patients (RM-493-012) and the latter LERP-deficiency obesity patients (RM-493-015).

## Studies RM-493-012 and RM-493-015

Both pivotal phase III studires were one year, multicentre, global, open label, non-randomised study **(RM-493-012)** including a 2-12 week initial dose titration and a double-blind placebo controlled 8-week withdrawal period in which patients would randomly be administered placebo for a duration of four week to assess efficacy of setmelanotide in POMC deficiency obesity (RM-493-012) and LEPR deficiency obesity **(RM-493-015),** respectively.

### *Methods*

The study design is presented below.




*The last two weeks of the Open Label Dose Titration Phase in which the therapeutic dose for an individual patient is established will be considered the first two weeks of Open Label Treatment. Subsequently patients will then receive an additional 10 weeks of active treatment in the Open Label Treatment for a total combined duration of 12 weeks, before transitioning into the Double Blind Withdrawal Phase.

**Figure 9. Study design**

## *Study Participants*

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

*Inclusion*

- Bi-allelic, homozygous or compound heterozygous (a different gene mutation on each allele) genetic status for either the POMC, PCSK1 or LEPR genes, with the loss-of-function (LOF) variant for each allele conferring a severe obesity phenotype.
- Age 6 years and above.
- If adult age ≥18 years, obesity with BMI ≥30 kg/m$^2$; if child or adolescent, obesity with BMI ≥95th percentile for age on growth chart assessment.
- Female participants of child-bearing potential or male participants with female partners of child-bearing potential had to agree to the use contraception as outlined in the protocol.

*Exclusion*

- Recent intensive (within 2 months) diet and/or exercise regimen with or without the use of weight loss agents including herbal medications, that had resulted in weight loss or weight stabilization, though patients could be considered if they had ended such a regimen at least 1 month ago
- Prior gastric bypass surgery resulting in >10% weight loss durably maintained from the baseline pre-operative weight with no evidence of weight regain
- Diagnosis of a DSM-III disorder that might interfere with study compliance, suicidal ideation or recent suicide attempts
- History of significant liver disease or liver injury or current liver assessment for an etiology other than non-alcoholic fatty liver disease (NAFLD)
- History or presence of impaired renal function
- History or close family history (parents or siblings) of skin cancer or melanoma, or patient history of ocular-cutaneous albinism
- Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions, determined as part of a screening comprehensive skin evaluation performed by a qualified dermatologist

## *Treatments*

A dose titration phase in the pivotal trials was to determine a patient's so-called Therapeutic Dosing (TD). The TD was defined as a weight-loss over two weeks of 2-3 kg for and adult patient and 1-2 kg for paediatric patients combined with a decrease of hunger score to a range of 0-2, was achieved. Once TD was achieved the subject was expected to continue on this dose throughout the duration of the trials, and this TD would also be carried over in the extension study if the patient decided to enrol. The final dose titration schedule during the up-titration phase of the pivotal trials is shown in Table 4.

**Table 4: Dose Titration Schedule**

| Dose Titration Week | Adult Dose (mg) | Adolescent Dose (mg) | Pediatric Dose (mg) |
|---|---|---|---|
| 1-2 | 1.0 | 0.5 | 0.5 |
| 3-4 | 1.5 | 1.0 | 1.0 |
| 5-6 | 2.0 | 1.5 | 1.5 |
| 7-8 | 2.5 | 2.0 | 2.0 |
| 9-10 | 3.0 | 2.5 | 2.5 |
| 11-12 | NA | 3.0 | NA |

NA: not available

During the dose titration, increments of 0.5 mg dose increases were done at weekly intervals to determine an individual's therapeutic dose, up to the approved maximum dose in the specific country of the participating site.

Thereafter, patients continued active treatment at their specific optimal therapeutic dose for an additional 10 weeks, for a total combined dosing duration of 12 weeks at the individual patient's therapeutic dose.

The two-week titration schedule in which a patient's therapeutic dose is reached was counted as part of the treatment phase, allowing patients to have an effective 12 weeks (2 + 10 open-label) of treatment before entering the double-blind withdrawal period. Following the dose titration and 10-week open label active treatment phases, only patients who lost at least 5 kg (or 5% if baseline < 100 kg) of weight from baseline, and who continued to show tolerability to setmelanotide, continued in the remainder of the study. Patients who do not exhibit the required weight loss of at least 5 kg (5% if < 100 kg at baseline) were taken off active treatment. The onset of the placebo period was variable for each patient in order to mask the actual timing of the withdrawal period; patients, investigators, and investigation sites remained blinded as to when placebo treatment was administered.

During the 8-week withdrawal period, patients were administered placebo for 4 weeks with different timing. Given that the elimination half-life is 11 hours and that the majority of the drug is eliminated after 55 hours, a carryover effect is considered minimal due to the 4-week withdrawal period. As such any weight gains seen during this latter period can be considered attributable to the withdrawal of setmelanotide.

Following the withdrawal period, patients went on to complete approximately 1 year of treatment at the therapeutic dose (the primary endpoint defined as 52-weeks after achieving their relative therapeutic dose). It was anticipated that the patient's therapeutic dose, established during the period of dose titration, would be administered throughout the study.

The study drug was provided as a sterile solution for injection with a nominal concentration of 10 mg/ml. In study RM-394-012 all but one batch of investigational product and one batch of placebo used a preservative free formulation, whereas the latter two batches as well as all batches used in RM-394-015 were of the preservative containing formulation. As no significant PK differences were apparent between both batches this likely did not have an influence on the efficacy or safety results.

Concomitant drugs were allowed provided they did not pose a safety risk, could significantly impact the efficacy assessments or could have and anorectic effect (whether intended or as unintended non-rare side effect).

## *Objectives*

The primary objective of both studies was to demonstrate statistical and clinically meaningful effects of the treatment on percent body weight change after 1 year of treatment. The null hypothesis for this objective was that the proportion of patients achieving at least 10% of weight loss after one year would be at most 5%, based on a historical control value, versus the hypothesis that this proportion will be at least 5%.

The secondary objectives included the safety and tolerability of treatment, the hunger score for patients 12 years and older, percent change in body fat mass, glucose parameters, waist circumference and reversal of hunger and weight during the double-blind withdrawal period.

Tertiary objectives included percent change in total body mass, non-bone lean mass, and bone density, fasting lipid states, PK of the investigative product, C-reactive protein, dose response throughout titration, QoL and health status changes.

Hunger and neurocognition changes in patients aged 6 to 11 years of age and change in pubertal development were seen as exploratory objectives. Other exploratory objectives included bone age assessed change in growth and development and ABPM, skin pigmentation measured by spectrophotometer, energy expenditure, and 24-hour pharmacokinetic profile for patients participating in these sub-studies. Further areas of exploration were hormonal, neuroendocrine, metabolic and anti-inflammatory analytes and biomarker assays, a PK/PD response employing a suitable endocrine biomarker predictive of setmelanotide target engagement, agonism and efficacy through activation of the MC4R and (if feasible) correlations of bi-allelic or loss-of-function POMC and PCSK1 genetic mutations and POMC deficiency due to diverse allelic variants with the magnitude of setmelanotide efficacy endpoints.

## *Outcomes/endpoints*

The primary protocol-defined endpoint was the proportion of patients in the full analysis set (FAS) who met the ≥10% weight loss threshold (responders) after approximately 1 year of treatment, compared to the proportion from historical data (at most, 5% responders in the null population).

The key secondary endpoints were:

- Mean percent change in body weight from baseline in the Designated User Set (DUS) population, whereby the second success criterion for the study is defined as a 10% observed mean weight loss from baseline to 1 year of treatment in this population.
- Mean percent change in weekly average of daily hunger score (most hunger over the last 24-hours) from baseline in patients ≥12 years of age in the DUS population.
- Met responder threshold of ≥25% improvement from baseline in hunger threshold (responders) in the FAS population. The relevance of this threshold was not clearly justified.

Other (non-key) secondary, tertiary and exploratory endpoints related to efficacy mainly included:

- Hunger was assessed daily throughout the study; patients ≥12 years of age self-report their hunger by responding to three questions and patients 6 to 11 years of age self-report their hunger each morning just prior to dosing by responding to one question
- Two global hunger questions were administered to assess patients' perceptions of their current status and change from baseline at key timepoints

- Body composition was assessed including total body weight loss, fat loss, and non-bone lean mass, measured in kg as well as percent change from baseline at the end of 1 year of treatment
- Glucose parameters as measured by fasting glucose, HbA1c and OGTT with a focus on parameters of insulin sensitivity over time were assessed
- Waist circumference was measured according to US National Heart Lung and Blood Institute criteria over the course of the study.
- To further assess improvements in weight and hunger related to treatment with setmelanotide in this ultra-rare patient population, a placebo withdrawal period was implemented to allow each patient to serve as their own control.
- Lipids (fasting cholesterol and triglycerides) were assessed during treatment with setmelanotide throughout the study.
- Changes in pubertal development for patients who had yet to reach Tanner Stage V was evaluated over the course of the study
- Changes in growth and development in patients <18 years of age were assessed with regular height, weight and body mass index (BMI) determinations (including Z score calculations) and annual bone maturation evaluations were performed during the study, as available
- Limited number of patients were expected to participate in various sub-studies (ABPM, skin color quantification, energy expenditure, and 24-hour PK profile); therefore, it was anticipated that no definitive conclusions would be determined regarding the effects of setmelanotide on these parameters. However, trends over time were explored

### *Sample size*

A minimum of 10 patients per study was foreseen as it was expected that treatment with setmelanotide for 1 year would be associated with a TRUE underlying probability of at least 10% weight loss at 1 year of at least 50%. That assumption yielded at least 94% power to yield a statistically significant (alpha=0.05 and 0.025 1-sided, due to discreteness of the binomial distribution) difference from the null hypothesis 5% value for 10 subjects. If the true probability of at least 10% weight loss at 1 year was 40%, then power was ~83%. The minimum observed proportion of N=10 patients with at least 10% weight loss at 1 year that would have yielded statistical significance (alpha=0.05 and 0.025 1-sided, due to discreteness of the binomial distribution) was 0.3 (3 of 10).

### *Randomisation*

No randomisation was employed in these studies and all patients were assigned to active treatment except during the double-blind withdrawal phase.

### *Blinding (masking)*

Both studies were open-label, except for the 8-week double-blind, placebo-controlled variably timed withdrawal period.

All patients and study-related staff remained blinded to study drug and patient assignation. The Investigator, study site staff, clinical research organization staff providing site management and CRO

Medical Monitor did not have access to the actual treatment sequence being administered during the 8-week double-blind placebo-controlled phase, except in the case of an emergency.

## *Statistical methods*

Five study populations were defined:

- The FAS (Full Analysis Set) population was defined as all patients who received any study drug and had at least one baseline assessment (including those who did and did not demonstrate ≥5 kg weight loss or 5% of body weight [if weight was <100 kg at baseline] over 12-week open label treatment period and proceeded into the double blind, placebo-controlled withdrawal period).
- The FAS was the population used for the primary endpoint analysis.
- The DUS (Designated Use Set) population was defined as all patients who received any study drug, demonstrated ≥5 kg weight loss or 5% of body weight (if baseline weight was <100 kg) over 12-week open-label treatment period, and proceeded into the double-blind, placebo-controlled withdrawal period.
- The Completers' Set (CS) population was defined as all patients in the DUS population who demonstrated both ≥5 kg weight loss or 5% of body weight (if baseline weight was <100 kg) over 12-week open-label treatment period and continued in the study on active treatment to complete a full year (approximately) of treatment.
- The Per-Protocol (PP) population was defined as the subset of patients in the FAS population with no major protocol violations and was exploratory in nature.
- The SAS (Safety Analysis Set) population was defined as all patients who received any study drug injections at least one post-dose safety assessment. This population may be identical to the FAS and is the primary safety and PK analysis population.

The main analyses were planned to be done on the 'Pivotal Set', defined as the first patients to enrol in and complete each trial (expected to encompass ~10 patients at minimum), while all patients whom enrolment from the pivotal set onward were designated the 'Supplemental Set'. The 1-year assessment of the former would be done separately and pooled with any data available from the latter whereby data from supplemental patients with less than 1 year of data available would be imputed using a linear model. Once all supplemental patients have reached 1 year of data availability the same analyses will be re-ran with the true 1-year data points.

*General Methods*

Baseline data were those last measurements obtained before administration of the first dose of investigative product, with the exception of hunger scoring for which the data collected on Day 1 of treatment could be considered as baseline if the average weekly hunger score was not collected prior to treatment start.

Primary analysis was on the impact at the end one year of treatment. Additional analyses will be performed on the specific treatment intervals separately (screening, titration, initial 12-open label treatment period, the 8-week double blind period and the 32-week open label treatment period) and were not part of the present application (pending).

Supplemental exploratory analyses are to be examined for data collected during the screening period, as well as the dose titration period as to explore the baseline variability of POMC deficiency subjects as well as the therapeutic dose response during titration. Hunger and weight variability/stability or

loss/gain, as well as patient medical history will be examined from before study entry, during the 4 weeks of screening and the 2-12 weeks of titration. These analyses were not part of the present application (pending).

*Co-variates and multiplicity*

As there was only a single primary efficacy analysis multiplicity was not considered and given the likely underpowered nature of any withdrawal period analysis (thus making them supportive/descriptive only) adjustment for multiplicity was not necessary. For secondary endpoint onward multiplicity could be a concern but would be difficult to address multiplicity by rigorous statistical approaches given the extremely limited number patients in the studied population.

Therefore nominal-p-values were to be used to interpret each endpoint separately, despite the fact that this may increase probability of Type I errors occurring for the endpoints considered. An attempt to alleviate this issue was made by using a step-down approach if statistical significance is achieved in the primary endpoint:

The first key secondary endpoint is change from baseline in body weight at approximately 1-year in the DUS population.

↓

The second key secondary endpoint is change from baseline in weekly "most hunger in the last 24 hours" hunger scores over approximately 1-year of treatment in the DUS population.

↓

The third key secondary endpoint is the categorical percent of responders' analysis of hunger (using the 25% improvement in hunger threshold) in the FAS population at approximately 1-year.

*Missing data*

If data for primary of key secondary endpoints was missing imputation with a linear model would be used, unless sufficient data points weren't available in which case the longitudinal mixed model for analysis was employed, if the cause of missing data was not related to the treatment itself. If treatment-related a 1-year weight change of 0 kg will be imputed. Supplemental patients with less than 3 months of data available will not be considered in the combined cohort analyses.

*Primary endpoint evaluation*

The primary endpoint was analysed via the exact binomial test which will test whether the percentage of patients who reach at least 10% weight loss is greater than 5%. One-sided, 95% CIs were calculated using the exact Clopper-Pearson method.

If statistical significance is achieved, the proportion of patients in the FAS population who show ≥10% weight loss at approximately 1 year will be numerically compared (point estimate) to the 35% proportion of responders according to success criteria and no formal statistical analysis will be performed.

At the time of the final analysis (pending), a linear mixed model repeated measures analysis of variance with a fixed term for time and baseline weight and a random effect for subjects will be used to assess the primary efficacy endpoint at approximately 1-year. All weight measurements obtained during the study will be included in the model. An unstructured covariance matrix will be used to model the expected different variances among the participants. In the event the mixed model does not converge with an unstructured covariance matrix a compound-symmetric then Toeplitz covariance

matrix will be employed instead. Additionally, a paired t-test will be derived from the model and compared to no change (0% mean percent weight change from baseline) and will use Satterthwaite's degrees of freedom estimates (1-sided, compared to alpha of 0.05 for the primary success of this endpoint; a comparison to an alpha of 0.025 will also be provided).

The assumption of normality will be assessed via a visual diagnostic of closeness to normality, not as a conditional test associated with efficacy endpoint analyses. Graphical assessments of residuals from the model fit may be examined. If a substantial departure from normality is observed, a transformation such as log (post/pre) or rank or other non-parametric test may be used to analyse the data as a sensitivity analysis; however, the analysis on the original scale of observation will be reported.

*Key Secondary endpoint evaluation*

Analyses of the key secondary endpoints will be supported by way of running the pre-specified key secondary analyses in the DUS, FAS and CS populations, and hunger specifically by additional morning hunger and average hunger assessments.

Once the linear mixed model repeated measures analysis of variance of the primary endpoint is concluded and found to be statistically significant, the mean percent change from baseline at the end of 1-year of treatment in the DUS population will be numerically compared (point estimate) to the ≥10% mean change from baseline in body weight; no formal statistical analysis will be performed.

The secondary endpoint also be performed in the FAS population, as a sensitivity analysis, using a non-parametric 1-sample Wilcoxon signed rank approach, which should mitigate the issues raised by the occurrence of a bimodal distribution.

The second key secondary endpoint, the mean percent change from baseline in weekly average hunger in the DUS population, was to be analysed in a similar manner using a linear mixed model for repeated measures analysis of covariance with weekly average hunger percent change from baseline as the outcome and fixed terms for time and baseline hunger and a random effect for subject. "Hunger in the morning" and "average hunger over a 24-hour period" will be analysed in the same manner as additional secondary endpoints.

If the above analysis proves to be statistically significant the mean percent change in hunger from baseline at the end of approximately 1-year of treatment in the DUS population will be numerically compared (point estimate) to a 25% mean change from baseline in hunger. The choice of a 25% reduction in hunger score was based on patient reported outcome measures and bodyweight. Based on these data the appropriate threshold for a relevant change in hunger score is 13.9% and 15.4% (for the PROMs) and 27% for bodyweight.

Similar as for the first key secondary endpoint, sensitivity analysis will be provided by performing the same analysis in the FAS.

The third key secondary endpoint is the proportion of patients in the FAS population who achieve at least a 25% hunger improvement from baseline threshold compared to the null hypothesis that 5% of patients will achieve this threshold at the end of approximately 1-year of treatment. This will be analysed via the exact binomial test which will test whether the percentage of patients who reach at least 25% hunger improvement is greater than 5%.

Once the third key secondary analysis is complete, and if it reaches statistical significance, the proportion of patients in the FAS population who show ≥25% hunger improvement will be numerically compared (point estimate) to the 35% proportion of responders at the end of approximately 1-year of treatment.

## *Results*

Both pivotal studies were submitted as individual clinical study report (data cut-off: 09 July 2019), with completed pivotal cohorts. In addition, individual addenda were provided with an updated data cut-off (30 April 2020), including ongoing supplemental cohorts. The presented results account for the completed pivotal and ongoing supplement cohorts.

## *Study RM-493-012 (POMC deficiency)*

### Participant flow

As of 30 April 2020, a total of 15 patients have been enrolled in the study; 10 pivotal patients (9 POMC and 1 PCSK1 deficiency patients) and 5 supplemental patients (all with POMC deficiency). Of the 10 former patients, 9 have completed the foreseen 1-year treatment period and 1 patient discontinued treatment due to lack of efficacy. Of the 5 supplemental patients, 2 have finished the protocol-defined 1 year of treatment, 2 still have treatment ongoing and 1 discontinued the study due to a protocol violation as it was discovered that the patient did not have a biallelic mutation. Consequently, the clinical database is still open and will only be locked once all participants have completed the 1-year treatment.

### Recruitment

Patients recruitment started on 14 February 2017.

### Conduct of the study

The original protocol was amended 13 times, mainly to accommodate regional regulations of specific individual participating countries.

For example, specific inclusion criteria were implemented including age inclusion criteria of 9 years instead of 6 years and specific BMI criteria, in addition to other country-specific protocol changes in some countries. However, these amendments did not exclude any patients of being recruited. Likewise, the change in dose for patients aged 9-11 years had no impact, as no patients were included within this age-range in the concerned country.

A maximal dose limit of 2.5 mg was initially imposed by some regulatory authorities in their respective national centres, since at the time when the concerned test sites were inducted, there was no clinical experience with a dosing >2.5 mg/kg. Other sites remained at a potential maximal dose of 3.0 mg/kg/. A protocol amendment was later accepted to allow this higher top dose, based on clinical experience.

The applicant changed the primary endpoint from a mean change analysis to a proportional responder endpoint, while the pivotal trials were already ongoing.

The above changes are further discussed in section 2.5.3 of this report.

## Baseline data

Baseline data for the study is provided in Table 5 and Table 6. Only limited data was available for the supplemental patient whom enrolled after 09 July 2019: it concerned a male subject 8 years of age at enrolment, with a baseline weight of 55.7 kg and BMI of 27.24 kg/m.

**Table 5: Demographic and Baseline Characteristics (RM-493-012)**

| Parameter | Pivotal Cohort (N=10) | Supplemental Cohort (N=5) | Total (N=15) |
|---|---|---|---|
| Age at Enrollment (years) | | | |
| N | 10 | 5 | 15 |
| Mean (SD) | 18.40 (6.17) | 14.80 (8.73) | 17.20 (7.02) |
| Median | 16.50 | 11.00 | 16.00 |
| Q1, Q3 | 15.00, 22.00 | 10.00, 17.00 | 11.00, 22.00 |
| Min, Max | 11.0, 30.0 | 7.0, 29.0 | 7.0, 30.0 |
| Age Categories, n (%) | | | |
| <12 years | 2 (20.0) | 3 (60.0) | 5 (33.3) |
| ≥12 years | 8 (80.0) | 2 (40.0) | 10 (66.7) |
| Sex, n (%) | | | |
| Male | 5 (50.0) | 4 (80.0) | 9 (60.0) |
| Female | 5 (50.0) | 1 (20.0) | 6 (40.0) |
| Race, n (%) | | | |
| White | 7 (70.0) | 1 (20.0) | 8 (53.3) |
| Other | 3 (30.0) | 4 (80.0) | 7 (46.7) |
| Arab | 1 (10.0) | 1 (20.0) | 2 (13.3) |
| Moroccan | 1 (10.0) | 0 | 1 (6.7) |
| NA | 1 (10.0) | 0 | 1 (6.7) |
| Not Reported | 0 | 1 (20.0) | 1 (6.7) |
| Turkish | 0 | 2 (40.0) | 2 (13.3) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 1 (10.0) | 1 (20.0) | 2 (13.3) |
| Not Hispanic or Latino | 8 (80.0) | 3 (60.0) | 11 (73.3) |
| Unknown | 1 (10.0) | 1 (20.0) | 2 (13.3) |

| Parameter | Pivotal Cohort (N=10) | Supplemental Cohort (N=5) | Total (N=15) |
|---|---|---|---|
| Country, n (%) | | | |
| United States | 1 (10.0) | 0 | 1 (6.7) |
| France | 1 (10.0) | 1 (20.0) | 2 (13.3) |
| Germany | 7 (70.0) | 0 | 7 (46.7) |
| Canada | 1 (10.0) | 0 | 1 (6.7) |
| Spain | 0 | 2 (40.0) | 2 (13.3) |
| Belgium | 0 | 2 (40.0) | 2 (13.3) |
| Gene Type, n (%) | | | |
| POMC | 9 (90.0) | 4 (80.0) | 13 (86.7) |
| PCSK1 | 1 (10.0) | 1 (20.0) | 2 (13.3) |
| Weight (kg) | | | |
| N | 10 | 5 | 15 |
| Mean (SD) | 118.70 (37.52) | 96.37 (30.10) | 111.26 (35.81) |
| Median | 114.95 | 100.50 | 114.40 |
| Q1, Q3 | 106.30, 139.10 | 83.67, 104.00 | 83.67, 138.00 |
| Min, Max | 55.9, 186.7 | 55.7, 138.0 | 55.7, 186.7 |
| Height (cm) | | | |
| N | 10 | 5 | 15 |
| Mean (SD) | 169.60 (13.96) | 160.20 (14.02) | 166.47 (14.23) |
| Median | 170.00 | 156.00 | 167.00 |
| Q1, Q3 | 159.00, 175.00 | 156.00, 165.00 | 156.00, 175.00 |
| Min, Max | 145.0, 195.0 | 143.0, 181.0 | 143.0, 195.0 |
| BMI ($kg/m^2$) | | | |
| N | 10 | 5 | 15 |
| Mean (SD) | 40.41 (9.05) | 36.68 (6.34) | 39.17 (8.21) |
| Median | 40.99 | 36.91 | 39.40 |
| Q1, Q3 | 33.79, 49.11 | 34.38, 42.12 | 33.79, 43.67 |
| Min, Max | 26.6, 53.3 | 27.2, 42.7 | 26.6, 53.3 |

| Parameter | Pivotal Cohort (N=10) | Supplemental Cohort (N=5) | Total (N=15) |
|---|---|---|---|
| Waist Circumference (cm) | | | |
| N | 10 | 5 | 15 |
| Mean (SD) | 121.80 (18.95) | 110.66 (17.35) | 118.09 (18.62) |
| Median | 122.50 | 109.30 | 121.00 |
| Q1, Q3 | 112.00, 128.00 | 103.00, 122.00 | 104.00, 128.00 |
| Min, Max | 86.0, 150.0 | 87.0, 132.0 | 86.0, 150.0 |

**Table 6: Baseline Characteristics in the pivotal cohort for the daily hunger score in patients below 12 years and 12 years and above and CGIS score in patients aged below 12 years (RM-493-012)**

| | |
|---|---|
| **Daily Hunger Score (average over 24hrs for >= 12 years)** | |
| N | 8 |
| Mean (SD) | 6.80 (0.720) |
| Median | 6.90 |
| Q1, Q3 | 6.0, 7.0 |
| Min, Max | 6.0, 8.0 |
| N | 7 |
| No hunger | 2.00 (28.60) |
| Mild hunger | 1.00 (14.30) |
| Moderate hunger | 1.00 (14.30) |
| Severe hunger | 3.00 (42.90) |
| **Daily Hunger Score (< 12 years)** | |
| N | 2 |
| Mean (SD) | 2.20 (1.18) |
| Median | 2.20 |
| Q1, Q3 | 1.00, 3.00 |
| Min, Max | 1.00, 3.00 |
| **CGIS Score, ages < 12 years, n (%)** | |
| N | 2 |
| No hunger | 0.00 |
| Mild hunger | 0.00 |
| Moderate hunger | 1.00 (50.00) |
| Severe hunger | 1.00 (50.00) |

## Numbers analysed

As of 9 July 2019, the different sets of efficacy evaluation are presented in Figure 9. As of 30 April 2020, 4 supplemental patients had either finished 1 year of treatment or were ongoing. The FAS and DUS at the time of this report included these 4 supplemental subjects, however as two of them were still undergoing treatment, their 52-week data was imputed. No supplemental patients were included in the second or third key secondary endpoint analyses.

