PPD

STATISTICAL ANALYSIS PLAN

STUDY SPONSOR:	Rhythm Pharmaceuticals, Inc. 222 Berkeley Street 12th Floor Boston, MA 02116 Tel: (857) 264-4280
PROTOCOL TITLE:	A Phase 3, Double Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Setmelanotide in Patients with Acquired Hypothalamic Obesity
PROTOCOL NUMBER:	RM-493-040
PPD	
NAME OF TEST DRUG:	Setmelanotide
PHASE:	Phase 3
METHODOLOGY:	Double Blind, Randomized, Placebo-Controlled
ANALYSIS PLAN DATE:	11 March 2025
ANALYSIS PLAN VERSION:	Version 4.0
AUTHOR:	PPD

APPROVAL SIGNATURE PAGE

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PPD **Author:** PPD

Approval Signature	Job Title
PPD	PPD

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Approval Signature	Job Title
PPD	PPD

Approval Signature	Job Title
PPD	PPD

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
α-MSH	alpha-melanocyte-stimulating hormone
ABPM	Ambulatory blood pressure monitoring
ADA	Anti-drug antibody
AE	Adverse event
ANCOVA	Analysis of covariance
BMI	Body mass index
BP	Blood pressure
CDI-2	Children's Depression Inventory-2
CGIC	Caregivers Global Impression of Change
CGIS	Caregivers Global Impression of Severity
CI	Confidence Interval
CMH	Cochran–Mantel–Haenszel
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CCI	[redacted]
ECG	Electrocardiogram
CCI	[redacted]
EOT	End of treatment
EU	European Union
ETT	Early Termination of Treatment
CCI	[redacted]
FAS	Full Analysis Set
FSH	Follicle-stimulating hormone
CCI	[redacted]
HO	Hypothalamic obesity
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board

Abbreviation	Definition
IRT	Interactive response technology
IWQOL	Impact of Weight on Quality of Life
LEPR	Leptin receptor
LTE	Long-term extension
MAR	Missing-at-random
MC4R	Melanocortin 4 receptor
MCMC	Markov chain Monte Carlo
MHP	Mental health professional
MI	Multiple Imputation
mITT	Modified Intention-to-Treat Analysis Set
PCSK1PK	Proprotein convertase subtilisin/kexin type 1
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PHQ	Patient Health Questionnaire
PK	Pharmacokinetic
POMC	Pro-opiomelanocortin
QD	Once daily
RD	Retrieved dropouts
SA	Safety Analysis Set
SAP	Statistical analysis plan
SD	Standard deviation
SFV	Safety Follow up visit
SoA	Schedule of Assessments
T4	Free thyroxine
TEAE	Treatment-emergent adverse event
US	United States

1. INTRODUCTION

This statistical analysis plan (SAP) summarizes the planned efficacy and safety analyses for study RM-493-040, which is a Phase 3, Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Setmelanotide in Patients with Acquired Hypothalamic Obesity (HO). This SAP is based on protocol version 5.1, (19 September 2024).

CCI [redacted]

1.1. Background Information from Protocol

Acquired HO is a severe, devastating form of obesity that affects approximately 5,000 to 10,000 patients in the United States (US) and is believed to have similar incidence and prevalence in the European Union (EU; Teng 2021; Roth 2015). Acquired HO develops after injury to the hypothalamus, most often as a result of a tumor (e.g., craniopharyngiomas, gliomas, pituitary adenomas, hamartomas), and/or the surgery or radiation therapy used to treat the tumor (Hochberg 2010). Other much rarer causes of injury include inflammatory conditions involving the hypothalamus such as sarcoidosis or trauma. Craniopharyngiomas represent the most common tumor associated with the development of HO and account for 5% to 15% of pediatric intracranial tumors, and occur with 2 peaks of incidence, one during childhood (10 to 19 years of age [29%]) and the second in adulthood (30 to 49 years of age [25%]) (Muller 2022).

Patients with acquired HO develop an aggressive form of obesity characterized by a high degree of sudden, severe, and sustained weight gain that is generally unresponsive to lifestyle or medical intervention. The weight gain is most dramatic in the first 6-12 months after injury and then continues for the next 8 to 12 years before plateauing (Sterkenburg 2015). Hyperphagia may occur in approximately 50% of patients along with lethargy due to decreased energy expenditure, and psychosocial disorders spanning from depression to aggressive behavior (Muller 2011).

Central melanocortin signaling has been extensively discussed as the primary element of energy homeostasis (Holland 2019). In patients with hypothalamic lesions, leptin signaling is often disturbed and results in reduced melanocortin signaling. This has been associated with hyperphagia and excessive weight gain. (Enriori 2016; Roth 2010; Roth 1998; Patel 2002; Shaikh 2008). In patients with craniopharyngioma or post-surgical treatment for it, levels of alpha-melanocortin-stimulating hormone (α-MSH) were found to be significantly reduced (Roth 2010; Roth 2011). Reduced serum α-MSH levels suggest melanocortin pathway deficiency, which might explain lower energy expenditure in peripheral tissues due to reduced fat and muscle fatty acid oxidation (Roth 2010; Roth 2011; An 2007).

Setmelanotide, a potent melanocortin 4 receptor (MC4R) agonist, is a synthetic 8 amino acid, cyclic peptide that binds with high affinity to the human MC4R and is efficient in activating MC4R. While not an analog, it retains the specificity and functionality of the naturally occurring pro-opiomelanocortin (POMC)-derived neuropeptide, αMSH, which is the endogenous ligand for the MC4R.

Setmelanotide is authorized for marketing in the US, UK, Israel, the EU, and Canada. Refer to the current Investigator's Brochure (IB) for additional information.

1.2. Study Objectives

This SAP is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

The study objectives for RM-493-040 are:

Primary:

- To evaluate the efficacy of setmelanotide on change in body mass index (BMI).

Key Secondary Objectives:

- To evaluate the efficacy of setmelanotide on the 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

Other Secondary Objectives:

- To evaluate changes in hunger and in symptoms of hyperphagia in response to setmelanotide
- To evaluate changes in additional parameters of body weight
- To evaluate changes in quality of life in response to setmelanotide treatment
- To evaluate changes in waist circumference following treatment with setmelanotide compared to placebo

- To evaluate changes in cardiometabolic parameters following treatment with setmelanotide compared to placebo

Safety Objectives:

- To evaluate the safety and tolerability of setmelanotide compared to placebo
- To evaluate the effect of setmelanotide on blood pressure (BP)

CCI

1.3. Study Design

1.3.1. Synopsis of Study Design

This is a Phase 3, double-blind, multi-center, placebo-controlled, randomized 2:1 (active to placebo), registrational trial, designed to assess the efficacy and safety of setmelanotide on weight loss and hunger in patients ≥4 years of age with acquired HO. Approximately 120 patients (at least 12 from sites in Japan) are planned to be enrolled at up to 35 clinical sites in North America, Europe, and Japan).

The study will consist 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 post-treatment period completion for a total study duration of up to 70 weeks in total. Patients who complete the end of treatment visit and remain enrolled may be eligible to participate in a long-term extension study or open-label bridging visits if the long-term extension is not yet available. For those eligible, bridging visits would occur at the clinic every 12 weeks in addition to the ~70 week duration noted above.

The Screening Period will last up to 8 weeks (from Day -56 to -1 with a minimum of 3 weeks to allow for the completion of all necessary tests and evaluations, including the collection of CCI baseline data for 2-3 weeks prior to randomization). Upon providing informed consent, patients will complete all screening procedures as listed in the Schedule of Assessments (SoA) (Table 1-1) to determine if they meet the study criteria.

Eligible patients will be enrolled into the Treatment Period that will last up to 60 weeks. During the Treatment Period, patients will attend the in-clinic visits and may attend at-home telehealth visits at Weeks 8, 16, 20, 28, 36, 44, 52 at the discretion of the investigator. Detailed assessment information is provided in the SoA (Table 1-1).

The End of Treatment (EOT) visit will occur as an in-person clinic visit after 52 weeks on a therapeutic regimen, which is the final planned week of dosing with trial treatment. At the EOT, patients who complete 52 weeks of on a therapeutic regimen and complete assessments through the EOT visit may be eligible to enter an open-label long-term extension (LTE) trial or attend Bridging visits with open-label setmelanotide if the LTE is not yet available.

All patients who discontinue treatment prematurely should attend an early termination of treatment (ETT) Visit as soon as possible after the last dose of trial treatment. Patients who discontinue treatment but remain enrolled in the trial should continue to complete all assessments (as Retained Dropouts). These patients will be required to complete the safety follow-up visit (SFV) as applicable following the ETT.

Patients who discontinue treatment prematurely are not eligible to enroll in the optional LTE trial. Exceptions may be made in consultation with the Sponsor.

Patients who discontinue prematurely and withdraw from the trial will not be required to complete the SFV following the ETT.

