CLINICAL REVIEW

Application Type	505(b)1 NDA Efficacy Supplement
Application Number(s)	213793 S-009
Priority or Standard	Priority
Submit Date(s)	June 20, 2025
Received Date(s)	June 20, 2025
PDUFA Goal Date	Original: 12/19/2025; Revised (Major Amendment): March 20, 2026
Division/Office	Diabetes, Lipid Disorders, and Obesity (DDLO); Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Reviewer Name(s)	Ginger Winston, MD
Review Completion Date	March 19, 2020
Established/Proper Name	Setmelanotide
(Proposed) Trade Name	IMCIVREE
Applicant	Rhythm Pharmaceuticals, Inc.
Dosage Form(s)	10 mg/ml solution
Applicant Proposed Dosing Regimen(s)	Starting dosage for adult and pediatric patients aged 4 years and older is 0.5 mg once daily for 2 weeks. Maintenance dose for adult and pediatric patients aged 6 years and older is 3 mg subcutaneously once daily. Maintenance dosage for pediatric patients aged 4 to less than 6 years is determined by body weight.
Applicant Proposed Indication(s)/Population(s)	IMCIVREE is a melanocortin 4 (MC4) receptor agonist indicated to reduce excess (b) (4) and maintain weight reduction long term in adults and pediatric patients 4 years and older with acquired hypothalamic obesity.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	To reduce excess body weight and maintain reduction long term in adults and pediatric patients aged 4 years and older with acquired hypothalamic obesity.

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
aHO	acquired hypothalamic obesity
AR	adverse reaction
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRO	contract research organization
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	good clinical practice
HO	Hypothalamic obesity
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
SAE	serious adverse event

SAP	statistical analysis plan
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Setmelanotide (RM-493) is a synthetic, cyclic octapeptide that functions as a melanocortin-4 receptor (MC4R) agonist. Setmelanotide is more potent and has a longer half-life in humans (approximately 11 hours) than the short-lived alpha-melanocyte stimulating hormone (α-MSH) ligand.

Setmelanotide is currently approved in the United States (U.S.) under the trade name IMCIVREE, to reduce excess body weight and maintain weight reduction long term in adult 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).

IMCIVREE is currently approved in adults and pediatric patients 6 years and older at the recommended maintenance dose of 3 mg once daily. Recommended maintenance dose for pediatric patients aged 2 to less than 6 years is determined by body weight. Dose escalation is recommended to minimize gastrointestinal symptoms, and current labeling allows for maintenance dose flexibility based on tolerability.

The current application seeks to gain an indication for IMCIVREE "to reduce excess [redacted] (b) (4) and maintain reduction long term in adults and pediatric patients 4 years and older" with acquired hypothalamic obesity (HO). The proposed starting dosage for adults and pediatric patients aged 4 years and older with acquired HO is 0.5 mg injected subcutaneously (SC) once daily for 2 weeks. Recommended maintenance dosage for adults and pediatric patients aged 6 years and older is 3 mg once daily. Recommended maintenance dose for pediatric patients aged 4 to less than 6 years is determined by body weight.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness (SEE) to support approval of IMCIVREE to reduce in excess body weight and maintain weight reduction long term in adults and pediatric patients 4 years and older with acquired HO. This conclusion is based on results from a single randomized, double-blind, placebo-controlled clinical trial that demonstrated clinically meaningful weight loss in patients with acquired HO. The trial was adequately designed to demonstrate efficacy, and the results were statistically significant. Confirmatory evidence comes from trials that demonstrated the effectiveness of setmelanotide for weight

reduction in the related indications of obesity resulting from POMC, PCSK1, and LEPR deficiency and BBS. The Applicant provided adequate data showing a similar mechanism of action of setmelanotide in acquired HO as the approved indications for obesity due to POMC, PCSK1, and LEPR deficiency and BBS.

In the adequate and well-controlled trial 040, the LS mean difference (95% CI) between the setmelanotide and placebo groups in mean percent BMI change from baseline at approximately Week 52 was -18.40% (-21.94, -14.85). Secondary endpoints, such as the proportion of patients achieving clinically meaningful BMI change of at least 5%, were supportive of the primary result conclusions. Given the rarity of the condition, the trial size (N=142) was appropriate. Given the expected natural history of the condition (early and aggressive weight gain), weight loss would be highly unlikely to occur in the absence of effective intervention.

Confirmatory evidence comes from trials that demonstrated the effectiveness of setmelanotide for weight reduction in the related indications for obesity due to POMC, PCSK1, LEPR deficiency and BBS. The Applicant provided adequate data showing a similar mechanism of action of setmelanotide in acquired HO as for POMC, PCSK1, and LEPR deficiency and BBS, specifically: 1) engaging residual MC4R in the paraventricular nucleus of the hypothalamus, and 2) engaging MC4R expressed in several extrahypothalamic regions of the CNS.

The single randomized, double-blind, placebo-controlled trial with confirmatory evidence from related indications are adequate for SEE. This review serves as the primary clinical review, Cross-Discipline Team Leader (CDTL) review, and the Decisional Memo. It summarizes the major issues related to approvability and labeling of the sNDA. All review disciplines and consultants recommend approval. For additional details regarding methods and results, refer to the individual discipline reviews and consult reviews referenced in this document.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Setmelanotide (brand name IMCIVREE) is a peptide agonist to the human melanocortin-4 receptor (MC4). It is currently approved in the U.S. 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 POMC, PCSK1, or LEPR deficiency, and BBS. The Applicant proposes to expand the indication to include patients with acquired hypothalamic obesity (HO). It is the recommendation of this medical reviewer, based on results of double-blind, placebo-controlled trial RM-493-040 and confirmatory evidence from approved indications, that setmelanotide be approved to reduce excess body weight and maintain weight reduction long term in adult and pediatric patients aged 4 years and older with acquired HO.

Acquired HO is a rare condition caused by structural damage to the hypothalamus most often resulting from tumors of the hypothalamus and/or related treatment. Craniopharyngiomas are the most common tumors associated with the development of acquired HO. Patients with acquired HO experience rapid and sustained weight gain that generally has been unresponsive to lifestyle or medical intervention. There is currently no approved drug treatment for acquired HO.

In a randomized, double-blind, placebo-controlled clinical trial, the LS mean difference (95% CI) between setmelanotide and placebo groups in percent BMI change from baseline to approximately Week 52 was -18.40% (-21.94, -14.85), with a two-sided p-value <0.001. The weight loss observed was clinically meaningful and would not be expected to occur in the absence of effective intervention given the natural history of the acquired HO. Secondary endpoints were supportive of the primary endpoint result. The efficacy of weight reduction with setmelanotide treatment in acquired HO is supported by confirmatory evidence from trials that demonstrated the effectiveness of setmelanotide for weight reduction in mechanistically related indications for obesity due to POMC, PCSK1, LEPR deficiency and BBS.

Overall, setmelanotide was well tolerated with treatment emergent adverse events (TEAEs) similar to the known safety profile for the indications of POMC, PCSK1, LEPR deficiency and BBS. In trial RM-493-040, frequent adverse reactions more common in the setmelanotide group compared to placebo group were hyperpigmentation disorders (58% vs. 10%, respectively), nausea (55% vs. 25%), vomiting (38% vs. 19%), headache (37% vs. 31%), and development of darkening of melanocytic nevus (15% vs. 6%). There was a higher frequency of serious adverse events (SAEs) of acute adrenal insufficiency in the setmelanotide group compared to placebo (5% vs. 0%, respectively). This adverse reaction is monitorable, and to address it in labeling, acute adrenal insufficiency was added to Warnings and Precautions (Section 5). There was a higher frequency in the setmelanotide group compared to placebo of hypernatremia (5% vs. 4%) and hyponatremia (6% vs. 2%). Of note, patients with acquired HO often have concomitant diabetes insipidus and are therefore at increased risk of developing sodium abnormalities. The risk of sodium imbalance is monitorable and is addressed in labeling by addition of sodium imbalance to Warnings and Precautions (Section

5).

In summary, the benefit-risk for setmelanotide once daily for weight reduction and maintenance in adult and pediatric patients ages 4 years and older with acquired HO is favorable. The weight reduction benefit is statistically significant and clinically meaningful, and safety concerns can be adequately addressed through labeling.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acquired hypothalamic obesity (HO) is caused by structural damage to the hypothalamus most often resulting from tumors of the hypothalamus and/or the surgery or radiation therapy to treat the tumors[1] • Acquired HO affects approximately 5,000 to 10,000 patients in the United States[2] • Craniopharyngiomas are the most common tumors associated with the development of acquired HO[1] • Craniopharyngiomas have 2 peak age ranges, childhood (5-9 years) and older adults (55-69 years) [3] • The weight gain in acquired HO is most dramatic in the first 6 to 12 months after the inciting hypothalamic injury and continues for the next 8 to 12 years before plateauing [4,5]	Acquired HO is a serious medical condition caused by structural damage to the hypothalamus (most often due to tumors and/or related surgery or radiation treatment) and is characterized by rapid and sustained weight gain that is generally unresponsive to lifestyle interventions.

[1] Roth CL and McCormack SE. Acquired hypothalamic obesity: A clinical overview and update. Diabetes Obes Metab. 2024;26(Suppl. 2):34-45.
[2] Teng H, Liu Z, Yan O, et al. Nomograms for predicting overall survival among patients with craniopharyngiomas at initial diagnosis: A SEER population-based analysis. Int J Gen Med. 2021;14:3517-27.
[3] Momin AA, Recinos MA, Cioffi G, et al. Descriptive epidemiology of craniopharyngiomas in the United States. Pituitary. 2021 Aug;24(4):517-522.
[4] Müller HL. Management of hypothalamic obesity. Endocrinol Metab Clin North Am. 2020 Sep;49(3):533-52.
[5] Sterkenburg AS, Hoffmann A, Gebhardt U et al. Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood onset craniopharyngioma: newly reported long-term outcomes. Neuro Oncol. 2015 Jul;17(7):1029-38.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Patients with acquired HO experience rapid and sustained weight gain that generally has been unresponsive to lifestyle or medical intervention	
Current Treatment Options	• Currently, there is no approved drug treatment for acquired HO.	There is currently no approved drug treatment option for patients with acquired HO.
Benefit	• In trial RM-493-040 (referred to as trial 040), the LS mean difference (95% CI) between setmelanotide and placebo groups in percent BMI change from baseline to approximately Week 52 was -18.40% (-21.94, -14.85) (two-sided p-value <0.0001). • The primary endpoint of mean percent change in BMI is clinically important because it is associated with improvement in obesity-related comorbidities (i.e., insulin-resistance, hyperlipidemia, hypertension). • Confirmatory evidence comes from mechanistically related, approved indications of obesity due to POMC, PCSK1, LEPR deficiency and BBS in patients ages 2 years and older shows clinically meaningful weight reduction.	The efficacy results from trial 040, along with confirmatory evidence from mechanistically-related approved indications met the evidentiary standard. Results from trial 040 provide strong evidence of the clinically significant weight reduction of setmelanotide in adults and pediatric patients ages 4 years and older with acquired HO. Clinically significant weight reduction is considered ≥5% mean weight loss from baseline versus placebo.
Risk and Risk Management	• In trial 040, the safety profile of setmelanotide was generally consistent with the known safety profile in currently approved indications. • The safety database was of acceptable quality and in general reflected the Division's advice during product development. • The most important safety concerns based on prior experience with setmelanotide were skin hyperpigmentation, injection site reactions,	Overall, setmelanotide was well tolerated in trial 040. The common adverse events were skin hyperpigmentation, gastrointestinal disorders (nausea, vomiting, constipation), headache, new melanocytic nevus formation and darkening of existing nevi. Acute adrenal insufficiency was added to Warnings and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea), headache, melanocytic nevus and spontaneous penile erection. • In trial 040 the most common adverse reactions were as follows: ○ skin hyperpigmentation ○ gastrointestinal disorders (nausea, vomiting, constipation) ○ headache ○ new melanocytic nevus formation and darkening of existing melanocytic nevi • There was an imbalance in SAEs due to adrenal insufficiency, with a higher frequency in setmelanotide group compared to placebo (5% vs 0%, respectively). To address this potential risk "Acute adrenal insufficiency in patients with acquired HO" was added to Warnings and Precautions. • There was a higher frequency of patients with treatment-emergent adverse events (TEAE) of hypernatremia (5%vs. 4%) and hyponatremia (6% vs. 2%). To address this potential risk, "Sodium imbalance in patients with acquired HO and central diabetes insipidus" was added to Warnings and Precautions.	Precautions (Section 5) to address an imbalance in serious adverse events of adrenal insufficiency. Sodium imbalance in patients with acquired HO and central diabetes insipidus was added to Warnings and Precautions (Section 5) to address the higher frequency of patients with TEAEs of hyponatremia and hypernatremia in the setmelanotide group compared to placebo. Overall, risks associated with setmelanotide therapy in patients with acquired HO can be adequately addressed through labeling.

1.4. Patient Experience Data

See Section 6.1.2.2 for discussion of patient reported outcome data pertaining to hunger.

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		Section 6.1.2.2
		☒	Patient reported outcome (PRO)	
		☒	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☒	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		Section 6.1.2.2 and review completed by the Division of Clinical Outcomes Assessment
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Acquired HO is a rare disease with an estimated prevalence of 5,000 to 10,000 people in the U.S. It is caused by structural damage to the hypothalamus most often resulting from tumors of the hypothalamus and pituitary, and/or the surgery or radiation therapy to treat these tumors.[6] Structural damage to the hypothalamus leads to disruption of key nuclei that govern body weight regulation including the arcuate nucleus. The arcuate nucleus contains neuronal populations that express proopiomelanocortin (POMC), a precursor of the hormone α-melanocyte-stimulating hormone (α-MSH) which is associated with inhibition of food intake and stimulation of energy expenditure.[7] The hormone α-MSH activates melanocortin 4 (MC4) receptors expressed on the paraventricular nucleus (PVN) of the hypothalamus. While most of the effects of α-MSH are mediated in the hypothalamus, it also acts extrahypothalamic sites (see Table 33 in the Appendix for a list of hypothalamic and extra-hypothalamic MC4R sites that regular energy hemostasis).

Craniopharyngiomas and associated therapies are the most common causes of acquired HO. In one registry study in the U.S., 86% of patients reported having developed HO as a result of a brain tumor or surgical treatment of a brain tumor, with 72% of tumors being craniopharyngiomas, followed by astrocytomas (7%) and pituitary macroadenomas (7%).[8] There are two peak age ranges for craniopharyngioma diagnosis; one in childhood (5-9 years) and another in older adults (55-69 years).[9] Approximately 30 to 50% of craniopharyngiomas occur in childhood.[10,11] Severe obesity occurs in about 50% of craniopharyngioma survivors. [3, 12]

Acquired HO is characterized by rapid weight gain that is most dramatic within the first year following surgical intervention and continues for 8 to 12 years.[3] Patients develop severe obesity and some patients experience hyperphagia, which is an insatiable hunger or desire to eat that does not subside after consuming food. The severe obesity is associated with increased risk of morbidities, such as cardiovascular disease, type 2

[6] Roth CL and McCormack SE. Acquired hypothalamic obesity: A clinical overview and update. Diabetes Obes Metab. 2024;26(Suppl. 2):34-45.
[7] Vohra MS, Benchoula K, Serpell CJ, Hwa WE. AgRP/NPY and POMC neurons in the arcuate nucleus and their potential role in treatment of obesity, European Journal of Pharmacology (2022) 915. doi.org/10.1016/j.ejphar.2021.174611.
[8] Rose SR, Horne VE, Bingham N, Jenkins T, Black J, Inge T. Hypothalamic obesity: 4 years of the international registry of hypothalamic obesity disorders. Obesity (Silver Spring). 2018;26(11):1727-1732.
[9] Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2014- 2018. Neuro Oncol. 2021 Oct 5;23(12 Suppl 2)
[10] Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. Neuro Oncol. 2012; 14(Suppl 5): v1-v49
[11] Karavitaki N, Cudlip S, Adams CB, Wass JA. Craniopharyngiomas. Endocr Rev. 2006; 27(4): 371-397.
[12] Muller HL, Emser A, Faldum A, et al. Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma. J Clin Endocrinol Metab. 2004; 89(7): 3298-3305.

diabetes mellitus, and non-alcoholic fatty liver disease. Risk factors for severe obesity include large hypothalamic tumors or surgical resections of the hypothalamus affecting several medial and posterior hypothalamic nuclei and satiety signaling pathways.[3,13]

Overall, acquired HO is a serious condition that leads to intractable severe obesity and is associated with obesity-related comorbidities.

2.2. Analysis of Current Treatment Options

There are no approved drug therapies for the treatment of acquired HO. Lifestyle interventions, including dietary modifications, physical activity and behavioral interventions, are the standard of care for weight reduction in patients with acquired HO. However, lifestyle interventions have failed to result in consistently meaningful and sustained reductions in BMI.[3,14] Historically, acquired HO has been refractory to pharmacologic therapy.[15] Various classes of weight reduction drugs have been used off-label for the treatment of HO, including stimulants (e.g., phentermine) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs).[8, 11] With the exception of a phase 3 randomized controlled trial that evaluated the GLP-1 RA exenatide, most trials evaluating treatment for HO are small, due to the rarity of the disease.[11, 16]

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

IND 112595 for the setmelanotide drug development program was submitted on October 12, 2011. Setmelanotide was granted orphan drug designation (ODD) by FDA on April 4, 2016, for treatment of POMC deficiency due to mutations in the POMC gene. FDA also granted ODD status to setmelanotide for the treatment of LEPR deficiency obesity on November 27, 2017, and for the treatment of BBS on September 19, 2019.

On May 1, 2017, FDA granted Breakthrough Therapy Designation (BTD) for setmelanotide for

[13] Bereket A, Kiess W, Lustig RH, Muller HL, Goldstone AP, Weiss R, et al. Hypothalamic obesity in children. Obes Rev (2012) 13(9):780–98.
[14] Roth CL and Zenno A. Treatment of hypothalamic obesity in people with hypothalamic injury: new drugs are on the horizon. Front Endocrinol. 14:1256514.
[15] van Iersel L, Brokke KE, Adan RAH, Bulthuis LCM, van den Akker ELT, van Santen HM. Pathophysiology and individualized treatment of hypothalamic obesity following craniopharyngioma and other suprasellar tumors: a systematic review. Endocr Rev. 2019; 40(1):193-235.
[16] Roth CL, Perez FA, Whitlock KB, Elfers C, Yanovski JA, Shoemaker AH, et al. A phase 3 randomized clinical trial using a once-weekly glucagon-like peptide-1 receptor agonist in adolescents and young adults with hypothalamic obesity. Diabetes Obes Metab (2021) 23(2):363–73.

the treatment of obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway. NDA 213793 (IMCIVREE) was submitted on March 27, 2020, and approved on November 25, 2020, for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1, or LEPR deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or VUS. NDA 213793/Supplement 001 was submitted on September 16, 2021, for the addition of an indication for chronic weight management in adult and pediatric patients 6 years of age and older with BBS. The supplement was approved on June 16, 2022.

NDA 213793/Supplement 007 was submitted on June 26, 2024, to expand the weight reduction indication for patients with obesity due to POMC, PCSK1, LEPR deficiency or BBS to 2 to <6 years of age. The supplement was approved on December 20, 2024.

On September 2, 2022, the Applicant submitted a request for BTD for the HO indication. On October 27, 2022, FDA granted BTD for setmelanotide for treatment of chronic weight management in adult and pediatric patients with HO (defined as obesity due to injury to the hypothalamus).

The Applicant submitted the original protocol for RM-493-040 to IND 112595 on November 2, 2022.

(b) (4)

3.2. Summary of Pre-submission/Submission Regulatory Activity

The following key meetings and correspondence related to this application occurred between the FDA and the Applicant:

- Type C guidance meeting (End-of-phase 2 meeting; October 4, 2022):
    - Data were reviewed from the phase 2 proof-of-concept study for patients with HO (trial RM-493-030) and feedback was provided for the Applicant's plan for a phase 3 randomized, placebo-controlled trial.
        - The Agency recommended limiting enrollment in the phase 3 trial to patients 6 years and older (instead of the proposed 4 years and older) because the majority of cases of HO are due to craniopharyngiomas and associated therapies, which have a bimodal age distribution with one peak in children 5 to 14 years of age. The Applicant provided their rationale for including patients 4 to < 6 years of age and the Agency concluded that the data submitted were sufficient to support the proposed age range. The Agency indicated, however, that age may be a

review issue if very few patients are enrolled in the 4 to <6 year age group.
    - The Applicant agreed to increase trial size from the proposed size of 75 patients to 120 patients (2:1 randomization) to allow for a more thorough assessment of safety.
    - The Applicant agreed to modify the study design to extend the placebo-controlled period from 6 months to 1 year.
    - The Agency recommended that the Applicant conduct qualitative interviews to support the content validity of the Daily Hunger Questionnaire.
- On May 21, 2024, the Applicant submitted a request for Orphan Drug Designation for the treatment of acquired HO.
- On January 31, 2025, the Applicant submitted a pre-sNDA written responses only (WRO) meeting request for the proposed indication. In the WRO letter dated March 26, 2025, the Agency strongly recommended that the Applicant include additional confirmatory evidence (CE) to demonstrate substantial evidence of effectiveness.
- In an Advice/Information request letter dated February 21, 2025, the Agency provided comments regarding the revised statistical analysis plan (SAP) submitted December 18, 2024. In the SAP the Applicant proposed to conduct formal hypothesis testing on the ‘ (b) (4) (initial 120 patients enrolled in trial 040). The Applicant proposed that the success/failure conclusions of trial 040 would be based on results from this (b) (4) . The Applicant also stated that the primary and secondary analysis would be conducted on the modified intent to treat (mITT) population, defined as all randomized subjects exposed to at least 1 dose of study treatment. In the Advice/Information request (dated February 21, 2025) the Agency stated, “your formal hypothesis testing should follow the primary estimand and include the mITT population, not the (b) (4)
- Type D Pre-sNDA guidance meeting (June 2, 2025)
    - The Applicant presented topline data from trial RM-493-040 and discussed their proposal for providing confirmatory evidence (CE) to demonstrate substantial evidence of effectiveness.
        - In pre-meeting written comments, the Agency stated that it would be possible that clinical evidence from related approved indications for setmelanotide could serve as CE if the Applicant provided adequate data showing a similar mechanism of action as in acquired HO. During the type D meeting, the Applicant provided data to support a shared mechanism of action with approved indications (POMC/PCSK1/LEPR deficiency and BBS).
        - The Agency indicated that the imbalance in serious adverse events raised safety concerns and would be a review issue potentially impacting approvability.
        - The Agency advised the Applicant that there were concerns regarding the

interpretability of the hunger assessment, and that if the Applicant proposed to include hunger assessment results in the label, they would need to provide the following:

- Justification that the mechanism of weight reduction in HO is primarily related to reduction in hunger;
- Evidence to support the clinical relevance of the chosen hunger thresholds or within-patient changes in hunger observed in the hunger assessments;
- Evidence to support the validity and reliability of the hunger assessment in the target age groups

- On November 6, 2025, a major amendment review extension letter was sent to the Applicant.

3.3. Foreign Regulatory Actions and Marketing History

Setmelanotide is authorized for marketing in Canada, European Economic Area, Great Britain, and Israel under the trade name IMCIVREE. In the European Economic Area and Great Britain, setmelanotide is indicated for treatment of obesity and the control of hunger associated with genetically confirmed BBS, loss-of-function biallelic POMC, including PCSK1 or biallelic LEPR deficiency in adults and children 2 years of age and older.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI conducted inspections of two domestic clinical investigators (CIs): Drs. Ashley Shoemaker (Site #004) and Susan Phillips (Site #005). See the OSA review in DARRTS dated November 4, 2025. In their review, OSI concluded that based on the overall inspection results of the CIs and the regulatory assessments, the data collected by the CI sites and submitted by the Applicant were verifiable. In addition, that OSI report stated that the clinical data submitted by the Applicant appeared acceptable in support of the respective indication.

4.2. Product Quality

There are no proposed changes to the drug product in this supplement. This application is recommended for approval from the chemistry, manufacturing, and controls (CMC) review perspective. See review from the Office of Pharmaceutical Quality dated October 15, 2025.

4.3. Clinical Microbiology

No new microbiology information was provided with this supplement.

4.4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted or required to support this application.

4.5. Clinical Pharmacology

The Office of Clinical Pharmacology reviewed this supplement (see full review in DAARTS dated March 13, 2026) and determined that the submitted clinical pharmacology data supported approval of setmelanotide for the indication of weight reduction and maintenance in adult patients and pediatric patients ages 4 years and older with aHO. The Applicant conducted phase 3 trial 040 in patients with aHO to support dosing in the proposed population along with a population pharmacokinetic (PK) approach for predicting daily exposures. The following issues pertain to labeling:

1. The pharmacology review team determined that IMCIVREE is not recommended for use in acquired HO patients with end stage renal disease (ESRD) or severe renal impairment because there is a lack of data in this sub-population with HO. No dose adjustment is required for patients with mild or moderate renal impairment.

2. The Applicant's recommended dosage in the label differs from the dosage in trial 040 as follows:
   - Adults and pediatric patients ages 6 years and older: Dosage titration to maintenance dose was every one week in the trial 040 and every 2 weeks in the Applicant's proposed label. Given concerns for gastrointestinal (GI) tolerability the Applicant's proposed label dosage is acceptable.

   - Pediatric patients aged 4 to <6 years: In the Applicant's proposed labeling the weight-based maximum doses had lower maximum doses, slower titration, and different body weight cutoffs than used in trial 040. There were 2 patients in trial 040 in the age 4 to <6 year age group. Both patients were age 4 (PTIDs (b) (6) and (b) (6)). **PTID** (b) (6) had a baseline weight of 57.8 kg and achieved a max dose of 3 mg on study day 304 however the patient had dosages held related to TEAEs and required de-escalation of doses so to the final maintenance dosage was 2.5 mg once daily. **PTID** (b) (6) was 33.8 kg at baseline and achieved a max dose of 2 mg on Day 22, however, the patient required dose de-escalations on 2 occasions because of the family's concern for weight loss.

   In response to an IR dated August 4, 2025, the Applicant provided the following reasons for the lower maximum doses, slower titration, and different body weight cutoffs than used in trial 040 for patients ages 4 to <6 years:

"1.The IMCIVREE PI is already complex with several different dosing regimens based on age or age and weight. The complexity will increase with a 3rd indication and a 4th clinical trial section. Therefore, given that the dosing regimen in the USPI for the younger patients are 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). However, note that the dosing in patients with HO aged 6 years and older is different than in the other indications as this patient population has a higher background rate of nausea and vomiting and slower titration was better tolerated in clinical studies."

The pharmacology team's review of the Applicant's population PK analysis confirmed that the simulations are acceptable to support the newly proposed dosage and administration.

Reviewer comment: This reviewer considers the Applicant's responses in addition to the dosage experiences of the 2 patients in the 4 to <6 age range in trial 040 adequate support for the Applicant's proposed label dosages in patients aged 4 to <6 years.

4.6. Devices and Companion Diagnostic Issues

No companion device or diagnostic is included in this application.

4.7. Consumer Study Reviews

See review from the Division of Medication Error, Prevention Analysis (DMEPA) in DAARTs dated September 10, 2025. DMEPA reviewed the prescribing information (PI), patients package insert (PPI), and Instructions for Use (IFU) and did not identify areas of vulnerability that may lead to medication errors.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 1 shows a brief description of trial 040, the primary focus of the current review. Clinical trial data from approved indications for chronic weight management in POMC, PCSK1, LEPR deficiency and BBS, are used as confirmatory evidence in this application. Table 2 provides a description of the following relevant trials used as confirmatory evidence: RM-493-012, -015, -022, -023, and -033. Trials RM-493-012 and -015 were previously reviewed in the original NDA submission 213793 for the indication of chronic weight management in POMC, PCSK1, and LEPR deficiency obesity for ages 6 years and older (see review in DAARTs dated November 24, 2020). Trials RM-493-014 and -023 were previously reviewed in sNDA 213793/001 for the indication of chronic weight management in patients with BBS ages 6 years and older (see review in DAARTs dated June 15, 2022). Trial 033 was previously reviewed in sNDA 213793/007 for the expanded age of 2 to <6 years for the indications of weight reduction in POMC, PCSK1, and LEPR deficiency and BBS (see review in DAARTs dated December 19, 2024).