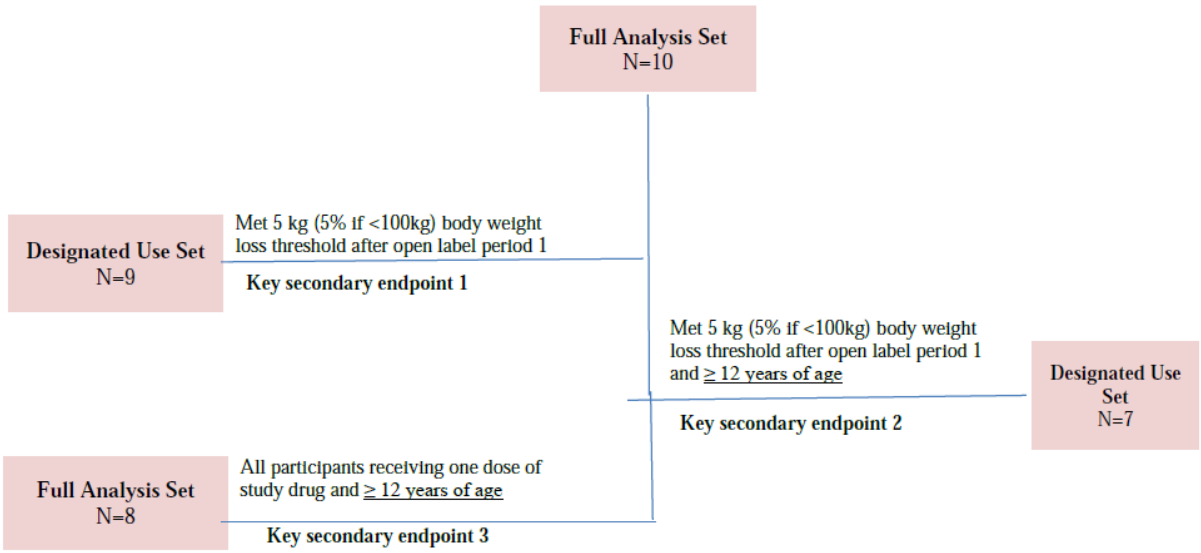



**Figure 10: Sets of Efficacy evaluation (study RM-493-012) as of 9 July 2019**

## Outcomes and estimation

*Primary Endpoint*

A total of 8 of the 10 pivotal subjects and 4 of the supplemental subjects (2 of which did not yet reach 52 weeks of treatment and for whom data were thus imputed) reached the primary endpoint with a p-value of less than 0.0001. For the pivotal cohort the results were replicated in the DUS and CS population where 8 of 9 patients (88.9%) reached the primary endpoint. See Table 7.

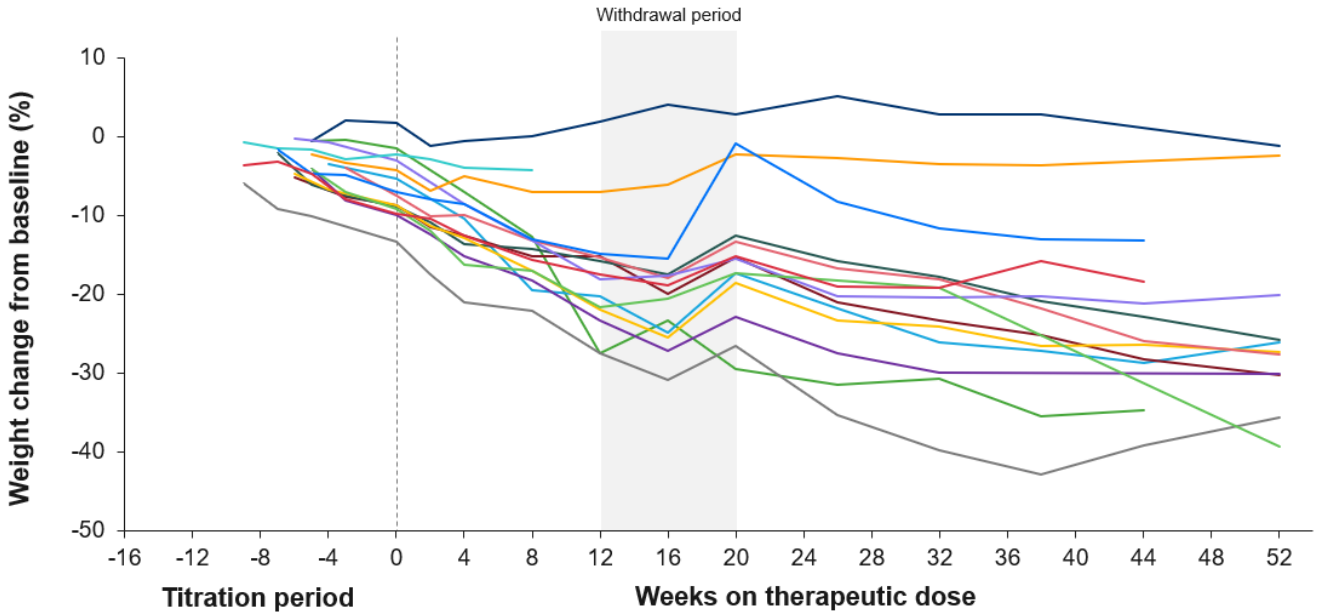
**Table 7: Body Weight (kg) – Proportion of Patients Achieving at Least 10% Weight Loss from Baseline at 52 Weeks from Therapeutic Dose - Pivotal and Supplemental Cohorts (FAS)**

| Parameter | Statistics | Pivotal (N=10) | Supplemental (N=4) | Total (N=14) |
|---|---|---|---|---|
| Patients Achieving at Least 10% Weight Loss from Baseline at Week 52 | n (%) | 8 (80.0) | 4 (100.0) | 12 (85.7) |
| | 90 % CI | (49.31, 96.32) | (47.29, 100.00) | (61.46, 97.40) |
| | p-value | <.0001 | <.0001 | <.0001 |

*Key Secondary Endpoints*

The key secondary endpoint was evaluated in the DUS population, which showed a mean negative weight change from baseline to Week 52 of +/- 26%. An overall continuous pattern of weight loss during treatment was seen, with overall clear weight regain during the blinded withdrawal period. A total of 92.3 percent of the overall DUS population (pivotal + evaluable supplemental patients) achieved a minimum of 10% weight loss from baseline to Week 52, whereas the pivotal patient cohort in isolation managed an 89% success rate in this regard. The Week 52 data for two supplemental patients was imputed as they did not yet complete one year of treatment.

Results (including patients from the supplemental cohort) are provided in Figure 10 and Table 8:




Time point at week 0 is indicated with a dashed line and defined as when a participant received their first therapeutic dose of setmelanotide. Withdrawal period consists of 4 weeks of active drug and then 4 weeks of placebo. One patient received treatment in reverse order during the withdrawal period; patient received placebo between weeks 12 and 16 and setmelanotide thereafter. Data are graphed by the planned timing of each visit.

**Figure 11: Percentage Change of Weight from Baseline by Visit (Pivotal & Supplemental Patients, DUS Population) – Shaded area represents the 8-week blinded withdrawal period.**

**Table 8: Body Weight (kg) – Percent Change from Baseline at Calendar Week 52 from First Dose - Pivotal and Supplemental Cohorts (DUS)**

| Parameter | Statistic | Pivotal (N=9) | Supplemental (N=4) | Total (N=13) |
|---|---|---|---|---|
| Percent Change from Baseline to ~Week 52 (%) | n | 9 | 4 | 13 |
| | Mean (SD) | -25.565 (9.879) | -26.25 (10.648) | -25.77 (9.671) |
| | Median | -27.31 | -25.06 | -27.31 |

| Parameter | Statistic | Pivotal (N=9) | Supplemental (N=4) | Total (N=13) |
|---|---|---|---|---|
| | Q1, Q3 | -30.2, -25.8 | -34.7, -17.8 | -30.2, -20.1 |
| | Min, Max | -35.6, -2.4 | -39.4, -15.5 | -39.4, -2.4 |
| | Least Squares Mean[1] | -25.39 | -26.26 | -25.66 |
| | 90% CI[a] | (-28.80, -21.98) | (-32.94, -19.58) | (-28.40, -22.91) |
| | p-values | <0.0001 | 0.0006 | <.0001 |
| Achieved at Least 10% Weight Loss from Baseline at ~Week 52 | n (%) | 8 (88.9) | 4 (100) | 12 (92.3) |

The second key secondary was the mean percent change in hunger from baseline to the Week 52 of treatment, as measured by the worst 'most hunger' in 24 hours. This endpoint was evaluated in the DUS cohort subjects that were 12 years or older, due to the incompatibility of the hunger assessment tools with younger aged subjects. Overall these patients managed to achieve a mean decrease in appetite of 27%, however, only 3 of the 8 evaluable subjects (43%) managed to achieve a decrease in hunger score of 25% or more. See Table 9.

**Table 9: Daily Hunger Scores – Percent Change from Baseline at 52 Weeks from Therapeutic Dose (Ages >= 12 Years) - Pivotal and Supplemental Cohort (DUS Population)**

| Parameter | Statistic | Total (DUS, N=8) |
|---|---|---|
| | | Worst (Most) Hunger in 24 Hours |
| Percent Change from Baseline to Week 52 (%) | n | 7 |
| | Mean (SD) | -27.06 (28.113) |
| | Median | -14.29 |
| | Q1, Q3 | -54.70, -3.50 |
| | Min, Max | -72.2, -1.4 |
| | LS Mean | -27.77 |
| | 90% CI | (-40.58, -14.96) |
| | P-value | 0.0005 |
| Subjects Achieving at Least 25% Hunger Improvement from Baseline at Week 52 | n (%) | 3 (42.9%) |

The third key secondary endpoint evaluated the proportion of patients ≥12 years achieving at least 25% improvement in hunger scores following 1 year of treatment with setmelanotide in the FAS population. Half of the pivotal FAS cohort managed to reach this endpoint [n=4 (50%), 90%CI:19.29-80.71, p=0.004]. No data on supplemental cohort patients was available as only one supplemental subject was >12 years and the patient did not have baseline hunger assessment available.

Results from other secondary/tertiary/exploratory endpoints (cut-off date: 09 July 2019) can be summarised below:

- At Week 52, patients in the pivotal DUS population had a mean negative change in waistline circumference of 15%.
- Overall a mean weight gain of 5.5 kilograms was noted when pivotal cohort patients underwent the 4-week setmelanotide withdrawal during the 8-week blinded withdrawal period.
- During the 4-week setmelanotide withdrawal period the pivotal cohort DUS subjects saw a mean increase in worst hunger score in 24 hours of 2.2 units increase, though this change was not statistically significant.
- Of the overall weight loss, a mean of 74% was due to loss of body fat, with no appreciable loss of bone density or non-bone lean body mass.
- The mean BMI in the pivotal DUS patients changed -27.82% from Baseline to week 52.
- Observed energy expenditures showed net reductions at the relevant assessment points, consistent with the weight loss achieved.

### *Study RM-493-015 (LEPR Deficiency)*

## Participant flow

As of the of 30 April 2020 a total of 12 patients have been enrolled in the study; 11 pivotal patients and 4 supplemental patients of which 3 patients had not yet finished 1 year of treatment and 1 of which was <12 years of age. The latter paediatric patient was not included in the second or third key secondary endpoint analyses as they were below the age thresholds for these analyses.

Of the 11 former patients 10 have completed the foreseen 1-year treatment period and 1 subject discontinued due to an AE (said patient's W52 data was thus imputed using a linear model). Of the 4 supplemental patients, 1 had finished the protocol-defined 1 year of treatment and 3 were still under treatment. Consequently, the clinical database is still open and will only be locked once all participants have completed the 1-year treatment.

## Recruitment

Patients recruitment started on 8 January 2018.

## Conduct of the study

The original protocol was amended five times, mainly to accommodate regional regulations of specific individual participating countries. Specifically, protocol amendment related to the inclusion of two global hunger questions did not affect the key secondary endpoint as collection of responses was achieved by using a different questionnaire.

A maximal dose limit of 2.5 mg was initially imposed by some regulatory authorities in their respective national centres, due to the fact that at the time when the concerned test sites were inducted, there was no clinical experience with a dosing >2.5 mg/kg. Other sites remained at a potential maximal dose of 3.0 mg/kg/. A protocol amendment was later accepted to allow this higher top dose, based on clinical experience.

The applicant changed the primary endpoint from a mean change analysis to a proportional responder endpoint, while the pivotal trials were already ongoing.

The above changes are further discussed in section 2.5.3 of this report.

## Baseline data

Baseline data for this study is provided in Table 10 and Table 11. Only limited data is available for 2 patients from the supplemental cohort whom enrolled after the 9 July 2019: it concerned an 8-year-old white female, with a baseline weight and BMI of 44.6 kg and 28.06 kg/m$^2$, and the other was a 20-year-old white male with a baseline weight and BMI of 159.3 kg, and 68.04 mg/m$^2$.

**Table 10 Demographic and Baseline Characteristics (RM-493-015)**

| Parameter | Pivotal Cohort (N=11) | Supplemental Cohort (N=4) | Total (N=15) |
|---|---|---|---|
| Age at Enrollment (years) | | | |
| N | 11 | 4 | 15 |
| Mean (SD) | 23.73 (8.39) | 16.00 (6.78) | 21.67 (8.52) |
| Median | 23.00 | 16.50 | 23.00 |
| Q1, Q3 | 15.00, 31.00 | 10.50, 21.50 | 13.00, 25.00 |
| Min, Max | 13.0, 37.0 | 8.0, 23.0 | 8.0, 37.0 |
| Age Categories, n (%) | | | |
| <12 years | 0 | 1 (25.0) | 1 (6.7) |
| ≥12 years | 11 (100.0) | 3 (75.0) | 14 (93.3) |
| Sex, n (%) | | | |
| Male | 3 (27.3) | 3 (75.0) | 6 (40.0) |
| Female | 8 (72.7) | 1 (25.0) | 9 (60.0) |
| Race, n (%) | | | |
| White | 10 (90.9) | 2 (50.0) | 12 (80.0) |
| Other | 1 (9.1) | 2 (50.0) | 3 (20.0) |
| Unknown | 0 | 2 (50.0) | 2 (13.3) |
| South Asian | 1 (9.1) | 0 | 1 (6.7) |

| Parameter | Pivotal Cohort (N=11) | Supplemental Cohort (N=4) | Total (N=15) |
|---|---|---|---|
| Ethnicity, n (%) | | | |
| Not Hispanic or Latino | 11 (100.0) | 2 (50.0) | 13 (86.7) |
| Unknown | 0 | 2 (50.0) | 2 (13.3) |
| Country, n (%) | | | |
| France | 4 (36.4) | 2 (50.0) | 6 (40.0) |
| Germany | 3 (27.3) | 1 (25.0) | 4 (26.7) |
| Canada | 0 | 1 (25.0) | 1 (6.7) |
| United Kingdom | 1 (9.1) | 0 | 1 (6.7) |
| Netherlands | 3 (27.3) | 0 | 3 (20.0) |
| Weight (kg) | | | |
| N | 11 | 4 | 15 |
| Mean (SD) | 133.27 (26.02) | 130.26 (70.25) | 132.46 (39.28) |
| Median | 132.30 | 133.92 | 132.30 |
| Q1, Q3 | 115.47, 153.40 | 76.56, 183.97 | 108.57, 159.27 |
| Min, Max | 89.4, 170.4 | 44.6, 208.7 | 44.6, 208.7 |
| Height (cm) | | | |
| N | 11 | 4 | 15 |
| Mean (SD) | 166.73 (7.42) | 153.00 (19.82) | 163.07 (12.76) |
| Median | 166.00 | 156.50 | 166.00 |
| Q1, Q3 | 159.00, 171.00 | 139.50, 166.50 | 158.00, 171.00 |
| Min, Max | 157.0, 180.0 | 126.0, 173.0 | 126.0, 180.0 |
| BMI ($kg/m^2$) | | | |
| N | 11 | 4 | 15 |
| Mean (SD) | 48.17 (10.45) | 52.06 (20.30) | 49.21 (13.02) |
| Median | 46.63 | 55.22 | 46.63 |
| Q1, Q3 | 38.52, 60.21 | 35.24, 68.88 | 38.52, 61.84 |
| Min, Max | 35.8, 64.6 | 28.1, 69.7 | 28.1, 69.7 |

| Parameter | Pivotal Cohort (N=11) | Supplemental Cohort (N=4) | Total (N=15) |
|---|---|---|---|
| Waist Circumference (cm) | | | |
| N | 11 | 4 | 15 |
| Mean (SD) | 129.45 (18.41) | 125.83 (39.73) | 128.49 (24.15) |
| Median | 133.00 | 124.75 | 129.50 |
| Q1, Q3 | 112.00, 149.00 | 99.25, 152.40 | 112.00, 149.00 |
| Min, Max | 104.0, 154.0 | 78.5, 175.3 | 78.5, 175.3 |

**Table 11: Baseline Characteristics in the pivotal cohort for the daily hunger and PGIS score in patients 12 years and above (RM-493-015)**

| | |
|---|---|
| **Daily Hunger Score (average over 24hrs for >= 12 years)** | |
| N | 11 |
| Mean (SD) | 5.4 (1.13) |
| Median | 5.7 |
| Q1, Q3 | 5.0, 6.0 |
| Min, Max | 3.0, 7.0 |
| **PGIS Score, ages >= 12 years, n (%)** | |
| N | 11 |
| No hunger | 2.00 (18.20) |
| Mild hunger | 3.00 (27.30) |
| Moderate hunger | 1.00 (9.10) |
| Severe hunger | 5 (45.50) |

## Numbers analysed

A summary of the analysis sets and the number of patients included as of 9 July 2019 are shown in the below diagram. As of 30 April 2020, 4 supplemental patients had either finished 1 year of treatment or were ongoing. The FAS and DUS at this point in time included respectively 4 and 3 of these supplemental subjects, however as three of them were still undergoing treatment at the time of data extraction their 52-week data was imputed. Only 3 of the 4 supplemental patients were included in the second or third key secondary endpoint analyses as one of these patients was <12 years.

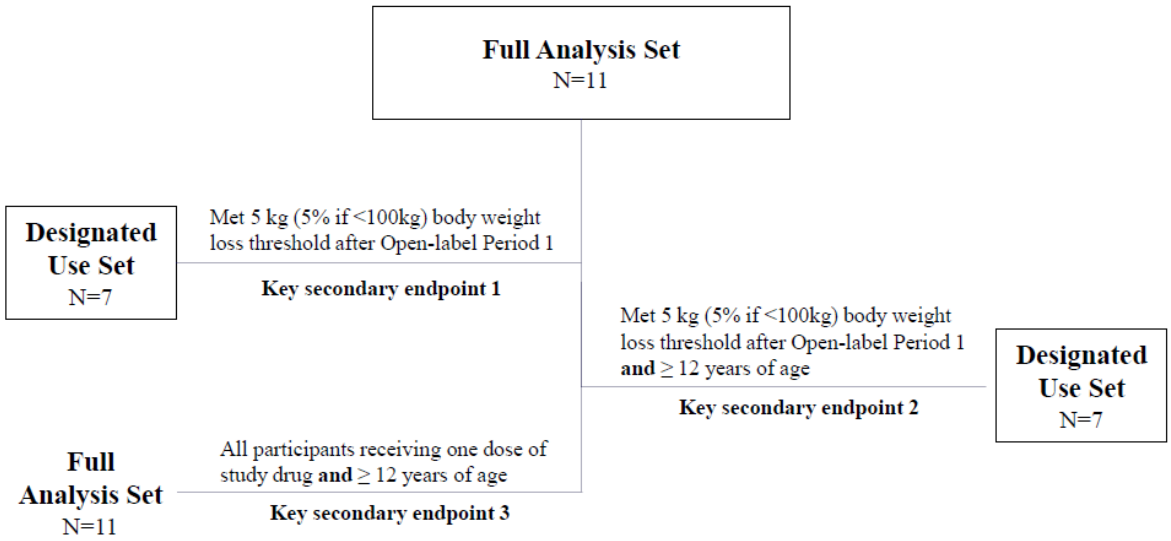



**Figure 12: Sets of Efficacy evaluation (study RM-493-015) as of 9 July 2019**

## Outcomes and estimation

*Primary Endpoint*

A total of 5 of the 11 pivotal subjects and 4 of the supplemental subjects (3 of which did not yet reach 52 weeks of treatment and for whom data were thus imputed) reached the primary endpoint with a p-value of less than 0.0001. For the pivotal cohort the results were replicated in the DUS and CS population where 4 of 9 patients reached the primary endpoint. See Table 12.

A fairly significant proportion of patients (55%) failed to reach the primary endpoint. One of these patients discontinued due to an adverse event of Grade 1 eosinophilia and the last data point collected was at Visit 3 (Day 57 of treatment = Week 8) where the subject showed a -1.4% decrease in weight from baseline. Three patients presented with weight decreases versus baseline between -0.1% and -9.8% at Week 59 visit, with maximal weight losses between -5.7% and -15.3% at earlier timepoints, and it was suspected that these patients were not following the prescribed regimen of study drug based on their aberrant setmelanotide PK data. Two other patients had decreases of -0.9% and -2.5% versus baseline at last assessment, with maximal weight losses of -5.9% and -3.7% measured at prior timepoints, without apparent reason or clarification for their reduced performance.