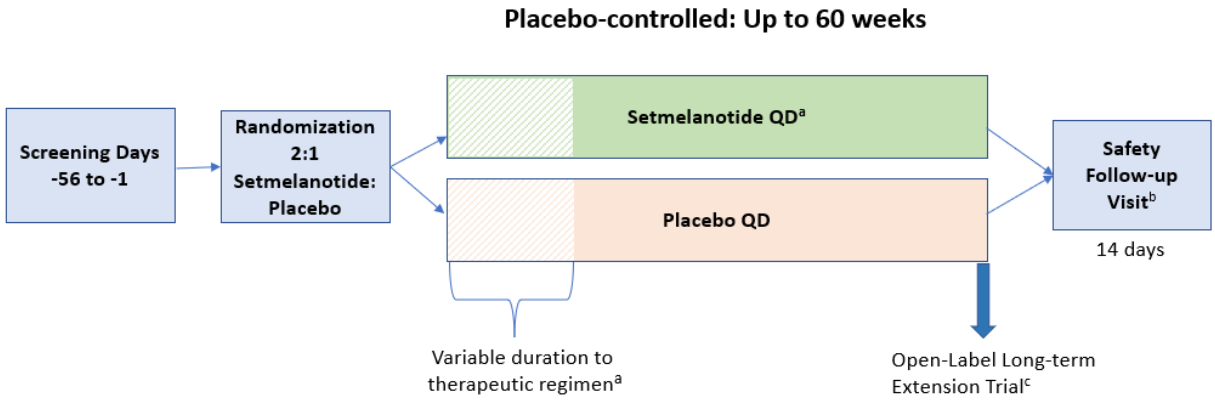
If the ETT Visit occurs 4 weeks or later following the last dose of trial treatment, then the ETT Visit will replace the SFV if no adverse events (AEs) are being monitored.

An SFV will occur as an in-person visit 14 days (±4 days) after the last dose of trial treatment. The SFV is not required for patients who complete the treatment period and either:

- Enroll in the LTE (or bridging visits if the LTE is not yet available) or transition to another qualified Rhythm study (e.g., managed access)
- Transition to a commercially available Rhythm MC4R agonist regimen

The trial design schema is shown in Figure 1.

Figure 1 Study Design Schematic



a. CCI [redacted]. See Protocol Section 5.5.3 for dose and escalation scheme CCI [redacted].

b. The SFV is only required for patients who prematurely discontinue treatment or for patients who complete the trial and do not enroll in the LTE or Bridging Visits.

c. Patients who complete the trial and trial assessments may be eligible to participate in the LTE (or receive open-label setmelanotide and attend Bridging Visits if the LTE is not yet available).

1.3.2. Randomization Methodology

Patients who are eligible to enter the trial will be randomized in a blinded manner on Day 1 in a 2:1 ratio (setmelanotide:placebo), stratified by age group (≥18 years old, ≥12 and <18 years old, <12 years old) and subpopulation (Japanese vs non-Japanese), to receive either setmelanotide or placebo. The randomization schedule will be generated by the Sponsor or its designee, and trial personnel will use a web-based interactive response technology (IRT) system to obtain the patient number for each eligible patient.

The patient, Investigator, and the Sponsor will be blinded to trial treatment assignment. Full details for the blinding and unblinding are provided in the separate Blinding and Unblinding Plans.

1.3.3. Stopping Rules and Unblinding

At the initiation of the study, study site personnel will be instructed on the method for breaking the blind. To conduct the primary analysis, the Sponsor will be unblinded when 120 patients have completed the study. To ensure the integrity of the study at the site level, investigators and patients will remain blinded after the unblinding of the sponsor.

Emergency unblinding for AEs may be performed through the IRT system. The IRT system will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's intervention assignment is warranted. Patient safety must always be the first consideration in making such a determination.

If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor or Contract Research Organization (CRO) Medical Monitor before unblinding a patient's intervention assignment unless this could delay emergency treatment for the patient. The date and reason for the unblinding by the Investigator must be recorded. If a patient's intervention assignment is unblinded, the Sponsor must be notified by the Investigator within 24 hours of occurrence. The Investigator should not reveal to the Sponsor the patient's treatment allocation unless the Sponsor requests this information for safety purposes.

For any unexpected serious adverse event (SAE) that is treatment-related (e.g., possible or probable), the blind will be lifted by the Sponsor only for that specific patient. The blind will be maintained for persons responsible for the ongoing conduct of the trial (such as the monitors, investigators, etc.) and those responsible for data analysis and interpretation of results at the conclusion of the trial (such as biometrics personnel). Unblinded information will only be accessible to those who need to be involved in the safety reporting to Health Authorities, the Independent Ethics Committee (IEC), and/or Institutional Review Board (IRB). Investigators will receive only blinded information unless unblinded information is judged necessary for safety reasons.

This trial or any site may be suspended or terminated, if in the opinion of the Sponsor, there is sufficiently reasonable cause. The Sponsor will provide written notification documenting the reason for cohort/site/trial termination to the Investigator.

Circumstances that may warrant suspension or termination include, but are not limited to:

At the Trial level

- Determination of unexpected, significant, or unacceptable risk to patients
- Plans to modify, suspend or discontinue the development of the trial medication

At the Site level

- Failure to enroll patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficiently complete and/or evaluable data

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigator, the IECs/ IRBs, the regulatory authorities, and any CRO(s) used in the study about the reason for suspicion or termination, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the trial patients and should ensure appropriate patient therapy and/or follow-up.

Should the trial be closed prematurely, all trial materials must be returned to the Sponsor or designee.

1.3.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1-1.

Table 1-1 Schedule of Assessments

Trial Period/ Procedure*	Screen-ing	Treatment Period															EOT†† (after 52 weeks on a therapeutic regimen)		ETT	SFV[2]	Bridg-ing Visits**
Clinic Visit Number		V1[1]	Call	V2	V3†	V4	V5†	V6†	V7	V8†	V9	V10†	V11	V12†	V13	V14†	V15††	V16††			Every 12 weeks
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	1	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 weeks +4 days		±4	±2 weeks
Informed consent/assent[3]	X																				
Inclusion/exclusion criteria review	X	X																			X
Medical history	X	X																			
Diagnostic history[4]	X	X																			
Randomization		X																			
Physical examination[5]	X	X				X							X				X††	X	X	X	X
Comprehensive skin examination[6]	X			X													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	X
Weight[8]	X	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	X		X
Vital signs[10]	X	X		X	X	X	X	X†	X	X†	X	X†	X	X†	X	X†	X	X	X	X	X
ECG (12-lead)[11]	X																				

Trial Period/ Procedure*		Treatment Period															EOT†† (after 52 weeks on a therapeutic regimen)		ETT	SFV [2]	Bridg-ing Visits**
Clinic Visit Number	Screen-ing	V1[1]	Call	V2	V3†	V4	V5†	V6†	V7	V8†	V9	V10†	V11	V12†	V13	V14†	V15††	V16††			Every 12 weeks
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	1	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 weeks +4 days		±4	±2 weeks
Pregnancy test[12]	X	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																				X[34]
IGF1[14]		X				X			X			X			X		X††	X	X		X[34]
Estradiol, Testosterone		X															X††	X	X		X[34]
CCI	X	X				X			X								X††	X	X		
Safety laboratory tests[15]	X	X		X		X			X				X				X††	X	X	X	X
CCI	X	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		
CCI	X	X		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	X
CDI-2[19]	X	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	X
CGIS or PGIS[20] (Global Hunger)		X					X				X						X††	X			X
CGIC or PGIC[20] (Global Hunger)									X								X††	X	X		X

Trial Period/ Procedure*		Treatment Period															EOT†† (after 52 weeks on a therapeutic regimen)		ETT	SFV[2]	Bridg-ing Visits**
Clinic Visit Number	Screen-ing	V1[1]	Call	V2	V3†	V4	V5†	V6†	V7	V8†	V9	V10†	V11	V12†	V13	V14†	V15††	V16††			Every 12 weeks
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	1	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 weeks +4 days		±4	±2 weeks
CCI		X				X											X††	X	X		
IWQOL-Lite-CT **or** IWQOL-Kids (Parent Proxy)[21]		X				X											X††	X	X		X (Week 12, then every 24 weeks)
CCI		X							X								X††	X	X		
CCI		X							X								X††	X	X		X (Week 12, then every 24 weeks)
CCI		X							X								X††	X			
CCI		X															X††	X			
PK (trough)[23]		X				X			X								X††	X	X		
ADA[23]		X				X			X								X††	X	X	X	X
CCI	X[24]	CCI																			
Telephone call[25]			X																		X[25]
Dispense/Return study drug[26]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X††	X	X		X
Study drug administration[27]		Daily																			Daily
Injection site inspection[28]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X††	X	X		X

Trial Period/ Procedure*		Treatment Period															EOT†† (after 52 weeks on a therapeutic regimen)		ETT	SFV[2]	Bridge-ing Visits**
Clinic Visit Number	Screen-ing	V1[1]	Call	V2	V3†	V4	V5†	V6†	V7	V8†	V9	V10†	V11	V12†	V13	V14†	V15††	V16††			Every 12 weeks
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	1	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 weeks +4 days		±4	±2 weeks
Drug compliance assessment[29]		X	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 medication review	Continuous from signing of ICF through completion of trial participation																				
ABPM sub-trial[31]	X[31]								X[31]								X[31††]				
CCI		X															X††		X		
Informed Consent for CCI																	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; CCI; ETT = Early Termination of Treatment; CCI; FSH = follicle-stimulating hormone; CCI; 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; V = Trial Visit Number.

* CCI See Protocol 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.

** Patients who complete the EOT Visit and remain enrolled may be eligible to participate in the LTE or open-label Bridging visits (if the LTE is not yet available). Bridging Visits occur at the clinic every 12 weeks (until either the LTE or a post-trial access program is available, commercial drug is available in the region, or the trial ends). Additional visits may be scheduled at the discretion of the Investigator.

