Office of Clinical Pharmacology Review

NDA Number	213793;SDN 489; Supplement 0009
Link to EDR	\\CDSESUB1\evsprod\NDA213793\0441
Submission Date	6/20/2025
Submission Type	Priority Review
Brand Name	Imcivree
Generic Name	Setmelanotide
Dosage Form and Strength	Solution for injection as 1 mL multiple-dose vial. Strength: 10mg/mL
Route of Administration	Subcutaneous injection
Proposed Indication	IMCIVREE is indicated to reduce body weight and maintain weight reduction long term in adult and pediatric patients aged 4 years and older with acquired hypothalamic obesity
Applicant	Rhythm Pharmaceuticals, Inc
Associated IND	112595
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1. EXECUTIVE SUMMARY

Imcivree (setmelanotide) is indicated for to reduce excess body weight and maintain weight reduction long term in adults and pediatric patients 2 years of age and older with syndromic or monogenic obesity due to:

- Bardet-Biedl syndrome (BBS).
- Pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).

Rhythm Pharmaceuticals Inc submitted a supplemental New Drug Application (sNDA) 213793 (Supplement 9) for Imcivree injection for the treatment of Acquired Hypothalamic Obesity (HO). The FDA granted Breakthrough Designation for the HO indication on October 27, 2022. The sparse PK data in patients with HO comes from the phase 3 study in patients with HO (Study RM-493-040) and the long-term extension study (Study RM-493- 022 (in which HO patients transitioned from the phase 2 study (Study RM-493-030)). Both phase 3 and phase 2 studies used the commercial formulation (preserved setmelanotide/mPEG-DSPE formulation). The Applicant submitted the population PK analysis to support dosing in patients 4 years of age and above with HO, which will be the focus of this review.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology and the Division of Pharmacometrics have reviewed the information in NDA213793 Supplement 9 and found it acceptable and recommends approval of this supplement with the revised labeling recommendation (see section 2.4).

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The clinical pharmacology information comprised of a population PK analysis to confirm daily exposures are supportive for the proposed dosing regimen of setmelanotide in patients with Acquired Hypothalamic Obesity (HO).
General dosing instructions	• Recommended starting dosage injected subcutaneously for: ○ Adults and pediatric patients aged 4 years and older with acquired HO is 0.5 mg (0.05 mL) once daily. ○ Maintenance dose is dependent on age and body weight cutoff: for 6 years and older the maximum dose is 3 mg once daily while for 4 to < 6 years of age the maximum

	dose is 0.5 mg, 1 mg, 1.5 mg and 2 mg for each of 15-20 kg, 20-30 kg, 30-40kg and ≥40 kg body weight bands respectively (see Section 2.2).
Dosing in patient subgroups (intrinsic and extrinsic factors)	Imcivree is not recommended for use in Acquired Hypothalamic Obesity patients with end stage renal disease (ESRD) or severe renal impairment (see section 2.2.2 and section 2.4). No dose adjustment is required for patients with mild or moderate renal impairment.
Labeling	The Applicant proposed changes to section 2.2 and 12.3. In general, the changes appear reasonable. See section 2.4 of this review for specific labeling recommendations which are pending agreement with Applicant.
Bridge between the to-be-marketed and clinical trial formulations	Both phase 3 and phase 2 studies used the commercial formulation (preserved setmelanotide/mPEG-DSPE formulation).

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Clinical Pharmacology Information

The Applicant conducted the phase 3 study RM-493-040 in patients with Acquired Hypothalamic Obesity (HO) to support dosing in this population along with using population PK approach for predicting daily exposures. The Applicant updated their previously reviewed population PK model with data from 89 HO patients. The overall aim of this population PK analysis was to evaluate the proposed setmelanotide dosing in adult and pediatric patients from 4 years of age and older with HO.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Acquired Hypothalamic Obesity (HO)

- Select patients for treatment with IMCIVREE who have acquired HO

Recommended Dosage in Patients with Acquired Hypothalamic Obesity

Adults and Pediatric Patients Aged 6 Years and Older

- The recommended starting dosage is 0.5 mg (0.05 mL) injected subcutaneously once daily for 2 weeks in adults and pediatric patients aged 6 years and older.
- Monitor patients for gastrointestinal (GI) adverse reactions during dosage initiation and titration.

- If the starting dosage is:
    - Not tolerated, discontinue the product.
    - Tolerated for 2 weeks, increase the dosage as presented in Table 1.

Table 1: Recommended Dosage in Adults and Pediatric Patients Aged 6 Years and Older

Week	Daily dose	Volume to be injected
Week 1-2	0.5 mg once daily	0.05 ml once daily
Week 3-4	1 mg once daily	0.1 ml once daily
Week 5-6	2 mg once daily	0.2 ml once daily
Week 7 and onward	3 mg once daily	0.3 ml once daily

Pediatric Patients Aged 4 to Less Than 6 Years

- The recommended starting dosage is 0.5 mg (0.05 mL) injected subcutaneously once daily for 2 weeks in pediatric patients aged 4 to less than 6 years.
- Monitor patients for GI adverse reactions during dosage initiation and titration.
- If the starting dosage is:
    - Not tolerated, discontinue the product.
    - Tolerated for 2 weeks, increase the dosage based on baseline body weight, as presented in Table 2.

Table 2: Recommended Dosage Based on Baseline Body Weight in Pediatric Patients Aged 4 to Less Than 6 Years

Patient Weight/Treatment Week	Daily Dose	Volume to be Injected
15 kg to less than 20 kg		
Week 1 and onward	0.5 mg once daily	0.05 mL once daily
20 kg to less than 30 kg		
Weeks 1-2	0.5 mg once daily	0.05 mL once daily
Week 3 and onward	1 mg once daily	0.1 mL once daily
30 kg to less than 40 kg		
Weeks 1-2	0.5 mg once daily	0.05 mL once daily
Weeks 3-4	1 mg once daily	0.1 mL once daily
Week 5 and onward	1.5 mg once daily	0.15 mL once daily
Greater than or equal to 40 kg		
Weeks 1-2	0.5 mg once daily	0.05 mL once daily
Weeks 3-4	1 mg once daily	0.1 mL once daily
Weeks 5-6	1.5 mg once daily	0.15 mL once daily
Weeks 7 and onward	2 mg once daily	0.2 mL once daily

2.2.2 Therapeutic individualization

For the previously approved genetic obesity indications (*BBS or POMC, PCSK1, or LEPR Deficiency*):

Patients with severe renal impairment have a higher exposure of setmelanotide relative to patients with normal kidney function. Reduce the recommended starting and maintenance dosage of IMCIVREE in adults and pediatric patients 2 years of age and older with severe renal impairment and *BBS or POMC, PCSK1, or LEPR Deficiency* (eGFR 15-29 mL/min/1.73 m^2). The use of IMCIVREE in pediatric patients aged 2 to less than 6 years with weight less than 20 kg and severe renal impairment is not recommended.

IMCIVREE is not recommended for use in patients with end stage renal disease (eGFR less than 15 mL/min/1.73 m^2).

The recommended dosage in patients with mild (eGFR of 60-89 mL/min/1.73 m^2) or moderate renal impairment (eGFR of 30-59 mL/min/1.73 m^2) is the same as those with normal kidney function.

Current supplement in patients with hypothalamic obesity (HO):

- Dosage in severe renal impairment in patients with HO: IMCIVREE is not recommended for use in HO patients with severe renal impairment (eGFR 15 to less than 30 mL/min/1.73 m^2) or end stage renal disease (eGFR less than 15 mL/min/1.73 m^2).

- The recommended dosage in patients with HO and mild (eGFR of 60-89 mL/min/1.73 m^2) or moderate renal impairment (eGFR of 30-59 mL/min/1.73 m^2) is the same as those with normal kidney function.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

Section 2.2 Dosage and administration:

The Applicant proposed a new dosing table for the HO population that used different body-weight tiered dosing and different age cutoffs than what was used in study RM-493-040 (See section 4.2). The OCP team identified the discrepancy and communicated clarifying questions to the Applicant via an information request on August 4, 2025. The Applicant responded on August 13, 2025 (see response-to-request-for-information-s-009-2025-08-04) stating that

1. *Therefore, given that the dosing regimen in the USPI for the younger patients is more conservative than that specified in the RM-493-040 protocol, using the same regimen will help reduce the risk of medication errors.*
2. *Of the 120 pivotal patients in Study RM-493-040, 2 were aged 4 to <6 years at baseline and randomized to the setmelanotide group (Patient* (b) (6) *and Patient* (b) (6)*, both aged 4 years at baseline). Therefore, there are minimal actual data in clinical trial patients to inform the dosing.*

3. *The updated population PK model confirms that exposure is weight-based and consistent across all indications (RPI0105; Module 5.3.5.3). Therefore, consistent dosing is appropriate for the younger age group (4 to <6 years). See the population PK review for further details (Section 4.3)*

The Agency's review of the Applicant's population PK analysis confirms that the simulations are acceptable to support the newly proposed dosage and administration as in Table 1 and Table 2.

Section 2.4 Recommended Dosage in Patients with Renal Impairment:

For the Hypothalamic Obesity Indication under review, Applicant has not proposed any change to the currently approved dosing regimen in patients with renal impairment. The proposal for dosing in HO patients with ESRD or mild or moderate renal impairment is acceptable. In patients with HO and mild or moderate renal impairment, the general dosing schedule is the same as the HO population with normal renal function. This is acceptable due to minimal PK changes that were deemed not clinically significant based on the updated population PK analysis.