Table 1. List of Clinical Trials Relevant to NDA 213793 Supplement 009

Trial	NCT number	Endpoints	Trial Design	Drug regimen	N	Treatment Duration	Study Population	No. Centers and Countries
RM-493-040	NCT05774756	*Primary*: Mean % change in BMI from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo *Key Secondary:* • Proportion of adult patients with ≥5% reduction in BMI, or pediatric patients with BMI z-score reduction of ≥0.2 points from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo therapeutic regimen of setmelanotide compared to	Double-blind, randomized, placebo-controlled	Setmelanotide or placebo equivalent initiated at 0.5 mg SQ once daily and dose escalated to 1.0 mg once daily within 1 week. Dose then escalated each week by 0.5 or 1.0 mg to achieve the individual patient's therapeutic regimen. Dosage was weight-based for patients < 6 years of age.	N=142 Patients < 18 years of age: n= 76	52 Weeks	Patients age ≥4 years of age with acquired HO defined as: - diagnosis of craniopharyngioma or other brain lesion affecting the hypothalamic region and has undergone surgery, or chemotherapy or radiation therapy involving the hypothalamus at least 6 months before Screening, or - documented injury to the hypothalamus at least 6 months before screening for which surgery/radiation is not indicated	28 centers enrolled patients in the U.S., Canada, Germany, Japan, Netherlands, U.K.

		placebo • Mean change in weekly average of the daily most hunger score in patients ≥12 years from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo						

Table 2. Clinical Trials Used as Confirmatory Evidence

Trial*	Objective(s) of the Trial	Trial Design	Dosing	N	Treatment Duration	Disease/Condition
RM-493-033	*Primary:* • Mean percent change in BMI from baseline to Week 52 • Proportion of patients with decrease in BMI Z-score of ≥ 0.2 from baseline to 52 weeks. *Key Secondary*: • Change from baseline to 52 weeks in: - Mean absolute change in BMI-Z-score - Mean change in percent of the 95th percentile of BMI	Open label (patients ages 2 to <6 years old)	Weight-based	12	52 weeks	POMC deficiency LEPR deficiency BBS

	- Mean change in vital signs and laboratory evaluations - Mean change in bone age • Frequency and severity of AEs					
RM-493-012	*Primary*: • To demonstrate statistically significant and clinically meaningful effects of setmelanotide on percent body weight change in patients with POMC deficiency obesity at the end of 1 year of treatment *Key Secondary*: To assess the effect of setmelanotide, over one year, on: • Safety and tolerability of setmelanotide • Hunger for patients ≥ 12 years • Percent change in body fat mass	Open-label with 8-week double blind placebo-controlled withdrawal period	Up to 12-week dose titration to therapeutic dose level (Max 3.0 mg) followed by 10 weeks at therapeutic dose followed by 8-week double blind placebo withdrawal and 32 weeks continued treatment at therapeutic dose	14	52 weeks	POMC deficiency LEPR deficiency BBS
RM-493-015	*Primary:* • To demonstrate statistically significant and clinically meaningful effects of setmelanotide on percent body weight change in patients with LEPR deficiency obesity at the end of 1 year of treatment	Open-label weight 8-week double blind placebo-controlled withdrawal period	Up to 12-week dose titration to therapeutic dose level (max 3 mg) followed by	13	52 weeks	LEPR deficiency

	Key Secondary: To assess the effect of setmelanotide, over one year, on: • Safety and tolerability of setmelanotide • Hunger for patients ≥ 12 years • Percent change in body fat mass		10 weeks at therapeutic dose followed by 8-week double blind placebo withdrawal and 32 weeks continued treatment at therapeutic dose			
RM-493-023	*Primary:* • Assess the effect of setmelanotide on the proportion of patients ≥ 12 years who achieved a clinically meaningful reduction from baseline in body weight *Key Secondary:* • Assess the effect of setmelanotide on mean percent change from baseline in body weight after 52 weeks • Assess the effect of setmelanotide on the mean percent change from baseline in the weekly average of the daily hunger score	Randomized, double-blind, placebo-controlled followed by an open-label treatment period	Setmelanotide or placebo QD via SC injection for the first 14 weeks. Starting dose 2 mg with increase to 3 mg for patients ≥16 years Starting dose 1 mg with increase to 2 mg for patients <16 years of	44 with BBS (8 with Alstrom)	52 weeks	BBS and Alstrom syndrome

			age). After the 14-week double-blind treatment period, all patients received open label Setmelanotide QD via SC injection for 38 weeks. SC injection			
RM-493-022	*Primary:* To characterize safety and tolerability of setmelanotide in patients who have completed a previous trial on treatment with setmelanotide for obesity associated with genetic defects upstream of the MC4R in the leptin-melanocortin pathway and with obesity related to other abnormalities in the MC4R pathway *Key Exploratory:* To assess the effect of setmelanotide, long-term, on: • Maintained or continued improvement in weight-related parameters	Open label extension trial	Patients start the trial on the same dose of setmelanotide they were taking at completion of the index trial. Dose changes considered for safety/tolerability reasons or for efficacy.	N/A	Up to 7 years	

			Ages ≥ 18 years: Dose can be titrated up to: 4 mg for weight >50 kg to < 60 kg 5 mg SC daily in patients with body weight > 60 kg			

*Trials RM-493-012 and -015 were reviewed in the original NDA 213793 submission.
Trial RM-493-033 was reviewed in the supplemental NDA 213793/S007 submission.
Trial RM-493-023 were reviewed in the supplemental NDA 213793/S001 submission.

5.2. Review Strategy

This review focuses on trial 040, a phase 3 randomized, double-blind, placebo-controlled trial that investigated setmelanotide for treatment of acquired HO in pediatric and adult patients ages 4 years and older. The FDA statistical team conducted an independent review of the efficacy results of trial 040 (see review in DAARTs). The safety results were verified by this clinical reviewer with assistance from the FDA Office of Computational Services (OCS) as notated in specific tables. Of note, the Applicant's analyses in the original submission (dated June 20, 2025) were insufficient to evaluate the efficacy results because they included only the first 120 patients enrolled in the trial (see further discussion in Section 6.1.2; subsection "Data Quality and Integrity"). On November 6, 2025, a major amendment review extension letter was sent to the Applicant. On March 9, 2026, the Applicant submitted complete efficacy and safety results for the full patient population in trial 040.

Confirmatory Evidence
Confirmatory evidence comes from trials that demonstrated the effectiveness of setmelanotide for weight reduction in the related indications of obesity due to POMC, PCSK1, LEPR deficiency and BBS. The Applicant provided adequate data showing a similar mechanism of action of setmelanotide in acquired HO as approved indications of weight reduction and maintenance in obesity due to POMC, PCSK1, and LEPR deficiency and BBS, specifically: 1) low or absent α-MSH production, 2) engaging residual MC4Rs in the paraventricular nucleus of the hypothalamus, and 2) engaging MC4Rs expressed in several extrahypothalamic regions of the CNS.

Acquired HO arises from anatomical damage to the arcuate nucleus of the hypothalamus where POMC neurons produce α-MSH, and where hypothalamic MC4 receptors reside. Study data show that in HO, the anatomical damage to the arcuate nucleus of the hypothalamus leads to a state of low α-MSH.[17,18] Low or absent α-MSH is also a feature of approved indications for POMC deficiency, LEPR deficiency, PCSK1 deficiency, and BBS.

Setmelanotide's efficacy is dependent on MC4R activation, as demonstrated by the complete loss of efficacy in MC4R knockout mice. The Applicant provides literature supporting the expression of MC4Rs in hypothalamic and extra-hypothalamic regions of the central nervous system (CNS) that impact food intake and energy expenditure. See Table 33 in the Appendix for a list of hypothalamic and extra-hypothalamic MC4Rs that regulate energy homeostasis.

[17] Roth CL, Enriori PJ, Gebhardt U, et al. Changes of peripheral alpha-melanocyte-stimulating hormone in childhood obesity. Metabolism. 2010;59:186-94.

[18] Roth CL, Eslamy H, Werny D, Elfers C, Shaffer ML, Pihoker C, Ojemann J, Dobyns WB. Semiquantitative analysis of hypothalamic damage on MRI predicts risk for hypothalamic obesity. Obesity (Silver Spring). 2015 Jun;23(6):1226-33. doi: 10.1002/oby.21067. Epub 2015 Apr 17. PMID: 25884561; PMCID: PMC5029599.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Trial RM-493-040

6.1.1. Study Design

Overview and Objective

Trial 040 is the adequate and well-controlled trial to confirm the efficacy and safety of setmelanotide in pediatric and adult patients ≥4 years of age with acquired HO.

Primary Objective: To evaluate the efficacy of setmelanotide on change in BMI.

Key Secondary Objectives:

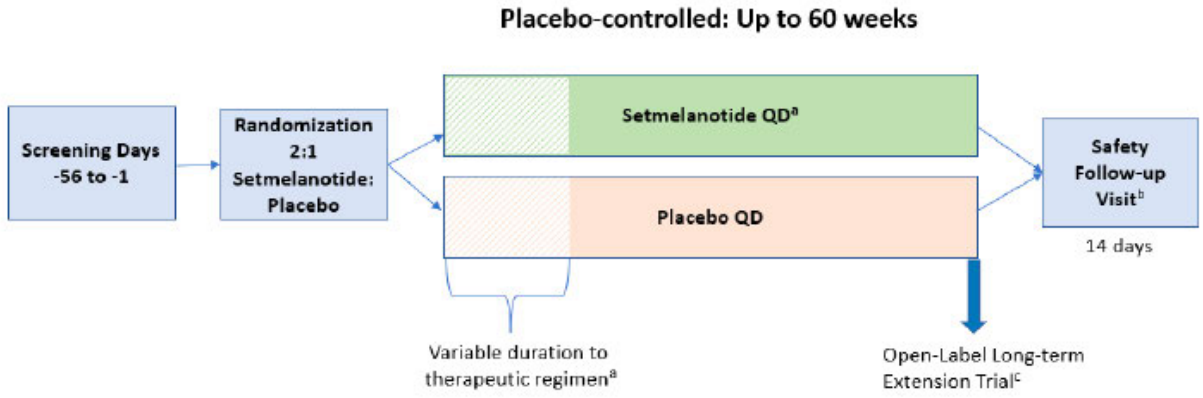
- To evaluate the efficacy of setmelanotide on proportion of patients with ≥5% reduction in BMI or ≥0.2-point reduction in BMI z-score
- To evaluate changes in hunger in response to setmelanotide

Trial Design

Trial 040 was a phase 3, randomized, double-blind, multicenter, placebo-controlled trial that investigated treatment of acquired HO with setmelanotide compared to placebo. The trial consisted of a screening period of up to 8 weeks, a treatment period of up to 60 weeks, and a safety follow-up visit approximately 2 weeks after the end-of-treatment for a total trial duration of up to 70 weeks. During the treatment period, patients were evaluated every 4 weeks via either in-clinical visits or at-home telehealth visits. The end of treatment (EOT) visit occurred after 52 weeks on a therapeutic regimen. At the EOT visit, patients who completed 52 weeks on a therapeutic regimen and completed assessments through the EOT visit could be eligible to enter an open-label extension (LTE) study or attend Bridging visits with open-label setmelanotide if the LTE was not yet available. Of note, the safety follow-up visit was not required for patients who completed the treatment period and either enrolled in the LTE, transitioned to another qualified trial managed by the Applicant, or transitioned to a commercially available MC4R agonist regimen from the Applicant.

All patients who discontinued treatment prematurely were to attend an early termination of treatment (ETT) visit as soon as possible after the last dose of study treatment. Patients who discontinued treatment but remained enrolled in the trial were to continue to complete all assessments as “retained dropouts”.

Figure 1. Study Design Schematic, Trial 040



Source: Applicant CSR for trial RM-493-040, Figure 1.

Reviewer Comment: Trial 040 was initially planned to enroll approximately 120 patients (at least 12 from sites in Japan) in a 2:1 randomization. The trial enrolled an initial 120 non-Japanese patients from 4/26/2023 to 2/29/2024 (described by the Applicant as the 'pivotal cohort'). Sites in Japan were added after the trial began and the enrollment period was extended to allow for 12 patients to be enrolled from Japan. The Japanese sites started enrollment in 7/11/2024 and enrolled 12 patients. As a result of the extended enrollment period, the Applicant stated in response to an information request that an additional 11 non-Japanese patients enrolled from 1/30/2024 to 2/19/2024 (total N=143).

Treatment Assignment: Patients were randomized in a 2:1 ratio (setmelanotide:placebo), stratified by age group (<12 years old, ≥12 and <18 years old, ≥18 years old) and subpopulation (Japanese vs non-Japanese), to receive either setmelanotide or placebo.

Trial Locations: There were 31 study sites, and 28 sites enrolled patients. Sites were in the U.S., Germany, United Kingdom, Canada, Japan, and Netherlands.

Reviewer comment: It is this reviewer's opinion that trial locations outside of the U.S. do not raise issues with respect to the applicability of results to the U.S. population. Of note, eligibility criteria were the same for trials conducted in Japan and non-Japanese sites.

Dose Selection: The doses of setmelanotide investigated in trial 040 were based on effective doses identified in prior clinical trials and the pharmacokinetics (PK) results from previous clinical trials. The dose levels are age- and weight-based to ensure exposure was similar to that observed for adult dosages of 2 mg to 3 mg daily.

Study treatments: All patients initiated study treatment (setmelanotide or placebo) at a dose of 0.5 mg QD and dose escalated to 1.0 mg QD within 1 week. Doses were escalated as appropriate based on the patient's age and weight at enrollment (Table 3) to achieve the individual patient's therapeutic regimen. Each weekly dose escalation could be extended over 2

weeks as needed based on tolerability.

Table 3. Setmelanotide Dosing in Trial 040

Starting Dose			Dose Escalation Based on Tolerability				
			Escalation Steps				Maximum Dose
Age (years)	Weight (kg)	Dose	Dose (+1 week)	Dose (+1 week)	Dose (+1 week)	Dose (+1 week)	
<6	<20	0.5 mg	1.0mg	1.5 mg (max)			1.5 mg
<6	20 to <25	0.5 mg	1.0 mg	1.5 mg	2.0 mg (max)		2.0 mg
<6	25 to <30	0.5 mg	1.0 mg	1.5 mg	2.0 mg	2.5 mg (max)	2.5 mg
<6	≥30	0.5 mg	1.0 mg	2.0 mg	3.0 mg (max)		3.0 mg
≥6	≥30	0.5 mg	1.0 mg	2.0 mg	3.0 mg (max)		3.0 mg

Source: Applicant CSR for Trial RM493-040, Table 2

Dose modification, dose discontinuation: If a patient's weight decreased to below 15 kg during the trial, the Investigator and Sponsor were to discuss the patient's status and determine if the patient should continue the current dose, decrease the dose, or discontinue treatment with setmelanotide temporarily or permanently. A dose reduction to 0.25 mg QD could be considered in such cases or in cases of safety or tolerability concerns.

Administrative Structure: Trial 040 was monitored by an independent Data Safety Monitoring Board (DSMB) that operated under a DSMB charter and met periodically to review the cumulative safety data from the trial and make recommendations to continue to modify the trial if needed.

Procedures and Schedules: See Appendix for a full schedule of events

Concurrent medications: All concomitant medications were to be kept at a stable dose throughout the trial unless dose change was necessary due to a change in the patient's condition. During the trial, any required increase in hormonal replacement therapy >25% was to be discussed with the Sponsor. Medications considered necessary for the patient's safety and wellbeing could be given during the trial at the discretion of the treating physician after discussion with the Medical Monitor. As per the eligibility criteria, medications approved for the weight reduction were permitted if the patient had <2% weight loss in the previous 3 months, the doses were stable for at least 3 months prior to randomization, and the patient intended to continue the same dose throughout the trial.

Treatment compliance: Treatment adherence was monitored throughout the trial via e-diary.

Subject completion, discontinuation, or withdrawal: Patients who either discontinued

treatment or withdrew from the trial before completing the trial attended an Early Termination of Treatment (ETT) Visit as soon as possible after the last dose of trial treatment. Patients who prematurely discontinue treatment may have also completed the Safety Follow-up Visit (SFV), if applicable. Patients who prematurely discontinued study drug treatment were requested to complete all scheduled study visits for assessments following completion of the ETT.

Inclusion Criteria:

- Patient has documented evidence of acquired HO defined as:
  − Diagnosis of craniopharyngioma or other brain lesion affecting the hypothalamic region and has undergone surgery, or chemotherapy, or radiation therapy involving the hypothalamus at least 6 months before Screening, OR
  − Documented injury to the hypothalamus at least 6 months before Screening for which surgery/radiation is not indicated.
- Aged 4 years and older at time of enrollment
- Documented weight gain associated with the hypothalamic injury either before therapy or following therapy (surgery and/or following chemotherapy or radiotherapy), and a body mass index (BMI) of ≥30 kg/m2 for patients ≥18 years of age, or BMI ≥95th percentile for age and sex for patients 4 to <18 years of age based on the US Centers for Disease Control and Prevention criteria.
- Patients must meet the contraception requirements unless otherwise indicated.
- Ability to communicate well with the Investigator, understand and comply with the requirements of the trial, and understand and sign the written informed consent and/or assent for patients aged <18 years, a parent/legal guardian that can sign.
- If receiving hormone replacement therapy (i.e., thyroid hormones, glucocorticoids, growth hormone or other medications known to affect metabolism or weight/body composition), the dose of such therapy has remained stable for at least 2 months prior to Screening.
  Note:
  - Changes in dose of ≤25% may be permissible, with the Sponsor's approval. If results of free thyroxine (FT4) warrant changes in therapy >50% or the addition of new medication the patient is screen failed and can be reassessed after 2 months.
  - This does not apply to patients experiencing adrenal crisis.

Key Exclusion Criteria:

- Diagnosis of Prader-Willi syndrome or Rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, neuroendocrine tumor syndrome (ROHHADNET).
- Weight loss >2% in the previous 3 months for patients aged ≥18 years or >2% reduction in BMI for patients aged 4 to <18 years.
  - NOTE: Dietary and/or exercise regimens, with or without the use of medications, supplements or herbal treatments associated with weight loss (e.g., orlistat,

lorcaserin, phentermine, topiramate, naltrexone, bupropion, glucagon-like peptide-1 [GLP-1] receptor agonists, etc.) are allowed if:

- the regimen and/or dose has been stable for at least 3 months prior to randomization
- the patient has not experienced weight loss >2% (for patients ≥18 years) or >2% BMI (for patients aged 4 to <18 years) during the previous 3 months, and
- the patient intends to keep the regimen and/or dose stable throughout the course of the trial.

- Bariatric surgery or procedure (e.g., gastric bypass/band/sleeve, duodenal switch, gastric balloon, intestinal barrier, etc.) within the last 2 years. All patients with a history of bariatric surgery or procedures must be discussed with and receive approval from the Sponsor prior to enrollment.
- Diagnosis of severe psychiatric disorders (e.g., schizophrenia, bipolar disorder, personality disorder), or Major Depressive Disorder (MDD) within the previous 2 years, or Screening Patient Health Questionnaire (PHQ)-9/PHQ-A score ≥15, or any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS), or a Children's Depression Inventory-2 (CDI-2) T-score ≥70 during Screening, or lifetime history of suicide attempts, or any suicidal behavior in the last month.
- Glycated hemoglobin (HbA1c) >11.0% at Screening.
- Current, clinically significant pulmonary, cardiac, metabolic, or oncologic disease considered severe enough to interfere with the trial and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor or contract research organization (CRO) monitor to determine eligibility.
- End stage renal disease (GFR <15 mL min/1.73 m2) in any age or glomerular filtration rate (GFR) <30 mL/min/1.73 m2 during Screening in patients <12 years of age (GFR calculated using the Bedside Schwartz Formula for patients <18 years of age).
- Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a comprehensive skin evaluation performed by the Investigator during Screening. Any concerning lesions identified during Screening will be biopsied and results known to be benign prior to enrollment. If the pre-treatment biopsy results are of significant concern, the patient is not eligible for trial participation.
- History or close family history (parents or siblings) of skin cancer or melanoma (not including noninvasive, infiltrative basal or squamous cell lesion), or patient history of ocular-cutaneous albinism.
- Patients with obesity attributable to other genetic or syndromic conditions (e.g., PPL [POMC, PCSK1, LEPR, collectively], BBS) prior to the hypothalamic injury.
- Cognitive impairment that, in the Investigator's opinion, precludes participation in the trial and completion of trial procedures or questionnaires.

Reviewer Comments: During a teleconference with the Sponsor on October 4, 2022, the

Division raised concerns regarding the rationale for the lower age limit of 4 years in trial 040. The Division noted that most cases of HO, excluding genetic syndromes of obesity, are due to craniopharyngiomas and associated therapies, which have a bimodal age distribution with one peak in children between 5 and 14 years of age and a second peak in older adults between 65 and 74 years or 50 and 74 years of age (depending on the data source). The Division recommended limiting enrollment to patients 6 years and older. In response, the Sponsor indicated that while uncommon, craniopharyngiomas with associated hypothalamic obesity can develop in patients <6 years of age and that earlier intervention for these patients is beneficial clinically. The Division agreed in general with the rationale, however communicated to the Sponsor that inclusion of patients 4 to 6 years of age may be a review issue if there were not an adequate number of patients enrolled in this age group.

In an information request dated September 12, 2025, the Division asked the Applicant to clarify how investigators ensured that obesity occurred secondary to hypothalamic injury in trial 040 rather than being a pre-existing condition. The Applicant provided the following response, which this reviewer considers acceptable:

"Patient historical weight and height data both pre- and post-hypothalamic injury or tumor growth were systematically reviewed by the contract research organization (CRO) medical monitor at screening to confirm weight gain that was temporally associated with hypothalamic injury. In most cases there were clear growth charts showing normal growth (height and weight) progression for participants, until the point of hypothalamic injury. In the rare instances where historical weight records were unavailable, the principal investigator's clinical judgment was utilized to adjudicate the diagnosis of hypothalamic obesity. During screening, the medical monitor evaluated recorded weights and issued queries when temporal association with surgery or hypothalamic injury was unclear. Subsequently, the clinical monitor conducted source data verification during site visits, crosschecking entered data with source documentation to ensure accuracy, consistency, and compliance with data quality standards."

Study Endpoints

Primary Endpoint:

- Mean percent change in BMI from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

Key Secondary Endpoints:

- The proportion of patients with ≥5% reduction in BMI in adult patients (≥18 years of age), or BMI z-score reduction of ≥0.2 points in pediatric patients (<18 years of age) from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
- The proportion of all patients with ≥5% reduction in BMI from baseline after

approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

- Mean change in the weekly average of the daily most hunger score in patients ≥12 years old from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

Pertinent Other Secondary Endpoints:

- Mean BMI z-score and BMI percentile reduction in patients <18 years of age from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
- Mean change in the weekly average of the Symptoms of Hyperphagia composite score from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
- Change in waist circumference from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
- The difference in change in cardiometabolic parameters including blood pressure (BP), lipid profile, glycated hemoglobin (HbA1c), liver function and C-reactive protein from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
- Mean change in physical functioning score and total score for the Impact of Weight on Quality of Life-Lite (IWQOL) (IWQOL-Lite-CT in patients ≥18 years and IWQOL-Kids in patients 11 to <18 years), from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

Pertinent Exploratory Endpoints:

- Mean change in Impacts of Hyperphagia composite score from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
- Mean change from Baseline in total score for EuroQol-Five Dimension (EQ-5D-5L) in caregivers of patients after 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

Reviewer comment: The Applicant initially proposed that trial 040 be a 1-year trial consisting of a 6-month, placebo-controlled period followed by a 6-month, single-blind period. The Division advised the Applicant that a 1-year, randomized, placebo-controlled trial was needed to meet the statutory standard for substantial evidence of effectiveness and that it was feasible to conduct such a trial in the HO population. The Applicant revised the study design to align with the Division's request.

At the end of phase 2 meeting, the Applicant was informed that the reliability of the hunger parameter tools would be an issue of review. The Agency advised the Applicant to ensure the adequacy of the patient reported outcome (PRO) tool when collecting hunger data for all

evaluated age range.

Statistical Analysis Plan

See the statistical analysis review (in DARRTS dated February 19, 2026) for a detailed review of statistical analysis procedures. Discussed below are issues with the statistical analysis plan (SAP) that have clinical relevance.

Primary estimand framework: In the primary estimand framework described in the SAP, the primary efficacy analysis was to be executed using the modified intention-to-treat (mITT) analysis set which was defined as all randomized patients receiving at least one dose of study drug. However, the formal hypothesis testing indicated that the success/failure conclusion of the trial would be based on the (b) (4)) for the first planned analysis. In Advice/Information Request communication dated April 1, 2025, the Agency informed the Applicant that the formal hypothesis testing should follow the primary estimand and include the mITT population (N=142), not the (b) (4)).

Primary efficacy timepoint: In the SAP version 4.0, the Applicant stated that to identify the primary timepoint, which is the timepoint after approximately 52 weeks of therapeutic drug treatment, the following steps were used:

- The number of days from therapeutic dose start date for all on-site visits excluding bridging visits were calculated
- The non-missing, on-site visit occurring closest to Day 365 within a window of 305 to 425 days from therapeutic dose start date was selected
- If multiple results were equidistant from Day 365 (from the therapeutic dose start date), the latest of these equidistant results was selected
- If no results had been reported within Days 305 to 425 from therapeutic dose start date, then the primary timepoint was considered missing.

Reviewer Comment: In an IR (dated October 17, 2025), the Agency informed the Applicant that their defined window of (b) (4) to 425 days was too long and contradicted the primary efficacy analysis of mean percent change in BMI from baseline after approximately 52 weeks. The Agency informed the Applicant that it would be acceptable to define a window of 358 to 425 days. The Agency requested that the Applicant perform additional analyses using a time window of day 358 to day 425, and that data points outside of this time window should be marked as missing and primary analysis use washout imputation for the primary endpoint and key secondary endpoints. The Applicant provided revised analyses using the primary timepoint window of day 358 to day 425.

Handling of dropouts or missing data – Missing data were imputed for height and body weight. As height was only measured at Screening for patients ≥21 years, BMI was calculated using the last available height measurement prior to weight collection (LOCF). For weight, a retrieved

dropout (RD) approach was planned. However, due to insufficient RD to provide a reliable multiple imputation model, a wash-out imputation method was utilized. For wash-out imputation, placebo patients were first imputed assuming missing-at-random (MAR) regressing on baseline weight, Visit 2 weight, Visit 4 weight, Visit 7 weight, Visit 9 weight, Visit 11 weight, and primary timepoint weight. This accounted for planned on-site visits as well as a combined primary timepoint. Once the placebo patients were imputed under MAR as indicated above, the observed placebo patients were combined with the setmelanotide patients needing imputation of the primary timepoint. The setmelanotide patients were then imputed assuming missing-not-at-random (MNAR) using placebo-based imputation (jump to reference method) regressing only on baseline value and primary timepoint value.

Protocol Amendments

The original protocol (submitted November 2, 2022) was amended 6 times. A summary of substantive changes to the protocol is provided in this section.

Amendment 1/Version 2 (December 7, 2022)

- No major revisions.

Amendment 2/Version 3 (March 9, 2023)

- Added the proportion of all patients with ≥5% reduction in BMI as a key secondary endpoint
- Elevated waist circumference and cardiometabolic endpoints to secondary endpoints
- Revised exclusion criterion #7 to permit adult and pediatric patients ≥12 years with glomerular filtration rate (GFR) <30 mL/min/1.73 m^2 to be enrolled

Amendment 3/Version 4 (August 2023)

- Added Japan to global study and specified number of Japanese patients

Amendment 4/Version 5 (February 8, 2024)

- Permitted Bridging Visits following EOT to permit eligible patients to continue open label setmelanotide until they transition from parent study; included assessments and clarity on dosing during Bridging Visits.
- Included exclusion criterion of hypersensitivity to setmelanotide or any excipients in the investigational product to ensure additional patient safety.
- Included dosing for patients who were both <6 years of age and >30 kg.

Amendment 5/Version 5.1 (September 2024) – US only protocol

- Clarified that the results of the Impacts of Hyperphagia and Symptoms of Hyperphagia questionnaires would be analyzed using a composite score; revised endpoint measurement from total score to composite score; removed age restriction on the caregiver version of the questionnaire.
- Clarified that the EOT occurs after 52 weeks on a therapeutic regimen

Amendment 6/Version 6 (December 19, 2024) – Global protocol

- Same revisions as Version 5.1 but for the Global protocol
- Specified that exclusion criterion #2 (Weight loss >2% in the previous 3 months for

patients aged ≥18 years or >2% reduction in BMI for patients aged 4 to <18 years) is not applicable at the time of inclusion/exclusion review for the LTE/Bridging eligibility.

Reviewer comment: The protocol amendments did not impact confidence in the adequacy of trial design, conduct, or results.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attested that trial 040 was conducted in accordance with the applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. The Applicant attested that investigators were responsible for providing oversight of the conduct of the trial at the site and adherence to requirements of 12 Code of Federal Regulations (CFR). The Applicant also attested that an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) reviewed and approved the protocol, informed consent form (ICF), investigator brochure, and other relevant documents (e.g., advertisements) prior to trial initiation. Amendments to the protocol required IRB/IEC approval before implementation.

Financial Disclosure

The Applicant reported no financial interests with clinical investigators in trial 040. Refer to Appendix for financial disclosure overview.