† 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 Protocol Section 6.8.6.

†† The EOT visit occurs after 52 weeks on a therapeutic regimen. CCI

1. CCI

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 EOT Visit and enroll in the optional LTE. For LTE eligibility, see Protocol 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 CCI . Additional considerations for reducing pain in distress in patients younger than 18 years of age are included in Protocol Appendix 2.
4. CCI
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 Protocol 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 Protocol 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 Protocol Section 6.8.6 before the morning meal (fasted).
16. Blood samples will be collected prior to dose administration for CCI .
17. See Protocol Section 6.6.4. Hunger Questionnaires and Symptoms of Hyperphagia Questionnaire will be recorded during the trial 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. CCI
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 Protocol 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 and can self-report 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. During the trial, these questions should be completed before dosing and at home using the e-diary. For patients who continue to Bridging visits, these questions should be completed at the clinic before dosing and the morning meal. See Protocol Section 6.6.4.2.

21. CCI [redacted]

23. Samples for ADA (anti-setmelanotide and anti-αMSH) and PK (trough) will be collected at timepoints per the SoA. 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. Any patient with a positive anti-setmelanotide ADA will be followed every 3 months after the ADA sample analysis until resolution of the ADA.

24. CCI [redacted]

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. For patients who continue to Bridging visits, a telephone call will be scheduled for the beginning of Week 2 to confirm proper dose escalation. Additional calls to patients may occur throughout dose escalation to a therapeutic regimen. See Protocol Section 5.5.3.

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. Patients in Bridging visits will record compliance on paper forms.

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 Protocol Section 6.8.2 for patients <12 years of age and regional applicability. 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 EOT Visit (occurs after 52 weeks on a therapeutic dose). The ABPM device will measure BP (systolic and diastolic) and heart rate (HR) in 30-minute intervals for each 24-hour period. CCI [redacted]

32. CCI [redacted] separate ICF/Assent for this assessment. A CCI [redacted] will be taken at the Day 1 Visit. If CCI [redacted] is not available at the clinic, this procedure may be skipped. If a patient discontinues before the EOT Visit, CCI [redacted] should be performed at the ETT Visit. See Protocol Section 6.7.4.

33. CCI [redacted]

34. Lab tests to be conducted only as needed at the discretion of the Investigator.

1.4. Efficacy, Pharmacokinetic, and Safety Endpoints

1.4.1. Efficacy Endpoints

The primary efficacy endpoint is the mean percent change from baseline in BMI after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo.

The key secondary efficacy endpoints are:

- The proportion of patients with ≥5% reduction in BMI in adult patients (≥18 years of age), or a 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

The other secondary efficacy endpoints are:

- The proportion of patients with a ≥2-point reduction in the weekly average of the daily most hunger score from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
- The 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
- The proportion of patients with a ≥10% reduction in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
- The proportion of patients with a ≥10% reduction in weight from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
- Mean percent change in weight in patients ≥18 years from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
- 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
- The proportion of patients aged ≥4 to <18 years of age with ≥0.2-point reduction of BMI Z-score from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

- The proportion of patients with BMI <30 kg/m2 (patients aged ≥18 years) or <95th percentile (patients aged <18 years) 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 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.

- 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 BP, CCI [redacted] liver function and CCI [redacted] from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

CCI [redacted]

1.4.2. Pharmacokinetic Parameters

Descriptive summaries will be provided on the pharmacokinetic endpoints, details will be documented in a separate Pharmacokinetic Analysis Plan (PKAP).

1.4.3. Safety Parameters

The safety endpoints are:

- Safety and tolerability assessed by the frequency and severity of AEs, AEs of special interest, vital signs, and laboratory evaluations from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

- Change in ambulatory BP and heart rate (HR) from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo (in patients ≥12 years)

2. ANALYSIS POPULATIONS

2.1. Population Definitions

The following analysis populations will be used in the statistical analyses:

- **Screening Analysis Set:** is defined as all patients who signed the informed consent form.
- **Safety Analysis Set (SA):** is defined as all patients who received at least 1 dose of study treatment (placebo or setmelanotide). Analyses performed on the safety set will be based on patients according to the treatment received.
- **Full Analysis Set (FAS):** is defined as all randomized patients. Analyses performed on the FAS will be based on treatment as randomized.
- **Modified Intention-to-Treat Analysis Set (mITT):** is defined as all randomized patients who are exposed to at least 1 dose of study treatment. Analyses performed on the mITT will be based on treatment as randomized.
- **Per-Protocol Set (PP)**: is defined as all patients in the mITT without any major protocol violations that warrant exclusion as determined by Sponsor in process described in Section 2.2.

The mITT is the primary population for the analysis of efficacy data. The PP will be used for sensitivity analyses of primary and key secondary efficacy endpoints. The SA is the primary population for the analysis of safety endpoints.

2.2. Protocol Violations

At the discretion of the Sponsor, major protocol violations, as determined by a review of the data prior to unblinding of the study results and the conduct of statistical analyses, may result in the removal of a patient's data from the PP Set. The Sponsor or designee will be responsible for producing the final protocol violation file (formatted as a Microsoft Excel file), in collaboration with the data monitoring group (or designee) as applicable; this file will include a description of each protocol violation and clearly identify whether or not this violation warrants exclusion from the PP Set. This file will be finalized prior to database lock and unblinding.

All protocol violations will be presented in a data listing.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

The sample size is mainly driven by the primary efficacy hypothesis with the safety database taken into consideration. With the planned sample size of ~120 patients (~80 patients in setmelanotide group vs ~40 patients in placebo group), the trial provides ~99.5% power to detect a treatment difference (treatment - placebo) of -10% in percent change of BMI from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide at 2-sided alpha of 0.05, assuming a common standard deviation of 10% (estimated from trial RM-493-030), a dropout rate of 20%, and 2:1 randomization.

It is planned to enroll ~12 patients from Japan within the ~120 patients. Using the Method 1 described in PMDA guidance, simulation studies (nsim = 100000 runs) confirmed that the sample size of 12 Japanese patients will provide 80.1% probability that $D_{Japan}/D_{all} > 0.5$ (D: Difference between study drug and placebo for the primary endpoint).

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the date of randomization which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. The last day of study medication is designated with an "L" (e.g., Day 14L). Post-treatment study days are numbered relative to the last dose and are designated as Day 1P, Day 2P, etc.

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, pharmacokinetic, and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of patients, mean, median, standard deviation (SD), minimum, and maximum values will be presented.

Unless stated otherwise, all relevant statistical tests will be conducted at the 2-sided, 0.05 level of significance.

3.3. Computing Environment

All statistical analyses will be performed using SAS statistical software Version 9.4 or higher, unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1 or later. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version September 1, 2022 or later.

3.4. Baseline Definitions

For all analyses, baseline will be defined as the last available measurement prior to randomization for patients randomized into either the setmelanotide or placebo group.

3.5. Methods of Pooling Data

Pooling of data is not applicable to this study.

3.6. Adjustments for Covariates

For efficacy analyses, including the primary analysis, where an analysis of covariance (ANCOVA) model, with an unequal variance to account for possible unequal residual variances, will be utilized and multiple age groups and subpopulation (Japanese vs. non-Japanese) are considered, adjustments will be made for the relevant age groups and subpopulation (Japanese vs. non-Japanese) for that given analysis. For example, the primary analysis on BMI for all patients in mITT would be adjusted for age groups of ≥18 years old, ≥12 and <18 years old, and <12 years old and subpopulation (Japanese vs. non-Japanese), whereas key secondary endpoint of mean change in weekly average of daily most hunger score in patients ≥12 will be adjusted for age groups of ≥18 years old and ≥12 and <18 years old) and subpopulation (Japanese vs. non-Japanese).

For ANCOVA models run on change as opposed to percent change, such as key secondary endpoint of change in most hunger score, adjustments will be made for baseline values.

3.7. Multiple Comparisons/Multiplicity

No multiplicity adjustments are required for the primary analysis as this study has only 1 primary endpoint. This controls the overall alpha at 0.05, 2-sided.

There are 3 key secondary efficacy endpoints planned in the trial. Based on the rarity of this disease, and the small number of patients to be enrolled in this trial, the ability to use extremely rigorous statistical approaches to address multiplicity for these key secondary endpoints is limited. Therefore, for publication, nominal-p-values will be used to interpret each endpoint separately in this small trial. The Sponsor acknowledges that this approach may increase the probability of potential Type 1 error for the set of 3 key secondary efficacy endpoints being analyzed. Therefore, if the primary endpoint is successfully met, then the Sponsor intends to apply a step-down (i.e. sequential testing/fixed sequence testing) on the 3 key secondary endpoints to control the overall Type 1 error, if needed for this purpose.

The following order will be used for sequential testing purposes:

- 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 from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide treatment 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 treatment compared to placebo.