However, the review team has determined that the use of IMCIVREE is not recommended in patients with severe renal impairment and HO, due to the following reasons:

1. There is a lack of PK data in this sub-population with HO
2. The approved dosing schedule for patients with genetic obesity and severe renal impairment stratifies two different doses based on age 6-12 years and 12 years and older (1 and 2 mg respectively), while the proposed dosage regimen for patients with HO have the same starting dose of 0.5 mg for ages 6 years and older through adulthood. In addition, the Applicant has not proposed any dose reduction for patients with HO and severe renal impairment, despite the higher predicted exposures for this sub-population.
3. The starting dose of 0.5 mg for all patients with HO without renal impairment represents a lower dose limit that precludes any further reduction due to limitation in the use of safe to administer dose below the 0.5 mg. The chances of a dosing error due to the lack of lower dose strength is unacceptable according to the review team (See DMEPA review).

Section 12.3 Pharmacokinetics.

The Applicant proposed to include PK estimates from the earlier conducted study in healthy participants as follows:

Following once-daily (QD) SC dosing of setmelanotide to healthy adults with obesity, steady-state plasma concentrations of setmelanotide increased slowly, reaching maximum concentrations at a median T_{max} of 8 h after dosing. (b) (4) *. Steady-state plasma concentrations of setmelanotide were achieved within 2 days of QD administration of* (b) (6) *mg*.

The clinical pharmacology team noted that in the previous labeling revision the Applicant accepted updated population PK estimates representative of the patient populations rather than PK data from healthy subjects. It was unclear how adding the healthy PK data in the label is useful or actionable to prescribers. Hence the OCP team recommends deletion of the newly proposed language pertaining to the PK data in healthy subjects.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Setmelanotide injection for subcutaneous use is marketed in the US as IMCIVREE (NDA 213793) by the Applicant, Rhythm Pharmaceuticals, Inc. The Applicant submitted Supplement 9 for Imcivree injection for the treatment of hypothalamic obesity (HO). The FDA granted Breakthrough designation for the HO indication on October 27, 2022. The PK data in patients with HO comes from the phase 3 study in patients with HO (Study RM-493-040) and the long-term extension study (Study RM-493- 022 (in which HO patients transitioned from the phase 2 study (Study RM-493-030)). Both Phase 3 and phase 2 studies used the commercial formulation (preserved setmelanotide/mPEG-DSPE formulation).

3.2 General Pharmacology and Pharmacokinetic Characteristics

Mechanism of action

Setmelanotide is an MC4 receptor agonist with 20-fold less activity at the melanocortin 3 (MC3) and melanocortin 1 (MC1) receptors. MC4 receptors in the brain are involved in regulation of hunger, satiety, and energy expenditure. Based on nonclinical evidence, setmelanotide may re-establish MC4 receptor pathway activity to reduce food intake and promote weight loss through decreased caloric intake and increased energy expenditure in patients with obesity due to HO, BBS, or POMC, PCSK1, or LEPR deficiency associated with insufficient activation of the MC4 receptor. The MC1 receptor is expressed on melanocytes, and activation of this receptor leads to accumulation of melanin and increased skin pigmentation independently of ultraviolet light.

Pharmacokinetics

The mean steady state setmelanotide Cmax,ss, AUCtau, and trough concentration for a 3-mg dose administered subcutaneously once daily was 31 ng/mL, 373 h*ng/mL, and 5 ng/mL, respectively simulated using individual PK model parameters from 109 adult patients with normal renal function. Steady-state plasma concentrations of setmelanotide were achieved within 2 days with daily dosing of 1-3 mg setmelanotide. The accumulation of setmelanotide in the systemic circulation during once-daily dosing over 12 weeks was approximately 30%. Setmelanotide AUC and Cmax increased proportionally following multiple-dose subcutaneous administration in the proposed dose range (1-3 mg).

Absorption

After subcutaneous injection of IMCIVREE, plasma concentrations of setmelanotide reached maximum concentrations at a median t_{max} of 8 h after dosing.

Distribution

The mean apparent volume of distribution of setmelanotide after subcutaneous administration of IMCIVREE 3 mg once daily was estimated to be 75.2 L. Protein binding of setmelanotide is 79.1%.

Elimination

The effective elimination half-life ($t_{½}$) of setmelanotide was approximately 11 hours. The total apparent steady state clearance of setmelanotide following subcutaneous administration of IMCIVREE 3 mg once daily was estimated to be 7.15 L/h in a typical male patient weighing 120 kg (actual body weight) with normal renal function.

Metabolism

Setmelanotide is expected to be metabolized into small peptides by catabolic pathways.

Excretion

Approximately 39% of the administered setmelanotide dose was excreted unchanged in urine during the 24-hour dosing interval following subcutaneous administration of 3 mg once daily.

Specific Populations

No clinically significant differences in the pharmacokinetics of setmelanotide were observed based on sex or disease. The effect of age 65 years or older, pregnancy, or hepatic impairment on the pharmacokinetics of setmelanotide is unknown.

Pediatric Patients

IMCIVREE has been evaluated in pediatric patients aged 2 to less than 6 years, 6 to less than 12 years, and aged 12 to 17 years. Simulations were performed using population pharmacokinetic analysis for pediatric patients aged 2 to less than 6 years, following the maximum recommended doses in each of the body weight groups - 2 mg, 1.5 mg, 1 mg, and 0.5 mg in patients weighing ≥40 kg, 30 to <40 kg, 20 to <30 kg, and 15 to <20 kg, respectively. The analyses suggest that AUC and C_{max} in pediatric patients aged 2 to less than 6 years are 52% and 75% higher in patients weighing ≥40 kg, 45% and 63% higher in patients weighing 30 to <40 kg, 24% and 38% higher in patients weighing 20 to <30 kg, and 17% and 14% lower in patients weighing 15 to <20 kg as compared to patients greater than or equal to 18 years (3 mg dose). For patients aged 6 to less than 12 years, the setmelanotide AUC and C_{max} were 88% and 89% higher compared to patients greater than or equal to 18 years. For patients aged 12 to 17 years, the setmelanotide AUC and C_{max} were both 26% higher as compared to patients greater than or equal to 18 years

Patients with Renal Impairment

Exposure parameters, AUC_{0-t} and AUC_{0-inf}, were approximately 13%-15%, 34%-35%, and 86%-96% higher for patients with mild, moderate, and severe renal impairment, respectively, as compared to patients with normal renal function

Renal impairment did not appear to affect plasma protein binding. The average fraction unbound (f_u) was approximately 0.2 and was independent of renal function.

Drug Interaction Studies

In vitro assessment of drug-drug interactions

Setmelanotide has low potential for pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP), transporters and plasma protein binding.

In vivo assessment of drug-drug interactions

No clinical studies evaluating the drug-drug interaction potential of setmelanotide have been conducted.

Immunogenicity

Across five clinical trials with an exposure time of at least 52 weeks, 4 of 245 subjects (1.6%) were positive for antibodies against setmelanotide. Anti-setmelanotide antibodies prevalence by genetic deficiency: BBS 3/50 (6.0%), AS 1/8 (12.5%), POMC deficiency (0/16), PCSK1 deficiency (0/2), LEPR deficiency (0/21), and acquired HO (0/142). Reported titers among ADA-positive subjects were generally low.

In five clinical trials with an exposure time of at least 52 weeks anti-α-MSH antibodies were measured in 17 of 245 subjects (6.9%). Anti-α-MSH antibodies by genetic deficiency: BBS 5/50 (10.0%), AS 1/8 (12.5%), POMC 1/16 (6.3%), LEPR 6/21 (28.6%), PCSK1 0/2 (0%), HO 4/142 (2.8%). The reported titer of ADA against α-MSH were generally low.

In patients with acquired HO, BBS, or in patients with POMC, PCSK1, or LEPR deficiency, there is insufficient information to characterize the ADA response to setmelanotide or α-MSH and the effects of ADA on pharmacokinetics, pharmacodynamics, safety, or effectiveness of setmelanotide products.

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 information provides supportive evidence of effectiveness. The Applicant conducted study RM-493-040 in patients with HO to support dosing in this population along with a population PK analysis. The applicant updated their previously reviewed population PK model with new pediatric data from 89 subjects with Acquired Hypothalamic Obesity (HO). The overall aim of this analysis was to evaluate proposed setmelanotide dosing in adult and pediatric patients from 4 years of age and older with HO. Specifically, key objectives included: Quantify intrinsic and extrinsic sources of variability in setmelanotide PK, including differences in disposition between rare genetic diseases of obesity (RGDO) and HO populations. Data from12 clinical studies were pooled to support population PK model development. The complete PK analysis dataset included 513 subjects. Setmelanotide PK were well described by a one-compartment model with zero-order input. Final model estimates were: apparent clearance (CL/F) 7.19 (95% confidence interval (CI): 6.86, 7.53) L/h, apparent volume of distribution (V/F) 73.1 (95% CI: 70.1, 76.3) L, and duration of zero-order absorption into the central compartment (D2) 5.82 (95% CI: 5.44, 6.23) h for a reference subject, i.e., a 120 kg male subject with RGDO, and IBW of

60 kg, eGFR of 90 mL/min/1.73m^2, and receiving the preserved setmelanotide formulation. Setmelanotide CL/F was modeled to vary with weight according to a fixed allometric scaling relationship with an exponent of 0.75. Setmelanotide V/F was modeled to vary with IBW according to a fixed allometric scaling relationship with an exponent of 1. The interindividual variability (IIV) estimates (percent coefficient of variation (CV%)) were CL/F = 28.6%, V/F = 26.9%, and D2 = 49.7%. The estimate of residual unexplained variability (RUV) was 1.61 ng/mL (standard deviation (SD), additive) with 200% CV%.