Patient Disposition

There were 161 patients screened, 143 randomized (setmelanotide, n=95; placebo, n=48), and 142 treated (setmelanotide, n=94 and placebo, n=48). One patient decided not to participate after randomization but prior to dosing. Of note, the trial enrolled an initial 120 non-Japanese patients from April 26, 2023, to February 29, 2024. Sites in Japan were added after the trial began and the enrollment period was extended to allow for 12 patients to be enrolled from Japan. The Japanese sites started enrollment on July 11, 2024, and enrolled 12 subjects. As a result of the extended enrollment period, an additional 11 non-Japanese patients were enrolled from 1/30/2024 to 2/19/2024 bringing the total enrollment to N=143. The Applicant's initial application included complete efficacy and safety data on the initial 120 non-Japanese patients. As part of a major amendment, the Applicant was requested to provide complete efficacy and safety data on the total study population (N=142).

The percentages of patients who completed treatment were similar in the setmelanotide and placebo groups (89.4% and 87.5%, respectively) (Table 4), as were the percentages who discontinued treatment because of TEAEs (5.3% vs. 6.3%, respectively). Table 5 shows TEAEs by SOC and PT leading to treatment discontinuation for the safety population (excludes the 1 patient who was randomized but did not start study drug). A higher percentage of patients in

the setmelanotide group compared to placebo had treatment discontinuations in the following notable SOCs: “Gastrointestinal disorders” (2.1% vs. 0%, respectively), and “Skin and subcutaneous tissue disorders” (2.1% vs. 0%, respectively). There was one patient death during the 52-week treatment period in the setmelanotide group (see Section 8.4.1 for description of this case).

Table 4. Patient Disposition, Randomized Population, Trial 040

	Setmelanotide (N=95) n(%)	**Placebo (N=48) n(%)**
Patients randomized	95 (100)	48 (100)
Patients treated	94 (94)	48 (100)
Safety analysis set	94 (100)	48 (100)
Study status		
Completed treatment	84 (89.4)	42 (87.5)
Discontinued treatment	10 (10.6)	6 (12.5)
Completed study	84 (89.4)	44 (91.7)
Primary reason for treatment discontinuation		
Adverse event	5 (5.3)	3 (6.3)
Withdrawal by patient	5 (5.3)	2 (4.2)
Withdrawal by parent/guardian	0	1 (2.1)
Primary reason for study discontinuation		
Death	1 (1.1)	0
Adverse event	3 (3.2)	2 (4.2)
Withdrawal by patient	4 (4.3)	1 (2.1)
Withdrawal by parent/guardian	1 (1.1)	1 (2.1)
Physician decision	1 (1.1)	0 (0.0)
Had at least 1 Bridging Visit	82 (87.2)	43 (89.6)

Source: Applicant table 14.1.1.1 submitted March 10, 2026 (in response to IR dated November 6, 2025)

Table 5. TEAEs Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial 040

	Setmelanotide N = 94 n(%)		**Placebo N = 48 n(%)**	
Any AE	**5**	**(5.3)**	**3**	**(6.3)**
Gastrointestinal disorders	**2**	**(2.1)**	**0**	**(0.0)**
Gastroesophageal reflux disease	1	(1.1)	0	(0.0)
Nausea	1	(1.1)	0	(0.0)

	Setmelanotide N = 94 n(%)		Placebo N = 48 n(%)	
Vomiting	1	(1.1)	0	(0.0)
Skin and subcutaneous tissue disorders	**2**	**(2.1)**	**0**	**(0.0)**
Skin hyperpigmentation	2	(2.1)	0	(0.0)
General disorders and administration site conditions	**1**	**(1.1)**	**1**	**(2.1)**
Injection site pruritus	1	(1.1)	0	(0.0)
Injection site reaction	0	(0.0)	1	(2.1)
Musculoskeletal and connective tissue disorders	**1**	**(1.1)**	**0**	**(0.0)**
Muscle spasms	1	(1.1)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**1**	**(1.1)**	**1**	**(2.1)**
Rhinorrhea	1	(1.1)	0	(0.0)
Dyspnea	0	(0.0)	1	(2.1)
Immune system disorders	**0**	**(0.0)**	**1**	**(2.1)**
Hypersensitivity	0	(0.0)	1	(2.1)

Source: Applicant Table 14.3.1.6A submitted March 9, 2026, in response to IR. Confirmed by clinical reviewer analysis, FDA Studio Analysis, adae.xpt dataset submitted March 9, 2026.

Reviewer comment: TEAEs leading to treatment discontinuation in the setmelanotide group were primarily related to known adverse reactions of setmelanotide, specifically nausea, vomiting, and skin hyperpigmentation.

Protocol Violations/Deviations

There were no major protocol deviations, specifically there were no reported deviations related to subject entry criteria, withdrawal criteria or study drug treatment. Categories of minor protocol deviations included: visit procedures (incorrect sequence of collecting data, dermatologist not evaluating new moles, visit performed out-of-window); lab samples (timing of sample collection).

Demographic Characteristics

Table 6 shows baseline demographic characteristics. The patient population was majority female (60%), with a similar proportion of male and female patients in each treatment group. There was a higher proportion of pediatric patients (53.5%, age <18 years) than adults (46.5%). Within the pediatric population, there was a higher proportion of adolescents (31%, ages 12 to <18 years) compared to children <12 years of age (22.5%). The proportion of patients in each age group was similar between treatment groups. Most patients were White (75%), followed by Asian (11%), and Black or African American (5%). Baseline BMI was similar between treatment

groups (36 kg/m^2). Most patients were enrolled in the United States (62%).

Table 6. Baseline Demographic Characteristics, Trial 040

	Setmelanotide (N=94) n(%)	Placebo (N=48) n(%)	Total (N=142) n(%)
Sex			
Female	54 (57.4)	31 (64.6)	85 (59.9)
Male	40 (42.6)	17 (35.4)	57 (40.1)
Age (years) at Enrollment			
Mean (SD)	20.6 (13.4)	22.9 (16.3)	21.4 (14.4)
Median (Min, Max)	17.0 (4.0, 65.0)	16.0 (4.0, 66.0)	17.0 (4.0, 66.0)
Age Category (years)			
< 12 Years	20 (21.3)	12 (25.0)	32 (22.5)
>= 12 Years and < 18 Years	29 (30.9)	15 (31.2)	44 (31.0)
>= 18 Years	45 (47.9)	21 (43.8)	66 (46.5)
Race			
American Indian or Alaskan Native	0 (0)	0 (0)	0 (0)
Asian	11 (11.7)	5 (10.4)	16 (11.3)
Black or African American	6 (6.4)	1 (2.1)	7 (4.9)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)
Other	6 (6.4)	6 (12.5)	12 (8.5)
White	71 (75.5)	36 (75.0)	107 (75.4)
BMI (kg/m^2)			
Mean (SD)	36.0 (9.2)	36.4 (8.8)	36.1 (9.0)
Median (Min, Max)	34.0 (21.3, 69.2)	34.6 (21.3, 70.0)	34.0 (21.3, 70.0)
BMI percent of 95th percentile, ages < 18 years			
n	49	27	76
Mean (SD	131.7 (28.9)	129.9 (24.4)	131.0 (27.2)
Median (Min, Max)	98.0, 209.6	97.2, 189.9	97.2, 209.6
BMI Z-score, ages < 18 years			
n	49	27	76
Mean (SD	3.7 (1.8)	3.4 (1.3)	3.6 (1.6)
Median (Min, Max)	2.0, 10.4	1.9, 7.5	1.9, 10.4
Country			
Canada	5 (5.3)	3 (6.2)	8 (5.6)
Germany	8 (8.5)	4 (8.3)	12 (8.5)
United Kingdom	9 (9.6)	1 (2.1)	10 (7.0)
Japan	8 (8.5)	4 (8.3)	12 (8.5)

	Setmelanotide (N=94) n(%)	Placebo (N=48) n(%)	Total (N=142) n(%)
Netherlands	7 (7.4)	5 (10.4)	12 (8.5)
United States	57 (60.6)	31 (64.6)	88 (62.0)

Source: FDA Office of Computational Services analysis, Analysis Studio, Custom Table Tool and Applicant Table 14.1.2.1.1

Baseline Clinical Characteristics

The etiology of acquired HO was craniopharyngioma in most patients (77%), with a similar proportion in each treatment group (Table 7).

Table 7. Summary of Tumor Type, Trial 040

	Setmelanotide (N=94) n(%)	Placebo (N=48) n(%)
Craniopharyngioma	73 (77.7)	37 (77.1)
Germinoma	6 (6.4)	1 (2.1)
Astrocytoma	4 (4.3)	3 (6.3)
Glioma	4 (4.3)	4 (8.3)
Hamartoma	1 (1.1)	2 (4.2)
Other*	6 (6.4)	1 (2.1)

Source: Applicant Adhoc Table 29 in response to Information Request dated September 12, 2025.
*Other – One each of the following diagnoses: hypothalamic glioma pilocytic astrocytoma, arachnoid cyst, heterogeneous mass in the suprasellar region involving the hypothalamus and optic chiasm, ependymoma, mature teratoma, cavernous hemangioma, either craniopharyngioma or astrocytoma, choriocarcinoma (from Applicant response to IR sent 8/10/2025).

Most patients reported baseline medical diagnoses consistent with hypothalamic injury (Table 8), as follows: diabetes insipidus (total 80%), with a higher percentage in the setmelanotide group compared to placebo (83% vs. 75%, respectively); central hypothyroidism (total 64%) with similar percentages in each treatment group; growth hormone deficiency (61%), with a higher percent in the setmelanotide group compared to placebo (65% vs. 54%, respectively).

Table 8. Baseline Medical History Reported in ≥10% of Patients, Trial 040

System organ class Preferred term	Setmelanotide (N=94) n(%)	Placebo (N=48) n(%)	Total (N=142) n(%)
Endocrine disorders	94 (100.0)	46 (95.8)	140 (98.6)
Diabetes insipidus	78 (83.0)	36 (75.0)	114 (80.3)
Central hypothyroidism	60 (63.8)	31 (64.6)	91 (64.1)
Growth hormone deficiency	61 (64.9)	26 (54.2)	87 (61.3)
Hypopituitarism	49 (52.1)	21 (43.8)	70 (49.3)

System organ class Preferred term	Setmelanotide (N=94) n(%)	Placebo (N=48) n(%)	Total (N=142) n(%)
Secondary hypogonadism	37 (39.4)	17 (35.4)	54 (38.0)
Adrenal insufficiency	28 (29.8)	11 (22.9)	39 (27.5)
Secondary adrenocortical insufficiency	18 (19.1)	11 (22.9)	29 (20.4)
Adrenocorticotropic hormone deficiency	17 (18.1)	7 (14.6)	24 (16.9)
Hypothyroidism	17 (18.1)	5 (10.4)	22 (15.5)
Precocious puberty	5 (5.3)	8 (16.7)	13 (9.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	84 (89.4)	43 (89.6)	127 (89.4)
Craniopharyngioma	65 (69.1)	34 (70.8)	99 (69.7)
Metabolism and nutrition disorders	65 (69.1)	38 (79.2)	103 (72.5)
Hyperlipidemia	8 (8.5)	6 (12.5)	14 (9.9)
Type 2 diabetes mellitus	8 (8.5)	5 (10.4)	13 (9.2)
Psychiatric disorders	44 (46.8)	27 (56.2)	71 (50.0)
Depression	15 (16.0)	10 (20.8)	25 (17.6)
Anxiety	13 (13.8)	10 (20.8)	23 (16.2)
Attention deficit hyperactivity disorder	10 (10.6)	5 (10.4)	15 (10.6)
Insomnia	6 (6.4)	6 (12.5)	12 (8.5)
Vascular disorders	14 (14.9)	9 (18.8)	23 (16.2)
Hypertension	6 (6.4)	7 (14.6)	13 (9.2)

Source: Primary reviewer analysis using OCS Analysis Studio, Custom Table Tool.

Reviewer comment: Most patients had baseline comorbid diseases consistent with hypothalamic damage and secondary hypopituitarism, including diabetes insipidus, central hypothyroidism and growth hormone deficiency. Consistent with epidemiologic data, craniopharyngiomas were the most common tumors leading to the diagnosis of acquired HO in trial 040. While the incidence of craniopharyngiomas among Black or African Americans in the U.S. is higher than Whites[19], the proportion of Black of African American patients enrolled in trial 040 was lower than Whites or Asians.

Table 9 shows the frequency of patients taking weight reduction medications at baseline. A similar proportion of patients were taking at least one medication associated with weight reduction at baseline in the setmelanotide and placebo groups (46% vs. 44%, respectively).

[19] Momin, A.A., Recinos, M.A., Cioffi, G. et al. Descriptive epidemiology of craniopharyngiomas in the United States. Pituitary 24, 517–522 (2021). https://doi.org/10.1007/s11102-021-01127-6

Overall, the most common concomitant weight reduction medications were in the glucagon-like peptide-1 (GLP-1) receptor agonist class, with a lower percent in the setmelanotide compared to placebo groups (20% vs. 27%, respectively).

Table 9. Baseline Weight Reduction Medications, Trial 040

	Setmelanotide (N=94) n (%)	Placebo (N=48) n (%)
Subjects with at Least One Medication	**43 (46)**	**21 (44)**
GLP-1 receptor agonists	**19 (20)**	**13 (27)**
Liraglutide	13 (14)	7 (15)
Semaglutide	12 (13)	7 (15)
Centrally Acting Sympathomimetics	**10 (11)**	**6 (13)**
Dexamfetamine	5 (5)	2 (4)
Methylphenidate	2 (2)	0
Dexamfetamine Sulfate	1 (1)	3 (6)
Lisdexamfetamine Mesilate	1 (1)	1 (2)
Methylphenidate Hydrochloride	1 (1)	0
Oxytocin And Analogues	10 (11)	1 (2)
Oxytocin	10 (11)	1 (2)
Centrally Acting Drugs	**8 (9)**	**3 (6)**
Phentermine	5 (5)	0
Bupropion Hydrochloride/naltrexone hydrochloride	2 (2)	1 (2)
Bupropion/naltrexone	1 (1)	1 (2)
Phentermine Hydrochloride/topiramate	1 (1)	1 (2)
Phentermine/topiramate	1 (1)	0
Biguanides	**7 (7)**	**6 (13)**
Metformin	7 (7)	5 (10)
Metformin Hydrochloride	0	1 (2)
Other Antiepileptics	**5 (5.3)**	**1 (2)**
Topiramate	5 (5.3)	1 (2)
Other Immunostimulants	**5 (5.3)**	**0**
Naltrexone	4 (4.3)	0
Naltrexone Hydrochloride	2 (2.1)	0
Other Blood Glucose Lowering Drugs, Excl. Insulins	**4 (4.3)**	**1 (2)**
Tirzepatide	4 (4.3)	1 (2)

Source: Applicant response to Information Request dated September 12, 2025, Applicant Adhoc Table 28.

Reviewer comment: Approximately half of the patients in trial 040 were taking at least one weight reduction medication at baseline, and the proportion was similar between the setmelanotide and placebo groups. As per the eligibility criteria, medications approved for the weight reduction were permitted if the patient had <2% weight loss while taking the drug in the previous 3 months prior to screening, the drug doses were stable for at least 3 months prior to randomization, and the patient intended to continue the same dose throughout the

trial. There are currently no approved weight reduction medications for the treatment of acquired HO. Overall, the proportion of patients taking at least 1 weight reduction medication at baseline was balanced between treatment groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was monitored by having patients document dose administration via an electronic diary. Compliance was similar in the setmelanotide and placebo groups (84% and 87%, respectively) as of data cut-off December 24, 2025. Compliance was defined as the number of doses administered divided by the duration of treatment in days. Table 10 shows pertinent concomitant medications taken at baseline by ≥25% of patients. Most patients were taking concomitant medications consistent with underlying hypothalamic and pituitary damage. The percent of patients taking concomitant glucocorticoids, which can lead to weight gain, was similar in the setmelanotide and placebo groups (89% vs. 87%, respectively.)

Table 10. Pertinent Concomitant Medications Taken by ≥25% of Patients, Trial 040

	Setmelanotide (N=94)	Placebo (N=48)	Total (N=142)
Glucocorticoids	84 (89.4)	42 (87.5)	126 (88.7)
Hydrocortisone	78 (83.0)	38 (79.2)	116 (81.7)
Hydrocortisone sodium succinate	24 (25.5)	14 (29.2)	38 (26.8)
Vasopressin and analogues	82 (87.2)	37 (77.1)	119 (83.8)
Desmopressin	66 (70.2)	30 (62.5)	96 (67.6)
Somatotropin and somatotropin agonists	68 (72.3)	28 (58.3)	96 (67.6)
Somatotropin	60 (63.8)	25 (52.1)	85 (59.9)
Thyroid hormones	88 (93.6)	41 (85.4)	129 (90.8)
Levothyroxine	61 (64.9)	26 (54.2)	87 (61.3)
Levothyroxine sodium	32 (34.0)	15 (31.3)	47 (33.1)
Additional drugs			
Estradiol	23 (24.5)	7 (14.6)	30 (21.1)
Metformin	18 (19.1)	11 (22.9)	29 (20.4)

Source: Table 2 from Applicant's response to information request dated January 9, 2026.

6.1.2.1. Efficacy Results – Primary Endpoint

For detailed review of the statistical analyses for efficacy endpoints, refer to the FDA statistical review dated February 19, 2026, and addendum dated March 16, 2026 by Dr. Yuhao Li (Office of Biostatistics, Division of Biometrics II). The LS mean difference (95% CI) in percent BMI change from baseline at Week 52 was -18.40% (-21.94, -14.85) for setmelanotide vs. placebo

(Table 11). The setmelanotide group achieved statistically significant superiority to the placebo group for the primary endpoint.

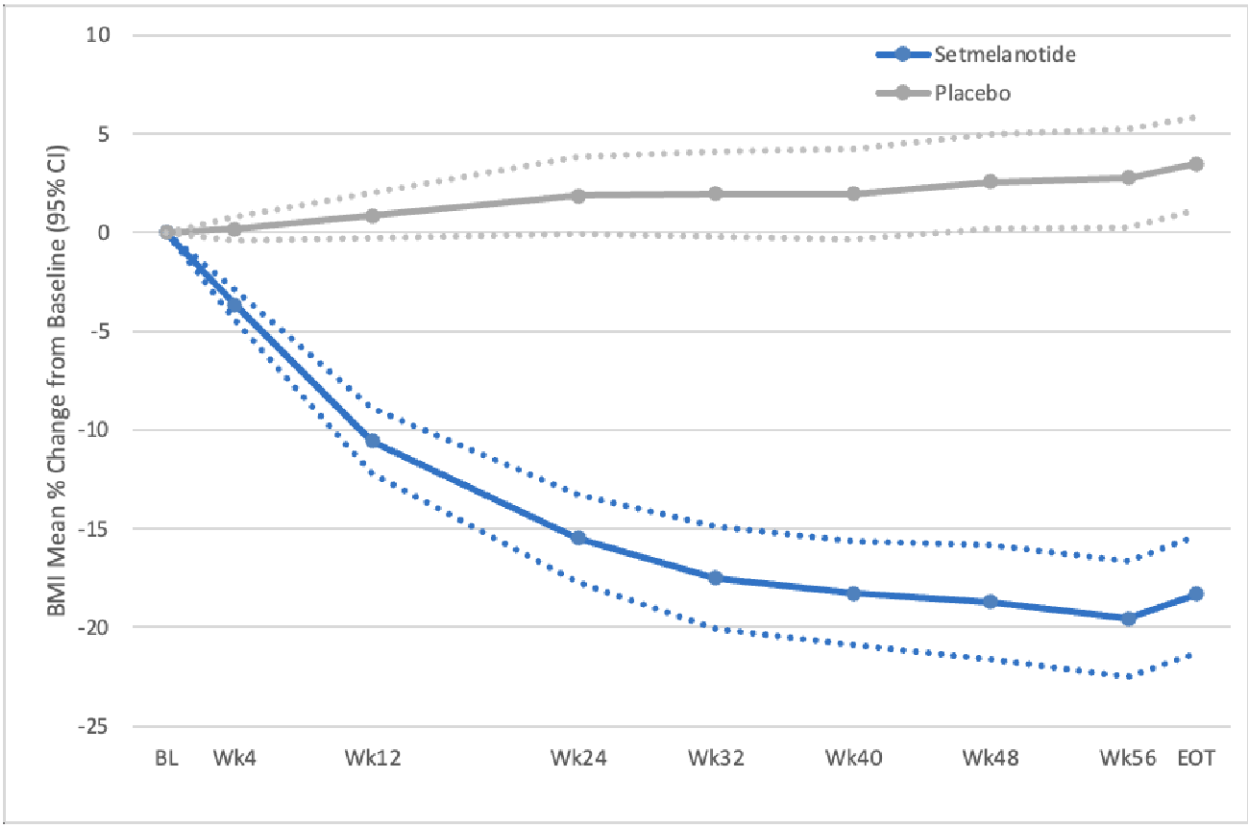
Table 11. Primary Efficacy Results: Mean Percent Change in BMI from Baseline to Approximately 52 Weeks, Trial 040[1]

	Setmelanotide N=94	**Placebo N=48**
Baseline BMI, Mean (SD)	36.04 (9.18)	36.35 (8.77)
Week 52 Missing BMI, n (%)	12 (12.77)	3 (6.25)
Percent Change from Baseline to Week 52*, LS Mean (SE)	-15.84 (1.52)	2.55 (0.98)
Comparison to Placebo*, LS Mean difference (95% CI), Two-sided P-value	-18.40% (-21.94, -14.85) <.0001	

[1] All randomized and dosed patients, N=142
Source: FDA statistical reviewer's analysis: adsl,xpt, adwthgw.xpt
* The LS Mean estimate is based on an ANCOVA model adjusted for baseline BMI and a stratification factor of age group (≥18 years old, ≥12 and <18 years old, and <12 years old) after imputing missing data with washout imputation method for weights and last observation carried forward imputation for heights.
**The missing BMI is defined as the BMI missing due to the missing of weights.

Figure 1 shows mean percent change in BMI over time by treatment group (N=120, initial cohort submitted by Applicant). Within 4 weeks of treatment, there is a separation in the setmelanotide and placebo curves. The setmelanotide curve continues to descend throughout the treatment period. However, the placebo curve rises during the treatment period reflecting a slight increase in mean percent change in BMI over time, consistent with natural history of acquired HO.

Figure 1: Mean Percent Change in BMI from Baseline by Visit , Trial 040



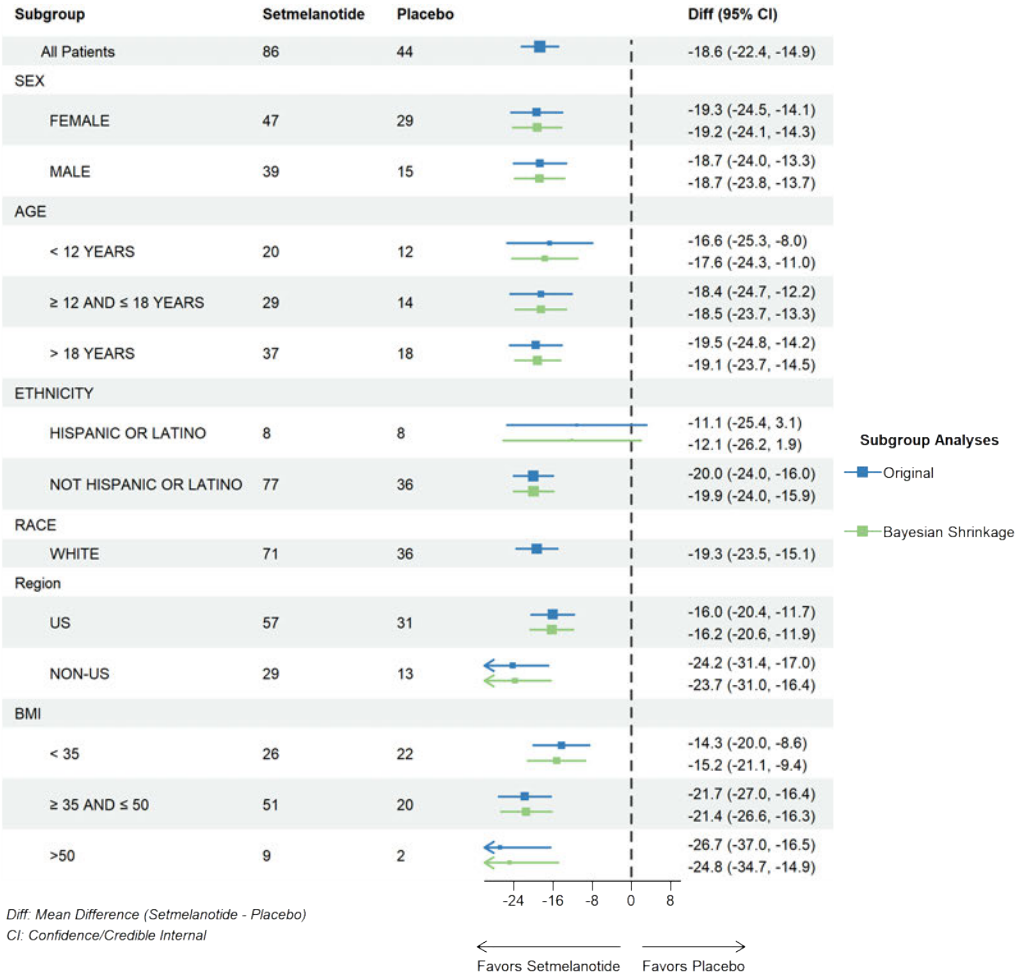
Source: Applicant CSR for Trial RM-493-040, Figure 3, N=120

Reviewer Comment: The placebo-adjusted difference in the mean percent change in BMI from baseline to approximately Week 52 for setmelanotide vs. placebo was statistically significant and clinically meaningful in favor of setmelanotide.

Subgroup Analyses

Subgroup analyses on percent change in BMI from baseline after Week 52 were conducted with respect to the baseline characteristics: sex, age group (<12, 12 to <18, and >18 years), ethnicity, race, region, and BMI. Subgroup estimates of LSMean difference favor setmelanotide. Figure 2 shows subgroup analyses for the initial 130 subjects enrolled in trial 040 (from FDA Statistical Review dated February 19, 2026). Of note, this figure does not include the 12 patients enrolled at the Japanese site. Subgroup LS mean estimates by sex, age, race, region and BMI favor setmelanotide. Of note, for race there were 6 Black or African American subjects randomized to the setmelanotide group 1 subject to the placebo group. Among the 6 Black or African American setmelanotide-treated subjects, 5 demonstrated BMI reductions of -4.12%, -11.52%, -22.58%, -11.21%, and -12.22%, while weight data at week 52 were missing for 1 subject. The single Black or African American placebo-treated subject experienced a BMI reduction of 0.02%. While the 95% confidence interval for the Hispanic or Latino subgroup crosses zero, the number of subjects in this subgroup was small.

Figure 2. Forest Plot of Subgroup Analyses of Primary Efficacy Results, N=130



Source: Statistical reviewer analysis from review dated February 19, 2026; adsl.xpt, advs.xpt, adallw.xpt
*Asian and Black or African American race subjects are not shown in this Figure 3 due to insufficient sample sizes for subgroup analyses (b)(4) Asian subjects in the treatment group vs. (b)(4) in the placebo group; 6 Black or African American subjects in the treatment group vs. 1 in the placebo group). All subjects are not Native Hawaiians or Other Pacific Islanders.
*1 setmelanotide-treated subject with unknown ethnicity is not included in the subgroup analyses.
**Size of black square (point estimate) in the forest plot is proportional to the precision (i.e., inverse of variance) of the estimates.

Sensitivity Analyses

A sensitivity analysis was performed for 8 patients <21 years with missing height values and reported weights. The missing height values were imputed using linear regression of longitudinal height measurements over time. In addition, a 2-way tipping point analyses was performed as a sensitivity analysis under the primary estimand to quantify the robustness of missing data assumptions and provide a worst-case boundary. See Statistical review in DAARTs dated February 19, 2026, for discussion of sensitivity analyses.

Data Quality and Integrity

Overall, the quality of the data and programs was low, and the analyses initially submitted by the Applicant were insufficient to evaluate the efficacy results. Issues with data quality and analyses include the following:

- To calculate pediatric BMI Z-scores, the Applicant assumed of a birth date of January 1st, and this was not mentioned or discussed in the original NDA submission.
- In the original NDA submission under folder "0441", macro codes for primary analyses and imputations were missing. Codes for primary analyses did not align with the SAP assuming unequal variance.
- Corrections on efficacy evaluation of Hunger Score including key secondary analyses were submitted after 50 days from the original NDA submission.
- The SAP version 4 submitted in the original NDA submission contained a critical contradiction. In Section 2.1 (Population Definitions), the mITT was defined, and it was stated that mITT would be used as the primary population for the analysis of efficacy data. However, in Section 3.12 (Interim Analyses, Timing of Planned Analyses, and Cohorts), the set of pivotal cohorts was defined and claimed to be used in formal hypothesis testing and success/failure.
- The Applicant combined adult and pediatric results in analyses of secondary cardiometabolic endpoints. These analyses are not clinically interpretable because the cut-offs for normal range values for cardiometabolic endpoints differ between adults and pediatric populations and within the pediatric population.

