CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213793Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	213793
Link to EDR	\\Cdsesub1\evsprod\NDA213793\213793.enx
Submission Date	27 MAR 2020
Submission Type	505(b)(1)
Brand Name	IMCIVREE (Proposed)
Generic Name	Setmelanotide Injection
Dosage Form and Strength	• 10 mg in a 1 mL vial
Route of Administration	Subcutaneous injection
Proposed Indication	Indicated for the treatment of obesity (b) (4) associated with 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 older.
Applicant	Rhythm Pharmaceuticals, Inc.
Associated IND	IND-112595
OCP Review Team	Suryanarayana Sista, PhD; Eliford Kitabi, PhD; Katarzyna Drozda, PharmD, MS; Christian Grimstein, PhD; Justin Earp, PhD; Jayabharathi Vaidyanathan, PhD
OCP Final Signatory	Shirley Seo, PhD

Table of Contents

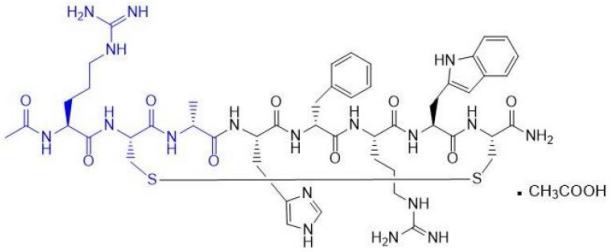
List of Tables

List of Figures

1. EXECUTIVE SUMMARY

This is an original NDA submitted by Rhythm Pharmaceuticals on 27 Mar 2020, seeking marketing approval for IMCIVREE (Setmelanotide) injection for the treatment of obesity (b) (4) associated with pro-opiomelanocortin (POMC), including PCSK1, deficiency obesity or leptin receptor (LEPR) deficiency obesity in adults and children 6 years of age and older. In this document, the names RM-493, Setmelanotide and IMCIVREE are used interchangeably.

IMCIVREE (setmelanotide) is a formulation of setmelanotide available as a 10 mg/mL multi-dose vial. Setmelanotide is a synthetic, cyclic octapeptide (8-amino acid-containing peptide) that functions as a selective agonist to the human melanocortin-4 receptor (MC4R). Setmelanotide binds with high affinity (inhibitory constant [K_i] = 2.1 nM) to MC4R and is efficient in activating this receptor (50% effective concentration [EC_{50}] = 0.27 nM). Chemically, it is Acetyl-L-arginyl-L-cysteinyl-D-alanyl-L-histidinyl-D-phenylalanyl-L-arginyl-L-tryptophanyl-L-cysteinamide cyclic (2→8)-disulfide and has the empirical formula $C_{49}H_{68}N_{18}O_9S_2$ (anhydrous, free base) and a molecular weight of 1117.3 Daltons (anhydrous, free base). Setmelanotide has the following primary structure:



IMCIVREE drug product is formulated as (b) (4) solution (pH 5 - 6) with excipients mPEG-2000-DSPE (N-(Carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl glycero-3-phosphoethanolamine sodium salt), carboxymethylcellulose sodium (CMC), mannitol, phenol, benzyl alcohol and sodium edetate. The proposed commercial formulation is a sterile solution intended for subcutaneous (SC) injection.

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

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

The Melanocortin-4 receptor (MC4R) has been identified as the dominant MC receptor involved in body weight, hunger, and energy homeostasis regulation. Due to its mechanism of action, setmelanotide has the potential to restore lost activity in the MC4R pathway by bypassing the defects upstream of the MC4R and directly activating MC4R neurons in the hypothalamus below such defects, thereby re-establishing weight and appetite control in patients with POMC and LEPR obesity.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology data submitted to NDA 213793 and found it acceptable to support approval of IMCIVREE for the treatment of obesity (b) (4) associated with pro-opiomelanocortin (POMC) deficiency obesity, including PCSK1, or leptin receptor (LEPR) deficiency obesity in adults and children 6 years of age and older. Key review issues with specific recommendations and comments are summarized below:

<table>
<tr><th>Review Issues</th><th>Recommendations and Comments</th></tr>
<tr><td>Supportive evidence of effectiveness</td><td>The primary evidence of effectiveness for the proposed dosing regimen were obtained from data from 2 efficacy trials in patients with POMC or LEPR deficiency obesity, which showed that IMCIVREE was effective in the treatment of obesity and (b) (4) associated with POMC deficiency obesity, including PCSK1, or LEPR deficiency obesity in adults and children 6 years of age and older.
8 out of 10 POMC patients and 5 out of 11 LEPR patients achieved a ≥ 10% weight loss after 1 year of setmelanotide treatment. This weight loss was also accompanied by clinically meaningful reductions in hunger over 1-year treatment in these patients.</td></tr>
<tr><td>General dosing instructions</td><td>IMCIVREE should be injected once daily, at the beginning of the day (b) (4), without regard to the timing of meals. IMCIVREE should be injected subcutaneously in the abdomen, thigh, or arm, rotating to a different site each day. If a dose is missed, the once daily regimen should be resumed as prescribed with the next scheduled dose. IMCIVREE must not be administered intravenously or intramuscularly. The recommended starting and titration doses of IMVICREE are listed in the Table below:
<table>
<tr><th>Week</th><th>Daily Dose</th></tr>
<tr><td colspan="2">Patients aged ≥ 12 years</td></tr>
<tr><td>Weeks 1-2</td><td>2 mg q.d.</td></tr>
<tr><td>Week 3 and beyond</td><td>3 mg q.d.</td></tr>
<tr><td colspan="2">Patients aged 6 - 12 years</td></tr>
<tr><td>Weeks 1-2</td><td>1 mg q.d.</td></tr>
<tr><td>Week 3 and beyond</td><td>2 mg q.d.</td></tr>
<tr><td>If clinical response is insufficient, and IMCIVREE is well tolerated</td><td>3 mg q.d.</td></tr>
</table>
The proposed doses in pediatric populations are supported by population PK and exposure-response analysis.</td></tr>
<tr><td>Dosing in patient subgroups</td><td>• Dose adjustment of setmelanotide is not required for mild renal impairment.
• Setmelanotide is not recommended in patients with moderate and severe renal impairment.</td></tr>
<tr><td>Bridge between the “to-be-marketed” and clinical trial formulations</td><td>The to-be-marketed formulation is the same as the clinical trial formulation that was used in several clinical pharmacology studies. The to-be-marketed formulation was also used in all the Phase 3 clinical studies.</td></tr>
</table>

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

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

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

The MC4R has been identified as the dominant MC receptor involved in body weight, hunger, and energy homeostasis regulation. Setmelanotide has the potential to restore lost activity in the MC4R pathway by bypassing the defects upstream of the MC4R and directly activating MC4R neurons in the hypothalamus below such defects. Thus, setmelanotide bypasses the upstream genetic defects in this critical MC4R signaling pathway to re-establish weight and appetite control in patients with POMC and LEPR obesity.

A summary of the PK and PD characteristics of IMCIVREE is presented below.

Absorption:	• Following SC injection of setmelanotide, plasma concentrations of setmelanotide reached maximum concentrations at a median T_{max} of 8.0 h after dosing. • Steady-state plasma concentrations of setmelanotide is achieved within 2 days with daily dosing of 1-3 mg setmelanotide • The accumulation of setmelanotide in systemic circulation during once-daily dosing over 12 weeks was approximately 30%. • Setmelanotide generally exhibits dose proportional PK following multiple-dose SC administration in the proposed dose range (1-3 mg).
Distribution:	• The mean apparent volume of distribution after SC administration is about 49 L, and the plasma protein binding of setmelanotide is 79.1%.
Metabolism:	• Setmelanotide does not appear to be metabolized by human hepatic microsomes and hepatocytes. Trace amounts of two urine metabolites, M19 (2%) and M7 (<1%) were observed in a small number of subjects.
Excretion:	• The total apparent steady-state clearance of setmelanotide is about 4.86 L/h. • At steady state, approximately 39% of the administered setmelanotide dose was renally eliminated as unchanged drug within 24 hours post-dose

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed starting dose of IMCIVREE is as follows:

(b) (4)

2.2.2 Therapeutic individualization

Based on findings from individual studies and population PK analyses, other than body weight, no other intrinsic factors affected the PK of setmelanotide after IMCIVREE administration. Dose adjustment of setmelanotide is not required for mild renal impairment. Setmelanotide is not recommended in patients with moderate and severe renal impairment. Setmelanotide was not evaluated in hepatic impairment.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following preliminary labeling concepts be included in the final package insert:

Label Section	Acceptable to OCP?			Recommendation
	A	AWE	U	
2 DOSAGE AND ADMINISTRATION 2.1 Recommended Dosage	☐	☑	☐	• **Recommended Dosage [1]** (b) (4) [redacted]

				• [redacted] (b) (4)
8 USE IN SPECIFIC POPULATIONS 8.6 Renal Impairment	☑	☐	☐	• No dose adjustments are required in patients with mild renal impairment. Setmelanotide is not recommended in patients with moderate and severe renal impairment
12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics	☐	☑	☐	• **Energy Expenditure** Short-term administration of IMCIVREE in 12 healthy obese subjects increased resting energy expenditure and shifted substrate oxidation to fat, [redacted] (b) (4)
12.3 Pharmacokinetics	☐	☑	☑	• The accumulation of setmelanotide in systemic circulation during once-daily dosing over 12 weeks was approximately 30%. [redacted] (b) (4)

A = Acceptable; AWE=Acceptable with minor edits; U=Unacceptable/substantive disagreement (must provide comment);

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

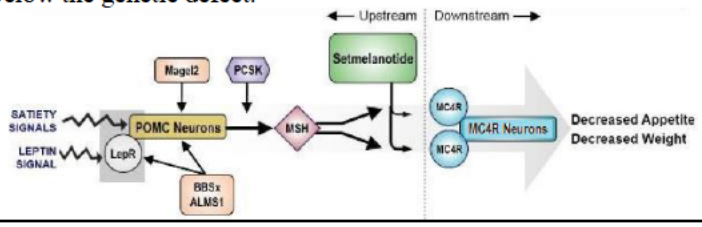
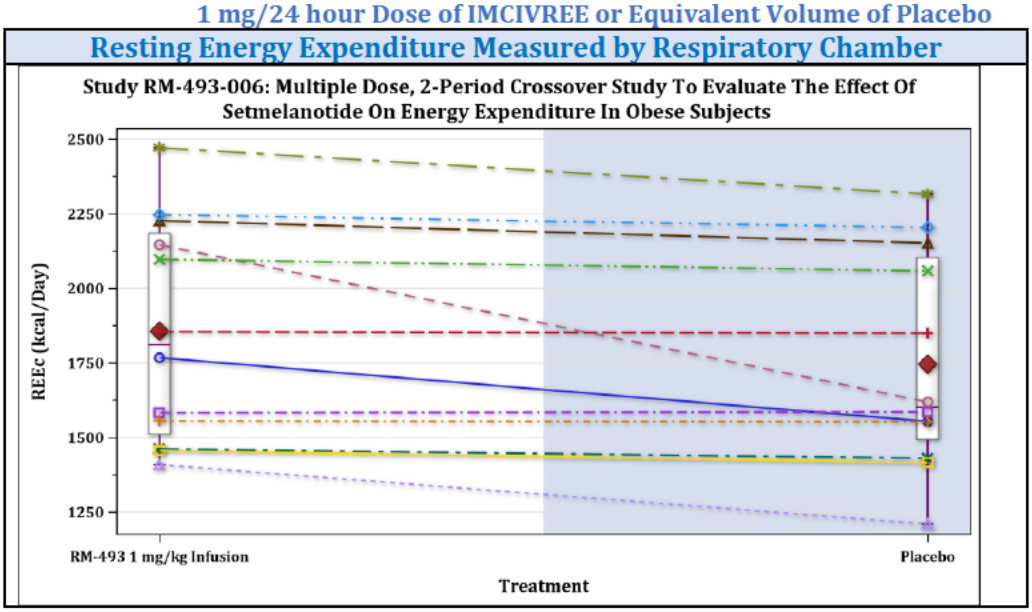
3.1 Overview of the Product and Regulatory Background

The clinical development program for IMCIVREE comprised of 13 studies: 6 Phase 1/1b/2a studies, 4 Phase 2 studies, 2 Phase 3 studies, and 1 long-term extension study. A total of 424 subjects participated in these clinical studies, including healthy obese volunteers (n = 313), patients with POMC, PCSK1 or LEPR (n = 64), patients with Prader-Willi syndrome (n = 39) and Bardet-Biedl syndrome and Alström syndrome patients (n=7).

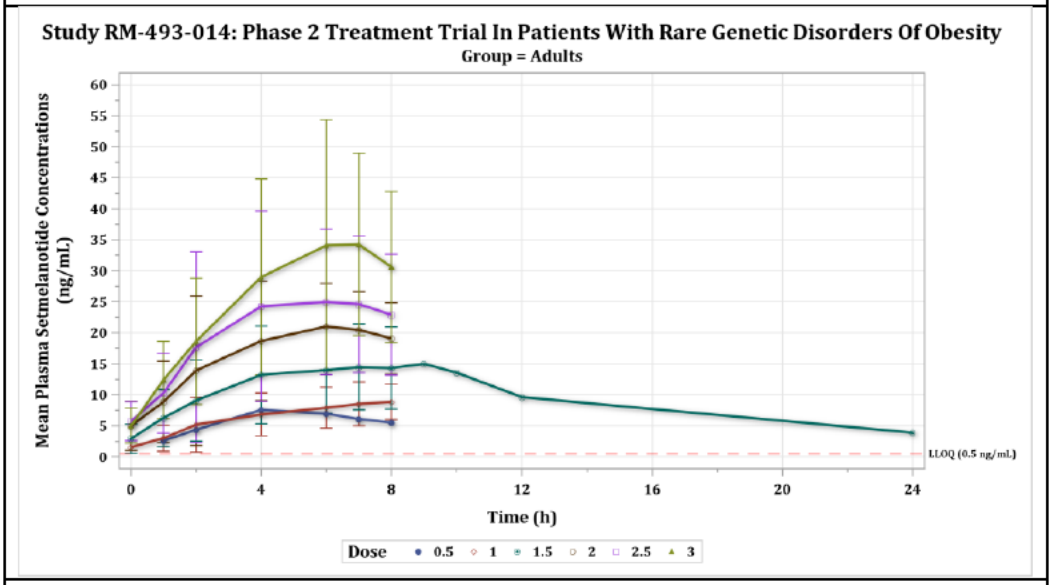
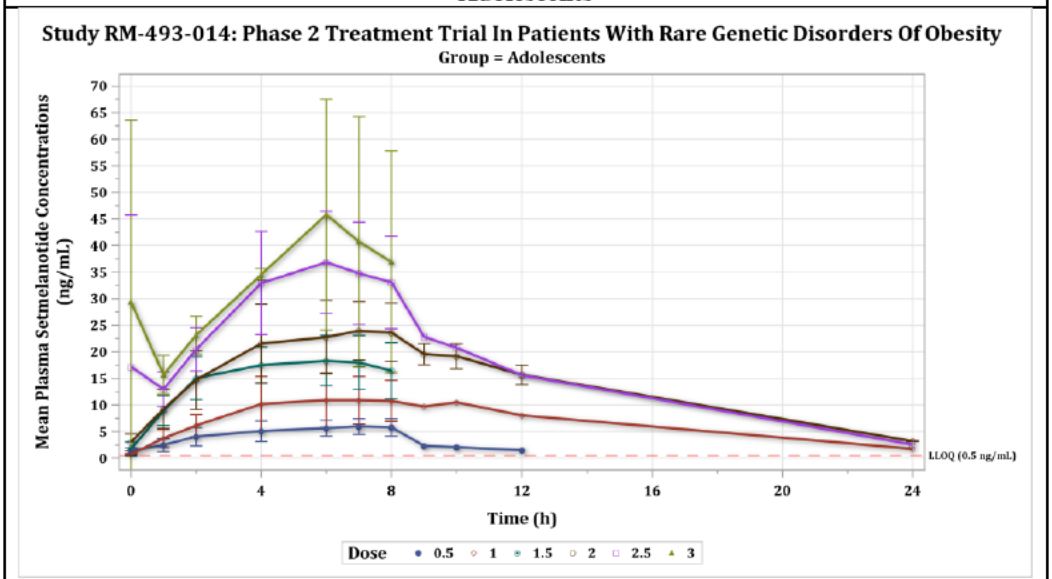
The regulatory history regarding these communications is summarized below:

Dates	Communication/Meeting Type	Key Communication Points
18 Dec 2015	Grant Request for Breakthrough Designation	• Agency granted breakthrough designation request after determining that setmelanotide for the treatment of proopiomelanocortin (POMC) deficiency obesity meets the criteria for Breakthrough Therapy designation.
01 May 2017	Grant Request for Expanded Breakthrough Designation	• Agency's revised breakthrough indication for setmelanotide for "the treatment of obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway." During a May 1, 2017 teleconference, the Sponsor had agreed to request the withdrawal of Breakthrough Designation for POMC deficiency obesity, since this condition is a subset of the indication granted with the current request.
27 Aug 2018	Type B Meeting	• Agreement of clinical pharmacology data package.
27 Nov 2018	Type B Meeting	• Bridging strategy for a proposed (b) (4) compared to the daily formulation
07 Aug 2019		• Request for Rolling Submission granted
27 Sep 2019	Type B Meeting (Pre-NDA)	• Agreement on the Immunogenicity package and Clinical Pharmacology package for NDA

3.2 General Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	The MC4 pathway serves a critical role in the control of food intake and energy balance. Its activity decreases appetite and caloric intake, and increases energy expenditure, with melanocortin 4 receptors (MC4R) acting as the final step in the signaling pathway. Under normal conditions, POMC neurons are activated by brain satiety signals, including those resulting from the hormone leptin acting through LEPR. POMC neurons produce a protein, which is specifically processed by the PCSK1, enzyme, into melanocyte stimulating hormone, or MSH, the natural ligand, or activator, for MC4R. When genetic mutations disrupt this pathway, the result is hyperphagia and severe obesity. Setmelanotide has the potential to restore lost function in this pathway by activating the intact MC4 pathway below the genetic defect. 
Active Moieties	Setmelanotide
Pharmacodynamics	Short-term administration of setmelanotide increases resting energy expenditure (REE) and shifts substrate oxidation to fat in obese individuals. **Figure 1 Mean Resting Energy Expenditure by Treatment following 1 mg/24 hour Dose of IMCIVREE or Equivalent Volume of Placebo**  *(Source: Reviewer generated graph)* Setmelanotide increased resting energy expenditure (REE) vs. placebo by 6.4% on average by 111 kcal/24h. Total daily energy expenditure (EE) trended higher while the thermic effect of a test meal and exercise EE did not differ significantly. The 23-hour non-exercise respiratory quotient was lower during setmelanotide treatment (0.833 ± 0.021 vs. 0.848 ± 0.022, p=0.02). No adverse effect on heart rate or blood pressure was observed.
General Information	

Bioanalysis	Setmelanotide concentrations in plasma were determined using validated LC-MS/MS assay. The validation range was 50 – 2000 pmol/L, with the lower limit of quantification (LLOQ) being 0.5 ng/mL.
Effect of Intrinsic Factors on Pharmacokinetics	Except body weight, PopPK analysis did not identify age, patient status (healthy obese vs. Rare Genetic Disorders of Obesity (RGDO)), and gender to have any clinically relevant impact on the PK or PD of setmelanotide. Setmelanotide apparent clearance after SC dosing (CL/F) varied with weight according to a fixed allometric relationship.
Dose Proportionality	Based on power regression analysis, setmelanotide C_{max} and $AUC_{0-\infty}$ were proportional over the range of 0.5 – 3.0 mg. There was a 5.71-fold increase in mean C_{max} and a 5.78-fold increase in mean $AUC_{(0\text{-last})}$ for the overall 6-fold increase in dose between 0.5 mg and 3 mg.
Intra-Subject Variability	PK: Estimates of intra-individual variability (IIV) (CV%) from the PopPK model were 28.7% for CL/F, 26.5% for apparent volume of distribution after SC dosing (V/F), and 52.3% for duration of zero-order absorption into central compartment (D2).
Renal or Hepatic Impairment	Eleven (11) subjects with mild renal impairment were included in the phase 3 trial. The popPK model suggests a trend towards 15% lower CL/F in patients with mild renal impairment, indicating a small effect of mild renal impairment on setmelanotide PK. Setmelanotide has not been studied in patients with moderate or severe renal impairment. *In vitro* evidence demonstrated that setmelanotide is not metabolized to any measurable degree by human liver microsomes (nor by human kidney microsomes or hepatocytes). No dedicated study was conducted with setmelanotide in hepatic impaired patients. Setmelanotide is not recommended for use in patients with severe hepatic impairment.
Pediatric	Pediatric simulations were carried out with the assumption that patients had normal renal function and the weight/age/sex distribution was randomly sampled from historical growth data over the desired age range. Based on the simulation, exposures in the 6 to <12-year-old group in general tended to be higher than those in the 12 to 17-year-old group at each setmelanotide QD dose. This was a direct result of the relationship between CL/F increasing with increasing body weight and the fixed dosing regimen.
Drug-Drug Interaction	*In vitro* results with human biomaterials indicated that the potential for setmelanotide to cause drug interactions is low. The Sponsor did not conduct any drug-drug interaction studies with setmelanotide.
Absorption	
Steady-State PK	The mean steady state $C_{max,ss}$ and $AUC_{(0\text{-}\tau)}$ following a 3 mg QD dose is 37.9 ng/mL and 495 h*ng/mL, respectively. Mean setmelanotide trough concentration for 3 mg QD is 6.77 ng/mL. Steady-state plasma concentrations of setmelanotide were achieved within 2 days of QD dosing. **Table 1 Steady-State Setmelanotide PK Parameters in Patients with Rare Genetic Disorders of Obesity (Study 014)** **Dose (mg)** / **N** / **$AUC_{0\text{-last}}$ (ng·h/mL)** / **AUC_{tau}[a] (ng·h/mL)** / **C_{max} (ng/mL)** / **C_{trough}[a] (ng/mL)** 0.5 mg / 13 / 35.8 / / 6.65 / 0.857 (18) 1.0 mg / 25 / 59.3 / 149 (1) / 10.4 / 1.52 (22) 1.5 mg / 22 / 106 / 308 (1) / 17.5 / 3.12 (26) 2.0 mg / 29 / 146 / 319 (2) / 25.1 / 4.37 (45) 2.5 mg / 19 / 188 / 330 (1) / 32.8 / 14.6 (56) 3.0 mg / 10 / 207 / / 38.0 / 13.4 (51) [a]Numbers in parenthesis indicates number of observations available

	Figure 2 **Mean Setmelanotide Concentration (±SD) Versus Time following 0.5 – 3.0 mg subcutaneous doses of IMCIVREE in Adult (Top Panel) and Adolescent Patients (Bottom Panel)** **Adults**  **Adolescents**  *(Source: Reviewer generated graph)*
T_{max}	Following SC injection of setmelanotide, plasma concentrations of setmelanotide reach maximum concentrations at approximately 8.0 h after dosing.
ADME	
Distribution	The mean apparent volume of distribution after SC administration of setmelanotide estimated from the Population PK model was 48.7 L. Plasma protein binding of setmelanotide is 79.1%.
Metabolism	The Sponsor did not conduct human metabolism studies with IMCIVREE. Setmelanotide does not appear to be metabolized by human hepatic microsomes, hepatocytes, or kidney microsomes.
Excretion	At steady state, approximately 39% of the administered setmelanotide dose was renally eliminated as unchanged drug during the 24-hour dosing interval following SC administration of 3.0 mg QD. The total apparent steady state clearance of setmelanotide following administration of 3.0 mg SC QD is estimated from population PK model to be 4.86 L/h. The effective half-life of setmelanotide is approximately 11 hours.

Immunogenicity	
Incidence	Anti-drug antibodies (ADA) to setmelanotide have not been detected in any clinical studies. A small number of samples tested positive for antibodies to α-MSH (2.5%), which were present both pre-treatment and post-treatment with setmelanotide.
Impact on PK	No relationship was found between any ADA parameters assessed (ADA to setmelanotide, neutralizing ADA to setmelanotide and antibodies to α-MSH) and PK or PD of setmelanotide.
Impact on Efficacy and Safety	Clinically meaningful association between immunogenicity and drug exposure, efficacy, or risk of adverse events (AEs) were not observed for setmelanotide.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The clinical pharmacology data presented in this NDA provides supportive evidence of effectiveness for IMCIVREE to for the treatment of obesity (b) (4) associated with POMC, including PCSK1, deficiency obesity or LEPR deficiency obesity in adults and children 6 years of age and older. The data from two phase 3 safety/efficacy studies (Studies RM-493-012 and RM-493-015) provided evidence of effectiveness of setmelanotide in producing clinically and statistically significant improvements in weight loss (b) (4) compared to baseline (see Clinical review by Dr. Galescu in DARRTS).

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed general dosing regimen is appropriate for the POMC and LEPR deficiency obesity patients. No dedicated dose-finding study was conducted in these patients. The starting dose of 2 mg in adults was selected based on clinical experience gained during the pivotal Phase 3 studies.

Due to limited available clinical data for doses of 2 mg and higher, and a theoretical concern that patients with MC4R pathway deficiencies might be especially sensitive to MC4R agonists, a cautious approach to the dosing regimen was followed at the time of study initiation. Adult dosing in Phase 3 pivotal studies were started at 1 mg, with dose increments of 0.5 mg every 2 weeks, until a therapeutic dose that resulted in weight loss or maximum dose of 3 mg was achieved. The starting setmelanotide dose was 0.5 mg in the pediatric patients (6 to 17 years of age) with dose increments of 0.5 mg and increasing up to a maximum dose of 3 mg. Frequent medical evaluation was needed with these small increments as it took 10 to 12 weeks to achieve a therapeutic dose resulting in weight loss. As subsequent clinical data from patients receiving doses up to 3 mg/day did not show any additional safety concerns, sponsor proposed an adult starting dose of 2 mg/day to allow for a quicker response to treatment.

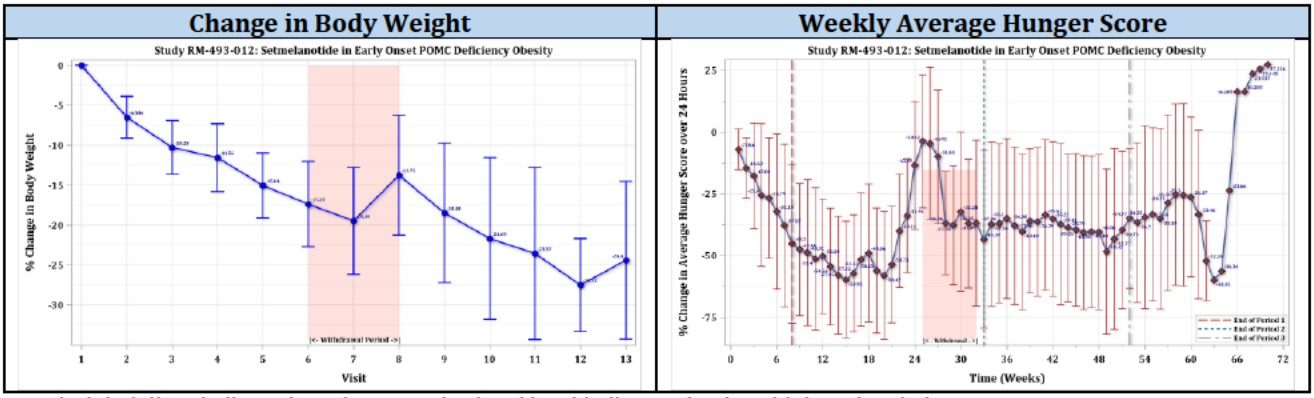
Study 012 and Study 015 were conducted in POMC and LEPR deficiency obesity patients, respectively. The primary endpoint in both studies was defined as the proportion of patients in the pivotal cohort in the full analysis set (FAS) population who met the ≥10% weight loss threshold (responders) after approximately 1 year of treatment. Eight (8) of the 10 patients with POMC/PCSK1 deficiency obesity and Five (5) of the 11 patients with LEPR deficiency obesity in the FAS Population achieved at least 10% weight loss after approximately 52 weeks of treatment with setmelanotide. This clinically meaningful body weight loss was accompanied with improvements in hunger score in POMC and LEPR obesity patients which was evaluated as secondary endpoint in both the studies.

The mean profiles of patients who met the ≥10% weight loss threshold is shown in Figure 3 and Figure 4. Longitudinal measurement of hunger score is also shown in the figures.

The drug's effectiveness is supported by exposure-response analyses which determined that at the proposed starting and maintenance doses, setmelanotide concentrations were at the plateau of the exposure-response curve. The EC_{50} (concentration needed to achieve half of the maximum efficacy = 7.8×10^{-20} ng/mL) was very small compared to the observed average concentration at the recommended starting and maintenance doses (C_{av} = 20.62 ng/mL).

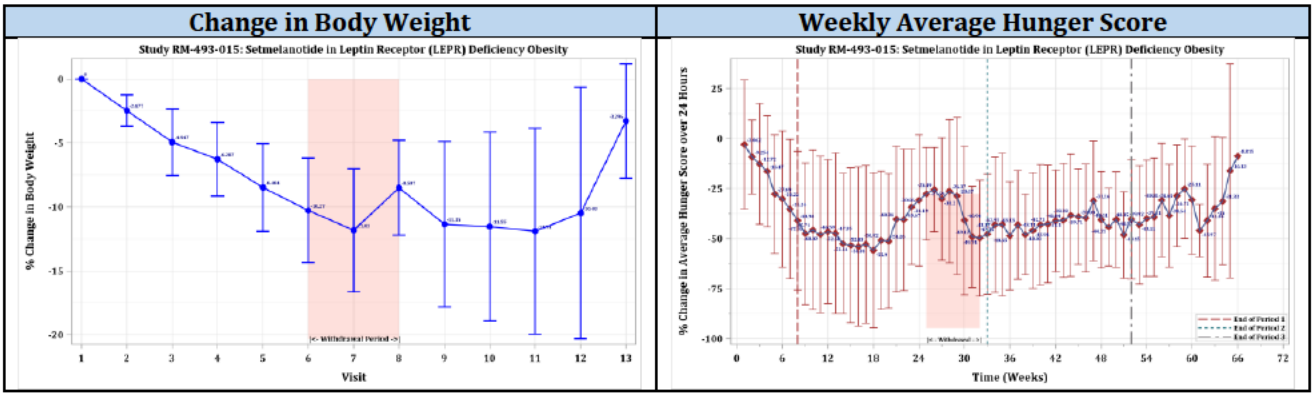
The proposed doses are also supported by the observed safety findings. Setmelanotide is generally well tolerated, with most adverse experiences being mild in nature. Nausea and vomiting were the predominantly reported adverse events followed by injection site reactions, and hyperpigmentation. It appears that if the initial nausea is tolerated, patients should be able to adhere to the proposed simplified dosing regimen.

Figure 3 Mean Absolute Weight Change from Baseline (Left Panel) and Weekly Average Hunger Score (Right Panel)in Study 012



Vertical dash lines indicate dose change, and colored band indicates placebo withdrawal period.
(Source: Reviewer generated graph)

Figure 4 Mean Absolute Weight Change from Baseline (Left Panel) and Weekly Average Hunger Score (Right Panel)in Study 015



Vertical dash lines indicate dose change, and colored band indicates placebo withdrawal period.
(Source: Reviewer generated graph)

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Based on the population PK (PopPK) model, using allometric scaling, baseline body weight but not renal function was found to be significant intrinsic covariates associated with setmelanotide exposure. Subjects with mild renal impairment had 19% (-6.5% to 47%) higher setmelanotide steady state AUC compared to those with normal renal function. Similarly, compared to subjects weighing 90 kg, subjects weighting 50

kg had 55% (38% - 73%) higher steady state AUC and subjects weighing 200 kg had 45% (39% - 52%) lower AUC. Due to the strong correlation between age and body weight (younger patients having lower body weight), the applicant's simulations indicated that pediatric subjects tend to be over-exposed compared to adults at the same setmelanotide dose. For this reason, the applicant proposes lower starting and maintenance doses for pediatric subjects. The applicant did not perform exposure-response analyses for efficacy nor for safety.

The following key review question was addressed from a dosing regimen and /or management perspective:

3.3.3.1 Does population PK and exposure-response modeling and simulation support the proposed labelling for specific populations?