The applicant further performed simulations to evaluate the exposures in pediatrics at the various proposed dose levels. These data are shown in the population PK Review (Section 4.3).

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

The Applicant conducted Study RM-493-040, a Phase 3, double-blind, multicenter, placebo-controlled, randomized 2:1 (active to placebo), registrational study designed to assess the efficacy and safety of setmelanotide in patients ≥4 years of age with acquired hypothalamic obesity (HO).

All patients were initiated at a dose of 0.5 mg once daily (QD) and dose escalated to achieve the individual patient's therapeutic regimen. The target therapeutic regimen varied by age and weight:

- Patients <6 years:
  - <20 kg: maximum 1.5 mg QD
  - 20 to <25 kg: maximum 2.0 mg QD
  - 25 to <30 kg: maximum 2.5 mg QD
  - ≥30 kg: maximum 3.0 mg QD
- Patients ≥6 years: All patients were allowed to receive a maximum 3.0 mg QD dose. Dose escalation occurred weekly in increments of 0.5 or 1.0 mg based on tolerability. Study drug was administered by subcutaneous (SC) injection QD in the morning.

However, the proposed dosing schedule under section 2 for patients with HO is different than that used in this pivotal phase 3 trial.

For section 2.2, Dosage and Administration, the Applicant proposed a new dosing table for the HO population the used different body-weight tiered dosing the age cutoffs different than what was used in study RM-493-040 (See section 4.2). The OCP team identified the discrepancy and communicated clarifying questions to the Applicant via an information request on August 4, 2025. The Applicant responded on August 13, 2025 (see response-to-request-for-information-s-009-2025-08-04) stating that:

1. *Therefore, given that the dosing regimen in the USPI for the younger patients is more conservative than that specified in the RM-493-040 protocol, using the same regimen will help reduce the risk of medication errors.*

2. *Of the 120 pivotal patients in Study RM-493-040, 2 were aged 4 to <6 years at baseline and randomized to the setmelanotide group (Patient (b) (6) and Patient (b) (6), both aged 4 years at baseline). Therefore, there are minimal actual data in clinical trial patients to inform the dosing.*
3. *The updated population PK model confirms that exposure is weight-based and consistent across all indications (RPI0105; Module 5.3.5.3). Therefore, consistent dosing is appropriate for the younger age group (4 to <6 years). See the population PK review for further details (Section 4.3)*

The Agency's review of the applicant's population PK analysis confirms that the simulations are acceptable to support the newly proposed dosage and administration Table 1 and Table 2.

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

None proposed for renal impairment in this supplement. According to the current Prescribing Information for Imcivree, no dose reduction is necessary for patients with mild and moderate renal impairment. A dose reduction is necessary for patients with severe renal impairment with genetic obesities while the use of Imcivree is not recommended for patients with end stage renal disease.

The review team agrees with the proposed dosing in mild/moderate renal impairment and in end stage renal disease. However, in this current supplement for therapy of patients with HO, since the Applicant has not determined a specific dose reduction for patients with HO and severe renal impairment, along with the limitations described in section 2.4, the review team could not recommend the use of Imcivree in HO patients with severe renal impairment (See section 2.4).

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The pharmacokinetic (PK) samples collected in Study RM-493-040 were analyzed using a validated liquid chromatography TM.4204 with tandem mass spectrometry (LC-MS/MS) assay, which detected RM-493 (setmelanotide). The LC-MS/MS method was developed and validated by (b) (4) The bioanalytical work was conducted in compliance with Good Clinical Practice (GCP) guidelines and Standard Operating Procedures (SOPs) written in accordance with ICH M10 Bioanalytical Method Validation and Study Sample Analysis guidance.

Method Summary

The summary of the bioanalytical method validation is presented below:

Briefly, RM-493 was extracted from human EDTA K_2 plasma using automated protein precipitation in a 96-well format with RM-493 ($^{13}C_{11}$,$^{15}N_2$) as the internal standard. Next, RM-493 and internal standard were identified and quantified using a Sciex API 6500 mass spectrometer equipped with a Turbo Ionspray interface and tandem mass spectrometry detection in positive ion mode over a standard curve range of 0.5 to 200 ng/mL. The concentrations were calculated using peak area ratios, and the linearity of the calibration curve was determined using linear regression analysis employing a $1/x^2$ weighting.

Validation Performance

The interassay accuracy (% bias) during validation ranged from -0.44% to 3.22%. The interassay precision (% coefficient of variation) during validation was 2.16% to 10.72%. The interassay precision and interassay accuracy values passed all predefined acceptance criteria.

Key Validation Parameters:

- Calibration Curve Range: 0.5 to 200 ng/mL
- Linearity: $r^2 \geq 0.9960$
- Calibration Curve Goodness of Fit: Biases: -0.90% to 1.30%
- Between-Run Accuracy and Precision: Mean Biases: -0.44% to 3.22%; CV: 2.16% to 10.72%
- Within-Run Accuracy and Precision: Mean Biases: -6.00% to 15.67%; CV: 0.94% to 9.70%
- Run Size Evaluation (192 samples): Mean Biases: -0.33% to 2.93%; CV: 1.71% to 3.34%
- Recovery of Analyte: 89.05%, 89.39%, and 89.80%; CV: 0.68% to 14.74%
- Recovery of Internal Standard: 88.58%; CV: 0.87% and 12.57%
- Dilution Integrity (20-fold dilution): Bias: -1.28%; CV: 1.30%
- Matrix Selectivity: No significant interference observed in 8 out of 8 tested matrices (including hyperlipemic and 5% hemolyzed matrices)
- Carryover: No significant carryover observed for analyte or internal standard
- Reinjection Reproducibility: 91h24min at 4°C
- Freeze-Thaw Stability: 4 cycles at -20°C and -80°C
- Short-Term Stability in Matrix: 23h00min at room temperature; 120h02min at 4°C
- Long-Term Stability in Matrix: 9, 120, 307, and 584 days at -20°C; 9, 120, 307, 584, and 770 days at -80°C
- Stability in Whole Blood: 120 minutes in ice/water bath (centrifugation at 4°C and room temperature)
- Post-Preparative Stability: 144h51min at 4°C

Study Sample Analysis

A total of 1,259 samples were received from August 10, 2023, to March 26, 2025. Of these, 417 samples were analyzed between March 28, 2024, and April 10, 2025. The interval from first sample draw date (April 26, 2023) to last analysis date (April 10, 2025) was 715 days. Adequate long-term stability (770 days at -80°C) was established to cover the storage period.

Incurred Sample Reanalysis (ISR)

Incurred sample reanalysis was conducted for Study RM-493-040, and the results indicated that the assay method performed according to established ISR acceptance criteria with (b) (4)% ((b) (4)) of ISR results within (b) (4)% difference.

Conclusion

The performance of the analytical method was successfully demonstrated during validation and study sample analyses. The analyte is stable under all conditions tested. From these results, the reported values for the study samples are determined to be reliable. The method for the determination of RM-493 in human EDTA plasma was proven to be precise, accurate, sensitive, and selective over the validated range of 0.5 to 200 ng/mL.

4.2 Clinical PK and/or PD Assessments

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

Study Design

The Applicant conducted Study RM-493-040, a Phase 3, double-blind, multicenter, placebo-controlled, randomized 2:1 (active to placebo), registrational study designed to assess the efficacy and safety of setmelanotide in patients ≥4 years of age with acquired hypothalamic obesity (HO).

A total of 143 patients (95 in the setmelanotide group and 48 in the placebo group) were enrolled, including 12 patients from Japan. Of the 143 enrolled patients, 120 either completed the end-of-treatment (EOT) visit or discontinued treatment prematurely and are included in the analyses (Pivotal Cohort). The study consisted of:

- Screening Period: Up to 8 weeks
- Treatment Period: Up to 60 weeks (including dose titration phase of up to 8 weeks plus 52 weeks of treatment with a therapeutic regimen)
- Safety Follow-up Visit (SFV): Approximately 2 weeks after the last dose of study treatment for patients who did not continue to open-label extension

Dosing:

All patients initiated study treatment at 0.5 mg once daily (QD) and dose escalated to achieve the individual patient's therapeutic regimen. The target therapeutic regimen varied by age and weight:

- Patients <6 years:
  - <20 kg: maximum 1.5 mg QD
  - 20 to <25 kg: maximum 2.0 mg QD
  - 25 to <30 kg: maximum 2.5 mg QD
  - ≥30 kg: maximum 3.0 mg QD

- Patients ≥6 years: All patients were allowed to receive a maximum 3.0 mg QD dose. Dose escalation occurred weekly in increments of 0.5 or 1.0 mg based on tolerability. Study drug was administered by subcutaneous (SC) injection QD in the morning.

Efficacy Assessments:

Efficacy and safety assessments were performed approximately every 4 weeks via either in-clinic visits or at-home telehealth visits. The EOT visit occurred after 52 weeks on a therapeutic regimen. The primary Endpoint was Mean percent change in BMI from baseline after approximately 52 weeks on a therapeutic regimen. See Clinical team review in DARRTS for final efficacy conclusions.