3.8. Subgroup Analysis

Subgroup analyses may be conducted to investigate the similarities across different age brackets, Japanese/non-Japanese patients, sex, race, ethnicity, and regions. The following designations may apply:

Age Brackets

- Patients <12 years old (i.e., 4-11 years old)
- Patients ≥ 12 and < 18 years old (i.e., 12-17 years old)
- Patients ≥ 18 years old

Japanese/Non-Japanese Status

- Japanese
- Non-Japanese

Sex

- Male
- Female

Race

- White
- Black
- Other (other races will be included if number of patients is greater than or equal to 10)

Ethnicity

- Hispanic or Latino
- Not Hispanic or Latino

Region

- North America (Canada, United states)
- Europe (Germany, Netherlands, United Kingdom)
- Japan

Analysis of the primary efficacy, and appropriate secondary and exploratory efficacy endpoints may be repeated for these subgroups should sufficient numbers of patients exist.

For subgroup analyses where the subgroup variable is a term in the model, these terms will be excluded from the model for that subgroup analysis and individual estimates will be generated for each grouping.

Any such analyses or descriptive summaries to be generated will be outlined in the sections below.

3.9. Withdrawals, Dropouts, Loss to Follow-up

Patients who are withdrawn or discontinued from the study will not be replaced.

3.10. Missing, Unused, and Spurious Data

Missing data will be handled for height and body weight and, by extension, their derivatives (BMI, BMI Z-Score, BMI P95), daily hunger scores, and adverse event dates.

Imputation of other missing questionnaire data will be applied for the derivation of summary scores, dependent on the questionnaire and imputation rules of the questionnaire.

Unless otherwise specified, all other study data will be summarized as reported (missing data will not be imputed).

3.10.1. Height

Given that height will be measured only at screening for patients 21 years of age or older, for visits where weight is collected but height is not, BMI will be calculated using the last available height measurement prior to weight collection (LOCF). The same approach is planned to be used for patients less than 21 years old as this will provide a conservative estimate of the BMI (as height is expected only to increase over the course of the study yet will be held constant in this approach, resulting in higher/more conservative BMI).

3.10.2. Weight

For analyses of weight and its derivatives (BMI, BMI Z-Score, BMI P95), including the primary and key secondary efficacy analyses, multiple imputation (MI) will be used to model missing weight measurements at the primary timepoint (after 52 weeks of therapeutic treatment). BMI, BMI Z-score, and BMI P95 will then be derived based upon the imputed weight and available height records.

Weight will be imputed using a retrieved dropout (RD) approach utilizing the following steps:

- If non-monotone missingness is observed in the full set of observations (inclusive of on-treatment completers), Markov Chain Monte Carlo will first be utilized on the full set of observations according to treatment arm to impute intermediate values and to generate a monotone missingness pattern.

- From there, or if a monotone pattern is naturally observed in the data, 2 subsets will be generated:
    - Subset 1: patients classified as off-treatment at primary timepoint (RDs or non-RDs)
    - Subset 2: on-treatment completers
- Monotone regression MI will then be applied to Subset 1 according to treatment arm, regressing on baseline weight, Visit 2 weight, Visit 4 weight, Visit 7 weight, Visit 9 weight, Visit 11 weight, and primary timepoint weight. This will result in 100 complete Subset 1 datasets (either as result of impute = 100 MCMC and impute = 1 Monotone, or, impute = 100 Monotone, missingness structure dependent).
- The complete Subset 1 data will be combined with Subset 2 data to give a wholly complete dataset, representative of all patients (Subset 1 and Subset 2)

Should there be insufficient RD to provide a reliable multiple imputation model, a wash-out imputation method will be utilized.

For wash-out imputation, placebo patients will first be 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 accounts for planned on-site visits as well as a combined primary timepoint as outlined in Table 3-1 below.

If non-monotone missingness is observed, MCMC MI will be utilized according to treatment arm to impute intermediate values and to generate a monotone missingness pattern. From there, or if a monotone pattern is naturally observed in the data, MI utilizing monotone regression will be executed.

Once the placebo patients have been imputed under MAR as directed above, the observed placebo patients will be combined with the setmelanotide patients needing imputation of the primary timepoint. The setmelanotide patients will then be imputed assuming missing-not-at-random (MNAR) using placebo-based imputation (jump to reference method) regressing only on baseline value and primary timepoint value.

Under either imputation method, should there be a patient death while on study, the patient will be considered as a treatment failure and the effective change and percent change from baseline will be set to 0 once the imputation is complete.

Regardless of if RD MI or wash-out MI is utilized, one hundred imputed datasets will be generated via SAS PROC MI. Each of the imputed datasets will then be analyzed according to the relevant statistical test outlined in the sections below. Resulting estimates will be combined using Rubin's rule (SAS PROC MIANALYZE) to produce inferential results.

3.10.3. Daily Hunger

For analyses of the daily hunger score questionnaire in patients ≥12 years of age, MI will be used to model missing measurements at the primary timepoint. The methods outlined above for

weight will be utilized for the daily hunger score questionnaire. The multiple imputation will function at the weekly average of daily hunger score level and not at the daily level scores.

MI approach for the daily hunger score questionnaire will be independent of the MI approach for weight; that is, while we would expect similar missingness between weight and daily hunger questionnaire domains, alternate approaches are acceptable. For example, if RD approach does not converge for weight and therefore wash-out imputation is used for weight, but RD approach does converge for daily hunger score, then RD approach will be used for hunger score even if "alternate" in approach to weight.

3.10.4. Adverse Event Dates

When tabulating adverse event data, partial dates will be handled as follows:

- If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment.
- If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent.
- A missing onset date will be coded as the day of treatment.

3.10.5. Concomitant Medication Dates

While concomitant medication dates will not be directly imputed, partial concomitant start and stop dates will be considered for purposes of identifying prior and/or concomitant status. In general, partial dates with any ambiguity towards prior/concomitant status will be considered concomitant; only partial dates that can clearly indicate prior status will be considered as such.

3.11. Visit Windows

Every effort should be made to ensure that all visits occur according to the protocol SOA, including any dropouts.

3.11.1. Therapeutic Dose Start Date and Primary Timepoint

Efficacy data will be summarized formally at the primary timepoint, after 52 weeks on therapeutic dose.

Setmelanotide or placebo equivalent will be administered at starting doses in all patients and subsequently up-titrated towards the target therapeutic dose, CCI [redacted] dependent. CCI [redacted]

CCI [redacted].

To identify the primary timepoint, the following steps will be utilized:

- Calculate the number of days from therapeutic dose start date for all on-site visits excluding bridging visits
- The non-missing, on-site visit occurring closest to day 365 within a window of 305 to 425 days from therapeutic dose start date will be selected
- If multiple results are equidistant from Day 365 (from the therapeutic dose start date), the latest of these equidistant results is selected
- If no results have been reported within days 305 to 425 from therapeutic dose start date, then the primary timepoint is considered missing

3.11.2. Efficacy Windowing for Patients

As noted in Section 3.10.2, RD MI and washout MI methodologies will impute based on results from baseline, Visit 2, Visit 4, Visit 7, Visit 9, Visit 11, and the primary timepoint. To ensure that captured data is used to the greatest extent possible, expanded windows as compared to the SOA will be considered. Note that visit windowing and use of on-site additional, unscheduled, or early termination visits will only occur if the specific visit as recorded and tabulated per the CRF is missing. That is, for on-site Visits 2, 4, 7, 9, and 11, the value collected directly from the CRF will be used, regardless of timing of that visit. If there is no collected value for a given visit per the CRF, the missing value will be replaced from other, non-missing, on-site visits (excluding bridging visits) based on the target analysis windows outlined in Table 3-1. Similar to primary timepoint handling, if there are multiple records equidistant from the target day, the latest of the equidistant records will be utilized.

Table 3-1 Efficacy Windowing for MI Models

Visit	Visit 2	Visit 4	Visit 7	Visit 9	Visit 11
SoA Target Visit Day	22	78	162	218	274
Target Analysis Visit Window	14, 50	51, 120	121, 190	191, 246	247, 304

3.12. Interim Analyses, Timing of Planned Analyses, and Cohorts

No formal interim analysis is currently planned before the completion of the pivotal cohort for this study. However, various data cuts may occur after completion of the pivotal cohort in support of regulatory submissions. The timing of these data cuts and the number of patients included in each analysis will take into account specific requests from regulatory agencies and applicable regulatory guidance. The rationale of each analysis will be documented.

3.12.1. Timing of Planned Analyses and Cohorts

While this study is powered assuming 120 patients, there are additional Japanese Pharmaceuticals and Medical Devices Agency (PMDA) guidance under consideration. Namely,

12 Japanese patients are to be enrolled and dosed for regulatory considerations. It is expected that these 12 patients will not be enrolled within the first 120 dosed patients and that there may be slight over-enrollment in total patient count to achieve the 12 Japanese patients.

As such, there are two currently planned analyses for the RM-493-040 study.

The pivotal analysis is planned for when 120 patients have completed or discontinued from the study, in accordance. This analysis will focus on the pivotal cohort, defined as the first 120 subjects dosed in any region who have completed the trial and any patients who discontinued after receiving their first dose of study drug.

Any patients beyond this pivotal set of 120 patients at the time of the pivotal analysis will have their data combined with the data of the pivotal set of patients and be analyzed together as ‘all patients’ at the time of the pivotal analysis. Summaries of all patients at the time of the pivotal analysis will be considered as additional, supportive information.

Formal hypothesis testing and success/failure conclusion of the study will be based off the pivotal cohort.