One patient had a less dramatic weight regain in the placebo period than the other subjects, the patient did gain body mass, which was shed again after resumption of treatment.

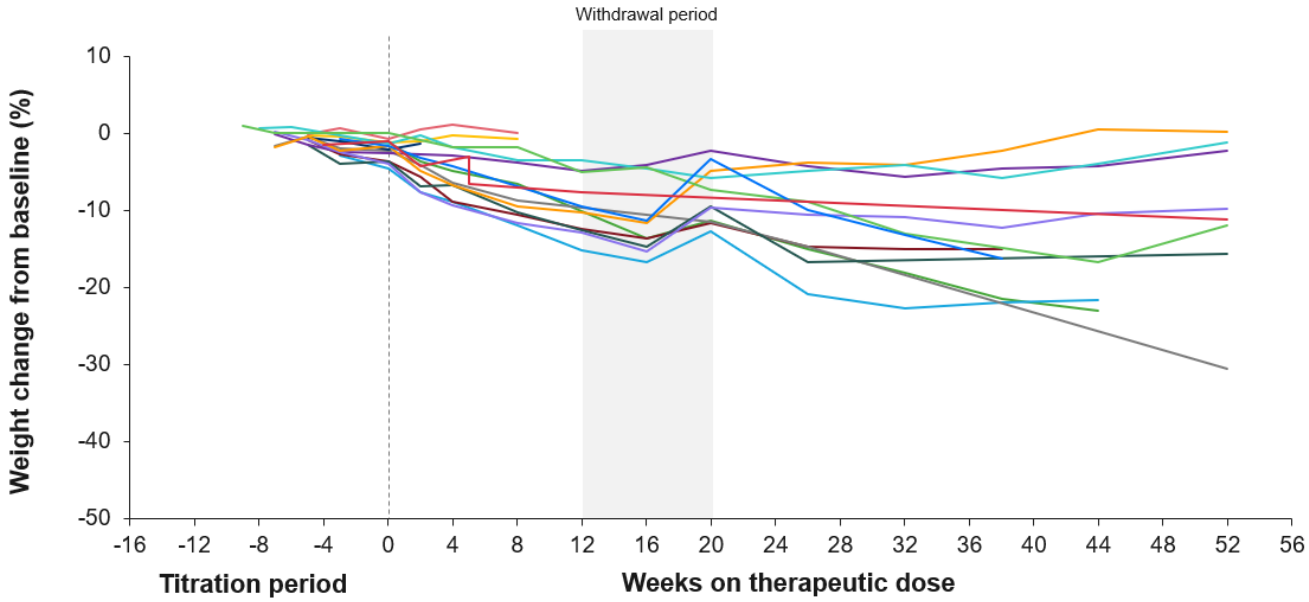
**Table 12: Body Weight (kg) – Proportion of Patients Achieving at Least 10% Weight Loss from Baseline at 52 Weeks from Therapeutic Dose - Pivotal and Supplemental Cohorts (FAS)**

| Parameter | Statistics | Pivotal (N=11) | Supplemental[a] (N=4) | Total (N=15) |
|---|---|---|---|---|
| Patients Achieving at Least 10% Weight Loss from Baseline at Week 52 | n (%) | 5 (45.5) | 4 (100.0) | 9 (60.0) |
| | 90 % CI[b] | (19.96, 72.88) | (47.29, 100.00) | (35.96, 80.91) |
| | p-value | <.0001 | <.0001 | <.0001 |

*Key Secondary Endpoints*

The key secondary endpoint was evaluated in the DUS population, which showed a mean negative weight change from baseline to W52 of +/- 13%. An overall continuous pattern of weight loss during treatment was seen, with overall clear weight regain during the blinded withdrawal period. A total of 70 percent of the overall DUS population (pivotal + evaluable supplemental patients) achieved a minimum of 10% weight loss from baseline to W52, whereas the pivotal patient cohort in isolation managed a 57.1% success rate in this regard due to the aforementioned 6 patients with less favourable or missing outcomes all being pivotal patients. The Week 52 data for three supplemental patients was imputed as they did not yet complete one year of treatment.

Results (including patients from the supplemental cohort) are provided in Figure 12 and Table 13:




Time point at week 0 is indicated with a dashed line and defined as when a participant received their first therapeutic dose of setmelanotide. Withdrawal period consists of 4 weeks of active drug and then 4 weeks of placebo. Data are graphed by the planned timing of each visit. Two Participants did not have weight measurements during the withdrawal period.

**Figure 13: Percentage Change of Weight from Baseline (Pivotal & Supplemental Patients, DUS Population, mean change of 9 patients) – Shaded area represents the 8-week blinded withdrawal period.**

**Table 13: Body Weight (kg) – Percent Change from Baseline at Calendar Week 52 Sensitivity Analysis ~Week 52 from First Dose - Pivotal and Supplemental Cohorts (DUS)**

| Parameter | Statistic | Pivotal (N=7) | Supplemental (N=3) | Total (N=10) |
|---|---|---|---|---|
| Percent Change from Baseline to ~Week 52 (%) | n | 7 | 3 | 10 |

| Parameter | Statistic | Pivotal (N=7) | Supplemental (N=3) | Total (N=10) |
|---|---|---|---|---|
| | Mean (SD) | -12.47 (8.919) | -13.17 (2.731) | -12.72 (7.421) |
| | Median | -15.28 | -11.95 | -13.80 |
| | Q1, Q3 | -21.0, -2.3 | -16.3, -11.3 | -16.3, -9.8 |
| | Min, Max | -23.3, 0.1 | -16.3, -11.3 | -23.3, 0.1 |
| | Least Squares Mean[1] | -12.47 | -13.21 | -12.76 |
| | 90% CI[a] | (-16.10, -8.83) | (-14.60, -11.83) | (-15.30, -10.22) |
| | p-values | <.0001 | <.0001 | <.0001 |
| Achieved at Least 10% Weight Loss from Baseline at ~Week 52 | n (%) | 4 (57.1) | 3 (100) | 7 (70) |

The second key secondary was the mean percent change in hunger from baseline to the Week 52 of treatment, as measured by the worst 'most hunger' in 24 hours. This endpoint was evaluated in the DUS cohort subjects that were 12 years or older, due to the incompatibility of the hunger assessment tools with younger aged subjects. Overall these patients managed to achieve a mean decrease in appetite of 50%, however, while 80% of evaluable subjects managed to achieve a decrease in hunger score of 25% or more. See Table 14.

**Table 14: Daily Hunger Scores – Percent Change from Baseline at 52 Weeks from Therapeutic Dose (≥12 Years of Age): Pivotal Cohort, Supplemental, and Total (Pivotal and Supplemental Cohorts Combined) - DUS**

| | | Worst (Most) Hunger in 24 Hours | | |
|---|---|---|---|---|
| **Parameter** | **Statistic** | **Pivotal Cohort (N=7)** | **Supplemental Cohort (N=3)** | **Total (N=10)** |
| Percent Change from Baseline to Week 52 (%) | n | 7 | 3 | 10 |
| | Mean (SD) | -43.7 (23.69) | -65.60 (4.275) | -50.27 (22.138) |
| | Median | -52.7 | -67.49 | -58.39 |

| | | Worst (Most) Hunger in 24 Hours | | |
|---|---|---|---|---|
| **Parameter** | **Statistic** | **Pivotal Cohort (N=7)** | **Supplemental Cohort (N=3)** | **Total (N=10)** |
| | Q1, Q3 | -64.0, -29.0 | -68.61, -60.71 | -66.71, -37.50 |
| | Min, Max | -67.0, 0.0 | -68.6, -60.7 | -68.6, 0.0 |
| | LS Mean | -41.93 | -57.32 | -50.29 |
| | 90% CI | (-54.76, -29.09) | (-121.11, 6.47) | (-63.81, -36.78) |
| | P-value | <0.0001 | 0.0593 | <0.0001 |
| Subjects Achieving at Least 25% Hunger Improvement from Baseline at Week 52 | n (%) | 5 (71.4) | 3 (100) | 8 (80.0) |

The third key secondary endpoint evaluated the proportion of patients ≥12 years achieving at least 25% improvement in hunger scores following 1 year of treatment with setmelanotide in the FAS population. About 79% of the total FAS population managed to reach this endpoint.

**Table 15: Daily Hunger Scores – Proportion of Patients Achieving at Least 25% Improvement in Daily Hunger (Worst, 'Most') from Baseline at 52 Weeks from Therapeutic Dose (≥12 Years of Age) – Pivotal Cohort and Total (Pivotal and Supplemental Cohorts Combined) FAS**

| | | Total (N=8) | | |
|---|---|---|---|---|
| **Parameter** | **Statistic** | **Morning Hunger** | **Worst (Most) Hunger in 24 Hours** | **Average Hunger over 24 Hours** |
| Subjects Achieving at Least 25% Hunger Improvement from Baseline at Week 52 | n (%) | 8.0 (72.7) | 3.0 (100.0) | 11.0 (78.6) |
| | 90% CI[a] | (43.56, 92.12) | (36.84, 100.00) | (53.43, 93.89) |
| | P-value1 | <0.0001 | 0.0001 | <0.0001 |

Results from other secondary/tertiary/exploratory endpoints (cut-off date: 09 July 2019) can be summarised below:

- At Week 52, patients in the pivotal DUS population had a mean negative change in waistline circumference of 7%.
- Overall a mean weight gain of 7 kilograms was noted when pivotal cohort patients underwent a 4-week IP withdrawal during the 8-week blinded withdrawal period.
- During the 4-week IP withdrawal period the pivotal cohort DUS subjects saw a mean increase in worst hunger score in 24 hours of 2.9 units increase, though this change was not statistically significant.
- Of the overall weight loss, a mean of 74% was due to loss of body fat, with no appreciable loss of bone density or non-bone lean body mass.
- The mean BMI in the pivotal DUS patients changed -13.2% from Baseline to week 52.
- Observed energy expenditures showed net reductions at the relevant assessment points, consistent with the weight loss achieved.

## Ancillary analyses

**Immunogenicity**

In the pivotal clinical studies, RM-493-012 and RM-493-015, ADA sampling strategies included collection of samples pre-treatment (identified as Screen, Day 1 or Day -1), and post-treatment at Day 14, Day 29 and every 2 weeks during the dose titration phase, then monthly thereafter in the maintenance phase. For any subject with a positive ADA to setmelanotide at the end of study or early termination, the subjects were to be assessed for ADA every 3 months until resolution or return to baseline.

The results to date demonstrate that no antibodies specific for setmelanotide were found in any of the samples from any of the clinical trials wherein ADA was assessed. Of the 79 screening positive samples that were assessed in the confirmatory assay, no samples (0/79) were confirmed positive for antibodies to setmelanotide. As a result, no samples to date have been tested in the neutralising antibody assay (NAb).

Consistent with the observation of no ADA to setmelanotide in the assays, there has been no observed clinical effect on PD or efficacy parameters, such as increased hunger or weight gain. However, given the issues observed in regard to the ADA assays used (see earlier discussion), no confirmative conclusions can be drawn from these findings at this point in time.

No patient in Study RM-493-012 had confirmed anti-α-MSH antibodies which is in line with the fact that POMC/PCSK1 deficiency patients lack α-MSH. In the RM-493-015, three LEPR patients confirmed anti-α-MSH samples were found, each in a different patient. Of these three samples was pre-treatment, while the others were temporally located in the titration phase, with inhibitions ranging from +31 to 38%. No effect on clinical response, setmelanotide concentration or safety could be ascribed to these findings, however.

**Glucose Metabolism**

With regards to glucose metabolism, overall results showed a positive trend. However, it should be noted that only 4 patients in the LEPR deficiency population completed the 52-week glucose measurement and the result should be interpreted with caution. Likewise, changes in HbA1c from a

median of 5.6% at baseline to 5.1% at week 52 was observed in patients with POMC deficiency. No LEPR patients had HbA1c measurements at follow-up.

**Other analyses**

Based on data on body weight and hunger score immediately before, during and after the placebo period the combined populations were confirmed to achieve a weight loss of 2.5 kg before, a weight gain of 5.9 kg during and a weight loss of 5.1 kg after the placebo period. The accompanying hunger scores were 3.8, 7.0 and 4.0 respectively. Even though these data are not statistically tested, there is a clear indication of a weight gain during the placebo period compared to the treatment period. This tendency was also shown in the spaghetti plots. Hence, an effect of setmelanotide on body weight and hunger is supported by this double-blind withdrawal period.

Analysis of the exploratory endpoints showed results that are in line with main results seen. Results on body composition indicated that the weight loss is primarily due to a reduction in fat mass while metabolic parameter analysis showed results indicative of an improvement in insulin sensitivity.

## Summary of main study(ies)

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

**Table 16: Summary of efficacy for trial RM-493-012**

| **Title: 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 Bi-Allelic Loss-of-Function POMC or PCSK1 Genetic Mutation** | | |
|---|---|---|
| Study identifier | RM-493-012<br>EudraCT number: 2016-002320-83 | |
| Design | This was a one year, multicentre, global, open label, non randomised study including a 2-12 week initial dose titration and a double-blind placebo controlled 8-week withdrawal period in which patients would randomly be administered placebo for a duration of four week to assess efficacy of setmelanotide in POMC deficiency obesity. | |
| | Duration of main phase: | 10 weeks at therapeutic dose followed by 8-week double blind placebo withdrawal period and 32 weeks continued treatment at therapeutic dose |
| | Duration of Run-in phase: | Up to 12-week dose titration to therapeutic dose level (maximum of 3.0 mg) |
| | Duration of Extension phase: | After completing approximately 1 year of dosing at the therapeutic dose, patients were eligible to |
| Hypothesis | The primary endpoint was the proportion of patients in the FAS who demonstrated at least 10% weight reduction at ~1 year (10-14 months post baseline) compared to baseline. The primary research hypothesis was that this proportion is at least 5%. The null hypothesis as that this proportion is at most 5%. | |
| Treatments groups | POMC deficiency | Treatment: setmelanotide<br>Duration: up to 52 weeks<br>Number enrolled: 15 (10 pivotal, 5 supplemental) |

<table>
<tr><td rowspan="4">Endpoints and definitions</td><td>Primary endpoint</td><td colspan="5">Proportion of patients who demonstrated at least 10% weight reduction at ~1 year compared to baseline</td></tr>
<tr><td>Key Secondary endpoint</td><td colspan="5">Mean percent change in body weight from baseline</td></tr>
<tr><td>Key Secondary endpoint</td><td colspan="5">Mean percent change in weekly average 'most hunger' score</td></tr>
<tr><td>Key Secondary endpoint</td><td colspan="5">Proportion of patients achieving ⩾25% improvement in weekly average 'most hunger' score</td></tr>
<tr><td>Data extraction date</td><td colspan="6">09 July 2019 (pivotal data)<br>30 April 2020 (supplemental data)</td></tr>
<tr><td colspan="7"><u>Results and Analysis</u></td></tr>
<tr><td>Analysis description</td><td colspan="6">Primary Analysis - Proportion of patients who demonstrated at least 10% weight reduction at ~1 year compared to baseline</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="6">Full Analysis Set (patients who received any of the study drug injections and at least one baseline assessment (included all pivotal cohort patients whether or not they demonstrated ⩾5kg weight loss or 5% of body weight [if baseline weight was <100kg] over the 12-week open-label treatment period and proceeded into the double-blind, placebo-controlled withdrawal).<br><br>Timepoint: 52 weeks</td></tr>
<tr><td rowspan="4">Descriptive statistics and estimate variability</td><td>Parameter</td><td>Statistic</td><td>Pivotal (N=10)</td><td>Supplemental[a] (N=4)</td><td>Total (N=14)</td></tr>
<tr><td rowspan="3">Patients Achieving at Least 10% Weight Loss from Baseline at Week 52</td><td>n (%)</td><td>8 (80.0%)</td><td>4 (100.0%)</td><td>12 (85.7%)</td></tr>
<tr><td>90% CI[b]</td><td>(49.31, 96.32)</td><td>(47.29, 100.00)</td><td>(61.46, 97.40)</td></tr>
<tr><td>p-value</td><td><.0001</td><td><.0001</td><td><.0001</td></tr>
<tr><td>Effect estimate per comparison</td><td colspan="6">N/A</td></tr>
<tr><td>Notes</td><td colspan="6">[a] The Supplemental Cohort was ongoing at the time of data cut. To be included in analysis, patients must have had at least 3 months of treatment. Two patients, (003-002 and 007-002 had not reached 52 weeks, so their 52-week data were imputed.<br>[b] Two-sided confidence interval (CI) obtained using Clopper-Pearson method and one-sided p-value obtained from exact binomial test, testing that at least 5% of patients in the population of interest would achieve 10% weight loss.</td></tr>
<tr><td>Analysis description</td><td colspan="6">Key Secondary analysis - Mean percent change in body weight from baseline</td></tr>
</table>

| | | | | | |
|---|---|---|---|---|---|
| Analysis population and time point description | Defined Use Set (subjects who received any of the study drug injections, demonstrated ≥5kg weight loss (or 5% of body weight if weight is < 100kg at baseline) over 12-week open label treatment period, and proceeded into the double-blind, placebo controlled withdrawal period.)<br><br>Timepoint: 52 weeks | | | | |
| Descriptive statistics and estimate variability | Parameter | Statistic | Pivotal (N=9) | Supplemental (N=4) | Total (N=13) |
| | Baseline body weight (kg) | Mean (SD) | 114.97 (37.774) | 94.47 (34.405) | 108.66 (36.664) |
| | | Median | 114.70 | 92.08 | 114.40 |
| | | Min, Max | 55.9, 186.7 | 55.7, 138.0 | 55.7, 186.7 |
| | ~Week 52 Body Weight (kg) | Mean (SD) | 83.076 (21.425) | 70.51 (27.349) | 79.21 (23.009) |
| | | Median | 82.70 | 75.90 | 82.70 |
| | | Min, Max | 54.5, 121.8 | 33.8, 96.5 | 33.8, 121.8 |
| | Percent Change from Baseline to ~Week 52 (%) | Mean (SD) | -25.565 (9.879) | -26.25 (10.648) | -25.77 (9.671) |
| | | Median | -27.31 | -25.06 | -27.31 |
| | | Min, Max | -35.6, -2.4 | -39.4, -15.5 | -39.4, -2.4 |
| | | LS Mean[a] | -25.39 | -26.26 | -25.66 |
| | | 90% CI[a] | (-28.80, -21.98) | (-32.94, -19.58) | (-28.40, -22.91) |
| | | p-value[a] | <.0001 | 0.0006 | <.0001 |
| Effect estimate per comparison | N/A | | | | |
| Notes | [a] Model based summary statistics from longitudinal mixed analysis of variance model with fixed effect for visit, baseline body weight and random effect for patient, one sided p-value from model. | | | | |
| **Analysis description** | **Key Secondary analysis - Mean percent change in weekly average 'most hunger' score** | | | | |
| Analysis population and time point description | Defined Use Set (subjects who received any of the study drug injections, demonstrated ≥5kg weight loss (or 5% of body weight if weight is < 100kg at baseline) over 12-week open label treatment period, and proceeded into the double-blind, placebo controlled withdrawal period.)<br><br>Timepoint: 52 weeks | | | | |
| Descriptive statistics and estimate variability | | | Total (N=8) | | |
| | Parameter | Statistic | Worst (most) hunger in 24 hours (N=7) | | |

| | | | |
|---|---|---|---|
| | Baseline hunger score | Mean (SD) | 8.1 (0.78) |
| | | Median | 8.0 |
| | | Min, Max | 7, 9 |
| | Week 52 Hunger Score | Mean (SD) | 5.3 (2.33) |
| | | Median | 5.5 |
| | | Min, Max | 2, 8 |
| | Percent Change from Baseline to week 52 (%) | Mean (SD) | -27.06 (28.113) |
| | | Median | -14.29 |
| | | Min, Max | -72.2, -1.4 |
| | | LS Mean[a] | -27.77 |
| | | 90% CI[a] | (-40.58, -14.96) |
| | | p-value[a] | 0.0005 |
| Effect estimate per comparison | N/A | | |
| Notes | [a] Model based summary statistics from longitudinal mixed analysis of variance model with fixed effect for visit, baseline body weight and random effect for subject, one sided p-value from model.<br>Percentages based on number of subjects with hunger diary data at both baseline and Week 52. | | |
| **Analysis description** | **Key Secondary analysis - Proportion of patients achieving ≥25% improvement in weekly average 'most hunger' score** | | |
| Analysis population and time point description | Full Analysis Set (patients who received any of the study drug injections and at least one baseline assessment (included all pivotal cohort patients whether or not they demonstrated ≥5kg weight loss or 5% of body weight [if baseline weight was <100kg] over the 12-week open-label treatment period and proceeded into the double-blind, placebo-controlled withdrawal).<br><br>Timepoint: 52 weeks | | |
| Descriptive statistics and estimate variability | Total (N=9) | | |
| | Parameter | Statistic | Worst (most) hunger in 24 hours |
| | Subjects Achieving at Least 25% Hunger Improvement from Baseline at Week 52 | n (%) | 4 (50.0%) |
| | | 90% CI[a] | (19.29, 80.71) |
| | | p-value[a] | 0.0004 |

| | |
|---|---|
| Effect estimate per comparison | N/A |
| Notes | [a] Two-sided confidence interval (CI) obtained using Clopper-Pearson method and one-sided p-value obtained from exact binomial test, testing that >= 5% of subjects in the population of interest will achieve >= 25% improvement in daily hunger score. |

**Table 17: Summary of efficacy for trial RM-493-015**

| **Title: 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 Bi-Allelic Loss-of-Function LEPR Genetic Mutation** | | |
|---|---|---|
| Study identifier | RM-493-015<br>EudraCT number: 2017-002005-36 | |
| Design | This was a one year, multicentre, global, open label, non randomised study including a 2-12 week initial dose titration and a double-blind placebo controlled 8-week withdrawal period in which patients would randomly be administered placebo for a duration of four weekto assess efficacy of setmelanotide in LEPR deficiency obesity | |
| | Duration of main phase:<br><br>Duration of Run-in phase:<br><br>Duration of Extension phase: | 10 weeks at therapeutic dose followed by 8-week double blind placebo withdrawal period and 32 weeks continued treatment at therapeutic dose<br>Up to 12-week dose titration to therapeutic dose level (maximum of 3.0 mg)<br><br>After completing approximately 1 year of dosing at the therapeutic dose, patients were eligible to enrol in a separate long-term extension study to continue receiving setmelanotide (Study RM-493-022) or they completed a final study visit approximately 30 days after their last dose. |
| Hypothesis | The primary endpoint was the proportion of patients in the FAS who demonstrated at least 10% weight reduction at ~1 year (10-14 months post baseline) compared to baseline. The primary research hypothesis was that this proportion is at least 5%. The null hypothesis as that this proportion is at most 5%. | |
| Treatments groups | LEPR deficiency | Treatment: setmelanotide<br>Duration: up to 52 weeks<br>Number enrolled: 15 (11 pivotal, 4 supplemental) |
| Endpoints and definitions | Primary endpoint | Proportion of patients who demonstrated at least 10% weight reduction at ~1 year compared to baseline |
| | Key Secondary endpoint | Mean percent change in body weight from baseline |
| | Key Secondary endpoint | Mean percent change in weekly average 'most hunger' score |

| | | |
|---|---|---|
| | Key Secondary endpoint | Proportion of patients achieving ⩾25% improvement in weekly average 'most hunger' score |
| Data extraction date | 15 July 2019 (pivotal data)<br>30 April 2020 (supplemental data) | |