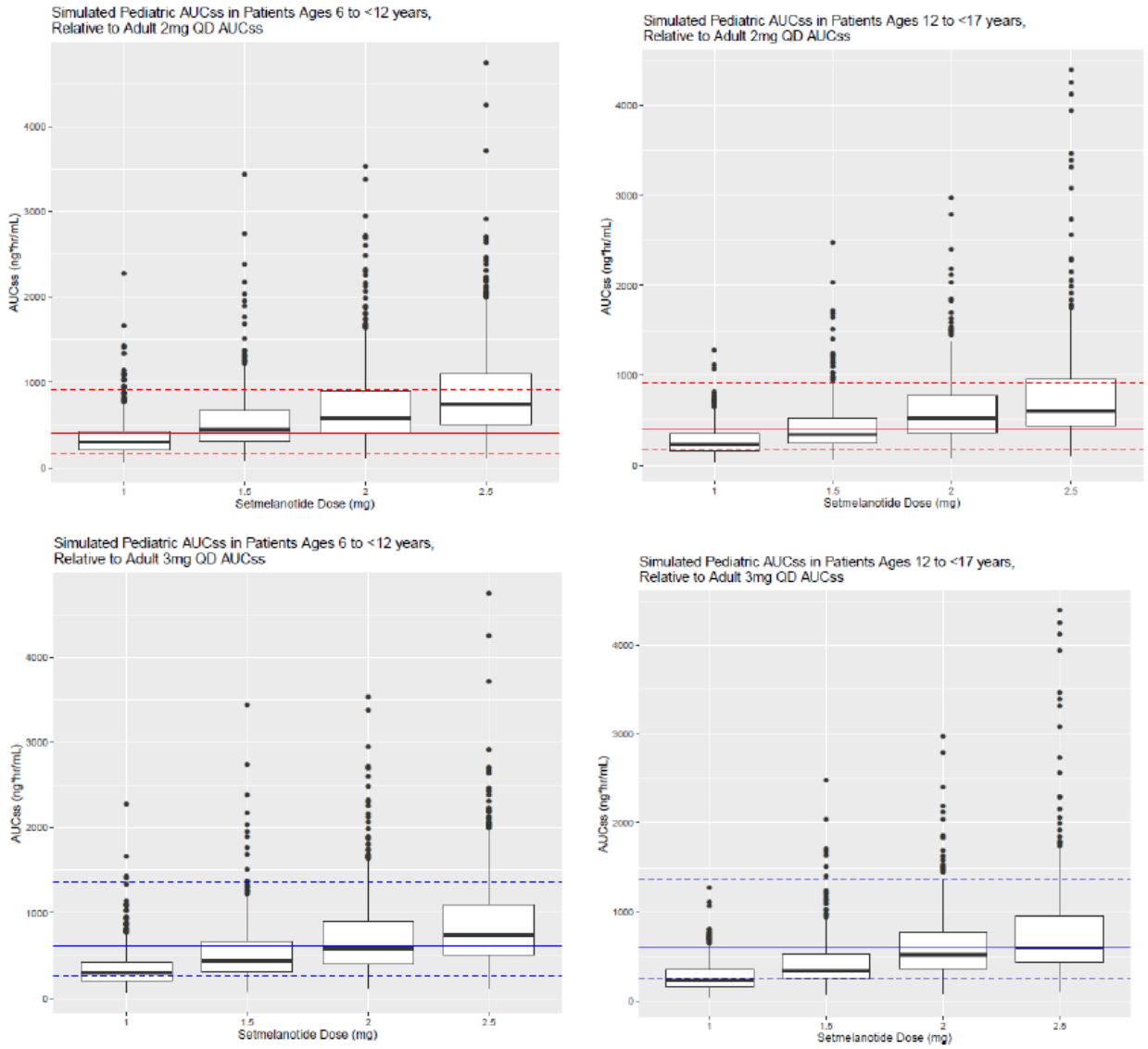
3.3.3.1.1 Pediatric subjects

Studies RM-493-012 (in POMC deficiency obesity) and RM-493-015 (in LEPR deficiency obesity) evaluated the PK of setmelanotide in pediatrics (n=4, Age: 6 to <12 years, body weight: 56 – 101 kg) and adolescents (n = 9, Age: 12 to 17 years). The body weights of patients between ages 12-17 years was 106-139 Kg in Study 012, while it was between 89-118 Kg in the Study 015. In pediatric patients, 6 to < 12 years, setmelanotide was initiated at 0.5 mg and maintenance dose ranged between 1.5 mg and 2 mg. Similarly, in adolescents (12-17 years), initial dose was 0.5 mg, but maintenance dose ranged between 1.5 mg and 2.5 mg. Exploration of individual weight profiles indicate that all pediatric patients lost weight immediately after start of treatment. The data also indicate that titrations were mainly based on tolerability rather than on a pre-specified target for weight loss. A maximum dose of 3 mg was prespecified in the protocol for those patients who could tolerate higher doses of setmelanotide.

On the other hand, findings from a PopPK model developed using PK data from these 2 studies concluded that patients aged 6 to <12 years of age would require a dose of 1.5 mg to match median adult exposures at the 2 mg dose and patients 12-17 years of age would require a dose of 2 mg. To approximate adult exposures at the 3 mg dose, patients aged 6 to <12 years of age would require a dose of 2 mg and patients aged 12-17 years of age would require a dose of 2.5 mg (Figure 5). These findings from model simulations suggest a higher starting dose would be warranted for pediatric subjects if an exposure matching principle was used. Though the safety profile of setmelanotide appears to be favorable in this patient population, the information is still limited, as only 4 subjects in the lower age group have been studied so far. The sponsor proposed (b) (4)

Because the Agency did not perform an exposure-vs-safety analyses and the relationship between exposure and adverse events is unknown, there is the possibility of a positive relationship between exposure and adverse events. Thus, a conservative approach to lower starting and maintenance doses in the lower age group of pediatric patients is appropriate, given the paucity of safety data in the 6 to <12 years of age subgroup (See Section 4.4 Pharmacometric Assessment for additional details). However, adolescents (12-17 years of age) may benefit from the same starting dose as adult subjects, as their baseline weight is comparable to adults and are predicted to have similar exposures as adults at the same starting dose. No significant safety events of interest were detected in adolescents in clinical trials.

Figure 5 Simulated Setmelanotide AUC_{ss} for Pediatric Patients



Key: Box and whisker plots, median line represents 50th percentile, box represent 25th and 75th percentile. Solid line represents the adult median, dotted line represent the median and 95% CI from the adult reference ranges.

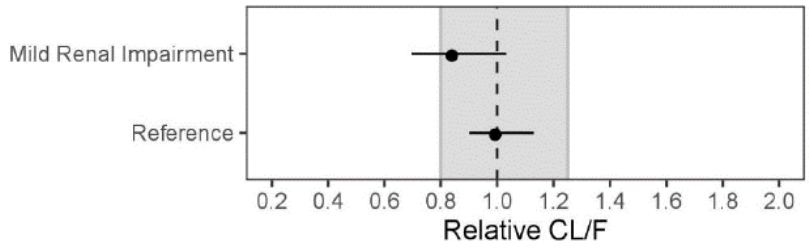
(Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Figure 7, page 58)

3.3.3.1.2 Renal impairment

The effect of renal function on setmelanotide CL/F was evaluated across a range of creatinine clearance of 60 to 90 mL/min utilizing the developed population PK model by using PK data from 11 patients with mild renal impairment. Subjects with creatinine clearance values above 90 mL/min were assumed to have normal renal function. The expected effect was a ~20% decrease in CL/F for a patient with a creatinine clearance of 75 mL/min (Figure 6). Evaluation of renal function as a categorical covariate on CL/F (mild impairment vs. normal renal function) showed that subjects with mild renal impairment had a ~15% lower CL/F as compared to those with normal renal function. This magnitude of change in clearance is not expected to be clinically significant and thus, no dose adjustment is recommended for patients with mild renal impairment.

Setmelanotide has not been studied in patients with moderate or severe renal impairment and thus, no dosing recommendations are proposed for these patients.

Figure 6 Effect of Mild Renal Function on Setmelanotide Clearance



(Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Figure 6, page 54)

Acceptability of proposed labelling for Renal Impairment:
The proposed labelling for mild renal impairment is acceptable. No dose adjustments are required in patients with mild renal impairment. The starting and maintenance doses in mild renal impaired subjects will result in exposures at the plateau of the dose response curve. Although mild renal impairment does not seem to be a significant PK covariate, approximately 40% of drug was eliminated unchanged in the urine. Thus, patients with moderate or severe renal impairment may have significantly higher exposure compared to patients with to normal renal function. Based on the lack of information, dosing in moderate and severe renal impairment is not recommended.

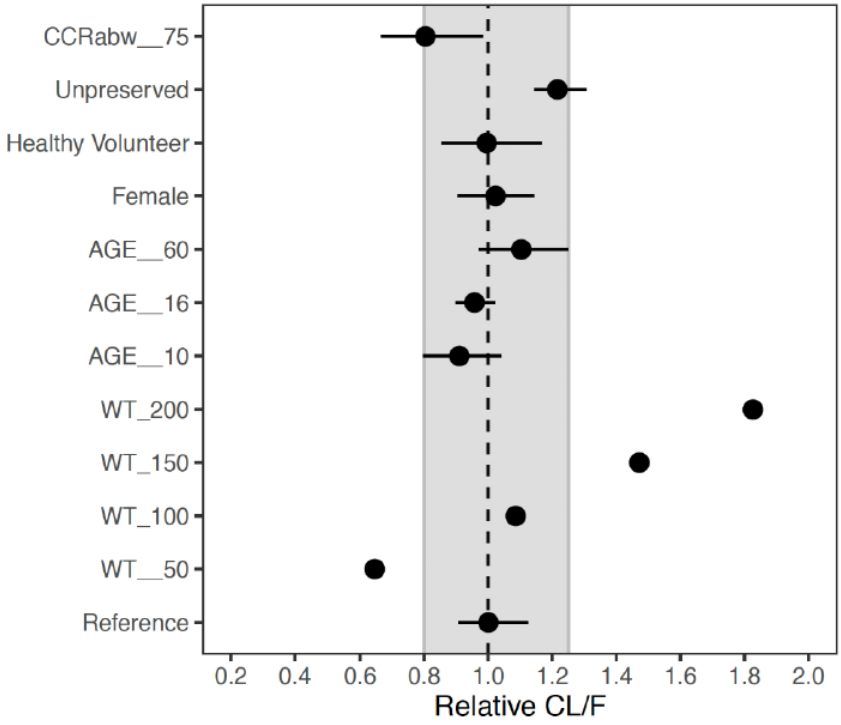
3.3.3.1.3 Hepatic Impairment

A study in hepatically impaired patients was not conducted, and setmelanotide is not indicated in patients with hepatic impairment.

3.3.3.1.4 Race, Sex, Body weight and Age

A fixed allometric relationships with exponents of 0.75 (CL/F) and 1.0 (V/F) was included for baseline body weight in the PopPK model. Based on the model and given the distribution of weight in the population PK database, the expected fold-changes in CL/F, relative to a 90 kg patient was a ~35% decrease for a 50 kg patient to an 83% increase for a 200 kg patient. Additionally, the model indicated that age was not a significant factor influencing clearance of setmelanotide (Figure 7), however a strong relationship between age and weight impacts recommendations for pediatric dosing.

Figure 7 Effect of Covariates on Setmelanotide Clearance



Key: Grey shaded area represents a range of 80-125% for reference. Point estimates and lines represent the median and 95% CI in the parameters, relative to the reference values. The reference CL/F represents a 25 year-old, 90kg, male patient with normal renal function receiving the preserved formulation.

(Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Figure 5, page 54)

3.3.3.1.5 Genomics

On May 05, 2020, the Office of Clinical Pharmacology/Division of Translational and Precision Medicine (OCP/DTPM) asked the applicant in an Information Request (IR) to provide the sequence variants interpretation for all subjects included in studies RM-493-012 and RM-493-015.

The FDA received response to the IR on May 20, 2020. DTPM has reviewed the pathogenicity assignment of the genetic variants in the POMC, PCSK1, and LEPR genes. We generally concur with the applicant's assessment of the pathogenicity of the genetic variants. For additional information please see the DTPM review in the Appendix 4.5.

3.3.4 Are there clinically relevant drug-drug interactions, and what is the appropriate management strategy?

No new drug-drug interaction study was carried out with setmelanotide. *In vitro* studies demonstrated that setmelanotide has low potential for pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP), transporters and plasma protein binding.

Setmelanotide showed no inhibition potential for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. The 50% inhibition concentration (IC_{50}) was >1 mM for CYP1A2, 2C9, 2C19 and 2D6, and >50μM for CYP3A4. The potential for time-dependent inhibition (TDI) of cytochrome P450 by setmelanotide showed that setmelanotide is not a time-dependent inhibitor of major

hepatic CYPs. Evaluation of the potential for cytotoxicity and induction of cytochrome P450 mRNA expression and enzyme activity (CYP1A2, CYP2B6 and CYP3A4) in human hepatocytes by setmelanotide showed that setmelanotide is not an inducer of these CYPs, nor is it cytotoxic up to 1 μM.

Assessment of the substrate and inhibitor potential of setmelanotide for transporters showed that setmelanotide is not a significant inhibitor of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), OATP1B1, OATP1B3, OAT1, OAT3, or OCT2 and is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. Setmelanotide is a not a substrate of MATE1 or MATE2K; setmelanotide is not an inhibitor of MATE1 or MATE2K. These results do not warrant a clinical drug interaction study.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 How is IMCIVREE identified and what are the analytical methods used to measure them in plasma?

Setmelanotide concentrations in plasma were determined using a validated LC-MS/MS assay. The validation range was 0.500 – 200 ng/mL, with the lower limit of quantification (LLOQ) being 0.500 ng/mL. A summary of validation parameters for the quantitation of setmelanotide in plasma is shown in Table 2.

4.1.1 How is IMCIVREE identified and what are the analytical methods used to measure them in urine?

Setmelanotide concentrations in urine were determined using a validated LC-MS/MS assay. The validation range was 2.00 - 800 ng/mL, with the lower limit of quantification (LLOQ) being 2 ng/mL. A summary of validation parameters for the quantitation of setmelanotide in urine is shown in Table 3.

Table 2 Summary Table of ELISA Method Validation for Quantitation of Setmelanotide (IMCIVREE) in Human Plasma

Validation Reports	Method Performance		
Setmelanotide in Human Plasma (original method) Title: Determination of RM-493 in Human Halt-Stabilized K_2-EDTA Plasma by LC-MS-MS (b) (4) Document #: 03221NK	Lower Limit of Quantification	0.500 ng/mL	
	Validated Range	0.500 to 200 ng/mL, using 0.5 mL plasma	
	Calibration Curve Concentrations (ng/mL)	0.500, 1.00, 2.50, 10.0, 25.0, 100, 180, and 200 ng/mL	
	QC Controls (validation)	0.500 (LLOQ), 1.50 (Low), 20.0, (Mid), 160 (High), and 1000 (Very High QC) ng/mL	
	Precision and Accuracy (Based on 6 replicates for each QC concentration for 3 runs)	Precision	Accuracy
	Intra-run	0.5 to 6.0% (LLOQ 17.9%)	-5.6 to 12.0% (LLOQ 17.4%)
	Inter-run	1.8 to 4.6% (LLOQ 13.6%)	--3.8 to 9.3%
	Dilution (10x) QC (1000 ng/mL)	Precision: 2.4% Accuracy: +1.0%	
	Benchtop stability extracted samples at 1°C	24 hours	
	Processed thawed/extracted stability at 22°C	66 hours	
	Recovery of setmelanotide and Internal Standard (0.500 – 200 ng/mL)	Setmelanotide: 29% to 46% Internal Standard: 29% to 45%	
	Short-term stability: stock and working solutions **Stock Solution (288 – 305 ug/mL)** 4° C Room Temperature **Stock Solution (10 ng/mL)** 4° C Room Temperature	 217 days 23 hours 140 days 16 hours	
	Long-term stability of plasma samples	See validation amendments	
	Freeze-thaw cycles	At least 5 freeze-thaw cycles	
	Re-injection reproducibility	Pass	
	Matrix factor; comparison of extracted spiked samples in matrix to matrix-free samples	Acceptable	
	Carry-over from control sample after ULOQ sample	None	
	Interference from 20 commonly used medications (acetaminophen, acetylsalicylic acid, brompheniramine, caffeine, cetirizine, chlorpheniramine, cimetidine, dextromethorphan, diphenhydramine, famotidine, ibuprofen, ketoprofen, loratadine, naproxen, omeprazole, phenylephrine, pseudoephedrine, ranitidine, salicylic acid, and triprolidine.)	None	
Amendment #1 (incorporating long-term stability to 124 days at -70°C) Document # 03221NK_am1	Long-term stability to 124 days at -70°C	High Control (160 ng/mL) Bias: -7.5% to -6.3% Low Control (1.50 ng/mL) Bias: -10.7% to -4.0%	
Amendment #2 (incorporating long-term stability to 203 days at -70°C) Document # 03221NK_am2	Long-term stability to 203 days at -70°C	High Control (160 ng/mL) Bias: -2.5% to 2.5% Low Control (1.50 ng/mL) Bias: 0.7% to 12.0%	

Validation Reports	Method Performance			
Amendment #3 (incorporating 116 h extract stability and long-term stability to 295 days (low QC) and 312 days (high QC) at -70°C) Document # 03221NK_am3	116 h extract stability at 22°C	Mean % Bias: High Control (160 ng/mL): +0.63% Low Control (1.50 ng/mL): -2.61%		
	Long-term stability to 295 days (low QC) and 312 days (high QC) at -70°C	High Control (160 ng/mL): Bias: -3.1% to +0.6% Low Control (1.50 ng/mL): Bias: +6.7% to +16.7%		
Amendment #4 (Extended extract stability to 144 h at 22°C) Document # 03221NK_am4	Extended extract stability to 144 h at 22°C	Mean % Bias: High Control (160 ng/mL): +1.9% Low Control (1.5 ng/mL): +0.7%		
Amendment #5 Extended long-term stability to 575 days (low QC) and 590 days (high QC) at -70°C Document # 03221NK_am5	Extended long-term stability to 575 days (low QC) and 590 days (high QC) at -70°C	High Control (160 ng/mL): Bias: -1.9% to +2.5% Low Control (1.50 ng/mL): Bias: -1.3% to +6.7%		
Amendment #6 Precision and accuracy equivalency for new reference standard (second lot #) Document # 03221NK_am6	Precision and accuracy equivalency for new reference standard (second lot #) LLOQ = 0.500 ng/mL QC Low = 1.50 ng/mL QC Med = 20.0 ng/mL QC High = 160 ng/mL		Precision	Accuracy
		LLOQ	9.4%	122%
		QC Low #1	5.9%	103%
		QC Low #2	8.2%	102%
		QC Med #1	1.8%	101%
		QC Med #2	2.4%	95.5%
		QC High #1	1.8%	98.8%
		QC High #2	1.6%	97.5%
Amendment #7 Additional validations to establish batch size, assess whole blood stability, assess matrix	Batch size determination	Max batch size established for 189 cycles		
	Precision and accuracy to establish batch size		Precision	Accuracy
		LLOQ	3.8%	-2.8%
effect in hemolytic and lipemic plasma and interference from additional common medications. Document # 03221NK_am7		QC Low	5.1%	+1.3%
		QC Med	2.2%	-1.0%
		QC High	1.7%	+1.3%
	Whole Blood Stability	Room Temperature: stable for up to 2 hours On Ice: stable for up to 2 hours		
	Calibration Curve Concentrations (ng/mL)	0.500, 1.00, 2.50, 10.0, 25.0, 100, 180, and 200 ng/mL		
	Matrix Effect: normal, hemolytic lipemic plasma Matrix factor Internal Std Normalized Matrix Factor	Setmelanotide: 0.895 – 1.09, Int Std: 0.894 – 0.968 0.49% - 4.16%		
	Interference from common medications: drospirenone, ethinyl estradiol, etonogestrel, levonorgestrel, medroxyprogesterone acetate, norgestimate, and norethindrone	None		

(Source: Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 4, pp 12-15

Table 3 Summary Table of ELISA Method Validation for Quantitation of Setmelanotide (IMCIVREE) in Human Urine

Validation Reports	Method Performance		
Setmelanotide in Human Urine (Original method) Title: Determination of RM-493 in Human CHAPS-Fortified Urine by LC-MS-MS 3/22/2012 (b) (4) Document No. 1004312	Lower Limit of Quantification	2.00 ng/mL	
	Validated Range	2.00-800 ng/mL, using 0.2 mL urine	
	Calibration Curve Concentrations (ng/mL)	2.00, 4.00, 10.0, 40.0, 100, 400, 720, and 800	
	QC Controls (validation)	2.00 (LLOQ), 6.00 (Low), 60.0 (Mid), 640 (High), and 4000 (Very High) ng/mL	
	Precision and Accuracy (Based on 6 replicates for each QC concentration for 3 runs)	Precision	Accuracy
	Intra-run	0.66 to 7.7% (LLOQ 9.1%)	-5.6 to 8.5%
	Inter-run	2.3 to 5.4% (LLOQ 7.6%)	-3.8 to 4.5%
	Dilution (10x) QC (4000 ng/mL)	Precision: 2.7%	
		Accuracy: -0.8%	
	Benchtop stability	24 hours at room temperature	
	Short-term stability of thawed/extracted samples	69 hours at room temperature	
	Recovery of Setmelanotide and Internal Standard	Setmelanotide: 81.81 to 88.11% Internal Standard: 78.52 to 88.47%	
	Short-term stability: stock and working solutions	48 days at 4°C; 23 hours at room temperature	
	Long-term stability of urine samples	11 days at-20°C	
	Freeze-thaw cycles	5	
	Re-injection reproducibility	Pass	
	Matrix Factor, comparison of extracted spiked samples in matrix to matrix-free samples	Acceptable	
	Carry-over from control sample after ULOQ sample	Not significant	

Validation Reports	Method Performance	
	Interference from 20 commonly used medications (acetaminophen, acetylsalicylic acid, brompheniramine, caffeine, cetirizine, chlorpheniramine, cimetidine, dextromethorphan, diphenhydramine, famotidine, ibuprofen, ketoprofen, loratadine, naproxen, omeprazole, phenylephrine, pseudoephedrine, ranitidine, salicylic acid, and triprolidine.	None
Amendment 1 (incorporating long-term stability to 114 days at -20°C and -70°C) Document No. 1004312_am1	Long-term stability to 114 days at -20°C and -70°C	At -20°C High control (640 ng/mL) Bias -4.7% to 7.2% Low Control (6.00 ng/mL) Bias 11.3% to 12.5% At -70°C High control (640 ng/mL) Bias -8.4% to 5.2% Low control (6.00 ng/mL) Bias 2.0% to 19.0%%
Amendment 2 (incorporating matrix effects, established batch sizes, and increased long-term stability at -20°C) Document No. 1004312_am2	Matrix Effect Batch size: established at 93 Long-term stability to 380 days at -20°C	IS-Normalized Matrix Factor (mean, CV%) Low Control (4 ng/mL) 0.984, 2.71% High Control (720 ng/mL) 1.02, 0.69% 93 At -20°C High control (640 ng/mL) Bias -6.7 to -3.8% Low Control (6.00 ng/mL) Bias -1.7 to 6.2%
Amendment 3 7/9/2014 (incorporating additional freeze/thaw cycle Document No. 1004312_am3	Freeze/thaw cycles % Bias Values: High 640 ng/mL Low 6.00 ng/mL	6 2.7% 4.2%

4.2 Biopharmaceutics

The final commercial IMCIVREE Injection product is a preserved, multi-dose setmelanotide (b) (4) solution with N-(carbonyl-methoxypolyethylene glycol 2000)- 1,2 –distearoyl-glycero-3-phospoethanolamine sodium salt (mPEG-2000-DSPE), and carboxymethyl cellulose sodium (CMC). The formulation contains 10 mg/mL setmelanotide and 100 mg/mL mPEG-2000-DSPE (b) (4) The formulation also contains mannitol and a preservative (b) (4) benzyl alcohol and sodium edetate. The unit formula for IMCIVREE Injection U-100 is provided in Table 4.

Table 4 Composition of the Commercial Formulation: Preserved Setmelanotide mPEG-DSPE/CMC Injection

Component	Composition, mg/mL
Setmelanotide[a] (b) (4)	10 mg
mPEG-2000-DSPE[b]	100 mg
Mannitol	11.0 mg
Carboxymethylcellulose sodium	8.0 mg
Phenol	5 mg
Benzyl Alcohol	10 mg
Sodium Edetate	1 mg
Water for Injection	q.s. to 1.0 mL

[a] (b)
[b] N-(Carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt

(Source: Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 1, Page 7)

4.3 Clinical PK and PD Assessments

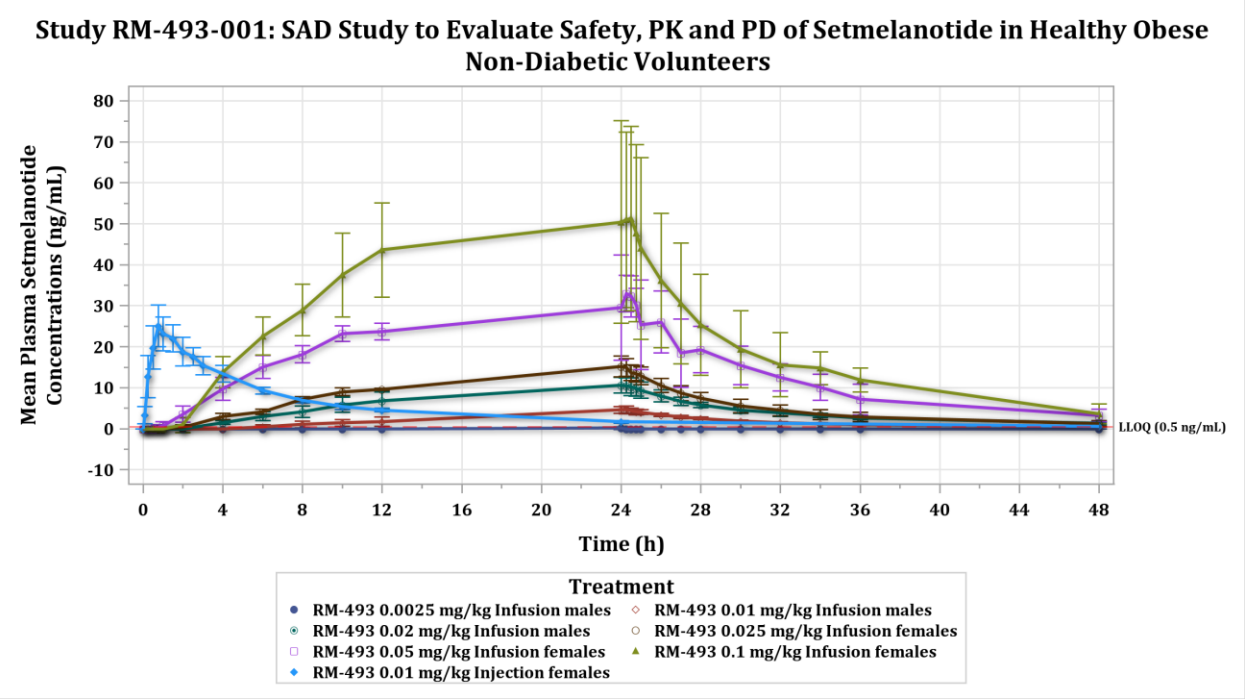
Study RM-493-001: *Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Setmelanotide Administered to Healthy Obese Non-Diabetic Volunteers*

This first-in-human (FIH) trial was conducted to evaluate the safety and tolerability of single doses of setmelanotide administered by SC continuous infusion and injection to healthy obese subjects. The other goals for this study were to evaluate the PK and PD profiles for single doses of setmelanotide. A total of 36 healthy obese non-diabetic volunteers, 13 White and 23 Black, 16 males and 20 females, aged between 20 and 53 years (mean = 35.6 years), participated in this study. The mean body weight of the population was 96.8 kg for the placebo group (n=22), 114.0 kg for the 0.0025 mg/kg group (n=3, males), 112.0 kg for the 0.01 mg/kg group (n=7), 104.3 kg for the 0.02 mg/kg group (n=4), and 95.3 kg for the 0.025 mg/kg group (n=3, females). The mean BMI was 33.0 kg/m^2 for the placebo group (n=22), 36.9 kg/m^2 for the 0.0025 mg/kg group (n=3, males), 34.8 kg/m^2 for the 0.01 mg/kg group (n=7), 32.3 kg/m^2 for the 0.02 mg/kg group (n=4), and 34.3 kg/m^2 kg for the 0.025 mg/kg group (n=3, females).

Serial blood samples were taken for the PK measurement of setmelanotide.

The mean setmelanotide exposure following administration of 0.0025, 0.01, 0.02, .025 and .05 mg/kg infusion doses of IMCIVREE and 0.01 mg/kg injection dose of IMCIVREE is presented in Figure 8.

Figure 8 **Mean (± SD) Setmelanotide Concentration Versus Time Following SC Infusion Doses of 0.0025, 0.01, 0.02, 0.025 and 0.05 mg/kg and 0.01 mg/kg SC Injection Dose of IMCIVREE**



(Source: Reviewer generated graph)

Since this study used an early formulation of setmelanotide that was not carried forward to pivotal trials and the dosing was based on per kg body weight instead of nominal daily dosing, the PK and PD findings from this study will not be discussed in detail.

Pharmacokinetics:
Setmelanotide appeared to exhibit two compartment pharmacokinetics following subcutaneous bolus injection or infusion over 24-hours.

A lag time was observed after continuous SC infusions of RM-493. The mean ±SD lag times varied from 0.74 ± 0.22 hr (for 0.05 mg/kg dose group) to 6.00 ± 2.83 hr (for the 0.01 mg/kg dose group). There was no lag time after administration of the SC bolus dose.

The mean T_{max} was approximately 24 hours (i.e., at the end of infusion) across all SC infusion dosing groups. Mean C_{max} ranged from 0.187 ng/mL (n = 1, 0.0025 mg/kg) to 64.75 ng/mL (n = 4, 0.1 mg/kg). After SC injections (0.01 mg/kg), the mean values for T_{max} and C_{max} were 25.4 ± 4.605 hr and 25.4 ± 4.605 ng/mL, respectively (Figure 8).

The mean (± SD) setmelanotide t½ was 8.98 ± 2.12 h across all dose groups (SC infusion and SC injection) and ranged from 5.59 to 12.9 hours across individual subjects.

Setmelanotide was excreted as unchanged parent drug into urine. Across all SC infusion dose groups (excluding the 0.0025 mg/kg male group which had mostly undetectable RM-493 plasma concentrations), the mean fraction of dose excreted unchanged was 27.35 ± 11.46% and ranged from 23 ± 5% (0.01 mg/kg in males) to 38 ± 4% (0.05 mg/kg administered to females). The mean renal clearance of setmelanotide was 43.98 ± 15.27 mL/min.

Pharmacodynamics:
Though signals of numerical effects of setmelanotide on parameters of hunger/satiety were observed, especially at the higher doses studied, few reached statistical significance The Sponsor hypothesized that this could be due to confounding issues associated with this data as some of the higher doses were also associated with a higher incidence of nausea.

Study RM-493-002: *Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Setmelanotide Administered to Healthy Obese Non-Diabetic Volunteers*

This trial was conducted to evaluate the safety and tolerability of multiple doses of setmelanotide when given by continuous subcutaneous (SC) infusion for 14 or 28 days or by SC injections every 12 hours (Q12 hours) for 14 days. The other goals for this study were to evaluate the PK and PD profiles for multiple doses of setmelanotide. A total of 57 subjects (age range: 19 – 57 years; 43 male and 14 females; weight range: 77.6 – 163.7 kg) were enrolled and randomly assigned study treatments within a specific cohort. Thirty-nine subjects received setmelanotide and 18 subjects received placebo.

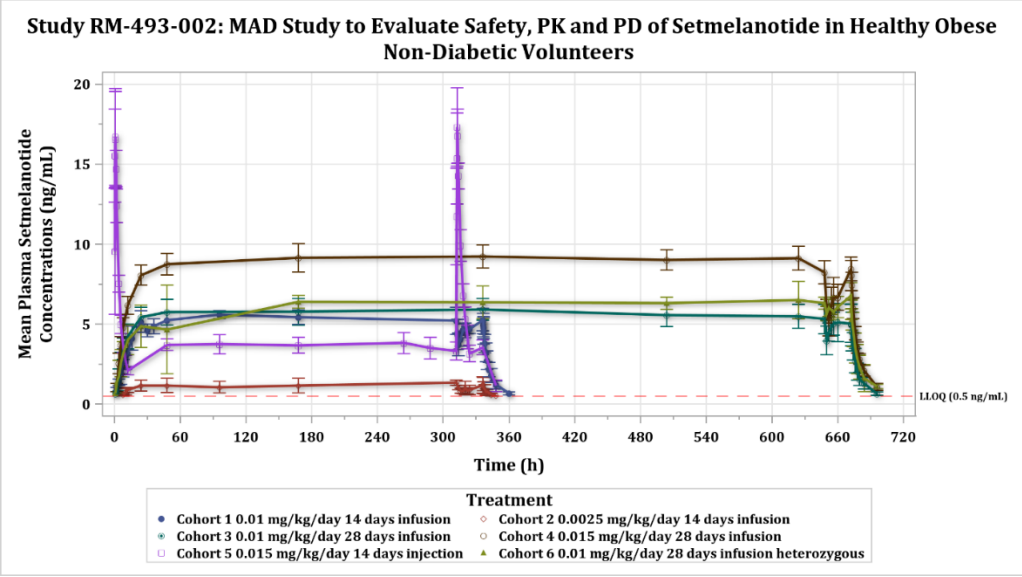
The RM-493 doses administered during this trial were, in chronological order:

- Cohort 1: 0.01 mg/kg/day for 14 days via SC infusion
- Cohort 2: 0.0025 mg/kg/day for 14 days via SC infusion
- Cohort 3: 0.01 mg/kg/day for 28 days via SC infusion
- Cohort 4: 0.015 mg/kg/day for 28 days via SC infusion
- Cohort 5: 0.015 mg/kg/day for 14 days via SC injection (0.0075 mg/kg every 12 hours)
- Cohort 6 (MC4R heterozygous subjects): 0.01 mg/kg/day for 28 days via SC infusion

Serial blood samples were taken for the PK measurement of setmelanotide.