An additional analysis is planned for when the 12 Japanese patients have completed or discontinued from the study. Analyses on all patients will be rerun at this time. To support access and regulatory considerations for the PMDA, specific primary, key secondary, and safety analyses may be run on just the Japanese patients with supportive consistency and exploratory evaluations. Any such analyses will be outlined in this SAP but will be subject to the additional analysis only and should not be considered as a core component of the regulatory package except for any PMDA submission.

4. STUDY ANALYSES

4.1. Disposition

Patient disposition will be tabulated by randomized group and include the number screened, the number randomized, the number treated in total, the number dosed with setmelanotide, the number dosed with placebo, the number in each patient population for analysis, and the number who withdrew prior to completing the treatment and reason(s) for withdrawal. Patient disposition will be summarized for the pivotal cohort of patients and all patients. A separate patient disposition will be provided for Japanese patients only.

A by-patient data listing of study completion information including the reason for premature treatment withdrawal will be presented for all patients.

4.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics information will be summarized by treatment group and overall. Age, height, weight, waist circumference, BMI, BMI P95, and BMI Z-Score at baseline will be summarized using descriptive statistics, as applicable. The number and percentage of participants in each age group (<12 years old, ≥12 to <18 years old, ≥18 years old), sex, ethnicity, race, and subpopulation (Japanese vs non-Japanese) will also be presented. Skin type as measured by the Fitzpatrick Classification Scale as defined in Table 4-1, will also be summarized. Patient demographics and baseline characteristics will be summarized for the mITT for pivotal patients and all patients. A separate summary of patient demographics and baseline characteristics will be provided for Japanese patients only.

Table 4-1 Fitzpatrick Classification Scale

Skin Type	Skin Color	Characteristics
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red or blond hair; blue, hazel, or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Dark Brown; mid-eastern skin types	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

Source: Fitzpatrick 1975

Patient demographic and baseline characteristics data will be provided in by-patient listings.

4.2.1. Medical and Diagnostic History

Medical history will be summarized in a table by MedDRA System Organ Class (SOC) and Preferred Term (PT) frequencies by treatment group and overall for the SA. Summaries will include pivotal and all patients.

A by-patient listing of medical history will be provided.

4.3. Efficacy Evaluation

In general, efficacy analyses will be conducted using the mITT population. Unless stated otherwise, the analysis on hunger score data will be provided for patients ≥12 years of age and <12 years of age. Descriptive summaries will be provided for both age groups for their corresponding questionnaire tools (due to the different hunger score questionnaire tools).

4.3.1. Primary Estimand

The population of the primary estimand is among participants (aged 4 years or older) with documented evidence of acquired HO and weight gain according to the inclusion/exclusion criteria. Participants will receive either active setmelanotide or placebo, where dose-escalation will occur based upon an CCI The primary analysis will be executed using the mITT analysis set, including all randomized patients receiving at least one dose of study drug, grouped as randomized.

The variable is mean percent change from baseline in BMI after 52 weeks of treatment with either setmelanotide or placebo.

Intercurrent events: Patients who discontinue treatment prior to study discontinuation will be handled via the treatment policy strategy, in which all collected measurements will be included in the statistical analyses. Other potential intercurrent events such as receiving the wrong treatment, treatment interruption, and non-adherence to study drug will also be handled via the treatment policy strategy whereby all collected measurements will be included in the statistical analyses.

Any on-study death will be handled via the composite strategy, in which death is considered a sufficiently unfavorable outcome and the patient will have their corresponding change and percent change from baseline artificially set to 0.

The population level summary is the difference between treatment groups (setmelanotide and placebo) in mean percent change from baseline in BMI at Week 52, obtained from an analysis of covariance (ANCOVA) model, with unequal variance to account for possible unequal residual variances, based on the outcomes of 100 imputed datasets combined using Rubin's Rule (Little and Rubin 2002). Multiple imputation assuming missing not at random (MNAR) will be used as the primary approach for missing data and will model the missing measurements based on known measurements from retrieved dropouts in the same treatment group. If insufficient retrieved dropouts exist to provide a reliable multiple imputation model, wash-out imputation will be used where missing values for subjects on active drug will be imputed with observed baseline and data from the placebo group. No intermediate values from the active treatment group would be used in this approach. Further technical details are found in Section 3.10.2.

The robustness of the primary estimand will be assessed through sensitivity analysis using two-dimensional tipping point.

4.3.2. Primary Efficacy Analysis

The primary efficacy endpoint of this study is the mean percent change from baseline in BMI after 52 weeks of treatment with the therapeutic regimen of either setmelanotide or placebo.

The statistical hypothesis for the primary efficacy endpoint is:

$$H0: \mu_t - \mu_p \geq 0 \text{ vs } H1: \mu_t - \mu_p < 0$$

where μ_t is the mean percent change in BMI from baseline after approximately 52 weeks on a therapeutic regimen in setmelanotide group, and μ_p is the mean percent change in BMI from baseline after approximately 52 weeks in placebo group.

The primary endpoint will be conducted on the mITT utilizing BMI values resultant from the multiple imputation process as outlined in Section 3.10.2. The difference between setmelanotide and placebo after 52 weeks on therapeutic dose will be estimated using an ANCOVA model with unequal variance to account for possible unequal residual variances. The model will be adjusted with stratification factors of age group (≥18 years old, ≥12 and <18 years old, and <12 years old) and subpopulation (Japanese and non-Japanese) as appropriate. This difference will be estimated for each of the 100 imputed datasets. The outcomes from the 100 imputed datasets will be combined using Rubin's Rule (Little and Rubin, 2002) through SAS PROC MIANALYZE to provide an overall estimate of least squares (LS) mean difference with corresponding 95% confidence intervals (CI) and p-value. The success criterion for the primary hypothesis requires the rejection of the null hypothesis at the 2-sided 0.05 significance level.

While formal hypothesis testing will be considered based on pivotal patients, the primary analysis will also be conducted for all patients.

The primary analysis will be repeated for Japanese patients to explore consistency of effect for the PMDA. Consistency will be determined as an observed treatment effect in Japanese patients of at least 50% of the observed, overall treatment effect (seen in all patients), in alignment with PMDA Method 1. All patients are the basis for comparison as this is the set of patients that consists of all 12 Japanese patients.

The actual, change from baseline, and percent change from baseline for observed values of BMI will be summarized descriptively by visit for pivotal and all patients in the mITT, as needed. Additional descriptive summaries will be provided by age category for pivotal and all patients as well as for Japanese/non-Japanese subgroup for all patients, as needed.

Percent change from baseline in BMI in observed values will be presented graphically by treatment group and visit, with standard error bars included, for the mITT for pivotal and all patients. The x-axis will include visit in weeks and the y-axis will represent the observed mean ± SE of percent change from baseline.

A by-patient listing for BMI observed values will be provided.

4.3.3. Sensitivity Analyses

4.3.3.1. Two-Dimensional Tipping Point Analysis

The two-dimensional tipping point analysis will be conducted for pivotal and all patients in the mITT with varying assumptions about the missing outcomes on the two treatment groups independently, including scenarios in which dropouts on setmelanotide group have worse outcomes than dropouts on placebo group. A penalty for the setmelanotide group and improvement on the placebo group will change by increments of 0.1 to 1, until the statistical significance is lost, i.e., until the p-value becomes >0.05.

4.3.4. Supplementary Analyses

4.3.4.1. Per-Protocol Population Analysis

The primary analysis may also be repeated for the PP population for both pivotal patients and all patients. The per-protocol analysis will only be provided if the number of excluded patients in PP population is at least 10% of the overall mITT set.

4.3.4.2. As-Observed Analysis

The primary analysis will also be repeated for the mITT population for both pivotal and all patients based on observed data only.

4.3.4.3. Last-Observation Carried Forward Analysis

A last-observation-carried-forward (LOCF) analysis will be conducted for pivotal and all patients in the mITT. For any patients missing the primary timepoint BMI value, the last available BMI value occurring at an on-site visit (including unscheduled, additional, or early termination on-site visits) will be carried forward and used as the primary timepoint value for analysis purposes.

4.3.5. Key Secondary Efficacy Analyses

Statistical testing will be performed on the key secondary endpoints according to the pre-specified hierarchical order as outlined in Section 3.7. Formal inference of efficacy tests will be based on the pivotal patients and stop once a result showing no statistical significance in favor of the study drug at the 2-sided alpha level of 0.05 is achieved.

The key secondary endpoints will rely upon the imputed values utilized for the primary efficacy endpoint (BMI/BMI Z-Score) or rely upon newly imputed values following same methodology as the primary efficacy endpoint (weekly average in daily hunger) as outlined in Section 3.10.3.

4.3.5.1. Proportion of BMI/BMI Z-Score Percent Change from Baseline

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 will be analyzed for pivotal patients in the mITT.

The BMI Z-score will be calculated for patients aged 4 to <18. These calculations will utilize the World Health Organization's WHO 2007 BMI SAS Macro Package. This macro package includes source code, three permanent datasets containing WHO 2007 references as required for calculation, and a readme.pdf with instructions. The patient age, sex, and BMI will be provided into this macro and the resulting BMI Z-Score will be produced and pulled directly into the appropriate CDISC compliant dataset.

Similar to the handling outlined in Section 3.10.1 if weight is collected but a corresponding height is not collected, the last available height record for that patient will be used in the calculation of BMI before this BMI is used as an input into the validated macro.