**Results and Analysis**

| | | | | | |
|---|---|---|---|---|---|
| **Analysis description** | **Primary Analysis - Proportion of patients who demonstrated at least 10% weight reduction at ~1 year compared to baseline** | | | | |
| Analysis population and time point description | Full Analysis Set (patients who received any of the study drug injections and at least one baseline assessment (included all pivotal cohort patients whether or not they demonstrated ⩾5kg weight loss or 5% of body weight [if baseline weight was <100kg] over the 12-week open-label treatment period and proceeded into the double-blind, placebo-controlled withdrawal).<br><br>Timepoint: 52 weeks | | | | |
| Descriptive statistics and estimate variability | Parameter | Statistic | Pivotal (N=11) | Supplemental[a] (N=4) | Total (N=15) |
| | Patients Achieving at Least 10% Weight Loss from Baseline at Week 52 | n (%) | 5 (45.5%) | 4 (100.0%) | 9 (60.0%) |
| | | 90% CI[b] | (19.96, 72.88) | (47.29, 100.00) | (35.96, 80.91) |
| | | p-value | <.0001 | <.0001 | <.0001 |
| Effect estimate per comparison | N/A | | | | |
| Notes | [a] The Supplemental Cohort was ongoing at the time of data cut. To be included in analysis, patients must have had at least 3 months of treatment. Three patients, (001-004, 007-003, and 008-001) had not reached 52 weeks; therefore, their 52-week data were imputed.<br>[b] Two-sided confidence interval (CI) obtained using Clopper-Pearson method and one-sided p-value obtained from exact binomial test, testing that at least 5% of patients in the population of interest would achieve 10% weight loss. Percentages based on number of patients with weight data at both baseline and Week 52. | | | | |
| **Analysis description** | **Key Secondary analysis - Mean percent change in body weight from baseline** | | | | |
| Analysis population and time point description | Defined Use Set (subjects who received any of the study drug injections, demonstrated ≥5kg weight loss (or 5% of body weight if weight is < 100kg at baseline) over 12-week open label treatment period, and proceeded into the double-blind, placebo controlled withdrawal period.)<br><br>Timepoint: 52 weeks | | | | |
| Descriptive statistics and estimate variability | Parameter | Statistic | Pivotal (N=7) | Supplemental (N=3) | Total (N=10) |

| | | | | | |
|---|---|---|---|---|---|
| | Baseline body weight | Mean (SD) | 131.74 (32.613) | 158.83 (50.051) | 139.87 (37.909) |
| | | Median | 120.53 | 159.27 | 136.97 |
| | | Min, Max | 89.4, 170.4 | 108.6, 208.7 | 89.4, 208.7 |
| | ~Week 52 Body Weight (kg) | Mean (SD) | 115.00 (29.60) | 138.64 (46.489) | 122.02 (34.515) |
| | | Median | 104.10 | 141.32 | 122.71 |
| | | Min, Max | 81.7, 149.9 | 90.9, 183.7 | 81.7, 183.7 |
| | Percent Change from Baseline to ~Week 52 (%) | Mean (SD) | -12.47 (8.919) | -13.17 (2.731) | -12.72 (7.421) |
| | | Median | -15.28 | -11.95 | -13.80 |
| | | Min, Max | -23.3, 0.1 | -16.3, -11.3 | -23.3, 0.1 |
| | | LS Mean[a] | -12.47 | -13.21 | -12.76 |
| | | 90% CI[a] | (-16.10, -8.83) | (-14.60, -11.83) | (-15.30, -10.22) |
| | | p-value[a] | <.0001 | <.0001 | <.0001 |
| Effect estimate per comparison | N/A | | | | |
| Notes | [a] Model based summary statistics from longitudinal mixed analysis of variance model with fixed effect for visit, baseline body weight and random effect for subject, one sided p-value from model. | | | | |
| **Analysis description** | **Key Secondary analysis - Mean percent change in weekly average 'most hunger' score** | | | | |
| Analysis population and time point description | Defined Use Set (subjects who received any of the study drug injections, demonstrated ≥5kg weight loss (or 5% of body weight if weight is < 100kg at baseline) over 12-week open label treatment period, and proceeded into the double-blind, placebo controlled withdrawal period.)<br><br>Timepoint: 52 weeks | | | | |
| Descriptive statistics and estimate variability | Parameter | Statistic | Pivotal (N=7) | Supplemental (N=3) | Total (N=10) |
| | Baseline hunger score | Mean (SD) | 7.0 (0.77) | 6.6 (1.88) | 6.9 (1.10) |
| | | Median | 7.0 | 6.4 | 6.9 |
| | | Min, Max | 6, 8 | 5, 9 | 5, 9 |
| | Week 52 Hunger Score | Mean (SD) | 4.1 (2.09) | 2.3 (0.60) | 3.5 (1.94) |
| | | Median | 3.0 | 2.5 | 2.8 |
| | | Min, Max | 2, 8 | 2, 3 | 2, 8 |
| | Percent Change from Baseline to week 52 (%) | Mean (SD) | -43.7 (23.69) | -65.60 (4.275) | -50.27 (22.138) |

| | | | | | |
|---|---|---|---|---|---|
| | | Median | -52.7 | -67.49 | -58.39 |
| | | Min, Max | -67, 0 | -68.6, -60.7 | -68.6, 0.0 |
| | | LS Mean[a] | -41.93 | -57.32 | -50.29 |
| | | 90% CI[a] | (-54.76, -29.09) | (-121.11, 6.47) | (-63.81, -36.78) |
| | | p-value[a] | <.0001 | 0.0593 | <.0001 |
| Effect estimate per comparison | N/A | | | | |
| Notes | [a] Model based summary statistics from longitudinal mixed analysis of variance model with fixed effect for week, baseline daily hunger score, and random effect for subject, one sided p-value from model.<br>Percentages were based on the number of patients with hunger diary data at both baseline and Week 52. | | | | |
| **Analysis description** | **Key Secondary analysis - Proportion of patients achieving ≥25% improvement in weekly average 'most hunger' score** | | | | |
| Analysis population and time point description | Full Analysis Set (patients who received any of the study drug injections and at least one baseline assessment (included all pivotal cohort patients whether or not they demonstrated ≥5kg weight loss or 5% of body weight [if baseline weight was <100kg] over the 12-week open-label treatment period and proceeded into the double-blind, placebo-controlled withdrawal).<br><br>Timepoint: 52 weeks | | | | |
| Descriptive statistics and estimate variability | Parameter | Statistic | Pivotal (N=11) | Supplemental (N=3) | Total (N=14) |
| | Subjects Achieving at Least 25% Hunger Improvement from Baseline at Week 52 | n (%) | 8 (72.7) | 3 (100) | 11 (78.6) |
| | | 90% CI[a] | (43.56, 92.12) | (36.84, 100.00) | (53.43, 93.89) |
| | | p-value[a] | <.0001 | .0001 | <.0001 |
| Effect estimate per comparison | N/A | | | | |
| Notes | [a] Two-sided confidence interval (CI) obtained using Clopper-Pearson method and one-sided p-value obtained from exact binomial test, testing that ≥5% of patients in the population of interest would achieve ≥ 25% improvement in daily hunger score. | | | | |

## Analysis performed across trials (pooled analyses and meta-analysis)

The proportion of patients achieving a ≥10% weight loss from baseline was lower among those with LEPR than with POMC deficiency obesity (60% versus 86%, respectively using the FAS population). Among patients that did not meet the primary endpoint, PK data for 3 LEPR deficiency patients showed

aberrant setmelanotide concentrations from approximately Visit 5 through Visit 12 leading to the suspicion that these patients were likely not taking study drug according to the prescribed regimen.

In the supportive investigator-led study RM-493-011, both of the POMC/PCSK1 deficiency patients lost at least 10% of body weight from screening to Visit 3 which is associated with approximately 3 months on study, while only one of the 3 LEPR deficiency patient lost at least 10% of body weight from screening to Visit 3.

Similarly, to the primary endpoint, the effect-size was far larger for the percentage change in individual body weight from baseline to Week 52 (%) (key secondary endpoint) in the POMC/PCSK1 deficiency patients than in the LEPR patient population, (mean ± SD) was -25.8% (±9.7) for POMC patients and -12.7% (±7.4) for LEPR deficiency obesity respectively using the DUS population). In the supportive RM-493-011 study similar outcomes were seen with mean decreases of -15% and -9% respectively among patients with POMC and LEPR deficiency at Month 3.

Differences in the overall weight-loss outcomes in the two pivotal trials could be explained by the fact that 3 patients in the LEPR-population had compliance issues (though there were two pivotal patients that had seemingly unexplainable less favourable responses to treatment) and 1 patient discontinued very early on in the study due to an AE. However, the same disparity of efficacy is replicated in the investigator-led supportive study (RM-493-011). The number of POMC and LEPR patients in study RM-493-011 was very low (n= 2 and 3 respectively) and thus it is not possible to clearly ascribe a causal effect to these findings. Nonetheless, seeing the difference in outcome scores repeated in two separate trials may indicate some process interfering in the efficacy of setmelatonide in LEPR patients. The CHMP recognised that given the ultra-rarity of these genetic disorders, that such finding cannot be further investigated in a clinical trial context. On the other hand, even though the performance in the LEPR population was markedly less than in the POMC/PCKS1 patients; overall patients still managed a respectable mean body weight change of -13% in a year of treatment. Moreover, patients that underwent the blinded withdrawal of setmelanotide did show a clear reversal of earlier weight loss gains, indicating that the product is having an overall positive effect in both populations.

As for the other key secondary endpoints, a reversed situation is observed for the percentage change in worst daily hunger score, with improvements in the LEPR patient population outpacing those in the POMC/PCSK1 population aged 12 years and above. The mean percent change from baseline to 52 weeks (mean ± SD) was -27.1% (±28.1) for POMC patients and -50.3% (±22.1) for LEPR deficiency obesity respectively using the DUS population). Proportion of patients achieving ≥25% improvement in worst hunger score was 50 % (n=4) for POMC patients and 78.6% (n=11) for LEPR deficiency obesity respectively using the FAS population. In contrast, in the investigator led study RM-493-011, better hunger management scores were reported for POMC patients (mean percent change from baseline (mean ± SD) to Month 3 in Hunger Score was -89.4% (±0.79) for POMC patients with POMC deficiency obesity and -64.1% (±17.44) for LEPR deficiency obesity patients) and thus no consistency on the hunger management scores is reported across the clinical studies.

In the supplemental cohort, the proportion of patients at 52 weeks achieving at least 10% weight loss compared to baseline was 85.7% and 60% in the POMC population and 60% in the LEPR population. In comparison, this was 80.0% and 45.5% in the pivotal population. The higher proportion meeting the endpoint in the supplemental cohort could be due to a shorter follow-up time and thereby lower number of patients not completing the study, as the change in bodyweight for those who withdraw from the study was set to 0 kg. However, as these patients are not part of the pivotal population no impact on the benefit risk balance of setmelanotide is expected.

## Clinical studies in special populations

No clinical studies in special populations were undertaken.

Both pivotal studies included paediatric subjects, and this is further presented and discussed in section 2.5.3 this report.

## *Supportive study(ies)*

**Study RM-493-011**

In study RM-493-011, eligible patients either had homozygous or compound heterozygous (different gene mutation on both alleles) POMC, LEPR, MC4R or PCSK1 gene mutations, heterozygous POMC/MC4R mutations, POMC hypermethylation (epigenetic) variants, Bardet-Biedl Syndrome or Älstrom's Syndrome. All subjects had to be obese, as defined by a BMI >30 kg/$m^2$ and not have any other curative option. A total of 30 patients were to be enrolled (initially only adult patients and once efficacy was established in adults, patients ≥12 years with POMC or LEPR mutations were to be enrolled). Treatments were provided subcutaneously according to dose titration scheduled to determine the TD level. A total of 7 patients enrolled, of which 2 POMC and 3 LEPR deficiency patients. All patients were still ongoing as of 19 February 2019, except for 1 LEPR patient who was withdrawn early due to a protocol violation.

Overall the mean % change in weight loss at Month 3 from screening for POMC/PCSK1 deficiency patients was ~15% and for LEPR deficiency patients ~9%, while the mean % change in weight loss from screening to 12 months for POMC/PCSK1 deficiency patients was ~30% and for LEPR deficiency patients ~9%. In addition, BMI and waist circumference were also less favourable within the first 3 months of study. Mean change ± SD from baseline in BMI for the POMC/PCSK1 deficiency patients was -7.73±0.75 and -3.59±1.82 for LEPR deficiency patients. Mean change ± SD from baseline in waist circumference for the POMC/PCSK1 deficiency patients was -11.50 ±6.36 and -6.67±4.04 for the LEPR deficiency patients.

In patients with LEPR deficiency, there was a weight loss during the first 52 weeks in two of the patients, where no substantial effect was seen in one of the patients, and after the first 52 weeks of treatment there was a tendency towards an increase in bodyweight, even though the dose was increase to 3 mg.

For the hunger-related secondary endpoint assessment showed that POMC and LEPR deficiency patients had a reduction in hunger-scores within 3 months for 1 POMC and 2 LEPR deficiency patients. However, better hunger management scores were reported for POMC patients (mean percent change from baseline (mean ± SD) to Month 3 in Hunger Score was -89.4% (±0.79) for POMC patients with POMC deficiency obesity and -64.1% (±17.44) for LEPR deficiency obesity patients).

**Study RM-493-022**

In the extension study RM-493-022, up to an additional 2 years treatment, or until drug was otherwise available through authorized use, patients had completed a prior study of setmelanotide for genetic obesity disorders upstream of the MC4 receptor in the melanocortin-leptin pathway. Visit 1 of this study coincided with the final visit of the index trial. Patients continued taking the same dose of setmelanotide that was being administered at completion of the Index Study, though dose level changes were allowed at any time based on safety or efficacy findings. As of 9 May 2019, the study was still ongoing, a total of 9 POMC/PCSK1 patients whom had finished Index study RM-493-012 and 6 LEPR patients whom had finished study RM-493-015 were enrolled for the extension study. One of the

former 9 patients discontinued prior to Week 37, while 5 patients had reached Week 89. All six LEPR patients had reached Week 25 at time of data extraction.

The baseline disposition of the POMC/PCSK1 patients was as follows: 4 females and 5 males, 12 to 27 years of age at time of enrolment in the extension Study. Mean body weight of the POMC/PCSK1 patients at enrolment in the RM-493-012 Index Study was 114.98 kg (range 55 to 186.7 kg) and mean body weight at enrolment in the extension Study was 83.61 kg (range 54.3 to 121.9 kg). One had an interruption of treatment for ~7 weeks prior to enrolling in the extension Study during which he experienced weight gain. For the 6 LEPR patients the baseline disposition was thus: 4 females and 2 males, 13 to 32 years of age at time of enrolment in the Extension Study. Mean body weight of the 6 LEPR deficiency patients at enrolment in the RM-493-015 Index Study was 125.43 kg (range 89.4 to 170.4 kg), their mean body weight at ~52 Weeks in the Index study was 110.22 kg (range 81.7 to 149.9 kg) and the mean body weight at enrolment in the extension Study was 121.87 kg (range 81.4 to 173.8 kg). Three LEPR deficiency patients requested a hiatus of treatment with setmelanotide after completing the Index Study before enrolment into the Extension Study and were off drug for approximately 4.5 months before resuming treatment in the Extension Study. This delay in enrolment into the Extension Study had a marked effect on the Extension Study baseline weight as patients gained weight during this period without treatment.

At Week 13 of the Extension study the 9 POMC/PCSK1 patients had mean change of +0.48 kg (+1.12%) compared to the Extension Study baseline and a mean change of -30.89 kg (-24.19%) compared to the Index Study baseline. At Week 25 a mean change of +1.78 kg (+2.53%) compared to the Extension Study baseline and a mean change of -29.59 kg (-23.42%) compared to the Index Study baseline was noted.

At Week 65 data of 7 patients was available showing a mean change of +3.86 kg (+5.93%) compared to the Extension Study baseline and a mean change of -34.17 (-25.41%) compared to the Index Study baseline.

At Week 89 of the Extension Study data of 5 patients was available showing a mean change of -0.46 kg (+0,14%) compared to the Extension Study baseline and a mean change of -40.22 kg (-30.20%) compared to the Index Study baseline.

Overall a fairly high variability was apparent in the individual patient weight curves, and though most patients maintained at least a 10% weight lost versus Index study baseline, with the overall trend being a continued weight loss versus Index baseline, some patients showed enormous spikes in weight. See Figure 14.

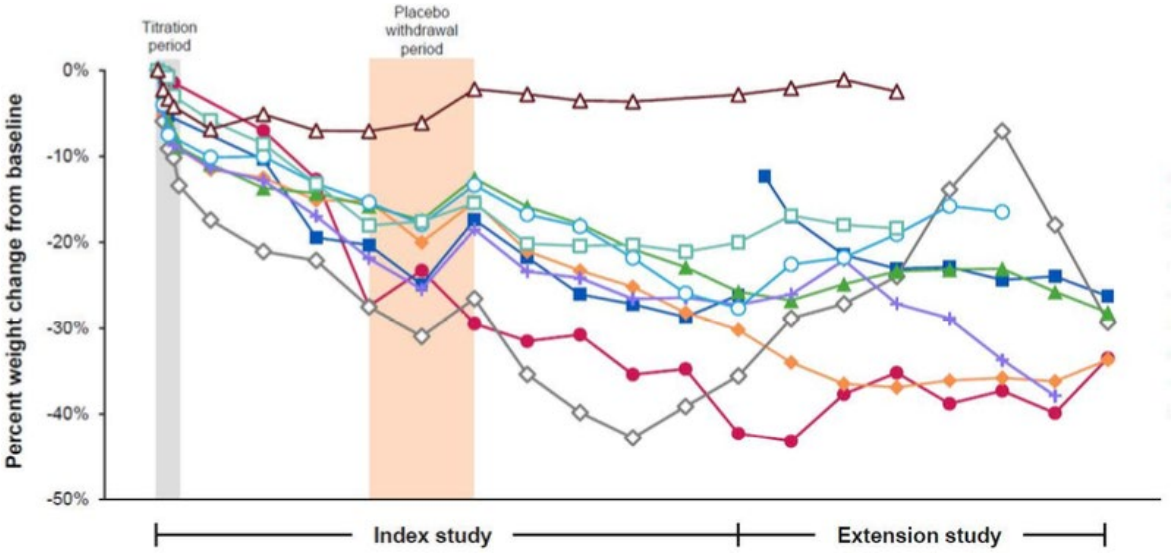



**Figure 14 : Percent Body Weight Change Over Time - Index Study Through Last Assessment in the Extension Study, Individual POMC/PCSK1 Patients**

Of the 6 LEPR deficiency patients currently enrolled the mean percent change in body weight at Week 13 was -2.18 kg (-1.88%) versus Extension study baseline and -5.75 kg (-4.47%) versus Index study baseline. At Week 25 these changes were a mean change of -1.58 kg (-1.77%) compared to the Extension Study baseline and -5.15 kg (-4.13%) compared to the Index Study baseline.

During the Index study RM-493-015, 3 subjects exhibited erratic setmelanotide PK values which were inconsistent with the weight loss noted, despite showing the expected weight progression early on during their dosing schedule. Neither achieved the Index primary endpoint and all three had a hiatus of ± 4.5 months between finishing the Index study and enrolment in the RM-493-022 Extension study, with significant weight gains noted during this period. Upon restart the patients were not administered their therapeutic Index dose but were instead treated with lower doses (ongoing as of Week 25). After 6 months of treatment one of these patients is showing a trend towards continued moderate loss of weight.

Overall there is currently little data, which does not yet allow to make any observations on outcomes or trends therein. See Figure 15.

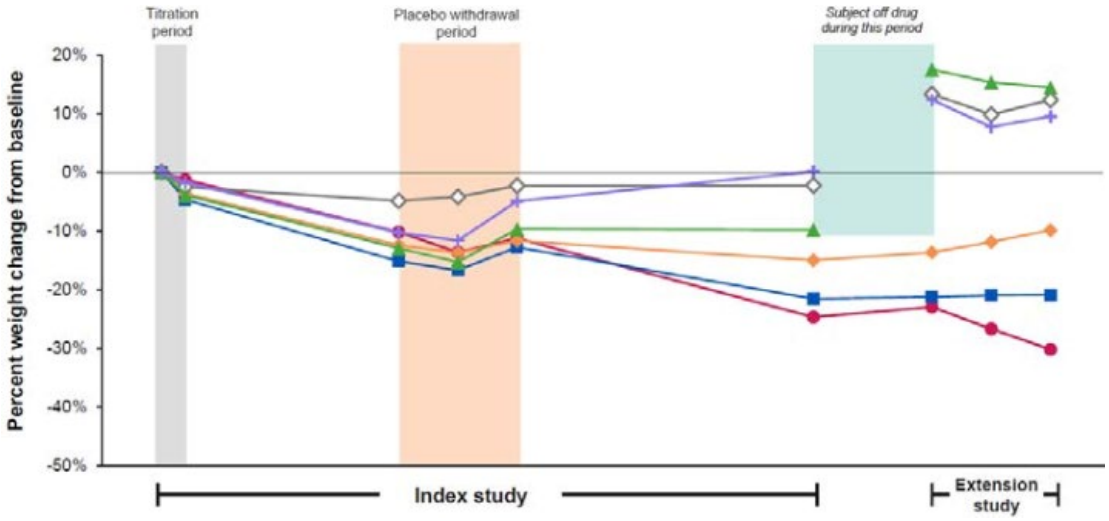



**Figure 15: Percent Change in Body Weight Over Time - Index Study Through Last Assessment in the Extension Study, Individual LEPR deficiency patients**

Based on the worst (most) hunger in 24 hours, the mean hunger score of the 7 POMC/PCSK1 patients ≥ 12 year was 8.0 at Index Study baseline and after ~1 year of treatment with setmelanotide in the Index Study the mean hunger score at Extension Study baseline was 6.4. During the Extension Study mean hunger score remained consistent for these 7 POMC/PCSK1 deficiency patients, and at Week 37 the mean hunger score was 6.3 but then tended to increase slightly over time. The mean hunger score of 5 of the 7 POMC/PCSK1 deficiency patients that completed Week 89 was 7.0. The mean hunger score of the 6 LEPR deficiency patients ≥12 year was 7.1 at Index Study baseline and the mean hunger score at Extension Study baseline was 5.7. During the Extension Study the mean hunger score was maintained during first 6 months of treatment in the Extension Study (5.7 at Week 25).

## 2.5.3. Discussion on clinical efficacy

The clinical efficacy consisted of two pivotal studies and two supportive studies. The proposed therapeutic indication relates to bi-allelic POMC/PCSK1/LEPR deficiency obesities, which are of an ultra-rare nature with a combined worldwide known incidence of less than 200 patients. Thus, any attempts with regards to discussion on adequate design, statistical considerations and interpretation of results are fraught with caveats stemming from an incessant paucity in total available data. This in turn hampers efforts towards robustness and implies that observed clinical effects could be as or even more important in any benefit/risk assessment as purely statistical considerations and outcomes, in contrast to trials in relatively abundant populations which allow robust statistical inference.