Pharmacokinetic (PK) and ADA assessment:

Blood samples were obtained to determine plasma concentrations of setmelanotide and anti-drug antibodies (ADA; anti-setmelanotide and anti-α-MSH). Trough samples were collected prior to the daily dose administration at specified clinic visits, including Day 1, Week 4, 8, 12, 24, 36, 52 and the End-of-Treatment (EOT) visit. No non-compartmental analysis was performed. PK parameters were calculated using population PK methods (See section 4.3).

GLP-1 Receptor Agonist Use:

Setmelanotide's effects on weight reduction were maintained regardless of prior and/or concomitant GLP-1 receptor agonist use:

- Prior and concomitant GLP-1 use: LSM difference -27.06%
- Prior GLP-1 use only: LSM difference -24.67

Safety:

Setmelanotide was well tolerated. The most commonly reported treatment-emergent adverse events (TEAEs) that occurred more frequently in setmelanotide-treated patients included nausea (53.2% vs. 27.1%), skin hyperpigmentation (55.3% vs. 8.3%), and vomiting (38.3% vs. 18.8%). Importantly, diarrhea (20.2% vs. 20.8%), injection site reactions (22.3% vs. 22.9%), and headache (36.2% vs. 31.3%) occurred at similar rates in both groups. For Final safety determinations see Clinical review in DARRTS.

Immunogenicity:

No Anti-setmelanotide antibodies prevalence was observed in patients with hypothalamic obesity (0/142). Reported titers among ADA-positive subjects were generally low. Out of the 142 samples tested only four tested as positive for Anti-a-MSH antibodies (2.8%). The reported titer of ADA against a-MSH were generally low. In patients with acquired hypothalamic (b) (4), there is insufficient information to characterize the ADA response to setmelanotide or a-MSH and the effects of ADA on pharmacokinetics, pharmacodynamics, safety, or effectiveness of setmelanotide products. For complete revisions to the immunogenicity section across all indications, see Immunogenicity review dated November 13, 2025, Reference ID: 5693221)

4.3 Population PK Review

The applicant's population PK Model was reviewed previously and found to be reasonable for simulating exposures for doses ranging from 0.5 to 3 mg in patients 2 years of age and older. With this submission the applicant is updating their population PK analysis with more pediatric data from Trial RM-493-040 in the acquired hypothalamic obesity population. As the structural model did not change and the parameter estimates are generally within 10% of the previously reviewed model, the aim of this review will focus solely on the change in estimate for CL as a function of eGFR and the updated corresponding simulation results.

Table 3 shows the nature of the population PK data entered into the analysis with this submission from 89 pediatric subjects with hypothalamic obesity weighing more than 30kg.

Table 3. Summary of new clinical trials included in the applicant's final population PK model.

Section	Patient Population	Age (years)	Setmelanotide / mPEG-DSPE Formulation	Subcutaneous Dose	Number of Subjects	
					Total	With PK
RM-493-040* (Phase 3)**						
<20 kg	HO	4-<6	Preserved	Titration every week: 0.5 up to 1.5 mg QD	—	—
20-<25 kg	HO	4-<6	Preserved	0.5 up to 2 mg QD	—	—
25-<30 kg	HO	4-<6	Preserved	0.5 up to 2.5 mg QD	—	—
≥30 kg	HO	≥6	Preserved	0.5 up to 3 mg QD	89	89

AS: Alström syndrome; BBS: Bardet-Biedl syndrome; HO: acquired hypothalamic obesity; LEPR: leptin receptor; PCSK1: proprotein convertase subtilisin/kexin type 1; POMC: pro-opiomelanocortin; PWS: Prader-Willi syndrome; QD: once daily; QW: once weekly; RGDO: rare genetic diseases of obesity
Source code: script/study-summary.R

(Source: Applicant's Population PK Report, RPF105, Table 1)

The applicant's final population PK parameters are shown in Table 4 and Table 5. The confidence interval for parameters provides confidence in the data to inform the estimates reliably and the final parameter estimates are within 10% of the previously reviewed model. Updated ETA (CL/F) plots are provided as eGFR had a higher degree of change in the parameter for this model and new simulations were performed Figure 1

Table 4. Final setmelanotide PPK model fixed effect parameter estimates.

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

Parameters estimated in the log domain were back-transformed for clarity

CI: confidence interval; HO: acquired hypothalamic obesity; RGDO: rare genetic diseases of obesity; SE: standard error

$CI = \text{estimate} \pm z_{\alpha/2} \cdot SE, \alpha = 0.05$

(Source: Applicants Population PK Report, RPF105, Table S9)

Table 5. Final setmelanotide PPK model random effect parameter estimates.

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

CI: confidence interval; Corr: correlation coefficient; CV: coefficient of variation; SD: standard deviation; SE: standard error; RUV: residual unexplained variability

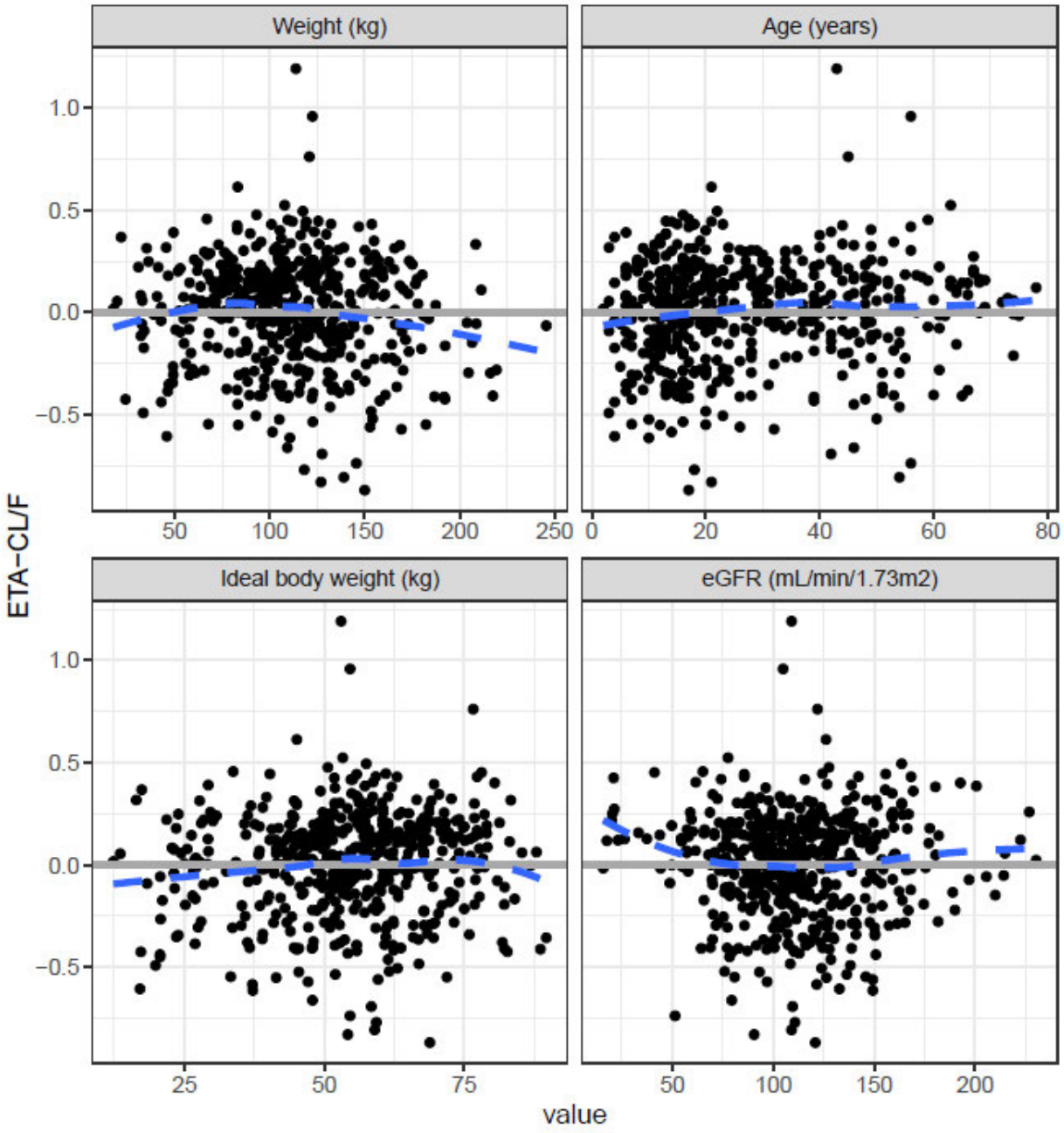
$CI = \text{estimate} \pm z_{\alpha/2} \cdot SE$, $\alpha = 0.05$

CV% of log-normal omega = sqrt(exp(estimate) - 1) · 100

CV% of sigma = sqrt(estimate) · 100

(Source: Applicant's Population PK Report, RPF105, Table S10)

Figure 1. Individual estimates of interindividual variability on setmelanotide apparent CL versus baseline continuous covariates. Black points represent data points with the blue dashed line representing a LOESS smooth through the data. The solid horizontal gray line (residual = 0) is included for reference. eGFR: estimated glomerular filtration rate.