The mean setmelanotide exposure following administration of 0.0025, 0.01, 0.015 mg/kg/day infusion doses of IMCIVREE and 0.015 mg/kg injection dose of IMCIVREE is presented in Figure 9.

Figure 9 Mean (± SD) Setmelanotide Concentration Versus Time Following Doses of 0.0025, 0.01, 0.015 mg/kg/day Infusion Doses and 0.015 mg/kg Injection Dose of IMCIVREE



(Source: Reviewer generated graph)

Pharmacokinetics:

In subjects receiving SC infusions, plasma setmelanotide concentrations reached a plateau by 24 to 48 hours after starting the infusion, suggesting that steady state is achieved by 24 to 48 hours. Following SC injection administered every 12 hours, setmelanotide steady-state concentrations were reached by 24 to 48 hours. Trough setmelanotide concentrations were reasonably consistent from Day 3 to the last day of

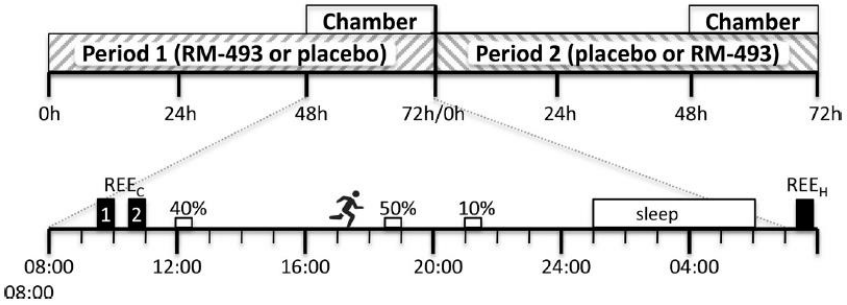
dosing (Day 14 or 28). Setmelanotide AUC and C_{max} increased with increasing dose in a roughly dose-proportional manner following single- and multiple-dose SC infusions.

However, the formulation used in this study was not carried forward to the pivotal program and additionally dosing in subsequent studies was based on fixed dosing as opposed to body weight-based dosing carried out in the current study. Further discussion about findings from this study will not be carried out as the findings do not contribute towards the labeling for the product.

Study RM-493-006 - *Multiple Dose, Energy Expenditure in Healthy Obese Subjects*

Study RM-493-006 was a double-blind, placebo-controlled, multiple-dose, 2-period, crossover study in healthy obese subjects to evaluate the effect of setmelanotide on resting energy expenditure (REE) measured in a room calorimeter during continuous SC infusion of setmelanotide. Subjects stayed for 24 hours in a metabolic chamber for the 3-day duration of each period, where they received active treatment during one period and placebo in another according to a randomization scheme. PK samples were drawn daily just before dosing. Urine over 24 hours was collected on the last day of treatment of both periods.

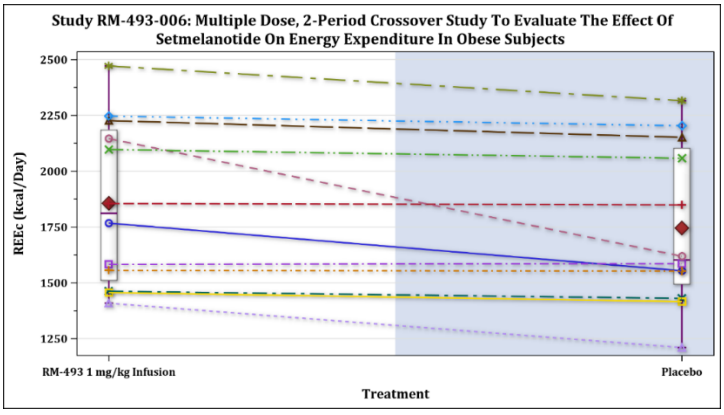
A total of 12 obese normotensive, nondiabetic, subjects with normal thyroid function at baseline participated in the study. The subjects were between the age of 18 and 50 years with a body mass index (BMI) between 30 and 40 kg/m^2. A schematic of the study design is shown below:



The primary outcome, resting energy expenditure measured by respiratory chamber (REEC) was defined as the average resting energy expenditure in the metabolic chamber from 09:30 (49.5-hour after starting treatment) to 10:00 and 10:30 to 11:00 while the subject was fasting, completely still, and awake in a seated position under the observation of the study personnel. The effect of setmelanotide vs placebo on REE is presented in Figure 10.

Setmelanotide increased resting energy expenditure vs. placebo by 6.4% (95% CI: 0.68 to 13.02 %), on average by 111 kcal/24h (95% CI: 15 to 207 kcal, p=0.03). Total daily energy expenditure trended higher while the thermic effect of a test meal and exercise energy expenditure did not differ significantly. The 23-hour non-exercise respiratory quotient was lower during setmelanotide treatment (0.833 ± 0.021 vs. 0.848 ± 0.022, p=0.02).

Figure 10 Effect of Setmelanotide Compared to Placebo on Resting Energy Expenditure



(Source: Reviewer generated graph)

Study RM-493-009: *Phase 1B/Phase 2A Safety and Efficacy of Setmelanotide in Obese Subjects*

Study RM-493-009 was a staged, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of setmelanotide when administered by SC injection. This study was conducted in three stages, with each new stage initiated after review of the safety, tolerability and weight loss from the initial ~4 weeks of the previous stage.

Stage A: A total of 25 obese subjects (14 male, 11 female) with a mean age of 40.3 years (range: 24 – 59 years), mean weight of 99.98 kg (range: 78.6 – 130.2 kg), and mean BMI of 33.92 kg/m^2 (range: 30.2 – 38.4 kg/m^2) participated in Stage A. Of the 25 subjects in this stage, 15 were Black or African American, 1 person was Native Hawaiian or Other Pacific Islander, 8 subjects were White, and 1 subject was classified as other.

Stage B: A total of 17 obese subjects (8 male, 9 female) with a mean age of 41.23 years (range: 23 – 62 years), mean weight of 97.27 kg (range: 79.3 – 116.8 kg), and mean BMI of 33.71 kg/m^2 (range: 30.3 – 38.6 kg/m^2) participated in Stage B. Of the 17 subjects in this stage, 9 were Black or African American, and 8 subjects were White.

Stage C: A total of 57 obese subjects (18 male, 39 female) with a mean age of 40.4 years (range: 21 – 60 years), mean weight of 98.63 kg (range: 77.7 – 124.1 kg), and mean BMI of 34.69 kg/m^2 (range: 30.4 – 39.6 kg/m^2) participated in Stage C. Of the 57 subjects in this stage, 20 were Black or African American, 1 person was Native Hawaiian or Other Pacific Islander, 30 subjects were White, 1 person was American Indian or Alaska Native, and 5 subjects were classified as other.

Compared to the mean setmelanotide concentration values of 5.74 ng/mL at 24 hours for the 0.75 mg BID treatment, (Stage A), the mean setmelanotide concentration values for QD treatments of 3.58 ng/mL at 1.5 mg QD (Stage B) and 4.74 ng/mL at 2.0 mg QD (Stage C) were lower.

The Sponsor reported that trough concentrations were collected during outpatient dosing in Stage B, with a significant number of patients and time-points demonstrating little evidence of drug exposure, and others with extremely variable setmelanotide concentrations. They report that despite intensive investigation with sites, no clear explanation was apparent, and hypothesized that there were challenges with drug administration and compliance during outpatient administration.

A summary of setmelanotide steady state PK parameters on Day 8 is presented in Table 5.

Table 5 Summary of Setmelanotide Steady State Pharmacokinetic Parameters from Study RM-493-009

Treatment	C_{max} (ng/mL)	t_{max} (h)	AUC_{24} (ng*h/mL)	C_{24} (ng/mL)	$t_{½}$ (h)	Fluctuation (%)
Stage A [a]						
0.75 mg BID (N=9)	14.2 (32.5)	4.50 (0.00, 8.50)	243 (40.4)	5.74 (47.3)	5.91 (23.9)	78.0 (24.8)
1.5 mg QD (N=9)	23.0 (15.0)	6.52 (4.50, 10.5)	271 (14.5)	3.58 (25.1)	7.55 (19.7)	174 (14.2)
Stage C [a]						
2.0 mg QD (N=12)	27.5 (24.9)	6.17 (4.17, 10.2)	347 (23.2)	4.74 (34.9)	7.73 (17.9)	158 (17.6)

Values are presented as arithmetic mean (%CV) for all parameters except T_{max} which is presented as median (min, max); [a] Day 8
(Source: CSR for Study RM-493-009, Table 6 Page 34)

Study RM-493-026: *Phase 1b Repeat-Dose Setmelanotide in Healthy Obese Subjects*

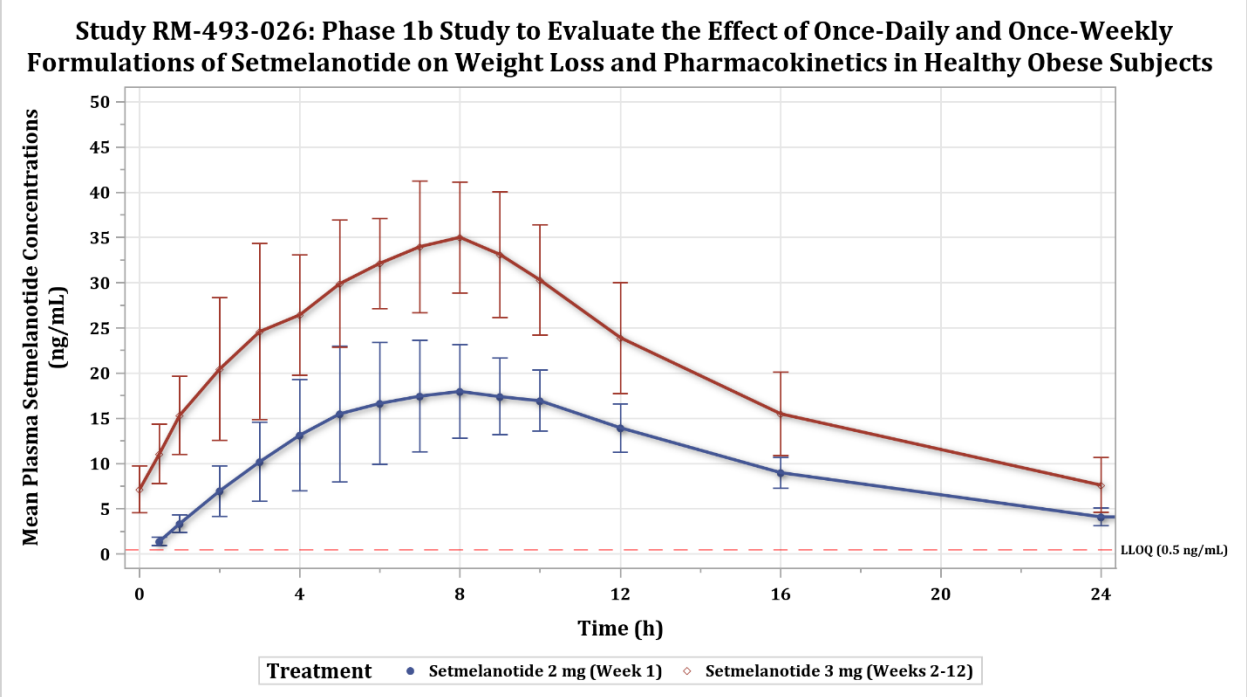
Study RM-493-026 was a randomized, double-blind, placebo-controlled study using a weekly setmelanotide formulation (QW) or matching placebo and a QD setmelanotide formulation or matching placebo in healthy, obese subjects. However, only data from the QD formulation were included in this submission. Subjects receiving the QD formulation were administered 2 mg for 1 week followed by 3 mg QD for 11 weeks. All subjects in this cohort were randomized in a 2:1 ratio to receive either setmelanotide or placebo and were stratified by gender and baseline BMI. Blood samples for 24-hour PK profiles were collected on Week 1 (Day 1) and Week 12. Trough samples were collected daily during Week 1. Trough samples were collected pre-dose each week for Weeks 2 through 12. Urine was collected on Week 1 (Day 1) and Week 12 over 24 hours. Blood samples were also collected for determination of ADA to setmelanotide.

A total of 13 obese subjects, 3 male and 10 females, between the ages of 34 and 54 years (mean=43.6 years), participated in this study. The mean body weight was 120.1 kg and the mean BMI was 43.8 kg/m^2.

Plasma concentration data were received for 11 subjects (9 setmelanotide- and 2 placebo-treated subjects). The 9 setmelanotide-treated subjects were included in the PK analysis.

As expected, mean setmelanotide concentrations at Week 12 were higher than those on Week 1 throughout the 24-h sampling period, due to the difference in dose between Week 1 (2 mg) and Weeks 2-12 (3 mg), as well as possible accumulation during QD dosing. The mean setmelanotide exposure following administration of 2 and 3 mg QD is presented in Figure 11.

Figure 11 Mean (±SD) Setmelanotide Concentration Versus Time on Day 1 Following Daily Administration of Setmelanotide 2 mg (Week 1) and 3 mg (Weeks 2-12)



(Source: Reviewer generated graph)

Pharmacokinetics:
Following the first injection of 2 mg setmelanotide on Day 1 of Week 1, the mean setmelanotide C_{max} was 19.7 ng/mL occurring at a median T_{max} of 8.5 h. The mean setmelanotide C_{max} was 37.9 ng/mL at a median T_{max} of 8.0 h on Day 1 of Week 12 after subjects were dosed with 3 mg setmelanotide. After normalizing to a 3 mg dose, the mean Week 12 C_{max} was higher than that on Week 1 suggesting some accumulation occurred during QD dosing over 12 weeks. The average setmelanotide concentrations during the 24-h dosing interval after multiple dosing through Week 12 (C_{avg}) was 20.6 ng/mL and the mean fluctuation in concentration during the dosing interval was 153%.

Accumulation was evident as seen by an increase in AUC during multiple dosing. The mean AUC_{tau} was 253 h*ng/mL on Day 1 of Week 1 (≈ 379 h*ng/mL when adjusted to a 3 mg dose) and 495 h*ng/mL on Week 12. Mean accumulation ratios were 1.29 for C_{max} and 1.31 for AUC_{tau}. These accumulation ratio values closely align with the theoretical accumulation factor of 1.23 to 1.33 for once-daily administration (tau = 24 h) after assuming linear PK with an apparent terminal $t_{1/2}$ of 10 to 12 h.

Based on data collected for 24 h during the Week 12 QD regimen, the steady-state apparent $t_{1/2}$ in this study ranged from 5.94 to 8.13 h. The effective half-life of setmelanotide was 11 h. At steady-state, the mean CLss/F was 6.21 L/h and the mean Vz/F was 62.7 L. (Table 6).

Table 6 Plasma Pharmacokinetic Parameters of Setmelanotide after Once-Daily Administration (2 mg Week 1; 3 mg Weeks 2-12)

Parameter	Week 1/Day 1 2 mg QD				Week 12/Day 1 3 mg QD			
	n	Mean	SD	CV%	n	Mean	SD	CV%
t_{max} (h)	6	8.50 (6.00-10.0)			6	8.00 (3.00-9.00)		
C_{max} (ng/mL)	6	19.7	2.80	14.2	6	37.9	5.31	14.0
NC_{max} (ng/mL)	6	29.6	4.20	14.2	-	-	-	-
C_{min} (ng/mL)	-	-	-	-	6	6.77	2.57	38.0
t_{min} (h)	-	-	-	-	6	12	13.1	110
C_{avg} (ng/mL)	-	-	-	-	6	20.6	3.47	16.8
AUC_{last} (h*ng/mL)	6	253	35.3	14.0	6	494	82.9	16.8
$NAUC_{last}$ (h*ng/mL)	6	379	52.9	14.0	-	-	-	-
AUC_{tau} (h*ng/mL)	6	253	35.4	14.0	6	495	83.3	16.8
$NAUC_{tau}$ (h*ng/mL)	6	379	53.0	14.0	-	-	-	-
$NAUC_{inf}$ (h*ng/mL)	6	432	67.1	15.5	-	-	-	-
$t_{1/2}$ (h)	6	6.18	0.613	9.92	6	7.11	0.999	14.1
CLss/F (L/h)	-	-	-	-	6	6.21	1.04	16.8
Vz/F (L)	-	-	-	-	6	62.7	6.66	10.6
Fluctuation (%)	-	-	-	-	6	153	28.3	18.4
RAC(C_{max})	-	-	-	-	6	1.29	0.126	9.78
RAC(AUC_{last})	-	-	-	-	6	1.31	0.125	9.60
RAC(AUC_{tau})	-	-	-	-	6	1.31	0.126	9.67

NC = Not calculated
NC_{max}, NAUC = PK parameters on Day 1 normalized to a 3 mg dose
t_{max} reported as median (min - max)
(Source: CSR for Study RM-493-026, Table 7 Page 53)

In vitro experiments showed that of the 4 potential metabolites of setmelanotide, M19, the free carboxylate, had 10-fold less activity than that of setmelanotide on MC1R, MC3R, MC4R, and MC5R.

The other metabolites were >1000-fold less active. Assessment of urine at steady-state showed that only two (M19 and M7) of the 4 metabolites were present. Metabolite M19 is formed after hydrolysis at the C-terminal amide that converts it to a carboxylic acid, and M7 is formed from cleavage of the arginine-tryptophan bond and further loss of the tryptophan. The urine data from this study were variable possibly due to the small sample size (n=6 subjects), M19 was estimated to represent ~2% of a 3.0 mg dose, M7 <1%, and parent setmelanotide was >30%.

The mean amount of setmelanotide excreted in urine over 24 h (A_e) was 0.685 mg on Day 1 of Week 1 and 1.17 mg on Day 1 of Week 12. The mean fraction of dose excreted in urine (F_e%, expressed as a percent) on Day 1, Week 1 was 34.3% compared to 39.1% on Day 1, Week 12. Mean renal clearance of setmelanotide (CL_R) calculated on Day1, Week 12 was 2.37 L/h, approximately 38% of total systemic clearance (Table 7).

Table 7 Urine Pharmacokinetic Parameters of Setmelanotide after Once-Daily Administration (2 mg Week 1; 3 mg Weeks 2-12)

	Week 1/Day 1 2 mg QD				Week 12/Day 1 3 mg QD			
Parameter	**n**	**Mean**	**SD**	**CV%**	**n**	**Mean**	**SD**	**CV%**
Total A_e (mg)	5*	0.685	0.0766	11.2	6	1.17	0.239	20.4
Total F_e (%)	5*	34.3	3.83	11.2	6	39.1	7.98	20.4
CL_R (L/h)	-	NC	NC	NC	6	2.37	0.328	13.9

*Subject (b) (6) had incomplete urine collection during the 12-24 h collection interval on Week 1/Days 1-2; Total A_e and F_e could not be estimated for this subject.
NC = Not calculated. CL_R was not estimated after the first dose on Week 1 since the 24-h urine sampling schedule did not allow single-dose renal elimination to be accurately determined.
(Source: CSR for Study RM-493-026, Table 8 Page 54)

All samples were negative for ADA to setmelanotide.

Study RM-493-011: *Phase 2 Study of Setmelanotide In Patients with Rare Genetic Disorders of Obesity*

Pharmacokinetics

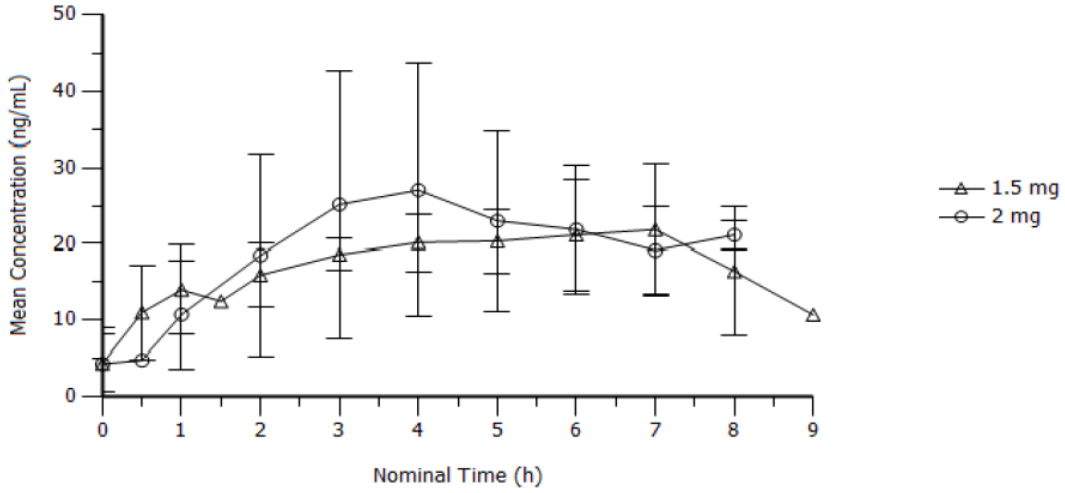
Study RM-493-011 was a Phase 2, open-label, uncontrolled, non-randomized, study with an additional long-term safety extension. The study planned to enroll up to 30 male and female patients identified with rare genetic obesity caused by a genetic mutation that impacts the leptin-melanocortin pathway (i.e., POMC, LEPR, MC4R, PCSK1 mutations, including heterozygous and epigenetic genetic defects in POMC, heterozygous MC4R mutations and patients with Bardet-Biedl and Alstrom's syndrome). Patients greater than or equal to 12 years of age with a POMC mutation or LEPR mutation were eligible for study participation after efficacy was established in adult patients.

A total of 7 patients were screened and enrolled and treated with at least 1 dose of setmelanotide in this ongoing study. Of the 7 patients who were enrolled, all had completed the dose titration period and 6 are ongoing in the extension period. One (1) patient discontinued due to a protocol violation. There are 2 female POMC patients with an average age of 23.0 years (20, 26 years), an average body weight of 153.9 kg (152.8, 155.0 kg) and an average BMI of 51.8 kg/m^2 (49.5, 54.1 kg/m^2). There are 3 LEPR patients (2 male and 1 female) with a mean age of 21.0 years (range: 15-22 years), mean body weight of 124.43 kg (range: 120.6 – 130.6 kg) and a mean BMI of 41.6 kg/m^2 (range: 39.9 – 44.2 kg/m^2). There were 2 patients with Epigenetic disease (1 male, 1 female) with an average age of 19.0 years (18, 20 years), an average body weight of 159.9 kg (137.6, 182.2 kg) and an average BMI of 46.7 kg/m^2 (38.1, 55.3 kg/m^2).

PK data were collected for 2 setmelanotide dose levels: 1.5 mg and 2.0 mg. PK data were collected on 2 study days for 2 of the 7 subjects. Otherwise, a single PK profile was included in the analysis.

Mean setmelanotide concentration-time profiles by dose are presented in Figure 12.

Figure 12 Mean (±SD) Setmelanotide Concentration Versus Time after Administration of 1.5 mg and 2 mg Doses of Setmelanotide to Patients With Rare Genetic Disorders of Obesity



(Source: CSR for Study RM-493-011, Figure 3, Page 56)

Mean C_{max} occurring at a median T_{max} of 3.50 hr obtained from 6 patients after the setmelanotide 1.5 mg dose was 24.8 ng/mL. Following a 2 mg dose in 3 patients, setmelanotide mean C_{max} was 28.1 ng/mL and

occurred at a median T_{max} of 4.05 hr. Mean AUC_{last} values were 111 h*ng/mL (n=6) and 153 h*ng/mL (n=3) after the 1.5 mg and 2.0 mg doses of setmelanotide, respectively. Mean pre-dose (C_{trough}) setmelanotide concentrations were 4.38 ng/mL after both 1.5 mg (n=6) and 2.0 mg (n=3) doses (Table 8).

Table 8 Plasma Pharmacokinetic Parameters of Setmelanotide after Doses of 1.5 mg and 2.0 mg

	Dose (mg)							
	1.5				2.0			
Parameter	**n**	**Mean**	**SD**	**CV%**	**n**	**Mean**	**SD**	**CV%**
T_{max} (h)	6		3.50 (2.00-7.00)		3		4.05 (4.00-7.00)	
C_{max} (ng/mL)	6	24.8	4.34	17.5	3	28.1	15.0	53.5
AUC_{0-8}(h*ng/mL)	2	115	10.8	9.42	2	201	48.8	24.3
AUC_{last} (h*ng/mL)	6	111	40.3	36.2	3	153	89.7	58.6
T_{last} (h)	6	6.49	2.42	37.3	3	7.67	0.577	7.53
C_{last} (ng/mL)	6	19.4	6.48	33.5	3	18.3	5.12	28.0
C_{trough} (ng/mL)	6	4.38	4.58	104	3	4.38	3.80	86.8

(Source: CSR for Study RM-493-011, Table 12, Page 57)

Study RM-493-014: *Phase 2 Study of Setmelanotide In Patients with Rare Genetic Disorders of Obesity*

Pharmacokinetics

Study RM-493-014 was a Phase 2, pilot study to assess initial (~3 month) safety and efficacy of setmelanotide in a group of populations of very rare genetic disorders of obesity, with the potential for responding patients to enter into a long-term extension phase. Study of the various populations was included in this protocol for administrative convenience since some of these genetic obesity disorders are so rare, with each population to be evaluated separately. The Sponsor anticipated that approximately 5 patients would be evaluated in each genetic disorder, and if substantial weight loss with good tolerability ("Proof of Concept") was demonstrated:
(i) Patients would be eligible to participate in the long-term phase (one-year extension); and
(ii) After consultation with regulatory agencies, additional evaluation of the effect of setmelanotide in each specific genetic disorder would continue in a pivotal study under a separate protocol.

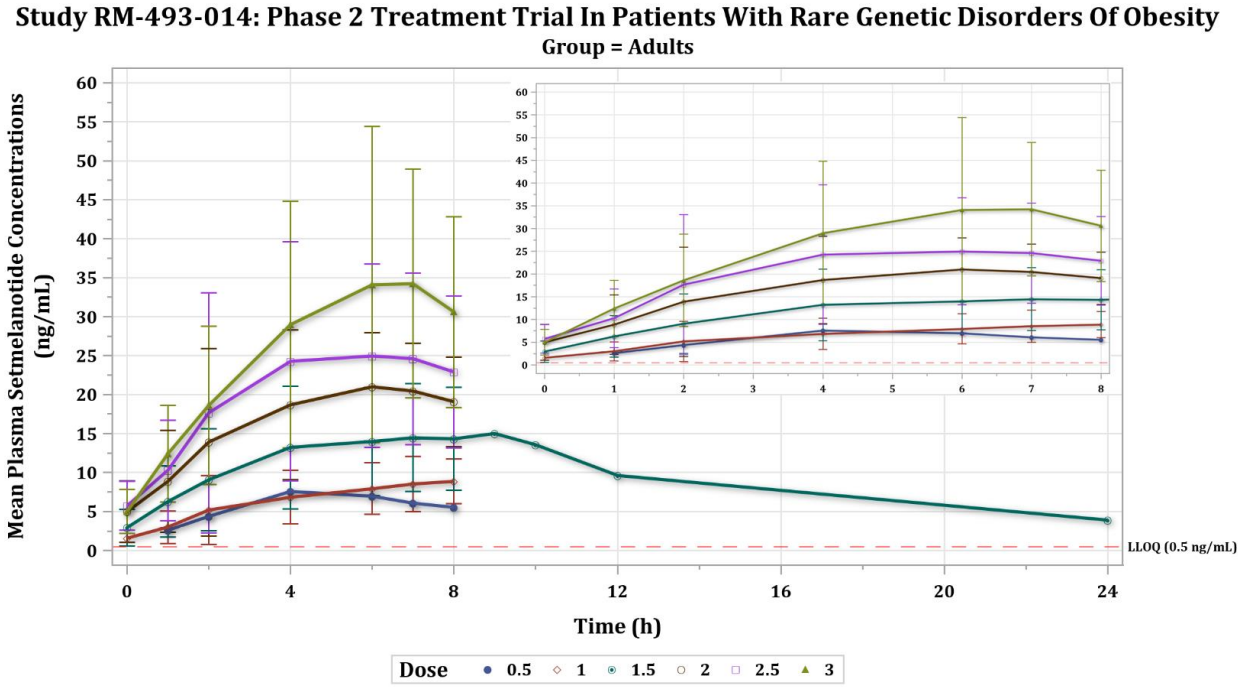
The study began with an initial period of dose titration where the individual patient's therapeutic dose was established by upwards dose titration in 2-week intervals. Patients continued on active treatment at their individually titrated therapeutic dose for an additional 10 weeks, for a total combined dosing duration of ~12 weeks at the individual patient's therapeutic dose. A second upwards dose titration may have been conducted if anticipated efficacy was not realized during the initial 10-week open label treatment phase. Patients demonstrating at least 5 kg weight loss (or 5% if baseline body weight <100 kg) at the end of the Open-Label Treatment Period were eligible to continue into the long-term extension phase.

A total of 40 patients were screened in this study, of whom 30 were enrolled and treated with at least 1 dose of setmelanotide. Twenty (20) of 30 patients completed the initial 12-week treatment phase. Five (5) patients withdrew from the initial 12-week treatment phase, all at the patient's/patient guardian's request, and 5 other patients were ongoing in the initial 12-week treatment phase as of 09 April 2019 (date of data cutoff) There are 22 female and 8 male patients with an average age of 29.1 years (range: 12 - 65 years), an average body weight of 125.1 kg (71, 204 kg) and an average BMI of 45.4 kg/m^2 (28, 80 kg/m^2). There were 4 patients with the Alström gene subtype, 10 patients with Bardet-Biedl syndrome (BBS) gene subtype, 1 patient with LEPR deficient obesity, 7 patients with PCSK1 subtype deficiency, 6 patients with POMC deficient obesity and 2 patients with Smith - Magenis Syndrome (SMS) gene subtype. Of the population, 25 were White, 4 Black or African American and 1 Asian.

PK data were collected for 6 setmelanotide dose levels: 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 mg.

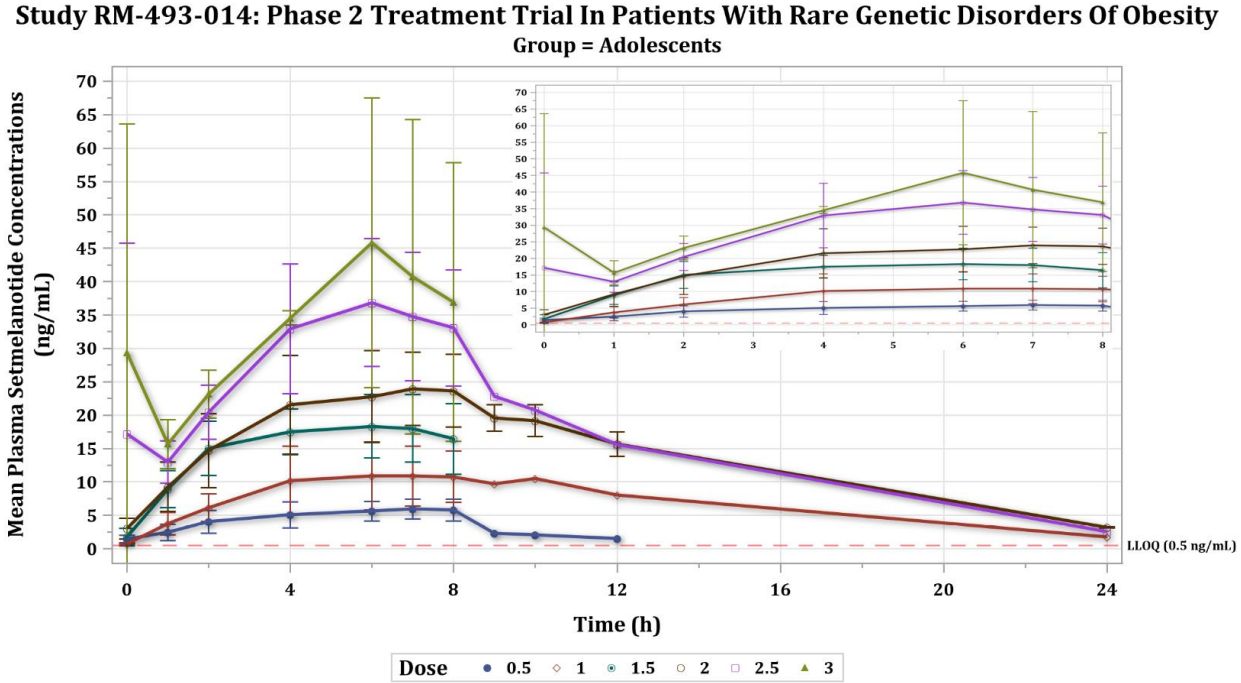
Mean setmelanotide concentration-time profiles by dose are presented in Figure 13 for adults and Figure 14 for adolescents.