### *Design and conduct of clinical studies*

Both trials were set up as Phase 3 open-label trials without a comparator, but including a double-blind placebo controlled 8-week withdrawal period in which patients would randomly be administered placebo for a duration of four weeks. Given that patients were allowed concomitant treatments, including those that may have had an effect on their body weight, this blinded withdrawal period was meant to ascertain that non-administration of setmelanotide would lead to weight gain in order to exclude the possibility that any weight losses seen would be purely due to causes unrelated to setmelanotide. The choice to not use a placebo control group was done for ethical considerations, as prior experience in the investigator led RM-493-011 trial had shown rapid weight losses in setmelanotide-treated POMC/LEPR deficiency obesity patients, and the fact that the number of known patients was very low and all of which have high unmet medical need and significant comorbidities due to their morbid obesity. Whereas the pivotal trial design is rather unconventional, the choice of a blinded withdrawal period was endorsed by the CHMP and considered adequately justified. The design of the pivotal studies gave the potential need to detangle the setmelanotide-effect on weight from all other potentially weigh-altering concomitant treatments that patients could be on during the trial. In the absence of available comparator, historical controls for bodyweight comparisons were used to support the efficacy evaluation. The choice of a historical 5% responder rate in the historical data was also chosen with a conservative approach. Historical data imply that in reality 0% of patients would show a 10% weight loss in 1 year, even with extreme measures. Still, the applicant assumed that a small proportion of patients (5%) might show 10% weight loss during a 1-year period. This choice was considered acceptable by the CHMP.

No dose finding studies had been undertaken and the choice of dosing was based on clinical observations made in the investigator-led RM-493-011 study and those in other indications currently under investigation (Bardet-Biedl and Ahlstrom syndrome related obesity).

The observationally informed choice of dosing regimen for the pivotal trials has methodological limitations and is not considered an optimal way of dose decision making. However, given the ultra-

rarity of the conditions and the particular pathophysiology which sets them apart from general obesity, it can be accepted that standard dose-finding approach has not been conducted due to lack of feasibility.

A maximal dose limit of 2.5 mg was initially imposed by some national competent authorities in their respective national centres, since at the time when the concerned test sites were inducted, there was no clinical experience with a dosing >2.5 mg Other sites remained at a potential maximal dose of 3.0 mg A protocol amendment was later accepted to allow this higher top dose, based on clinical experience. Despite more data collected with the upper dose of 2.5 mg which would thus logically become the upper dosing limit for the pivotal trials in absence of dose finding trials, an upper limit of 3.0 mg was implemented for the pivotal trials on direct request of another regulatory authority. Although the approach is not substantiated by the totality of the clinical data, the non-clinical data showed large safety margins, 150-fold higher than human exposure levels at this latter dose, thus indicating that this choice was likely safe and can thus be accepted.

Overall the choice of inclusion and exclusion criteria seems acceptable considering the objectives of the studies.

The CHMP agreed that strict adherence to the European guidelines on clinical evaluation of medicinal products used in weight management (EMA/CHMP/311805/2014) is not feasible as these conditions of obesity are different that than the general population of obese patients. Though most of the POMC/PCSK1/LEPR deficiency obesity patients will be of class II or III obesity, the limited availability of subjects would make it difficult to have a representative balanced sample of type I, II and III obesity subjects. Likewise, a separate analysis on the weight lowering effect and effect on glycaemic parameters for type 2 diabetes patients would generally not make sense in the studied populations as sub-analysis are statistically difficult given the extremely limited patient numbers.

The choice of primary and key secondary endpoints with regard to the weight loss thresholds were in accordance with the European guideline cited above. The applicant changed the primary endpoint from a mean change analysis to a proportional responder endpoint, while the pivotal trials were already ongoing. The rationale for this change was driven by the fact that the intended patient population may have represented a bimodal type, which would have potentially impacted sensitivity of the original primary endpoint. As such the choice to move towards a proportional endpoint is considered justified. As the mean-targeted endpoint was retained as a key secondary endpoint and given that both the original and new primary endpoints were met, the protocol amendment did not affect the validity of the results of the pivotal studies.

The choice of the DUS population for the evaluation of mean changes is valid given that the FAS population would include patients who do not meet the threshold for entering the blinded withdrawal phase and which could thus lead to a binomial distribution.

The primary analysis was performed on the pivotal patient sets, with separate analyses considering any supplemental patients and pooled pivotal + supplemental patients. If any supplemental patients had not yet achieved one year of treatment at the time of analysis, but had at least three months of treatment data available, then their missing 1-year data would be imputed using a linear model. Given the un-predictability of weight changes the choice of an LME imputation was considered questionable, but following a sensitivity analysis using an alternative LOCF imputation model it was shown that the choice of the former had not influenced the outcomes.

**Dosing recommendation in adult population**

Initially, the applicant proposed a simplified dosing regimen for the SmPC. The dosing schedule was not reflecting the titration schedule used in the pivotal trials. On the basis that patients with a deficient MC4R pathway may react strongly to the first introduction of setmelanotide, the recommended

setmelanotide dose for adults with POMC and LEPR deficiency obesity, as proposed by the applicant, was a starting dose of 2 mg subcutaneous injection QD, and if tolerated for 2 weeks, increase to 3 mg QD, aiming to achieve a normal BMI.

However, the CHMP noted that there was little evidence of safety concerns at doses up to 3 mg/day. In addition, the rapid weight loss seen during the trials was predominantly due to loss of fat, with no evidence of fluid loss or electrolyte disturbance. The higher recommended starting dose as used in the pivotal trials would possibly allow a quicker response to treatment and less patient and health care system burden.

Because the proposed simplified dosing regimen did not seem consistent with the clinical findings observed the pivotal trials, the CHMP considered the following recommendations:

- Since most adult patients reached a therapeutic dose higher than 1 mg and the safe profile of the product within the clinical dose range, it can be considered appropriate to forego 0.5 mg up-titration steps; the recommended initial starting dose is 1mg;

- For patient who did not reach TD at 2.0 mg to start with a dosing at 2.5 mg as this is the highest dose where more than 30% of patients in the pivotal trials reached their TD. The final up-titration to 3 mg should then only be used in those patients that still fail to see adequate weight control at a 2.5 mg dose.

The above revised dosing recommendation more realistically reflected the fact that only a minority of adult patients in the pivotal trials required a 3mg TD. Thus, a more granular final up-titration step (2.0 mg/2.5 mg/3mg), was recommended by the CHMP and implemented in section 4.2 of the SmPC by the applicant for the adult population to better reflect the clinical reality.

## *Efficacy data and additional analyses*

In POMC population and LEPR population the studies met the primary and key secondary endpoints. As those were single arm studies Historical controls were the same patients that were included in the two pivotal studies and not a cohort by its own. Based on this historical data, the median annual weight gain in those patients before entering the study was 5.6 kg and 6.7 kg in POMC and LEPR patients respectively. This is in contrast to the weight loss seen in the two studies. However, as changes in bodyweight are also age dependent, especially in children, such comparison should be considered relative rather than absolute.

The primary endpoint was met by the pivotal FAS cohort, the supplemental FAS cohort and the combined FAS cohort of the POMC/PCSK1 deficiency obesity patients, as more than 5% of all patients in each cohort achieved a 10% weight loss from baseline to W52 at a statistically significant level for both defined confidence levels, and the total amount of patients reaching this threshold was more than 35% of each individual and the pooled cohorts. Similarly, the LEPR patients also achieved these thresholds. See Table 7 and Table 12 for POMC/PCKS1 and LEPR populations, respectively. For both trials, sensitivity analyses using the pivotal DUS and CS populations confirmed success on all thresholds. Similarly, the key secondary endpoint of mean change at 52 weeks of treatment as measured in the DUS populations achieved both statistically significance versus a 0 null-hypothesis at an alpha of 0.05 and 0.025, and 35% of more of the subjects achieved an observed mean weight decrease of at least 10% versus baseline. See Table 8 and Table 13 for POMC/PCKS1 and LEPR populations, respectively.

Thus, overall both trials achieved both the primary endpoint and the closely related secondary mean weight change endpoint.

The first key secondary hunger-related endpoint (mean percent change in hunger from baseline to Week52 of treatment, as measured by the worst 'most hunger' in 24 hours) was met by both trial populations at all predefined confidence levels, as the mean percent change was both statistically significantly different form zero at both defined confidence levels and the observed mean hunger change exceeded the 25% threshold. Only data for pivotal patient cohorts were available. The second key secondary hunger endpoint was the proportion of subjects achieving at least 25% improvement in daily hunger from baseline at 52 weeks and was also met at both an alpha of 0.05 and of 0.025.

Other secondary and tertiary endpoints generally confirmed the primary and secondary outcomes. The decrease in BMI and the weight declines associated with setmelanotide were due to body fat loss, and not due to changes in bone density or lean body mass. Likewise, available energy expenditures were consistent with the weight loss effect of setmelanotide.

No formation of anti-setmelanotide antibodies was discovered and hence no causal influence on outcomes could be established. Three patients in the LEPR population developed anti-α-MSH antibodies, each at various discrete time points, with varying degrees of inhibitory potential, but no causal link to efficacy or safety observations could be made. Because the immunologic assays require further investigation, no definite conclusions can be drawn from these observations.

Long term data from both supportive (ongoing) studies are consistent with a maintenance of the effect of setmelanotide in both studied populations.

However, across the pivotal trials, the proportion of patients achieving a ≥10% weight loss from baseline was lower among those with LEPR than with POMC deficiency obesity (60% versus 86%, respectively using the FAS population). Among patients who did not meet the primary endpoint, PK data for 3 LEPR deficiency patients showed aberrant setmelanotide concentrations from approximately Visit 5 through Visit 12 leading to the suspicion that these patients were likely not taking study drug according to the prescribed regimen.

In supportive Investigator-sponsored Study RM-493-011, both of the POMC/PCSK1 deficiency patients lost at least 10% of body weight from screening to Visit 3 which is associated with approximately 3 months on study, while only one of the 3 LEPR deficiency patient lost at least 10% of body weight from screening to Visit 3.

Similarly, to the primary endpoint, the effect-size was far larger for the percentage change in individual body weight from baseline to Week 52 (%) (key secondary endpoint) in the POMC/PCSK1 deficiency patients than in the LEPR patient population, (mean ± SD) was -25.8% (±9.7) for POMC patients and -12.7% (±7.4) for LEPR deficiency obesity respectively using the DUS population). In the supportive RM-493-011 study similar outcomes were seen with mean decreases of -15% and -9% respectively among patients with POMC and LEPR deficiency at Month 3.

Differences in the overall weight-loss outcomes in the two pivotal trials could be explained by the fact that 3 patients in the LEPR-population had compliance issues (though there were two pivotal patients that had seemingly unexplainable less favourable responses to treatment) and 1 patient discontinued very early on in the study due to an AE. However, the same disparity of efficacy was replicated in the investigator-led supportive study (RM-493-011). The number of POMC and LEPR patients in study RM-493-011 was very low (n= 2 and 3 respectively) and thus it is not possible to clearly ascribe a causal effect to these findings. Nonetheless, seeing the difference in outcome scores repeated in two separate trials may indicate some process interfering in the efficacy of setmelanotide in LEPR patients. A likely explanation for this observation lays in the fact that in LEPR deficiency patients lose the ability to regulate both POMC and AGRP neurons, likely resulting in basal low levels of melanocortin tone. In addition, LEPR is expressed on other (non-melanocortin) neuronal populations both within the hypothalamus and in other areas involved in food reward such as the striatum and ventral tegmental

area. As such the hyperphagia and obesity in LEPR deficient patients is usually more severe than seen in POMC deficiency and is mediated by both melanocortin (setmelanotide-responsive) and melanocortin-independent (setmelanotide-unresponsive) pathways. This may explain the relatively less favourable weight outcomes experienced by these patients. Likewise, the patients' hunger feeling is relatively higher than that seen in POMC/PCSK1 subjects, meaning that similar changes therein would likely be subjectively experienced to a relatively larger degree.

The CHMP recognised that given the ultra-rarity of these genetic disorders, such finding cannot be further investigated in a clinical trial context. On the other hand, even though the performance in the LEPR population was markedly less than in the POMC/PCKS1 patients; overall patients still managed a respectable mean body weight change of -13% in a year of treatment. Moreover, patients that underwent the blinded withdrawal of setmelanotide did show a clear reversal of earlier weight loss gains, indicating that the product is having an overall positive effect in both populations. Interestingly, a reversed situation is observed for the percentage change in worst daily hunger score, with improvements in the LEPR patient population outpacing those in the POMC/PCSK1 population aged 12 years and above. The mean percent change from baseline to 52 weeks (mean ± SD) was -27.1% (±28.1) for POMC patients and -50.3% (±22.1) for LEPR deficiency obesity respectively using the DUS population). Proportion of patients achieving ≥25% improvement in worst hunger score was 50 % (n=4) for POMC patients and 78.6% (n=11) for LEPR deficiency obesity respectively using the FAS population. In contrast, in the investigator led study RM-493-011, better hunger management scores were reported for POMC patients (mean percent change from baseline (mean ± SD) to Month 3 in Hunger Score was -89.4% (±0.79) for POMC patients with POMC deficiency obesity and -64.1% (±17.44) for LEPR deficiency obesity patients) and thus no consistency on the hunger management scores is reported across the clinical studies. These findings across POMC and LEPR subgroups also remain to be elucidated.

In the supplemental cohort, the proportion of patients at 52 weeks achieving at least 10% weight loss compared to baseline was 85.7% and 60% in the POMC population and 60% in the LEPR population. In comparison, this was 80.0% and 45.5% in the pivotal population. The higher proportion meeting the endpoint in the supplemental cohort could be due to a shorter follow-up time and thereby lower number of patients not completing the study, as the change in bodyweight for those who withdraw from the study was set to 0 kg. However, as these patients were not part of the pivotal population, the CHMP considered that these findings did no impact on the benefit risk assessment in the intended patient population.

A total of three LEPR deficiency obesity patients were identified with mal-compliance issues, and several instances of mal-compliance were also noted in outpatient settings in Phase 2 PK/PD trials (see section 2.4.4). Additionally, the RM-493-022 extension trial included a number of POMC patients whom showed enormous weight spikes and subsequent falls suggestive of mal compliance, but not confirmed. No further information was made available to allow a proper investigation of these cases. Nevertheless, two categories of mal-/noncompliance were identified ie, patients who do not take the drug daily, as observed in the 2 LEPR patients (RM-493-011) and patients who take the drug in the evening before going to sleep rather than in the morning, as reported in 3 other LEPR patients (RM-493-015), likely resulted in the drug wearing off during the day and having minimal effect on hunger and weight loss. The variable pharmacokinetic (PK) profiles in the patients (RM-493-015) also suggested non-compliant dosing. In view of these findings potentially impacting on the efficacy of setmelanotide, the CHMP recommended to inform prescribers in 4.2 of SmPC that symptoms of POMC and LEPR deficiency obesity will return if compliance to the dosing regimen is not maintained.

### *Assessment of paediatric data on clinical efficacy*

There is currently a lack of clarity on the efficacy and safety outcomes in paediatric patients as no age-based sub-analysis was performed. Moreover, there is a tangible paucity of data in the 6-to-12-year-old age bracket, in particular for patients below the age of 11 years. This is however an issue that can be expected given the ultra-rare nature of the conditions under consideration. In clinical studies, 14 of the patients treated with setmelanotide were aged 6 to 17 years at baseline. Overall, efficacy and safety in these younger patients were similar to older patients studied. Clinically significant decreases in BMI were demonstrated. In patients who had not yet completed their growth, appropriate progression in pubertal development and increases in height were observed during the study period.

Given that POMC/LEPR-deficiency obesity is an ultra-rare condition with a high unmet medical need, which warrants treatment as early as possible, it can be accepted that in relation to the sought indication, data is available for a mere 3 patients aged between 6 and 10 years of age. The CHMP noted that the number of paediatric patients included were in line with the current PIP requirement of at least one patient in the 6-12-years age category. The applicant proposed to capture Tanner scores, bone age x-ray results and to perform a 6-12-years subgroup analysis as part of the proposed registry. This is in line with the CHMP recommendation to collect further long-term data.

With regard to data for patients below 6 years, the pivotal trial intended to recruit at least one patient <6 years was terminated without such a patient having been recruited. Instead, the applicant informed that a new protocol for this very young age group will be initiated as part of PIP modification. Since this age group is not included in the proposed indication, the CHMP recommended to provide the final study report for the planned paediatric study in patients aged 2 to <6 years of age, once available.

**Dosing recommendation in paediatric population**

A POPPK modelling was conducted to overcome the data paucity and support the proposed dosing recommendation in the paediatric population. Based on these data, the applicant suggested a flat dosing recommendation. However, the POPPK modelling did indicate that age and weight were important co-variates and that a weight-based dosing approach may be more appropriate in children. In addition, upon CHMP request for further validation of the POPPK model, it was found that the POPPK modelling was unable to properly describe the PK characteristics in this group. Given the sparsity of data and inherent issues thereof it was considered that dose extrapolation towards these young children could not be supported by the submitted data on POPPK modelling. As such, the CHMP recommended that the posology in the intended paediatric age range (6-12 years) should rely on the available clinical data. The CHMP thus did not recommend the proposed maximal dosing of 3 mg daily in this age bracket since no such doses were administered in the pivotal clinical trials. The upper limit of dosing in patients aged between 6 and 12 years of age should be limited to the highest dose used in the trials, which is 2.5 mg daily. By analogy to the proposed posology in adults, a granular final up-titration step was recommended by the CHMP (1 mg/2 mg/2.5 mg) with an initial starting dose of 0.5 mg or 1mg dose and implemented in section 4.2 of the SmPC by the applicant for the paediatric population to better reflect the clinical reality.

## 2.5.4. Conclusions on the clinical efficacy

The CHMP concluded that the efficacy of setmelanotide was demonstrated in patients with bi-allelic mutations of POMC/PCKS1 and LEPR deficiency obesity genes in the proposed dosing regimens for adult and paediatric (6-18 years) population.

## 2.6. Clinical safety

During the procedure, the CHMP raised concerns over the presentation of the safety data. Updated summaries of clinical safety were submitted with a common data cut off (10 November 2020).

The safety dataset comprises:

- All ongoing and completed studies from the clinical development programme to support the intended population (POMC and LEPR deficiency). These included healthy adult obese subjects, paediatric and adult patients with POMC or LEPR deficiencies obesity and adult patients with Prader Willi Syndrome (RM-493-010). See Tabular overview of the clinical studies with some studies being conducted in broader population of various genetic disorders (RM-493-011, RM-493-014, RM-493-0122); see 2.4.1 Tabular overview of the clinical studies

- Completed study RM-493-019, US Expanded Access for the use of setmelanotide in a single patient with partial lipodystrophy associated with leptin deficiency and multiple autoimmune diseases;

- Ongoing study, RM-493-023, a phase III trial in Bardet Biedl syndrome and Alström Syndrome patients with moderate to severe obesity.

When relevant, data on RM-493-023 are presented separately as "blinded group" since the study is still ongoing.

### Patient exposure

The overall extent of exposure by study number and duration of treatment is shown in Table 18.

**Table 18 Overall Extent of Exposure in the Setmelanotide Clinical Development Programme (cut off November 2020)**

| | Duration of Exposure to Setmelanotide (Months) | | | | |
|---|---|---|---|---|---|
| **Study Number** | **<1** | **1 to <6** | **6 to <12** | **≥12** | **Total** |
| RM-493-001 | 32 | 0 | 0 | 0 | 32 |
| RM-493-002 | 39 | 0 | 0 | 0 | 39 |
| RM-493-003 | 6 | 31 | 0 | 0 | 37 |
| RM-493-006 | 12 | 0 | 0 | 0 | 12 |
| RM-493-008 | 20 | 0 | 0 | 0 | 20 |
| RM-493-009 | 8 | 51 | 0 | 0 | 59 |
| RM-493-010 | 14 | 25 | 0 | 0 | 39 |
| RM-493-011 | 0 | 3 | 3 | 6 | 12 |
| RM-493-012 | 0 | 2 | 1 | 12 | 15 |
| RM-493-014 | 51 | 60 | 14 | 26 | 151 |
| RM-493-015 | 0 | 1 | 3 | 11 | 15 |
| RM-493-019 | 0 | 1 | 0 | 0 | 1 |
| RM-493-026 | 8 | 21 | 0 | 0 | 29 |
| RM-493-029 | 15 | 0 | 0 | 0 | 15 |
| Total | 205 | 195 | 21 | 55 | 476 |

As of 10 November 2020, a total of 476 subjects are known to have been exposed to at least 1 dose of setmelanotide, with 52 subjects exposed to blinded study drug (either setmelanotide or placebo) in an ongoing, blinded setmelanotide clinical study (RM-493-023).

Of the 476 subjects known to be exposed to setmelanotide, 228 were healthy obese subjects and 233 were patients with genetic forms of obesity. Of these latter 233 patients, a total of 35 had LEPR or POMC/PCSK1 deficiency obesity. Fifteen subjects were either healthy volunteers or subjects with renal impaired function (RM-493-029).

The overall extent of setmelanotide exposure by duration of treatment is shown in Table 19. The median time on treatment was 54 days, with a wide range of 1 to 1,970 days (64.6 months). A total of 76 (16%) patients received setmelanotide for at least 6 months, with 55 (12%) receiving setmelanotide for at least 1 year.

**Table 19 Overall Extent of Exposure in the Setmelanotide Clinical Development Program**

| **Parameter / Statistic** | **All Setmelanotide Treated Patients (N=476)** |
|---|---|
| Time on Treatment (days) | |
| n | 476 |
| Mean | 144.5 |
| SD | 278.94 |
| Median | 54.0 |
| Min, Max | 1, 1,970 |
| Duration of Exposure, n (%) | |
| <1 month | 205 (43.1) |
| 1 to <3 months | 151 (31.7) |
| 3 to <6 months | 44 (9.2) |
| 6 to <12 months | 21 (4.4) |
| 12 to <18 months | 12 (2.5) |
| ≥18 months | 43 (9.0) |

A total of 80 patients opted to continue setmelanotide treatment in an extension Study (RM-493-022), including 12 of 15 patients with POMC/PCSK1 deficiency obesity who completed pivotal index Study RM-493-012 and 12 of 15 patients with LEPR deficiency obesity who completed pivotal index Study RM-493-015. All exposures in RM-493-022 are presented in Table 20 within the relevant index studies.

**Table 20 Overall Extent of Exposure in the Setmelanotide Clinical Development Program**

| Study Number | Duration of Exposure to Setmelanotide (Months) | | | | |
|---|---|---|---|---|---|
| | <1 | 1 to <6 | 6 to <12 | ≥12 | Total |
| RM-493-001 | 32 | 0 | 0 | 0 | 32 |
| RM-493-002 | 39 | 0 | 0 | 0 | 39 |
| RM-493-003 | 6 | 31 | 0 | 0 | 37 |
| RM-493-006 | 12 | 0 | 0 | 0 | 12 |
| RM-493-008 | 20 | 0 | 0 | 0 | 20 |
| RM-493-009 | 8 | 51 | 0 | 0 | 59 |
| RM-493-010 | 14 | 25 | 0 | 0 | 39 |
| RM-493-011 | 0 | 3 | 3 | 6 | 12 |
| RM-493-012 | 0 | 2 | 1 | 12 | 15 |
| RM-493-014 | 51 | 60 | 14 | 26 | 151 |
| RM-493-015 | 0 | 1 | 3 | 11 | 15 |
| RM-493-019 | 0 | 1 | 0 | 0 | 1 |
| RM-493-026 | 8 | 21 | 0 | 0 | 29 |
| RM-493-029 | 15 | 0 | 0 | 0 | 15 |
| Total | 205 | 195 | 21 | 55 | 476 |

## *Adverse events*

As of 10 November 2020, the most common (i.e., incidence >10%) TEAEs among setmelanotide-treated patients in the setmelanotide are presented in Table 21.