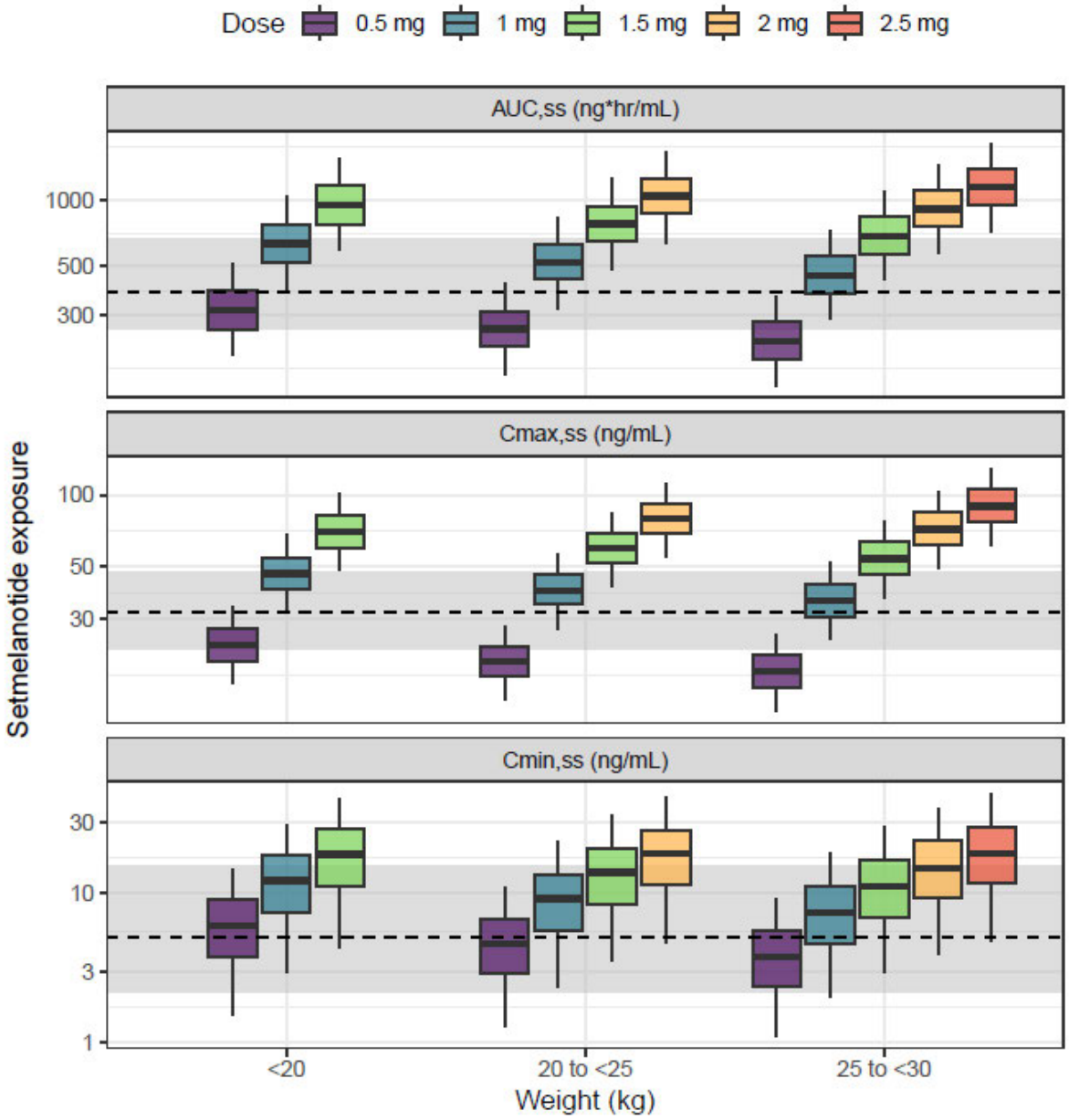


(Source: Applicant's Population PK Report, RPF105, Figure S31)

The applicant's updated simulation of exposures in pediatrics with varying degrees of renal function are shown below. Shrinkage for ETA (CL/F) was acceptable at 12.2% suggesting the variability in the data are preserved in the simulations for AUC.

Figure 2. Simulated setmelanotide exposure versus weight for pediatric subjects 4 to <6 years old with HO and normal renal function compared to exposure in adults with RGDO and normal renal function receiving 3 mg setmelanotide; stratified by exposure metric and dose.

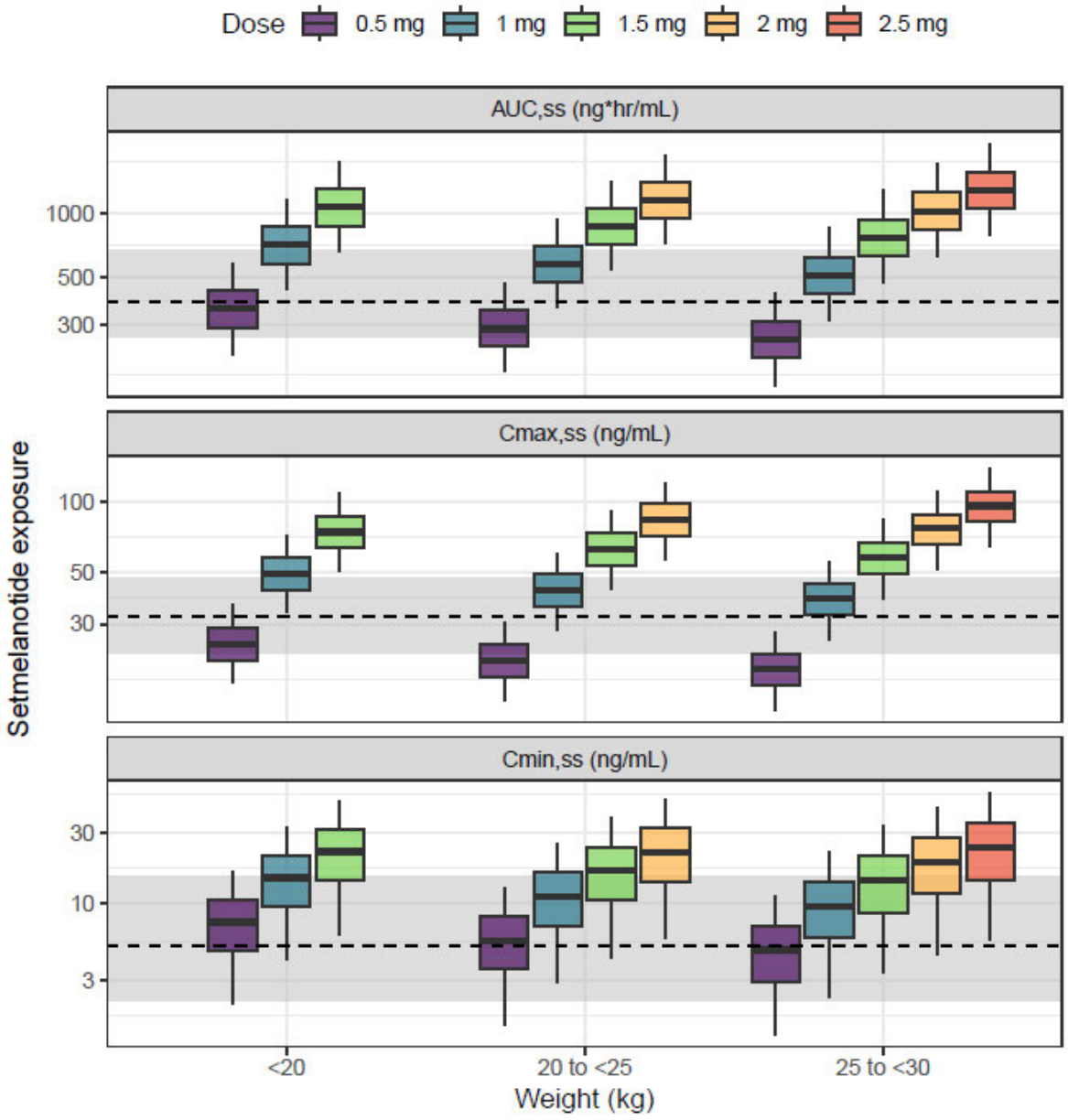
The median exposure values in subjects with HO are designated by solid lines in the center of the boxes. Boxes indicate the 25th and 75th percentiles with whiskers extending to the 5th and 95th percentiles of the exposure values. The horizontal dashed line indicates the median and the grey shaded region indicates the 5th and 95th percentiles of the reference exposure values. AUC,ss: area under the concentration-time curve for a dosing interval at steady state; $C_{max,ss}$: maximum concentration in the dosing interval at steady state; $C_{min,ss}$: minimum concentration in the dosing interval at steady state.



(Source: Applicant's Population PK Report, RPF105, Figure S46)

Figure 3. Simulated setmelanotide exposure versus weight for pediatric subjects 4 to <6 years old with HO and mild renal impairment compared to exposure in adults with RGDO and normal renal function receiving 3 mg setmelanotide; stratified by exposure metric and dose.