Figure 13 **Mean (±SD) Setmelanotide Concentration Versus Time (inset - for the first 8-hours) after Administration of 0.5 – 3.0 mg Doses of Setmelanotide to Adult Patients with Rare Genetic Disorders of Obesity**



(Source: Reviewer generated plot)

Figure 14 **Mean (±SD) Setmelanotide Concentration Versus Time (inset - for the first 8-hours) after Administration of 0.5 – 3.0 mg Doses of Setmelanotide to Adolescent Patients with Rare Genetic Disorders of Obesity**



(Source: Reviewer generated plot))

Mean C_{max} for combined visits ranged from 6.65 ng/mL (n=13) at a median (range) T_{max} of 7.00 h (3.90-8.12 h) after 0.5 mg to 38.0 ng/mL (n=10) at a T_{max} of 6.26 h (4.00-8.03 h) after 3 mg. The mean AUC_{last} ranged from 35.8 h*ng/mL (n=13) after 0.5 mg to 207 h*ng/mL (n=10) after 3 mg (Table 9). The median C_{trough} values were 0.727 ng/mL after 0.5 mg, 1.33 ng/mL after 1 mg, 2.50 ng/mL after 1.5 mg, 4.14 ng/mL after 2 mg, 7.3 ng/mL after 2.5 mg, and 6.68 ng/mL after 3 mg.

Table 9 Plasma Pharmacokinetic Parameters of Setmelanotide after Doses of 1.5 mg and 2.0 mg

Parameter	Dose (mg)											
	0.500				1.00				1.50			
	n	Mean (Median)	SD	CV%	n	Mean (Median)	SD	CV%	n	Mean (Median)	SD	CV%
T_{max} (h)	13	7.00 (3.90-8.12)			25	6.90 (1.95-10.9)			22	5.96 (1.98-8.10)		
C_{max} (ng/mL)	13	6.65	1.76	26.5	25	10.4	4.72	45.5	22	17.5	6.47	37.1
$AUC_{(0-t)}$ (h*ng/mL)	5	41.5	10.7	25.7	11	43.8	21.4	49.0	11	115	42.5	37.1
AUC_{last} (h*ng/mL)	13	35.8	10.7	30.0	25	59.3	31.8	53.7	22	106	62.2	58.6
T_{last} (h)	13	7.96	0.128	1.61	25	8.52	3.24	38.0	22	8.57	3.50	40.8
AUC_{tau} (h*ng/mL)					1	149			1	308		
C_{trough} (ng/mL)	18	0.857 (0.727)	0.731	85.3	22	1.52 (1.33)	1.26	82.7	26	3.12 (2.50)	2.16	69.4

Parameter	Dose (mg)											
	2.00				2.50				3.00			
	n	Mean (Median)	SD	CV%	n	Mean (Median)	SD	CV%	n	Mean (Median)	SD	CV%
T_{max} (h)	29	6.77 (1.97-8.25)			19	6.00 (2.00-8.23)			10	6.26 (4.00-8.03)		
C_{max} (ng/mL)	29	25.1	8.30	33.0	19	32.8	13.7	41.7	10	38.0	14.7	38.8
$AUC_{(0-t)}$ (h*ng/mL)	12	130	30.4	23.3	10	175	82.7	47.3	6	179	71.3	39.9
AUC_{last} (h*ng/mL)	29	146	69.6	47.6	19	188	84.8	45.0	10	207	81.9	39.5
T_{last} (h)	29	8.69	4.19	48.3	19	8.67	3.77	43.4	10	7.99	0.103	1.29
AUC_{tau} (h*ng/mL)	2	319	11.2	3.53	1	330						
C_{trough} (ng/mL)	45	4.37 (4.14)	2.94	67.3	56	14.6 (7.30)	27.4	188	51	13.4 (6.68)	20.4	152

Abbreviations: AUC: Area under the curve; C_{max}: Maximum concentration; C_{trough}: Trough plasma concentration; CV: Coefficient of variation; SD: Standard deviation; T_{max}: Time to maximum plasma concentration.
Note: T_{max} reported as median (min-max).
C_{trough} = the concentration at the end of the QD dosing interval for a given dose level. Anomalous high C_{trough} values were reported for Patient 011-112 between Visit 5 and Visit 11, which resulted in higher mean C_{trough} at the 2.5 and 3 mg doses; median values may be more representative of the C_{trough} at these dose levels.
(Source: CSR for Study RM-493-014, Table 9, Page 82)

Dose proportionality assessments showed that there was approximately proportional increase in mean C_{max} and AUC_{last} to the increase in dose for incremental increases in dose between 0.5 mg and 3 mg., There was a linear relationship between C_{max} and AUC_{last} versus dose, as shown in the 5.71-fold increase in mean C_{max} and a 5.78-fold increase in mean AUC_{last} for the overall 6-fold increase in dose between 0.5 mg and 3 mg (Table 10 and Figure 15).

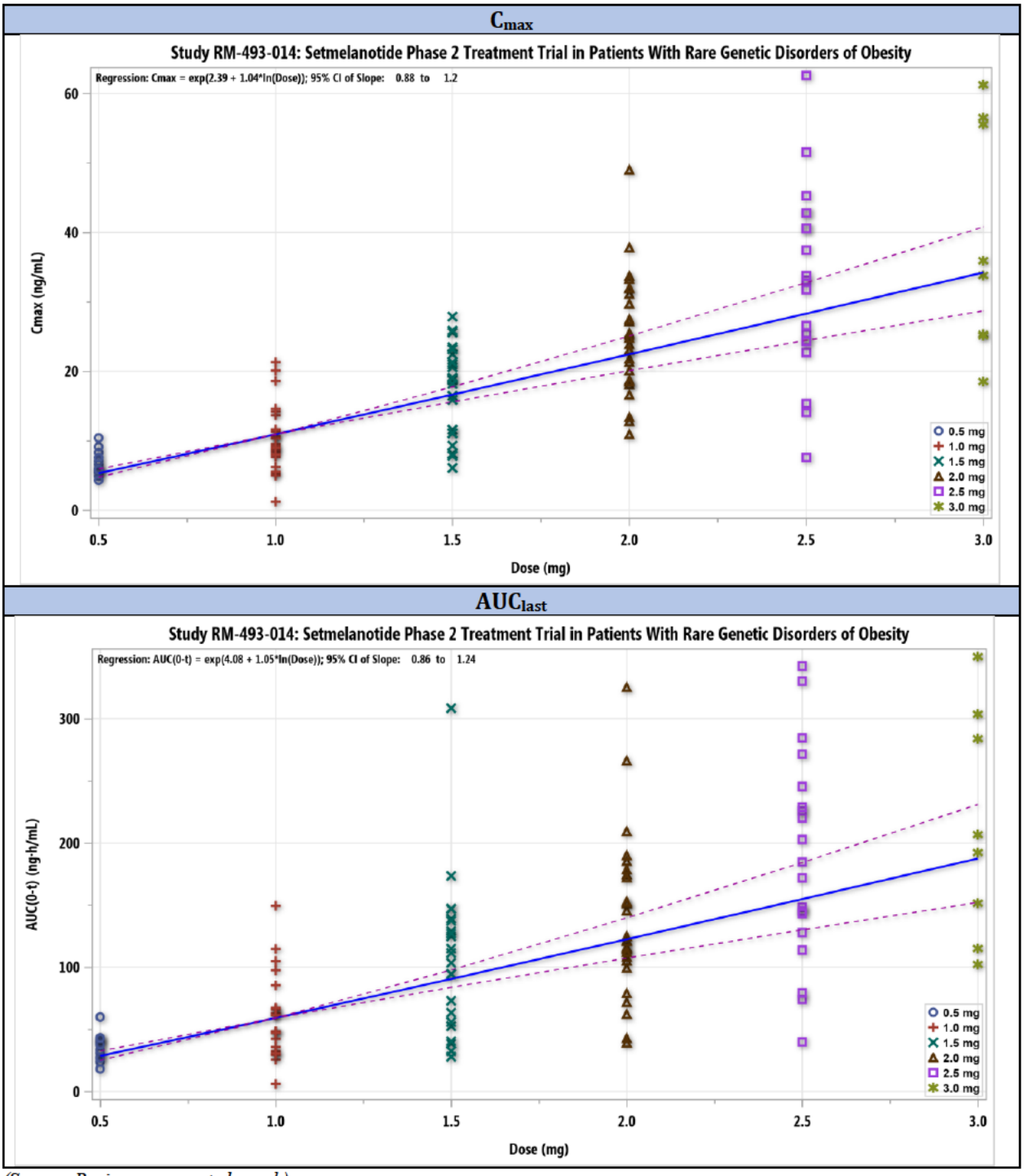
Table 10 Dose Proportionality of Setmelanotide C_{max} and AUC_{last} between Doses of 0.5 – 3.0 mg

Dose (mg)	Dose Ratio	Mean C_{max} (ng/mL)	C_{max} Ratio	Mean AUC_{last} (h*ng/mL)	AUC_{last} Ratio
0.5	2.00	6.65	1.56	35.8	1.66
1		10.4		59.3	
1	1.50	10.4	1.68	59.3	1.79
1.5		17.5		106	
1.5	1.33	17.5	1.43	106	1.38
2		25.1		146	
2	1.25	25.1	1.31	146	1.29
2.5		32.8		188	
2.5	1.20	32.8	1.16	188	1.10
3		38.0		207	
0.5	6.00	6.65	5.71	35.8	5.78
3		38.0		207	

Abbreviations: AUC: Area under the curve; C_{max}: Maximum concentration.

(Source: CSR for Study RM-493-014, Table 10, Page 84)

Figure 15 Dose Proportionality of Setmelanotide C_{max} and AUC_{last} between Doses of 0.5 – 3.0 mg



(Source: Reviewer generated graph)

Study RM-493-012: *Pivotal Phase 3 Study of Setmelanotide in POMC Deficient Obesity*

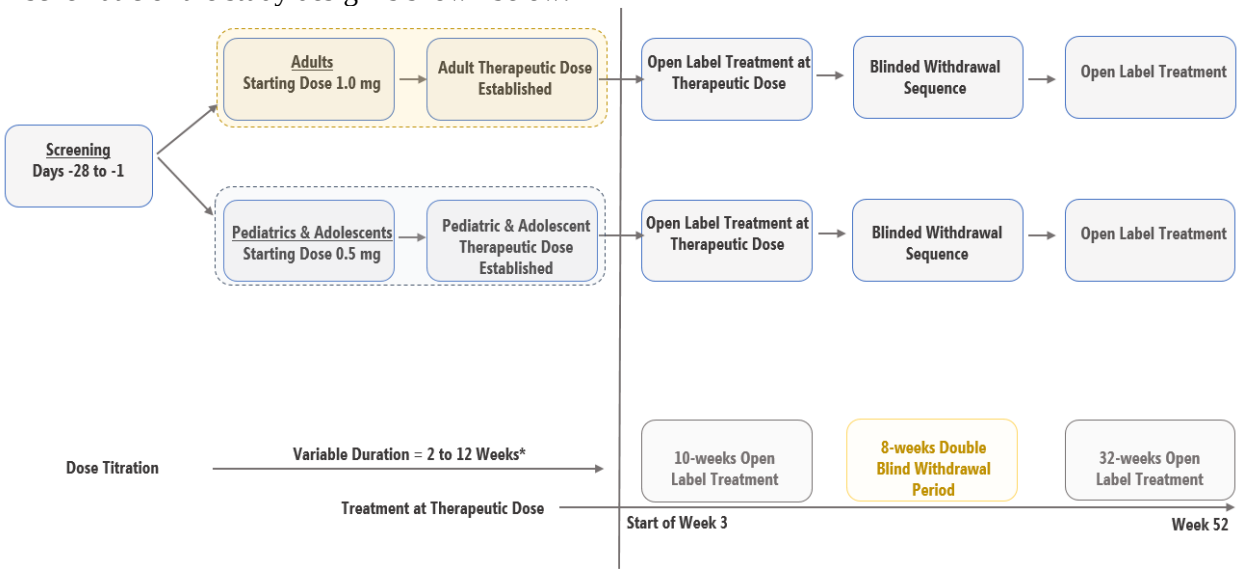
Pharmacokinetics:

Study RM-493-012 was a pivotal study to assess long-term (52 weeks) efficacy of setmelanotide in POMC deficiency obesity. For this global study, the maximum allowable dose differed across countries. The US, Canada and UK authorities approved a maximum daily dose of 3.0 mg, while Germany and France authorities initially approved a maximum daily dose of 2.5 mg. The study began with an initial period (dose titration) lasting 2 to 12 weeks (dependent upon number of dose escalations required to determine an individual's therapeutic dose). 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. For patients who achieved at least a 5 kg weight loss (or at least 5% weight loss if baseline body weight was <100 kg) at the end of the Open Label Treatment Period, they continued into the double-blind, variably-timed, placebo-controlled, withdrawal period lasting 8 weeks, inclusive of a 4-week of placebo treatment period. 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 investigative sites remained blinded as to when placebo treatment was administered. 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 pivotal cohort included 9 patients with POMC genetic mutations and 1 patient with PCSK1 genetic mutation. Of these 10 pivotal patients comprising the pivotal cohort, 9 completed the study and 1 withdrew from the study due to lack of efficacy. Of the 10 pivotal patients, 5 were male and 5 were female. The mean age of the group was 18.4 years (range: 11 – 30 years), and the mean body weight was 118.7 kg (range: 55.9 – 186.7 kg) and the mean BMI was 40.41 kg/m^2 (range: 26.6 – 53.3 kg/m^2). Of the 10 patients, 7 were White, 1 was Arab, 1 was Moroccan, 3 patients were categorized as other and 1 patient's category was not available.

In addition to this cohort, there were 4 supplemental patients, 1 male and 3 females. The mean age of this supplemental group was 17.0 years (range: 10 – 29 years), and the mean body weight was 106.5 kg (range: 83.7 – 138 kg) and the mean BMI was 39.0 kg/m^2 (range: 34.4 – 42.7 kg/m^2). Of the 4 supplemental cohort patients, 1 was White and 3 patients were categorized as other.

A schematic of the study design is shown below:

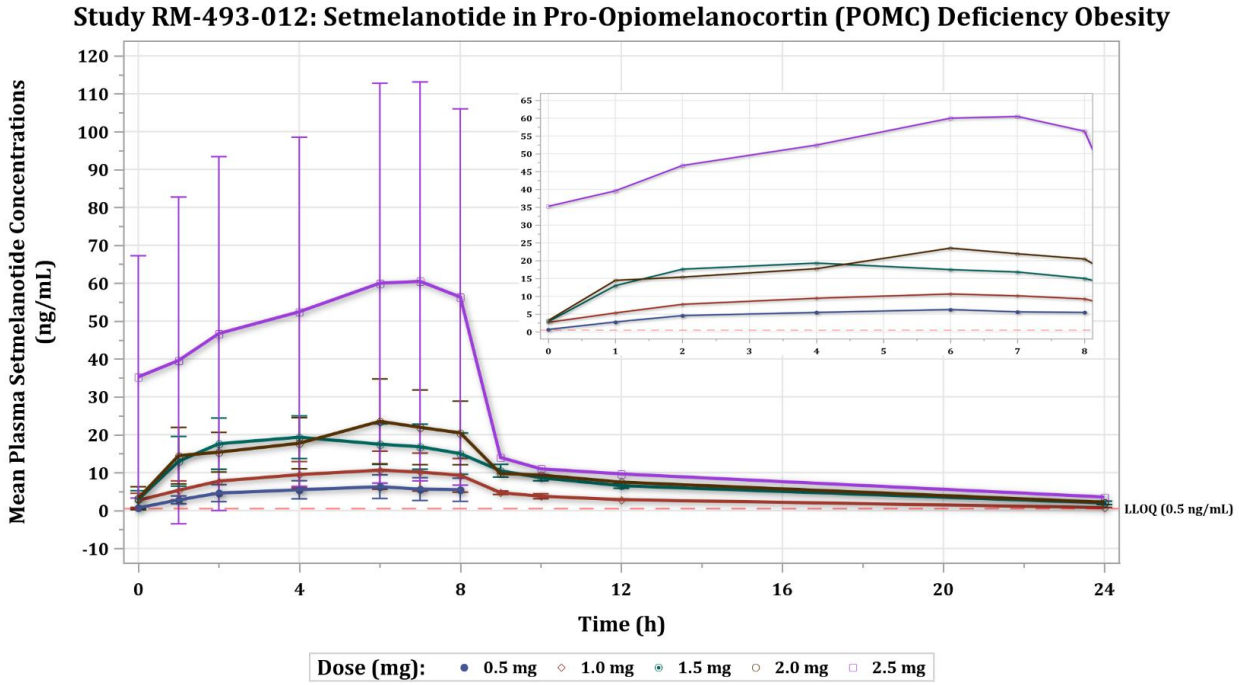


*The last 2 weeks of the Open Label Dose Titration Phase in which the therapeutic dose for an individual patient was established was considered the first 2 weeks of Open Label Treatment. Subsequently patients received an additional 10 weeks of active treatment in the Open label Treatment for a total combined duration of 12 weeks, before transitioning into the Double Blind Withdrawal Phase

Serial blood samples were taken for the PK measurement of setmelanotide. PK sample collections were limited in pediatric age participants (age 6 through age 11 years) to avoid excess blood volume reductions.

The mean setmelanotide exposure summarized by dose level are presented in Figure 16.

Figure 16 Mean (±SD) Setmelanotide Concentration Versus Time (inset - for the first 8-hours) by treatment following Doses of 0.5, 1.0, 1.5, 2.0 and 2.5 mg Setmelanotide in POMC Patients



(Source: Reviewer generated graph)

The mean C_{max} ranged from 6.47 ng/mL after 0.5 mg (n=4, 45.7% CV) to 24.5 ng/mL after 2.0 mg (n=6, 46.2% CV). The mean C_{max} after 2.5 mg, 24.4 ng/mL (n=3, 50.4% CV), was similar to that after 2.0 mg. The median T_{max} occurred between 4.01 h (range 1.00-8.02 h) after 1.5 mg and 7.03 h (range 5.80-8.00 h) after 2.5 mg. It should be noted that, given the limited PK sampling in most subjects, the C_{max} and T_{max} values may be underestimated. The mean AUC_{0-8} ranged from 38.3 h*ng/mL after 0.5 mg (n=4, 47.3% CV) to 143 h*ng/mL after 2.0 mg (n=6, 49.4% CV). As noted for C_{max}, the mean AUC_{0-8} after 2.5 mg, 138 ng/mL (n=3, 52.3% CV), was similar to that after 2.0 mg. Twenty-four (24) hour PK sampling occurred in only 2 subjects (4 profiles in each subject with 6 of 8 profiles occurring during dose titration). Estimates of AUC_{0-24} during the once-daily dosing interval ranged from 86.1 h*ng/mL after 1.0 mg (n=2, 8.85% CV) to 228 h*ng/mL after 2.5 mg (n=1). (Table 11).

Table 11 Plasma Pharmacokinetic Parameters of Setmelanotide by Dose

	Dose (mg)											
	0.500				1.00				1.50			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV %	n	Mean	SD	CV%
T_{max} (h)	4	6.07 (5.98-7.92)			10	5.99 (3.95-8.00)			20	4.01 (1.00-8.02)		
C_{max} (ng/mL)	4	6.47	2.96	45.7	10	11.5	4.66	40.4	20	22.4	4.94	22.0
C_{trough} (ng/mL)	6	0.715	0.825	115	15	1.83	1.54	84.3	61	3.10	2 .37	76.5
AUC_{0-8} (h*ng/mL)	4	38.3	18.1	47.3	10	66.7	27.7	41.6	20	130	32.3	24.9
AUC_{0-24} (h*ng/mL)	0	NC	NC	NC	2	86.1	7.63	8.85	4	185	34.3	18.5
AUC_{last} (h*ng/mL)	4	38.3	18.1	47.3	10	74.2	26.8	36.1	20	147	34.2	23.3
	Dose (mg)											
	2.00				2.50							
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV %				
T_{max} (h)	6	5.38 (1.00-7.00)			3	7.03 (5.80-8.00)						
C_{max} (ng/mL)	6	24.5	11.3	46.2	3	24.4	12.3	50.4				
C_{trough} (ng/mL)	6	5.40	7.47	138	7	7.26	5.44	75.0				
AUC_{0-8} (h*ng/mL)	6	143	70.7	49.4	3	138	72.3	52.3				
AUC_{0-24} (h*ng/mL)	1	167	NC	NC	1	228	NC	NC				
AUC_{last} (h*ng/mL)	6	159	61.7	38.9	3	180	77.7	43.2				

Note: T_{max} reported as median (range); Mean (SD) values for 2.5 mg dose exclude aberrant values for Subject (b) (6) mean values for AUC_{last} derived from mostly AUC_{0-8} values with a small number of AUC_{0-24} values. NC = Not calculated; For C_{trough} Dose represents prior dose.

(Source: CSR for Study RM-493-012, Table 21, Page 77)

Pharmacodynamics:

The primary objective of this study was to demonstrate a clinically meaningful effect on percentage of body weight change in patients with POMC deficiency obesity after 1 year of treatment with setmelanotide and show a statistical significance.

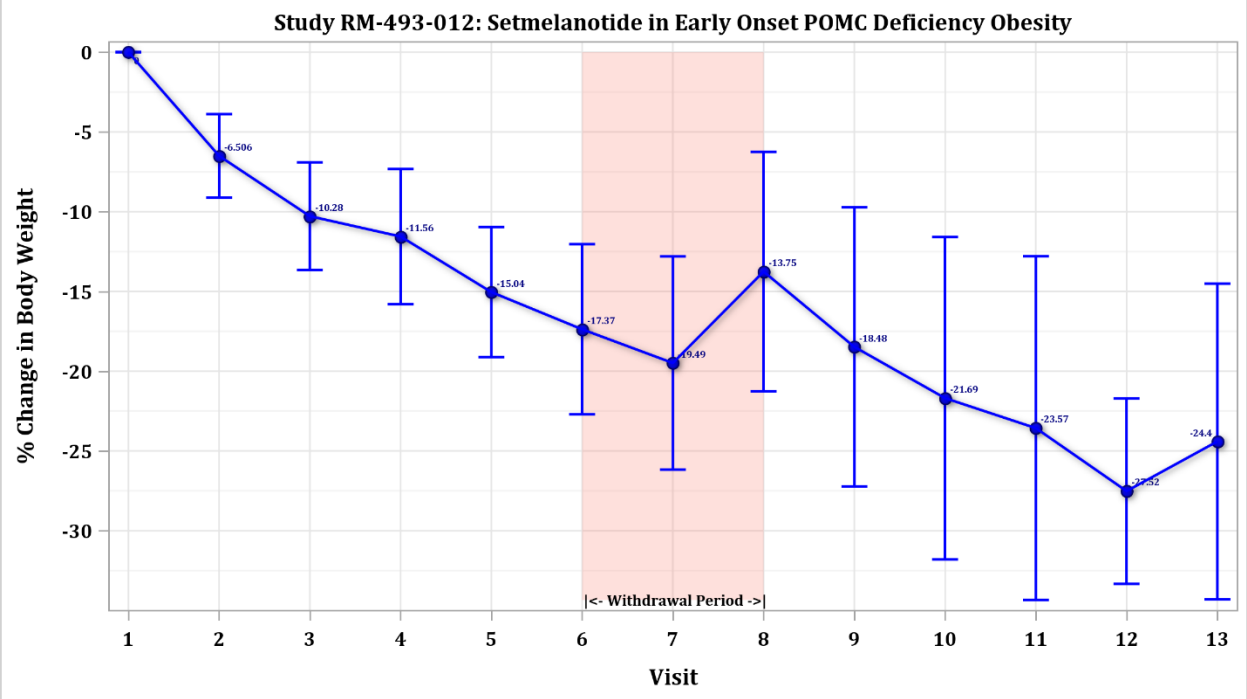
Several key analysis populations were defined in this study:

- The Full Analysis Set (FAS) 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 Designated Use Set (DUS) 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 primary endpoint in this study was defined as the proportion of patients in the pivotal cohort in the FAS population who met the ≥10% weight loss threshold (responders) after approximately 1 year of treatment.

After approximately 52 weeks of treatment with setmelanotide, 8 of the 10 pivotal patients with POMC/PCSK1 deficiency obesity in the FAS Population achieved at least 10% weight loss, demonstrating statistically significant ($p< 0.0001$) and clinically meaningful body weight loss after 1 year of treatment (Table 12, Figure 17).

Figure 17 Percent Change of Weight from Baseline by Visit Following Administration of Setmelanotide in POMC Patients



(Source: Reviewer generated graph)

Table 12 Proportion of POMC Patients Achieving at Least 10% Weight Loss from Baseline at 52 Weeks from Therapeutic Dose of Setmelanotide

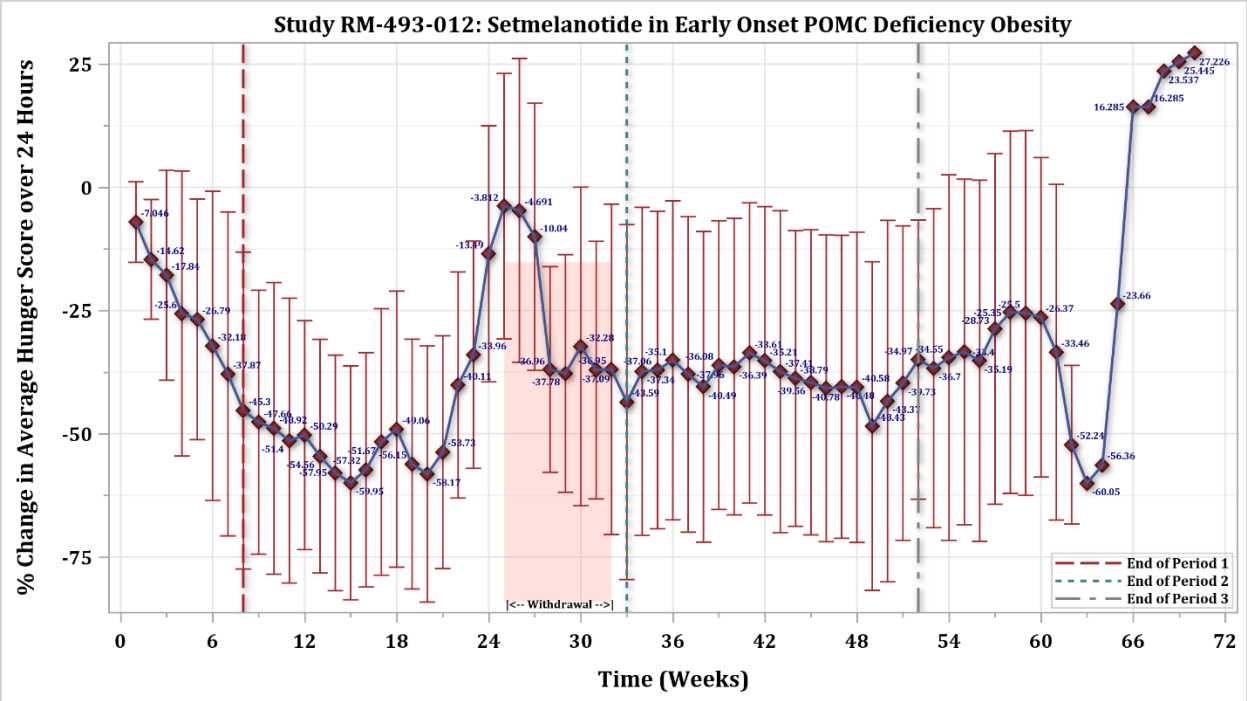
Parameter	Statistics	Total (N=10)
Subjects Achieving at Least 10% Weight Loss from Baseline at Week 52	n (%)	8 (80.0%)
	90 % CI[a]	(49.31, 96.32)
	p-value	<.0001

[a] 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.
Note: FAS population consisted of subjects 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).Weight was measured in triplicate at each visit.
Percentages based on number of subjects with weight data at both baseline and Week 52.

(Source: CSR for Study RM-493-012, Table 12, Page 62)

One of the secondary efficacy endpoints evaluated was hunger score. During the study 3 distinct daily hunger scores were collected: morning hunger, worst (most) hunger in 24 hours, and average hunger in 24 hours. Weekly average hunger score for analysis were determined from average of daily hunger scores. The hunger score used to assess study endpoints was the weekly average hunger score of the daily worst (most) hunger score in 24 hours (Figure 18). The second key secondary endpoint of this study was to evaluate the mean percent change in hunger scores for patients ≥12 years of age with POMC/PCSK1 deficiency obesity in the DUS population following 1 year of treatment with setmelanotide. The mean baseline score of the 7 patients ≥12 years of age in the DUS population was 8.1, the mean score at Week 52 following treatment with setmelanotide was 5.8, and the mean score percent change from baseline to Week 52 was -27.1% (p=0.0005) as shown in (Table 13).

Figure 18 Percent Change of Average Hunger Score from Baseline by Visit Following Administration of Setmelanotide in POMC Patients



(Source: Reviewer generated graph)

Table 13 Percent Change in Daily Hunger Scores from Baseline at 52 Weeks from Therapeutic Dose (≥12 Years of Age) – Pivotal Cohort (DUS Population)

		Total (N=7)		
Parameter	**Statistic**	**Morning Hunger**	**Worst (Most) Hunger in 24 Hours**	**Average Hunger over 24 Hours**
Baseline Hunger Score	n	7	7	7
	Mean (SD)	4.8 (2.63)	8.1 (0.78)	6.7 (0.71)
	Median	5.5	8.0	6.7
	Q1, Q3	2, 7	7, 9	6, 7
	Min, Max	1, 8	7, 9	6, 8
Week 52 Hunger Score	n	7	7	7
	Mean (SD)	2.7 (1.90)	5.8 (2.02)	4.4 (1.78)
	Median	3.0	6.0	4.1
	Q1, Q3	1, 3	4, 8	3, 6
	Min, Max	0, 6	3, 8	2, 7
Percent Change from Baseline to Week 52 (%)	n	7	7	7
	Mean (SD)	-10.8 (78.15)	-27.1 (28.11)	-32.2 (29.32)
	Median	-42.9	-14.3	-33.3
	Q1, Q3	-85, 55	-55, -3	-60, -7
	Min, Max	-100, 100	-72, -1	-76, 4
	LS Mean[a]	-11.08	-27.77	-33.11
	90% CI[a]	(-37.78, 15.62)	(-40.58, -14.96)	(-47.90, -18.31)
	P-value[a]	0.2447	0.0005	0.0006
Subjects Achieving at Least 25% Hunger Improvement from Baseline at Week 52	n (%)	4 (57.1%)	3 (42.9%)	4 (57.1%)

[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.

Note: DUS population consisted of subjects who received any injections of study drug, demonstrated ≥5kg weight loss [or 5% of body weight loss if weight was <100kg at baseline] during the 12-week open label treatment period, and proceeded into the double-blind, placebo-controlled withdrawal period. Hunger ranged from 0 to 10 on a Likert-type scale; 0 = not hungry at all and 10 = hungriest possible. Hunger score was captured in a daily diary, then averaged to calculate a weekly score for analysis. Questions on hunger questionnaire (ages >= 12) are: "in the last 24 hours, on average, how hungry do you feel?", "In the last 24 hours, how hungry did you feel when you were the most hungry?" (key secondary endpoint), and "This morning when you woke up for the day, how hungry did you feel?" Percentages were based on the number of patients with hunger diary data at both baseline and Week 52. The last value prior to the first dose was considered the baseline value. If the weekly average hunger score prior to the first administration of study drug was missing, the daily hunger score collected on Day 1 (first day of active dose) was used as "Baseline."

(Source: CSR for Study RM-493-012, Table 14, Page 65)

The proportion of patients ≥12 years of age achieving at least 25% improvement in hunger scores following 1 year of treatment with setmelanotide in FAS population was the third key secondary endpoint. Four (4) of the 8 patients (50%) in the FAS Population achieved at least 25% hunger score (worst 'most' hunger in 24 hours) improvement from baseline at Week 52 after treatment with setmelanotide (p= 0.0004, Table 14).

Table 14 Proportion of Subjects (≥12 years of age) Achieving at Least 25% Improvement in Daily Hunger Scores from Baseline at 52 Weeks from Therapeutic Dose of Setmelanotide – Pivotal Cohort (FAS Population)

		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 (%)	5 (62.5%)	4 (50.0%)	5 (62.5%)
	90% CI[a]	(28.92, 88.89)	(19.29, 80.71)	(28.92, 88.89)
	P-value[1]	<.0001	0.0004	<.0001

[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.

Note: FAS population consisted of patients who received any injections of study drug and at least 1baseline assessment (included those who did and did not demonstrate ≥5kg weight loss [or 5% of body weight if weight was <100kg at baseline] during the 12-week open-label treatment period and proceeded into the double-blind, placebo-controlled withdrawal period). Hunger scores ranged from 0 to 10 on a Likert-type scale; 0 = not hungry at all and 10 = hungriest possible. Hunger score was captured in a daily diary, then averaged to calculate a weekly score for analysis. Questions on hunger questionnaire (ages ≥ 12) are: "in the last 24 hours, on average, how hungry do you feel?", "In the last 24 hours, how hungry did you feel when you were the most hungry?" (key secondary endpoint), and "This morning when you woke up for the day, how hungry did you feel?"
Percentages were based on number of subjects with hunger diary data at both baseline and Week 52.