In general, protocol deviations were not believed to have a negative impact on trial results. Subject retention and trial completion were acceptable. There were no notable financial conflicts of interest.

6.1.2.2. Efficacy Results – Secondary Endpoints

The first key secondary endpoint was the proportion of adult subjects with ≥5% reduction in BMI, or pediatric subjects with ≥0.2 BMI Z-score reduction from baseline after approximately 52 weeks of treatment (Table 12). The percent of patients achieving this secondary endpoint was greater in the setmelanotide group compared to placebo (80.8% vs 23.2%, respectively). This finding is supported by responder analysis, which showed a higher frequency of patients in the setmelanotide group achieved ≥5% reduction in BMI from baseline after 52 weeks compared to the placebo group (75.8% vs. 9.7%, respectively).

Table 12. Key Secondary Endpoint Analysis Results for Change in BMI from Baseline, Trial 040

Key Secondary		**Setmelanotide N=94**	**Placebo N=48**
	Response Rate*(%)	80.84	23.17

Adult Subjects with ≥ 5% Reduction in BMI or Pediatric Subjects with ≥ 0.2 BMI Z-Score Reduction from Baseline After 52 weeks	Risk Difference (%), (95% CI), P-value*	-60.79, (-74.11, -47.47) <0.001	
Subjects with ≥ 5% Reduction in BMI from Baseline After 52 weeks	Response Rate*(%)	75.79	9.73
	Risk Difference (%), (95% CI), P-value*	-66.23, (-78.65, -53.81), <0.001	

Abbreviations: CI = confidence interval, SD = standard deviation, SE = standard error, BMI = body mass index, N = number of subjects in the treatment group, n = number of subjects.
* The response rate is calculated on average across multiple imputation datasets based on the same primary imputed dataset for BMI.
** The risk difference is calculated using Cochran-Mantel-Haenszel test with adjustment of stratification factors of age group and race group on the same primary imputed dataset for the primary endpoints.
Source: Sponsor's analyses; adsl.xpt, adallw.xpt, adwthgw.xpt

The second prespecified key secondary endpoint was the change from baseline in the weekly average of the daily "most hunger" score for subjects aged ≥12 years. Hunger was assessed in patients ages ≥12 years using the "Hunger Questions for Patients ≥12 Years of Age (version 3.0)". This clinical outcomes assessment (COA) consisted of 2 items. The secondary endpoint pertained to results for the following item: "In the last 24 hours, how hungry did you feel when you were the most hungry?". Patients rated their hunger on an 11-point numeric rating scale ranging from 0 to 10 (0 = not hungry at all and 10 = hungriest possible).

Table 13 shows the weekly average of the daily "most hunger" score in patients ages ≥12 years. The missing rates for this endpoint were high: 11% of patients had missing baseline data, and 27% of patients in the setmelanotide group and 25% of patients in the placebo group had missing data at Week 52 (among patients with an observed baseline score). Missing data at baseline were imputed using all observed scores at baseline under missing at random by normal distribution. Missing score data after week 52 were imputed using placebo-washout multiple imputation method. The LSMean difference (95% CI) in weekly average of daily "most hunger" score change from baseline at Week 52 was -0.82 (-1.62, 0.02) for setmelanotide vs. placebo (p = 0.045).

Table 13. Key Secondary Endpoint Results for Weekly Average of Daily Most Hunger Scores in Subjects ≥12 years

	Setmelanotide N=74	**Placebo N=36**
Subjects With Observed Baseline Score, n (%)	66 (89.18)	32 (88.88)
Baseline*, Mean (SD)	6.70 (2.20)	7.05 (2.03)
Subjects with Observed Score at Week 52, n (%)	54 (72.97)	27 (75.00)
Change from Baseline to Week 52^, LS Mean (SE)	-2.27 (0.25)	-1.44 (0.33)
Comparison to Placebo^, LS Mean difference (95% CI), Two-sided P-value	-0.82 (-1.62, -0.02) 0.045	

Abbreviations: CI = confidence interval, SD = standard deviation, SE = standard error, BMI = body mass index, N = number of subjects in the treatment group, n = number of subjects.
* The mean is computed using all observed baseline scores.
^ Missing data at baseline were imputed using all observed scores at baseline . Missing score data after week 52 were imputed using placebo-washout MI method. ANCOVA model with unequal variance to account for possible unequal residual variances was used to estimate the difference between treatment groups. The model was adjusted with the baseline weekly average hunger score, stratification factors of age group (≥18 years, and ≥12 and <18 years) and subpopulation (Japanese and non-Japanese).
Source: Reviewer's analysis; adsl.xpt, adallw.xpt, adwthgw.xpt

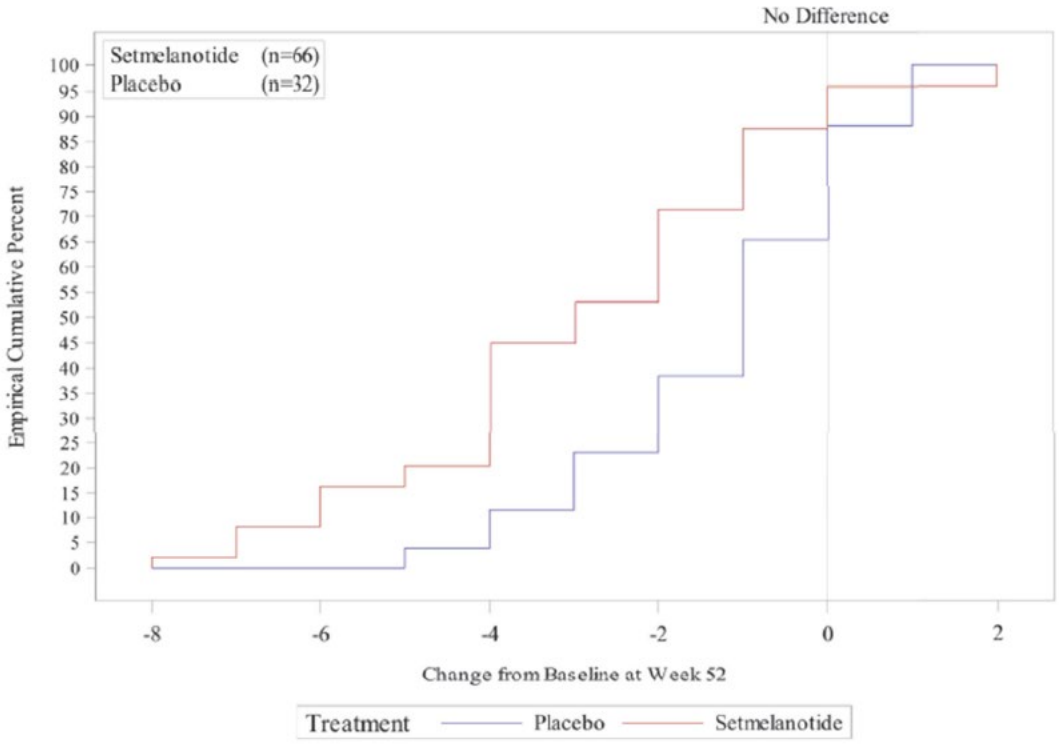
A consult was obtained from the Division of Clinical Outcome Assessment (DCOA) to assess whether the submitted COA data supported the hunger COA-related labeling claims. The Applicant submitted qualitative and quantitative summary reports for the "most hunger" item from the Hunger Questions for Patients ≥12 Years of Age. The DCOA reviewers concluded the following regarding the "most hunger" item:

- *The 'most hunger' item measured a clinically relevant and important concept (hunger severity) for the U.S. patients based on the concept elicitation portion of the exit interviews.*
- *The 'most hunger' item appeared to be well-understood in U.S. patients based on the cognitive portion of the exit interviews.*
- *The interpretability of the measurement properties of the item (i.e. reliability, validity, and ability to detect change) is difficult given the small sample size of the trial.*
- *The magnitude of the statistically significant treatment effect appears clinically meaningful to U.S. patients based on qualitative data and the empirical cumulative distribution function (eCDF) curves by treatment.*

Of note, the Applicant did not provide qualitative interview data to support the content validity of the "most hunger" item in the patients enrolled in Japan (N=12). Therefore, it is unknown what amount of change in the "most hunger" item score is meaningful to the Japanese patients. Among U.S. patients participating in exit interviews, most reported a (within person) mean change of -4.5 (range 2-7) on the 'most hunger' item as representing a meaningful

improvement. The cumulative distribution function (CDF) for change in weekly average "most hunger" score from baseline to Week 52 showed a separation between treatment and placebo groups across a range that likely includes a clinically meaningful change threshold (Figure 3).

Figure 3. Cumulative Distribution Function for Change in Weekly Average Most Hunger score by Treatment from Baseline to Week 52*



Source: Figure 1 in Applicant response to IR dated March 2, 2026

Reviewer comment: Based on DCOA evaluation of exit interviews, the "most hunger" item appears to measure a clinically relevant and important concept (hunger severity) for the U.S. patient population. The magnitude of the statistically significant treatment effect appears clinically meaningful to U.S. patients based on qualitative data and the eCDF curves by treatment group. This reviewer recommends including daily "most hunger" results in Section 14. However, the "most hunger" score should be excluded from the indications statement because this was not a primary efficacy endpoint.

Other Secondary Endpoints

Table 15 shows the proportion of patients with ≥10% BMI reduction from baseline at 52 weeks was greater in the setmelanotide group compared to placebo (60.9% vs. 4.7%, respectively). Of note, the proportion of subjects achieving ≥15% weight reduction was not pre-specified.

Table 14. Secondary Endpoint Analysis Results for Change in BMI from Baseline, Trial 040

Key Secondary		**Setmelanotide N = 94**	**Placebo N=48**
Subjects with ≥ 10% Reduction in BMI from Baseline After 52 weeks*	Response Rate*(%)	60.99	4.69
	Risk Difference (%), (95% CI),	-56.59, (-68.32, -44.85)	
Subjects with ≥ 15% Reduction in BMI from Baseline After 52 weeks*	Response Rate*(%)	50.12	2.15
	Risk Difference (%), (95% CI)	-47.75, (-58.85, -36.66)	

* Note: Subjects with ≥ 10% and ≥ 15% reduction in BMI from baseline after 52 weeks are not controlled for multiplicity. These outcomes are included in the product label to provide additional information.

Cardiometabolic parameters

The Applicant assessed the difference between study groups in the change in cardiometabolic parameters from baseline after approximately 52 weeks as a non-key secondary endpoint. However, the Applicant provided analyses that combined results for pediatric and adult patients. These data are not clinically interpretable given that the cut-off range for normal values differ between adult and pediatric patients. In addition, norms for pediatric patients differ based on age, sex, and/or height.

Hyperphagia and Quality of Life Scores

Non-key secondary endpoints that the Applicant included in the proposed label were as follows:

(b) (4)

DCOA reviewers concluded that the (b) (4) were inadequate to support labeling claims as they were not prespecified alpha-controlled endpoints.

Dose/Dose Response

See Section 7.1.4.

Durability of Response

The Applicant was able to demonstrate durability of effect throughout the 52-week planned treatment duration (see Figure 1, mean percent change in BMI over time).

Reviewer comment: The weight loss trajectory over the 52-week treatment period at the

intended maintenance dosage of setmelanotide is considered adequate to support durability of response.

Persistence of Effect

Persistence of effect was not assessed in this trial. However, like other weight reduction drugs, it is expected that withdrawal of treatment would lead to weight regain.

Additional Analyses Conducted on the Individual Trial

Not applicable

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

To achieve SEE, confirmatory evidence was used from the related indications of obesity due to POMC, PCSK1, and LEPR deficiency and BBS. The Applicant submitted confirmatory evidence from trials RM-493-033, -012, -015 and -23 for these related indications (see Section 5.1 for a description of each trial). Results of these trials are described in the current IMCIVREE label. Setmelanotide is approved to reduce excess weight and maintain weight reduction long term in patients 6 years and older with obesity due to POMC, PCSK1, and LEPR deficiency (November 2020, original NDA); for obesity due to BBS (June 2022, supplement 001); and obesity due to POMC,PCSK1, LEPR deficiency and BBS in patients ages 2 to <6 (December 2024, supplement 007). Overall, results from these trials confirm the efficacy of setmelanotide in achieving clinically meaningful weight reduction in these related indications.

Reviewer comment: The efficacy of setmelanotide in achieving clinically meaningful weight reduction in pediatric and adult patients ages 4 years and older with acquired HO is supported by confirmatory evidence from the related indications of obesity due to POMC, PCSK1 and LEPR deficiency, and BBS.

7.1.2. Secondary and Other Endpoints

Not applicable.

7.1.3. Subpopulations

Not applicable.

7.1.4. Onset, Duration, and Durability of Efficacy Effects

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

It is not expected that setmelanotide will be used substantially differently in the post-market setting compared to use in trial 040 for patients with acquired HO ages 4 years and older.

7.2.2. Other Relevant Benefits

Not applicable.

7.3. Integrated Assessment of Effectiveness

Results from trial 040 along with confirmatory evidence from trials that supported the approval of related indications for weight reduction in obesity due to POMC, PCSK1, LEPR deficiency and BBS provide SEE that treatment with setmelanotide results in statistically significant and clinically meaningful weight reduction in patients 4 years and older with acquired HO. It is acceptable to rely on a single randomized, double-blind, placebo-controlled trial with confirmatory evidence to provide SEE given the rarity of acquired HO and the expected natural history of the condition (early and aggressive weight gain) which results in weight loss being highly unlikely to occur in the absence of an effective intervention.

The findings in trial 040 support an indication for setmelanotide to reduce excess body weight and maintain weight reduction long term in adults and pediatric patients aged 4 years and older with acquired HO. The trial data do not support the Applicant's proposed indication to "reduce excess (b) (4) because the primary efficacy endpoint in trial 040 measured change in BMI not (D) (4) The trial data also do not support the proposed indication "to reduce (b) (4) because this was not a primary endpoint and there were limitations of the (b) (4) score used in trial 040. These limitations include interpretability of the measurement properties of the most hunger score (i.e., assessment of reliability, validity, and ability to detect change) given the small sample size of the trial.

Trial 040 showed the LS mean difference (95% CI) between setmelanotide and placebo groups in percent BMI change from baseline at Week 52 was -18.40% (-21.94, -14.85), p-value <0.001. This result was statistically significant and clinically meaningful. Efficacy data from trials RM-493-033, -012, -015, and -023 provided confirmatory evidence that clinically meaningful weight loss can be achieved with setmelanotide treatment in patients with mechanistically related indications of POMC, PCSK1, LEPR deficiency and BBS.

Overall, the BMI reduction achieved in trial 040 reflects a clinically meaningful benefit in pediatric and adult patients ages 4 years and older with acquired hypothalamic obesity, for

which there is currently no approved drug therapy.

8. Review of Safety

8.1. Safety Review Approach

This safety review focuses on trial 040, a phase 3, double-blind, randomized, placebo-controlled trial that investigated the efficacy and safety of setmelanotide compared to placebo in pediatric and adult patients aged 4 years and older with acquired HO.

Setmelanotide is currently approved to reduce excess body weight and maintain weight reduction long term in adult and pediatric patients aged 2 years and older with syndromic and monogenic obesity due to Bardet-Biedl syndrome (BBS), pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency. Currently labeled Warnings and Precautions include disturbance in sexual arousal, depression and suicidal ideation, hypersensitivity reactions, skin hyperpigmentation, darkening of pre-existing nevi, and development of new melanocytic nevi. The most common labeled adverse reactions include skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, and spontaneous penile erection.

Safety review issues identified prior to this safety review are the currently labeled Warnings and Precautions, as well as, injection site reactions, gastrointestinal disorders (nausea, vomiting, abdominal pain), and pediatric growth and development.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety population is defined as patients who took at least 1 dose of the investigational product. In the Applicant's NDA submission dated June 20, 2025, complete safety data were submitted for the initial 120 patients enrolled in trial 040. As part of a major amendment, the Applicant submitted updated safety data for the complete safety population (N=142) on March 9, 2026.

Table 16 shows the duration of exposure to study drug in trial 040 for the safety population. The mean weeks of exposure were similar between treatment groups. Most patients were exposed to study drug for greater than 12 months (this included drug titration), with similar percentages in the setmelanotide and placebo groups (89.4% vs. 89.6%, respectively).

Table 15. Duration of Exposure, Trial 040, Safety Population

	Setmelanotide (N=94)	Placebo (N=48)

Treatment Duration (Weeks)[1]		
n	94	48
Mean (SD)	54.9 (12.3)	54.9 (12.8)
Median	59.0	59.0
Min, Max	4.7, 62.1	3.3, 64.6
Duration of Exposure, n(%)		
<1 month	0	1 (2.1)
1 to <3 months	3 (3.2)	1 (2.1)
3 to <6 months	3 (3.2)	1 (2.1)
6 to <=12 months	4 (4.3)	2 (4.2)
>12 months	84 (89.4)	43 (89.6)

[1] Treatment duration prior to start of bridging visits
Source: Table 14.1.4.2 from Applicant's IR Response dated March 9, 2026.

Reviewer Comment: Mean duration of exposure was similar between treatment groups.

8.2.2. Relevant characteristics of the safety population:

Baseline demographic characteristics, disease characteristics and concomitant medications are summarized in in Section 6.1.2. The trial population sufficiently represents the expected target population.

8.2.3. Adequacy of the safety database:

In the context of the incidence of HO in the United States, I found the size of the safety database to be adequate. The database included exposure to appropriate doses of setmelanotide and the duration of treatment was adequate. Efforts were made to ensure adequate follow-up of all patients.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The initial application submitted June 20, 2025, did not contain complete efficacy and safety data for all patients who received at least one dose of the study drug in trial 040 (N=142). Instead, it contained efficacy and safety data for the initial 120 patients enrolled in trial 040. As part of a major amendment, the Applicant submitted complete efficacy and safety data for all patients who received at least 1 dose of study drug (N=142) on March 9, 2026. The submission integrity was fair. The overall quality of the submission was fair.

8.3.2. Categorization of Adverse Events

Adverse events were monitored throughout the trial and recorded in the eCRFs from the screening visit through the EOS visit. AEs that occurred after study drug initiation were

considered TEAEs. AEs were monitored until they were resolved or clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). The definition of AEs and SAEs provided by the Applicant were accurate.

As per the trial protocol, clinically significant changes in laboratory values, blood pressure, and pulse did not need to be reported as AEs. However, abnormal values that constituted a serious adverse event (SAE) or led to discontinuation of administration of the trial drug were reported and recorded as an AE.

All AEs were categorized using MedDRA version 25.1 or later. This reviewer determined that the AE coding from verbatim terms to preferred terms was appropriate in most cases.

8.3.3. Routine Clinical Tests

The safety assessment methods and time points that were described in the protocols appear reasonable and adequate for the population, disease, and indication investigated. The results of these assessments and analyses of results are presented in Section 8.4. For the Schedules of Activities for trial 040 see the Appendix.

8.4. Safety Results

8.4.1. Deaths

There were 2 reported patient deaths, both patients were in the setmelanotide-treatment group. One patient (ID (b) (6)) died due to uncontrolled seizures and had a history of a pre-existing seizure disorder. A second patient (ID (b) (6)) died of complications related to an ischemic stroke during the bridging visit period. Narratives for both deaths are provided below.

Patient (b) (6) was a 13-year-old male with a history of craniopharyngioma (date of diagnosis unknown) status post initial resection at age 3. During the same month as the resection, the patient was diagnosed with hydrocephalus, epilepsy, hemiparesis, facial paresis, and aphasia. The patient had additional craniopharyngioma resections at ages 4 and 5 years. At age 6 years the patient developed hypopituitarism and was later diagnosed with hypothyroidism, androgen deficiency, a bone metabolism disorder and an immune system disorder. Of note, the patient had a history of therapy-refractory epilepsy since his first tumor resection. During the screening period, prior to randomization, the patient was hospitalized for hyponatremia thought to be related to an elevated level of lacosamide (anti-seizure medication). The patient had an AE of seizure while hyponatremic. During the hospitalization for hyponatremia, the antiepileptic medication regimen was changed. On study day 3, the patient was hospitalized due to seizure activity (sodium in normal range) and the event was considered resolved on day 4. The investigator assessed that seizure activity was related to change in anti-epileptic medication and ineffective anti-epileptic medication. On Days 6

through 8, the patient was accidentally treated with setmelanotide 4 mg daily instead of 1 mg daily. The dose was decreased on 1 mg daily on Day 9. There were no reported AEs related to this overdosing. The patient's dose was escalated to a max dose of 3 mg on Day 54. His last dose of setmelanotide was reported on Day 309.

On Day 328, the patient was evaluated for ongoing tonic-clinic seizures resistant to anti-epileptic therapy. As per the clinical narrative, seizures were a known problem after the diagnosis of craniopharyngioma and related resections. The cranial MRI did not show an etiology of the seizures. The seizures became more resistant to emergency medication, and the treating physician and family decided to proceed with palliative care. On Day 329, the patient's sodium level on laboratory evaluation was 146 mmol/L and supra-therapeutic brivaracetam level of 1.81 µg/mL (normal range 0.5-0.9 µg/mL). The patient experienced repetitive status epilepticus. On Day 330, methylprednisolone and ampicillin/sulbactam were started for treatment of aspiration pneumonia. The patient received morphine and midazolam "continuously" and died on Day 348. The cause of death was reported as epilepsy, seizure therapy resistant.

Patient (b) (6) was a 6-year-old male whose death was related to acute ischemic strokes that occurred while he was participating in the open-label bridging visits in trial 040. The patient was diagnosed with a suprasellar pilomyxoid astrocytoma at 10 months of age and treated with excision and radiation therapy. His medical history also included hydrocephalus, ventriculo-peritoneal (VP) shunt placement, gastrostomy, diabetes insipidus, central hypothyroidism, secondary adrenocortical insufficiency, esophageal fistula, seizures, hemiparesis, elevated liver enzymes, and visual impairment. In (b) (6), he was found to have left carotid artery stenosis and diagnosed with Moyamoya disease. During trial 040, the patient's dose of setmelanotide was titrated up to a total daily of 3 mg daily, and the patient completed the double-blind, randomized treatment period. He was converted to open-label bridging visits on Day 414, and setmelanotide was re-titrated as per protocol.

On Day 544, the patient developed diarrhea without fever that worsened, and the patient went to the ER on Day 546. As per the clinical narrative provided by the Applicant, the patient showed signs of hypernatremic dehydration. Stool cultures were positive for astrovirus enteritis and labs included sodium 148 mmol/L. On Day 547 the patient experienced profound right-sided weakness. Laboratory tests showed a sodium of 159 mmol/L. MRI brain showed extensive left-sided predominant cortical stroke involving most of the left cerebral cortex, likely some involvement of the left basal ganglia, and questionable involvement of the thalamus. The patient had an emergent thrombectomy. He remained intubated after the procedure and there was concern for hemorrhage and swelling of a large volume of infarcted tissue. On Day 548, CT of the brain showed widespread infarcts (left greater than right), with re-occlusion on the left side and multiple new strokes on the right. The patient had an emergent left-sided decompressive hemicraniectomy. Laboratory tests included sodium 150 mmol/L. On Day 549 the patient had a bradycardic arrest and underwent cardiopulmonary resuscitation. The

patient's code status was changed on do not resuscitate (DNR) and the patient died on Day 551. Ischemic stroke was considered the cause of death. An autopsy was not performed.

Reviewer comment: Patient (b) (6) had a history of therapy-refractory epilepsy since his first tumor resection. It is therefore difficult to attribute the repetitive status epilepticus that led to the patient's death to setmelanotide therapy. Patient (b) (6) had a history of Moyamoya disease which is a rare, progressive vasculopathy of undetermined etiology characterized by progressive narrowing of the terminal intracranial portion of the internal carotid artery and circle of Willis. Patients with Moyamoya disease present with ischemic strokes or transient ischemic attacks (TIAs), and intracranial hemorrhages are also common due to the fragility of abnormal collateral vessels that develop. Of note, Moyamoya disease can be associated with head or neck irradiation. Based on this patient's history of Moyamoya disease, it is unlikely that this patient's death was related to setmelanotide treatment.

8.4.2. Serious Adverse Events

There was a higher frequency of SAEs in the setmelanotide group compared to placebo (28% vs. 6%, respectively) (Table 17). The greatest imbalance were in the '*Infections and infestations'* SOC and '*Endocrine disorders'* SOC. Each of these SOCs is discussed separately below along with SAEs of "hyponatremia" and "hypernatremia" in the *Metabolism and nutrition disorders* SOC.

Table 16. Serious Adverse Events by System Organ Class and Preferred Term, Frequency in Setmelanotide Group> Placebo, Trial 040

System Organ Class Preferred Term	Setmelanotide (N=94) n (%)	Placebo (N=48) n (%)
Any SAE	26 (27.7)	3 (6.2)
Infections and infestations	**11 (11.7)**	**0 (0.0)**
Cellulitis	2 (2.1)	0 (0.0)
Covid-19	2 (2.1)	0 (0.0)
Appendicitis	1 (1.1)	0 (0.0)
Gastroenteritis	1 (1.1)	0 (0.0)
Localized infection	1 (1.1)	0 (0.0)
Lower respiratory tract infection	1 (1.1)	0 (0.0)
Norovirus infection	1 (1.1)	0 (0.0)
Pyelonephritis	1 (1.1)	0 (0.0)
Streptococcal sepsis	1 (1.1)	0 (0.0)
Viral infection	1 (1.1)	0 (0.0)
Endocrine disorders	**5 (5.3)**	**0 (0.0)**
Adrenal insufficiency	3 (3.2)	0 (0.0)

System Organ Class Preferred Term	Setmelanotide (N=94) n (%)	Placebo (N=48) n (%)
Adrenocortical insufficiency acute	2 (2.1)	0 (0.0)
Nervous system disorders	**5 (5.3)**	**2 (4.2)**
Altered state of consciousness	1 (1.1)	0 (0.0)
Cerebral artery stenosis	1 (1.1)	0 (0.0)
Headache	1 (1.1)	0 (0.0)
Loss of consciousness	1 (1.1)	0 (0.0)
Seizure	1 (1.1)	0 (0.0)
Carotid artery aneurysm	0 (0.0)	1 (2.1)
Status migrainosus	0 (0.0)	1 (2.1)
Metabolism and nutrition disorders	**3 (3.2)**	**1 (2.1)**
Hypernatremia	2 (2.1)	1 (2.1)
Hyponatremia	1 (1.1)	0 (0.0)
Gastrointestinal disorders	**2 (2.1)**	**1 (2.1)**
Hematemesis	1 (1.1)	0 (0.0)
Nausea	1 (1.1)	0 (0.0)
Vomiting	1 (1.1)	1 (2.1)
Eye disorders	**1 (1.1)**	**0 (0.0)**
Vision blurred	1 (1.1)	0 (0.0)
General disorders and administration site conditions	**1 (1.1)**	**0 (0.0)**
Catheter site erosion	1 (1.1)	0 (0.0)
Hepatobiliary disorders	**1 (1.1)**	**0 (0.0)**
Cholecystitis	1 (1.1)	0 (0.0)
Immune system disorders	**1 (1.1)**	**0 (0.0)**
Anaphylactic reaction	1 (1.1)	0 (0.0)
Injury, poisoning and procedural complications	**1 (1.1)**	**0 (0.0)**
Concussion	1 (1.1)	0 (0.0)
Investigations	**1 (1.1)**	**0 (0.0)**
Blood sodium abnormal	1 (1.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**1 (1.1)**	**0 (0.0)**
Acute respiratory failure	1 (1.1)	0 (0.0)
Vascular disorders	**1 (1.1)**	**0 (0.0)**

System Organ Class Preferred Term	Setmelanotide (N=94) n (%)	Placebo (N=48) n (%)
Hypertension	1 (1.1)	0 (0.0)

Source: Clinical reviewer analysis, FDA Analysis Studio, adae.xpt submitted March 9, 2026, and Applicant Table 14.3.1.4A submitted March 9, 2026, in response to IR

Infections

A higher percent of subjects in the setmelanotide group compared to placebo experienced SAEs in the *Infections and infestations* SOC (11.7% vs. 0%, respectively). This included 5 adult patients with the following conditions: cellulitis, COVID-19 (in 2 patients), localized infection (foot ulcer on left toe), and pyelonephritis. And 5 pediatric patients with the following conditions: cellulitis, lower respiratory tract infection appendicitis, gastroenteritis, viral infection, streptococcal sepsis and norovirus infection.

Reviewer comment: While the frequency of SAEs in the *Infections and infestations* SOC was higher in the setmelanotide group compared to placebo, there was a wide spectrum of types of infections, and it is difficult to conclude that treatment with setmelanotide increased risk of a specific infectious etiology (e.g., viral or bacterial infections).