Analysis will be conducted using the following steps:

- Binomial proportions will be calculated for each treatment arm for each of the 100 imputed datasets. Analysis between arms will be conducted for each of the 100 imputed datasets with a Cochran-Mantel–Haenszel (CMH) test with adjustment of stratification factors of age group and subpopulation (Japanese and non-Japanese), as appropriate. For each MI dataset, the COMMONRISKDIFF option in PROC FREQ will calculate the adjusted estimate of the risk difference of success (setmelanotide minus placebo) over all strata with its 95% confidence interval (CI).

- The estimates of the risk difference and their standard errors for all the MI datasets will be input to PROC MIANALYZE.

- PROC MIANALYZE will output an overall estimate of the risk difference, its 95% CI, and a combined p-value.

- PROC MIANALYZE will also output overall estimates of the proportions of responders in each treatment arm, along with 95% CIs.

While formal hypothesis testing will be considered based on pivotal patients, this key secondary analysis will also be conducted for all patients.

This analysis will be repeated for the Japanese subpopulation to explore consistency of effect. Similarly to the primary endpoint, consistency will be claimed if the estimated treatment effect in the Japanese subpopulation is at least 50% of the observed, overall treatment effect in all patients.

This key secondary analysis will additionally be repeated for the PP population for pivotal patients only.

Descriptive statistics for the actual, change from baseline, and percent change from baseline in observed BMI Z-Score for patients <18 years of age will be provided by visit. Additional descriptive summaries will be provided for Japanese/non-Japanese subgroup for all patients, as needed.

Change from baseline in BMI Z-Score in observed values will be presented graphically by treatment group and visit, with standard error bars included, for the mITT for pivotal and all patients. The x-axis will include visit in weeks and the y-axis will represent the observed mean ± SE of percent change from baseline.

A by-patient listing for BMI Z-Score observed values will be provided.

4.3.5.2. Proportion of All Patients with ≥5% Reduction in BMI from Baseline

The proportion of pivotal patients with ≥5% reduction in BMI from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo will be analyzed following the same methodology described in Section 4.3.5.1 above for the mITT.

Similar to the above, formal analysis will be conducted based on pivotal patients, but the analysis will be repeated for all patients.

This analysis will also be repeated for the Japanese subpopulation to explore consistency of effect. Similarly to the primary endpoint, consistency will be claimed if the estimated treatment effect in the Japanese subpopulation is at least 50% of the observed, overall treatment effect in all patients.

This key secondary analysis will additionally be repeated for the PP population for pivotal patients only.

4.3.5.3. Daily Hunger Questionnaire Change from Baseline

Mean change from baseline in the weekly average of the daily hunger scores for pivotal patients ≥12 years old in the mITT after 52 weeks on therapeutic regimen will be analyzed to compare setmelanotide versus placebo.

Analysis will be conducted with an ANCOVA model, assuming unequal variance to account for possible unequal residual variances and adjusted with baseline weekly average of daily most hunger score and stratification factors of age group (≥18 years old, ≥12 and <18 years old) and subpopulations (Japanese and non-Japanese), as appropriate. The ANCOVA model will be run for each of the 100 imputed datasets (according to Section 3.10.3) and the outcomes from each of the 100 imputed datasets will be combined using Rubin's Rule to provide an overall estimate against the null hypothesis with corresponding confidence intervals and p-value.

Daily hunger questionnaire scores are recorded for 7 consecutive days before each scheduled trial visit.

Prior to analysis, daily hunger scores for each of the hunger assessments will be averaged separately for the 7 days immediately preceding the visit. The hunger score on the day of the visit will not be considered as prior to visit and thus the daily scores over the 7 days prior to, and not considering day of visit, will be considered. Only if all 7 days prior to randomization (baseline) are missing, will we consider the day of visit (Day 1). This will help to ensure non-missing baseline values for this key secondary endpoint.

Once these daily scores are identified, the weekly average of daily scores will be equal to the average of the daily scores over the 7 identified days. For a week of hunger scores to be considered evaluable, scores need to be recorded and available for analysis on at least 1 of 7 days to provide sufficient data to determine mean values. Unless specified otherwise, this will be applicable for all daily hunger score related analyses.

While formal hypothesis testing will be considered based on pivotal patients, the analysis will also be conducted for all patients.

This analysis will also be repeated for the Japanese subpopulation to explore consistency of effect. Similarly to the primary endpoint, consistency will be claimed if the estimated treatment effect in the Japanese subpopulation is at least 50% of the observed, overall treatment effect in all patients.

This key secondary analysis will additionally be repeated for the PP population for pivotal patients only.

The actual and change from baseline for observed values of weekly average of daily hunger scores will be summarized descriptively by visit for pivotal and all patients for the mITT, as needed. Additional descriptive summaries will be provided for the Japanese/non-Japanese subgroup for all patients, as needed.

Change from baseline in weekly average of daily hunger scores observed values will be presented graphically by treatment group and visit, with standard error bars included, for the mITT for pivotal and all patients. The x-axis will include visit in weeks and the y-axis will represent the observed mean ± SE of change from baseline.

A by-patient listing for observed hunger score responses will be provided.

4.3.6. Other Secondary Efficacy Endpoints

The other secondary endpoints will rely upon imputed values utilized for the primary and key secondary efficacy endpoints where applicable (BMI/BMI Z-Score/BMI P95/Weight/weekly average in daily hunger). Endpoints relating to domains that have not previously relied on multiply imputed values will be analyzed as observed. Any analyses relying upon imputed values will specify so in the sections below.

4.3.6.1. Daily Hunger Questionnaire Reduction

The proportion of pivotal patients ≥ 12 years of age achieving a ≥ 2-point reduction in the weekly average of daily most hunger score from baseline after approximately 52 weeks will be analyzed for the mITT. Binomial proportions will be calculated for each treatment arm for each of the 100 imputed datasets. Analysis between arms will be conducted for each of the 100 imputed datasets with a CMH test with adjustment of stratification factors of age group (≥18 years old, ≥12 and <18 years old) and subpopulation (Japanese and non-Japanese), as appropriate. This analysis will follow the same methodology as the first key secondary efficacy endpoint as outlined in Section 4.3.5.1.

This analysis will be repeated for all patients.

4.3.6.2. Symptoms of Hyperphagia (Patient/Caregiver Versions)

Daily Symptoms of Hyperphagia scores are recorded for 7 consecutive days before each scheduled trial visit.

Patients ≥12 years of age who are able to self-report CCI [redacted]

Caregivers of patients who are <12 years of age or of patients ≥ 12 years of age who cannot self-report will be administered CCI [redacted]

[redacted]

Analysis of the mean change in weekly average of symptoms of hyperphagia composite score after approximately 52 weeks will be analyzed separately for each of the questionnaires, assuming sufficient sample size, for pivotal and all patients in the mITT. The between-group comparison on the mean change from baseline will be conducted with an ANCOVA model, assuming unequal variance to account for possible unequal residual variances. The ANCOVA model will adjust for baseline score in both models with a stratification factor of age groups and subpopulations (Japanese and non-Japanese), as appropriate.

Descriptive summaries will be provided for weekly average composite score, change from baseline, and percent change from baseline for pivotal and all patients, as needed.

Subgroup analysis on the Symptoms of Hyperphagia based upon different baseline value data cutoffs may be explored as appropriate.

The Symptoms of Hyperphagia results will be presented in a by-patient listing.

4.3.6.3. Proportion of Patients with ≥10% Reduction in BMI from Baseline

The proportion of pivotal and all patients in the mITT achieving a ≥ 10% reduction in BMI from baseline after approximately 52 weeks will be analyzed. Binomial proportions will be calculated for each treatment arm for each of the 100 imputed datasets. Analysis between arms will be conducted for each of the 100 imputed datasets with a CMH test with adjustment of stratification factors of age group and subpopulation (Japanese and non-Japanese), as

appropriate. This analysis will follow the same methodology as the first key secondary efficacy endpoint as outlined in Section 4.3.5.1.

4.3.6.4. Proportion of Patients with ≥10% Reduction in Weight from Baseline

The proportion of pivotal and all patients in the mITT achieving a ≥ 10% reduction in weight from baseline after approximately 52 weeks will be analyzed. Binomial proportions will be calculated for each treatment arm for each of the 100 imputed datasets Analysis between arms will be conducted for each of the 100 imputed datasets with a CMH test with adjustment of stratification factors of age group and subpopulation (Japanese and non-Japanese), as appropriate. This analysis will follow the same methodology as the first key secondary efficacy endpoint as outlined in Section 4.3.5.1.

The actual, change from baseline, and percent change from baseline for observed values of weight will be summarized descriptively by visit for pivotal and all patients in the mITT, as needed.

Percent change from baseline in weight in observed values will be presented graphically by treatment group and visit, with standard error bars included, for the mITT for pivotal and all patients. The x-axis will include visit in weeks and the y-axis will represent the observed mean ± SE of percent change from baseline.

A by-patient listing of observed body weight will be provided.

4.3.6.5. Body Weight Percent Change from Baseline in Patients ≥18 Years of Age

Mean percent change in weight from baseline after approximately 52 weeks in pivotal and all patients ≥ 18 years in the mITT will be analyzed.

The between-group comparison on the mean percent change from baseline will be conducted with an ANCOVA model, assuming unequal variance to account for possible unequal residual variances. The ANCOVA model will adjust for the stratification factor of subpopulations (Japanese and non-Japanese), as appropriate.