**Table 21 Most Common (i.e., Incidence >10%) Treatment-Emergent Adverse Events among Setmelanotide-treated Patients in the Setmelanotide Clinical Program through 10 November 2020 (N=476), by MedDRA Preferred Term**

| Preferred Term | Setmelanotide (N=476) n (%) | Placebo (N=110) n (%) | Blinded (N=52) n (%) |
|---|---|---|---|
| Patients with at Least 1 TEAE | 426 (89.5) | 68 (61.8) | 51 (98.1) |
| Skin hyperpigmentation | 229 (48.1) | 5 (4.5) | 27 (51.9) |
| Nausea | 157 (33.0) | 9 (8.2) | 17 (32.7) |
| Headache | 125 (26.3) | 16 (14.5) | 11 (21.2) |
| Injection site erythema | 114 (23.9) | 11 (10.0) | 21 (40.4) |
| Injection site pruritus | 83 (17.4) | 1 (0.9) | 16 (30.8) |
| Vomiting | 59 (12.4) | 5 (4.5) | 14 (26.9) |
| Diarrhoea | 51 (10.7) | 4 (3.6) | 9 (17.3) |
| Fatigue | 51 (10.7) | 3 (2.7) | 6 (11.5) |
| Injection site induration | 51 (10.7) | 4 (3.6) | 12 (23.1) |
| Injection site pain | 49 (10.3) | 4 (3.6) | 13 (25.0) |

TEAEs occurring in >2% of setmelanotide-treated patients in the setmelanotide clinical program are summarized in Table 22.

**Table 22 Treatment-Emergent Adverse Events Occurring in >2% of Setmelanotide treated Patients in the Setmelanotide Clinical Program through 10 November 2020 (N=476), by MedDRA SOC and Preferred Term**

| System Organ Class/ Preferred Term | Setmelanotide (N=476) n (%) | Placebo (N=110) n (%) | Blinded (N=52) n (%) |
|---|---|---|---|
| Patients with at Least 1 TEAE | 426 (89.5) | 68 (61.8) | 51 (98.1) |
| Skin and subcutaneous tissue disorders | 265 (55.7) | 14 (12.7) | 33 (63.5) |
| Skin hyperpigmentation | 229 (48.1) | 5 (4.5) | 27 (51.9) |
| Dry skin | 18 (3.8) | 2 (1.8) | 3 (5.8) |
| Pruritus | 17 (3.6) | 1 (0.9) | 2 (3.8) |
| Skin lesion | 10 (2.1) | 0 | 1 (1.9) |
| Alopecia | 10 (2.1) | 0 | 0 |
| Skin discolouration | 10 (2.1) | 0 | 0 |

| | | | |
|---|---|---|---|
| General disorders and administration site conditions | 236 (49.6) | 29 (26.4) | 35 (67.3) |
| Injection site erythema | 114 (23.9) | 11 (10.0) | 21 (40.4) |
| Injection site pruritus | 83 (17.4) | 1 (0.9) | 16 (30.8) |
| Fatigue | 51 (10.7) | 3 (2.7) | 6 (11.5) |
| Injection site induration | 51 (10.7) | 4 (3.6) | 12 (23.1) |
| Injection site pain | 49 (10.3) | 4 (3.6) | 13 (25.0) |
| Injection site oedema | 43 (9.0) | 1 (0.9) | 5 (9.6) |
| Injection site bruising | 36 (7.6) | 2 (1.8) | 16 (30.8) |
| Injection site reaction | 14 (2.9) | 0 | 4 (7.7) |
| Asthenia | 12 (2.5) | 0 | 2 (3.8) |
| Influenza like illness | 10 (2.1) | 0 | 1 (1.9) |
| Gastrointestinal disorders | 226 (47.5) | 25 (22.7) | 34 (65.4) |
| Nausea | 157 (33.0) | 9 (8.2) | 17 (32.7) |
| Vomiting | 59 (12.4) | 5 (4.5) | 14 (26.9) |
| Diarrhoea | 51 (10.7) | 4 (3.6) | 9 (17.3) |
| Abdominal pain | 23 (4.8) | 4 (3.6) | 4 (7.7) |
| Abdominal pain upper | 21 (4.4) | 0 | 3 (5.8) |
| Dry mouth | 16 (3.4) | 2 (1.8) | 0 |
| Dyspepsia | 13 (2.7) | 0 | 0 |
| Constipation | 11 (2.3) | 4 (3.6) | 2 (3.8) |
| Gastrooesophageal reflux disease | 11 (2.3) | 1 (0.9) | 2 (3.8) |
| Nervous system disorders | 156 (32.8) | 23 (20.9) | 15 (28.8) |
| Headache | 125 (26.3) | 16 (14.5) | 11 (21.2) |
| Dizziness | 21 (4.4) | 1 (0.9) | 4 (7.7) |
| Infections and infestations | 107 (22.5) | 24 (21.8) | 22 (42.3) |
| Upper respiratory tract infection | 24 (5.0) | 13 (11.8) | 3 (5.8) |
| Nasopharyngitis | 21 (4.4) | 0 | 4 (7.7) |
| Gastroenteritis | 11 (2.3) | 2 (1.8) | 1 (1.9) |
| Musculoskeletal and connective tissue disorders | 84 (17.6) | 10 (9.1) | 11 (21.2) |
| Back pain | 32 (6.7) | 1 (0.9) | 4 (7.7) |
| Arthralgia | 20 (4.2) | 0 | 3 (5.8) |
| Pain in extremity | 19 (4.0) | 2 (1.8) | 2 (3.8) |
| Muscle spasms | 11 (2.3) | 1 (0.9) | 1 (1.9) |
| Reproductive system and breast disorders | 80 (16.8) | 5 (4.5) | 6 (11.5) |
| Spontaneous penile erection | 36 (7.6) | 2 (1.8) | 2 (3.8) |
| Erection increased | 13 (2.7) | 0 | 0 |

| | | | |
|---|---|---|---|
| Psychiatric disorders | 74 (15.5) | 0 | 6 (11.5) |
| Insomnia | 20 (4.2) | 0 | 1 (1.9) |
| Disturbance in sexual arousal | 10 (2.1) | 0 | 1 (1.9) |
| Anxiety | 10 (2.1) | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | 52 (10.9) | 7 (6.4) | 12 (23.1) |
| Cough | 13 (2.7) | 0 | 4 (7.7) |
| Rhinorrhoea | 10 (2.1) | 1 (0.9) | 3 (5.8) |
| Metabolism and nutrition disorders | 55 (11.6) | 6 (5.5) | 9 (17.3) |
| Decreased appetite | 40 (8.4) | 3 (2.7) | 2 (3.8) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 43 (9.0) | 1 (0.9) | 3 (5.8) |
| Melanocytic naevus | 33 (6.9) | 1 (0.9) | 1 (1.9) |

Note: TEAE = Treatment-Emergent Adverse Event. The blinded data up to the data cutoff date were summarized under the 'Blinded' group.
Note: Uncoded TEAEs are not presented.

The relationship of TEAEs to study drug was determined by the Investigator. A summary of treatment-related TEAEs, based on the Investigator's assessment, occurring in >2% of setmelanotide-treated patients is presented in Table 23.

**Table 23 Treatment-related Treatment-Emergent Adverse Events Occurring in >2% of Setmelanotide-treated Patients in the Setmelanotide Clinical Program through 10 November 2020 (N=493), by MedDRA SOC and Preferred Term**

| **System Organ Class/ Preferred Term** | **Setmelanotide (N=476) n (%)** | **Placebo (N=110) n (%)** | **Blinded (N=52) n (%)** |
|---|---|---|---|
| Patients with at Least 1 TEAE | 381 (80.0) | 37 (33.6) | 49 (94.2) |
| Skin and subcutaneous tissue disorders | 253 (53.2) | 6 (5.5) | 30 (57.7) |
| Hyperpigmentation disorders | 236 (49.6) | 5 (4.5) | 28 (53.8) |
| Pruritus | 11 (2.3) | 0 | 0 |
| General disorders and administration site conditions | 210 (44.1) | 18 (16.4) | 32 (61.5) |
| Injection site reactions (Rhythm grouped term) | 176 (37.0) | 12 (10.9) | 32 (61.5) |
| Fatigue | 41 (8.6) | 2 (1.8) | 5 (9.6) |
| Asthenia | 10 (2.1) | 0 | 1 (1.9) |
| Gastrointestinal disorders | 181 (38.0) | 10 (9.1) | 20 (38.5) |
| Nausea | 137 (28.8) | 2 (1.8) | 11 (21.2) |
| Vomiting | 45 (9.5) | 1 (0.9) | 8 (15.4) |
| Diarrhoea | 27 (5.7) | 1 (0.9) | 5 (9.6) |
| Dry mouth | 14 (2.9) | 2 (1.8) | 0 |
| Abdominal pain (Rhythm grouped term) | 22 (4.6) | 2 (1.8) | 3 (5.8) |

| | | | |
|---|---|---|---|
| Nervous system disorders | 109 (22.9) | 9 (8.2) | 9 (17.3) |
| Headache | 91 (19.1) | 6 (5.5) | 4 (7.7) |
| Dizziness | 13 (2.7) | 0 | 1 (1.9) |
| Reproductive system and breast disorders | 70 (14.7) | 2 (1.8) | 3 (5.8) |
| Disturbance in sexual arousal (Rhythm grouped term) | 60 (12.6) | 2 (1.8) | 2 (3.8) |
| Metabolism and nutrition disorders | 44 (9.2) | 5 (4.5) | 2 (3.8) |
| Decreased appetite | 40 (8.4) | 3 (2.7) | 1 (1.9) |
| Psychiatric disorders | 46 (9.7) | 0 | 3 (5.8) |
| Insomnia | 13 (2.7) | 0 | 0 |
| Disturbance in sexual arousal (Rhythm grouped term) | 15 (3.2) | 0 | 1 (1.9) |
| Musculoskeletal and connective tissue disorders | 29 (6.1) | 4 (3.6) | 4 (7.7) |
| Back pain | 11 (2.3) | 0 | 1 (1.9) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 29 (6.1) | 0 | 1 (1.9) |
| Hyperpigmentation disorders (Rhythm Grouped Term) | 24 (5.0) | 0 | 1 (1.9) |

Note: TEAE = Treatment-Emergent Adverse Event. The blinded data up to the data cut-off date were summarized under the 'Blinded' group.

## *Events of Special Interest (ESI)*

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

**Hyperpigmentation Disorders**

Approximately half (51% [244/476]) of setmelanotide-treated patients experienced a hyperpigmentation disorder, most commonly skin hyperpigmentation (48% [229/476]) and melanocytic naevus (7% [34/476]). Other hyperpigmentation disorders events were less commonly reported, including skin discoloration (2% [10/476]) and ephelides (1% [5/476]). All other hyperpigmentation disorders were reported for <1% of setmelanotide-treated patients. These events were expected due to the effect of the MC1R mechanism during treatment with an MC4R agonist such as setmelanotide.

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%). Twelve (3%) patients discontinued setmelanotide due to a hyperpigmentation disorder.

Hyperpigmentation disorders typically presented 2 to 3 weeks after initiation of setmelanotide treatment and remained ongoing during treatment. The onset of hyperpigmentation disorders was much less common later in treatment, particularly beyond treatment Month 6. Examination of the time of onset of hyperpigmentation disorders in the intended treatment population, in which most (89% [31/35]) patients received treatment for ≥6 months, suggest a similar pattern than that of the overall setmelanotide-treated population that included healthy obese subjects who received setmelanotide for a short duration, with 55% (125/228) receiving treatment for <1 month.

In pivotal Studies RM-493-012 and RM-493-015, melanin content measurements and skin color measurements were performed as a sub-study. Melanin content measurements were taken at 3 distinct body locations, central forehead, right upper buttock, and zygomatic process. Findings showed that mean melanin measurements increased in all 3 areas during treatment without an obvious relationship to sun exposure. However, a wide variability in measurements was seen in the relatively small number of patients who participated in the sub-study (N=22), precluding any firm conclusions to be drawn. Of note, no case of melanoma has been observed among setmelanotide-treated patients.

**Sexual events**

Overall, 72 (15%) of 476 setmelanotide-treated patients experienced a sexual disorder, most commonly spontaneous penile erection (8% [36/476]), erection increased (3% [13/476]), and disturbance in sexual arousal (2% [10/476]). Other sexual disorders reported occurred in <1% of setmelanotide-treated patients overall.

When only male patients are considered (N=193), the incidence of penile erection, erection increased, and ejaculation disorder was 19%, 7%, and <1%, respectively. None of these patients reported prolonged erections (greater than 4 hours) requiring urgent medical evaluation. When only female patients are considered (N=283), the incidence of disturbance in sexual arousal, female sexual arousal disorder, and libido increased was 4%, 1%, and 1%, respectively.

All sexual events were mild or moderate in intensity and non-serious. Four (<1%) patients each required a setmelanotide dose interruption due to a disturbance in sexual arousal. Disturbances in sexual arousal led to setmelanotide discontinuation for 2 (<1%) setmelanotide-treated patients.

Disturbances in sexual arousal typically presented within the first month after initiation of setmelanotide treatment. The onset of disturbances in sexual arousal was much less common later in treatment, particularly beyond treatment Month 2.

**Hypertension**

Six (1%) of 476 setmelanotide-treated patients experienced a hypertension event, with all such events being non-severe and non-serious. One (<1%) patient required a setmelanotide interruption because of a hypertension event; however, no patient discontinued setmelanotide because of such events. The patient requiring a dose interruption due to hypertension had Prader-Willi syndrome, a patient population in which hypertension is commonly seen.

Across patient populations, the incidence of hypertension was 3% (1/35), 2% (4/233), and <1% (2/228) among those with POMC/PCSK1 or LEPR deficiency obesity, other forms of genetic obesity, and healthy obese subjects.

**Depression**

Overall, 3% (15/476) of patients experienced a depression event, including depression (2% [9/476]) and depressed mood (2% [7/476]). (One patient experienced the events of both depressed mood and depression.) The depression event was severe for 4 patients, and serious for 1 patient. One (<1%) patient each required a setmelanotide dose reduction or discontinued setmelanotide due to a

depression event.

Although the number of patients in the intended treatment population is smaller, the incidence of depression events was higher in the population of patients with LEPR or POMC/PCSK1 deficiency obesity (26% [9/35]) than in the overall population of patients with genetic forms of obesity or healthy obese subjects (5% [11/233] and 2% [4/228], respectively). However, the duration of setmelanotide exposure was notably shorter in healthy obese subjects than in patients with LEPR or POMC/PCSK1 deficiency obesity or other genetic forms of obesity.

In the POMC/LEPR population, no overall worsening in depressive symptoms during setmelanotide treatment was evident based on review of available questionnaire data (including PHQ-9).

Regarding the use of antidepressants in the POMC/LEPR population, one patient received antidepressant therapy prior to initiating setmelanotide; the patient's antidepressant medication doses remained stable during setmelanotide treatment. Furthermore, 2 patients, both with relevant medical history (depression/behavioural disorder with suicidal ideation), initiated antidepressant medication during setmelanotide treatment.

**Suicidal Ideation**

A total of 4 setmelanotide-treated patients, 1 with POMC (study RM-493-012) and 3 with LEPR deficiency obesity (study RM-493-012) experienced suicidal ideation during setmelanotide treatment. In all 4 patients, the suicidal ideation during treatment occurred in conjunction with depression, and for 1 patient, the event was assessed as SAE, unrelated to treatment.

Based on C-SSRS scores in Studies RM-493-012 and RM-493-015, there is no evidence of progression or worsening to suggest that setmelanotide causes suicidal ideation or behaviour.

One additional patient (Study RM-493-023) experienced suicidal ideation, with this event assessed as serious. Thus, suicidal ideation was serious for 2 patients, of whom 1 was known to be treated with setmelanotide. No healthy obese subject experienced suicidal ideation.

**Nausea and Vomiting**

Overall, 33% (157/476) of patients experienced nausea, with the incidence of vomiting being lower (12% [59/476]). For most patients, nausea and vomiting were mild or moderate in intensity, and all cases were non-serious.

Three (<1%) of 476 patients each experienced severe nausea and vomiting. A total of 2% (8/476) and 2% (9/476) required a setmelanotide interruption due to nausea and vomiting, respectively. Furthermore, 2% (11/476) and 2% (8/476) of patients permanently discontinued setmelanotide due to nausea and vomiting, respectively, making these events the most common TEAEs leading to setmelanotide discontinuation.

Although the total number of setmelanotide-treated patients was smaller than in other populations, the incidence of nausea and vomiting was higher in the population of patients with LEPR or POMC/PCSK1 deficiency obesity (57% [20/35] and 29% [10/35], respectively) than in the overall population of patients with genetic forms of obesity (32% [74/233] and 12% [29/233], respectively) or healthy obese subjects (35% [79/228] and 12% [27/228], respectively). The higher incidence of nausea and vomiting in the indicated population may be reflective of the study designs, which included a setmelanotide dose titration period followed by a placebo withdrawal period before resumption of setmelanotide.

Onset of nausea and vomiting events among all setmelanotide-treated patients showed that the onset was found most common in the first month of setmelanotide treatment. The onset of nausea and vomiting was much less common later in treatment, particularly beyond treatment Month 6.

**Injection Site Reactions**

Overall, 39% (184/476) and 11% (12/110) of setmelanotide- and placebo-treated patients, respectively, experienced at least 1 TEAE representative of an injection site reactions (ISRs). Overall, the most common ISRs were injection site erythema (24% [114/476]), injection site pruritus (17% [83/476]), injection site induration (11% [51/476]), and injection site pain (10% [49/476]); all other ISRs occurred at an incidence <10%. All ISRs were mild or moderate in intensity and non-serious. Overall, <1% (4/476) and <1% (2/276) of patients required a setmelanotide dose interruption or discontinued setmelanotide, respectively, due to an injection site reaction.

ISRs were most commonly experienced within the first month after initiation of setmelanotide treatment. The incidence of ISRs was notably lower after the first month of treatment, with a relatively small number of ISRs occurring with setmelanotide administration in Month 5 and beyond.

Overall, 920 unique ISRs AE are included in the safety data across studies. Of these, 201 had either no end time or date recorded. Approximately three-fourths (77% [155/201]) were reported in ongoing setmelanotide clinical studies and may have an outcome date later on reported.

Seven (<1%) of the 920 ISRs reported across all studies resulted in temporary interruptions of setmelanotide administration. No ISRs TEAEs resulting in temporary interruptions of treatment were reported among patients with LEPR or POMC deficiency obesity.

## *Serious adverse event/deaths/other significant events*

There was one death reported in study RM-493-015. The cause of the death was a result of injuries sustained as a passenger in an automobile accident. This event occurred after participation in the study for approximately 36 weeks (Day 251) and was considered unrelated to study drug by the investigator.

SAE are presented in Table 24.

**Table 24: Serious Adverse Events in the Setmelanotide Clinical Program through 10 November 2020, by MedDRA SOC and Preferred Term**

| System Organ Class/ Preferred Term | Setmelanotide (N=476) n (%) | Placebo (N=110) n (%) | Blinded (N=52) n (%) |
|---|---|---|---|
| Patients with at Least 1 SAE | 24 (5.0) | 3 (2.7) | 2 (3.8) |
| Psychiatric disorders | 5 (1.1) | 0 | 1 (1.9) |
| Suicidal ideation | 1 (0.2) | 0 | 1 (1.9) |
| Depression | 1 (0.2) | 0 | 0 |
| Hallucination, auditory | 1 (0.2) | 0 | 0 |
| Major depression | 1 (0.2) | 0 | 0 |
| Panic attack | 1 (0.2) | 0 | 0 |

| | | | |
|---|---|---|---|
| Gastrointestinal disorders | 4 (0.8) | 0 | 0 |
| Pancreatitis | 2 (0.4) | 0 | 0 |
| Enteritis | 1 (0.2) | 0 | 0 |
| Melaena | 1 (0.2) | 0 | 0 |
| Infections and infestations | 2 (0.4) | 1 (0.9) | 0 |
| Diverticulitis | 0 | 1 (0.9) | 0 |
| Pelvic inflammatory disease | 0 | 1 (0.9) | 0 |
| Pneumonia | 1 (0.2) | 0 | 0 |
| Rotavirus infection | 1 (0.2) | 0 | 0 |
| Injury, poisoning and procedural complications | 2 (0.4) | 1 (0.9) | 0 |
| Muscle strain | 0 | 1 (0.9) | 0 |
| Road traffic accident | 1 (0.2) | 0 | 0 |
| Vaccination complication | 1 (0.2) | 0 | 0 |
| Metabolism and nutrition disorders | 3 (0.6) | 0 | 0 |
| Hypoglycaemia | 2 (0.4) | 0 | 0 |
| Diabetic ketoacidosis | 1 (0.2) | 0 | 0 |
| Hepatobiliary disorders | 1 (0.2) | 1 (0.9) | 0 |
| Biliary dyskinesia | 0 | 1 (0.9) | 0 |
| Cholecystitis | 1 (0.2) | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 2 (0.4) | 0 | 0 |
| Endometrial cancer stage I | 1 (0.2) | 0 | 0 |
| Melanocytic naevus | 1 (0.2) | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | 2 (0.4) | 0 | 0 |
| Pleurisy | 1 (0.2) | 0 | 0 |
| Pulmonary embolism | 1 (0.2) | 0 | 0 |
| Surgical and medical procedures | 2 (0.4) | 0 | 0 |
| Cholecystectomy | 1 (0.2) | 0 | 0 |
| Gastric banding reversal | 1 (0.2) | 0 | 0 |
| Cardiac disorders | 1 (0.2) | 0 | 0 |
| Acute myocardial infarction | 1 (0.2) | 0 | 0 |
| Endocrine disorders | 1 (0.2) | 0 | 0 |
| Adrenocortical insufficiency acute | 1 (0.2) | 0 | 0 |
| Eye disorders | 0 | 0 | 1 (1.9) |
| Blindness | 0 | 0 | 1 (1.9) |
| General disorders and administration site conditions | 1 (0.2) | 0 | 0 |
| Chest pain | 1 (0.2) | 0 | 0 |
| Immune system disorders | 0 | 0 | 1 (1.9) |
| Anaphylactic reaction | 0 | 0 | 1 (1.9) |

| | | | |
|---|---|---|---|
| Nervous system disorders | 1 (0.2) | 0 | 0 |
| Hypoaesthesia | 1 (0.2) | 0 | 0 |
| Pregnancy, puerperium and perinatal conditions | 1 (0.2) | 0 | 0 |
| Pregnancy | 1 (0.2) | 0 | 0 |

Note: TEAE = Treatment-Emergent Adverse Event. The blinded data up to the data cutoff date were summarized under the 'Blinded' group.
Uncoded TEAEs are not presented.

Treatment related SAE are presented in Table 25.

**Table 25 Treatment-related Serious Adverse Events in the Setmelanotide Clinical Program through 10 November 2020, by MedDRA SOC and Preferred Term**

| System Organ Class/ Preferred Term | Setmelanotide (N=476) n (%) | Placebo (N=110) n (%) | Blinded (N=52) n (%) |
|---|---|---|---|
| Patients with at Least 1 Treatment-related SAE | 2 (0.4) | 1 (0.9) | 1 (1.9) |
| General disorders and administration site conditions | 1 (0.2) | 0 | 0 |
| Chest pain | 1 (0.2) | 0 | 0 |
| Hepatobiliary disorders | 0 | 1 (0.9) | 0 |
| Biliary dyskinesia | 0 | 1 (0.9) | 0 |
| Immune system disorders | 0 | 0 | 1 (1.9) |
| Anaphylactic reaction | 0 | 0 | 1 (1.9)[1] |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 (0.2) | 0 | 0 |
| Endometrial cancer stage I | 1 (0.2) | 0 | 0 |

Note: TEAE = Treatment-Emergent Adverse Event. The blinded data up to the data cutoff date were summarized under the 'Blinded' group.
[1] The treatment assignment was unblinded for this patient, who was assigned to placebo; thus, this event is unrelated to setmelanotide.

Across the pivotal studies and supportive study RM-493-011, none of the SAEs were considered related to setmelanotide treatment and no patients discontinued therapy due to an SAE. Depression was the only SAE reported by more than 1 patient (n=3). There was 1 SAE of cholecystitis and another of cholecystectomy in the index studies RM-493-011 and RM-493-015, respectively, both occurring in POMC patients. In studies RM-493-012 and 014 The SAEs reported in studies 022 and 014 were all considered unrelated to study drug. In RM-493-014, one patient in study had 2 separate SAEs: an acute myocardial infarction and a gastrointestinal haemorrhage, and 1 patient had one SAE (enteritis). Generally, information on these cases did not allow to establish a causal association with setmelanotide.