(Source: CSR for Study RM-493-012, Table 15, Page 66)

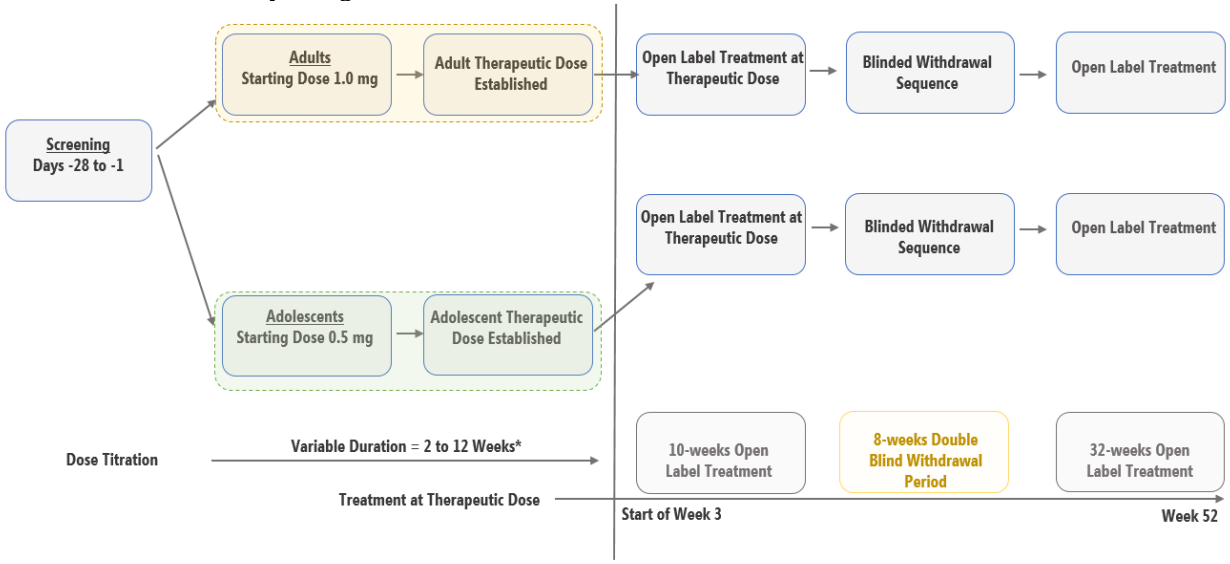
Study RM-493-015: *Pivotal Phase 3 Study of Setmelanotide in LEPR Deficient Obesity*

Study RM-493-015 was a pivotal study to assess long-term (52 weeks) efficacy of setmelanotide in LEPR deficiency obesity. For this global study, the maximum allowable dose differed across countries. The United Kingdom (UK) and the Netherlands authorities approved a maximum daily dose of 3.0 mg, while Germany and France authorities approved a maximum daily dose of 2.5 mg. There was an initial dose titration period lasting 2 to 12 weeks (dependent upon number of dose escalations required to determine an individual's therapeutic dose). 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. Patients who achieved at least a 5 kg weight loss (or at least 5% weight loss if baseline body weight was <100 kg) at the end of the Open Label Treatment Period continued into the double-blind, variably-timed, placebo-controlled, withdrawal period lasting 8 weeks, inclusive of a 4-week of placebo treatment period. 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 sites remained blinded as to when placebo treatment was administered. 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).

The pivotal cohort included 11 patients with LEPR deficient obesity. Of these 11 pivotal patients comprising the pivotal cohort, 9 completed the study. One patient died in an automobile accident (unrelated to study drug) and the other patient was withdrawn from the study due to Grade 1 eosinophilia, which was considered by the Investigator to be probably related to study drug. Of the 11 pivotal patients, 3 were male and 8 were female. The mean age of the group was 23.7 years (range: 13 – 37 years), and the mean body weight was 133.3 kg (range: 89.4 – 170.4 kg) and the mean BMI was 48.2 kg/m^2 (range: 35.8 – 64.6 kg/m^2). Of the 11 patients, 10 were White and 1 patient was a South Asian.

In addition to this cohort, there were 2 supplemental male patients. The average age of this supplemental group was 18.0 years (13 and 23 years), and the average body weight was 158.6 kg (108.6 and 208.7 kg) and the mean BMI was 56.1 kg/m^2 (42.4 and 69.7 kg/m^2). The race of these 2 supplemental cohort was classified as unknown.

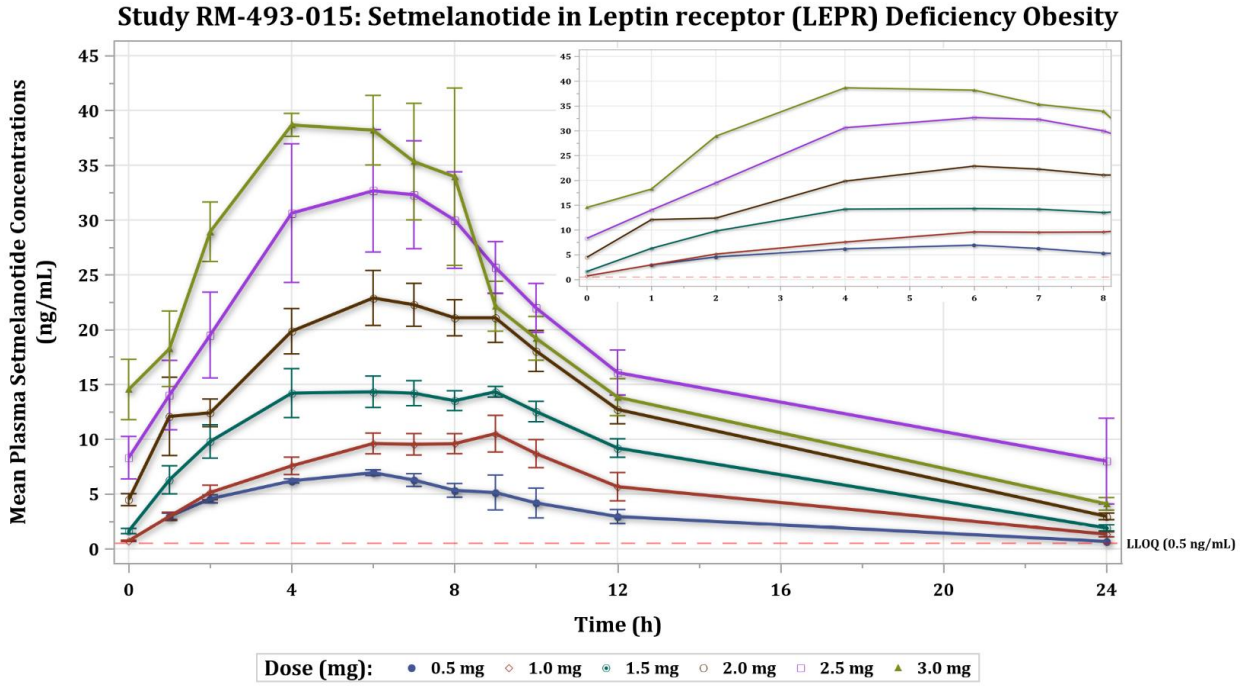
A schematic of the study design is shown below:



*The last 2 weeks of the Open Label Dose Titration Phase in which the therapeutic dose for an individual patient was established was considered the first 2 weeks of Open Label Treatment. Subsequently patients received 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

Serial blood samples were taken for the PK measurement of setmelanotide. Most PK profiles were collected over 8 hours, while 24-h PK samples (generally 2 to 4 subjects per dose level) were available in a smaller number of subjects. The mean setmelanotide concentrations after 3.0 mg were slightly lower than those observed after 2.5 mg at 9 h and later time points, likely due relatively small sample size and lower number of subjects with 9 to 24 h PK sampling (Figure 19).

Figure 19 Mean (±SD) Setmelanotide Concentration Versus Time (inset - for the first 8-hours) by treatment following Doses of 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 mg Setmelanotide in LEPR Patients



(Source: Reviewer generated graph)

Mean C_{max} ranged from 7.21 ng/mL after 0.5 mg (n=4) to 38.9 ng/mL after 3.0 mg (n=3). The median T_{max} occurred between 4.00 h (range 4.00-6.00 h) after 3.0 mg and 6.92 h (range 5.83-9.00 h) after 1 mg. The mean AUC_{0-8} ranged from 41.2 h*ng/mL after 0.5 mg (n=4) to 231 h*ng/mL after 3.0 mg (n=3). Estimates of AUC_{0-24} during the QD dosing interval ranged from 88.5 h*ng/mL after 0.5 mg (n=1) to 421 h*ng/mL after 3.0 mg (n=2) (Table 15).

Table 15 Plasma Pharmacokinetic Parameters of Setmelanotide in LEPR Obesity Patients by Dose

	Dose (mg)											
	0.5				1.0				1.5			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	4	6.00 (4.00-7.00)			13	6.92 (5.83-9.00)			12	6.48 (2.00-8.00)		
C_{max} (ng/mL)	4	7.21	0.342	4.74	13	10.4	3.22	30.8	12	17.0	6.52	38.4
C_{trough} (ng/mL)	4	0.544	0.374	68.7	11	1.35	0.599	44.3	16	2.49	0.891	35.8
$AUC_{0\text{-}8}$ (h*ng/mL)	4	41.2	1.50	3.65	13	53.0	19.0	35.8	12	91.8	34.9	38.0
$AUC_{0\text{-}24}$ (h*ng/mL)	1	88.5	NC	NC	4	148	47.6	32.1	4	218	35.0	16.0
AUC_{last} (h*ng/mL)	4	56.2	22.1	39.2	13	79.1	55.5	70.1	12	130	71.7	55.0
	Dose (mg)											
	2.0				2.5				3.0			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	15	6.00 (3.90-8.02)			10	6.03 (3.97-9.05)			3	4.00 (4.00-6.00)		
C_{max} (ng/mL)	15	23.9	8.38	35.1	10	31.1	12.9	41.3	3	38.9	2.62	6.72
C_{trough} (ng/mL)	32	4.80	2.56	53.4	32	4.87	2.71	55.6	11	5.85	1.44	24.7
$AUC_{0\text{-}8}$ (h*ng/mL)	15	133	47.7	35.9	10	166	56.0	33.7	3	231	11.9	5.16
$AUC_{0\text{-}24}$ (h*ng/mL)	4	316	70.9	22.5	4	418	48.3	11.6	2	421	62.6	14.9
AUC_{last} (h*ng/mL)	15	178	101	56.6	10	260	147	56.3	3	383	80.4	21.0

Note: T_{max} reported as median (range); Mean (SD) values for 2.0 mg dose exclude aberrant value for Subject (b) (6) Mean (SD) values for 2.5 and 3.0 mg doses exclude aberrant values for Subjects (b) (6) and (b) (6) NC = Not calculated. For C_{trough} Dose represents prior dose.

(Source: CSR for Study RM-493-015, Table 18, Page 77)

Pharmacodynamics:

The primary objective of this study was to demonstrate statistically significant and clinically meaningful effects of setmelanotide on percent body weight change in patients with LEPR deficiency obesity due to rare biallelic or loss-of-function mutations at the end of 1 year of treatment.

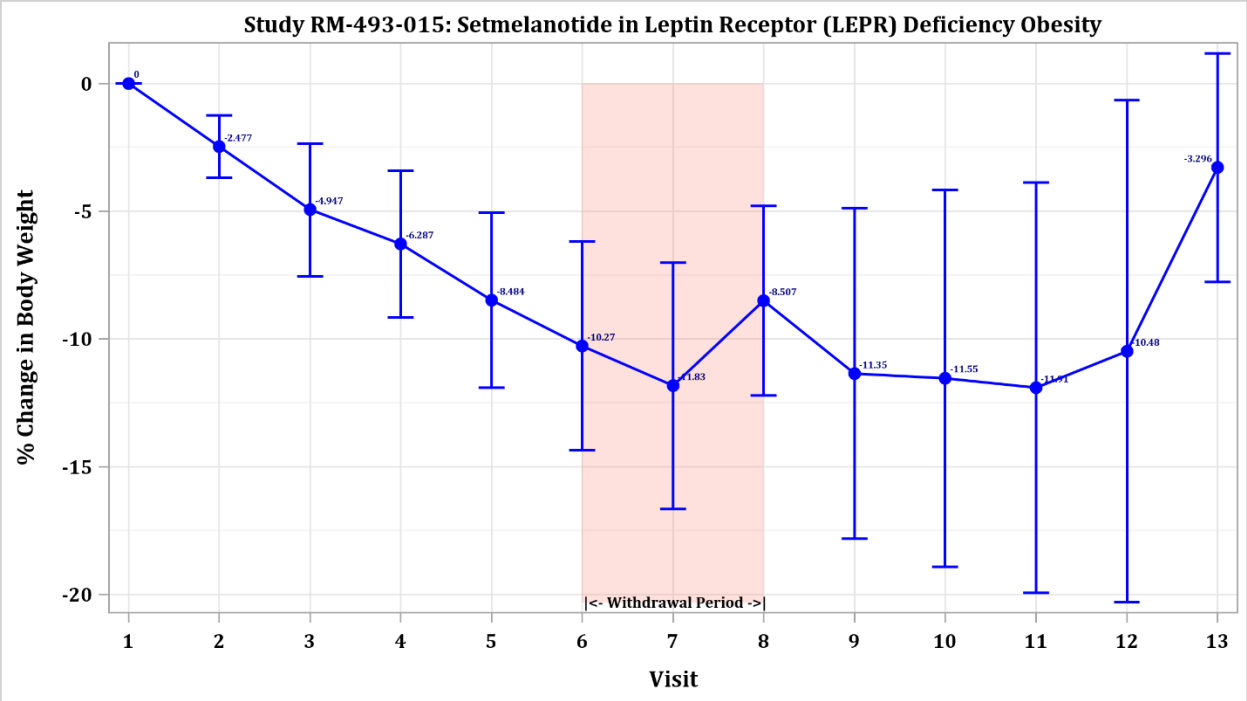
Several key analysis populations were defined in this study:

- The FAS 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 DUS 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 primary endpoint in this study was defined as the proportion of patients in the pivotal cohort in the FAS population who met the ≥10% weight loss threshold (responders) after approximately 1 year of treatment.

After approximately 52 weeks of treatment with setmelanotide, 5 of 11 patients achieved a ≥10% decrease from baseline in body weight at Week 52 (i.e., after 52 weeks of treatment with setmelanotide at the therapeutic dose) (Table 16, Figure 20).

Figure 20 Percent Change of Weight from Baseline by Visit Following Administration of Setmelanotide in LEPR Obesity Patients



(Source: Reviewer generated graph)

Table 16 Proportion of LEPR Obesity Patients Achieving at Least 10% Weight Loss from Baseline at 52 Weeks from Therapeutic Dose of Setmelanotide

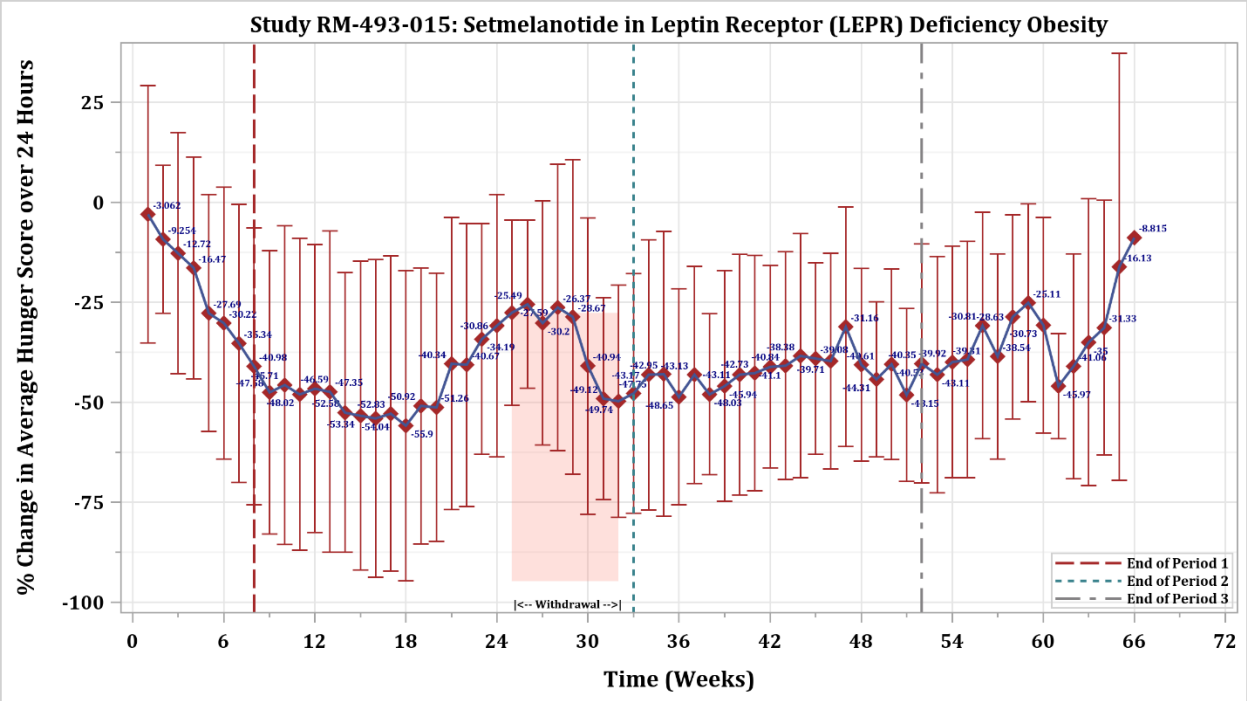
Parameter	Statistic	Total (N=11)
Subjects Achieving at Least 10% Weight Loss from Baseline at Week 52	n (%)	5 (45.5%)
	90% CI[1]	(19.96, 72.88)
	P-value[1]	0.0001

Note: FAS consisted of patients who receive any of the study drug injections and at least one baseline assessment (includes those who do and do not demonstrate ≥5 kg weight loss or 5% of body weight if weight is <100kg at baseline over 12-week open label treatment period and proceed into the double blind, placebo controlled withdrawal period).
Weight was measured in triplicate at each visit.
Percentages based on number of patients with weight data at both baseline and Week 52.
[1] 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 subjects in the population of interest will achieve 10% weight loss.

(Source: CSR for Study RM-493-015, Table 11, Page 65)

One of the secondary efficacy endpoints evaluated was hunger score. During the study 3 distinct daily hunger scores were collected: morning hunger, worst (most) hunger in 24 hours, and average hunger in 24 hours. Weekly average hunger score for analysis were determined from average of daily hunger scores. The hunger score used to assess study endpoints was the weekly average hunger score of the daily worst (most) hunger score in 24 hours (Figure 21). In the pivotal cohort in the DUS population, an LS mean percent change from baseline in hunger score of -41.9% was seen at Week 52 (i.e., after 52 weeks of treatment at the therapeutic dose) as shown in Table 17.

Figure 21 Percent Change of Average Hunger Score from Baseline by Visit Following Administration of Setmelanotide in POMC Patients



(Source: Reviewer generated graph)

Table 17 Percent Change in Daily Hunger Scores from Baseline at 52 Weeks from Therapeutic Dose (≥12 Years of Age) – Pivotal Cohort (DUS Population)

		Total (N=7)		
Parameter	**Statistic**	**Morning Hunger**	**Worst (Most) Hunger in 24 Hours**	**Average Hunger over 24 Hours**
Baseline Hunger Score	n	7	7	7
	Mean (SD)	3.8 (2.21)	7.0 (0.77)	5.4 (0.85)
	Median	3.6	7.0	5.7
	Q1, Q3	2, 6	6, 8	5, 6
	Min, Max	0, 6	6, 8	4, 7
Week 52 Hunger Score	n	7	7	7
	Mean (SD)	2.0 (1.27)	4.1 (2.09)	2.9 (1.27)
	Median	2.9	3.0	3.0
	Q1, Q3	1, 3	2, 5	2, 4
	Min, Max	0, 3	2, 8	2, 5
Percent Change from Baseline to Week 52 (%)	n	7	7	7
	Mean (SD)	-36.6 (47.16)	-43.7 (23.69)	-45.1 (23.78)
	Median	-51.7	-52.7	-53.8
	Q1, Q3	-76, 0	-64, -29	-64, -20
	Min, Max	-86, 50	-67, 0	-74, -17
	LS Mean[1]	-36.63	-41.93	-45.05
	90% CI[1]	(-61.08, -12.19)	(-54.76, -29.09)	(-59.88, -30.21)
	P-value[1]	0.0088	<.0001	<.0001

Note: DUS population consisted of patients who received any of the study drug injections, demonstrated ≥5 kg weight loss or 5% of body weight if weight was < 100kg at baseline over 12-week open label treatment period, and proceeded into the double-blind, placebo controlled withdrawal period. Hunger ranges from 0 - 10 on a Likert-type scale; 0 = not hungry at all and 10 = hungriest possible. Hunger score was captured in a daily diary; this was then averaged to calculate a weekly score for analysis. Questions on hunger questionnaire (ages ≥12) are: "in the last 24 hours, on average, how hungry do you feel?", "In the last 24 hours, how hungry did you feel when you were the most hungry?" (key secondary endpoint), and "This morning when you woke up for the day, how hungry did you feel?" Percentages based on number of patients with hunger diary data at both baseline and Week 52.

The last value prior to the first dose was considered the baseline value. Note that if the weekly average hunger score prior to the first administration of study drug was missing, the daily hunger score collected on Day 1 (first day of active dose) was used as "Baseline."

[1] Model based summary statistics from longitudinal mixed analysis of variance model with fixed effect for week, baseline daily hunger score and random effect for patient, one sided p-value from model.

(Source: CSR for Study RM-493-015, Table 13, Page 69)

The proportion of patients ≥12 years of age achieving at least 25% improvement in hunger scores following 1 year of treatment with setmelanotide in FAS population was the third key secondary endpoint. Eight (8) of the 11 patients (73%) in the FAS Population achieved at least 25% hunger score (worst 'most' hunger in 24 hours) improvement from baseline at Week 52 after treatment with setmelanotide (p<0.0001, Table 18).

Table 18 Proportion of Subjects (≥12 years of age) Achieving at Least 25% Improvement in Daily Hunger Scores from Baseline at 52 Weeks from Therapeutic Dose of Setmelanotide – Pivotal Cohort (FAS Population)

		Total (N=11)		
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 (%)	6 (54.5)	8 (72.7)	7 (63.6)
	90% CI[1]	(27.12, 80.04)	(43.56, 92.12)	(34.98, 86.49)
	P-value[1]	<.0001	<.0001	<.0001

Note: FAS consisted of patients who received any of the study drug injections and at least one baseline assessment (included 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 proceed into the double-blind, placebo-controlled withdrawal period). Hunger ranged from 0 - 10 on a Likert-type scale; 0 = not hungry at all and 10 = hungriest possible. Hunger score was captured in a daily diary, and this was then averaged to calculate a weekly score for analysis.
Questions on hunger questionnaire (ages ≥12) were: "in the last 24 hours, on average, how hungry do you feel?", "In the last 24 hours, how hungry did you feel when you were the most hungry?" (key secondary endpoint), and "This morning when you woke up for the day, how hungry did you feel?"

[1] 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.

(Source: CSR for Study RM-493-015, Table 14, Page 70)

4.3 Immunogenicity

Immunogenicity to setmelanotide was evaluated in a majority of the clinical trials in the development program. Anti-drug antibodies (ADA) to setmelanotide, neutralizing antibodies (NAb) to setmelanotide and antibodies to α-melanocortin stimulating hormone (α-MSH) were evaluated through validated assays. The incidence of screen positives was 79 of 1,148 samples in the screening assay (6.9%). 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 were tested in the neutralizing antibody assay (NAb). Antibodies specific for setmelanotide were not found in any of the samples from any of the clinical trials where ADA was assessed. There have been no observations of a rapid decline in measured setmelanotide concentrations, which would indicate a possible emergence of ADA to setmelanotide. This leads to the expectation that there would no impact of ADA on setmelanotide PK. In addition, there have been no observed clinical effects on PD or efficacy parameters, such as increased hunger or weight gain which is consistent with the observation of no ADA to setmelanotide as noted in the assays. There is no evidence of systemic allergic reactions or progression of skin reactions over time that would indicate the presence of ADA to the setmelanotide or its formulation components. There was a report of one case of mild eosinophilia in Subjec (b) (6) (Study 015) that led to discontinuation. This patient had pretreatment optical density (OD) values at or below the cut-point at screening and post-treatment with setmelanotide in the ADA assay, the setmelanotide PK concentrations appeared to be in alignment with other subjects, and there were no samples positive for anti-α-MSH antibodies. These data indicate there is no relationship between the eosinophilia and immunogenic response.

The acceptability of the immunogenicity data and associated analytical method is further deferred to the OBP review.

4.4 Pharmacometrics Assessment

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4.4.1 SUMMARY OF FINDINGS

The applicant identified body weight but not renal function to be a significant intrinsic covariate associated with setmelanotide exposure. Subjects with mild renal function had 19% (95% CI: -6.5% - 47%) higher setmelanotide steady state AUC compared to those with normal renal function. There were no subjects with moderate renal impairment in the development program. Subjects weighting 50 Kg had 55% (95% CI: 38% - 73%) higher steady state AUC compared to subjects with 90 Kg and subjects weighting 200Kg had 45% (95% CI: 39% - 52%) lower AUC. Due to the strong correlation between age and body weight (younger patients having lower weight), the applicant's simulations indicate that pediatric subjects tend to be over-exposed compared to adults at the same setmelanotide dose. For this reason, the applicant proposes (b) (4). Similarly, despite lack of data, the applicant proposes (b) (4) The purpose of this review is to assess if population PK and exposure-response analyses support the proposed labelling for specific populations.

4.4.1.1 Key review questions

4.4.1.1.1 Does population PK modeling and simulation data support the proposed labelling for specific populations?

4.4.1.1.1.1 Pediatric subjects

Yes, the proposed labeling for pediatric subjects is acceptable for treatment of RGDO. However, the recommendation for starting dose for adolescents is not acceptable. The reviewer's exposure-response analyses for efficacy determined a very small EC_{50} (concentration need to achieve half of the maximum efficacy = $7.8 \times 10^{-20}\ ng/mL$) compared to the range of observed concentration at the recommended starting and maintenance doses. This implies that at the proposed starting and maintenance doses, the concentrations (C_{av} = 20.62 ng/mL, see section 2.1) are at the plateau of the exposure-response curve and therefore maximum efficacy is expected. The reviewer did not perform exposure-vs-safety analyses but given a possibility for positive relationship between exposure and adverse events, a conservative approach (b) (4) The proposed doses are also supported by pediatric to adult exposure-matching PK simulations which indicate that acceptable proportions of pediatric subjects will attain exposures higher than the lower 10th percentiles of the adult exposures. However, adolescents may benefit from the same starting dose as adult subjects with no concerns for adverse events. This is because, the adolescents, with comparable baseline weight as adults are predicted to have the same exposure as adults at the same starting dose. Given the favorable safety profile observed in adults with the same exposure as adolescents at 2 mg dose, it is justified that adolescents should be initiated at the same dose as adults of 2 mg.

4.4.1.1.1.2 Moderate renal impairment

No, the proposed labelling (b) (4) Therefore, given the concerns for safety, it is better to be conservative and avoid setmelanotide for subjects with moderate renal impairment.

4.4.1.2 Recommendations

The applicant's proposed dose labelling is acceptable for treatment of RGDO, with a caution not to dose setmelanotide in patients with moderate renal impairment.

4.4.2 RESULTS OF SPONSOR'S ANALYSIS

4.4.2.1 Population PK Analysis

4.4.2.1.1 Review Summary

The applicant's population PK analysis is acceptable for prediction of exposures in specific populations and for exposure-response analyses. In brief, Setmelanotide plasma pharmacokinetics were adequately described by a one compartment model with zero-order absorption kinetics after subcutaneous injection. Both goodness-of-fit plots and prediction corrected visual predictive checks indicate that the final population PK model is adequate in characterizing the PK profile of Setmelanotide in adult and pediatric subjects 6 years and older. The inter-individual variability (IIV) for CL (28.7%), and V (26.5%) were small. IIV for D2 (duration of zero order absorption) was relatively high (52.3%). Eta Shrinkages for CL (27.7%), V (57.8%) and D2 (40.9%) are reasonable and support evaluation of covariates of CL. Although renal excretion account for about 40% elimination of unchanged Setmelanotide within 24 hours, creatinine clearance (CLCR) was not a significant covariate for clearance. Body weight was a covariate for CL and V with fixed allometric exponents of 0.75 and 1 respectively. Other covariates were; setmelanotide formulation on D2 and bioavailability (F), and sex, age, and healthy status on CL. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

The developed model was used to support labelling of Setmelanotide in the current submission as outlined in Table 19**.**

Table 19 Reviewer's Specific Comments on Applicant's Final Population PK model

Utility of the final model			Reviewer's Comments
Support applicant's proposed labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	Initial and maintenance doses are dependent on age group. Initial and maintenance doses for subjects (b) (4) (b) (4) are 1 mg and 2 mg respectively: in adults, the doses are 2 mg and 3 mg respectively	Through monte-carlo simulations the applicant's model shows that setmelanotide exposure, after 1 mg through 2.5 mg doses, exposures in pediatric subjects are within the 95% prediction interval for exposure in adults receiving 3 mg. Monte-carlo simulations for exposure matching are acceptable since the model predictive performance was reasonable as indicated by prediction corrected visual predictive checks (PcVPC)
	Extrinsic factor	Formulation was the only extrinsic factor with effect on setmelanotide bioavailability	
Derive exposure metrics for exposure-response analyses	Predicted exposures from the PK model were used for exposure vs response analyses		The applicant did not perform exposure-vs-response analyses. The reviewer has performed these analyses as described in section 2 (Population PD analyses)
Predict exposures at alternative dosing regimen	The model was used to assess predicted exposures at doses >= 2mg		

4.4.2.1.2 Introduction

The key objectives of the applicant's population PK analyses were to:

- To develop a population PK model from phase 1 to 3 studies.
- To estimate the effects of prespecified covariates which may be important predictors of setmelanotide PK.
- To use the resulting population PK model to determine an appropriate starting dose of setmelanotide in children (6 - 11yrs) and adolescents (12 - 17 yrs).

4.4.2.1.3 Model development

4.4.2.1.3.1 Data

The analyses were based on PK data from 8 phase 1-3 studies. The study design, study population, and timing of blood samples varied among the 8 clinical studies. Brief descriptions of the studies included are presented in addendum Table 26.

The final NONMEM data file for analysis contained 2711 PK observations from 120 subjects. Table 20 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 20 Summary of Baseline Demographic Covariates for Analysis

		STUDIES						
Characteristics	level	RM493008	RM493010	RM493011	RM493012	RM493014	RM493015	RM493026
N		22	40	7	12	30	13	9
RACE (n (%))	White	2 (9.1)	36 (90.0)	6 (85.7)	7 (58.3)	25 (83.3)	10 (76.9)	5 (55.6)
	Black or African	20 (90.9)	1 (2.5)	1 (14.3)	0 (0.0)	4 (13.3)	0 (0.0)	4 (44.4)
	Asian	0 (0.0)	3 (7.5)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	0 (0.0)	0 (0.0)	5 (41.7)	0 (0.0)	3 (23.1)	0 (0.0)
SEX (n (%))	Male	14 (63.6)	19 (47.5)	3 (42.9)	7 (58.3)	8 (26.7)	5 (38.5)	2 (22.2)
	Female	8 (36.4)	21 (52.5)	4 (57.1)	5 (41.7)	22 (73.3)	8 (61.5)	7 (77.8)
Formulation n (%)	Preserved	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	13 (100.0)	9 (100.0)
	Unpreserved	22(100.0)	40 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	No information	0 (0.0)	0 (0.0)	7 (100.0)	12 (100.0)	30 (100.0)	0 (0.0)	0 (0.0)
Baseline BMI (kg. /m^2), (Mean (Sd))		33.68 (3.24)	39.67 (11.86)	45.97 (7.02)	39.73 (8.35)	45.39 (10.10)	49.37 (11.43)	44.44 (7.06)
Baseline weight (Kg), (Mean (Sd))		99.68 (13.70)	97.72 (25.56)	142.99 (21.98)	114.27 (35.66)	125.08 (33.52)	137.17 (32.75)	120.62 (23.45)
Baseline ideal Weight (Kg), (Mean (Sd))		65.58 (8.59)	52.82 (13.37)	69.29 (9.28)	62.13 (12.44)	58.47 (12.94)	60.18 (7.68)	57.39 (7.42)
Baseline adjusted Weight (Kg), (Mean (Sd))		79.22 (9.84)	70.78 (13.61)	98.77 (10.83)	82.99 (20.58)	85.11 (19.06)	90.97 (14.64)	82.68 (11.81)
Baseline height (Cm), (Mean (Sd))		171.42 (7.88)	158.12 (13.19)	176.54 (8.59)	167.87 (13.48)	165.39 (12.50)	166.69 (7.27)	164.41 (6.70)
Baseline age (yrs.), (Mean (Sd))		39.23 (8.49)	26.35 (9.48)	20.29 (3.40)	17.08 (6.37)	29.13 (16.81)	22.85 (8.21)	43.78 (6.80)

Source: Reviewer's independent analyses

4.4.2.1.3.2 Base Model

The base model was a population PK model developed using setmelanotide PK data from 29 adult subjects who were healthy and obese and another 91 subjects with rare genetic disorders of obesity (RGDO) (See table of studies). The base PK model was a one-compartment structural model with zero-

order absorption from subcutaneous administration site and linear elimination kinetics. The model was parameterized in apparent clearance (CL/F), apparent central compartment volume (V/F), duration of zero order absorption (D2). Relative bioavailability (F) from administration site was fixed to 1 and between subject variability for F was estimated. Clearance and volume parameters were allometrically scaled using body weight. coefficients for WT were fixed to literature values of 0.75 for CL and 1 for V. Allometric scaling was supported by a significant difference in objective function value between a model with and without allometric scaling ($\Delta\ OFV = -50$). Estimated model parameters are given in Table 21 below.