Endocrine disorders – Adrenal insufficiency

In the *Endocrine disorders* SOC, there were 3 SAEs of "adrenal insufficiency" and 2 SAEs of "adrenocortical insufficiency" in the setmelanotide group and no SAEs in the placebo group. All 5 patients had an underlying history of adrenal insufficiency and included 2 adult and 3 pediatric patients. Given the imbalance in these SAEs between treatment groups the narratives for each patient are provided below. Table 18 provides abbreviated descriptions of the SAEs of acute adrenal insufficiency.

Adrenocortical insufficiency acute: PT ID (b) (6) was an 8-year-old male with a history of craniopharyngioma status post resection, a CSF reservoir, adrenocortical insufficiency, diabetes insipidus, central hypothyroidism, growth hormone deficiency, moyamoya disease (s/p cerebral revascularization), and hemiparesis likely secondary to Moyamoya disease. As per planned dose escalation, the patient initiated setmelanotide 0.5 mg QD on Day 1, increased to 1 mg QD on Day 8, 2 mg QD on Day 15, and 3 mg QD on Day 22.

This patient had 2 SAEs during the trial. Concomitant medications at the time of the events included desmopressin, cholecalciferol, amitriptyline, hydrocortisone sodium succinate, diphenhydramine, somatropin, indomethacin, acetylsalicylic acid, omeprazole, ondansetron, and levothyroxine. The first SAE was cerebral artery stenosis diagnosed on Day 267, most likely related to the underlying Moyamoya disease. As part of this SAE the patient was hospitalized for right frontotemporal craniotomy for indirect revascularization. The second SAE was an adrenal crisis. Symptoms started on study Day 394 when the patient noted feeling more

fatigued than usual, he reported participating in “hard play during physical education class and recess”. On Day 395 his fatigue progressed. On Day 396, he developed emesis and was given a stress dose of hydrocortisone, but emesis continued. On Day 397 he was taken to the ER and diagnosed with adrenal crisis and treated with stress dose hydrocortisone. Setmelanotide dosing was temporarily discontinued on Days 397 to 400. Of note, patient had been on a steady dosage of setmelanotide 3 mg daily since Day 22. On Day 398 his laboratory tests were significant for acidosis. He developed an altered mental status that was attributed to hyponatremia (reported serum sodium level 123 mmol/L). His sodium levels fluctuated and some of his routine doses of desmopressin were held along with other medications. On Day 400 his sodium level normalized, and he was discharged home on Day 401.

Adrenal insufficiency: PT ID (b) (6) was a 13-year-old female with a history of craniopharyngioma status post radical tumor resection and tumor relapse, as well as hypopituitarism (including hypothyroidism, diabetes insipidus, adrenal insufficiency, growth hormone deficiency). Concomitant medications at the time of the adrenal insufficiency event included desmopressin, dexamfetamine, colecalciferol, hydrocortisone, levothyroxine sodium, somatropin, and estradiol. The patient initiated setmelanotide 0.5 mg QD on Day 1, and titrated to 1 mg QD on Day 9, 2 mg QD on Day 16, and 3 mg QD on Day 23.

On study Day 84 the patient experienced chills followed by severe headache and dizziness. She was unable to stand, and experienced back pain and nausea without stomachache or vomiting. Per the narrative, the patient was experiencing “extra stress because her parents were on vacation”. The patient was given additional doses of hydrocortisone and paracetamol without improvement. On the evening of Day 84, the patient was hospitalized because of “severe adrenal insufficiency”. She was treated with hydrocortisone and on Day 85 she reported an improvement in the headache and dizziness. Neurological exam showed no abnormalities. Laboratory results were grossly normal, this included sodium, glucose, white blood cell count, hemoglobin, c-reactive protein, potassium, and creatinine. The patient missed a dose of setmelanotide on Day 84, but per clinical narrative this was not related to the AE. On Day 86, the patient was discharged from the hospital. Setmelanotide was held on Day 85 and resumed at 3 mg daily on Day 86.

Adrenocortical insufficiency acute: Patient ID (b) (6) was a 17-year-old female with history of craniopharyngioma status and surgical resection followed by relapse, hypopituitarism (including diabetes insipidus, adrenocortical insufficiency, growth hormone deficiency and hypothyroidism), visual impairment, celiac disease, migraines and depression. The patient initiated setmelanotide 0.5 mg QD on Day 1, but experienced tolerability issues leading to the dose being held on Day 8, reduced to 0.25 mg on Day 16 and held again on Day 19. The dose was restarted Day 20 and incrementally titrated up to max dose of 3 mg QD on Day 334. Concomitant medications at the time of the event included hydrocortisone, levothyroxine, dydrogesterone + estradiol, somatropin, desmopressin, sumatriptan, macrogol, and dexamfetamine.

On Day 89, the patient reported not feeling well and experienced diarrhea. The dosage of setmelanotide at that time was 2 mg QD and had been titrated up from 1.5 mg QD on Day 72. On Day 90 she left for a school trip and on Day 92 she vomited up all her medication and was taken to the hospital and admitted for Addison's crisis (preferred term adrenocortical insufficiency acute). The patient did not administer setmelanotide on that day. The patient was given IV hydrocortisone and approximately 30 minutes after administration, the patient reported improvement in her headache and she "started to feel better". She was discharged from the hospital on Day 90 (same day as she presented). She resumed study drug on Day 91.

Reviewer comment: The Division sent an IR (dated September 8, 2025) requesting the Applicant to clarify if patient ID (b) (6) had a history of Addison's disease (primary adrenal insufficiency). In response, the Applicant stated that the patient had "a history of secondary adrenocortical insufficiency (secondary to hypothalamic damage due to craniopharyngioma and the associated treatment)." The Applicant stated that the patient was enrolled at a site "located in the Netherlands and the verbatim term of 'Addisonian crisis' is interchangeably used by the medical community for acute events of both primary and secondary adrenocortical insufficiency."

Adrenal insufficiency: Patient ID (b) (6) was a 36 y/o female with history of craniopharyngioma complicated by central hypothyroidism, adrenal insufficiency, diabetes insipidus, growth hormone deficiency, unilateral blindness, hypogonadism, hyperuricemia, and lymphedema. Medical history also included hypercalcemia, metabolic dysfunction associated liver disease, and migraines. Concomitant medications at the time of the SAE were allopurinol, luliconazole, pregabalin, somapacitan, levothyroxine sodium, desmopressin acetate, hydrocortisone, and valproate sodium. Dosing of setmelanotide was initiated at 0.5 mg QD on Day 1 titrated to 2 mg QD on Day 29, and max dose of 3 mg on Day 50.

On Day 19 the subject was febrile to 104 degrees Fahrenheit and developed redness and swelling on her right lower limb, she experienced loss of appetite and received an additional dose of hydrocortisone. On Day 20, the setmelanotide was not administered because of poor appetite. On Day 21, she was admitted to the hospital for cellulitis of the right lower limb and adrenal insufficiency. She was treated with hydrocortisone and ceftriaxone. She was discharged from the hospital on Day 38. The patient was administered setmelanotide during the hospitalization.

Adrenal insufficiency: Patient ID (b) (6) was a 20-year-old female with history of germ cell tumor in the hypothalamus, central hypothyroidism, adrenal insufficiency, secondary hypogonadism, diabetes insipidus and growth hormone deficiency. Setmelanotide was initiated at 0.5 mg QD on Day 1, and titrated up to 1 mg on Day 22, then held Days 53-54 due to the acute adrenal insufficiency SAE described below, resumed at an increased dosage of 2 mg QD on Day 55, then held again for safety reasons Days 56-61 and Day 63.

On Day 51, the subject experienced cold symptoms with fever and decreased appetite. On Day 53, the patient was evaluated in the ER and diagnosed with influenza and discharged with oseltamivir. Laboratory results included an elevated creatinine kinase level of 877 U/L (reference range 41-153 U/L), elevated C-reactive protein at 8.9 mg/dL (RR <0.14 mg/dL), and a positive influenza A antigen test. The subject did not take the study drug on Days 53 or 54. On Day 54 the subject experienced vomiting, and on Day 55 the vomiting persisted, and she was hospitalized with diagnosis of adrenal insufficiency and treated with steroids. Laboratory results included an elevated creatinine kinase level of 1091 U/L (RR, 41-153 U/L). Setmelanotide was held on Days 56 through 62 because of severe nausea. She was discharged on Day 60.

Table 17. Serious Adverse Events of Acute Adrenal Insufficiency, Trial 040

Patient ID	Treatment arm	Age (years)	Baseline adrenal insufficiency	Trial day of SAE	Comments
(b) (6)	Setmelanotide	8	Yes	397	Symptoms started with fatigue and then patient developed emesis prior to hospitalization.
	Setmelanotide	13	Yes	84	Symptoms prior to hospitalization were chills, nausea, headache, dizziness, and back pain.
	Setmelanotide	17	Yes	90	Initial symptoms were diarrhea, vomiting, and headache.
	Setmelanotide	36	Yes	21	Patient experienced a concomitant cellulitis.
	Setmelanotide	20	Yes	55	Hospitalization for acute adrenal insufficiency was preceded by influenza and vomiting.

Source: Clinical reviewer generated from Applicant CSR for trial RM-493-040

In response to an IR dated September 8, 2025, the Applicant provided narratives for SAEs of acute adrenal insufficiency across the setmelanotide development program (excluding trial 040). All the SAEs reported in the IR response occurred within Trial 022 (an open-label extension trial). Table 19 provides a list of the SAEs of acute adrenal insufficiency that occurred across the setmelanotide development program (excluding trial 040).

Table 18. Serious adverse events of Acute Adrenal Insufficiency Across the Setmelanotide Development Program[1]

PTID in LTE trial 022	Index Trial prior to LTE Trial 022	Age (years)	Baseline adrenal insufficiency	Genetic deficiency	Total treatment duration[2] (years)	Study day of SAE[3]	Comments
(b) (6)	Trial 011 (Patient ID (b) (6)	20	Yes	POMC/PCSK1/LEPR deficiency	7.6 years	451	On the day of hospitalization for adrenal insufficiency the patient experienced diarrhea and fever.
	Trial 012 (Patient ID (b) (6)	16	Yes	POMC/PCSK1/LEPR deficiency	5.4 years	1080	Patient had 3 events of acute adrenal insufficiency: 2 events in setting seizure and 1 in setting of hypoglycemia.
	Trial 030 (Patient ID (b) (6)	9	Yes	POMC/PCSK1/LEPR deficiency	2.9 years	617	Patient may have experienced a coinciding viral infection at time of acute adrenal insufficiency event.

Source: Clinical reviewer generated from Applicant's response to IR dated September 8, 2025
[1]All patients were enrolled in LTE trial 022 at the time of the acute adrenal insufficiency events
[2] Total treatment duration includes index trial and LTE trial 022
[3] Study Day of the LTE trial 022
Abbreviations: LTE – long term extension

Reviewer comments: There was an imbalance in the percentage of patients with SAEs of acute secondary adrenal insufficiency in trial 040, with 5 patients in the setmelanotide treatment group and no patients in the placebo group. All patients had an underlying history of adrenal insufficiency. On review of the clinical narratives, preceding events of infection were potential triggers for 2 of the SAEs; influenza in PTID (b) (6), and cellulitis in PTID (b) (6)

(b) (6). The triggers for acute adrenal insufficiency in the remaining 3 patients (PTIDs (b) (6), (b) (6)) are uncertain. All 3 patients experienced gastrointestinal (GI) symptoms (nausea and/or vomiting) either preceding or concurrent with the adrenal insufficiency SAEs. It is difficult to conclude that the GI symptoms were related to setmelanotide given that they may have been symptoms associated with acute adrenal insufficiency.

Across the setmelanotide development program, there were 3 additional patients with SAEs of acute adrenal insufficiency, all events occurred during the long-term extension (LTE) trial 022. The trigger for acute adrenal insufficiency in one patient (ID (b) (6)) may have been a viral infection and in another patient (ID (b) (6)) the trigger may have been stress related to seizure activity and hypoglycemia. Because the SAEs of acute adrenal insufficiency that occurred across the development program (excluding trial 040) were all in open label extension trial 022, the safety data are not placebo-controlled and therefore interpretation is limited.

Overall, given the imbalance in acute adrenal insufficiency SAEs in placebo-controlled trial 040 it is the opinion of this reviewer that acute adrenal insufficiency be included in the label in Section 5 (Warnings and Precautions).

Metabolism and Nutrition Disorders - Hyponatremia and Hypernatremia

During the treatment period for trial 040, there were 2 SAEs of hypernatremia in the setmelanotide group (2.1%) and 1 SAE in the placebo group (2.1%). There were 2 SAEs of hyponatremia (2.1%) in the setmelanotide group and no events of hyponatremia in the placebo group (0%). Of note, during the open-label period after completion of trial 040, there was one SAE of hypernatremia and one SAE of hyponatremic seizure as of the March 26, 2025, data cut-off. Narratives for SAEs of hypernatremia and hyponatremia in patients treated with setmelanotide during the treatment period for trial 040 and the open label extension period are provided below.

Patient ID (b) (6) (Hypernatremia): 22 y/o female with history of craniopharyngioma status post excision and related hypopituitarism, central hypothyroidism, diabetes insipidus, delayed puberty, hyperphagia and weight gain. Pertinent concomitant medications included desmopressin, hydrocortisone sodium succinate, levothyroxine, medroxyprogesterone, fludrocortisone, estradiol, somatropin. On Study Day 180, the subject's home sodium level was reported as 160 (no units provided) which prompted a hospital evaluation. As per the subject's family, the patient was not urinating the usual amount and not reaching the goal of 2 liters fluid intake per day for the few weeks prior to this event. The subject went to the emergency room where the sodium level was reported as 152. The subject was admitted to the hospital for "acute worsening of hypernatremia (Grade 2/moderate) with no secondary symptoms". While hospitalized the subject's sodium increased to 159 mmol/L. The patient was treated with desmopressin and intravenous fluids. Of note, the patient's growth hormone treatment had

recently been resumed (date not provided by Applicant) and the trial investigator suspected that the patient's desmopressin dosage may have become ineffective in the setting of resumption of growth hormone. No action was taken with study drug.

Patient ID (b) (6) **(Hypernatremia):** 6 y/o male with history of craniopharyngioma status post excision and secondary hypothyroidism, adrenal insufficiency, diabetes insipidus, and growth hormone deficiency. Concomitant medications included hydrocortisone, levothyroxine, topiramate, desmopressin, and dexamphetamine. On Day 6, the patient experienced intermittent nausea and vomiting which were recorded as AEs (both Grade 2/moderate). Sodium level on Day 8 was recorded as 130 mmol/L with no AE reported. After discussion with the trial investigator, the study drug was temporarily interrupted to allow time for symptom resolution. Symptoms of nausea and vomiting were considered resolved on Day 11. On Day 15, the patient resumed study drug at 0.25 mg which was increased to 0.5 mg on Day 22. On Day 43, the patient had "breakthrough episodes of vomiting." On Day 44, the patient was "unable to hold down water, could not tolerate oral desmopressin" and was taken the emergency room. And admitted to the pediatric intensive care unit for management of hypernatremia, dehydration and acidosis. The peak sodium level was 158 mmol/L. The patient was treated for hypernatremia.

Of note - The patient's mother reported that the patient experienced 3 episodes of vomiting on Day 1 on the way home from the study site. As per the Applicant's narrative, the family stated that the cause of the vomiting was motion sickness during travel and/or stomach upset related to antibiotic use for an ear infection. Sodium level was recorded as 155. Adverse events (non-serious) of vomiting (Grade 2/moderate) and hypernatremia (Grade 2/moderate) were recorded. Desmopressin dose was adjusted and repeat sodium level on Day 4 was 133 mmol/L. An AE of hyponatremia (Grade 2/moderate) was reported.

Patient ID (b) (6) **(Hyponatremia during treatment period; and Hypernatremia during open label period):** 12 y/o male with history of optic glioma, secondary adrenocortical insufficiency, diabetes insipidus, central hypothyroidism, and cerebral hemorrhage related to an arteriovenous malformation. Pertinent concomitant medications included levothyroxine, desmopressin, hydrocortisone, and hydrocortisone sodium succinate. On Day 99, the patient's fluid intake was approximately 20 oz more than usual, and on Day 100 his sodium level was 127 mmol/L. The patient's family was advised to administer stress dose hydrocortisone if he became symptomatic, reduce overall fluid daily goal by 24-30 oz, give half the dose of desmopressin, and recheck sodium in 1 to 2 days. On Day 102, the patient's sodium was 126 mmol/L. Patient's mother indicated that fluid restriction at school was challenging. Patient developed a headache at school and was advised to drink more fluid. Patient developed vomiting and was evaluated at the emergency room where sodium level of 122 mmol/L. Patient was admitted to the pediatric intensive care unit where he was treated for hyponatremia (Grade 3/Severe) and levels normalized on Day 104. The study drug was temporarily discontinued on Day 103 and resumed on Day 107 at a dose of 1 mg daily.

On Day 480 during open-label treatment with setmelanotide (after completion of trial 040) the patient had an MRI of the spine and was fasting for the imaging test. On Day 481, the patient had a recorded sodium level of 177 mmol/L and was admitted to the pediatric intensive care unit. The patient experienced an altered mental status. The MRI demonstrated metastasis, and the suspected diagnosis was pilocytic astrocytoma with leptomeningeal dissemination. Hypernatremia was corrected while hospitalized. The study drug was temporarily discontinued starting Day 480 until next steps for treatment progression of malignancy were confirmed.

PTID (b) (6) **(Hyponatremia)**: 7-year-old male with history of craniopharyngioma, adrenocorticotropic hormone deficiency, diabetes insipidus, hypothyroidism, growth hormone deficiency cerebrospinal fluid reservoir placement and ventricular drainage. Pertinent medications were levothyroxine, somatropin, and desmopressin. Prior to the onset of the serious adverse event, the patient had an AE of hyponatremia (Grade 2/moderate) with a sodium value of 129 mmol/L that was recorded as ongoing. On Day 86, the patient was admitted to the hospital after a day of vomiting, headache, and diarrhea. The patient's mother doubled his regular hydrocortisone doses. The patient's blood sodium was 127 mmol/L (hemolyzed potassium) and he was hospitalized due to an abnormal blood sodium level (Grade 3/severe) that was considered secondary to gastroenteritis. The patient was discharged home on Day 87. On Day 88 the sodium level was 123, however the patient reported no more headache, diarrhea, or vomiting. Given these results, the patient was re-hospitalized. Desmopressin doses were adjusted. On Day 91, the patient was "feeling well" but sodium levels were 150 and then repeat level 140 mmol/L. The patient resumed his regular desmopressin and hydrocortisone doses. The events of gastroenteritis and abnormal blood sodium were considered recovered/resolved.

Hyponatremia SAE during open-label extension:
Patient ID (b) (6) **(Hyponatremic Seizure during open-label extension)**: 13 y/o female with history of germinoma status post craniotomy in (b) (6), complicated by development of hypopituitarism, diabetes insipidus, and secondary adrenocortical insufficiency. Concomitant medications included somatropin, desmopressin, levothyroxine and semaglutide. On Day 497 while receiving open-label setmelanotide, the patient experienced vomiting. On Day 498, the patient presented to the emergency room with headache and diffuse abdominal pain for 2-3 days, as well as symptoms of nausea and vomiting. The sodium level was reported as 127 mmol/L. On the morning of Day 499, the sodium level improved with recorded values that day of 129, 133, and 141. Patient was being prepared for discharge from the emergency room when she experienced a seizure. CT scan of the brain showed a focal midline pontine calcification and more generalized bilateral basal ganglia calcification. The patient experienced two additional seizures later that morning. After the third seizure, the patient continued to have decorticate posturing and bilateral foot tremors and remained unresponsive.

The patient was transferred to another hospital and admitted to the intensive care unit and

intubated. MRI of the brain showed no evidence of acute intracranial pathology and lobular separated cystic non-enhancing lesion measuring 13x12x12 mm likely corresponding to a previously observed lesion. The patient had an EEG that identified no seizure activity and cerebrospinal fluid analysis was negative for infection. On Day 502, the patient was extubated. On Day 503, the patient was awake, followed commands ad moved all extremities. Sodium levels fluctuated during the remainder of the hospitalization, at one point the patient again experienced hyponatremia and headache with sodium level of 124 mmol/L. On Day 511 the patient was discharged from the hospital. Study drug was restarted on Day 514. The event was categorized as 'hyponatremia seizure'.

Reviewer comment: Overall, there was an imbalance in SAEs of hyponatremia during the treatment period in trial 040, with a higher percent in the setmelanotide group compared to placebo (2.1% vs. 0%). The event of hyponatremia in PTID (b) (6) appears related to increased fluid intake in the setting of taking desmopressin. The patient may have increased his fluid intake because he was experiencing a headache. While the etiology of the headache is uncertain, headache is a potential adverse reaction related to setmelanotide therapy. The event of hyponatremia in PTID (b) (6) was in the setting of symptoms of nausea, diarrhea, headache that may have been related to a gastroenteritis though these symptoms are also potentially related to setmelanotide.

While the percentage of cases of hypernatremia was balanced between the setmelanotide and placebo groups, the second SAE of hypernatremia (PTID (b) (6)) may have been related to decreased oral intake and inability to tolerate desmopressin in the setting of nausea and vomiting which are symptoms potentially related to setmelanotide.

While events that occurred during the OLE are not included in the treatment-emergent SAEs for trial 040, there was a notable SAE of 'hyponatremic seizure' that occurred during the OLE (PTID (b) (6)). The patient had a history of DI and developed hyponatremia while taking desmopressin in the setting of nausea, vomiting, and abdominal pain which are all potential side effects of setmelanotide treatment. The etiology of the seizure activity is uncertain; hyponatremia and correcting the low sodium level too quickly are potential causes.

Overall, these events of hypernatremia and hyponatremia highlight the potential for sodium imbalances to occur in patients with acquired HO and concomitant diabetes insipidus on desmopressin therapy who experience treatment side effects such as nausea, vomiting, and headache. An association with setmelanotide cannot be excluded. It is therefore the opinion of this reviewer that hypernatremia and hyponatremia be included as potential risks related to setmelanotide treatment in Section 5 of the label (Warnings and Precautions). Providers and patients should be advised to monitor sodium levels and hydration status when there is a change in fluid intake potentially related to setmelanotide treatment.

<u>Hypersensitivity</u>

There was one SAE of 'anaphylactic reaction' (PTID (b) (6)) that occurred in a 6-year-old male patient with history of a CNS germ cell tumor with hypothalamic and pituitary involvement, diabetes insipidus, and adrenal insufficiency. The anaphylactic reaction (throat swelling, diffuse rash, abdominal pain) occurred immediately after eating pistachio ice cream. Based on the temporal relationship, the most likely cause of the anaphylactic reaction was exposure to pistachio.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 20 shows the TEAEs leading to treatment discontinuation during trial 040. A slightly lower percent of patients discontinued treatment in the setmelanotide group compared to placebo (5.3% vs. 6.3%, respectively).

Table 19. TEAEs Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial 040

System Organ Class Preferred Term	Setmelanotide N=94 n(%)	Placebo N=48 n (%)	Overall N=142 n (%)
At Least 1 TEAE Leading to Study Drug Withdrawal	**5 (5.3)**	**3 (6.3)**	**8 (5.6)**
Gastrointestinal disorders	**2 (2.1)**	**0**	**2 (1.4)**
Gastroesophageal reflux disease	1 (1.1)	0	1 (0.7)
Nausea	1 (1.1)	0	1 (0.7)
Vomiting	1 (1.1)	0	1 (0.7)
Skin and subcutaneous tissue disorders	**2 (2.1)**	**0 (0.0)**	**2 (1.4)**
Skin hyperpigmentation	2 (2.1)	0 (0.0)	2 (1.4)
General disorders and administration site conditions	**1 (1.1)**	**1 (2.1)**	**2 (1.4)**
Injection site pruritus	1 (1.1)	0 (0.0)	1 (0.7)
Injection site reaction	0	1 (2.1)	1 (0.7)
Musculoskeletal and connective tissue disorders	**1 (1.1)**	**0**	**1 (0.7)**
Muscle spasms	1 (1.1)	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	**1 (1.1)**	**1 (2.1)**	**2 (1.4)**
Rhinorrhea	1 (1.1)	0	1 (0.7)
Dyspnea	0	1 (2.1)	1 (0.7)
Immune system disorders	**0**	**1 (2.1)**	**1 (0.7)**
Hypersensitivity	0	1 (2.1)	1 (0.7)

Source: Applicant Table 14.3.1.6A (submitted March 9, 2026, in response to IR dated November 6, 2025) confirmed by Clinical reviewer.

8.4.4. Significant Adverse Events

Significant events are discussed in the Section 8.4.2 (Serious Adverse Events) and Section 8.4.5 (Treatment Emergent Adverse Events and Adverse Reactions).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Table 22 shows TEAEs by SOC and PT with frequency of SOC in setmelanotide group greater than placebo, frequency of SOC ≥3% in any arm, and frequency of PT at least 2% greater in the setmelanotide group compared to placebo. The most frequent SOCs were *Gastrointestinal disorders*, *Skin and subcutaneous tissue disorders* and *Infections and infestations*. Of note, on narrative review of the TEAEs of hypernatremia, this reviewer concluded that there were 7 subjects in the setmelanotide group (7.4%), and 2 subjects in the placebo group (4.2%) with TEAEs of hypernatremia (see discussion in **Section 8.4.6,** Laboratory Findings, Chemistry subsection). Table 20 shows the percentage of subjects with hypernatremia reported by the Applicant in their IR response dated March 9, 2026.

Table 20. TEAEs by SOC and PT with Frequency of SOC in Setmelanotide Group >Placebo, SOC ≥3% in Any Arm, and Frequency of PT at least 2% greater in the Setmelanotide group compared to Placebo, Safety Population, Trial 040

System Organ Class Preferred Term	Setmelanotide N = 94 n (%)	Placebo N = 48 n (%)	Risk Difference (RD) RD (95% CI)	Forest Plot
Any AE	94 (100.0)	44 (91.7)	8.33 (0.51, 16.15)	
Gastrointestinal disorders	**71 (75.5)**	**27 (56.3)**	**19.28 (2.77, 35.79)**	
Nausea	52 (55.3)	12 (25.0)	30.32 (14.47, 46.16)	
Vomiting	36 (38.3)	9 (18.8)	19.55 (4.77, 34.33)	
Constipation	11 (11.7)	3 (6.3)	5.45 (-3.99, 14.89)	
Skin and subcutaneous tissue disorders	**61 (64.9)**	**18 (37.5)**	**27.39 (10.64, 44.15)**	
Skin hyperpigmentation	53 (56.4)	4 (8.3)	48.05 (35.34, 60.76)	
Dry skin	5 (5.3)	1 (2.1)	3.24 (-2.84, 9.31)	
Infections and infestations	**56 (59.6)**	**22 (45.8)**	**13.74 (-3.5, 30.98)**	
Upper respiratory tract infection	15 (16.0)	7 (14.6)	1.37 (-11.06, 13.8)	
Covid-19	12 (12.8)	5 (10.4)	2.35 (-8.61, 13.31)	
Gastroenteritis	8 (8.5)	1 (2.1)	6.43 (-0.51, 13.37)	

System Organ Class Preferred Term	Setmelanotide N = 94 n (%)	Placebo N = 48 n (%)	Risk Difference (RD) RD (95% CI)	Forest Plot
Ear infection	5 (5.3)	0 (0.0)	5.32 (0.79, 9.84)	
Otitis media	5 (5.3)	1 (2.1)	3.24 (-2.84, 9.31)	
Localised infection	3 (3.2)	0 (0.0)	3.19 (-0.35, 6.74)	
Tonsillitis	3 (3.2)	0 (0.0)	3.19 (-0.35, 6.74)	
Nervous system disorders	**48 (51.1)**	**20 (41.7)**	**9.40 (-7.83, 26.62)**	
Headache	34 (36.2)	15 (31.2)	4.92 (-11.4, 21.24)	
Dizziness	11 (11.7)	2 (4.2)	7.54 (-1.08, 16.15)	
Migraine	3 (3.2)	0 (0.0)	3.19 (-0.35, 6.74)	
Respiratory, thoracic and mediastinal disorders	**26 (27.7)**	**13 (27.1)**	**0.58 (-14.91, 16.06)**	
Oropharyngeal pain	10 (10.6)	2 (4.2)	6.47 (-1.94, 14.89)	
Metabolism and nutrition disorders	**23 (24.5)**	**8 (16.7)**	**7.80 (-5.86, 21.46)**	
Decreased appetite	11 (11.7)	1 (2.1)	9.62 (1.97, 17.27)	
Hyponatremia	6 (6.4)	1 (2.1)	4.30 (-2.08, 10.68)	
Hypernatremia	5 (5.3)	1 (2.1)	3.24 (-2.84, 9.31)	
Injury, poisoning and procedural complications	**19 (20.2)**	**8 (16.7)**	**3.55 (-9.76, 16.85)**	
Skin abrasion	3 (3.2)	0 (0.0)	3.19 (-0.35, 6.74)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**17 (18.1)**	**5 (10.4)**	**7.67 (-3.96, 19.3)**	
Melanocytic naevus	14 (14.9)	3 (6.2)	8.64 (-1.29, 18.58)	
Reproductive system and breast disorders	**14 (14.9)**	**5 (10.4)**	**4.48 (-6.77, 15.72)**	
Erection increased	4 (4.3)	1 (2.1)	2.17 (-3.57, 7.91)	
Genital pain	4 (4.3)	0 (0.0)	4.26 (0.19, 8.33)	
Endocrine disorders	**7 (7.4)**	**2 (4.2)**	**3.28 (-4.47, 11.03)**	
Adrenal insufficiency	3 (3.2)	0 (0.0)	3.19 (-0.35, 6.74)	
Ear and labyrinth disorders	**6 (6.4)**	**0 (0.0)**	**6.38 (1.45, 11.31)**	
Eustachian tube dysfunction	3 (3.2)	0 (0.0)	3.19 (-0.35, 6.74)	

Source: Applicant Table 14.3.1.2A submitted March 9, 2026, as part of IR dated November 6, 2025, and verified by Clinical reviewer using FDA Analysis Studio, Safety Explorer; adae.xpt dataset.