## *Laboratory findings*

Overall, 4% (21/476) of setmelanotide-treated patients had a blood and lymphatic system disorder reported as a TEAE, including anemia (9 patients; 2%), eosinophilia (3 patients; <1%), and

leukocytosis, and neutropenia (each 1 patient; <1%). One (<1%) patient each also had iron deficiency anemia, coagulopathy, lymphadenopathy, and microcytic anemia reported as a TEAE.

Within the Investigations SOC, 1 (<1%) patient had neutrophil count increased reported as a TEAE. Of these events, all 3 cases of eosinophilia and 1 case of anemia were considered by the Investigator to be setmelanotide-related.

All of these events were non-serious, and, with the exception of 1 case of severe anemia, all were mild or moderate in intensity. Three (<1%) had setmelanotide interrupted due to a hematologic TEAE, anemia in 2 (<1%) patients and eosinophilia in 1 (<1%) patient. One (<1%) of 476 patients discontinued setmelanotide due to a hematologic TEAE, eosinophilia.

Hypoglycaemia was the most commonly reported clinical chemistry TEAE (4 patients; <1%). One (<1%) patient each reported hypercholesterolemia, hyperglycemia, hypertriglyceridemia, hyponatremia, and hypophosphatemia. Within the Investigations SOC, clinical chemistry test abnormalities reported as TEAEs included blood creatine phosphokinase increased (6 patients (including 2 healthy obese subjects and 4 with genetic forms of obesity); 1%) and alanine aminotransferase increased (2 patients; <1%); all other clinical chemistry test abnormalities were reported as TEAEs for 1 (<1%) patient only. Clinical chemistry TEAEs that were considered by the investigator to be setmelanotide-related included blood creatine phosphokinase increased (2 patients; <1%) and blood bilirubin increased, blood uric acid increased, hypoglycemia, and gamma-glutamyl transferase increased (each 1 patient; <1%). All of these events were non-serious, and most were mild or moderate in intensity.

Additionally, 1 LEPR patient experienced renal failure on day 16 of treatment (during titration period at the 1.5-mg dose) and considered by the investigator to be setmelanotide-related. This event was assessed by the Investigator as mild, Grade 1 and resolved w/o sequelae or additional treatment needs and did not require hospitalization; and was assessed as non-serious. One other patient in extension Study RM-493-022 experienced "chronic kidney disease stage 3" on Day 142, and this event was considered unrelated to setmelanotide by the investigator.

Severe clinical chemistry TEAEs included hypoglycaemia (2 patients; <1%) and 1 case each of blood creatinine phosphokinase increased, blood phosphorus increased, and hypertriglyceridemia. Clinical chemistry TEAEs leading to study drug interruption, each in 1 patient, included blood calcium decreased, blood creatine phosphokinase increased, blood magnesium decreased, blood phosphorus decreased, blood potassium decreased, and hypertriglyceridemia. Only 1 patient discontinued setmelanotide because of a clinical chemistry TEAE (hypoglycemia).

## *Safety in special populations*

No elderly patients were included in the pivotal or supportive RM-493- 011 and RM-493-022 studies.

In paediatric patients (aged <12 years), the TEAEs experienced in this group were considered mild to moderate in intensity. TEAEs considered treatment-related were consistent with those reported across other age groups. Common TEAEs reported were injection site reactions, skin hyperpigmentation, and nausea. See Table 26 .

Three paediatric patients experienced SAEs, each considered unrelated to study drug. First patient had pleuritis and a second SAE of major depressive disorder. Second patient experienced hypoglycemia due to a suspected adrenal crisis, and of the third patient had a panic attack.

**Table 26 Most Common (i.e., Incidence >10%) Treatment-Emergent Adverse Events Among Setmelanotide-treated Patients in the Setmelanotide Clinical Program through 10 November 2020 (N=476), by Age Category, by MedDRA Preferred Term**

| Preferred Term | Age <12 years (N=11) n (%) | Age 12 to <18 years (N=63) n (%) | Age ≥18 years (N=402) n (%) |
|---|---|---|---|
| Patients with at Least 1 TEAE | 9 (81.8) | 61 (96.8) | 356 (88.6) |
| Skin hyperpigmentation | 6 (54.5) | 38 (60.3) | 185 (46.0) |
| Nausea | 3 (27.3) | 19 (30.2) | 135 (33.6) |
| Headache | 3 (27.3) | 21 (33.3) | 101 (25.1) |
| Injection site erythema | 5 (45.5) | 21 (33.3) | 88 (21.9) |
| Injection site pruritus | 2 (18.2) | 17 (27.0) | 64 (15.9) |
| Vomiting | 2 (18.2) | 9 (14.3) | 48 (11.9) |
| Diarrhoea | 2 (18.2) | 13 (20.6) | 36 (9.0) |
| Fatigue | 0 | 10 (15.9) | 41 (10.2) |
| Injection site induration | 0 | 16 (25.4) | 35 (8.7) |
| Injection site pain | 1 (9.1) | 9 (14.3) | 39 (9.7) |

Pregnancy was reported in 1 patient and this led to drug discontinuation. The patient had received 55 doses of setmelanotide.

## *Immunological events*

No evidence of systemic allergic reactions or progression of skin reactions over time, that would indicate the presence of ADA to setmelanotide or its formulation components was reported. There has been one case of mild eosinophilia in Study RM-493-015 that led to drug discontinuation.

Overall, the analysis of a number of immunogenicity samples is still pending.

Based on the currently available data from the clinical trials RM-493-012 and RM-493-015, it has been observed that 68% (19 out of 28) of adult and paediatric patients with POMC- or LEPR-deficiency were screened positive for antibody to setmelanotide. These 68% of patients who screened positive for antibodies to setmelanotide were inconclusive for antibodies to setmelanotide in the confirmatory assay. There was no observation of a rapid decline in setmelanotide concentrations that would suggest the presence of anti-drug antibodies. Furthermore, approximately 23% of adult and paediatric patients with LEPR-deficiency (3 patients) confirmed positive for antibodies to alpha-MSH that were classified as low-titer and non-persistent. Of these 3 patients (13%), 2 tested positive post-Imcivree treatment and 1 was positive pre-treatment. None of the patients with POMC-deficiency were confirmed to have antibodies to alpha-MSH.

## *Safety related to drug-drug interactions and other interactions*

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

### *Discontinuation due to adverse events*

A total of 60 (9%) of 638 patients in the setmelanotide clinical program, including 50 (11%) of 476 setmelanotide-treated patients, 5 (5%) of 110 placebo-treated patients, and 5 (10%) of 52 patients for whom study drug remains blinded, have discontinued study drug due to a TEAE.

The most common type of TEAEs leading to setmelanotide discontinuation in the 476 setmelanotide treated patients were gastrointestinal disorders (19 patients; 4%), including nausea (11 patients; 2%), vomiting (8 patients; 2%), and abdominal pain and upper abdominal pain (each 2 patients; <1%).

Other TEAEs leading to setmelanotide discontinuation for >1 patient were skin hyperpigmentation (12 patients; 3%), headache (7 patients; 2%), fatigue (4 patients; <1%), and back pain, muscle spasms, melanocytic naevus, musculoskeletal chest pain, and ventricular tachycardia (each 2 patients; <1%). In the 2 cases of ventricular tachycardia that led to setmelanotide discontinuation, both occurred in healthy obese subjects, were moderate in intensity and transient, each resolving in <1 minute after onset, and were considered by the Investigator to be unrelated to setmelanotide.

Discontinuation of setmelanotide due to TEAEs was uncommon in the intended treatment population, with 1 LEPR patient in study RM-493-015 and 2 patients with POMC in study RM-493-022 discontinuing setmelanotide due to a TEAE, 1 each due to eosinophilia, headache, and hypoglycemia. Of these 3 events, eosinophilia was considered by the investigator to be setmelanotide-related, with the other 2 events considered unrelated.

### *Post marketing experience*

Setmelanotide was approved in the United States on 27 November 2020 for chronic weight management in adult and paediatric patients 6 years of age and older with obesity due to POMC, PCSK1, or LEPR deficiency. This approval occurred after the cut-off date for the safety report included in this application, and no post-marketing data are yet available.

## 2.6.1. Discussion on clinical safety

Safety data from 15 clinical Phase 1, 2 and 3 studies (ongoing and completed) have been presented. These included both healthy obese subjects, patients with POMC-, PSCK1- and LEPR-deficiency and other rare genetic disorders associated with obesity. Nevertheless, the safety database for setmelanotide is still limited, both in sample size – which is inherent to orphan diseases - and in duration of exposure which makes it difficult to detect rare adverse reactions and those associated with prolonged or cumulative exposure. The overall number of subjects treated in the intended population included 2 POMC patients (study 011) and 15 POMC/PCSK1 patients (study 012) as well as 3 LEPR patients (study 011) and 15 LEPR patients (study 015). Among those patients, the majority (30 patients) had been exposed for ≥12 months.

The number of paediatric subjects included in the pivotal studies is also very limited of which only 11 patients who were younger than 12 years old.

There are additional safety data in other populations with a total of 476 exposed subjects (233 had genetic forms of obesity); 76 of those have been treated for at least 6 months and 55 have been treated for at least 1 year. Among all setmelanotide-treated patients/subjects (n=476), 74 (≈16%) patients were <18 years; 40% were male and 60% were female. Considering the target group (POMC/LEPR deficiency) being a very rare disease with a prevalence <1/1.000.000; the safety database is considered sufficient to support the present application.

A total of 80 patients opted to continue setmelanotide treatment in an extension Study (RM-493-022), including 12 of 15 patients with POMC/PCSK1 deficiency obesity who completed pivotal index Study RM-493-012 and 12 of 15 patients with LEPR deficiency obesity who completed pivotal index Study RM-493-015. Thus the long term data are also limited. The CHMP considered acceptable to include in the pharmacovigilance plan, an observational Registry (PASS) with a primary objective, the assessment of long-term safety of setmelanotide as prescribed in routine practice for patients with bi-allelic homozygous POMC or LEPR deficiency obesity according to the approved prescribing information. The focus will be on characterising and quantifying the important potential risks of special interest, as well as describing the safety in populations underrepresented or excluded in the clinical trials.

The intended treatment population has several comorbidities, and there was no placebo comparative group in the pivotal studies. This design did not allow a proper differentiation of the comorbidity symptoms from drug-related AEs, thus complicating the characterisation of the safety profile of setmelanotide.

All patients included in the pivotal studies and supportive study RM-493-011 experienced at least 1 TEAE and also experienced at least 1 treatment-related TEAE.

Overall, the most common TEAEs among setmelanotide-treated patients, with the corresponding incidence among placebo-treated patients, were: skin hyperpigmentation: 48% (229/476) versus 5% (5/110); nausea: 33% (157/476) versus 8% (9/110); headache: 26% (125/476) versus 15% (16/110); injection site erythema: 24% (114/476) versus 10% (11/110) and injection site pruritus: 17% (83/476) versus <1% (1/110). Similar pattern was observed with the treatment related TEAEs (see Table 21).

There was one death reported in a LEPR patient in study RM-493-015. This was considered unrelated to study drug by the investigator.

Across the pivotal studies and supportive study RM-493-011, none of the SAEs were considered related to setmelanotide treatment and no patients discontinued therapy due to an SAE.

As of 10 November 2020, a total of 60 (9%) of 638 patients in the setmelanotide clinical program, including 50 (11%) of 476 setmelanotide-treated patients, 5 (5%) of 110 placebo-treated patients, and 5 (10%) of 52 patients for whom study drug remains blinded, have discontinued study drug due to a TEAE.

Approximately half (51% [244/476]) of setmelanotide-treated patients experienced a hyperpigmentation disorder, most commonly skin hyperpigmentation (48% [229/476]) and melanocytic naevus (7% [34/476]). Other hyperpigmentation disorders events were less commonly reported, including skin discoloration (2% [10/476]) and ephelides (1% [5/476]). Skin darkening typically occurred 2 to 3 weeks after initiation of setmelanotide treatment. Additional data did not reveal any differences of skin colour dependent of previous or ongoing sun exposure. There is no evidence for the development of melanoma with setmelanotide. However, given the limited exposure and underlying mechanism, this event (apparition of new melanocytic lesions or evolution of such lesions) is considered as an important potential risk in the RMP and is intended to be monitored through the proposed PASS. In addition, a warning in section 4.4 has been added to annually perform skin examination before and during treatment with setmelanotide. In addition, skin hyperpigmentation is an identified risk and is included in the SmPC as a very common adverse reaction.

Spontaneous penile erections, an effect associated with MC4R agonism, have also been reported in about one third of setmelanotide-treated males in the pivotal studies. These were mild in nature and resolved quickly without need for intervention, and setmelanotide treatment was continued. 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. None of the patients reported prolonged

erections (greater than 4 hours) requiring urgent medical evaluation. Nevertheless, given the clinical significance of priapism, prolonged penile erections are considered as an important potential risk in the RMP and a warning has been included in the SmPC to consider seek emergency medical attention for potential treatment of priapism. All relevant drug related sexual events have been included in section 4.8 of the SmPC (including erection increased and sexual arousal as commonly and uncommonly reported, respectively).

Some drugs that target the CNS have been associated with depression or suicidal ideation, but the exact mechanism is not known. Patients with severe obesity are known to have both depression and suicidal ideation and behaviours so therefore, the background rate of depression and suicidal ideation in the setmelanotide studies is not unexpected. Depression is considered as an important potential risk in the RMP and is included as a common adverse drug reaction in the SmPC. A warning has been added in the SmPC to monitor each medical visit for any depressive symptoms and consider discontinuing treatment if patients experience suicidal thoughts or behaviours. This risk is to be followed up in the proposed PASS. Overall, a total of 4 patients experienced suicidal behaviour. No new cases of suicidal behaviour have been reported during the procedure. This risk is to be followed up in the proposed PASS. In addition, the C-SSRS scale is included in the assessment of patients in clinical trials.

Nausea and vomiting were reported respectively very commonly and commonly with setmelanotide in the pivotal studies and supportive study RM-493- 011, and less commonly in the other studies. One patient had needed dose-reduction. Another 21 patients had temporary discontinued setmelanotide; most often nausea and vomiting. The majority of gastrointestinal AEs leading to temporary discontinuation of study drug were mild or moderate in severity and resolved. None of the patients with vomiting as an adverse event to setmelanotide developed associated electrolyte disturbances. Nausea and vomiting are added as adverse drug reactions in the SmPC.

A total of 38.6% of the patients treated with setmelanotide had at least one Injection site reaction. This is more than the double of the frequency among the placebo-treated patients. The most common ISRs (each reported in >5%) were erythema, pruritus, induration, pain, oedema, bruising, swelling and 'injection site reaction'. These consisted of 43% of all reported ISRs. As 476 patients reported a total of 920 ISRs, suggesting several patients must have experienced $\geqslant$2 ISRs. All ISRs were reported to be mild or moderate and non-serious, which is reassuring. A total of 6 patients experienced a total of 7 ISRs resulting in temporary treatment discontinuation. Three (3) of these patients were healthy obese and 4 patients had 'Genetic obesity' thus, none had POMC/LEPR. Compared to healthy obese, it may be expected that patients for which the treatment is intended to treat the underlying condition may be more prone to tolerate mild (and moderate) ISRs, and this may be the explanation that none of the POMC/LEPR patients discontinued treatment due to ISRs.

Whilst the applicant considered the reported cases of alopecia as unrelated to setmelanotide, the CHMP noted that alopecia was commonly reported in several clinical trials (e.g. studies RM-493-011, 012 and 022). Since this event may be suggestive of a potential drug relationship through cross-reactivity with the MC1R or the MC2R and a causal relationship cannot be excluded (given the available conflicting literature), alopecia has been added in section 4.8 of the SmPC.

Across patient populations, the incidence of hypertension was 3% (1/35), 2% (4/233), and <1% (2/228) among those with POMC/PCSK1 or LEPR deficiency obesity, other forms of genetic obesity, and healthy obese subjects. No signal of worsening hypertension was found while being treated concomitantly with setmelanotide and antihypertensive medications. In general, patients that were on antihypertensive medications prior to study start remained on stable doses of antihypertensive medication throughout the study. However, given the limited long-term data and the fact that MC4R agonists are linked to an increase in sympathetic tone, a pharmacodynamic effect on HR and BP can be

anticipated, appropriate warnings have been included to monitor heart rate and blood pressure, especially in case of overdose.

Overall, no trends or clinically meaningful changes were observed in clinical laboratory assessments throughout the studies.

No development of anti-setmelanotide antibodies was noted in analysed samples, however 3 LEPR patients did have anti-α-MSH anti-bodies at distinct timepoints. No efficacy or safety events could be associated with the appearance of these anti-bodies, but nonetheless their potential impact on outcomes is as of yet unknown. In addition, the suitability of the assays used in the immunologic analysis is yet to be addressed, the validity of these findings remains to be confirmed (see sections 2.4.4 and 2.4.5).

No elderly patients were included in the pivotal or supportive studies. Hence no safety data is available in this population.

Very limited information is available on pregnancy with one case report during treatment with setmelanotide. Since rapid weight gain or weight loss is not desirable during pregnancy, the CHMP recommended to not start setmelanotide, during pregnancy or while attempting to get pregnant. However, if a patient who is taking setmelanotide has reached a stable weight and becomes pregnant, consideration should be given to maintaining setmelanotide. Lastly, 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.

There is no information on the presence of setmelanotide or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. However, setmelanotide is excreted at low levels in the milk of rats treated during the preweaning lactation period. The use of setmelanotide is not recommended while breastfeeding.

A single case of overdose was reported, whereby a patient in study RM-394-012 received a 5 mg instead of a 0.5 mg dose during the dose titration phase. Section 4.9 of the SmPC adequately addressed this concern.

The overall risk of abuse is considered low based on the current safety profile and expected medical supervision.

No formal withdrawal or rebound study has been conducted. However, based on the pivotal data, weight gain during the placebo period in the integrated group was similar to the weight lost, after setmelanotide was resumed. This finding is suggestive of the absence of rebound or withdrawal symptoms since the weight gain during the reversibility period was within physiologic expectations.

## *Assessment of paediatric data on clinical safety*

The number of paediatric patients in the safety set was very limited, especially in regard to children younger than 11 years with only partial data. This is however an issue that can be expected given the ultra-rare nature of the conditions under consideration. Nevertheless, the CHMP noted that paediatric data in very young patients had accumulated to an amount that is significantly beyond the agreed PIP prerequisites (at least one patient in the 6-12 years age category). All but one of the 6 evaluable patients (3 of which were between 6 and 10 years) reached the primary endpoint without major drug-related safety concerns. The CHMP thus concluded that the safety in the paediatric population, including those younger than 11 years has been sufficiently addressed to support this application. The applicant proposed to capture Tanner scores, bone age x-ray results and to perform a 6-12 year subgroup analysis as part of the proposed registry. This is in line with the CHMP recommendation to

collect further long-term data. In addition, a warning is included in the SmPC to periodically assess response to setmelanotide therapy due to the possible impact of weight loss on growth and maturation.

### 2.6.2. Conclusions on the clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC. Appropriate measures including additional pharmacovigilance activities and risk minimisation activities (see 2.7) have been put in place to ensure safe and effective use of the product in the recommended indication.

## *2.7. Risk Management Plan*

### *Safety concerns*

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | None |
| Important potential risks | Melanoma<br>Prolonged penile erections<br>Depression (including suicidal ideation) |
| Missing information | Use in pregnant/breastfeeding women<br>Use in hepatic impairment<br>Use in severe renal impairment<br>Long-term use |

### *Pharmacovigilance plan*

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation | | | | |
| None | | | | |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances | | | | |
| None | | | | |
| **Category 3** - Required additional pharmacovigilance activities | | | | |

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| A Registry of Patients with POMC or LEPR Deficiency Obesity Treated with Setmelanotide | **Primary objective:**<br>To assess the long-term safety of setmelanotide as prescribed in routine practice for patients with biallelic homozygous POMC or LEPR deficiency obesity according to the current local prescribing information.<br><br>**Secondary objectives:**<br>To document the incidence and characteristics of AESIs including the following:<br>• Prolonged penile erection<br>• Depression (including suicidal ideation)<br>To document AESI and new adverse event occurrence in special populations, including:<br>• Patients with hepatic impairment<br>• Patients with severe renal impairment<br>• Use in pregnancy and breastfeeding<br><br>**Exploratory objective:**<br>To document any cases of melanoma and their characteristics | Melanoma<br><br>Prolonged penile erection<br><br>Depression (including suicidal ideation)<br><br>Patients with hepatic impairment<br><br>Patients with severe renal impairment<br><br>Use in pregnancy and breastfeeding<br><br>Long term use | Protocol submission<br><br>Start of data collection<br><br>First annual progress report<br><br>Second annual progress report<br><br>Third annual progress report<br><br>Fourth annual progress report<br><br>Completion of enrolment<br><br>First annual interim analysis report<br><br>Fifth annual progress report<br><br>Second annual interim analysis report<br><br>Sixth annual progress report<br><br>Third annual interim analysis report<br>Seventh annual progress | 30 Sep 2021<br><br>31 Mar 2022<br><br>31 Mar 2023<br><br>31 Mar 2024<br><br>31 Mar 2025<br><br>31 Mar 2026<br><br>31 Mar 2026<br><br>30 Sep 2026<br><br>31 Mar 2027<br><br>30 Sep 2027<br><br>31 Mar 2028<br><br>30 Sep 2028<br><br>31 Mar 2029 |

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| | | | report | |
| | | | Fourth annual interim analysis report | 30 Sep 2029 |
| | | | Eighth annual interim analysis report | 31 Mar 2030 |
| | | | Last (fifth) annual interim analysis report | 30 Sep 2030 |
| | | | Last (ninth) annual progress report | 31 Mar 2031 |
| | | | End of data collection: +9 years | 31 Mar 2031 |
| | | | Final study report: +6 months | 30 Sep 2031 |

## *Risk minimisation measures*

| Safety concern | Risk minimisation measures |
|---|---|
| Melanoma | Routine risk minimisation measures:<br>Routine risk communication:<br>• SmPC sections 4.4 and 4.8<br>• PL section 2, 4<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• 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.<br>• PL section 2 recommends a skin examination be conducted prior and during treatment.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Legal status: prescription only medication<br><br>No additional risk minimisation measures |

| Safety concern | Risk minimisation measures |
|---|---|
| Prolonged penile erections | Routine risk minimisation measures:<br>Routine risk communication:<br>• SmPC section 4.4<br>• PL section 2 and 4<br>Routine risk minimization specific clinical measures to address the risk:<br>• SmPC section 4.4 includes the statement that patients who have an erection lasting greater than 4 hours should seek emergency medical attention.<br>• PL section 2 recommends patients seek urgent medical care if they experience an erection lasting greater than 4 hours.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Legal status: prescription only medication<br><br>No additional risk minimisation measures |
| Depression (including suicidal ideation) | Routine risk minimisation measures:<br>Routine risk communication:<br>• SmPC section 4.4<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• 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.<br>.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Legal status: prescription only medication<br><br>No additional risk minimisation measures |

| Safety concern | Risk minimisation measures |
|---|---|
| Use in pregnant/breastfeeding women | Routine risk minimisation measures:<br>Routine risk communication:<br>• SmPC section 4.6<br>• PL section 2<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• 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.<br>• SmPC section 4.6 notes that if breastfeeding, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from IMCIVREE therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Legal status: prescription only medication<br><br>No additional risk minimisation measures |
| Use in hepatic impairment | Routine risk minimisation measures:<br>Routine risk communication:<br>• SmPC sections 4.2 and 5.2<br>• PL section 2<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• SmPC sections 4.2 and 5.2 note that setmelanotide should not be administered to patients with hepatic impairment.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Legal status: prescription only medication<br><br>No additional risk minimisation measures |

| Safety concern | Risk minimisation measures |
|---|---|
| Use in severe renal impairment | Routine risk minimisation measures:<br>Routine risk communication:<br>• SmPC sections 4.2 and 5.2<br>• PL section 2<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• SmPC sections 4.2 and 5.2 recommend IMCIVREE not be administered to patients with severe renal impairment<br>Other routine risk minimisation measures beyond the Product Information:<br>• Legal status: prescription only medication<br><br>No additional risk minimisation measures |
| Long-term use | Routine risk minimisation measures:<br>Routine risk communication:<br>• None<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• None Other routine risk<br>minimisation measures beyond the Product Information:<br>• Legal status: prescription only medication<br><br>No additional risk minimisation measures |

### *Conclusion*

The CHMP and PRAC considered that the risk management plan version 0.6 is acceptable.