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Table 21 Estimated model parameters and covariate effects for the base model

PK Parameter (Unit)	NONMEM Parameter	Estimate	95%CI*
CL/F (L/hr)	$\exp(\theta_1)$	5.49	(5.11, 5.89)
V/F (L)	$\exp(\theta_2)$	56.3	(53.3, 59.4)
$D2$ (hr)	$\exp(\theta_4)$	5.26	(4.79, 5.78)
$CL/F \sim AllometricExponent$	θ_6	0.750 FIX	
$V/F \sim AllometricExponent$	θ_7	1.00 FIX	
IIVvar $CL/F(\omega^2_{CL/F})$	$\Omega_{1,1}(\eta_1)$	0.0826 (%CV=29.4)	(0.0520, 0.113)
IIVcov $CL/F, V/F(\omega_{CL/F}, \omega_{V/F})$	$\Omega_{2,1}$	0.00467	(-0.00819, 0.0175)
IIVvar $V/F(\omega^2_{V/F})$	$\Omega_{2,2}(\eta_2)$	0.0362 (%CV=19.2)	(0.0168, 0.0555)
IIVcov $CL/F, D2(\omega_{CL/F}, \omega_{D2})$	$\Omega_{3,1}$	0.0345	(-0.00446, 0.0735)
IIVcov $V/F, D2(\omega_{V/F}, \omega_{D2})$	$\Omega_{3,2}$	0.0190	(-0.00393, 0.0419)
IIVvar $D2(\omega^2_{D2})$	$\Omega_{3,3}(\eta_3)$	0.180 (%CV=44.4)	(0.131, 0.229)
$Res_{proportional}(\sigma^2)$	$\Sigma_{1,1}(\varepsilon_1)$	0.0782 (%CV=28.5)	(0.0753, 0.0811)
$Res_{additive}(\sigma^2)$	$\Sigma_{2,2}(\varepsilon_2)$	1.55 (SD=1.24)	(1.48, 1.62)

*95%CI derived from standard errors obtained from the NONMEM $COVARIANCE step

θ_3 (Ka) was fixed to a very small value and θ_5 (F1) was fixed to 0 to ensure all drug was absorbed through the zero-order process into the central compartment. Typical values for CL/F and V/F represent a 90kg individual. IIV=interindividual variability, CV=coefficient of variation, SD=standard deviation

Source: Applicant's population PK modeling report (Report Number: RPI0101F-Report-v1.1-Final; Page 30 of 215)

Inter-individual variability (IIV) was modeled assuming a log-normal distribution for patient level random effects. The base model included variance covariances among the IIVs. Residual variability was modeled as a combined additive plus proportional residual error on setmelanotide concentration. Model evaluations and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

4.4.2.1.3.3 Covariate Analysis

Covariate model building proceeded through investigation of plots of covariates versus inter-individual random effects. No obvious trends were observed. Despite the lack of obvious relationships, the applicant employed the Full Covariate Model (FCM) building technique to develop a full covariate model. With FCM, physiologically plausible relationships are included into the model with emphasis on parameter estimation rather than stepwise hypothesis testing. Figure 22 shows the covariates included in the full model. Additional covariates (other than body weight) in the full model included age, renal function, sex, and health status on CL/F. The model also included effect of formulation on D2.

Figure 22 Parameterization of the full covariate model

$$CL/F_i = exp(\theta_1) \times \left(\frac{WT_i\ kg}{90\ kg}\right)^{\theta_{11}} \times \left(\frac{AGE_i\ yr}{25\ yr}\right)^{\theta_6} \times \left(\frac{CCRabw_i\ mL/min}{90\ mL/min}\right)^{\theta_7} \times exp(\theta_8 \times SEX_i) \times exp(\theta_9 \times HEALTHY_i) \times exp(\eta_{1i})$$

$$V/F_i = exp(\theta_2) \times \left(\frac{WT_i\ kg}{90\ kg}\right)^{\theta_{12}} \times exp(\eta_{2i})$$

$$D2_i = exp(\theta_3) \times exp(\theta_5 \times FORM_{ij}) \times exp(\eta_{3i})$$

$$F = 1 \times exp(\theta_{10})^{FORM_{ij}}$$

where

- SEX=0 for males and SEX=1 for females. HEALTHY=0 for patients and HEALTHY=1 for healthy obese subjects. FORM=0 for preserved formulation and FORM=1 for preservative-free or missing formulation for individual *i* at time *j*.
- θ_7 is the estimated power parameter for the effect of CCRabw, normalized to a reference value of 90 mL/min. θ_7 was only estimated in patients with mild renal impairment.

4.4.2.1.3.4 Final Model

4.4.2.1.3.4.1 Final model parameters and diagnostics

The FCM was the final model and the parameter estimates for the final covariate model are listed in Table 22. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 23. The Visual Predictive Check (VPC) plot for the final covariate model with adult and pediatric data are given in Figure 24 and Figure 25.

Table 22 Parameter Estimates of Applicant's Final Model

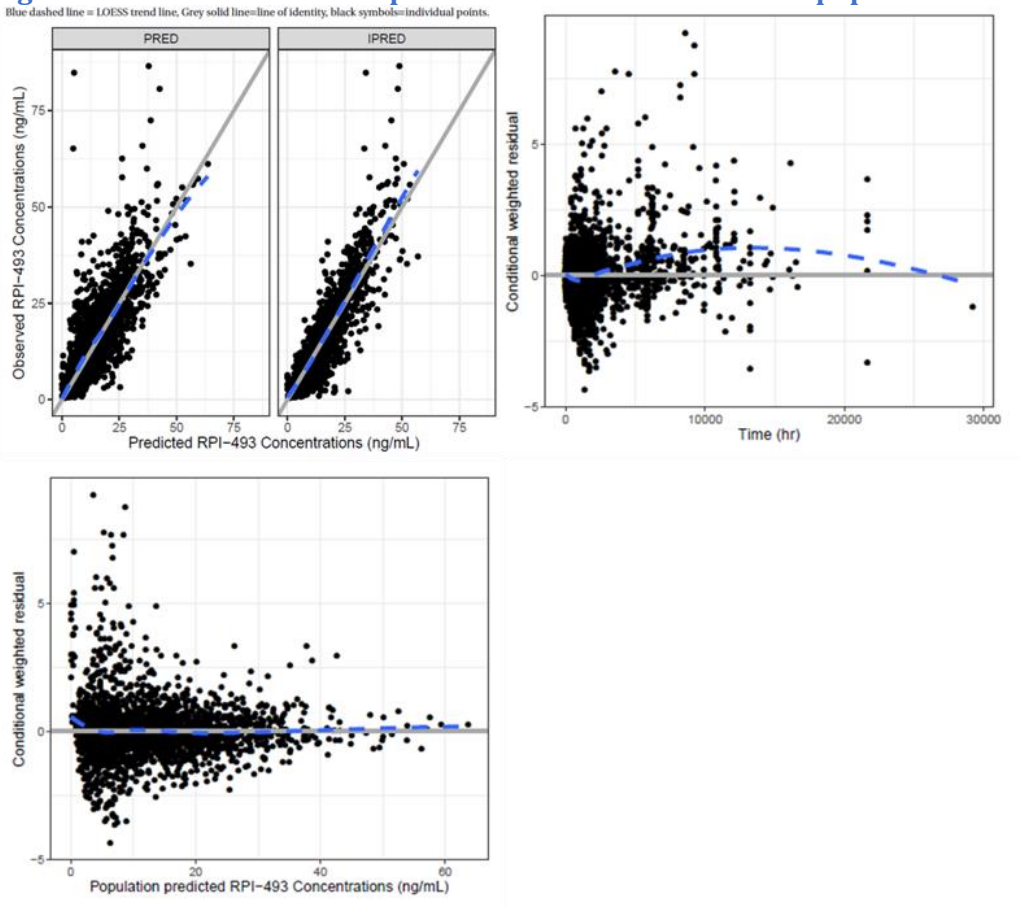
PK Parameter (Unit)	NONMEM Parameter	Estimate	95%CI*	Effective N	Rhat
CL/F (L/hr)	$\exp(\theta_1)$	4.86	(4.36, 5.44)	1550	1
V/F (L)	$\exp(\theta_2)$	48.7	(44.6, 52.7)	882	1.01
$D2$ (hr)	$\exp(\theta_4)$	5.35	(4.50, 6.43)	5480	1
$D2 \sim FORM$	$\exp(\theta_5)$	1.01	(0.783, 1.28)	5040	1
$CL/F \sim Age$	θ_6	0.105	(-0.0453, 0.259)	22000	1
$CL/F \sim CCRabw$	θ_7	1.21	(0.127, 2.28)	9740	1
$CL/F \sim Sex$	$\exp(\theta_8)$	1.02	(0.905, 1.15)	6050	1
$CL/F \sim Healthy$	$\exp(\theta_9)$	0.996	(0.854, 1.16)	21700	1
$F \sim FORM$	$\exp(\theta_{10})$	0.826	(0.769, 0.880)	336	1.02
$CL/F \sim AllometricExponent$	θ_{11}	0.750 FIX		40000	1
$V/F \sim AllometricExponent$	θ_{12}	1.00 FIX		40000	1
IIVvar $CL/F(\omega^2_{CL/F})$	$\Omega_{1,1}(\eta_1)$	0.0790 (%CV=28.7)	(0.0583, 0.109)	15500	1
IIVcov $CL/F, V/F(\omega_{CL/F}, \omega_{V/F})$	$\Omega_{2,1}$	0.0217	(-0.00861, 0.0516)	1080	1.01
IIVvar $V/F(\omega^2_{V/F})$	$\Omega_{2,2}(\eta_2)$	0.0679 (%CV=26.5)	(0.0395, 0.113)	1920	1
IIVcov $CL/F, D2(\omega_{CL/F}, \omega_{D2})$	$\Omega_{3,1}$	0.00495	(-0.0336, 0.0475)	2230	1
IIVcov $V/F, D2(\omega_{V/F}, \omega_{D2})$	$\Omega_{3,2}$	-0.0204	(-0.0740, 0.0195)	1690	1
IIVvar $D2(\omega^2_{D2})$	$\Omega_{3,3}(\eta_3)$	0.242 (%CV=52.3)	(0.163, 0.363)	2680	1
$Res_{proportional}(\sigma^2)$	$\Sigma_{1,1}(\varepsilon_1)$	0.0736 (%CV=27.6)	(0.0665, 0.0810)	1420	1
$Res_{additive}(\sigma^2)$	$\Sigma_{2,2}(\varepsilon_2)$	1.69 (SD=1.3)	(1.39, 2.08)	1460	1

*95%CI derived from 40000 NONMEM BAYES iterations

θ_3 (Ka) was fixed to a very small value to ensure all drug was absorbed through the zero-order process into the central compartment. Typical values for CL/F, V/F, and D2 all represent the preserved formulation. Typical value for CL/F represents a 25 year old, 90kg, male patient with normal renal function. Typical value for V/F represents a 90kg individual. IIV=interindividual variability, CV=coefficient of variation, SD=standard deviation, Rhat - Gelman-Rubin Convergence Diagnostic, Neff - Number of independent samples accounting for autocorrelation.

Source: Applicant's population PK modeling report (Report Number: RPI0101F-Report-v1.1-Final; Page 33of 215)

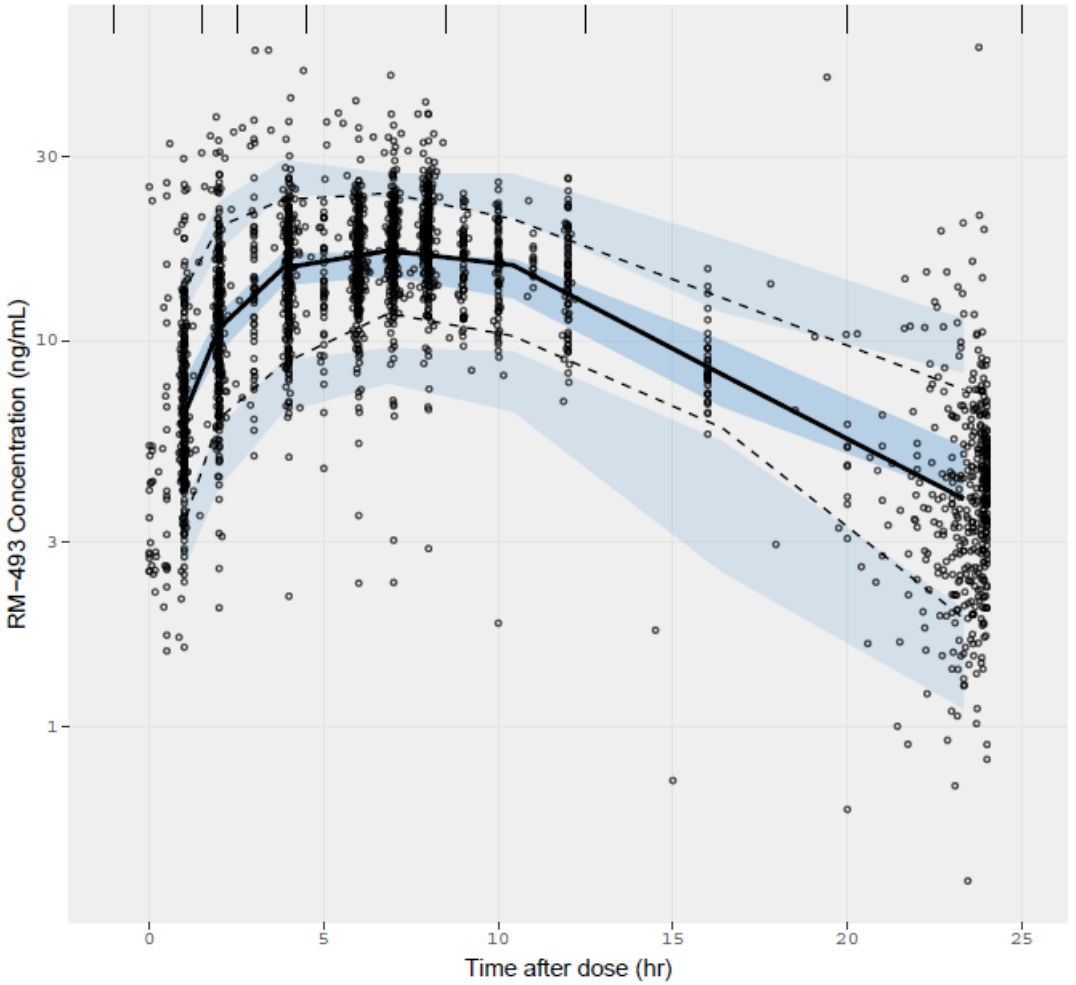
Figure 23 Goodness of fit plot for the final Setmelanotide population PK model



Source: Applicant's population PK modeling report (Report Number: RPI0101F-Report-v1.1-Final; Page 113 - 116 of 215)

Figure 24 Prediction corrected visual predictive check of the final model

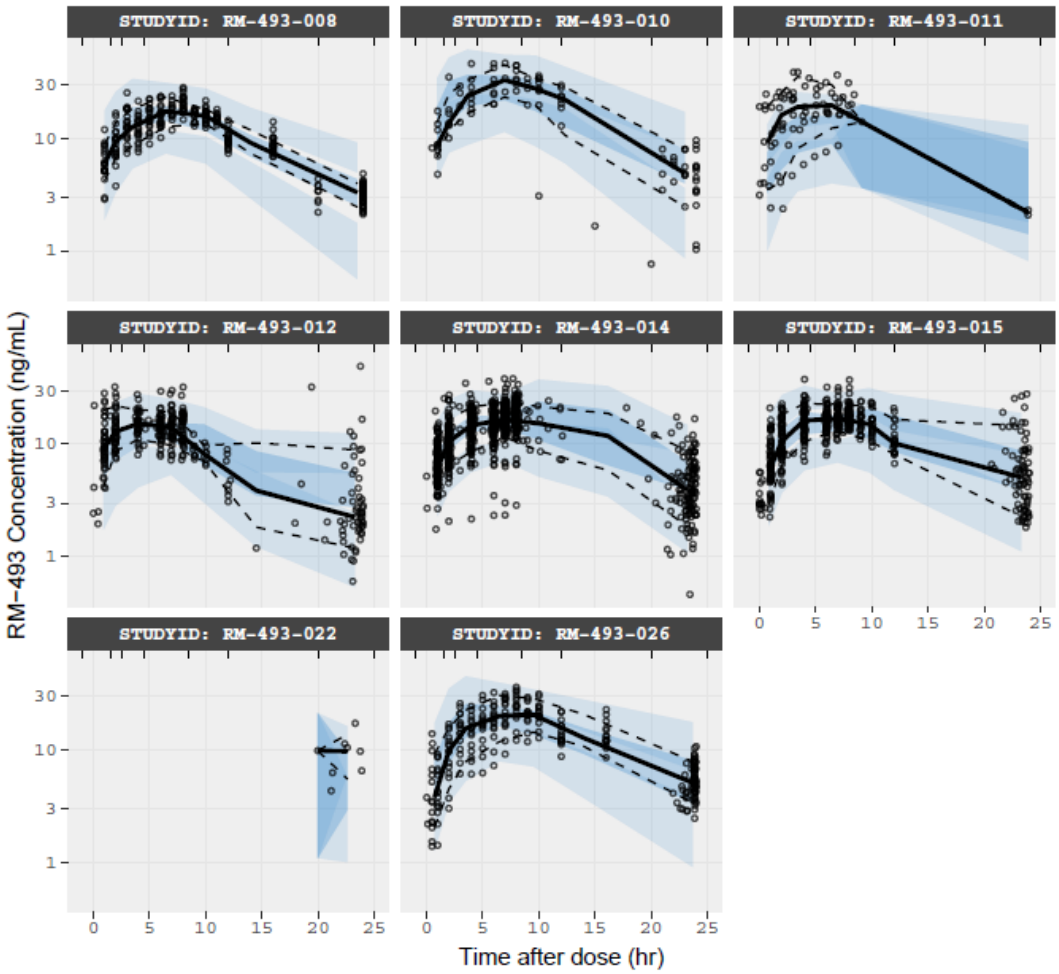
pcVPC of concentrations vs. time after dose. Black lines represent the median and 90% interval of the observed data. Blue shaded regions represent the 95% CI of the 10th, 50th, and 90th prediction intervals.



Source: Applicant's population PK modeling report (Report Number: RPI0101F-Report-v1.1-Final; Page 126 of 215)

Figure 25 Prediction corrected visual predictive check of the final model stratified by Studies

pcVPC of concentrations vs. time after dose stratified by study. Black lines represent the median and 90% interval of the observed data. Blue shaded regions represent the 95% CI of the 10th, 50th, and 90th prediction intervals.



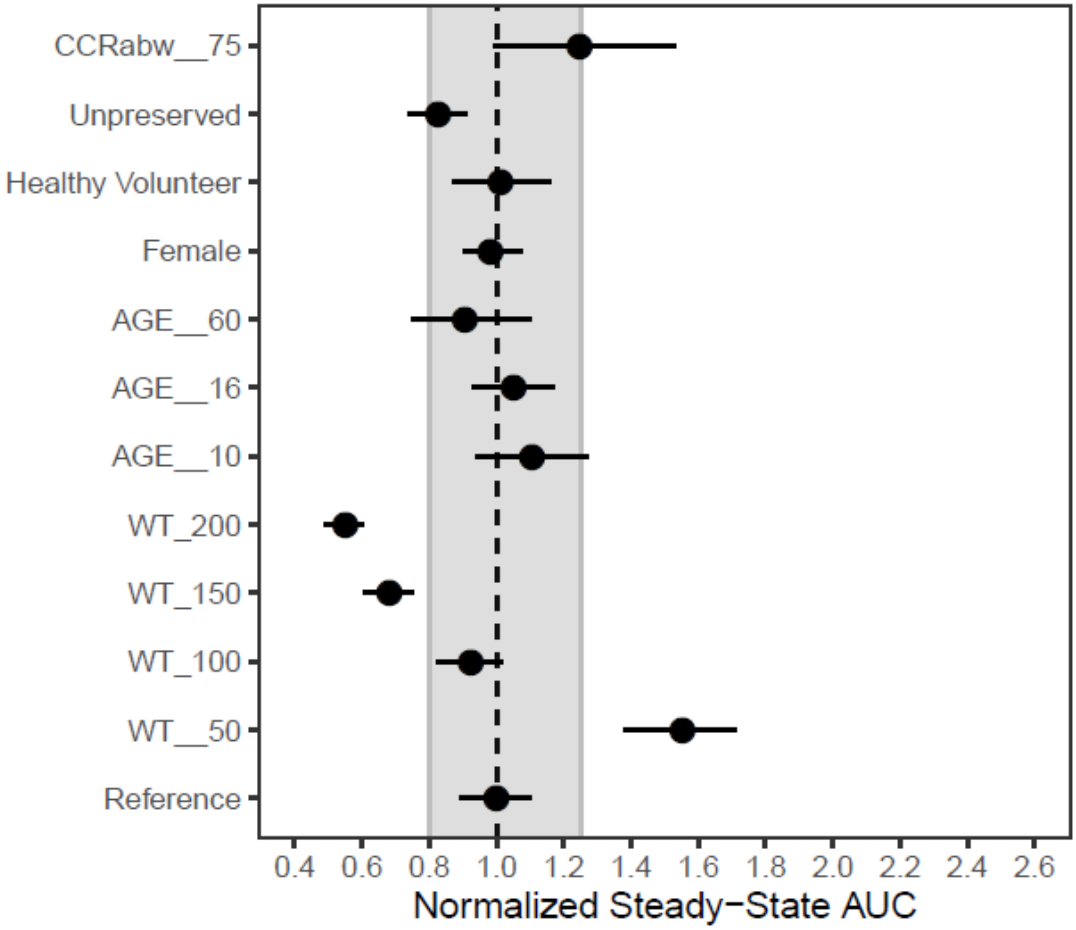
Source: Applicant's population PK modeling report (Report Number: RPI0101F-Report-v1.1-Final; Page 127 of 215)

4.4.2.1.3.5 Magnitudes of covariate effects

Magnitudes of covariate effects on setmelanotide AUC relative to reference covariate values are shown in Figure 26. Significant covariate effects are observed for body weight, renal function, and unpreserved formulation. Compared to reference weight of 90Kg, subjects with 50 kg and greater than 150 Kg have higher and lower AUC respectively. Similarly, compared to subjects with normal renal function, subjects with mild renal function have higher AUC. Furthermore, subjects who took unpreserved formulation have significantly lower AUC compare to preserved formulation.

On the other hand, Female have marginally lower AUC compared to males and compared to reference age of 25 years, subjects with 10 years and 60 years have marginally higher and lower AUC respectively.

Figure 26 Full PK model covariate effects on steady state AUC



Relative AUCss values were calculated using a setmelanotide 2.0 mg QD dose and simulated estimates of AUCss at various perturbations of sex, weight, formulation, patient status, and renal function, normalized to the AUCss of a typical 25-year-old, 90 kg, male patient, with normal renal function and receiving the preserved formulation of setmelanotide. Symbols represent the median relative AUCss and lines represent 95% confidence interval. Grey shaded area represents a 0.8 - 1.25 reference range

Source: Applicant's population PK modeling report (Report Number: RPI0101F-Report-v1.1-Final; Page 151 of 215)

4.4.2.1.3.6 Matching of pediatric to adult setmelanotide exposures

The applicant performed Monte-Carlo simulations of exposures in pediatric subjects using the final population PK model and a virtual subject population, created by randomly sampling weight/sex per age from a dataset of historical growth in patients with RGDO. The simulated pediatric exposures after 1, 1.5, 2, and 2.5 mg doses were compared to post-hoc estimates of the population PK dataset for subjects 17-60 years. Pediatric subjects were all assumed to have normal renal function. At each dose, the applicant compared the proportion of pediatric subjects who exceeded the lower 10th percentile of adult exposure. Table 23 shows the probability of exceeding the lower 10th percentile of adult exposure at different doses. Table 23 shows that initiating setmelanotide at 1 mg in pediatric subjects will result in only about 90% of 6-12 years old and 65% of 12-17-year olds exceeding the lower 10th percentile of 2 mg adult exposures. Table 23 also shows that titrating dose to 2 mg will result in 98% of 6-12 years old and 90% of 12-17 years old exceeding lower 10th percentile of 3mg adult exposures.

Table 23 Probability of simulated pediatric exposure exceeding lower 10th percentile of adult exposure

Age Group (year)	Pediatric Dose (mg)	AUCss (ng*hr/mL)	CMAXss (ng/mL)	CMINss (ng/mL)	Adult Dose (mg)
6 to <12	1.0	0.894	0.896	0.820	2
6 to <12	1.5	0.996	0.992	0.897	2
6 to <12	2.0	0.998	0.998	0.941	2
6 to <12	2.5	1.00	0.998	0.983	2
12 to <17	1.0	0.649	0.622	0.733	2
12 to <17	1.5	0.936	0.907	0.873	2
12 to <17	2.0	0.994	0.994	0.918	2
12 to <17	2.5	1.00	1.00	0.952	2
6 to <12	1.0	0.560	0.522	0.637	3
6 to <12	1.5	0.893	0.879	0.807	3
6 to <12	2.0	0.981	0.985	0.875	3
6 to <12	2.5	1.00	0.992	0.940	3
12 to <17	1.0	0.236	0.169	0.476	3
12 to <17	1.5	0.646	0.586	0.722	3
12 to <17	2.0	0.900	0.887	0.823	3
12 to <17	2.5	0.988	0.992	0.890	3

Source: Applicant's population PK modeling report (Report Number: RPI0101F-Report-v1.1-Final; Page 78 of 215)

4.4.2.1.4 Reviewer's comments

The reviewer finds the applicant's model development steps and identification of covariate effects to be acceptable for prediction of exposures in specific populations and for exposure-response analyses. Therefore, the reviewer did not perform independent exploration of covariate effects. The reviewer repeated the applicant's analyses and found similar results as those reported by the sponsor.

4.4.3 REVIEWER'S ANALYSES

4.4.3.1 Exposure-response analyses for efficacy

Exposure-response analyses for efficacy were conducted in order to determine if differences in setmelanotide exposures due to PK covariates (e.g. renal impairment and body weight) translates to meaningful differences in treatment outcomes. The specific objectives of exposure-response analyses are given below.

4.4.3.1.1 Objectives

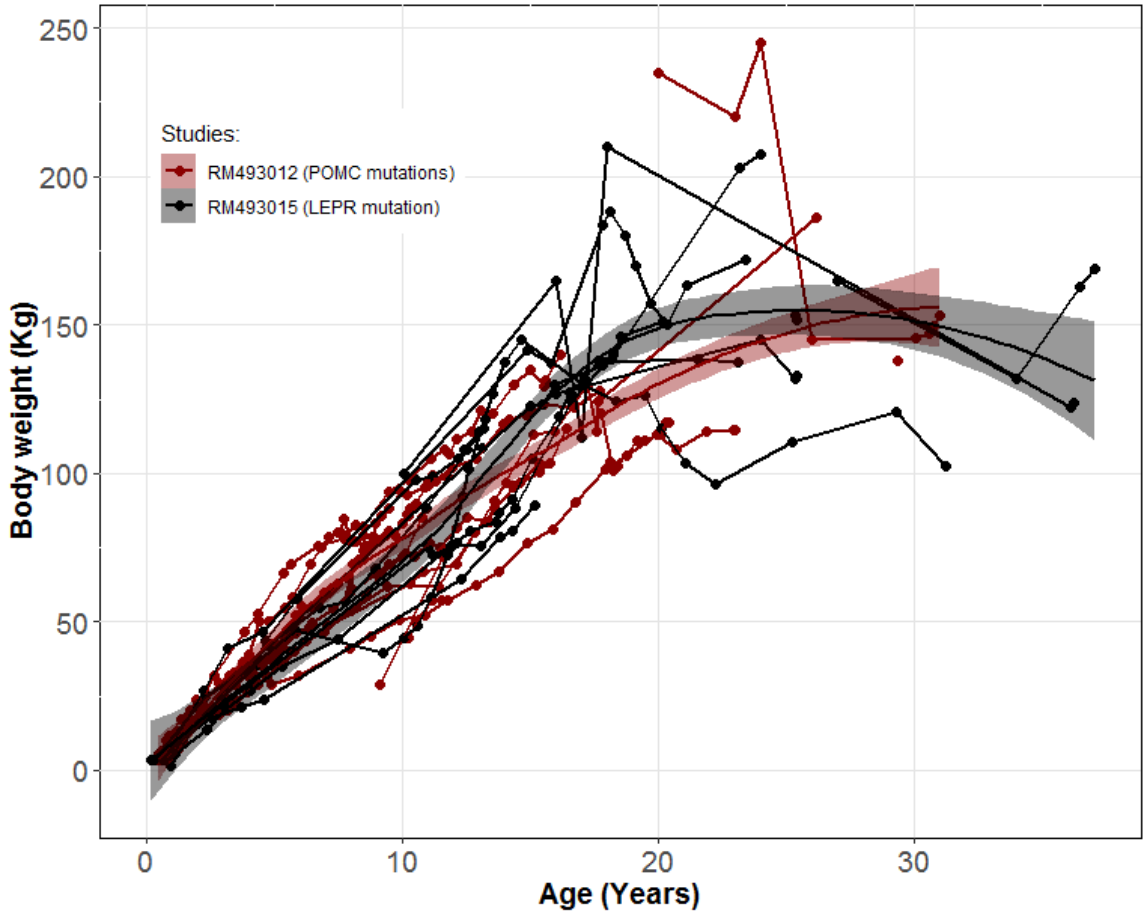
Objective of the reviewer's exposure-response analyses were:

1. To develop a model that can adequately describe historical growth data for subjects with RGDO.
2. To develop a model that can adequately describe weight changes during different treatment epochs.
3. To characterize variability in treatment related weight loss.
4. To determine factors associated with the variability in treatment related weight loss.

4.4.3.1.2 Data

Historical growth data were available from 14 subjects with POMC/PSK1 genetic disorders (Study RM493012) and 13 subjects with LEPR disorder (Study RM493015). The data is shown in Figure 27. The data shows identical growth rate between subjects with POMC/PSK1 and those with LEPR genetic mutations.

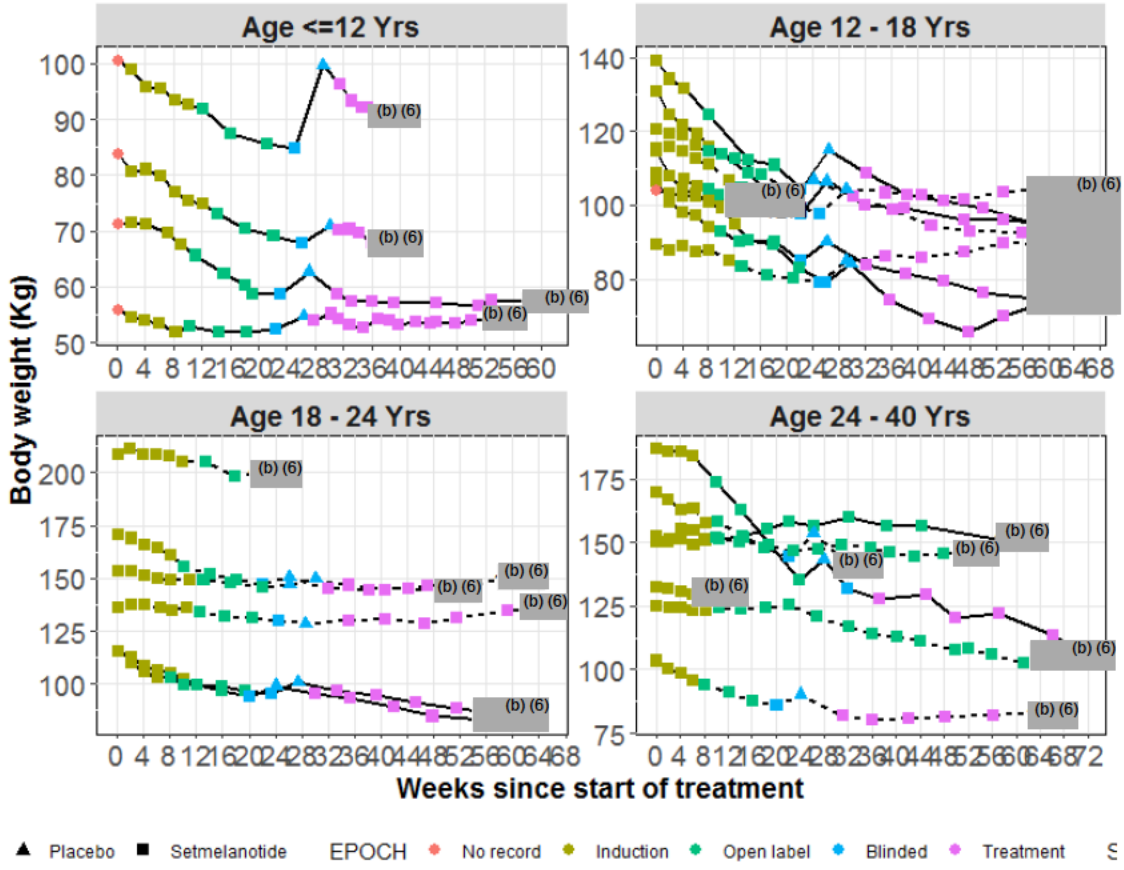
Figure 27 Probability of simulated pediatric exposure exceeding lower 10th percentile of adult exposure



Source: Reviewer's independent analyses

Data for weight profiles at different treatment epochs were available from 13 subjects in studyRM493012 and 13 subjects in study RM492015. The data is shown in Figure 28. The figure shows that for most subjects, weight loss occurs during treatment induction and open label epochs. But during blinded epoch (subjects receives placebo treatment) most subjects gain weight. Finally, most subjects lose weight again when setmelanotide is re-started during the treatment epoch.