Table 21 shows adverse reactions with frequency ≥5% in the setmelanotide group and at least

1% greater in the setmelanotide group compared to placebo. This reviewer used combined terms “hyperpigmentation disorders”, “headache”, and “local administration reaction” to capture similar preferred terms. PTs included in the combined terms for “skin hyperpigmentation disorders” and “headache” are listed in the footnote of Table 23. The most frequent adverse reactions were “skin hyperpigmentation disorders”, “nausea”, “vomiting”, “headache”, “upper respiratory tract infection”, and “melanocytic naevus”.

Table 21. Adverse Reactions Occurring in ≥5% of Setmelanotide-treated Patients and at Least 1% Greater in the Setmelanotide Group, Trial 040

Preferred Term	Setmelanotide N = 94 n (%)	Placebo N = 48 n (%)	Risk Difference RD (95% CI)
Hyperpigmentation disorders[a]	55 (58.5)	5 (10.4)	48.1 (34.9, 61.3)
Nausea	52 (55.3)	12 (25.0)	30.3 (14.5, 46.2)
Vomiting	36 (38.3)	9 (18.8)	19.6 (4.8, 34.3)
Headache[b]	35 (37.2)	15 (31.2)	5.9 (-10.4, 22.3)
Upper respiratory tract infection	15 (16.0)	7 (14.6)	1.4 (-11.1, 13.8)
Melanocytic naevus	14 (14.9)	3 (6.2)	8.6 (-1.3, 18.6)
Covid-19	12 (12.8)	5 (10.4)	2.4 (-8.6, 13.3)
Constipation	11 (11.7)	3 (6.2)	5.5 (-3.9, 14.9)
Decreased appetite	11 (11.7)	1 (2.1)	9.6 (1.9, 17.3)
Dizziness	11 (11.7)	2 (4.2)	7.5 (-1.1, 16.2)
Oropharyngeal pain	10 (10.6)	2 (4.2)	6.5 (-1.9, 14.9)
Gastroenteritis	8 (8.5)	1 (2.1)	6.4 (-0.5, 13.4)
Back pain	7 (7.4)	1 (2.1)	5.4 (-1.3, 12.0)
Arthralgia	6 (6.4)	2 (4.2)	2.2 (-5.3, 9.7)
Hyponatremia	6 (6.4)	1 (2.1)	4.3 (-2.1, 10.7)
Dry skin	5 (5.3)	1 (2.1)	3.2 (-2.8, 9.3)
Ear infection	5 (5.3)	0 (0.0)	5.3 (0.8, 9.8)
Hypernatremia	5 (5.3)	1 (2.1)	3.2 (-2.8, 9.3)
Injection site swelling	5 (5.3)	1 (2.1)	3.2 (-2.8, 9.3)
Otitis media	5 (5.3)	1 (2.1)	3.2 (-2.8, 9.3)

Source: Clinical reviewer analysis, FDA Analysis Studio, Safety Explorer; adae.xpt dataset submitted March 9, 2026, in response to IR dated November 6, 2025, and Applicant Table 14.3.1.2A submitted March 9, 2026.
[a]Hyperpigmentation disorders includes - skin hyperpigmentation, skin discolouration, nail pigmentation, ephelides, and pigmentation disorder
[b]Headache includes headache and migraine

Of note, in the current label for IMCIVREE for the approved indications of monogenic and

syndromic obesity, “injection site reactions” are listed as a common adverse reaction. However, in trial 040 the frequency of the OCMQ (narrow) term “local administration reaction” was similar between the setmelanotide and placebo groups (53.2% vs. 54.2%, respectively) (Table 22).

Table 22. Frequency of OCMQ (Narrow) Term Local Administration Reaction, Trial 040, Safety Population

OCMQ term Preferred terms	Setmelanotide N=94 n (%)	Placebo N=48 n (%)
Local Administration Reaction	**52 (55.3)**	**26 (54.2)**
Injection site reaction	22 (23.4)	11 (22.9)
Injection site erythema	16 (17.0)	6 (12.5)
Injection site pruritus	16 (17.0)	8 (16.7)
Injection site pain	11 (11.7)	7 (14.6)
Injection site induration	8 (8.5)	2 (4.2)
Injection site edema	7 (7.4)	4 (8.3)
Injection site swelling	5 (5.3)	1 (2.1)
Injection site bruising	4 (4.3)	2 (4.2)
Injection site hemorrhage	3 (3.2)	0 (0.0)
Injection site discoloration	1 (1.1)	0 (0.0)
Injection site mass	1 (1.1)	2 (4.2)
Injection site nodule	1 (1.1)	0 (0.0)
Vaccination site pain	1 (1.1)	0 (0.0)
Incision site pain	0 (0.0)	1 (2.1)

Source: Reviewer analysis, OCS Analysis Studio, Safety Explorer; adae.xpt dataset submitted March 9, 2026, in response to IR dated November 6, 2025.

Reviewer comment: Common adverse reactions in trial 040 (skin hyperpigmentation, nausea, vomiting, and headache) are consistent with currently labeled common adverse reactions in the IMCIVREE label. However, the frequency of injection site reaction-related PTs was similar between the setmelanotide and placebo groups in trial 040, unlike currently labeled indications.

8.4.6. Laboratory Findings

As per protocol for trial 040, laboratory abnormalities that were clinically relevant were reported as TEAEs. In the initial NDA submission, the Applicant’s analyses of laboratory data combined results from adult and pediatric patients. These analyses were not interpretable because the adult and pediatric populations have different cut-off ranges for normal values, and normal ranges also vary within the pediatric population based on age, sex, and/or height. In a response to an IR dated January 5, 2026, the Applicant provided descriptive statistics for clinical laboratory data (actual values and changes from baseline) for subjects aged ≥18 years.

Liver Laboratories

Among subjects aged ≥18 years there were no clinically meaningful differences between the 2 treatment groups in shifts from baseline for liver laboratory parameters (AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin) during the treatment period for trial 040. Table 23 shows subjects with liver enzyme values exceeding specified levels. There were 2 subjects with AST and/or ALT >3x ULN in the setmelanotide group and no subjects in the placebo group (4.4% vs. 0%, respectively). The narratives for these 2 patients in the setmelanotide group are provided below (PTIDs 007-005 and 018-001).

Table 23. Subjects Age ≥18 Years with Liver Enzyme Values Exceeding Specified Levels, Safety Population, Trial 040

Laboratory Parameter	Criteria	Setmelanotide (N=45) n (%)	Placebo (N=21) n (%)
ALT	>3 x ULN	1 (2.2)	0
	>5 x ULN	0	0
AST	>3 x ULN	1 (2.2)	0
	>5 x ULN	0	0
AST and/or ALT	>3 x ULN	2 (4.4)	0
Total bilirubin	>2 x ULN	0	1 (4.8)
Alkaline phosphatase	>1.5 x ULN	2 (4.4)	0

Source: Applicant Table 14.3.2.7.1 submitted March 9, 2026, in response to IR dated November 6, 2025.

Table 24 shows the PTs related to abnormal liver enzymes for adult and pediatric patients. The frequency of the combined term “liver enzyme abnormality” (consisting of PTs “ALT increased” “AST increased” “liver function test abnormal” and “hepatic enzyme increased”) was higher in the setmelanotide group compared to placebo (6.4% vs. 0%, respectively).

Table 24. Frequency of Preferred Terms Related to Liver Enzyme Abnormalities, Safety Population, Trial 040

	Setmelanotide (N=94) n (%)	Placebo (N=48) n (%)
Liver enzyme abnormality	6 (6.4)	0 (0.0)
ALT increased	4 (4.3)	0 (0.0)
AST increased	2 (2.1)	0 (0.0)
Liver function test abnormal	1 (1.1)	0 (0.0)
Hepatic enzyme increased	1 (1.1)	0 (0.0)

Source: Clinical reviewer analysis, FDA Analysis Studio, Safety Explorer; adae.xpt dataset submitted March 9, 2026, in response to IR dated November 6, 2025.

In response to an IR dated September 8, 2025, the Applicant provided clinical narratives for the 4 patients who reported TEAEs of "ALT increased" and/or "AST increased" (total of 6 events). Table 25 provides clinical information for these events. All patients with TEAEs "ALT increased" and/or "AST increased" were randomized to the setmelanotide group (2 pediatric and 2 adults). Most of the ALT and AST elevations were mild.

Table 25. Description of TEAEs related to Elevated Liver Enzymes

Patient ID	Treatment group	TEAE Preferred Term	Age at enrollment (years)	Peak lab value reported	Study drug interrupted due to TEAE	Lab abnormality resolved
(b) (6)	Setmelanotide	ALT increased	16	2x ULN	No	Yes
	Setmelanotide	ALT increased	48	1.1x ULN	No	Yes
		AST increased		1.1x ULN		
	Setmelanotide	ALT increased	12	4.7x ULN	No	Yes
	Setmelanotide	ALT increased	32	1.5x ULN**	Yes	Yes
		AST increased		3.9x ULN**		

Source: Applicant response to IR dated September 8, 2025.
*Patient (b) (6) also experienced an increase in AST to peak value 2.2x ULN though this was not recorded as a TEAE by the Applicant
**As per the Applicant's response to IR dated January 5, 2026, the ALT and AST values increased further than indicated in the table however were not reported.

The following narratives are for patients who experienced AST and/or ALT elevations ≥3X ULN:

Patient ID (b) (6) – 12 y/o male with history of optic glioma, secondary adrenal insufficiency, diabetes insipidus, central hypothyroidism and metabolic dysfunction-associated steatotic liver disease (MASLD). Concomitant medications at the time of the liver enzyme TEAE included loratadine, saccharomyces boulardii, dietary supplements, krill oil, vitamins not otherwise specified (NOS), sambucus nigra fruit, lisdexamfetamine mesylate, ascorbic acid, colecalciferol, levothyroxine, desmopressin, hydrocortisone, and hydrocortisone sodium succinate. Baseline ALT level was elevated 1.8x ULN (52 U/L, normal range (NR) 5-30 U/L). Baseline AST level was in normal range. Patient had a peak ALT value 4.7x ULN (142 U/L) at Visit 2 (Day 23). The AST also peaked on that day at 2.2x ULN (86 U/L, NR 0-39 U/L), however, this was not recorded as a TEAE by the Applicant. No action was taken with study drug in response to liver enzyme abnormalities. Of note, ALT and AST values were in normal range at the end of the treatment period. The values provided for direct bilirubin, total bilirubin, and alkaline phosphatase were in

normal range for this patient. GGT was elevated to 2x ULN. Given the patient's underlying diagnosis of MASLD and resolution of liver enzyme abnormalities without change in study drug, it is possible that the enzyme abnormalities were related to MASLD.

Patient ID (b) (6) - 32-year-old female with history of craniopharyngioma status post multiple resections, central hypothyroidism, diabetes insipidus, central adrenal insufficiency, growth hormone deficiency and secondary hypogonadism. Concomitant medications at the time of the events included: hydrocortisone, levothyroxine sodium, desmopressin, somatropin, estradiol, progesterone, trazodone, bupropion, venlafaxine, alprazolam, naratriptan, galcanezumab, fexofenadine, levosalbutamol, budesonide/formoterol, montelukast, fluticasone, tiotropium, linaclotide, famotidine, phentermine, naltrexone, tirzepatide, magnesium, and riboflavin.

The AST level peaked to 3.9x ULN (166 U/L, NR 14-43) on Day 23. The ALT also peaked on that day to 1.5x ULN (79 U/L, NR 10-53 U/L). The study drug was interrupted because of these laboratory abnormalities on Day 25. As per the clinical narrative provided by the Applicant, on Day 29 the grade of the preferred term "AST increased" increased from 1 to 2, and the grade of "ALT increased" increased from 2 to 3, however, the laboratory values related to these grade changes were not reported. The TEAEs were reported as resolved on Day 39 and study drug was resumed on Day 43 with no further liver enzymes abnormalities reported. AST and ALT values were in normal range for Visits 4 (Day 80) through end of treatment visit. Total and direct bilirubin levels were in normal range during the treatment period. The patient completed the trial treatment period on Day 414.

Reviewer comment: While there was a higher frequency of TEAEs related to increased AST and/or ALT laboratory values in the setmelanotide group compared to the placebo group, the elevations were generally mild. There were 2 patients in which elevations in AST and/or ALT were >3x ULN. One patient (ID (b) (6)) had a medical history of MASLD which is a potential alternate explanation for the liver enzyme abnormality. The second patient (ID (b) (6)) had study drug interrupted due to the liver enzyme elevation, and it is possible that the elevation was related to study drug however the patient resumed study drug after the liver enzyme elevation resolved and enzyme values remained in normal range. Overall, there were a small number of mild elevations in liver enzymes (<3x ULN). It cannot be concluded that the cases of AST and/or ALT elevations ≥3x ULN were related to study drug.

Hematology

Among patients ages ≥18 years in trial 040, there were no clinically meaningful differences between the 2 treatment groups in shifts from baseline for any hematology parameter. The frequency of patients with OMCQ term "anemia" was higher in the setmelanotide group compared to placebo (3.2% vs. 0%, respectively) (Table 26). There were no SAEs of anemia.

Table 26. Preferred Terms in the Narrow OCMQ term "Anemia" by Age Group, Safety Population, Trial 040

OCMQ Preferred terms	Setmelanotide N=94 n (%)	Placebo N=48 n (%)
Anemia	**3 (3.2)**	**0 (0.0)**
Anemia	2 (2.1)	0 (0.0)
Hemoglobin decreased	2 (2.1)	0 (0.0)
Hematocrit decreased	1 (1.1)	0 (0.0)

Clinical reviewer analysis, FDA Analysis Studio, Safety Explorer; adae.xpt dataset submitted March 9, 2026, in response to IR dated November 6, 2025.

Reviewer comment: While there was a slightly higher frequency of the OMCQ term "anemia" in the setmelanotide group compared to placebo, the number of events was small and given the complexity of the patient population it is difficult to conclude that these events were related to study drug.

Chemistry

Among patients ages ≥18 years, there were no clinically meaningful differences between the 2 treatment groups in shifts from baseline for the following chemistry parameters: potassium, bicarbonate, albumin, BUN, creatinine, phosphate, magnesium, calcium.

There was an imbalance in TEAEs of "hypernatremia and "hyponatremia". Table 27 shows subjects with TEAEs (including SAEs) related to serum sodium abnormalities. This table is based on review of clinical narrative data provided by the Applicant in response to IR dated January 26, 2026. It is the conclusion of this reviewer that there were 7 subjects with TEAEs of hypernatremia in the setmelanotide group and 2 subjects in the placebo group (7.4% vs. 4.2%, respectively). This differs from the Applicant's position that there were 5 subjects in the setmelanotide group and 2 subjects in the placebo group (5.3% vs. 4.2%, respectively). This reviewer also concludes that there were 6 subjects with TEAEs of hyponatremia in the setmelanotide group and 1 subject in the placebo group, which is consistent with the Applicant's position (6.4% vs. 2.1%, respectively).

Of note, there were 4 patients who experienced multiple events of hyponatremia and hypernatremia. All patients had a baseline history of diabetes insipidus, except for 1 patient (PTID (b) (6)). See **Section 8.4.2** for discussion of SAEs of hyponatremia and hypernatremia.

Table 27. Subjects with Sodium Imbalance Treatment-Emergent Adverse Events and Serious Adverse Events, Safety Population, Trial 040

Patient ID	TEAE or SAE	Treatment Arm	Age* (Years)	DI	Sodium Abnormality	Trial Day	Comments
(b) (6)	SAE	Setmelanotide	22	yes	Hypernatremia	181	Detected on home test, no secondary symptoms; desmopressin dose thought to be

							no longer effective due to recent resumption of growth hormone
(b) (6)	SAE	Setmelanotide	12	yes	Hyponatremia	103	Days 99-102 had increased fluid intake (difficulty with fluid restriction goals) associated with hyponatremia at home; Day 103 had headache at school, encouraged to drink more water then started vomiting which prompted emergency room visit
	TEAE	Multiple events of both hypo- and hypernatremia throughout the trial					
	SAE	Setmelanotide	6	yes	Hypernatremia	44	Day 43 episodes of vomiting, unable to tolerate oral water or desmopressin, required hospitalization for fluid and sodium management
	TEAE	Multiple events of both hypo- and hypernatremia throughout the trial					
	SAE	Setmelanotide	7	yes	Hyponatremia	86	Occurred in the setting of vomiting, diarrhea and headache, attributed to gastroenteritis
	TEAE	Multiple events of both hypo- and hypernatremia throughout the trial					
	SAE	Placebo	10	yes	Hypernatremia	247	Missed and delayed doses of desmopressin the day prior
	TEAE	Setmelanotide	16	yes	Hypernatremia	362	In the setting of an SAE documented as 'altered state of consciousness', the patient was evaluated for fever, vomiting, lethargy, confusion, and decreased oral intake; found to have hypernatremia; was suspected to have meningitis
	TEAE	Setmelanotide	13	no	Hyponatremia	289	No description provided
	TEAE	Setmelanotide	6	yes	Hypernatremia	4 events between Day 27 to 273	
	TEAE	Setmelanotide	7	yes	Hyponatremia	2 events on Day 50 and 321	
	TEAE	Setmelanotide	13	yes	Multiple events of both hypo- and hypernatremia between Day 78 to 267		
	TEAE	Placebo	59	yes	Hyponatremia	218	Noted to have headache and blurry vision on day 216
	TEAE	Placebo	9	yes	Hypernatremia	Multiple events of hypernatremia throughout the trial	

Source: Generated by DPMH clinical reviewer and this clinical reviewer based on Applicant response to IR dated January 21, 2026, and NDA 213793/S-009, Module 5, 14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events, RM-493-040-report-body-2
Abbreviations: DI: concomitant Diabetes Insipidus
*Age at enrollment in years

Reviewer Comment: A higher percentage of patients in the setmelanotide group experienced TEAEs of hypernatremia and hyponatremia compared to the placebo group in trial 040. However, it is difficult to attribute causation of these TEAEs of sodium imbalance directly to setmelanotide, particularly given that all but 1 patient had underlying diabetes insipidus (DI). Some patients experienced sodium abnormalities related to exacerbation of underlying DI due to acute infectious illness (e.g., gastroenteritis, viral illness) or alterations in desmopressin dosing. It cannot be ruled out that setmelanotide contributed to headache experienced by 1 patient with an SAE of hypernatremia (PTID (b) (6)) and vomiting in another patient with SAE of hypernatremia (PTID (b) (6)). In these cases, it is possible that setmelanotide triggered adverse reactions that exacerbated DI. However, it cannot be concluded based on the data provided that setmelanotide directly caused hypernatremia or hyponatremia. It is also notable that there was a higher frequency of patients with DI at baseline in the setmelanotide group compared to placebo (83% vs. 75%, respectively). Given the potential for setmelanotide to cause adverse reactions (such as nausea, vomiting and headache) that exacerbate DI, this reviewer recommends adding risk of sodium imbalance in patients with DI to Section 5 (Warnings and Precautions).

8.4.7. Vital Signs

There were no clinically significant differences in vital signs (blood pressure, heart rate, respiratory rate, temperature) between the setmelanotide and placebo treatment groups in trial 040. There were no significant imbalances in TEAEs related to vital sign abnormalities. A 24-hour ambulatory blood pressure monitoring (ABPM) assessment was conducted at select sites in North America and Europe. Patients wore the monitor for a 24-hour period before each of the following visits: Day 1, Week 24, and Week 60. Results of the ABPM are shown in Table 28. There were small mean reductions in diastolic blood pressure (-1.45 mmHg [SD 6.05]) and systolic blood pressure (-1.58 mmHg [SD 9.50]) in the setmelanotide group. Conversely, mean systolic blood pressure increased in the placebo group from baseline (+2.25 mmHg [SD 9.56]). There was a mean reduction in heart rate from baseline in the setmelanotide group (-7.81 bpm [SD 15.762]).

Table 28. Mean Change from Baseline to End of Treatment in 24-Hour Ambulatory Blood Pressure Parameters, Trial 040

Parameter	Statistic	Setmelanotide (N=94)	Placebo (N=48)

24-Hr Diastolic Blood Pressure (mmHg)	n	30	13
	Mean (SD)	-1.45 (6.051)	-0.03 (11.597)
	Median	-0.62	0.68
	Min, Max	-11.5, 8.6	-34.3, 13.6
24-Hr Systolic Blood Pressure (mmHg)	n	30	13
	Mean (SD)	-1.58 (9.504)	2.25 (9.558)
	Median	-1.68	3.31
	Min, Max	-19.9, 17.6	-21.7, 15.1
24-Hr Heart Rate (bpm)	n	30	13
	Mean (SD)	-7.81 (15.762)	-2.49 (10.654)
	Median	-7.17	-0.72
	Min, Max	-53.9, 16.0	-34.7, 7.4
	Min, Max	-12.2, 8.8	-35.0, 12.8

Source: Applicant CSR for Trial RM-493-040, Table 41

Reviewer comment: There was no evidence of vital sign abnormalities related to setmelanotide therapy.

8.4.8. Electrocardiograms (ECGs)

In trial 040, 12-lead ECGs were performed at screening only as per the protocol.

8.4.9. QT

The Applicant conducted a thorough QT study as a post-marketing requirement (Study RM-493-032). The Interdisciplinary Review Team (IRT) for Cardiac Safety Studies reviewed the study and concluded that at a dose 2.3 times the maximum recommended dose (3 mg), setmelanotide did not prolong the QTcF (see DARRTs IRT review dated 4/5/2023).

8.4.10. Immunogenicity

The Applicant had a postmarking commitment (PMC) to improve the performance and repeatability of the setmelanotide confirmatory ADA assay to ensure that the confirmatory ADA assay can reliably test for the presence of ADA in clinical samples (PMC 3973-4). This PMC was fulfilled on 5/2/2023. There were no patients with confirmed positive anti-drug antibodies to RM-493 in trial 040. See review from the Office of Pharmaceutical Quality Research (OPQR) dated October 2, 2025. The OPQR review team concluded that, "overall, setmelanotide demonstrates a low immunogenicity risk, with findings supporting that immunogenicity does not impact its clinical benefit-risk profile."

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Hyperpigmentation disorders

Hyperpigmentation related to setmelanotide treatment is a result of agonism of the MC1 receptor, which is associated with increased eumelanin secretion. Eumelanin is a dark pigment that absorbs UV light and is photo protective. The MC1 receptor agonist plays a role in the ability of the melanocytes to recover from UV damage.[20]

The frequency of the combined term "hyperpigmentation disorders" (which included the PTs "skin hyperpigmentation", "ephelides", "nail pigmentation", "skin discoloration", and "pigmentation disorder") was higher in the setmelanotide group compared to placebo (58.5% vs. 10.4%, respectively). The increased risk of skin hyperpigmentation with setmelanotide therapy is consistent with currently labeled adverse reactions for IMCIVREE.

Melanocytic Nevi
Per protocol a comprehensive skin exam was performed at screening, Week 8, and end of treatment (Week 60) or early termination of treatment. If any new concerning lesion or changes in existing lesions were identified during the treatment period, the lesions were to be evaluated by a dermatologist and biopsied if clinically indicated. There was a higher percent of patients in the setmelanotide group that reported the PT "melanocytic naevus" compared to the placebo group (14.9% vs. 6.2%, respectively). The PT "melanocytic naevus" included verbatim terms for new nevi formation, nevi that were enlarging, and pre-existing nevi that

[20] Wolf Horrell EM, Boulanger MC, D'Orazio JA. Melanocortin 1 Receptor: Structure, Function, and Regulation. Front Genet. 2016 May 31;7:95.

were darkening. In the setmelanotide group there were 6 pediatric patients (ages <18 years) and 9 adult patients with a new or changing melanocytic naevus.

The Applicant provided a listing of patients who developed new moles, or changes in existing moles (e.g., darkening or enlargement) with descriptions of the moles and whether dermatologic evaluations were completed (see Appendix). Eight patients were referred to a dermatologist for further evaluation of moles. Two patients had biopsies and pathology showed "compound dysplastic nevi with mild to moderate cytologic atypia extending to the base". The patient was recommended to follow-up with dermatology every three months.

Melanoma across the Setmelanotide Development Program
As of the data cutoff date of March 26, 2025, a total of 2 patients treated with setmelanotide across the once daily setmelanotide development program, including 1 patient in the commercial setting, had an SAE of melanoma. One patient, with the diagnosis of BBS, had an SAE of malignant melanoma (Grade 3) diagnosed after the patient transitioned from receiving setmelanotide 3.0 mg in LTE trial 022 to receiving commercial setmelanotide. The melanoma was identified during routine clinical trial skin examination at the end of the study visit for LTE trial 022. The patient had fair skin type (Fitzpatrick 2) and as per the Applicant's clinical narrative (provided in the Summary of Clinical Safety), the patient "was deemed as a high-risk individual with reported and documented evidence of significant ultraviolet (UV) light exposure." The patient's fair skin type and significant UV light exposure are potential risk factors for the development of melanoma.

In the post-marketing setting, one patient with BBS was diagnosed with superficial spreading melanoma stage 1. Approximately 5 months after initiating treatment with setmelanotide a dermatological examination showed hyperpigmentation (mainly on the upper hemisphere and photo-exposed areas) and a few nevi on the trunk and back, 2 of which were suspicious (right 3 mm and left 6 mm). The 2 suspicious lesions were biopsied, and results of the right lesion showed a superficial spreading melanoma with maximum thickness of 0.6 mm. The stage was reported as pT1a. Results for the left lesion showed a "predominantly dermal compound nevus with healthy margins". Setmelanotide was discontinued by the physician due to lack of beneficial effects and the occurrence of adverse reactions. This patient had a strong history of UV exposure and photodamage as risk factors.

Reviewer Comment: Skin hyperpigmentation is a known risk associated with setmelanotide treatment. There were 2 patients in trial 040 who had biopsies because of abnormal skin exams and each patient had a compound dysplastic nevus with mild to moderate cytologic atypia. Based on the currently recommended management of histologically dysplastic nevi, there is ample evidence that mildly or moderately histologically dysplastic nevi are not

melanoma precursors and do not require re-excision when biopsy removes the entire visible lesion.[21]

There have been 2 patients treated with setmelanotide across the once daily setmelanotide development program diagnosed with melanoma. Both patients had other risk factors for development of melanoma (fair skin type, strong history of UV light exposure, photodamage).

The current label for IMCIVREE includes "Skin Pigmentation, Darkening of Pre-Existing Nevi, and Development of New Melanocytic Nevi" in Warnings and Precautions (Section 5.4) with a recommendation to "perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmentary lesions." It is the opinion of this reviewer that the current recommendation for full body skin exam prior to initiation and periodically during treatment with IMCIVREE be retained.

8.5.2. Disturbance in sexual arousal

Treatment with setmelanotide has previously been associated with sexual AEs, most notably intermittent spontaneous penile erections. Disturbance in sexual arousal is listed in the Warnings and Precautions section of the current label for IMCIVREE. In trial 040, the frequency of the combined term containing PTs "spontaneous penile erection" and "increased penile erections" was higher in the setmelanotide group compared to placebo (7% vs. 4%, respectively for the combined term). There were no reported AEs related to disturbance in sexual arousal in female patients.

Reviewer comment: This reviewer recommends reporting the frequency of the PTs "spontaneous penile erection" and "increased penile erections" in trial 040 in Section 6 of the label (Clinical Trial Experience).

8.5.3. Injection site reactions

In trial 040 the frequency of the OCMQ term "local administration reaction" was similar between the setmelanotide and placebo groups (53.2% vs. 54.2%, respectively) (Table 24 in Section 8.4.5). The current IMCIVREE label lists injection site reactions as a common adverse reaction. This was not observed in trial 040.

Reviewer comment: The frequency of injection site reactions was similar between the setmelanotide and placebo groups in trial 040.