4.3.6.6. BMI Z-Score and BMI Percentile Reduction from Baseline in Patients <18 Years of Age

BMI percent of the 95th percentile will rely upon the Center for Disease Control's (CDC) 2000 CDC Growth Chart Provided Source Code and Datasets. Similar to the macro utilized for BMI Z-score generation outlined in Section 4.3.5.1, the patient age, sex, and BMI will be provided into this CDC macro. The CDC macro will utilize these inputs to generate the calculated percent of the 95th percentile which will be pulled directly into the appropriate CDISC compliant dataset.

The mean reduction in BMI Z-Score after approximately 52 weeks on therapeutic regimen in pivotal and all patients <18 years of age in the mITT and in BMI percentile in pivotal and all patients <18 years in the mITT will be analyzed. Analyses for each item will be conducted separately.

Analysis will be conducted with an ANCOVA model, assuming unequal variance to account for possible unequal residual variances and adjusted with baseline score and stratification factors of age groups (<12 years old, ≥12 and <18 years old) and subpopulation (Japanese and non-Japanese), as appropriate. The ANCOVA model will be run for each of the 100 imputed datasets and the outcomes from each of the 100 imputed datasets will be combined using Rubin's Rule to provide an overall estimate against the null hypothesis with corresponding confidence intervals and p-value.

Descriptive summaries for the BMI percentile reduction actual, change from baseline, and percent change from baseline will be provided by visit for pivotal and all patients <18 years of age in the mITT, as needed.

Change from baseline in BMI percentile reduction in observed values will be presented graphically by treatment group and visit, with standard error bars included, for the mITT for pivotal and all patients <18 years of age. The x-axis will include visit in weeks and the y-axis will represent the observed mean ± SE of percent change from baseline.

BMI percent of 95th percentile results will be presented in a by-patient listing.

4.3.6.7. BMI Z-Score Reduction in Patients Aged ≥4 to <18 Years

The proportion of pivotal and all patients aged ≥4 to <18 years achieving a ≥0.2-point reduction of BMI Z-score from baseline will be analyzed for the mITT. Binomial proportions will be calculated for each treatment arm for each of the 100 imputed datasets Analysis between arms will be conducted for each of the 100 imputed datasets with a CMH test with adjustment of stratification factors of age group (≥12 and <18 years old, <12 years old) and subpopulation (Japanese and non-Japanese), as appropriate. This analysis will follow the same methodology as the first key secondary efficacy endpoint as outlined in Section 4.3.5.1.

4.3.6.8. Proportion of Patients with BMI <30 kg/m^2 (≥18 years) or <95th percentile (<18 years)

For consistency with BMI percent of 95th percentile analyses, a subject's 95th BMI percentile will be based upon the CDC macro as outlined in Section 4.3.6.6 and is age and sex dependent.

The proportion of patients with BMI <30 kg/m2 (patients aged ≥18 years) or <95th percentile (patients aged <18 years) after approximately 52 weeks will be analyzed. Binomial proportions will be calculated for each treatment arm for each of the 100 imputed datasets. Analysis between arms will be conducted for each of the 100 imputed datasets with a CMH test with adjustment of stratification factors of age group (≥12 and <18 years old, <12 years old) and subpopulation (Japanese and non-Japanese), as appropriate. This analysis will follow the same methodology as the first key secondary efficacy endpoint outlined in Section 4.3.5.1.

Patient BMI percentiles will be included on the BMI percent of 95th percentile by-patient listing.

4.3.6.9. Quality of Life

Quality of life will be assessed using the Impact of Weight on Quality of Life-Lite-Clinical Trials questionnaires (IWQOL-Lite-CT or IWQOL-Kids).

The IWQOL-Lite-CT will be administered to patients ≥18 years of age. The IWQOL-Lite-CT is a validated 20-item self-report measure of obesity-specific quality of life questionnaire. The IWQOL-Lite-CT yields a Total score and 3 composite scores: Physical (7 items), Physical Function (5 items), and Psychosocial (13 items).

Mean change in physical functioning score and total score for the IWQOL (IWQOL-Lite-CT in pivotal and all patients ≥18 years in mITT), from baseline will be analyzed with an ANCOVA model adjusted for baseline score and subpopulation (Japanese and non-Japanese), as appropriate.

The IWQOL-Kids will be administered to patients between the ages of 11 and <18. The IWQOL-Kids is a validated 27-item self-report measure of weight-related quality of life for youth. It provides a total score inclusive of 4 domains: physical comfort, body esteem, social life, and family relations.

Mean change in total score for the IWQOL-Kids in pivotal and all patients between the ages of 11 and <18 in the mITT will be analyzed with an ANCOVA model adjusted for baseline score and subpopulations (Japanese and non-Japanese), as appropriate.

Descriptive summaries will be presented for both the IWQOL and IWQOL-Kids actual and change from baseline by visit for pivotal and all patients of relevant age in the mITT, as needed.

By-patient listings will be provided for IWQOL-Lite-CT and IWQOL-Kids.

4.3.6.10. Waist Circumference

Change in waist circumference from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo will be analyzed.

The between-group comparison will be conducted for pivotal and all patients in the mITT using an ANCOVA model adjusted with baseline measurement and a stratification factor of age groups (<12 years old, ≥12 and <18 years old, and ≥18 years old) and subpopulations (Japanese and non-Japanese), as appropriate.

The actual, change from baseline, and percent change from baseline for waist circumference will be summarized descriptively by visit for pivotal and all patients in the mITT, as needed.

Change from baseline in waist circumference will be presented graphically by treatment group and visit, with standard error bars included, for the mITT for pivotal and all patients. The x-axis will include visit in weeks and the y-axis will represent the observed mean ± SE of percent change from baseline.

By-patient listing will be provided based on reported results.

4.3.6.11. Cardiometabolic Parameters

The difference in change in cardiometabolic parameters including blood pressure, CCI [redacted] liver function and CCI [redacted] from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo will be analyzed.

Mean change in each cardiometabolic parameter from baseline will be analyzed for pivotal and all patients in the mITT with an ANCOVA model adjusted with baseline measurement and stratification factors of age group (≥18 years old, ≥12 and <18 years old, <12 years old) and subpopulation (Japanese and non-Japanese), as appropriate.

The actual, change from baseline, and percent change from baseline for each cardiometabolic parameter will be summarized descriptively by visit for pivotal and all patients in the mITT, as needed.

A by-patient listing will be provided for each cardiometabolic parameter based on reported results.

4.3.7. Exploratory Efficacy Endpoints

4.3.7.1. CCI [redacted]

[redacted]

4.3.7.2. CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

4.3.7.3. CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.3.7.4. CCI [redacted]

CCI [redacted]

4.3.7.5. CCI [redacted]

CCI [redacted]

4.3.7.6. CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

4.4. Pharmacokinetic Evaluations

PK analysis will be conducted by the Sponsor designee and analysis will be specified in a separate PKAP. However, PK concentration listings will be provided based on the mITT where relevant profile are obtained.

4.5. Safety Analysis

Safety analyses will be conducted using the SA Set.

4.5.1. Drug Exposure

Drug exposure will be summarized for pivotal and all patients by treatment group across the entire length of the study. The number of doses administered, total dose received in mg, treatment duration in weeks, and percentage of dosing compliance will be summarized using descriptive statistics (N, mean, SD, median, minimum, maximum, and 95% confidence intervals). A separate summary for Japanese patients will be provided.

Treatment duration will be defined in weeks as (date of last dose – date of first dose + 1) / 7.

Dosing compliance percentage will be defined as (number of doses administered / the duration of treatment in days) * 100.

A by-patient listing for dosing will be provided.

4.5.2. Adverse Events

All AEs will be coded using the MedDRA coding system (Version 24.0 or later) and displayed in tables by treatment received and in data listings using system organ class and preferred term. AE grade assessment will be based on investigator reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0.

Analyses of AEs will focus on those events that are considered treatment-emergent, where treatment-emergent is defined as any 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 to be related to study drug exposure.

The number and percentage of pivotal and all patients with any treatment-emergent AE (TEAE), with any TEAE assessed by the Investigator as related to treatment (definite, probable, or possible relationship), with any serious TEAE, with any serious related TEAE, with any TEAE leading to study drug withdrawal, or with any TEAE leading to death will be summarized by treatment received, as needed. The aforementioned summaries will be repeated for Japanese patients, as needed.

The number and percentage of pivotal and all patients with treatment-related TEAEs leading to study discontinuation and non-serious TEAEs will also be summarized by treatment received, as needed.

TEAEs of special interest (Nausea, Vomiting, Diarrhea) will be identified and summarized by treatment received for pivotal and all patients, as needed. A separate summary will be provided for Japanese patients.

In these tabulations, each patient will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

All AEs occurring on-study will be listed in patient data listings. Listings will also be provided for the following: drug product related TEAEs, serious TEAEs, drug product related serious TEAEs, TEAEs leading to study drug withdrawal, events of special interest, and deaths.

4.5.3. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be measured as shown in the SoA (Table 1-1) according to the age of the patient (child <12 or adult ≥12). Results of the C-SSRS will be provided in a shift table for pivotal and all patients assessing shifts from the baseline most severe ideation to most severe ideation during follow-up, as needed.

A by-patient listing including the ideation, intensity of ideation, behavior, and number of attempts will be provided.