Figure 28 Weight profiles at different epochs of setmelanotide treatment. The profiles are stratified by age of patients at the start of treatment



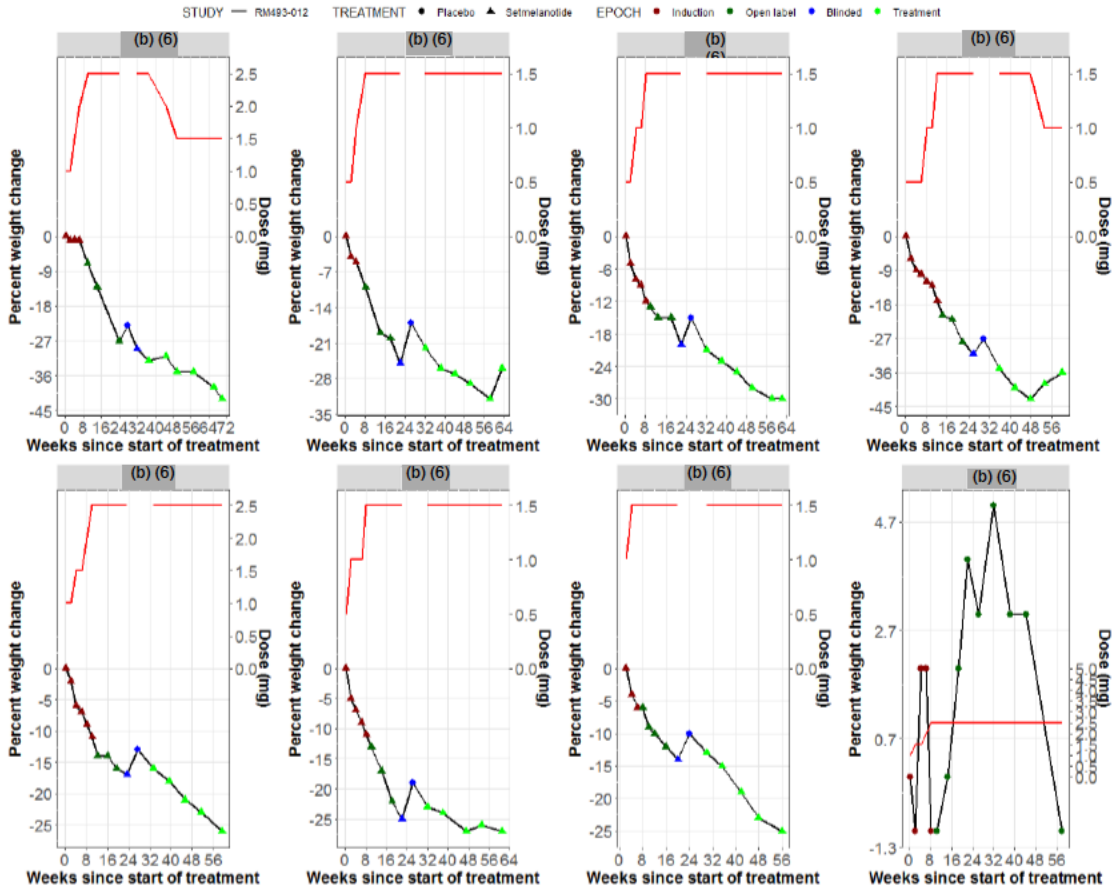
Source: Reviewer's independent analyses

4.4.3.1.3 Exploration of dose-response relationships.

In the induction epoch setmelanotide was initiated at a lower dose (0.5mg or 1 mg) and titrated to maintenance dose (2 mg, 2.5 mg or 3 mg). This offers an opportunity to explore dose-response relationships. It is expected that the rate of weight loss would increase when dose is increased. This was investigated by visual inspection of plots of weight change over-time overlaid on plots of dose titration (Figure 29, Figure 30, Figure 31, Figure 32).

The following observations were made from Figure 29: Subject (b) (6) did not lose weight until when dose was titrated from 1 mg to 2mg. Subject (b) (6) did not lose weight despite increasing dose from 1 to 2.5 mg. For most other subjects, weight loss occurred at the same rate since the start of treatment. Rate of weight loss seems to be the same across the individuals.

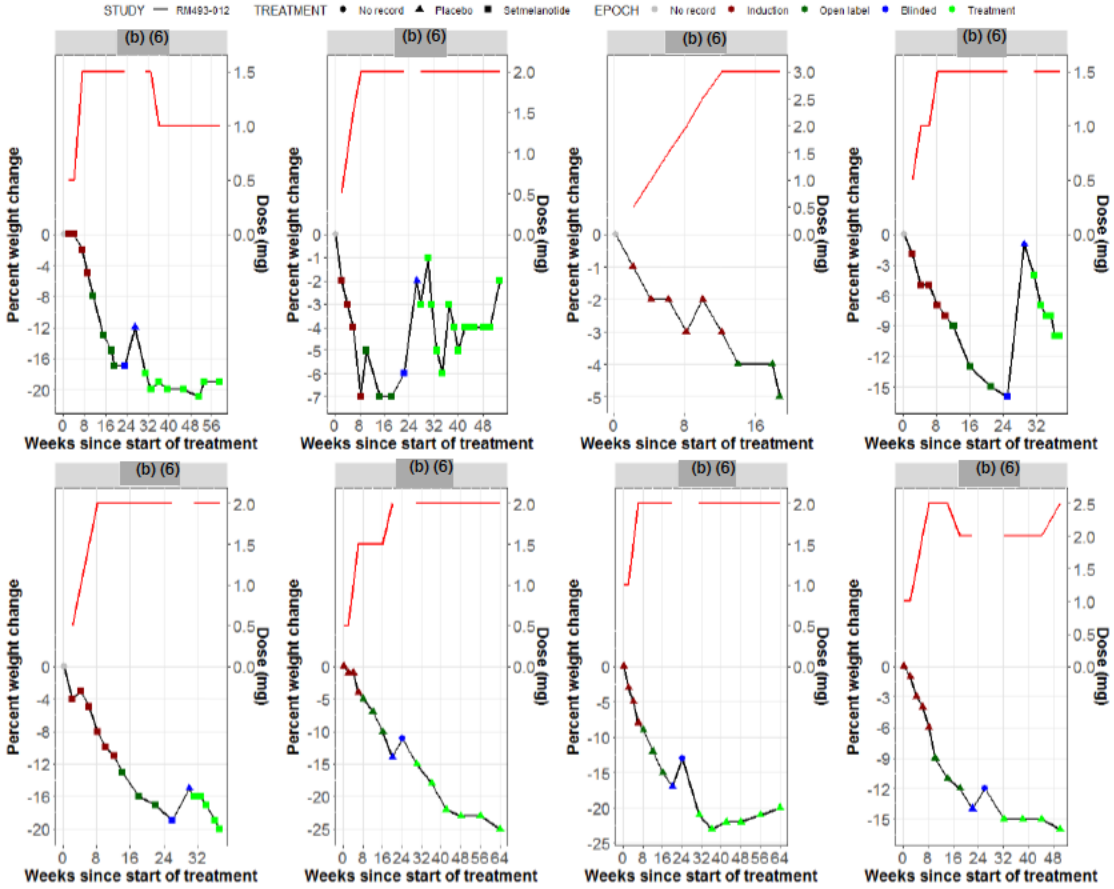
Figure 29 Weight change plot overlaid on dose titration plot (1)



Reviewer's independent analyses

The following observations were made from Figure 30: Subject (b) (6) did not lose weight until when dose was titrated from 0.5 mg to 1.5mg. Dose was titrated down to 1 mg during the treatment epoch without rebound weight gain. Subject (b) (6) lost weight since the start of treatment and despite decreasing the dose from 2.5 mg to 2 mg there were no rebound weight gain. For most other subjects, weight loss seemed to occur at the same rate since the start of treatment across the individuals.

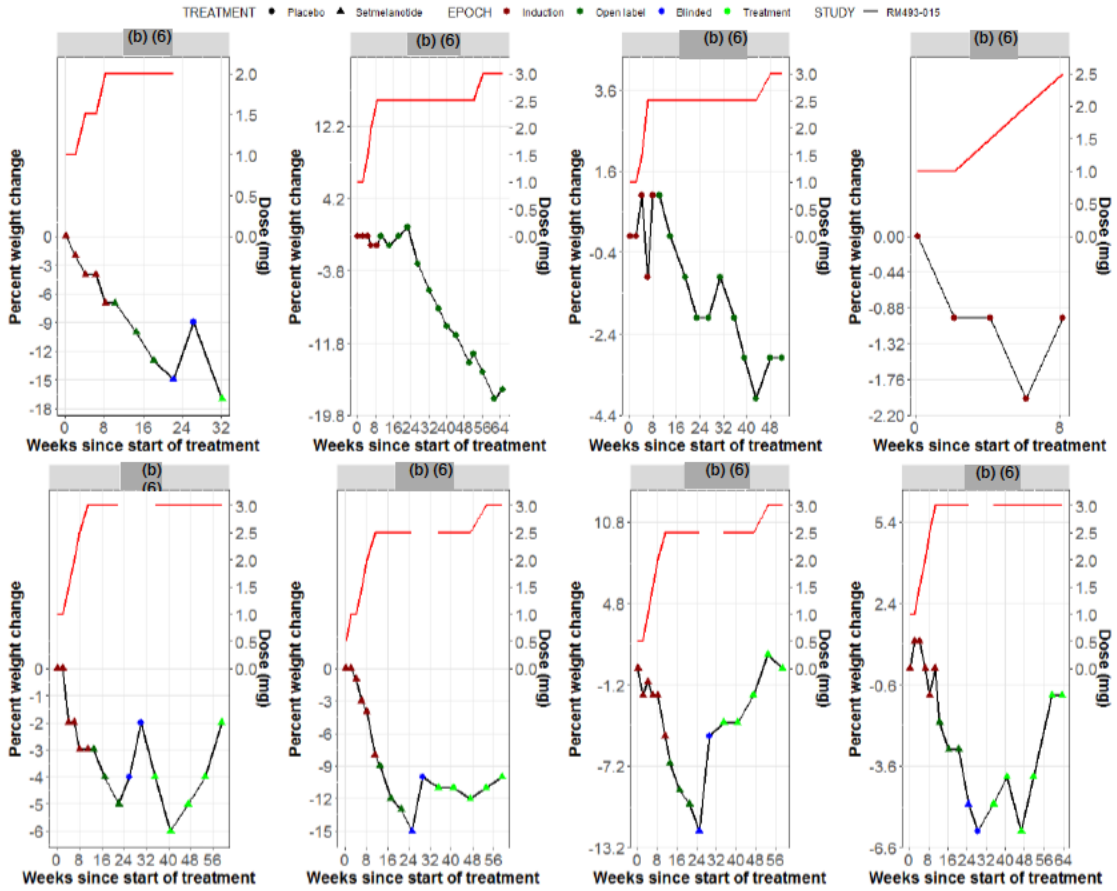
Figure 30 Weight change plot overlaid on dose titration plot (2)



Reviewer's independent analyses

The following observations were made from Figure 31: Subject (b) (6) did not lose weight for the first 8 and 24 weeks respectively despite dose titration to 2.5 mg. Subjects (b) (6) lose weight immediately after treatment. The other 3 subjects lost weight after dose titration.

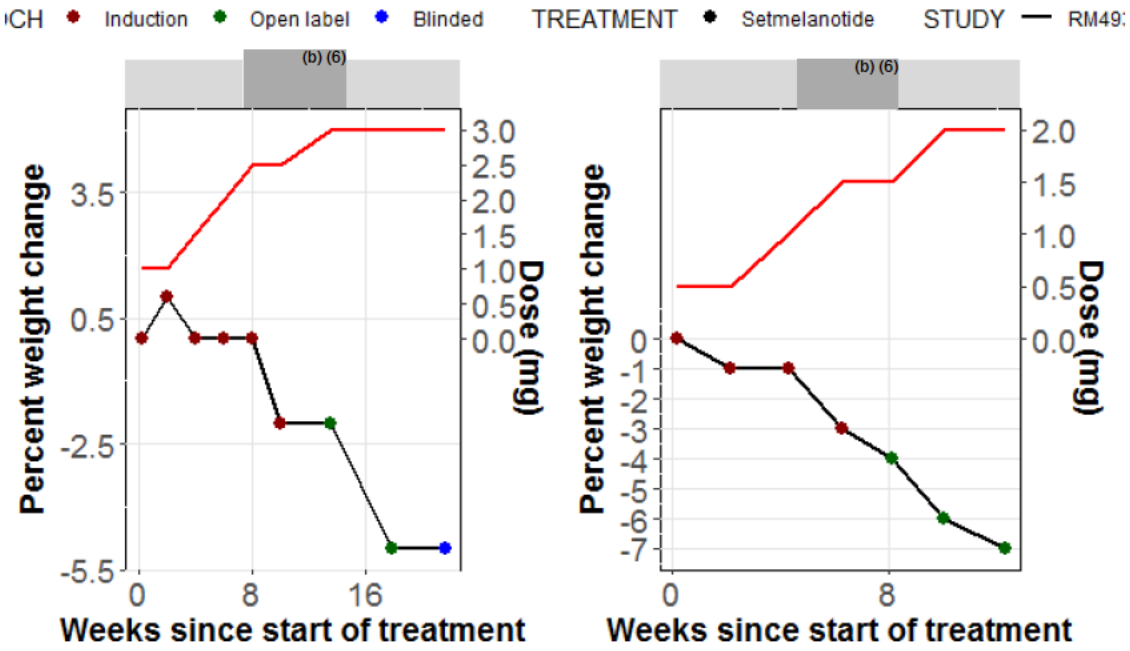
Figure 31 Weight change plot overlaid on dose titration plot (3)



Reviewer's independent analyses

The following observations were made from Figure 32: Subject (b) (6) lost weight after titration while subject (b) (6) immediately lost weight after treatment initiation.

Figure 32 Weight change plot overlaid on dose titration plot (4)



Reviewer's independent analyses

Overall, the exploratory plots do not show a consistent relationship between dose titration and weight loss. For some subjects, weight loss occurs immediately after starting treatment with lowest dose, while for other subjects, weight loss occurred after dose titration. Thus exposure-response relationships were evaluated by modeling of concentration versus weight relationship using population methods.

4.4.3.1.4 Modeling historical growth.

Compartment modeling was used to analyze the historical growth data. A one compartment model parameterized by KIN (rate constant of weight gain) and KOUT (rate constant of weight loss) was tested and found adequate to describe the observed data. Based on **Figure 27**, weight was considered to increase to steady state for every subject in the dataset. Since not every subject had reached steady state weight before treatment, a steady state parameter (SSWT) was estimated. The weight compartment was initialized at birthweight. Since birth weight was not known for all subjects, the birth weight parameter (BASEWT) was fixed to 3.5 Kg and its inter-individual variability was estimated. Empirical estimates of birthweight were confined to be between 2.5 Kg to 5 Kg. Being an unidentifiable parameter, KIN was not estimated but calculated from estimated SSWT and KOUT (KIN = SSWT/KOUT). NONMEM version 7.4 was used for estimation of model parameters. Individual subject parameters were estimated using the method of POPULATION WITH UNCONSTRAINED ETA as described in NONMEM user's guide (Introduction to NONMEM 7.3.0, Robert J. Bauer, ICON development solutions, Hanover, Maryland, November 20, 2013). The medians of the estimated and calculated model parameters are given in Table 24.

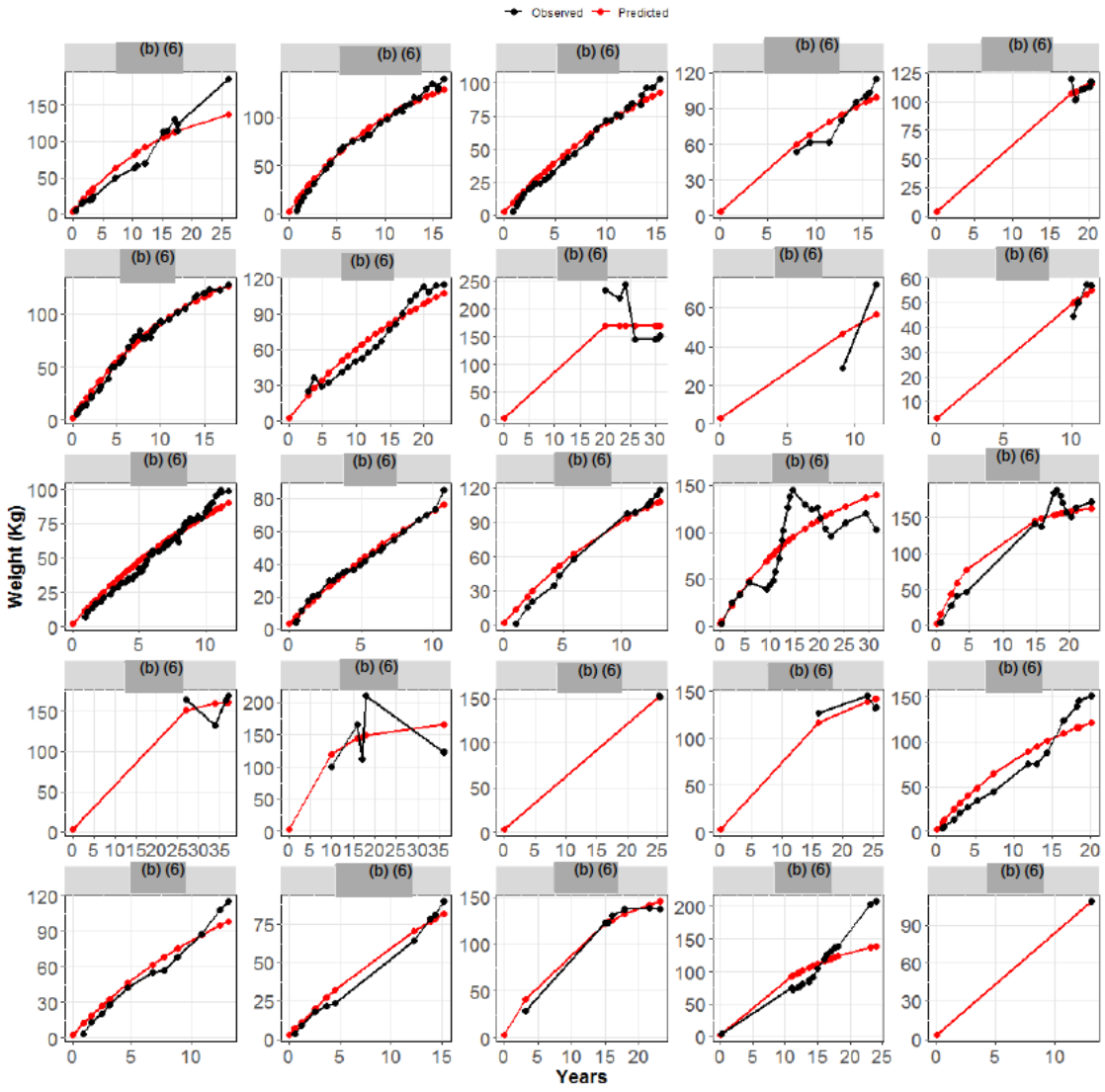
Table 24 Medians and Inter-quartile (IQR) ranges of parameter values for the historical growth model

Parameters	Median	IQR
BASEWT	3.29	2.5 - 3.49
SSWT	169.11	169.05 - 169.29
KIN	0.0012	0.001 - 0.0016
KOUT	0.000007	6e-06 - 1e-05

Reviewer's independent analyses

Figure 33 shows observed, and model predicted growth curves for each individual. Generally, there is good agreement between observed and predicted data.

Figure 33 Observed and model predicted growth curves from the historical growth data and model



Reviewer's independent analyses

4.4.3.1.5 Modeling weight profiles during setmelanotide treatment.

4.4.3.1.5.1 Dataset preparation

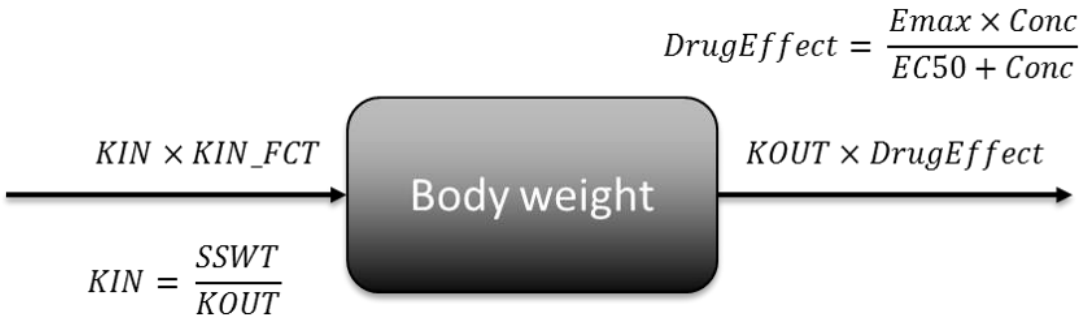
For each subject empirical bayes estimates of PK parameters and individual historical growth parameters were joined to the weight loss dataset. The weight loss dataset contained the following information: Weight profiles during setmelanotide treatment, setmelanotide dosing, and intrinsic and extrinsic covariates. Two subjects were excluded from analysis for lack of PK information. Another 4 subjects were excluded from analysis for the following reasons: Subject (b) (6) did not lose weight despite dose titration to 2.5 mg; Subject (b) (6) did not lose weight despite being on maximum tolerable dose for almost 20 weeks; Subject (b) (6) received treatment for 5 weeks and lost less than 2.5% of baseline body weight; subject (b) (6) regained weight after placebo treatment and did not lose weight after re-initiation of setmelanotide. The final dataset contained 11 subjects from study RM493012 and 10 subjects from study RM493015.

4.4.3.1.5.2 Structural model.

The same structural model for historical growth was used to describe weight profile after treatment. To account for treatment related weight loss two submodels were tested; for the first submodel drug effect was modelled to decrease KIN, while for the second submodel drug effect increased KOUT. The second submodel provided better fit to the data than the first model. However, plots of predicted overlaid to observed weight profiles indicated underprediction of weight gain during placebo treatment. This implied that the KIN parameter estimated from historical growth data was smaller than it should be during treatment. For this reason, a parameter for KIN adjustment (KIN_FCT) was introduced and estimated.

Drug effect was assumed to follow an E_{max}-relationship with parameters E_{max}, and EC_{50} to be determined. A schematic representation of the model is given in Figure 34.

Figure 34 Schematic representation of the concentration vs weight model



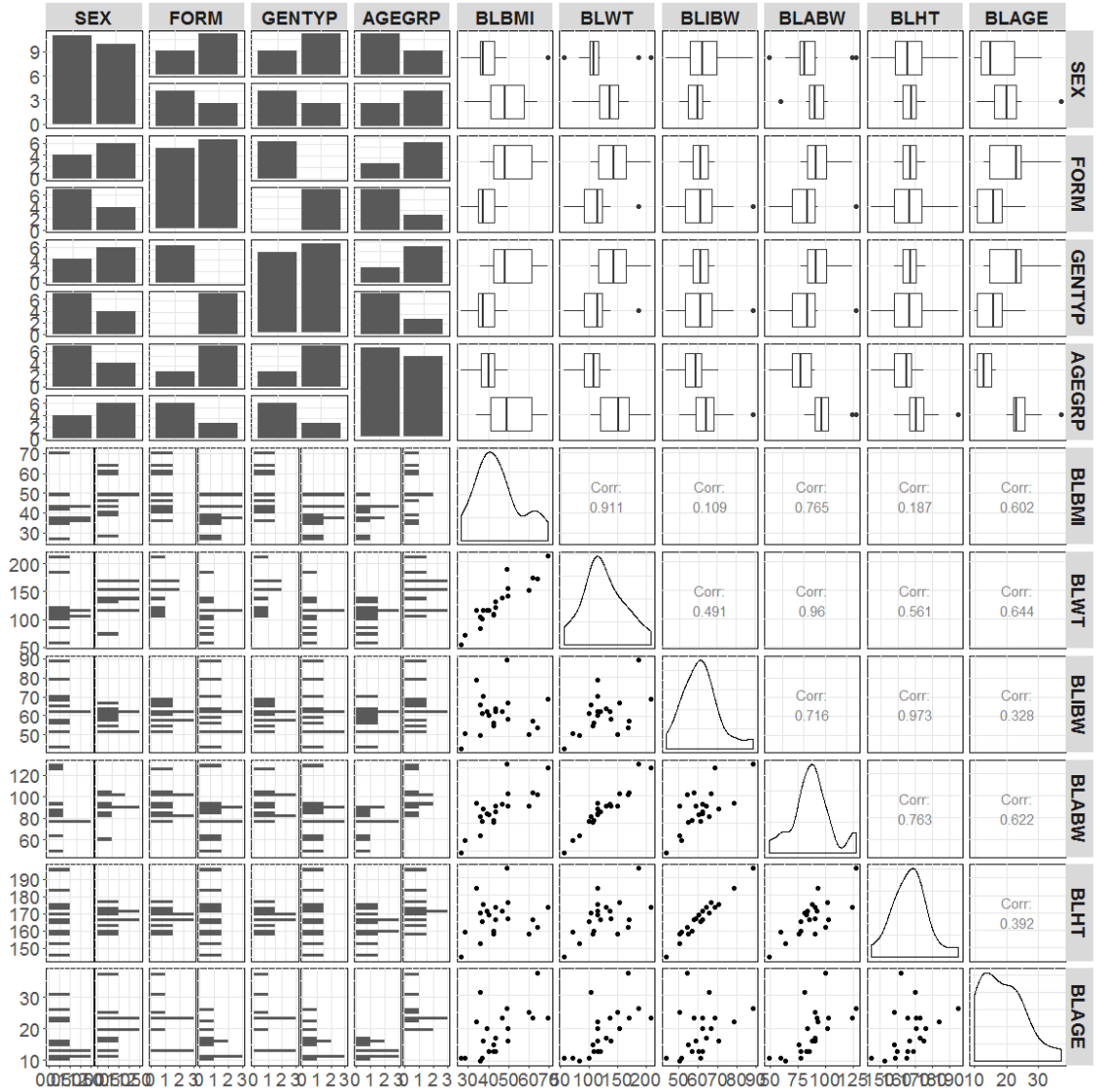
Source: reviewer's independent analysis

During the modeling exercise it was discovered that model objective function minimized successfully only when EC_{50} was fixed to a very small value. For this reason, EC_{50} was fixed to 3.5×10^{-5} and E_{max} and KIN_FACT were estimated. Also, inter-individual variability for E_{max} and KIN_FACT were estimated. Next, E_{max}, KIN_FACT, and IIV parameters were fixed to allow robust estimation of EC_{50} and IIV for EC_{50}. The estimated EC_{50} was 7.8×10^{-20}, and was fixed to this value in all subsequent analyses.

4.4.3.1.5.3 Covariate model

Parameter-vs-covariate relationships were assessed by statistical analysis and visual inspection of ETA-vs-covariate plots. Correlation among covariates were assessed by statistical analysis and visual inspection of covariate-vs-covariate plots. Figure 35 shows correlated covariates.

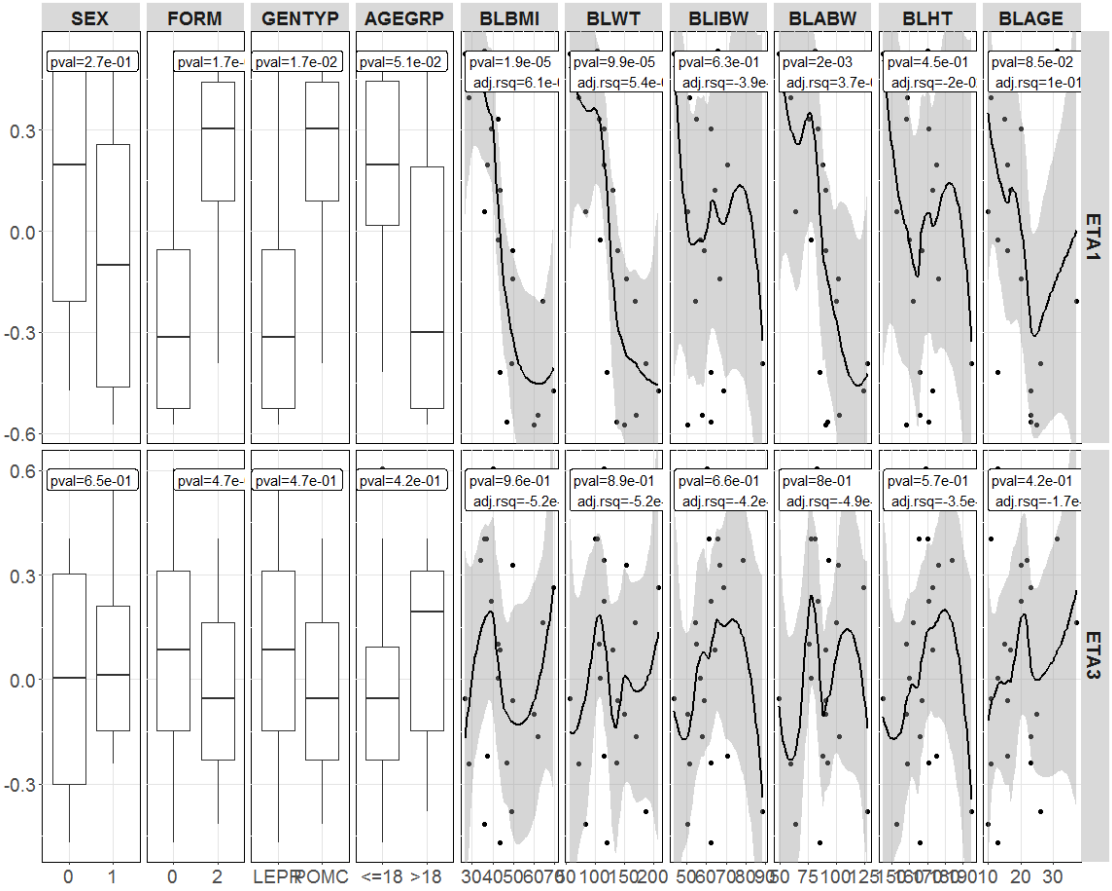
Figure 35 Covariate versus covariate plots



Reviewer's independent analyses

Figure 36 shows that covariates related to ETA for E_{max} (ETA1) are: formulation type (FORM), genotype (GENTYP), baseline BMI (BLBMI), weight (BLWT), adjusted body weight (BLABW) and age groups (AGEGRP). No covariate is related to ETA for KIN_FCT (ETA3).

Figure 36 Etas versus covariates plots for the base structural model of concentration vs weight



Reviewer's independent analyses

Covariate relations were added into the model in a stepwise manner. The effect of genotype on E_{max} was included first. This resulted in significant improvement in model fit as indicated by significant drop in objective function ($\Delta OFV = -7.56$). Inspection of covariate relations indicated that, after inclusion of genotype-E_{max} relationship, covariates still related with ETA1 were: BLBMI, BLWT, and BLADW. Due to correlations among BLBMI, BLWT, and BLADW, BLWT-E_{max} relationship was selected for inclusion into the model. This led to further improvement in model fit ($\Delta OFV = -24.1$). No further covariate-parameter relations were observed from subsequent covariate-vs-eta plots.