[21] Spaccarelli N, Drozdowski BA et al. Dysplastsic nevus part II: Molecular/genetic profiles and management. Journal of the American Academy of Dermatology, Volume 88, Issue 1, 13 – 20.

8.5.4. Gastrointestinal disorders

The most reported gastrointestinal disorders in trial 040 with frequency greater in the setmelanotide group compared to placebo were nausea (55.3% vs. 25.0%, respectively), vomiting (38.3% vs. 18.8%), and constipation (11.7% vs. 6.2%). There was 1 SAE of "nausea" in the setmelanotide group and none in the placebo group. There were 2 SAEs of "vomiting", one in each treatment group. Nausea and vomiting are listed as common adverse reactions in the current IMCIVREE label.

Reviewer comment: Nausea and vomiting are known adverse reactions associated with setmelanotide therapy. These adverse reactions are monitorable. It is the recommendation of this reviewer that nausea, vomiting, and constipation be included in the adverse reactions table for trial 040 in Section 6.

8.5.5. Psychiatric disorders

As with all centrally acting weight-loss drugs, depression and suicidality are AEs of interest. In trial 040, the frequency of the OCMQ broad term "depression" was lower in the setmelanotide group compared to placebo (13.8% vs. 18.8%, respectively, see Table 29). The frequency of the SOC "psychiatric disorders" was lower in the setmelanotide group compared to placebo (26.6% vs. 29.2%, respectively) (Table 30).

Table 29. Frequency of OCMQ (Broad) Term "Depression", Safety Population, Trial 040

OCMQ (broad) Preferred term	Setmelanotide N=94 n(%)	Placebo N=48 n(%)
Depression	**13 (13.8)**	**9 (18.8)**
Depression	5 (5.3)	3 (6.2)
Depressive symptoms	5 (5.3)	5 (10.4)
Anhedonia	1 (1.1)	0 (0.0)
Depressed mood	1 (1.1)	0 (0.0)
Self-injurious ideation	1 (1.1)	0 (0.0)
Adjustment disorder with depressed mood	0 (0.0)	1 (2.1)

Source: Reviewer generated analysis using FDA Analysis Studio, Safety Explorer; adae.xpt dataset submitted March 9, 2026, in response to IR dated November 6, 2025.

Table 30. Subjects in Psychiatric Disorders SOC, Safety Population, Trial 040

System Organ Class Preferred term	Setmelanotide N=94 n(%)	Placebo N=48 n(%)

Psychiatric disorders (SOC)	**25 (26.6)**	**14 (29.2)**
Depression	5 (5.3)	3 (6.2)
Depressive symptom	5 (5.3)	5 (10.4)
Sleep disorder	4 (4.3)	2 (4.2)
Insomnia	3 (3.2)	0 (0.0)
Anxiety	2 (2.1)	0 (0.0)
Attention deficit hyperactivity disorder	2 (2.1)	1 (2.1)
Irritability	2 (2.1)	1 (2.1)
Affective disorder	1 (1.1)	0 (0.0)
Anhedonia	1 (1.1)	0 (0.0)
Defiant behavior	1 (1.1)	0 (0.0)
Depressed mood	1 (1.1)	0 (0.0)
Hallucination, auditory	1 (1.1)	0 (0.0)
Libido decreased	1 (1.1)	0 (0.0)
Self-injurious ideation	1 (1.1)	0 (0.0)
Terminal insomnia	1 (1.1)	0 (0.0)
Adjustment disorder with depressed mood	0 (0.0)	1 (2.1)
Obsessive-compulsive disorder	0 (0.0)	1 (2.1)
Restlessness	0 (0.0)	1 (2.1)

Source: Reviewer generated analysis using FDA Analysis Studio, Safety Explorer; adae.xpt dataset submitted March 9, 2026, in response to IR dated November 6, 2025.

There were no SAEs in the *Psychiatric disorders* SOC. Of note, there was one TEAE with PT "self-injurious ideation" in the setmelanotide group. In response to an information request dated October 10, 2025, the Applicant provided the narrative below for this TEAE.

Patient ID (b) (6) **("self-injurious ideation") -**This patient was 7-year-old female with relevant medical history of depression under the care of a psychologist and psychiatrist. On study day 127 an AE of "self-injurious ideation" was reported (verbatim description: 'thoughts of being "better off dead" in time of extreme anger'). The event was reported as occurring during an episode of extreme anger. Per protocol, the Columbia-Suicide Severity Rating Scale (C-SSRS) and Children's Depression Inventory-2 (CDI-2) were administered and did not meet the threshold for referral to a mental health provider. Further follow-up was solicited from the Investigator who indicated that, per the clinic notes, the patient's parents reported that there was no true suicidal ideation, and that the child said this in anger to elicit a reaction when she was denied something she wanted. The patient completed the double-blind treatment period and continued to receive setmelanotide treatment during bridging visits.

Reviewer comment: The frequency of TEAEs related to depression was lower in the setmelanotide group compared to the placebo group in trial 040.

8.5.6. Growth and development

The Division of Pediatrics and Maternal Health (DPMH) was consulted to assess the effects of setmelanotide on linear growth and development in trial 040 (see DPMH review in DAARTs dated February 26, 2026). There were 76 patients enrolled in trial 040 aged 4 to <18 years of age. Of note, the Applicant only collected the year of birth for patients because full date of birth was considered a "prohibited subject identifier in clinical trials" in some jurisdictions in which the trial was conducted (see Applicant response to IR request dated October 10, 2025). In the absence of full date of birth, all growth and development analyses were conducted based on an assigned date of July 1st during the year of birth. As a result, the DPMH reviewer states, *"the precise age of each pediatric patient in the trial may by underestimated or overestimated by 1 day to 6 months. Therefore, the interpretation of pubertal development and linear growth velocity are limited based on the potential for comparison of patients to age-matched peers with up to 6 months difference."*

Pubertal development:
The DPMH reviewer concluded that there were several limitations in assessing pubertal development as follows:

- *The definitions of 'precocious' or 'delayed' are determine by age cut-offs. Because the patient ages in this trial may be inaccurate up to 6 months, the assessments of precocious and delayed may be inaccurate.*
- *It is unclear which patients underwent physician assessment as opposed to self-assessment (for Tanner Stages). Therefore, there may have been inconsistency in how Tanner Stages were assigned.*
- *The protocol stated that if a female patient reached menarche during the trial, the Tanner exam at EOT could be skipped. The rationale for this is unclear. While menarche typically occurs later in the progression of puberty, it does not indicate the end of pubertal development. Therefore, menarche does not warrant skipping a Tanner Stage assessment. This may have unnecessarily contributed to the number of patients missing Tanner Stage EOT data.*
- *Patients in this trial were known to have underlying endocrinopathies (e.g. hypothyroidism, growth hormone deficiency, secondary hypogonadism) that may have impacted their pubertal development patterns which limits interpretation based on expected norms for age and sex. This limitation is mitigated to some degree by having a disease-matched placebo arm for comparison.*
- *Given the number of prepubertal patients throughout the trial and post-pubertal pediatric patients at the start of the trial, ultimately there were 17 (of 35) pediatric patients in the setmelanotide group and 6 (of 18) in the placebo group that were*

undergoing pubertal development during the trial. This small number of patients in each cohort limits the interpretation of the available data.

As per the DPMH review, *"the percentage of patients with pubertal development stages that appeared to be normal for age and sex at end of treatment compared to baseline were 89% (31/35) in the setmelanotide group and 89% (16/18) in the placebo group."* The DPMH reviewer concluded, "*While there were several limitations in assessing pubertal development based on the data provided, ultimately there was no signal of abnormal pubertal development associated with treatment with setmelanotide*."

Linear Growth Velocity

Of the 76 pediatric patients in trial RM-493-040, 66 had available end of treatment (EOT) height data for review. The primary metric for analysis was the height Z-score, standardized deviations from age- and sex- adjusted means. As indicated in the DPMH review, a change in height Z-score over time for an individual patient that is less than 0.5 standard deviations from baseline is generally considered not clinically significant.[22] The DPMH reviewer found that the percentage of pediatric patients with a decrease in the World Health Organization (WHO) height Z-score of greater than 0.5 over the 56 to 60-week trial was 12% in the setmelanotide group and 9% in the placebo group (see Table 31). Of note, there were a small number of patients with a decrease of greater than 0.5. The DPMH reviewer concluded that there were limitations to assessment of the height Z-score, including: 1) patient ages in the trial may be inaccurate up to 6 months because only year of birth was recorded, 2) patients had underlying endocrinopathies (e.g. hypothyroidism, growth hormone deficiency) that may have impacted their linear growth patterns. However, despite these limitations, the reviewer concluded that there was no signal of abnormal linear growth velocity associated with treatment with setmelanotide.

Table 31. Summary of WHO Height Z-score Changes in Pediatric Patients after 56 to 60 weeks, Trial 040

	Setmelanotide n=43	**Placebo n=23**
Height Z-score		
Less than 0.5	84% (n=36)	74% (n=17)
Increase of greater than 0.5	5% (n=2)	17% (n=4)
Decrease of greater than 0.5	12%	9%

[22] Childress AC, Cutler AJ, Patel M, Oh C. Analysis of Growth Velocity in Children with Attention-Deficit/Hyperactivity Disorder Treated for up to 12 Months with Serdexmethylphenidate/Dexmethylphenidate. J Child Adolesc Psychopharmacol. 2023 May;33(4):134-142.

	(n=5)	(n=2)

Source: DPMH Clinical reviewer generated based on Applicant's response to IR dated October 21, 2025.

8.6. Safety Analyses by Demographic Subgroup

Treatment-emergent adverse events were assessed by sex and age (<12 years, 12 to <18 years, ≥18 years) subgroups. Overall, the frequency of common TEAEs by sex were similar. Of note, for patients <12 years of age, the frequency of the following PTs was lower in the setmelanotide group compared to placebo: vomiting (45% [n=9] vs. 50% [n=6], respectively) and nausea (40% [n=8] vs. 50% [n=6]). Otherwise, the frequency of common TEAEs were similar by age group. The patient numbers within race and ethnicity subgroups were too small to conclude meaningful differences. See the Appendix for forest plots of subgroup analyses for the following SOCS: *Gastrointestinal disorders, Skin and subcutaneous tissue disorders, Infections and infestations.*

8.7. Specific Safety Studies/Clinical Trials

Not applicable

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

See Section 8.5.1 for discussion of post-marketing cases of melanoma.

8.8.2. Human Reproduction and Pregnancy

There were no pregnancies during trial 040.

8.8.3. Pediatrics and Assessment of Effects on Growth

See **Section 8.5.6** for assessment of growth in trial 040.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was 1 patient in trial 040 who had an accidental overdose of setmelanotide due to study drug administration error during the dose titration period. The patient was 13 years old and on study day 6 received a 4 mg dose instead of a 0.5 mg dose of setmelanotide. No TEAEs were reported due to the overdose. The FDA Controlled Substance Staff (CSS) was consulted regarding the abuse potential of setmelanotide during the original NDA review (see consult in DARRTs under IND 112595, submitted April 8, 2016). CSS concluded that based on data at that time, setmelanotide did not produce abuse-related signals that would necessitate an abuse potential assessment.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

During the post marketing period, the label for IMCIVREE was updated to include Hypersensitivity within the Contraindications, Warnings and Precautions, and Adverse Reactions sections (see Labeling Approval Letter dated 11/15/2023). This labeling update was based on cases of hypersensitivity in the post marketing period that were reviewed by the Division of Pharmacovigilance (DPV) and Division of Pulmonology, Allergy, and Critical Care (DPACC).

There was one post-marketing case of melanoma reported (for full case narrative see Applicant response to IR dated October 24, 2024). The patient was a 36-year-old male diagnosed with BBS who experienced a superficial spreading of melanoma (SSM) stage 1. On (b) (6), the patient initiated setmelanotide 3 mg daily. On (b) (6), a biopsy of a right paravertebral nevus revealed melanoma 0.3 cm with thickness measured 0.6 mm. Setmelanotide was discontinued by the physician on (b) (6), due to lack of beneficial effects and occurrence of adverse reactions. See **Section 8.5.1** for further discussion of this event.

Reviewer comment: The Division of Dermatology reviewed the post-marketing case of melanoma described above and concluded that it is difficult to determine a causal link between the reported case and setmelanotide given the known incidence and prevalence of melanoma.

8.9.2. Expectations on Safety in the Postmarket Setting

We do not anticipate significant off-label use of setmelanotide based on labeling that clearly states it is indicated for acquired hypothalamic obesity with limitation of use that it is not approved for general obesity.

8.9.3. Additional Safety Issues From Other Disciplines

Not applicable.

8.10. Integrated Assessment of Safety

Common safety issues observed in trial 040 were consistent with the known safety profile of setmelanotide for the indications of weight reduction and maintenance in POMC, PCSK1, LEPR deficiency and BBS in adult and pediatric patients ages 2 years and older. Specifically, the most common safety events in trial 040 were skin hyperpigmentation, gastrointestinal disorders (nausea, vomiting), headache, and melanocytic nevus formation or darkening.

The AEs of special interest are listed below:

- Skin hyperpigmentation: A higher frequency of patients in the setmelanotide group experienced an AE included in the group germ “hyperpigmentation disorders”

compared to the placebo group (58% vs. 10%, respectively). Skin hyperpigmentation is a known adverse reaction of setmelanotide therapy, and it is not known to be associated with increased risk of malignancy. This reviewer agrees with the current IMCIVREE labeling recommendation in Section 5.4 (Warnings and Precautions) to inform patients or caregivers that they should have a full body skin examination before starting and during treatment with IMCIVREE to monitor changes.

- Gastrointestinal disorders: The most common GI disorders reported in trial 040 were nausea and vomiting. There was a higher frequency of patients in the setmelanotide group compared to placebo who experienced TEAEs of "nausea" (55% vs. 25%, respectively) and "vomiting" (38% vs. 19%, respectively). The events of nausea and vomiting associated with setmelanotide use are monitorable.
- Psychiatric disorders: Given the centrally acting mechanism of action of setmelanotide, psychiatric AEs were of interest. There was a lower frequency of AEs in the setmelanotide group compared to placebo in the *Psychiatric disorders* SOC (27% vs. 29%, respectively) and OCMQ (broad) term "depression" (14% vs. 19%, respectively).
- Disturbances in Sexual Arousal: In trial 040, the frequency of the combined term containing PTs "spontaneous penile erection" and "increased penile erections" was higher in the setmelanotide group compared to placebo (7% vs. 4%, respectively for the combined term).
- Injection site reactions: In trial 040 the frequency of the OCMQ term "local administration reaction" was similar between the setmelanotide and placebo groups (53% vs. 54%, respectively).
- Growth and development: There was no evidence of abnormal pubertal development or growth associated with setmelanotide treatment in pediatric patients.

There was a higher frequency of SAEs in the setmelanotide group compared to placebo, most notably SAEs of acute adrenal insufficiency, hypernatremia and hyponatremia. While there was no evidence that setmelanotide directly caused these events, it is possible that the study drug may have triggered adverse events that led to these SAEs. This reviewer therefore recommends adding the following Warnings and Precautions to the Section 5 of the label:

- "Acute Adrenal Insufficiency in Patient with Acquired Hypothalamic Obesity" – In patients with secondary adrenal insufficiency, monitor for clinical signs of acute adrenal insufficiency.
- "Sodium Imbalance in Patients with Acquired Hypothalamic Obesity and Central Diabetes Insipidus" – In patients with acquired HO and concomitant diabetes insipidus(DI)/arginine vasopressin (AVP) deficiency, monitor serum sodium levels with changes in fluid intake and hydration status. Adjust the doses of concomitant therapies for DI/AVP deficiency as needed.

Generally, this reviewer finds that the AE profile of setmelanotide in adult and pediatric patients (ages 4 years and older) in trial 040 acceptable and potential adverse reactions are monitorable.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

This PI review includes a high-level summary of the major changes to the PI as compared to the Applicant's draft PI. There are several important differences between the Applicant's proposed labeling received on June 20, 2025, and the FDA approved language[1], as outlined below.

- Section 1 (Indications and Usage):
  - The Applicant initially proposed the following language: "IMCIVREE is indicated to reduce excess (b) (4) This was revised to remove language regarding (b) (4) given that data to support these claims were not provided in the supplement submission.
  - The applicant proposed "acquired hypothalamic (b) (4) as the intended use, however we revised this to "acquired hypothalamic obesity" for consistency with previous agency advice and to avoid broadening the population beyond those studied in clinical trials.
  - The Division did not agree with the Applicant's proposal to revise the order of the conditions for which setmelanotide is indicated and reverted to the previous order, as recommended in previous labeling negotiations.

  [Note: We removed reference to an FDA-approved test as noted in the Applicant's August 13, 2025, communication regarding the marketing status of (b) (4) (this does not pertain to the acquired HO indication).]
- Section 2 (Dosage and Administration)
  - We added that IMCIVREE is not recommended for use in adults and pediatric patients aged 4 years and older with acquired HO and severe renal impairment.
- Section 5 (Warnings and Precautions)
  - The Division relocated the incidence rates of adverse reactions listed in subsections 5.1 (Disturbance in Sexual Arousal), 5.2 (Depression and Suicidal Ideation) and 5.4 (Skin Hyperpigmentation, Darkening of Pre-Existing Nevi, and Development of New Melanocytic Nevi) to Section 6 to align with specific indications.
  - The Applicant proposed to add subsection 5.6 "(b) (4) " and subsection 5.7 (b) (4)

[redacted] (b) (4) „.

- Subsection 5.6: The title was revised to “Acute Adrenal Insufficiency in Patients with Acquired Hypothalamic Obesity” and removed [redacted] (b) (4)
- Subsection 5.7: The title was revised to “Sodium Imbalance in Patients with Acquired Hypothalamic Obesity and Central Diabetes Insipidus” and removed [redacted] (b) (4)

- Section 6 (Adverse Reactions)
  - We revised the applicant’s proposed HO safety population to include the full treatment population (n=142) and clarified the table of most common adverse reactions to combine related terms rather than discrete MedDRA preferred terms.
  - As noted above, we relocated rates for selected adverse events of interest in subsections according to indication, including additional events of disturbance in sexual arousal for hypothalamic obesity.
- Section 8 (Use in Specific Populations)
  - Revised Subsection 8.4 (Pediatric Use) to include a summary of the basis of approval for the pediatric population with acquired HO and clarified the pediatric populations approved for other indications.
- Section 10 (Overdosage):
  - Included language recommended by America’s Poison Centers.
- Section 12 (Clinical Pharmacology)
  - Subsection 12.1 (Mechanism of Action): While the applicant proposed revisions to this section they purport to reflect the current understanding of the mechanism of action of the product, since they did not provide new data to support these revisions, we retained the current language and incorporated the acquired HO indication as part the statement related to re-establishing the MC4 receptor pathway to reduce food intake and promote weight loss.
  - Subsection 12.6 (Immunogenicity): We revised the applicant’s proposed rates of anti-drug antibodies across all five clinical trials (including acquired HO) based on FDA’s analysis of these data.
- Section 14 (Clinical Studies)
  - Table 9 - Primary and Key Secondary Efficacy results revised to include the complete patient population in trial 040 (N=142) and revised Table 9 to reflect the data presentation used in other products approved for weight reduction.
  - The following figures and tables proposed by the Applicant were revised of removed:
    - Applicant’s Figure 1 removed – Title [redacted] (b) (4)

[redacted]: These data were relocated to Table 9. Removed the [redacted] from the table.

- Added new Figure 1 – Title *"Cumulative Distribution of Percent Change from Baseline in BMI after 52 Weeks on Therapeutic Regimen in Patients Aged ≥4 Years with Acquired HO (Trial 1)"*
- Applicant's Figure 2 removed – Title, "BMI Mean Percent Change and Hunger Mean Change from Baseline After 52 Weeks on Therapeutic Regimen in Patients Aged ≥4 Years with Acquired HO"
- Table 10 revised – Title, *"Daily Hunger Scores – Change from Baseline After 52 Weeks on Therapeutic Regimen in Patients Aged [redacted] Years with Acquired Hypothalamic [redacted]"*. [redacted] were removed because changes in scoring were not supported by qualitative exit interview data.
- Table 11 removed: Title, "[redacted]". The instrument used to measure [redacted] was not validated.
- Table 12 removed – Title, "[redacted]". This information was not interpretable since it combined results for pediatric and adult patients.
- Table 13 removed – Title, "[redacted]". This instrument was not validated to support these claims.

- We made additional revisions throughout the labeling to align with current labeling regulations and guidances and to improve clarity and readability.

1 For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.

11. Risk Evaluation and Mitigation Strategies (REMS)

Not Applicable

12. Postmarketing Requirements and Commitments

Not applicable.

13. Appendices

13.1. References

The following references are from the Applicant for Appendix Table 33:

Adank DN, Lunzer MM, Lensing CJ, Wilber SL, Gancarz AM, Haskell-Luevano C. Comparative in vivo investigation of intrathecal and intracerebroventricular administration with melanocortin ligands MTII and AGRP into mice. ACS Chem Neurosci. 2018;9(2):320-7.

Boghossian S, Park M, York DA. Melanocortin activity in the amygdala controls appetite for dietary fat. Am J Physiol Regul Integr Comp Physiol. 2010;298(2):R385-R393.

Campos CA, Shiina H, Ritter RC. Central vagal afferent endings mediate reduction of food intake by melanocortin-3/4 receptor agonist. J Neurosci. 2014;34(38):12636-45.

Chen P, Williams SM, Grove KL, Smith MS. Melanocortin 4 receptor-mediated hyperphagia and activation of neuropeptide Y expression in the dorsomedial hypothalamus during lactation. J Neurosci. 2004 Jun 2;24(22):5091-100.

Cowley MA, Pronchuk N, Fan W, Dinulescu DM, Colmers WF, Cone RD. Integration of NPY, AGRP, and melanocortin signals in the hypothalamic paraventricular nucleus: evidence of a cellular basis for the adipostat. Neuron. 1999 Sep;24(1):155-63.

Fortin SM, Chen J, Grill HJ, Hayes MR. The mesencephalic trigeminal nucleus controls food intake and body weight via hindbrain POMC projections. Nutrients. 2021 May 13;13(5):1642.

Gavini CK, Jones WC 2nd, Novak CM. Ventromedial hypothalamic melanocortin receptor activation: regulation of activity energy expenditure and skeletal muscle thermogenesis. J Physiol. 2016 Sep 15;594(18):5285-301.

Giraudo SQ, Billington CJ, Levine AS. Feeding effects of hypothalamic injection of melanocortin 4 receptor ligands. Brain Res. 1998 Nov 2;809(2):302-6.

Kim MS, Rossi M, Abusnana S, Sunter D, Morgan DG, Small CJ, et al. Hypothalamic localization of the feeding effect of agouti-related peptide and alpha-melanocyte-stimulating hormone. Diabetes. 2000 Feb;49(2):177-82.

Lerma-Cabrera JM, Carvajal F, de la Torre L, de la Fuente L, Navarro M, Thiele TE, et al. Control of food intake by MC4-R signaling in the lateral hypothalamus, nucleus accumbens shell and ventral tegmental area: interactions with ethanol. Behav Brain Res. 2012 Sep 1;234(1):51-60.

Liu J, Garza JC, Li W, Lu XY. Melanocortin-4 receptor in the medial amygdala regulates emotional stress-induced anxiety-like behaviour, anorexia and corticosterone secretion. Int J Neuropsychopharmacol. 2013 Feb;16(1):105-20.

Monge-Roffarello B, Labbe SM, Lenglos C, Caron A, Lanfray D, Samson P, et al. The medial preoptic nucleus as a site of the thermogenic and metabolic actions of melanotan II in male rats. Am J Physiol Regul Integr Comp Physiol. 2014 Jul 15;307(2):R158-66.

Richardson J, Cruz MT, Majumdar U, Lewin A, Kingsbury KA, Dezfuli G, et al. Melanocortin signaling in the brainstem influences vagal outflow to the stomach. J Neurosci. 2013 Aug 14;33(33):13286-99.

Shukla C, Britton SL, Koch LG, Novak CM. Region-specific differences in brain melanocortin receptors in rats of the lean phenotype. Neuroreport. 2012 Jul 11;23(10):596-600.

Skibicka KP, Grill HJ. Hypothalamic and hindbrain melanocortin receptors contribute to the feeding, thermogenic, and cardiovascular action of melanocortins. Endocrinology. 2009 Dec;150(12):5351-61.

Roseberry AG. Altered feeding and body weight following melanocortin administration to the ventral tegmental area in adult rats. Psychopharmacology (Berl). 2013 Mar;226(1):25-34.

Williams DL, Kaplan JM, Grill HJ. The role of the dorsal vagal complex and the vagus nerve in feeding effects of melanocortin-3/4 receptor stimulation. Endocrinology. 2000 Apr;141(4):1332-7.

13.2. Tables

Table 32. Hypothalamic and Extra-hypothalamic MC4Rs that Regulate Energy Homeostasis

	Brain Region	MC4R Expression?	Set-induced cFOS[a]?	Impacts Food Intake?	Impacts Energy Expenditure?	Literature Reference*
Hypothalamic	PVH	Y	Y	Y	Y	Giraudo1998, Cowley 1999, Kim 2000
	DMH	Y	Y	Y	Y	Kim 2000, Chen 2004
	LHA	Y	Y	Y	N	Kim 2000, Lerma-Cabrera 2012, Shukla 2012
	RCh	Y	Y	Y	N	Skibicka 2009
	VMH	Y	Y	N	Y	Kim 2000, Gavini 2016
	ARC	Y	Y	N	ND	Kim 2000
Extra-hypothalamic	MPO	Y	Y	Y	Y	Kim 2000, Monge-Roffarello 2014
	CeA	Y	Y	Y	ND	Boghossian 2010, Kim 2000
	MeA	Y	Y	Y	Y	Liu 2013
	VTA	Y	Y	Y	ND	Roseberry 2013, Lerma-Cabrera 2012
	DMV	Y	Y	Y	ND	Williams 2000, Richardson 2013
	NTS	Y	Y	Y	Y	Campos 2014, Richardson 2013, Skibicka 2009
	Mes5	Y	Y	Y	ND	Fortin 2021
	Intrathecal	NA	NA	Y	Y	Adank 2018

Source: Applicant, Clinical Overview

* See citations in Section 13.1 (References)

Abbreviations: ARC=arcuate nucleus; CeA = central amygdala nucleus; DMH = dorsomedial nucleus of the hypothalamus; DMV = dorsal motor vagal nucleus; LHA = lateral hypothalamic area; MC4R = melanocortin-4 receptor; MeA = medial amygdala; Mes5 = mesencephalic trigeminal nucleus; MPO = medial preoptic nucleus; N = no; NA = not applicable; ND = not done; NTS = nucleus of the solitary tract; PVH = paraventricular hypothalamic nucleus; RCh = retrochiasmatic area; VMH = ventromedial hypothalamic nucleus; VTA = ventral tegmental area; Y = yes.