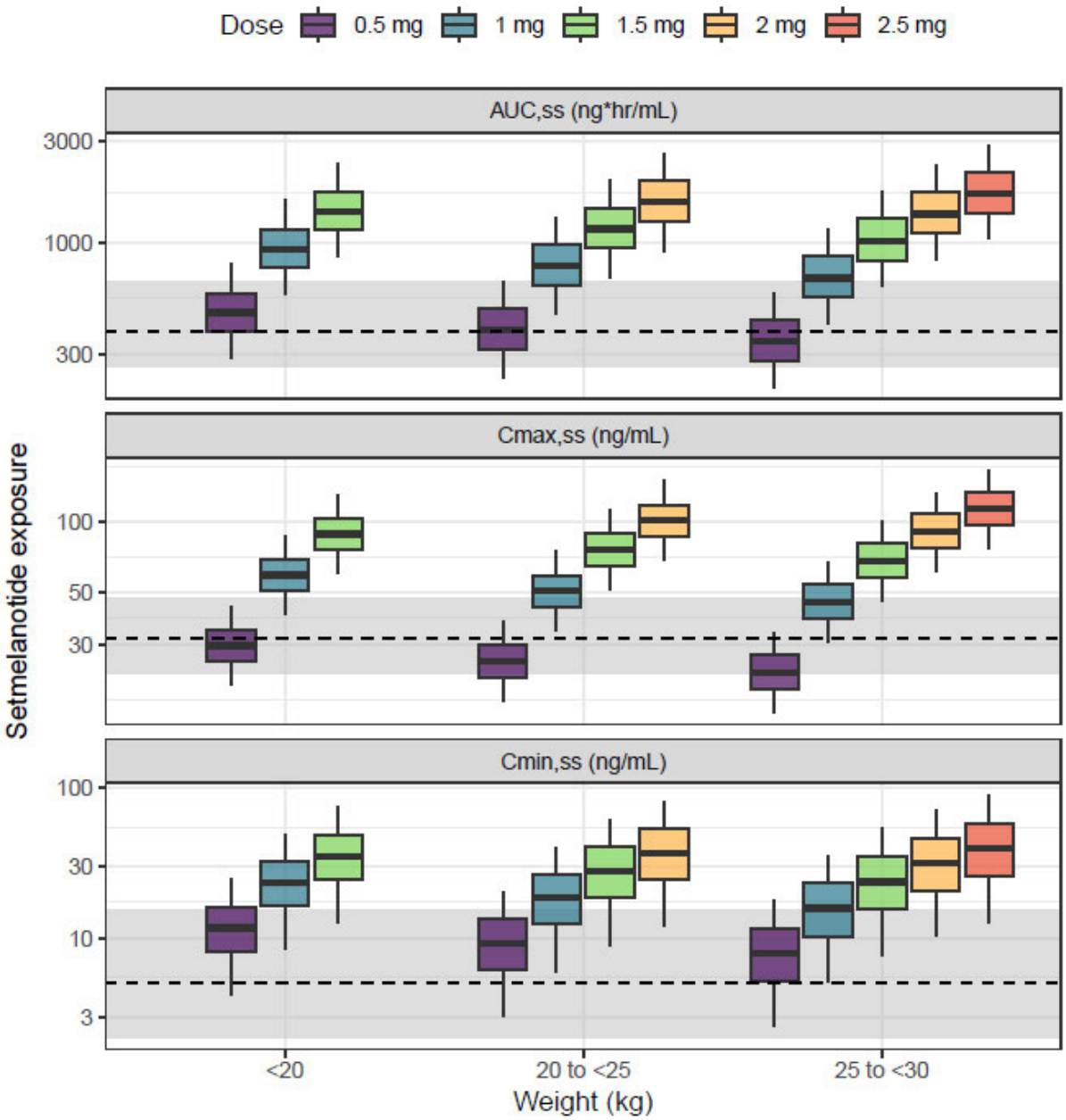
The median exposure values in subjects with HO are designated by solid lines in the center of the boxes. Boxes indicate the 25th and 75th percentiles with whiskers extending to the 5th and 95th percentiles of the exposure values. The horizontal dashed line indicates the median and the grey shaded region indicates the 5th and 95th percentiles of the reference exposure values. AUC,ss: area under the concentration-time curve for a dosing interval at steady state; $C_{max,ss}$: maximum concentration in the dosing interval at steady state; $C_{min,ss}$: minimum concentration in the dosing interval at steady state.



(Source: Applicant's Population PK Report, RPF105, Figure S47)

Figure 4. Simulated setmelanotide exposure versus weight for pediatric subjects 4 to<6 years old with HO and moderate renal impairment compared to exposure in adults with RGDO and normal renal function receiving3 mg setmelanotide; stratified by exposure metric and dose.

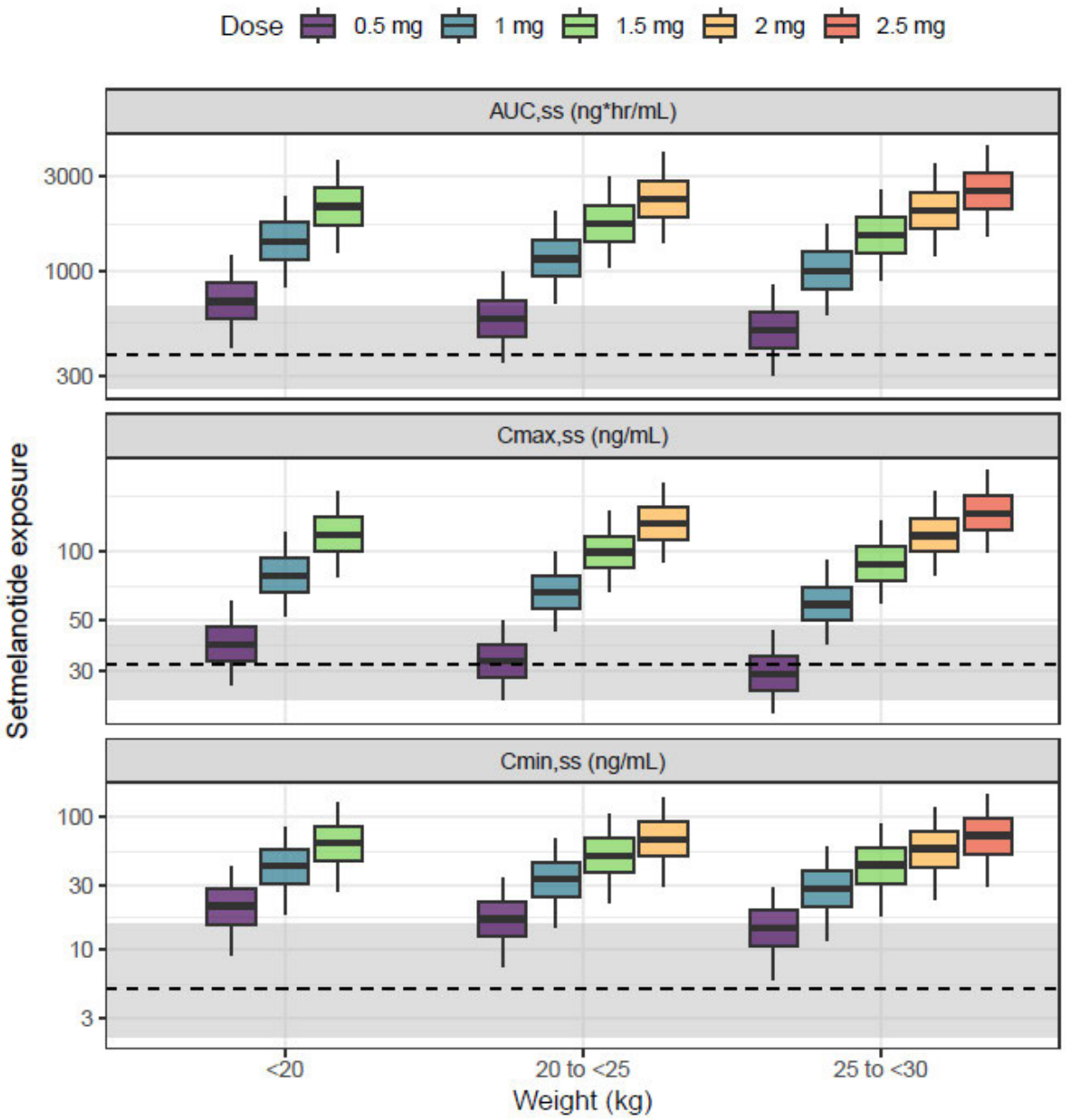
The median exposure values in subjects with HO are designated by solid lines in the center of the boxes. Boxes indicate the 25th and 75th percentiles with whiskers extending to the 5th and 95th percentiles of the exposure values. The horizontal dashed line indicates the median and the grey shaded region indicates the 5th and 95th percentiles of the reference exposure values. AUC,ss: area under the concentration-time curve for a dosing interval at steady state; $C_{max,ss}$: maximum concentration in the dosing interval at steady state; $C_{min,ss}$: minimum concentration in the dosing interval at steady state.



(Source: Applicant's Population PK Report, RPF105, Figure S48)

Figure 5. Simulated setmelanotide exposure versus weight for pediatric subjects 4 to<6 years old with HO and severe renal impairment compared to exposure in adults with RGDO and normal renal function receiving 3 mg setmelanotide; stratified by exposure metric and dose.