4.4.3.1.5.4 Final model

The covariate model after inclusion of genotype and baseline body weight as covariates on E_{max} was the final model. Backward exclusion of covariates was not performed. Parameter estimates for the final model are given in Table 25. The parameters are well estimated as indicated by precision estimates (Relative standard error). The table shows that the population average for maximum decrease in body weight is about 28 Kg (LEPR subjects) and POMC subjects would lose 32% more weight on average compared to LEPR subjects. The table also shows that E_{max} is higher for subjects with low BLWT compared to subjects with high BLWT, e.g. typical E_{max} for subjects weighting 90 Kg would be $28.6 \times (90/115)^{-0.84} = 35$Kg.

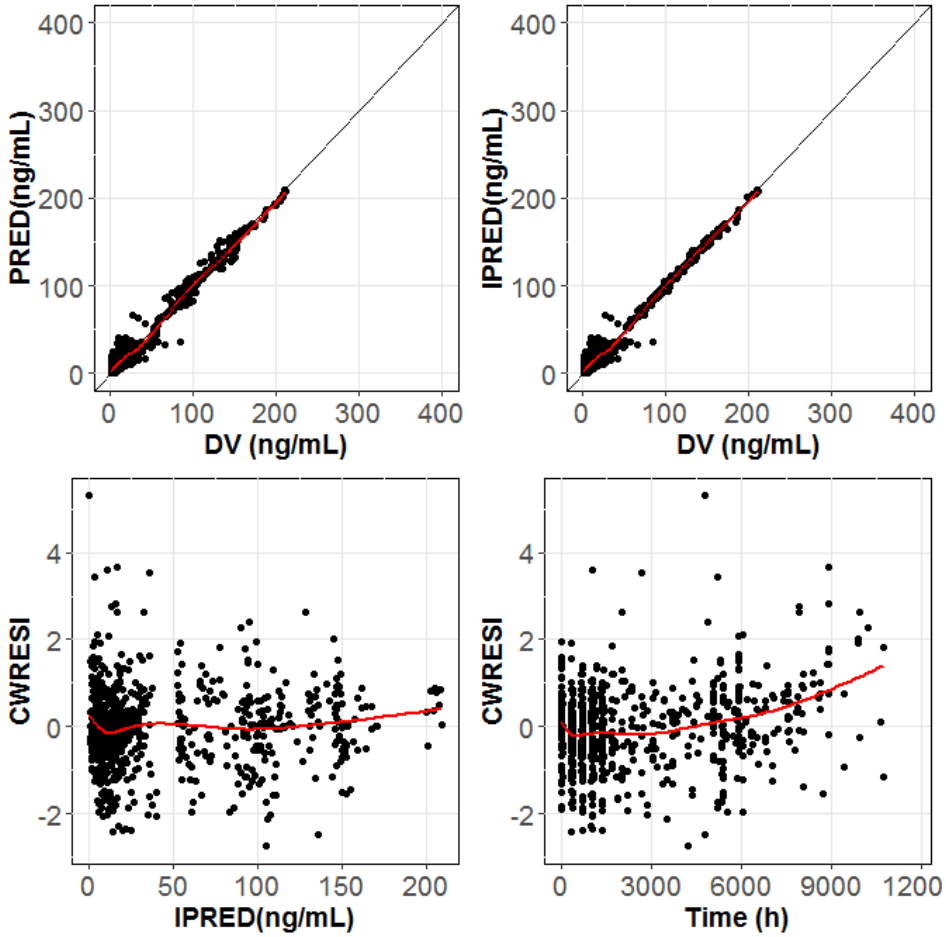
Table 25 Parameter estimates and objective function Values final model of concentration vs weight

Parameters	Descriptions	Estimates (RSE)
OFV	Objective function value	3938.2
Emax (Kg)	Maximum weight loss	28.6 (3%)
Ec50 (ng/mL)	Concentration for half of Emax	7.8E-20 (fixed)
KIN_FCT	Ratio of rate constant of weight gain during treatment to before treatment	16.8 (3%)
ADDWT (Kg)	Additive body weight residuals	1.6 (44%)
PROPWT (%CV)	Proportional body weight residuals	0.018 (37%)
GENTYP_EFFECT	Ratio of Emax in POMC to Emax in LEPR	1.32 (25%)
BLWT_EFFECT	Exponent for effect of baseline body weight on Emax (BLWT/115)^BLWT_EFFECT	-0.84 (12%)
BSV Emax (%CV)	Between subject variability for Emax	7.0% (47%)
BSV EC50(%CV)	Between subject variability EC50	33.3% (fixed)
BSV KIN_FCT (%CV)	Between subject variability KIN_FCT	11.1% (19%)

Reviewer's independent analyses

Figure 37 shows the goodness of fit plots for the final model. In general, the final model provided adequate fit of the observed data.

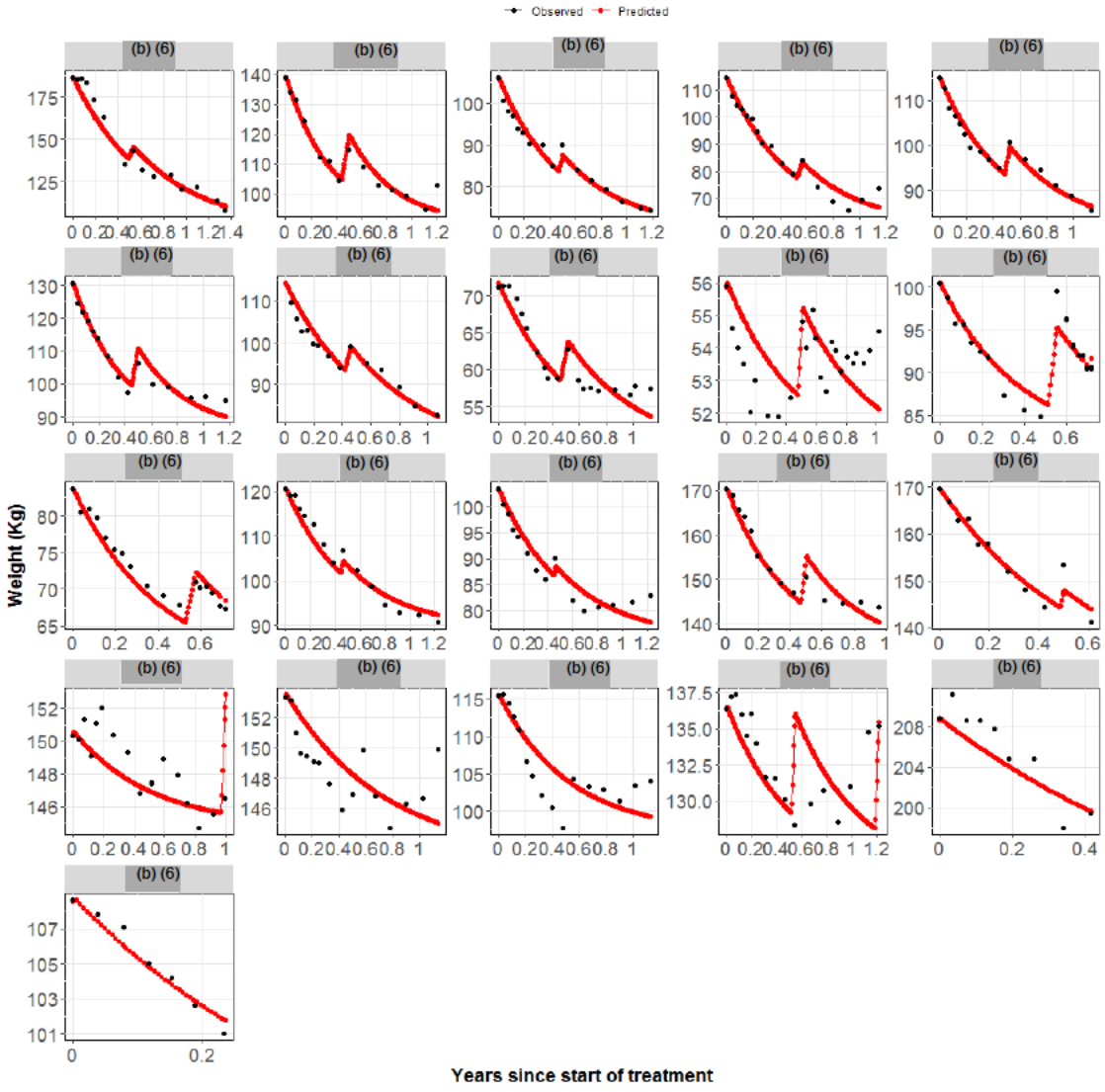
Figure 37 Goodness-of-fit plots for the final model of concentration vs weight



Reviewer's independent analyses

Figure 38 shows observed, and model predicted weight profiles for each individual during setmelanotide treatment. Generally, there is good agreement between observed and predicted data.

Figure 38 Observed and model predicted weight profiles during setmelanotide treatment



Reviewer's independent analyses

4.4.3.1.6 Reviewer's conclusion on exposure-response analyses

The exposure-response analyses have determined that weight loss in patients with RGDOB after setmelanotide treatment can be described by an indirect response model with drug effect affecting the rate of weight loss. Drug effect is described by an E_{max} model and the results indicates that setmelanotide exposures at the proposed doses (C_{av} = 20.62 ng/mL) are at the plateau of the dose response curve. These results imply that variability in treatment responses may not be due to PK covariates but to covariates for the Emax parameter. Therefore, increasing setmelanotide dose based on PK covariates is not supported. But to be conservative for safety, dose reductions proposed by the applicant for specific populations (pediatrics (b) (4) *are supported.*

Addendum tables

Table 26 Summary of Studies with PK Sampling Included in Population PK Analysis

Study # / Phase	Description	Population	Formulation	Doses	Subjects Enrolled / Subjects with PK	PK and PD Objectives
Single Dose Studies						
RM-493-008 Part 1/ Phase 1 USA	Part 1 Open label, 2-period crossover, single dose PK	Adults > 18 years	Setmelanotide saline*and Setmelanotide/mPEG-DSPE (preservative free)	SC injection 1.5 mg single dose	8 / 8	Determine the PK of single dose administration of mPEG-DSPE formulation
Multiple Doses Studies						
RM-493-008 Part 2 Phase 1 USA	Placebo controlled, double blind, randomized, dose titration	Healthy obese Adults >18 years	Setmelanotide/ mPEG-DSPE (preservative-free)	SC injection 1.5 mg QD for 4 days 1.0 mg QD for 2 days followed by	14 / 12	Characterize safety, tolerability and PK of setmelanotide/mPEG-DSPE following multiple administration.
RM-493-026 Phase 1B	Randomized, placebo controlled Once weekly formulation	Obese adults Adults >18 years	Setmelanotide/ mPEG-DSPE (preserved) Setmelanotide- QW**	SC injection QD formulation 2.0 mg QD or placebo Week 1 followed by 3 mg	50 / 9	PK, safety and tolerability Urine collection Assess immunogenicity (QD dosing)
Patient Studies						
RM-493-010 Phase 2 USA	Randomized, double-blind, placebo controlled, crossover pilot study Safety and efficacyin Prader-Willi Syndrome (PWS)	Subjects with PWS Adults > 18 years	Setmelanotide/mPEG-DSPE (preservative-free)	SC injection Part 1 single-blind 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. Assess immunogenicity
				Part 2: double-blind placebo, 1.5 mg, or 2.5 mg QD for 4 weeks	20	Characterize the PK of setmelanotide in patients. Develop a population PKmodel of setmelanotide in patients. Assess immunogenicity

Study # / Phase	Description	Population	Formulation	Doses	Subjects Enrolled / Subjects with PK	PK and PD Objectives
				Part 3 Sub-Study: double-blind, placebo withdrawal 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.
				Part 4 open label extension 0.5 mg and 1.5 mg for 2 weeks	8	Multiple dose PK during a 24-hour steady state interval (sub-study)
RM-493-011 Phase 2 Investigator initiated Germany	Open label, dose titration Trial in are genetic disorders	Heterozygous POMC deficiency, LEPR and Epigenetic deficiency and PCSK1 >12 years	Setmelanotide/ mPEG-DSPE (preservative free and preserved)	SC-injection Part 1 - baseline (2 days) Part 2 - dosage findings (Weeks 2 - 4) dose titration from 0.5 mg to 1 mg, 1.5 mg and 2 mg Part 3 - outpatient	10 / 7 (2 - POMC; 3 - LEPR; and 2 - Epi-genetic)	PK collected on final visit of Part 3, Assess safety and Immunogenicity

Study # / Phase	Description	Population	Formulation	Doses	Subjects Enrolled / Subjects with PK	PK and PD Objectives
RM-493-012 Phase 3 Germany, UK, France, USA, Canada, Spain, Belgium	Open label, double-blind, placebo-controlled withdrawal period Safety and efficacy in POMC Patients	Early on-Set POMC Deficiency obesity due to i-allelic, loss of function POMC or PCSK1 genetic mutation >6 years	Setmelanotide/ mPEG-DSPE (preservative free and preserved)	SC injection *Adults* - Initial dose 1.0mg titrated up to 3.0 mg QD Dose titration with incremental increases of 0.5 mg every 2 weeks *Adolescents* - initial dose 0.5mg titrated up to 3 mg QD *Pediatric* - initial dose 0.5 mg titrated up to 2.5 mg Followed by 10 -	12 / 12 4 (2 - Both; 1 - Preservative Free; 1- Preserved) 4 (1 - Preserved, 3 - Both) 4 (Preserved)	Characterize the PK in adults, adolescents and pediatrics patients Develop a population PK model of setmelanotide in patients All Patients ≥12 years at titration visit: 8-hour PK profile. Subset (optional for ≥12 years adults): 24-hour PK profile Trough samples all patients at all visits Assess immunogenicity in patients

Study # / Phase	Description	Population	Formulation	Doses	Subjects Enrolled / Subjects with PK	PK and PD Objectives
RM-493-014 Phase 2 (on-going) USA UK	Phase 2 safety study in rare genetic disorder's (Basket)	>12 years of Age 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 *Adults* - 1.0 to 3.0 g QD, increments 0.5 mg every 2 weeks *Adolescents* - 0.5 to 3 mg QD increments 0.5 mg every 2 weeks *Pediatric* - 0.5 to 2.5 mg QD	27 / 27 15 (5-Both;7 Preserved;3 Preservative Free) 12 (2 - Both; - Preserved;3 Preservative Free)0	Characterize the PK adults in patients. Develop a population PK model of setmelanotide in patients (24-hours PK profiles during titration phase) Assess immunogenicity in patients Characterize the PK in adolescent patients. Develop a population PK model of setmelanotide in patients (8-hour PK profiles during titration phase) Assess immunogenicity in patients Characterize the PK pediatrics in patients. Develop a population PK model of setmelanotide in patients. (trough samples at clinic visits). Assess immunogenicity in patients
RM-493-015 Phase 3 Germany, UK, France, Netherlands, USA	An Open Label Double-Blind Placebo-Controlled Withdrawal Period	>6years old, in LEPR deficiency. obesity due allelic, loss-of-function LEPR gene mutations.	Setmelanotide/ mPEG-DSPE (preserved)	SC injection *Adults* - Initial dose 1.0mg titrated up to 3.0 mg QD	14 / 13 9 (9 - Preserved)	Characterize the PK in adult patients. Develop a population PK model of setmelanotide in patients (All Patients ≥12 years at titration visit:8-hour PK profile. Subset (optional for ≥ 12 years adults): 24-hour PK profile. Trough samples all patients at all visits). 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 ado-descent patients. Patients 6 to 11 years - full PK profile at dose titration visit. Assess immunogenicity in adolescents.
				Pediatrics - initial dose 0.5 mg titrated up to 2.5 mg Dose titration with incremental increases of 0.5mg every 2 weeks	0	Characterize the PK in pediatric patients. Assess immunogenicity in pediatrics
RM-493-022 Germany (Ongoing)	Extension study	>6 years	Setmelanotide/ mPEG-DSPE (preserved)	SC injection Same dose as index study. Dose adjustments (either increase or decrease were made in increments of 0.5 mg. Max 3 mg - US Canada	16 / 10	Characterize the PK of setmelanotide following long- term administration. Assess immunogenicity.

4.5 Genomics and Targeted Therapy Review

EXECUTIVE SUMMARY

On March 27, 2020, FDA received a New Drug Application (NDA 213793) for setmelanotide. Setmelanotide is a melanocortin-4 receptor (MC4R) agonist. The proposed indication is for the treatment of obesity (b) (4) associated with 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 older.

Variants in the POMC, PCSK1, and LEPR genes affect the MC4R pathway and cause rare genetic disorders of obesity that start early in childhood and progress over time.
The Office of Clinical Pharmacology/Division of Translational and Precision Medicine (OCP/DTPM) has reviewed the pathogenicity assignment of the genetic variants in the POMC, PCSK1, and LEPR genes. We generally concur with the applicant's assessment of the pathogenicity of the genetic variants.

4.5.1 BACKGROUND

POMC deficiency obesity is caused by loss of function (LoF) mutations in the POMC gene. Mutations in POMC are very rare in the general population. In humans, null mutations in POMC gene lead to hyperphagia, early onset obesity, isolated adrenocorticotrophin (ACTH) deficiency, and hypopigmentation of skin and hair. Heterozygous carriers of null mutations have a significantly higher risk of being obese or overweight (PMID: 21633175).

Mutations in the PCSK1 gene result in missing melanocortin stimulating hormone (MSH) neuropeptide synthesis and/or processing (PMID: 11874690). Rare congenital deficiency of PCSK1 has been reported in less than 20 unrelated probands (carrying homozygous or compound heterozygous mutations) who presented with malabsorptive diarrhea, failure to thrive during early infancy associated with high mortality rate, severe early-onset obesity, polyphagia, central diabetes insipidus, hypogonadism, hyperproinsulinemia and other endocrine dysfunctions (PMID: 24890885).

Congenital leptin-receptor deficiency is characterized by severe, early-onset obesity associated with hyperphagia. Subjects are born with a normal birth weight but show rapid weight gain in the first months of life, which results in severe obesity. The key features are hyperphagia and impaired satiety (PMID: 21633175). About 3% of patients with severe obesity have LoF mutations in the LEPR gene.
Setmelanotide is a synthetic, cyclic octapeptide (8-amino acid-containing peptide) that functions as a MC4R agonist. According to the applicant, setmelanotide has the potential to restore lost activity in the MC4R pathway by bypassing the defects upstream of the MC4R and directly activating MC4R neurons in the hypothalamus below such defects. Thus, setmelanotide bypasses the upstream genetic defects in this critical MC4R signaling pathway to re-establish weight and appetite control in patients with POMC (including PCSK1) and LEPR obesity.

The applicant identified (b) (4) as the Rhythm-preferred CLIA-LDT laboratory for post-NDA genetic testing. The American College of Medical Genetics and Genomics (ACMG) guidelines were utilized by (b) (4) for the interpretation of sequence variants and the impact on pathogenicity in the POMC, PCSK1, and LEPR genes. ACMG developed recommendation for classification and use of standard terminology- "pathogenic", "likely pathogenic", "uncertain significance", "likely benign", and "benign"- to describe variants identified in genes that cause Mendelian disorders (PMID: 25741868).

4.5.2 SUBMISSION CONTENTS RELATED TO GENOMICS

On May 05, 2020, DTPM asked the applicant in an Information Request (IR) to provide the document with the sequence variants interpretation for all subjects included in studies RM-493-012 and RM-493-015. The FDA received response to the IR on May 20, 2020. DTPM has reviewed the pathogenicity assignment of the genetic variants in the POMC, PCSK1, and LEPR genes.

4.5.3 REVIEW OF EVIDENCE FOR SEQUENCE VARIANT INTERPRETATION

4.5.3.1 American College of Medical Genetics and Genomics (ACMG) pathogenicity classification

In 2015, ACMG in collaboration with the Association for Molecular Pathology (AMP), and the College of American Pathologists, published revised guidelines for the interpretation of sequence variants (PMID: 25741868). These recommendations primarily apply to the genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. The ACMG guidelines recommend the use of specific standard terminology- "pathogenic", "likely pathogenic", "uncertain significance", "likely benign", and "benign"- to describe variants identified in genes that cause Mendelian disorders. In addition, ACMG describes a process for classifying variants into five pathogenicity categories based on criteria using typical types of variant evidence (e.g., population data, computational data, functional data, segregation data; see Table 27 and Table 28).

Table 27 American College of Medical Genetics and Genomics (ACMG) criteria for classifying pathogenic and benign variants

Evidence of pathogenicity	
Very strong	
PVS1	Certain types of variants (e.g., nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single exon or multiexon deletion) can often be assumed to disrupt gene function by leading to a complete absence of the gene product by lack of transcription or nonsense-mediated decay of an altered transcript.
Strong	
PS1	Same amino acid change as a previously established pathogenic variant regardless of nucleotide change (e.g., Val→Leu caused by either G>C or G>T in the same codon)
PS2	De novo (both maternity and paternity confirmed) in a patient with the disease and no family history
PS3	Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product
PS4	Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product
Moderate	
PM1	Located in a mutational hot spot and/or critical and well-established functional domain (e.g., active site of an enzyme) without benign variation
PM2	Absent from controls (or at extremely low frequency if recessive) (Table 6) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium
PM3	For recessive disorders, detected in trans with a pathogenic variant
PM4	Protein length changes as a result of in-frame deletions/insertions in a nonrepeat region or stop-loss variants
PM5	Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before
PM6	Assumed de novo, but without confirmation of paternity and maternity
Supporting	
PP1	Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease
PP2	Missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease
PP3	Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.)
PP4	Patient's phenotype or family history is highly specific for a disease with a single genetic etiology
PP5	Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation
Evidence of benign impact	
Stand-alone	
BA1	Allele frequency is >5% in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium
Strong	
BS1	Allele frequency is greater than expected for disorder
BS2	Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder, with full penetrance expected at an early age
BS3	Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing
BS4	Lack of segregation in affected members of a family
Supporting	
BP1	Missense variant in a gene for which primarily truncating variants are known to cause disease
BP2	Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis with a pathogenic variant in any inheritance pattern
BP3	In-frame deletions/insertions in a repetitive region without a known function
BP4	Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc.)
BP5	Variant found in a case with an alternate molecular basis for disease
BP6	Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation
BP7	A synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved

Source: Reviewer-generated table based on PMID: 25741868.

Table 28 American College of Medical Genetics and Genomics (ACMG) rules for combining criteria to classify sequence variants

Pathogenic
(i) 1 Very strong (PVS1) AND (a) ≥1 Strong (PS1–PS4) OR (b) ≥2 Moderate (PM1–PM6) OR (c) 1 Moderate (PM1–PM6) and 1 Supporting (PP1–PP5) OR (d) ≥2 Supporting (PP1–PP5) (ii) ≥2 Strong (PS1–PS4) OR (iii) 1 Strong (PS1–PS4) AND (a)≥3 Moderate (PM1–PM6) OR (b)2 Moderate (PM1–PM6) AND ≥2 Supporting (PP1–PP5) OR (c)1 Moderate (PM1–PM6) AND ≥4 Supporting (PP1–PP5)
Likely* pathogenic
(i) 1 Very strong (PVS1) AND 1 Moderate (PM1–PM6) OR (ii) 1 Strong (PS1–PS4) AND 1–2 Moderate (PM1–PM6) OR (iii) 1 Strong (PS1–PS4) AND ≥2 Supporting (PP1–PP5) OR (iv) ≥3 Moderate (PM1–PM6) OR (v) 2 Moderate (PM1–PM6) AND ≥2 Supporting (PP1–PP5) OR (vi) 1 Moderate (PM1–PM6) AND ≥4 Supporting (PP1–PP5)
Benign
(i) 1 Stand-alone (BA1) OR (ii) ≥2 Strong (BS1–BS4)
Likely* benign
(i) 1 Strong (BS1–BS4) and 1 Supporting (BP1–BP7) OR (ii) ≥2 Supporting (BP1–BP7)
Uncertain significance
(i) Other criteria shown above are not met OR (ii) the criteria for benign and pathogenic are contradictory

*Source: Reviewer-generated table based on PMID: 25741868. *The terms "likely pathogenic" and "likely benign" should be used to refer to >90% certainty of a variant either being disease-causing or benign.*

4.5.3.2 Summary of sequence variants interpretation

The (b) (4) laboratory utilized a next generation sequencing-based in vitro diagnostic for detection of germline nucleotide substitutions, short insertions and deletions, and copy number variants (CNVs) in POMC (including PCSK1) and LEPR genes. Inclusion criteria for patients' enrollment in the Phase 3 studies, RM493-012 and RM493-015, was based on bi-allelic, homozygous or compound heterozygous genetic status for either the POMC, PCSK1 or LEPR genes, with the LoF variant for each allele conferring a severe obesity phenotype. The (b) (4) laboratory utilized the 2015 ACMG guidelines for the interpretation of sequence variants in the POMC, PCSK1 and LEPR genes (see Table 29). Per the guidelines, all variants were placed into 1 of the 5 interpretation categories: "pathogenic", "likely pathogenic", "uncertain significance", "likely benign", and "benign". The results were reviewed independently by 2 technicians and patients with variants assigned into "pathogenic", "likely pathogenic", "uncertain significance" were included in Phase 3 studies.

Reviewer's comments: *The reviewer generally concurs with the applicant's assessment of the pathogenicity of the genetic variants presented in Table 3. Assessment of pathogenicity should be determined based on the entire body of evidence in aggregate (e.g., association with the phenotype, population frequency data, computational, and functional data). As part of the medical practice, clinicians consider multiple sources of information to form a diagnostic conclusion. In addition, clinicians are accustomed to making recommendations based on some level of uncertainty.*

Most of the observed variants in studies RM493-012 and RM493-015 were "private". Besides publication of a single case control study for a "private" mutation, no additional data were available in the published literature. The type of mutations (e.g., deletions, truncations, frameshift mutations) are highly

likely to cause disease and are considered to be pathogenic. Based on the ACMG guidelines, "likely pathogenic" category should be restricted to variants where the data support a high likelihood (>90% certainty) that variants are pathogenic. In contrast, when a variant does not fulfill criteria for using terms "pathogenic" or "likely pathogenic "and cannot be classified as "benign" or "likely benign", especially in the context of the observed phenotype, the variant assessment may default to categorization as a "variant of uncertain significance". Classification of variants with some level of uncertainty (e.g., likely pathogenic, variant of uncertain significance) may require a reevaluation based on accumulation of additional evidence.

Given that variant pathogenicity is not clearly established for many patients who may benefit from setmelanotide (i.e., patients carrying "variants of unknown significance"), clinical evaluation and implementation of the "stopping rule" might be beneficial for management of setmelanotide therapy (i.e., reevaluate drug risk/benefit if patient does not reach a certain weight loss goal within a given timeframe and consider drug discontinuation).

Table 29 Variant interpretation summary for studies RM4 012 and RM493-015

Trial	Patient	Gene	Zygosity	Variant	Predicted Effect	(b) (4) nterpretation	Reviewer's ACMG Assessment	Reviewer's Pathogenicity Agreement	Reviewer's Comment
RM493-012	(b) (6)	POMC	**Hom**	**c.-11C>A**	**Pre-Coding**	**Path**	**PVS1+PS3**	**Agree**	**Variant creates out-of-frame ATG initiation codon which could abolish translation of the wild-type protein and was confirmed by in vitro data**
			Hom	c.304C>T	p.Gln102*	Likely Path	PVS1+PM2+PP3	Agree	Variant is predicted to cause premature protein termination
			Hom	c.225delG	p.Lys76Serfs*82	Likely Path	PVS1+PM2	Agree	Variant causes frameshift
			Hom	c.251G>A	p.Trp84*	Path	PVS1+PS3+PM2	Agree	Variant is predicted to cause premature protein termination and in vitro data predicts marked truncation of POMC preprohormone
			Het/Het	c.-11C>A/c.403_404dupGG	Pre-Coding/p.Lys136Alafs*23	Path/Likely Path	PVS1+PS3/ PVS1+PM2	Agree/Agree	c.-11C>A creates out-of-frame ATG initiation codon; c.403_404dupGG causes frameshift mutation
			Hom	c.304C>T	p.Gln102*	Likely Path	PVS1+PM2	Agree	Variant is predicted to cause premature protein termination
			Het/Het	c.151A>T/c.296delG	p.Lys51*/p.Gly99Alafs*59	Likely Path/Likely Path	PVS1+PM2/ PVS1+PM2	Agree/Agree	c.151A>T/c.296delG cause premature protein termination leading to truncation of the POMC gene product
			Hom	c.158A>G	p.Asp53Gly	Likely Benign	BS1+BP4	Agree	The predicted phenotype for the variant was benign
			Hom	c.133-2A>C	Splicing	Likely Path	PVS1+PM2	Agree	Variant causes sequence change in the splice acceptor site of intron 3
		PCSK1	Hom		p.Tyr343*	Path	PVS1+PM2+PS3	Agree	Variant causes premature protein termination, in vitro data shows total lack of enzyme activity
RM493-015		LEPR	**Hom**	**c.2051A>C**	**p.His684Pro**	**Likely Path**	**PS3+PM2**	**Agree**	**Variant results in a complete loss of signaling**
			Het/Het	c.1874G>A/c.2051A>C	p.Trp625*/p.His684Pro	Likely Path/Likely Path	PVS1+PM2/PS3 +PM2	Agree/Agree	c.1874G>A is predicted to cause premature protein termination; c.2051A>C results in a complete loss of signaling
			Het/Het	c.2227T>C/c.2598-3_2607del13	p.Ser743Pro/Splicing	VOUS/Likely Path	PM2/PVS1+PM2	Agree/Agree	c.2227T>C supported by in silico data; c.2598-3_2607del13 supported by in silico data
			Hom	del of exons 6, 7 & portion of 8	-	Path	PVS1+PS3	Agree	Variant causes frameshift and lack of enzyme secretion
			Hom	c.1871dupA	p.Asn624Lysfs*21	Likely Path	PVS1+PM2	Agree	Variant causes frameshift in exon 13, in silico predicted a truncated LEPR protein lacking 521-amino acid fragment
			Het/Het	c.1264T>C/c.2131dupA	p.Tyr422His/p.Thr711Asnfs*18	VOUS/Likely Path	PM2/PVS1+PM2	Agree/Agree	c.1264T>C alters protein sequence (probably damaging); c.213dupA causes truncated protein
			Het/Het	c.1264T>C/c.2131dupA	p.Tyr422His/p.Thr711Asnfs*18	VOUS/Likely Path	PM2/PVS1+PM2	Agree/Agree	c.1264T>C alters protein sequence (probably damaging); c.213dupA causes truncated protein
			Hom	c.1604-8A>G	Intronic	VOUS		Agree	Variant causes frameshift and premature stop codon (in silico and RNA analysis)
			Het/Het	c.1753-1dupG/c.2168C>T	Splicing/p.Ser723Phe	Path/VOUS	PVS1+PS3+PP3/ PM2	Agree/Agree	c.1753-1dupG splice-site mutation in intron 13 causing the retention of an extra nucleotide in the mRNA and a frameshift with a premature stop codon (in silico and RNA analysis); c.2168C>T missense mutation in exon 16 (pathogenic based on silico prediction)

(b) (6)	Het/Het	c.1835G>A/c.2051A>C	p.Arg612His/p.His684Pro	VOUS/Likely Path	PM2/PS3+PM2	Agree/Agree	c.1835 G>A causes some residual enzyme activity; c.2051A>C results in a complete loss of signaling
	Hom	c.2385T>G	p.Tyr795*	Likely Path	PVS1+PM2	Agree	Variant is predicted to cause premature protein termination

ACMG- American College of Medical Genetics and Genomics; POMC- Pro-opiomelanocortin; PCSK1- Proprotein Convertase Subtilisin/Kexin Type 1; LEPR- Leptin Receptor; Hom- Homozygous; Het- Heterozygous; dup- duplication; del- deletion; Path-Pathogenic; VOUS- Variant of Uncertain Significance; PG- Prevention Genetics; *nonsense variant.

4.5.4 SUMMARY AND CONCLUSIONS

Human genetics studies have identified several diseases that are the result of genetic defects affecting the MC4R pathway, including POMC, PCSK1 deficiency obesity, and LEPR deficiency obesity. These MC4R pathway mutations cause rare genetic disorders of obesity that start early in childhood and progress over time and can become life-threatening in severity.

Setmelanotide is a synthetic, cyclic octapeptide that functions as a MC4R agonist. The applicant has conducted 2 pivotal Phase 3 studies, one in patients with POMC deficiency obesity (including 1 patient with PCSK1 deficiency obesity), study RM-493-012, and another in patients with LEPR deficiency obesity, study RM-493-015. Efficacy results from the pivotal studies demonstrated that setmelanotide induced clinically meaningful weight loss (b) (4) in these patient populations.

Implementation of the ACMG guidelines for classification and interpretation of sequence variants in the POMC, PCSK1, and LEPR genes was utilized by the (b) (4) laboratory.

DTPM has reviewed the pathogenicity assignment of the genetic variants in the POMC, PCSK1, and LEPR genes submitted as an IR. We concur with the applicant's assessment of the pathogenicity of the genetic variants.

Given that variant pathogenicity is not clearly established for many patients who may benefit from setmelanotide (i.e., patients carrying "variants of unknown significance"), clinical evaluation and implementation of the "stopping rule" might be beneficial for management of setmelanotide therapy (i.e., reevaluate drug risk/benefit if patient does not reach a certain weight loss goal within a given timeframe and consider drug discontinuation).

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