[a] From Hansen 2021

Table 33. Description of New Moles for TEAEs with Preferred Term Melanocytic Naevus, Trial 040 (Blinded Treatment Period)

Patient	Verbatim Term	Age	Location	Size (mm)	Pigmentation Description	Dermatologist Evaluation (Y/N)	Findings
(b) (6)	Mole (Day 215)	15	Upper Back	4	Right shoulder, ~4 mm, slightly raised	Y	Mole was biopsied, results: compound melanocytic nevus, dysplastic, with mild cytologic atypia. extending to base. Follow-up with derm every three months.
	New moles (Day 24)	28	Face	4	New moles on face, arms, and chest. Size are up to 4 mm. Description: Dark, round or ellipsoid, sharp edges.	N	
	New moles on neck (Day 51)	15	Neck	2	Hyperpigmented, uniform	N	
	Enlarged mole on scalp (nexus) (Day 106)	7	Scalp	7	Dark brown to black	Y	New nevus on the mid frontal scalp is soft in texture and has normal hair density. It does have benign features throughout. Discussion of removal versus monitoring, and decided to continue monitoring.
	New mole to right cheek (Day 287)	4	Face	1.5	Dark	N	
	New mole on gingiva above left incisor (Day 197)	34	Face	1	New mole in the gingiva above the left central incisor (noted on (b) (6)). Small uniformly dark flat macule.	N	
	2 moles near below left eye (Day 415)	37	Face	1	2 tiny lesions under left eye	N	
	New moles (Day 51)	24	Ears	2	Round Brown	Y	Neoplasm of uncertain behavior (ears)

			Upper Back	5	Round Brown	Y	Compound dysplastic melanocytic nevus, congenital type, with moderate cytologic atypia. The nevus extends to the deep specimen margin.
			Lower Back	10	Round Brown	Y	Actinic skin damage lentigines multiple benign melanocytic nevi of both upper extremities, both lower extremities, and trunk
			ght leg front	2	Round Brown	Y	Actinic skin damage lentigines multiple benign melanocytic nevi of both upper extremities, both lower extremities, and trunk
			Left leg back	2	und Brown pinpoint	Y	Actinic skin damage lentigines multiple benign melanocytic nevi of both upper extremities, both lower extremities, and trunk
(b) (6)	Compound dysplastic melanocytic nevus with moderate cytologic atypia, left posterior neck (Day 2)	24		Up to 10	Black	Y	Multiple benign nevi, melanocytic nevi
	Compound dysplastic melanocytic nevus with moderate cytologic atypia, left thigh (Day 2)						
	Compound dysplastic melanocytic nevus with moderate cytologic atypia, mid- upper back						

	(Day 2)						
	Compound dysplastic melanocytic nevus with moderate cytologic atypia, upper back (Day 2)						
	Numerous new nevi covering entire body, brown color, pinpoint size (0.5 mm) (Day 19)			Range from 0.5 to 1	Light brown to black	N	
(b) (6)	Developed new mole between nose and lips, left side, brown, 0.5 mm (Day 44)	6	Face	0.5	Brown	N	
(b) (6) (placebo)	New moles on face and ears (Day 22)	7	Face	2	Face and left ear, moles are dark brown	N	
(b) (6) (placebo)	New mole on anterior neck, 2 mm (Day 328)	10	Neck	2	ght brown freckle	N	
(b) (6) (placebo)	New mole (right lower lash line) (Day 457)		Face	3	Light brown	N	

Source: Applicant CSR Trial RM-493-040, Table 22

Table 34. Description of Changes in Existing Moles for TEAEs with Preferred Term of Melanocytic Naevus, Trial 040

Patient	Verbatim Term	Age	Description of Change	Dermatologist Evaluation (Y/N)	Findings
(b) (6)	Darkening of existing moles (Day 24)	28	Darkened	N	

	Moles on chest and abdomen increased in size (Day 105)		Other: 5 moles anterior chest and abdomen, very dark, larger than before measuring 4-5 mm.	N	
(b) (6)	Changes in moles - large moles and darkening (Day 80)	20	Other: 3 larger moles have darkened on left shoulder, right shoulder, and between shoulder blades. 3-5 mm	Y	Not available
	Darkening of moles (Day 19)	15	Darkened	N	
	Change in existing mole on left breast (2 mm diameter red raised lesion) (Day 262)	34	Other: more red, located on her left chest on top of the breast.	N	
	Darkening of pre-existing mole of right upper arm (Day 192)	23	Darkened	Y	Not available
	Darkening of moles (Day 54)	18	Darkened	N	
	Darkening of preexisting moles (Day 26)	24	Darkened [b]	Y	Not available
	Darkening of preexisting moles (Day 7)	6	Darkened	N	
	Darkening of moles (Day 29)	12	Darkened	N	
(placebo)	Raised mole at the base of skull (Day 218)	10	Other: 3 moles (one on back, neck, and arm) flat to slightly raised. No change in size or color.	N	
(b) (6) (placebo)	Pruritus on moles at the nape neck (Day 400)		Other: change in sensitivity, itchy so picking at them	N	
(b) (6) (placebo)	Darkening of moles (Day	30	arkened	N	

	31)				
(b) (6) (placebo)	Darkening of pre-existing moles near injection sites (Day 29)	6	arkened	N	

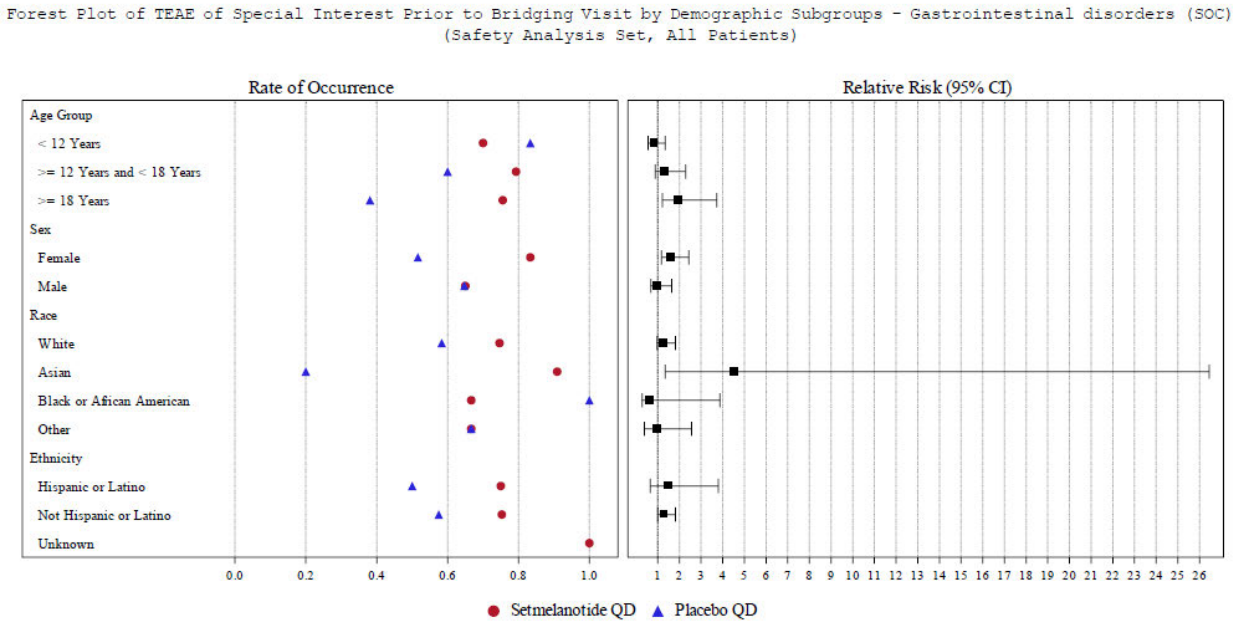
Abbreviations: HO = hypothalamic obesity; N = no; NR = not resolved; TEAE = treatment-emergent adverse event; Y = yes.
[a] Changes may be to new mole identified at an earlier visit and described in Table 22.
[b] Other changes noted in the data listing that do not appear to correlate to a new TEAE include: Other: darkening, right abdomen nevus changing shape and becoming oblong; other: increasing in size but some are becoming misshaped; and other: moles have darkened and increased in size.
Note: TEAEs were 'mapped' to reported changes in existing moles in Listing 16.2.9.3.5 as closely as possible based on study day for TEAE onset and study day most closely associated with the visit reported in Listing 16.2.9.3.5.
Source: Applicant CSR Trial RM-493-040, Table 23

Table 35. Mean and Mean Change from Baseline to End of Treatment in PHQ-9 Scores in Patients ≥18 Years of Age, Safety Analysis Set, Trial 040

Actual/Change	Statistic	Setmelanotide (N=94)	Placebo (N=48)
Actual Baseline Score	n	36	19
	Mean (SD)	1.8 (2.29)	2.5 (2.29)
	Median	1.0	2.0
	Min, Max	0, 9	0, 8
Change from Baseline to End of Treatment	n	36	19
	Mean (SD)	-3.0 (3.43)	-2.9 (2.77)
	Median	-2.0	-3.0
	Min, Max	-14, 2	-10, 0

Source: Applicant Table 14.3.4.1 and Table 14 in the Applicant response to information request dated November 6, 2025

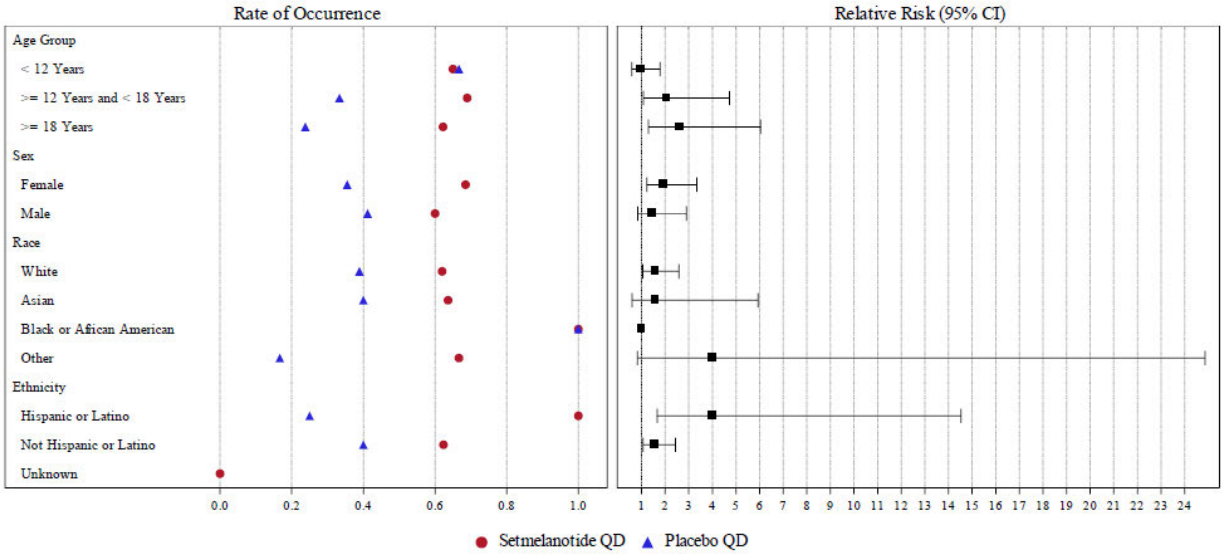
Figure 4. Forest Plots of Subgroup Safety Analyses



Source: Applicant IR response dated March 9, 2026

Reviewer comment: The event rate for males in the *Gastrointestinal disorders* SOC was balanced between the setmelanotide and placebo groups (65.0% vs. 64.7%, respectively). However, the frequency of the following notable PTs within the SOC (for males) was higher in the setmelanotide group compared to placebo: nausea (45.0% vs. 17.6%, respectively); vomiting (32.5% vs. 17.6%); diarrhea (20.0% vs. 17.6%).

Forest Plot of TEAE of Special Interest Prior to Bridging Visit by Demographic Subgroups – Skin and subcutaneous tissue disorders (SOC)
(Safety Analysis Set, All Patients)

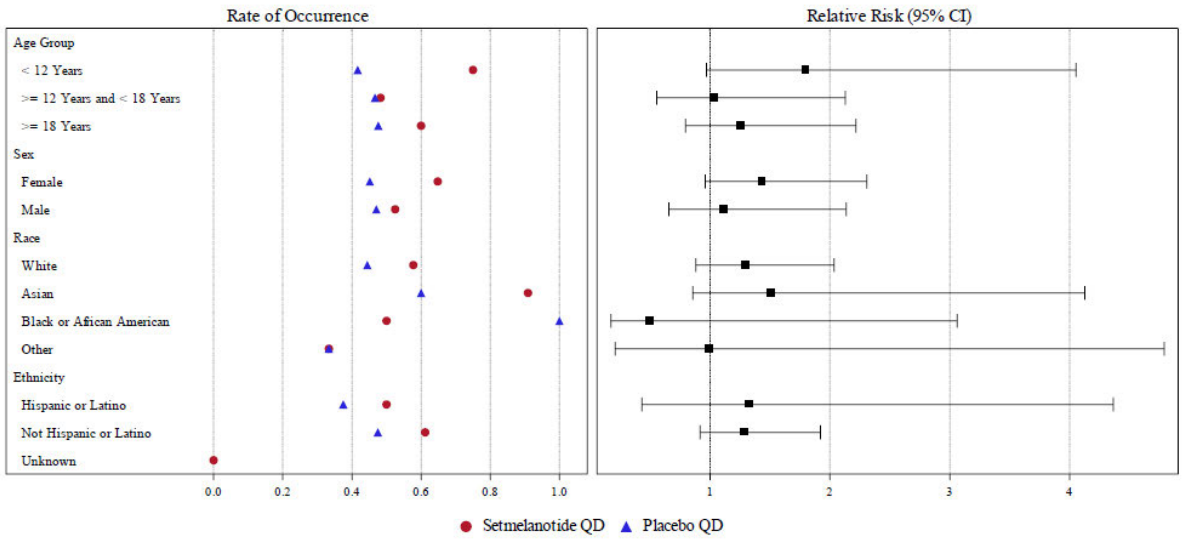


TEAE is defined as an AE with onset after the administration of study medication through the end of the study (14 days after last dose administered); any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study, or any event deemed related to study drug exposure.
Note: Relative risk and 95% confidence interval (CI) are estimated based on score confidence limits.
Source: Table t-14-3-1-2A, t-14-3-1-2-1A2 (Age subgroup), t-14-3-1-2-1A2 (Sex subgroup)

Source: Applicant IR response dated March 9, 2026

Reviewer comment: The event rate for the age group "<12 years" was relatively balanced in the *Skin and subcutaneous tissue disorders* SOC between the setmelanotide and placebo groups (65.0% vs. 66.7%, respectively). However, the frequency of the PT "skin hyperpigmentation" was higher in the setmelanotide group compared to placebo (55.0% vs. 16.7%, respectively).

Forest Plot of TEAE of Special Interest Prior to Bridging Visit by Demographic Subgroups - Infections and infestations (SOC)
(Safety Analysis Set, All Patients)



TEAE is defined as an AE with onset after the administration of study medication through the end of the study (14 days after last dose administered); any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study, or any event deemed related to study drug exposure.
Note: Relative risk and 95% confidence interval (CI) are estimated based on score confidence limits.
Source: Table t-14-3-1-2A, t-14-3-1-2-1A2 (Age subgroup), t-14-3-1-2-1A2 (Sex subgroup)

Source: Applicant IR response dated March 9, 2026

13.3. Financial Disclosure

Covered Clinical Study (Name and/or Number): Trial RM-493-040

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 100		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Schedule of Assessments for Trial RM-493-040

Trial Period/ Procedure*	Screening	Treatment Period																ETT	SFV[2]
Clinic Visit Number		V1	Call	V2[1]	V3†	V4	V5†	V6†	V7	V8†	V9	V10†	V11	V12†	V13	V14†	V15	V16 (EOT)		
Trial Day	-56 to -1	1	8	22	50	78	106	134	162	190	218	246	274	302	330	358	386	414		
Trial Week	-8 to -1	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60		
Visit Window (days)	-	-	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4		±4
Informed consent/assent[3]	X																			
Inpatient days (Japan only)**		X																		
Clinic call (weekly)			X																	
Inclusion/exclusion criteria review	X	X																		
Medical history	X	X																		
Diagnostic history[4]	X	X																		
Randomization		X																		
Physical examination[5]	X	X				X							X					X	X	X
Comprehensive skin examination[6]	X			X														X	X	
Fitzpatrick scale		X																		
Height[7]	X	X		X	X	X	X	X†	X	X†	X	X†	X	X†	X	X†	X	X	X	X
Weight[8]	X	X		X	X	X	X	X†	X	X†	X	X†	X	X†	X	X†	X	X	X	X
Waist circumference[9]	X	X		X		X			X			X†			X			X	X	

Trial Period/ Procedure*	Screening	Treatment Period																ETT	SFV[2]
Clinic Visit Number		V1	Call	V2[1]	V3†	V4	V5†	V6†	V7	V8†	V9	V10†	V11	V12†	V13	V14†	V15	V16 (EOT)		
Trial Day	-56 to -1	1	8	22	50	78	106	134	162	190	218	246	274	302	330	358	386	414		
Trial Week	-8 to -1	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60		
Visit Window (days)	-	-	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4		±4
Vital signs[10]	X	X		X	X	X	X	X†	X	X†	X	X†	X	X†	X	X†	X	X	X	X
ECG (12-lead)[11]	X																			
Pregnancy test[12]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FSH[13]	X																			
T4, Free T4, T3	X																			
IGF1[14]		X				X			X			X			X			X	X	
Estradiol, Testosterone (b) (4)		X																X	X	
(b) (4)	X	X				X			X									X	X	
Safety laboratory tests[15]	X	X		X		X			X				X					X	X	X
(b) (4)	X	X							X									X	X	
Hunger Questions[17]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
(b) (4)	X	X		X	X	X		X		X		X		X		X		X	X	
C-SSRS[18]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDI-2[19]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PHQ-A or PHQ-9[19]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Trial Period/ Procedure*	Screening	Treatment Period																ETT	SFV[2]
Clinic Visit Number		V1	Call	V2[1]	V3†	V4	V5†	V6†	V7	V8†	V9	V10†	V11	V12†	V13	V14†	V15	V16 (EOT)		
Trial Day	-56 to -1	1	8	22	50	78	106	134	162	190	218	246	274	302	330	358	386	414		
Trial Week	-8 to -1	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60		
Visit Window (days)	-	-	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4		±4
CGIS or PGIS[20] (Global Hunger)		X					X				X							X		
CGIC or PGIC[20] (Global Hunger)									X									X	X	
(b) (4)		X				X												X	X	
IWQOL-Lite-CT or IWQOL-Kids (Parent Proxy)[21]		X				X												X	X	
(b) (4)		X							X									X	X	
		X							X									X	X	
		X							X									X		
		X																X		
PK trough or profile[23]		X				X (Japan)[23]	X (Japan)[23]		X	X (Japan)[23]								X	X	
ADA[23]		X				X			X									X	X	X
(b) (4)	X[24]	(b) (4)																		
Telephone call[25]			X																	

Trial Period/ Procedure*	Screening	Treatment Period																ETT	SFV[2]
Clinic Visit Number		V1	Call	V2[1]	V3†	V4	V5†	V6†	V7	V8†	V9	V10†	V11	V12†	V13	V14†	V15	V16 (EOT)	
Trial Day	-56 to -1	1	8	22	50	78	106	134	162	190	218	246	274	302	330	358	386	414	
Trial Week	-8 to -1	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	
Visit Window (days)	-	-	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4		±4
Dispense/ Return study drug[26]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study drug administration[27]		Daily																		
Injection site inspection[28]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug compliance assessment[29]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event collection[30]	Continuous from signing of ICF through completion of trial participation																			
Concomitant medications review	Continuous from signing of ICF through completion of trial participation																			
ABPM sub-trial[31]	X[31]								X[31]									X[31]		
Body composition by DXA[32]		X																X	X	
Informed Consent for Patient/Caregiver Interviews[33]																		X		

Abbreviations: ABPM = Ambulatory Blood Pressure Monitoring; ADA = anti-drug antibody; CDI-2 = Children's Depression Inventory-2; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Days; ECG = electrocardiogram; EOT = End of Treatment; (b) (4)
ETT = Early Termination of Treatment; (b) (4) FSH = follicle-stimulating hormone; HbA1c = glycated

hemoglobin; IGF1 = Insulin-like Growth Factor 1; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical Trials version; LTE = Long-Term Extension; PHQ = Patient Health Questionnaire; PK = pharmacokinetic; SFV = Safety Follow-up Visit; T4 = free thyroxine; V = Trial Visit Number.

* Assessments/samples should be collected/obtained prior to administration of trial treatment. (b) (4) (b) (4) See Appendix 8 for a summary of the Patient and Safety Questionnaires, the timing relative to dosing, the location where the assessment should be conducted, and the method of data collection.

** All patients from sites in Japan will remain in the clinical research unit (CRU) for 24-hours after the first dose administration (from Day 1 through Day 2) for safety monitoring and PK sampling. The first 3 patients (adult or pediatric) from sites in Japan will be enrolled one at a time. Each of the 3 patients will be dosed for 2 weeks before the next patient initiates

† The Week 8, 16, 20, 28, 36, 44, and 52 visits may be scheduled in-clinic or as at home telehealth visits at the discretion of the Investigator. If these visits are conducted as telehealth visits, the following assessments are not required to be collected: height, weight, waist circumference (cm), vital signs. For patients on hormone replacement therapy, one or more of these visits may be required in-person. See Section 6.8.6.

1 All patients will initiate setmelanotide at 0.5 mg once daily (QD). The first dose will be administered in clinic. Dose titration will be made per Section 5.4.3.

2 The SFV visit will occur 14 days after the last dose of trial treatment (ETT) for patients who prematurely discontinue. The SFV is not required for patients who complete the Week 60 Visit and enroll in the optional LTE. For LTE eligibility, see Section 5.1.3.

3 Prior to the initiation of any trial procedures and assessments, signed informed consent and/or assent (as applicable) are required per protocol. A separate informed consent and/or assent (as applicable) will be required (b) (4) Additional considerations for reducing pain in distress in patients younger than 18 years of age are included in Appendix 2.

4 All patients must have documented evidence of prior hypothalamic injury on radiographic imaging, as confirmed by the clinical investigator, at least 6 months before Screening.

5 A complete physical examination will be conducted at Screening and at the EOT Visit (or at the ETT Visit, as applicable). At other time points, an abbreviated examination will be performed. The abbreviated examination should focus on heart, lungs, skin, and any areas of previous abnormal findings, noting any changes from baseline. In addition, Tanner Staging for assessment of pubertal development will be conducted for those patients who have yet to reach Tanner Stage V. Whenever possible, the same trained health care professional will conduct the exam and Tanner Staging.

6 A comprehensive skin examination will be performed by the Investigator. The skin examination should include a full body (head-to-toe skin examination). If any concerning lesions are identified during Screening, the patient should be referred to a dermatologist. Any concerning lesions will be biopsied by the dermatologist and results must be benign prior to the first dose of setmelanotide. If the pre-treatment biopsy results are of concern, the patient will be excluded from the trial. Additionally, any concerning lesion or change in an existing lesion during the course of the trial must be evaluated by the dermatologist and biopsied, if clinically indicated in the opinion of the dermatologist.

7 For patients ≥21 years of age, height is to be measured at screening only. For patients <21 years of age, height is to be measured at the time points listed in the Schedule of Activities (SoA). Height (cm) will be measured, without shoes, socks, or hats, using a wall-mounted stadiometer. For clinic visits, the stadiometer should be calibrated by site personnel on a daily basis prior to height assessment. All measurements will be done at each time point and recorded to the nearest half cm.

8 Weight (kg) is to be measured at the clinic using the same scale throughout the trial. Weight should be measured after patients have attempted to empty their bladders and after an overnight fasting. Patients are to wear light clothing or underwear and no shoes, with empty pockets, and will be weighed at approximately the same time of day. All measurements will be measured in triplicate and recorded to the nearest 10th of a kg if reported with a digital scale, or half kg with a mechanical scale, and will be measured in triplicate.

9 Waist circumference (cm) should be measured at approximately the same time at each visit. Patients should be standing and in light clothing and have emptied their bladder. Whenever possible, the same trial staff member should perform the measurement for a given patient to minimize variability.

[10] All blood pressure (BP) and heart rate (HR) measurements are to be obtained with the patient in the sitting position following at least 5 minutes of rest. All measurements will be taken in triplicate, approximately 2 minutes apart. When possible, BP should be taken in the non-dominant arm throughout the trial, using the same methodology (automated or manual). Body temperature (°C) and respiration rate (breaths/minute) will be obtained in the sitting position following at least 5 minutes of rest. Repeat measures and more frequent monitoring can be implemented for significant increases in BP or HR.

[11] At Screening, a single 12-lead ECG will be performed in the supine position following a period of at least 10 minutes of rest. See Section 6.8.5.

[12] A urine pregnancy test may be performed to expedite availability of results prior to dosing on Day 1. All in-clinic pregnancy tests per SoA will be serum tests; dosing may continue with results pending. At telehealth visits, urine pregnancy tests will be performed using pregnancy test kits. Additional pregnancy tests may be required according to local regulations and/or requirements.

[13] See Section 6.8.6 for FSH screening requirements.

[14] IGF1 labs will be drawn at Baseline and approximately every 3 months for patients taking growth hormones.

[15] Safety laboratory tests will be performed per Section 6.8.6 before the morning meal (fasted).

[16] Blood samples will be collected prior to dose administration for (b) (4) (b) (4)

[17] Hunger Questionnaires and Symptoms of Hyperphagia Questionnaire will be recorded using an at-home e-diary as follows: during the Screening Period for 7 consecutive days before the enrollment visit (Day 1) for 7 consecutive days before each scheduled trial visit, scheduled tele-health visit, or at the ETT visit as applicable. These questionnaires should be completed prior to the morning meal (fasted) before dosing and at home using the e-diary. (b) (4) (b) (4)

[18] The Baseline/Screening version of the C-SSRS scale is the initial form of the instrument to assess suicidality in a patient's lifetime and is administered at Screening. In order to be eligible for the trial, a patient at Screening cannot have a suicidal ideation of type 4 or 5, a suicide attempt during the patient's lifetime, or any suicidal behavior in the last month, as per the C-SSRS. After Screening, the 'Since Last Visit' version of the scale will be used to assess suicidality since the patient's last visit. If at any time during the trial a patient has a suicidal ideation of type 4 or 5, or any suicidal behavior, the patient should be referred to a mental health professional (MHP). The C-SSRS should be completed before dosing either in clinic or in the presence of trained nursing or site staff during telehealth visits, as applicable.

[19] The PHQ-A will be administered to patients 11-17 years of age and the PHQ-9 will be administered to patients ≥18 years of age. The CDI-2 will be administered to patients 7 to <12 years of age (self-report short form) and to caregivers of patients 7 to <12 years of age (parent version).
To be eligible for the trial, an individual patient's PHQ-A or PHQ-9 score must be <15 at Screening or a CDI-2 T-score <70. If at any time during the trial an individual patient's PHQ-A or PHQ-9 score is ≥10 or has a CDI-2 T-score ≥65, the patient should be referred to a MHP. See Sections 6.8.10.2 and 6.8.10.3.
The PHQ-9/PHQ-A and CDI-2 should be completed before dosing either in clinic or in the presence of trained nursing or site staff during telehealth visits, as applicable.

[20] The Global Hunger Questions for Patients ≥12 Years of Age consist of two parts: the Patient Global Impression of Severity (PGIS) and the Patient Global Impression of Change (PGIC). The Caregiver Reported Global Hunger Questions consist of the Caregiver Global Impression of Severity (CGIS) and the Caregiver Global Impression of Change (CGIC) and will be administered to caregivers of patients <12 years of age or to caregivers of patients who are unable to self-report. PGIS/CGIS only is administered at baseline. Both parts (PGIS/PGIC and CGIS/CGIC) are administered thereafter per the SoA. These questions should be completed before dosing and at home using the e-diary. See Section 6.6.4.2.

[21] (b) (4)

[22] (b) (4)

[23] Samples for ADA and PK (trough) will be collected at timepoints per the SoA (V1, V4, V7, EOT). All samples should be collected before study drug administration on the day of collection. Patients should be instructed to not administer study drug prior to the clinic visit. In addition to trough samples outlined in the SoA, additional PK profile samples will be collected pre-dose and post-dose for patients in Japan at Week1 and after 4 weeks on a therapeutic dose. The PK samples collected after 4 weeks on a therapeutic dose may be collected at a time designated by the Investigator. If these samples are requested during a permitted telehealth visit, that visit will be conducted in-person. See Section 6.8.7.1. Any patient with a positive ADA will be followed every 3 months after the ADA sample analysis until resolution of the ADA.

[24] (b) (4) (b) (4) See Section 6.7.3.

[25] Site personnel will call the patient on Day 8 to confirm the proper dose escalation has occurred and to collect AEs and any changes in concomitant medications. Additional calls to patients may occur throughout dose escalation to a therapeutic regimen. See Section 5.4.3.

[26] Patients/caregivers will return all (the number recorded) used vials to the clinic when they visit, and both clinic-administered study drug as well as outpatient study drug administration will be recorded in a trial e-diary.

[27] Patients/caregivers will draw up and self-administer/administer the drug once daily in the morning beginning the morning of Day 1 and for the duration of dosing. On days with clinic visits, the patients/caregivers will administer the drug in the clinic in the presence of the clinical staff following blood draws, and to assure proper technique.

[28] Injection site evaluations and scoring (by the clinical staff) will include identification and measurement of areas of erythema, edema, and induration, as well as the presence of localized pain, tenderness, and itching. Additional evaluation data can be collected at any visit in which there are injection site reactions, even if not a time point for formal assessment.

[29] A question querying whether the patient completed their daily injection will be asked via an e-diary.

[30] AEs will be recorded from the time a patient provides informed consent. AEs reported after dosing on Day 1 will be considered TEAEs.

[31] At applicable sites measuring ABPM, this assessment will be conducted outside of the clinic setting in patients ≥4 years of age, (See Section 6.8.2 for patients <12 years of age. Applicable to patients in North America/EU only – not applicable in Japan. ABPM assessments will require wearing the device at each time point for any 24-hour period prior to: the Day 1 Visit (from last day in Screening window), the Week 24 Visit, and the Week 60 Visit. The ABPM device will measure BP (systolic and diastolic) and heart rate (HR) in 30-minute intervals for each 24-hour period. (b) (4)

[32] (b) (4) (b) (4) (b) (4) who agree to sign a separate ICF/Assent for this assessment. A (b) (4) will be taken at the Day 1 Visit. If (b) (4) is not available at the clinic, this procedure may be skipped. If a patient discontinues before the EOT Visit, (b) (4) should be performed at the ETT Visit. See Section 6.7.4.

[33] (b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GINGER J WINSTON
03/19/2026 03:52:43 PM

JOHN M SHARRETTS
03/19/2026 04:29:00 PM