4.5.4. Patient Health Questionnaire (PHQ-9 or PHQ-A)

The PHQ-9 is a 9-item depression scale of the Patient Health Questionnaire used to assist clinicians in diagnosing depression as well as selecting and monitoring treatment and is administered to patients ≥18 years old. The PHQ-A is a modification of the PHQ-9 for adolescents (patients ages 11 to 17 years old). Each question has a score from 0 to 3, and all 9 scores are added to produce a total score.

The Patient Health Questionnaire-9 and PHQ-A will be measured as shown in the SoA (Table 1-1). The actual values and change from baseline of the total scores will be summarized with descriptive statistics by visit for pivotal and all patients, as needed.

A by-patient listing of the results of the individual 9 questions will be provided.

4.5.5. Children's Depression Inventory-2 (CDI-2)

The CDI-2 has both a self-report and a parent version. The CDI-2: Self-Report Short version is an efficient screening measure that contains 12 items. The self-report short version will be administered to patients 7 to <12 years of age according to the SoA (Table 1-1).

Items on the CDI-2 Parent form correspond to items on the self-report version and are suitably rephrased. Item selection for the parent forms was guided to maximize validity, and thus focused on observable manifestations of depression. The CDI-2 parent form consists of 17 items and the 4 choices provided for each item correspond to 4 levels of symptomatology: 0 (not at all), 1 (some of the time), 2 (often), or 3 (most of the time). The CDI-2 parent version will be administered to caregivers of patients 7 to <12 years of age according to the SoA (Table 1-1).

The actual values and change from baseline of the total scores will be summarized with descriptive statistics by visit for pivotal and all patients, as needed.

By-patient listings will be provided for each version of the CDI-2.

4.5.6. Global Hunger Questions

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 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 (Table 1-1).

The actual values and change from baseline of the total scores will be summarized with descriptive statistics by visit for pivotal and all patients, as needed. Shift tables will also be provided for pivotal and all patients for each version of the questionnaire, capturing shifts from baseline to each on study visit, as needed.

A by-patient listing of the results questions will be provided.

4.5.7. Thyroxine (T4), Free Thyroxine (T4), and T3

T4, Free T4, and T3 will be measured as shown in the SoA (Table 1-1).

A by-patient listing of the results of will be provided.

4.5.8. Injection Site Evaluations

Injection site evaluations will be performed according to the SoA (Table 1-1) and will be summarized for pivotal and all patients for all visits by treatment received according to severity (none, mild, moderate, severe) and type of reaction (erythema, edema, induration, itching, pain or tenderness, or other reaction), as needed. For patients reporting more than one occurrence of the same type of reaction, the most severe reaction will be used for the summary.

A by-patient listing will be provided for all injection site evaluations and will also include measurement (if applicable).

4.5.9. Laboratory Data

Clinical laboratory values will be expressed in the International System of Units (SI).

The actual value, change from baseline, and percent from baseline to each on-study evaluation will be summarized for each clinical laboratory parameter by visit and treatment received for pivotal and all patients, as needed. Clinical laboratory parameters include:

Hematology

Hematocrit, Hemoglobin, CCI , Mean Corpuscular Hemoglobin, Erythrocytes, Mean Corpuscular Volume, Platelets, Leukocytes, Differentials (absolute and percent; Basophils, Eosinophils, Neutrophils, Lymphocytes, Monocytes).

Chemistry

Glucose, Blood urea nitrogen, Uric acid, Creatinine, Creatine phosphokinase, Sodium, Potassium, Chloride, Bicarbonate, Calcium, Lactate dehydrogenase, Magnesium, Phosphate, Total bilirubin, Direct bilirubin, Alkaline phosphatase, Alanine transaminase, Aspartate transaminase, Albumin, Gamma-glutamyl transferase, Total protein.

Urinalysis

Color, clarity, leukocyte esterase, nitrite, urobilinogen, urine protein, pH, specific gravity, Urine ketones, Urine bilirubin, Urine glucose, Blood.

In the event of repeat values, the last non-missing value per study day/time will be used.

Abnormal evaluations will be summarized in a table by treatment received for pivotal and all patients, as needed.

Shift tables of change in abnormal status (low/normal/high) of laboratory parameters from baseline to every planned post-baseline visit will be presented for hematology and clinical chemistry by treatment received for pivotal and all patients, as needed.

All laboratory data, including pregnancy test results and FSH, will be provided in data listings.

4.5.10. 12-Lead Electrocardiogram

ECG results will be measured as shown in the SoA (Table 1-1).

All ECG data, including overall interpretation, will be provided in a by-patient data listing.

4.5.11. Vital Signs

Vital signs will be measured as according to the SoA (Table 1-1). Aside from those used in efficacy evaluations, the actual value, change from baseline, and percent change from baseline

of temperature, HR, systolic Blood Pressure (BP), diastolic BP, and respiratory rate will be summarized descriptively by visit and treatment received for pivotal and all patients, as needed.

A by-patient listing of all vital signs will be provided.

4.5.12. Physical Examination and Comprehensive Skin Examination

Physical and comprehensive skin examinations will be performed according to the SOA (Table 1-1). Results of the physical examinations will be provided in a shift table, summarizing the shift from baseline to each visit for pivotal and all patients by treatment received, as needed. Skin examination findings will be presented in a shift table, summarizing the shift from baseline to each visit for a given region by treatment received for pivotal and all patients, as needed.

A separate, by-visit descriptive summary of tanner staging assessment will be provided by treatment received for pivotal and all patients, as applicable.

Separate by-patient listings of all physical examination, tanner staging, and skin examination findings will be provided.

4.5.13. Concomitant Medications

A prior medication is defined as any medication that was started before the time of first dose date.

Concomitant medications are defined as medications either ongoing at the time of first dose date or which start on or after the first dose date but before drug discontinuation. A medication may be considered both prior and concomitant.

Concomitant medications will be assessed according to the schedule in Table 1-1 and coded using the WHO Drug Dictionary, version March 1, 2021, or later. The use of prior and concomitant medications will be included in separate summary tables by treatment received for pivotal and all patients, as needed. Prior and concomitant medications will be tabulated by Anatomical Therapeutic Chemical class and Preferred Term.

Prior and concomitant medications will also be included in a by-patient data listing.

4.5.14. Anti-RM-493 Antibody Measurements

Blood samples for Anti-RM-493 antibody assessment will be collected as shown in the SoA (Table 1-1).

Results will be provided in a by-patient listing, including the date of the assessment and result.

4.5.15. Ambulatory BP Monitoring (ABPM)

At select sites in North America and Europe, ABPM will be conducted outside of the clinic setting in all patients ≥4 years of age. For patients ≤12 years of age, both caregiver and Investigator will confirm feasibility of patient compliance in this assessment. The ABPM monitor will measure BP (systolic and diastolic), pulse pressure (mmHg), mean arterial blood pressure (mmHg) and HR in 30-minute intervals for each 24-hour period. ABPM assessments

will require patients to wear the monitor at each time point for any 24-hour period before Day 1 (conducted during Screening), Week 24, and EOT Visit (occurs after 52 weeks on a therapeutic dose), per SoA (Table 1-1).

Assuming sufficient patients, ABPM parameters will be summarized by visit, timepoint (Nighttime, daytime, 24 hours overall), and treatment received. Nighttime results will be defined to include all reported measurements between 8:00PM (20:00 hours) to 5:59AM (05:59 hours) the next day. Daytime results will be defined to include all reported measurements between 6:00AM (06:00 hours) to 7:59PM (19:59 hours).

Nighttime, daytime, and 24 hour overall values will be derived using the following steps:

> For derivation purposes, the reported collection time, in 24hour time system, will be mapped as Hour = Floor(Time). For example, times from 07:00-07:59 will be mapped to Hour=07:00. The hourly value will be equal to the average of non-missing values mapped to that specific hour. For example, since ABPM measurements are in 30-minute intervals, the 7:00 value may be defined as the average of the 7:00 and 7:30 collected values, as applicable.
>
> Once all hourly values are generated, the timepoint (nighttime, daytime, 24 hour overall) values will be derived as the average of all non-missing hourly values according to the timepoint definitions above.

Change from baseline in nighttime, daytime, and 24 hour overall values will be derived using the following steps:

> As noted above, hourly values will be generated for each of the 24 hours of ABPM monitoring. For post-baseline visits, each hourly value will first have its own change from baseline based upon the baseline value for the same hour. For example, change from baseline at 7:00 will be calculated as post-baseline 7:00 value minus baseline 7:00 value.
>
> Once all hourly change from baselines are derived, the timepoint (nighttime, daytime, 24 hour overall) change from baseline values will be derived as the average of all non-missing hourly change from baseline values according to the timepoint definitions above.

The actual observed and change from baseline in ABPM parameters will be summarized by timepoint, visit, and treatment received for pivotal and all patients, as needed.

A by-patient listing for all ABPM parameters will be provided.

5. CHANGES TO PLANNED ANALYSES

CCI

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7. APPENDIX

7.1. Appendix 1

The below is the list of the 120 pivotal patients in the mITT primary efficacy analysis cohort:

Note: One patient (Patient ID: PPD was randomized but never received any dose of test article, therefore, this patient will be excluded from the mITT analysis set.

Patient ID
PPD

PPD

PPD

PPD

PPD

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PPD

Electronic Record and Signature Disclosure created on: 10/6/2023 11:57:17 AM
Parties agreed to: PPD

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