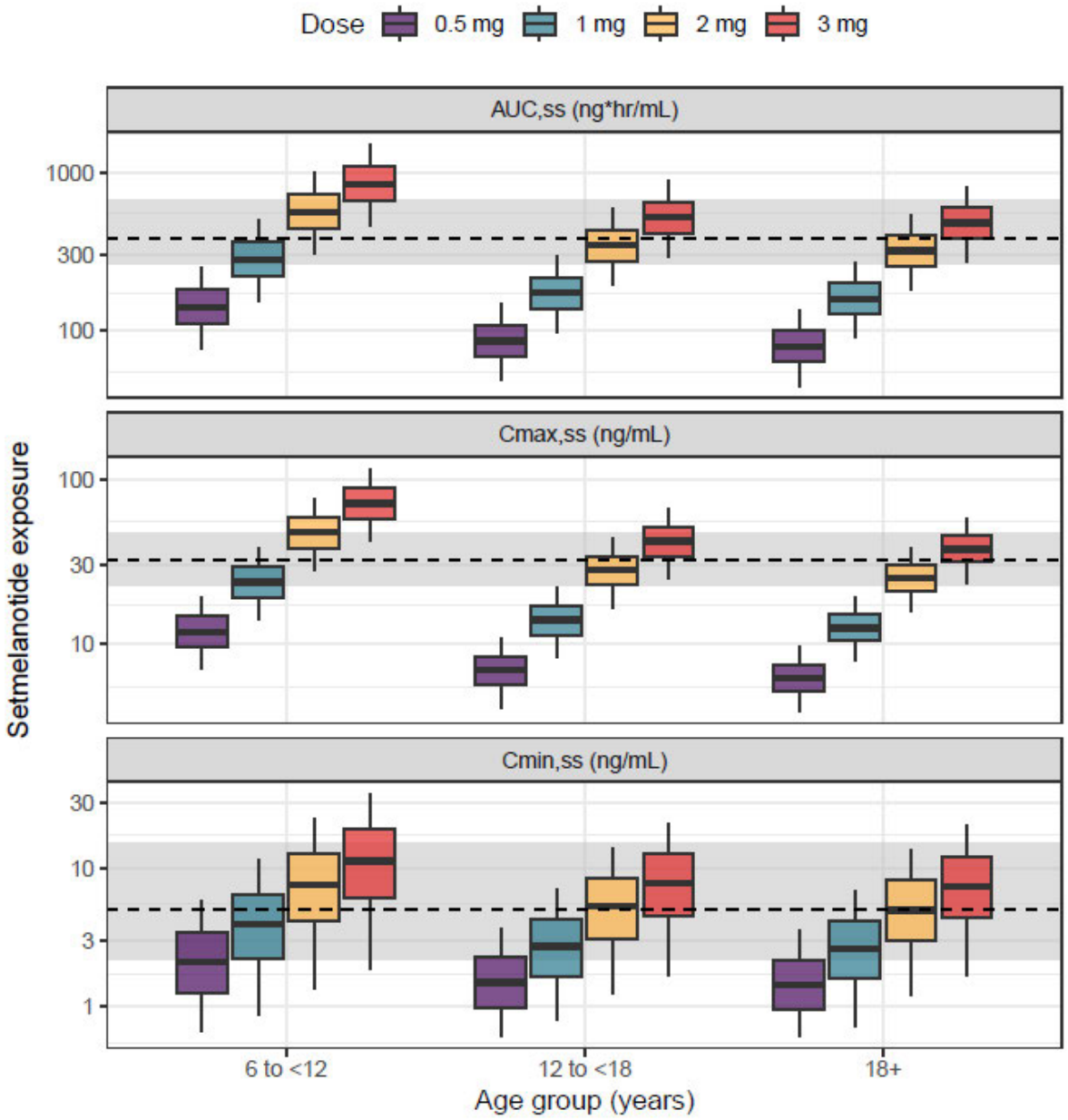
The median exposure values in subjects with HO are designated by solid lines in the center of the boxes. Boxes indicate the 25th and 75th percentiles with whiskers extending to the 5th and 95th percentiles of the exposure values. The horizontal dashed line indicates the median and the grey shaded region indicates the 5th and 95th percentiles of the reference exposure values. AUC,ss: area under the concentration-time curve for a dosing interval at steady state; $C_{max,ss}$: maximum concentration in the dosing interval at steady state; $C_{min,ss}$: minimum concentration in the dosing interval at steady state.



(Source: Applicant's Population PK Report, RPF105, Figure S49)

Figure 6. Simulated setmelanotide exposure versus age group for subjects ≥6 years old with HO and normal renal function compared to exposure in adults with RGDO and normal renal function receiving 3 mg setmelanotide; stratified by exposure metric and dose.

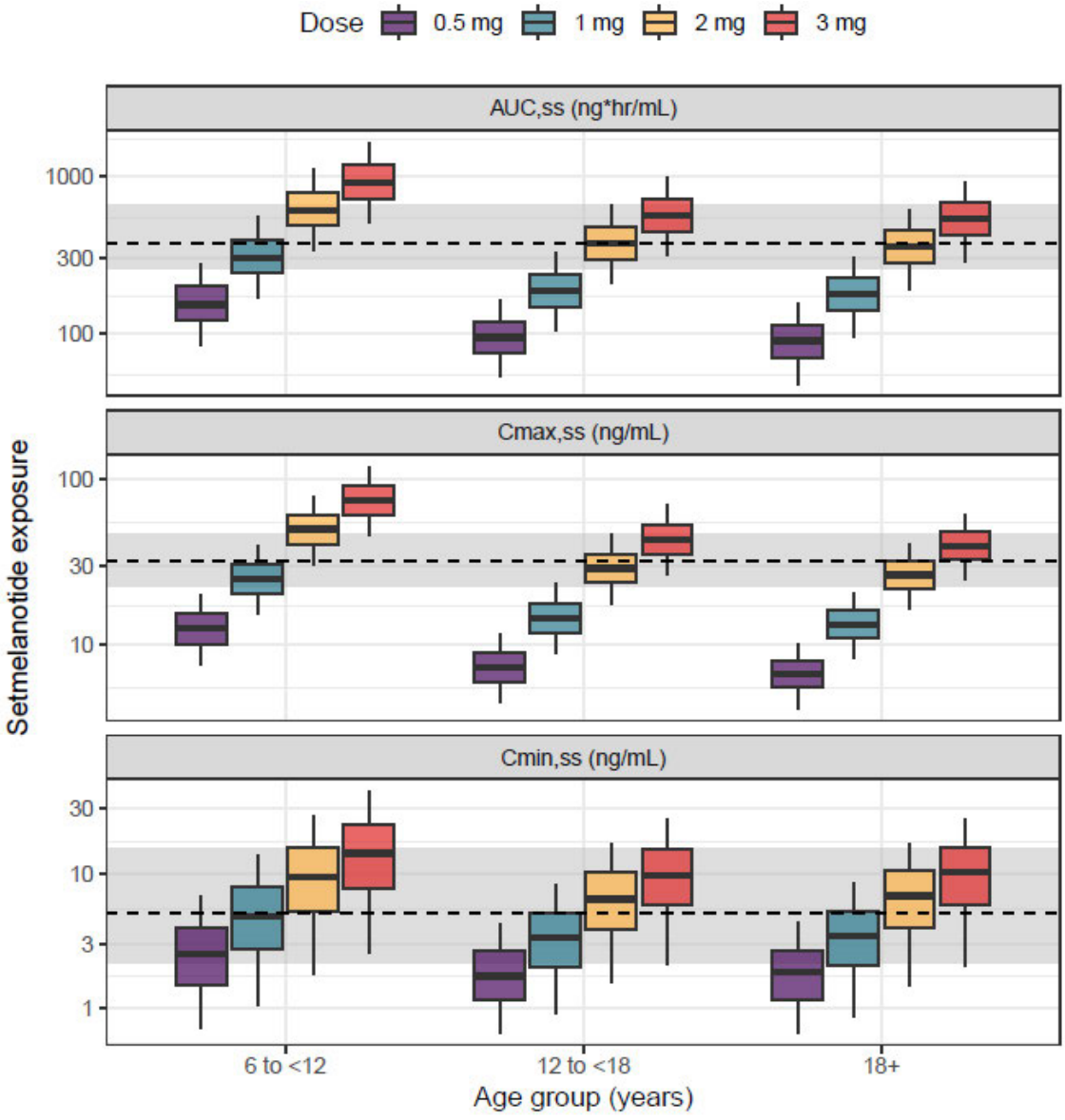
The median exposure values in subjects with HO are designated by solid lines in the center of the boxes. Boxes indicate the 25th and 75th percentiles with whiskers extending to the 5th and 95th percentiles of the exposure values. The horizontal dashed line indicates the median and the grey shaded region indicates the 5th and 95th percentiles of the RGDO reference exposure values. AUC,ss: area under the concentration-time curve for a dosing interval at steady state; $C_{max,ss}$: maximum concentration in the dosing interval at steady state; $C_{min,ss}$: minimum concentration in the dosing interval at steady state.



(Source: Applicant's Population PK Report, RPF105, Figure S50)

Figure 7. Simulated setmelanotide exposure versus age group for subjects ≥6 years old with HO and mild renal impairment compared to exposure in adults with RGDO and normal renal function receiving 3 mg setmelanotide; stratified by exposure metric and dose.