## *2.8. Pharmacovigilance*

### *Pharmacovigilance system*

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### *Periodic Safety Update Reports submission requirements*

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 25.11.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

## *2.9. New Active Substance*

The applicant compared the structure of setmelanotide with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers setmelanotide to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

## *2.10. Product information*

### 2.10.1. User consultation

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

### 2.10.2. Labelling exemptions

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

considering the very low number of patients, the QRD Group accepted the request for translation exemption, i.e. EN only for the outer carton and vial label of this medicinal product. The MAH should explore the possibility to increase the font size to 7 points.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

### 2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Imcivree (setmelanotide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

The indication claimed by the applicant is "Treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above."

POMC and LEPR genes are upstream of the MC4R pathway and patients suffering usually have no to sub-functional levels of the MC4R ligand α-MSH, released by POMC neurons in response to adipose-mediated energy homeostasis signals.

There are no available data on incidence of obesity due to POMC deficiency or LEPR deficiency. POMC (including PCKS1) and LEPR deficiencies can be confirmed only following genetic testing. Nonetheless, on the basis of worldwide literature, it is estimated that less than 200 cases have been reported with these genetic deficiencies. Complete POMC deficiency (biallelic mutations) results in loss of endogenous MC4R agonist. As the endogenous antagonist (AGRP) is not affected, this results in markedly reduced melanocortin tone, which manifests as hyperphagia (food-seeking behaviours), driving severe obesity.

LEPR deficiency obesity is caused by bi-allelic (either homozygous or compound heterozygous) loss of the LEPR. In LEPR deficiency, patients lose the ability to regulate both POMC and AGRP neurons, likely resulting in basal low levels of melanocortin tone. In addition, LEPR is expressed on other (non-melanocortin) neuronal populations both within the hypothalamus and in other areas involved in food reward such as the striatum and ventral tegmental area. As such the hyperphagia and obesity in LEPR deficient patients is usually more severe than seen in POMC deficiency (many patients do not survive) and is mediated by both melanocortin (setmelanotide-responsive) and melanocortin-independent (setmelanotide-unresponsive) pathways.

Early-onset extreme obesity, unrelenting hunger and hyperphagia are common clinical features of these genetic disorders. The hyperphagia generally begins in infancy, and severe obesity follows shortly thereafter. As patients grow and develop, paediatric weight curves demonstrate progressive and extreme weight gain, tracking >3 standard deviations above normal weights for age, usually leading to adult body mass index (BMI) values >40 kg/m2. POMC deficiency obesity patients often weigh over 100 kg by age 6 to 8 years, especially where there are bi-allelic POMC gene defects. This in turn contribute to increased mortality and morbidity in these populations, including various co-morbidity complications as well as global impairments in daily functioning and overall quality of life.

### 3.1.2. Available therapies and unmet medical need

There are currently no approved therapies nor products in development specifically for the obesity and hyperphagia associated with POMC/PCSK1 or LEPR deficiencies.

The most used weight management techniques used with these patients are caloric limitation through adapted nutritional strategies and gastric surgeries. However, clinical experience shows that neither of these treatments result in durable clinically relevant responses, as patients suffer unrelenting and unstoppable feelings of hunger.

As such, these patients currently experience a high unmet need of effective treatment for their ultra-rare condition.

Setmelanotide, an 8-amino acid cyclic peptide analogue of naturally occurring alpha-melanocyte stimulating hormone (α-MSH), is claimed to be a highly MC4R-specific agonist and is intended to restore energy expenditure and satiety signalling in the hypophysial MC4R pathway. It is to be administered once daily as a subcutaneous injection.

The proposed therapy aims to induce clinically relevant weight loss and suppression of hunger feeling in the targeted patient population.

### 3.1.3. Main clinical studies

Results from the pivotal cohort of two separate studies in POMC (RM-493-012) and LEPR (RM-493-015) were submitted to support this application. Both pivotal trials were still ongoing at time of submission and supplemental data were provided during the procedure. RM-493-012 and RM-493-015 were of identical design, both phase III open-label non-randomised trials with an 8-week placebo-controlled withdrawal period. Both studies included a 2- to 12-week titration period to establish a given patient's therapeutic dosing, after which patients would receive 10 further weeks of treatment at the therapeutic dose. When certain protocol-defined weight-milestones were reached patients would enter the blinded 8-week withdrawal period during which the patients would randomly enter a 4-week treatment period with placebo. This 8-week withdrawal period was meant to establish whether any weight and hunger effects seen were indeed related to the setmelanotide and not to other factors or protocol-allowed concomitant treatments. After the 8-week randomised withdrawal period the patients would restart treatment at her/his previously established therapeutic dose for an additional 32 weeks in order to complete one year of treatment.

## *3.2. Favourable effects*

The primary endpoint was met in both studies at all significance levels. In study RM-493-012, 80% of POMC patients achieved at least 10% weight loss from baseline at Week 52, which was significantly increased compared to a historical control of 5% untreated responders (p: <0.0001, 90% CI = [49.31, 96.32]). If the results (true + imputed) of all 4 supplemental patients were included these numbers remained statistically significant with 85.7% responders (p: <0.0001, 90% CI = [61.46, 97.40]). The secondary success criterion, a 10% observed mean weight loss from baseline to 1 year of treatment, was also met as more than 35% of all patients reached the primary endpoint. In study RM-493-015 (LEPR), the corresponding numbers were 45.5% (p: <0.0001, 90% CI = [19.96, 72.88]) and 60% (p: <0.0001, 90% CI = [35.96, 80.91]), indicating that both primary endpoint and associated study success criterion were also met. In both studies, sensitivity analyses using the pivotal DUS and CS study sets confirmed the outcomes.

The first key secondary endpoint, mean percent change in body weight, was also met in both studies at both defined significance levels. In study RM-493-012, the pivotal patients reported a LS mean weight change of -25.39% (p: <0.0001, 90% CI = [-28.8, -21.98]) and combined with the supplemental patient outcomes (true and imputed) the outcome became -25.66% (p: <0.0001, 90% CI = [-28.4, -22.91]). The associated success criterion was also met as the observed mean weight loss at 52 weeks was greater than 10%. In RM-493-015 study, these corresponding outcomes were -12.47% (p: <0.0001, 90% CI = [-16.10, -8.83]) and – 12.76% (p: <0.0001, 90% CI = [-15.30, -10.22]).

The second key secondary endpoint, mean percent change in hunger scores, was met in both studies at both defined success levels. In study RM-493-012 the pivotal DUS patients 12 years or older reported a LS mean weight change of -27.77% (p: <0.0001, 90% CI = [-40.58, -14.96]). The associated success criterion for this endpoint was also met as the observed mean hunger decrease at 52 weeks was greater than 25%. In the RM-493-015 study these corresponding outcomes were – 41.93% (p: <0.0001, 90% CI = [-54.76, -29.09]) and – 50.29% (p: <0.0001, 90% CI = [-63.81, -36.78]) in the combined pivotal and supplemental cohort outcomes.

The third key secondary endpoint, proportion of responders with a >25% response in hunger improvement from baseline at week 52, was met in both pivotal studies at all specific significance levels. In study RM-493-012, 50% of pivotal FAS patients 12 years or older achieved at least 25% hunger improvement from baseline at Week 52 (p: 0.0004, 90% CI = [19.29, 80.71]). The associated

success criterion for this endpoint was also met as more than 35% percent of patients met the endpoint. In study RM-493-015, these corresponding outcomes were 72.7% (p: <0.0001, 90% CI = [43.56, 92.12]) and 78.6% (p: <0.0001, 90% CI = [53.43, 93.89]) in the combined pivotal and supplemental cohort outcomes.

Ancillary analyses showed results on change in waist circumference, body composition by DEXA scan, BMI, energy expenditure, lipid profile and glucose metabolism that pointed in a positive direction. Furthermore, no bone mass loss was seen.

## *3.3. Uncertainties and limitations about favourable effects*

Given the ultra-rarity of these genetic conditions and thus the lack of available patients, it was difficult to implement a strongly powered statistical analysis. This should be factored when considering observed outcomes and uncertainties, such as for example potential bias induction.

Historical comparison of the key endpoints was provided by the historical pre-treatment data of the enrolled subjects in both pivotal trials. This comparison showed a median weight gain prior to entering the trials versus a median weight loss seen during the trials. However, as weight changes are also age dependent, such comparison should be considered relative rather than absolute.

Despite positive results in all primary and key secondary endpoints, comparison between the outcomes in the two studies showed that in general LEPR deficiency obesity patients have a less favourable response in regard to weight loss relative to POMC/PCSK1 deficiency obesity patients, whereas the situation is completely opposite in regards to improvements in hunger. It is likely that this may reflect the difference in POMC/PCSK1 and LEPR expression in the areas involved in food reward. The latter is expressed on other (non-melanocortin) neuronal populations both within the hypothalamus, as well as in the striatum and ventral tegmental area. These patients thus suffer from a more severe disease form, likely explaining the relatively less favourable weight outcomes as well as the seemingly contradictory better hunger outcomes by virtue of their base hunger-level being far reduced so that improvements are relatively experienced as more impactful.

Two patients in the LEPR deficiency obesity population had unexplainably less favourable responses, but it could be plausible that their uncontrolled diabetic state, as well as the use of prednisolone by one subject, may have contributed to such response.

Analyses investigating correlations of bi-allelic or loss-of-function POMC and PCSK1 genetic mutations and POMC deficiency due to diverse allelic variants with the magnitude of setmelanotide efficacy endpoints were also not undertaken and thus potential variability in response due to genetic factors is currently unknown.

Several cases of mal compliance were noted in the pivotal studies as well as in the outpatient settings in Phase II trials. Moreover, in the RM-493-022 extension some patients presented with temporary enormous weight spikes suggestive of mal compliance but not confirmed.

Currently there is a lack of knowledge on efficacy and dosing considerations in elderly, patients with moderate to severe renal impairment and patients with hepatic impairment since these special populations were not included in the clinical studies. Data on patients with mild renal impairment are available, but do not allow a proper dosing evaluation since no dosage adjustments were made

Likewise, no data are available in patients <8 years of age. The presented POPPK modelling did not allow for extrapolation towards the youngest children, limiting the maximum dosing to 2.5 mg as reported in the clinical trials for the paediatric population.

The observationally informed choice of dosing regimen for the pivotal trials had methodological limitations however standard a dose-finding approach has not been conducted due to the ultra-rarity of the condition and the lack of available subjects in this population.

No development of anti-setmelanotide antibodies was noted in analysed samples, however 3 LEPR patients did have anti-α-MSH anti-bodies at distinct timepoints. No efficacy or safety events could be associated with the appearance of these anti-bodies, but nonetheless their potential impact on outcomes is as of yet unknown. In addition, the suitability of the assays used in the immunologic analysis is yet to be addressed, the validity of these findings remains to be confirmed. Further investigations have thus been recommended by the CHMP on this aspect.

## *3.4. Unfavourable effects*

Approximately half of setmelanotide-treated patients experienced a hyperpigmentation disorder, most commonly skin hyperpigmentation (48% [229/476]) and melanocytic naevus (7% [34/476]). There is a clear underlying mechanism for hyperpigmentation linked to the activation of the MC1 receptor. Skin hyperpigmentation generally occurred within 2 to 3 weeks of treatment initiation, continued for the duration of treatment, and resolved upon drug discontinuation.

In the clinical trials with setmelanotide, there have been no cases of melanoma until now. New melanocytic lesions or evolution of such lesions to melanoma is an important potential risk in the RMP.

Spontaneous penile erections, an effect associated with MC4R agonism, have also been reported in about one third of setmelanotide-treated males in the pivotal studies. These were mild in nature and resolved quickly without need for intervention, and setmelanotide treatment was continued. 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. None of the patients reported prolonged erections (greater than 4 hours) requiring urgent medical evaluation. Nevertheless, given the clinical significance of priapism, prolonged penile erection is considered as an important potential risk in the RMP.

Overall, 3% (15/476) of patients experienced a depression event, including depression (2% [9/476]) and depressed mood (2% [7/476]). One patient experienced the events of both depressed mood and depression. The depression event was severe for 4 patients, and serious for 1 patient. One (<1%) patient each required a setmelanotide dose reduction or discontinued setmelanotide due to a depression event. Depression/suicidal ideation are to be considered important potential risks for setmelanotide in the RMP due to the experience from other centrally acting anti-obesity drugs, but overweight by itself also predisposes to depression.

Setmelanotide is administered by daily injections, which is both painful and inconvenient, especially for a treatment intended also for paediatric patients. Injection site reactions and nausea were very common but are considered manageable through appropriate SmPC risk minimisation measures.

## *3.5. Uncertainties and limitations about unfavourable effects*

The rate and extent of absorption in function of the injection site are uncertain. The SC injection has been limited to the abdomen region as observed in clinical trials.

The clinical safety data set is limited leading to a number of uncertainties: the number of patients treated in the intended indication is small so it is unlikely to detect rarer adverse reactions, and there is a need for longer-term data to detect adverse reactions associated with prolonged or cumulative

exposure. In addition, the paediatric safety data was very limited especially in regard to children younger than 11 years.

The pivotal studies were open-label studies and were performed without a comparative placebo group and in a patient population with several comorbidities. This made it challenging to determine the causal relationship to the treatment, and there were patient groups excluded from the clinical trials while they might be at a higher risk for developing some of the designated event of special interests as well as other excluded patient groups.

The effect of long-term or cumulative use of setmelanotide on hyperpigmentation is not known and subjects with a history or close family history of melanoma were not studied in clinical trials with setmelanotide. This will be further monitored long-term in the proposed PASS, although it is questioned if the targeted sample size of approximately 150 patients will be sufficient.

The risk of prolonged penile erections (>4 hours) as up until now is not fully characterised, there have only been reports of spontaneous erections of short duration that resolved without intervention, and there was no signal of prolonged penile erections in pre-clinical or clinical setmelanotide studies contrary to the rare case reports of priapism that have been reported with other MCR agonists.

Subjects with severe depression were not studied in the clinical trials and it is also difficult to determine whether the depression/suicidal ideation is linked to the underlying disease or the drug; this will further be followed-up in the proposed PASS.

Nausea is considered to be a manageable effect of setmelanotide, however the effect of the proposed simplified dosing on the risk of nausea has not been investigated.

ISRs are considered to be a manageable effect of setmelanotide, however limited information on the case reports may have limited the assessment on potential risk minimisation measures to address this risk.

The clinical impact of ADAs is unknown as more data are expected and the suitability of the assays is yet to be confirmed.

## 3.6. Effects Table

**Table 27: Effects Table for setmelanotide in the treatment of obesity and uncontrolled hunger associated with biallelic pro-opiomelanocortin (POMC) including Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), deficiency obesity or leptin receptor (LEPR) deficiency obesity in adults and children 6 years of age and above. (Data cutoff: March 2020, including both pivotal and supplemental patient data*)**

| Effect | Short Description | Unit | Treatment | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| Body Weight | Proportion of patients achieving ≥10% weight loss after 52 weeks of treatment compared to historical 5% responder rate | % | 85.7 (61.46, 97.40) | NA | Limited population<br>No sub analysis for special populations<br>Limited data in patients <11years | RM-493-012 FAS, n=14 |
| | | | 60 (35.96, 80.91) | NA | Limited population<br>Endpoint met but outcome relatively less favourable versus POMC/PCSK1 deficiency obesity patients<br>No sub analysis for special populations<br>Limited data in patients <11years | RM-493-015 FAS, n = 15 |
| Body Weight | Mean percent change in body weight from baseline statistically significant from zero | % | -25.66 (-28.40, -22.91) | NA | Limited population<br>No sub analysis for special populations<br>Limited data in patients <11years | RM-493-012 DUS, n = 13 |
| | | | -12.76 (-15.30, -10.22) | NA | Limited population<br>Endpoint met but outcome relatively less favourable versus POMC/PCSK1 deficiency obesity patients<br>No sub analysis for special populations<br>Limited data in patients <11years | RM-493-015 DUS, n = 10 |
| Hunger | Mean percent change in weekly average of daily hunger score from baseline statistically significant from zero | % | -27.77 (-40.58, -14.96) | NA | Limited population<br>Endpoint met but outcome relatively less favourable versus LEPR deficiency obesity patients<br>No sub analysis for special populations<br>No data in patients <12years | RM-493-012 DUS ≥ 12 years, n = 7 |
| | | | -50.29 (-63.81, -36.78) | NA | Limited population<br>No sub analysis for special populations<br>No data in patients <12years | RM-493-015 DUS ≥ 12 years, n = 10 |

| Effect | Short Description | Unit | Treatment | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| Hunger | Proportion of patients achieving ≥25% improvement in hunger after 52 weeks of treatment compared to historical 5% responder rate | % | 50.0 (19.29, 80.71) | NA | Limited population<br>Endpoint met but outcome relatively less favourable versus LEPR deficiency obesity patients<br>No sub analysis for special populations<br>No data in patients <12 years | RM-493-012 FAS ≥ 12 years, n = 8 |
| | | | 78.6 (53.43, 93.89) | NA | Limited population<br>No sub analysis for special populations<br>No data in patients <12 years | RM-493-015 FAS ≥ 12 years, n = 14 |
| **Unfavourable Effects** | | | | | | |
| Skin hyperpigmentation | Frequency | % | 77.1% | NA | - effect of long-term or cumulative use?<br>- subjects with (close family) history of melanoma excluded in the clinical trials | Studies 011/012/015 (n=35) |
| Prolonged penile erections (>4 hours) | Frequency, in males | % (absolute number on total) | 35.3% (6/17 patients) | NA | - none reported in the non-clinical and clinical studies until now but rare case reports with other MCR agonists: only reports of spontaneous short-lived erections with setmelanotide | Studies 011/012/015 (total n=35, males n= 17) |
| Depression | Absolute number of cases | Absolute number | 5 patients, 1 considered related by the Investigator, not by the applicant | NA | - subjects with severe depression excluded in the clinical trials<br>- very difficult to determine whether it is linked to the underlying disease or to the drug<br>- the applicant considers one of the reports not to be related contrary to the investigator<br>- role of concomitant use of antidepressants? | Studies 011/012/015 (n=35) |
| Suicidal ideation | Absolute number of cases | Absolute number | 6 patients, none related | | - very difficult to determine whether it is linked to the underlying disease or to the drug | Studies 011/012/015 (n=35) |
| Nausea | | | | | Although nausea is considered to be a manageable effect of setmelanotide, there is an uncertainty about it as the effect of the proposed simplified dosing on the risk of nausea has not been investigated. | |

Abbreviations: NA: not applicable

*Note that the aggregated data from the pivotal and supplemental study sets as presented here, including imputed results from supplemental patients that had not finished 52 Weeks of treatment at data cut-off yet, tend to show

higher outcomes compared to an analysis that only takes into account pivotal patients. The difference in analysis outcomes for the POMC/PCSK1 group is small, but larger for the LEPR patient group. This latter group had however 2 cases of mal-compliance and a discontinuation due to AE in the pivotal group, which likely explains the larger gap. Nonetheless, both aggregated and pivotal-only analyses show that all primary and key secondary endpoints are met.

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

Setmelanotide is a MC4R agonist with the potential to restore lost activity in the MC4R pathway aiming at re-establishing weight and appetite control in patients with POMC and LEPR obesity. There are no pharmacological treatment options for the patient populations and there is a substantial medical need.

The fact that all key endpoints in both the RM-493-012 and RM-493-015 trials were met, indicating not only statistical but also clinical significance, in a group of patients that prior to these results did not have any effective way to manage their morbid obesity and unrelenting hunger makes the efficacy outcomes of prime importance in face of the high unmet need in these ultra-rare genetic conditions. Equally important is the fact that the responses seem to be durable, with some variability, during follow-up of up to three years of treatment. Nonetheless, the data set is relatively limited, and this is inherent to the ultra-rarity of the proposed indications. Given the expected life-long nature of the treatment, the proposed pharmacovigilance plan to follow-up POMC and LEPR patients in a registry (PASS) is agreed upon. Particularly, data on weight trajectory and discontinuation are planned to be collected in this registry, and these are considered relevant to monitor the maintenance of the effect of setmelanotide in the indication applied for.

Some efficacy uncertainties were identified such as the relative less favourable hunger scores despite relative better weight scores in LEPR deficiency obesity patients versus POMC/PCSK1 deficiency obesity patients, the dosing choices and the lack of data in special populations, as well as the paucity of safety data in certain age groups. However, these are not expected to have a significant impact over the clinically proven benefits of setmelanotide in the intended treatment population. In particular, despite safety and efficacy data in children below the age of 11 years was limited, the number of patients is in line with the PIP requirement of at least one patient in the 6-12 years age category. Also, neither the originally proposed POPPK model, nor a model refitted to a two-compartment type, would be able to adequately support any kind of dosing extrapolation to young children, a titration to effect and acceptable tolerance can be supported by the limited clinical observations available.

The uncertainties regarding the limited clinical safety dataset (n=35) in the proposed indication is to be addressed by the proposed observational Registry (PASS). Moreover, there are safety data from a total of 377 exposed subjects including some preliminary data from the ongoing long-term extension study providing data for a total up to about 3 years in some POMC-patients that demonstrate a generally well tolerated and safe profile of setmelanotide with no patients who discontinued treatment due to drug-related AEs. The safety profile based on the limited data seems to be reassuring, but caution is warranted due to experience from other centrally acting anti-obesity products.

The important potential risks of melanoma, prolonged penile erections and depression/suicidal thoughts can be accepted taking into account the unmet medical need for which setmelanotide is used and the fact that these risks will be further monitored long-term in the proposed PASS. Overall, the safety issues noted are important, but this importance is not of such magnitude that it would overtly negatively influence the overall benefit of the treatment as shown by the highly favourable outcomes.

### 3.7.2. Balance of benefits and risks

Overall, the favourable outcomes, both in a statistical and clinically relevant sense, on body weight and hunger suppression in the ultra-rare conditions of POMC/PCSK1 deficiency obesity and LEPR deficiency obesity are promising for a patient population that until now suffers from a high unmet medical need due to the absence of an effective durable treatment for their condition. Although potential risks are identified these are not considered to outweigh the benefits of Setmelanotide in the proposed indication.

## *3.8. Conclusions*

The overall B/R of Imcivree is positive.

# 4. Recommendations

## *Outcome*

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Imcivree is favourable in the following indication:

Imcivree is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

## *Conditions or restrictions regarding supply and use*

Medicinal product subject to restricted medical prescription. (See Annex I: Summary of Product Characteristics, section 4.2)

## *Other conditions and requirements of the marketing authorisation*

**Periodic Safety Update Reports**

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

**Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the

agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

## *New Active Substance Status*

Based on the CHMP review of the available data, the CHMP considers that setmelanotide is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

## *Paediatric Data*

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0164/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.