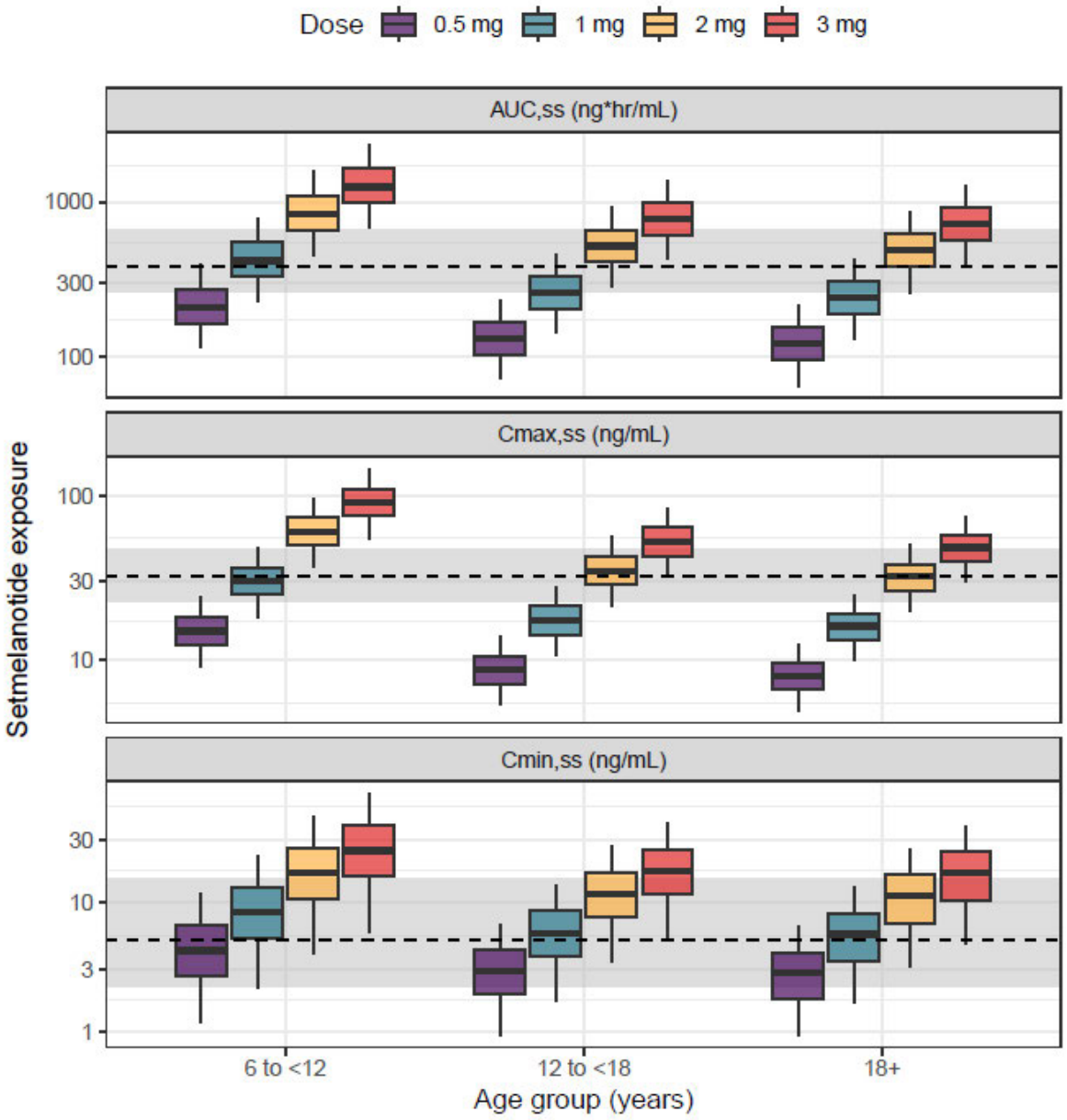
The median exposure values in subjects with HO are designated by solid lines in the center of the boxes. Boxes indicate the 25th and 75th percentiles with whiskers extending to the 5th and 95th percentiles of the exposure values. The horizontal dashed line indicates the median and the grey shaded region indicates the 5th and 95th percentiles of the RGDO reference exposure values. AUC,ss: area under the concentration-time curve for a dosing interval at steady state; $C_{max,ss}$: maximum concentration in the dosing interval at steady state; $C_{min,ss}$: minimum concentration in the dosing interval at steady state.



(Source: Applicant's Population PK Report, RPF105, Figure S51)

Figure 8. Simulated setmelanotide exposure versus age group for subjects ≥6 years old with HO and moderate renal impairment compared to exposure in adults with RGDO and normal renal function receiving 3 mg setmelanotide; stratified by exposure metric and dose.

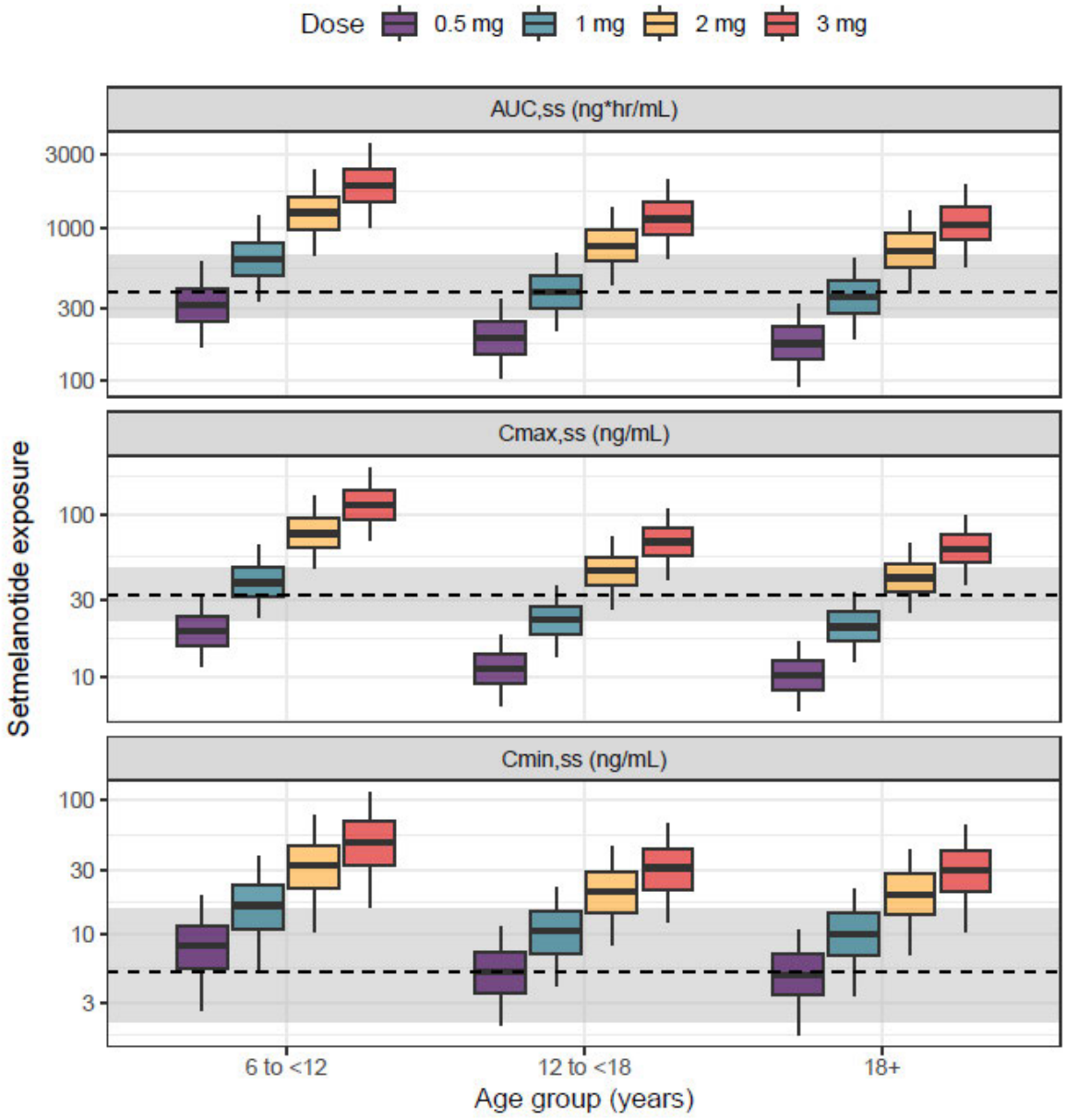
The median exposure values in subjects with HO are designated by solid lines in the center of the boxes. Boxes indicate the 25th and 75th percentiles with whiskers extending to the 5th and 95th percentiles of the exposure values. The horizontal dashed line indicates the median and the grey shaded region indicates the 5th and 95th percentiles of the RGDO reference exposure values. AUC,ss: area under the concentration-time curve for a dosing interval at steady state; $C_{max,ss}$: maximum concentration in the dosing interval at steady state; $C_{min,ss}$: minimum concentration in the dosing interval at steady state.



(Source: Applicant's Population PK Report, RPF105, Figure S52)

Figure 9. Simulated setmelanotide exposure versus age group for subjects ≥6 years old with HO and severe renal impairment compared to exposure in adults with RGDO and normal renal function receiving 3 mg setmelanotide; stratified by exposure metric and dose.

The median exposure values in subjects with HO are designated by solid lines in the center of the boxes. Boxes indicate the 25th and 75th percentiles with whiskers extending to the 5th and 95th percentiles of the exposure values. The horizontal dashed line indicates the median and the grey shaded region indicates the 5th and 95th percentiles of the RGDO reference exposure values. AUC,ss: area under the concentration-time curve for a dosing interval at steady state; $C_{max,ss}$: maximum concentration in the dosing interval at steady state; $C_{min,ss}$: minimum concentration in the dosing interval at steady state.



(Source: Applicant's Population PK Report, RPF105, Figure S53)

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