Rhythm Pharmaceuticals, Inc.
Protocol #: RM-493-035

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial: Multiple Independent Sub-studies of Setmelanotide in Patients with POMC/PCSK1, LEPR, NCOA1 (SRC1), or SH2B1 Gene Variants in the Melanocortin-4 Receptor Pathway

Statistical Analysis Plan

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CONTENTS

I.Introduction 5

A. Background 5
B. Protocol and Amendment History 5
C. Changes from Planned Analyses 7

II.Protocol Objectives and Study Endpoints 7

A. Estimand 10

III.Study Design 10

A. Design Overview 10
B. Study Population 12
C. Sample Size Determination 13
D. Treatment Randomization 13
E. Assessment Schedule 14

IV.Interventions 14

A. Treatment Administration 14

V.General Analytical Considerations 14

A. Data Sources 14
B. Blinding Considerations 14
C. Study Period 15
D. Definition of Baseline 15
E. Study Day 15
F. Analysis Window 15
G. Missing Data 16
H. Multiple Study Centers 17
I. Covariates Adjustment in Primary Analysis 17
J. Data Safety Monitoring Board 17
K. Multiple Adjustment 18
L. Analysis Sets 18
M. Subgroup of Analysis Population 19
N. Special Distribution Schedule 19
O. Data Display Characteristics 19
P. Blinded Review of Data 20
Q. Software Version 20

VI.Patient Accountability 21

A. Patient Demographic and Baseline Characteristics 21
B. Disposition 21
C. Protocol Deviations and Violation 21
D. Historic Measurements and Interventions 21

E. Medical History 22
F. Medical History Weight Loss Interventions .**Error! Bookmark not defined.**

VII. Efficacy Analyses 22

A. Efficacy Assessments 22
B. Primary Efficacy Analysis 23
C. Secondary Efficacy Analysis 26
D. [redacted] 28
E. Supplemental Analysis 29

VIII. Questionnaires 29

A. Hunger Questions 29
B. Global Hunger 31
C. [redacted] 32
D. [redacted] 33
E. [redacted] 35
F. Impact of Weight on Quality of Life (IWQOL) 35
G. Nutrition and Exercise Counseling 38

IX. Safety Analyses 38

A. Exposure 38
B. Adverse Events 39
C. Injection Site Evaluation 40
D. Clinical Laboratory Results 41
E. Vital Signs 41
F. Physical Examination 42
G. Prior and Concomitant Medications 42
H. Concomitant Procedures 42
I. Skin Examination 42
J. Hyperpigmentation 43
K. Sexual Function 43
L. Electrocardiogram 43
M. Columbia-Suicide Severity Rating Scale (C-SSRS) 44
N. Patient Health Questionnaire-9 (PHQ-9) 45
O. Children's Depression Inventory 2 (CDI-2) 45

X. References 46

XI. Appendix 1: Schedule of Assessment 47

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ACMG	American College of Medical Genetics
AE	Adverse Event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
[redacted]	[redacted]
[redacted]	[redacted]
IWQOL	Impact of Weight on Quality of Life
LP	Likely Pathogenic
MC4R	Melanocortin-4 Receptor
NCOA1	Nuclear Receptor Coactivator 1
P	Pathogenic
P/LP	Pathogenic, Likely Pathogenic
PCSK1	Proprotein Convertase Subtilisin/Kexin Type 1
PG	Prevention Genetics
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9
PK	Pharmacokinetic
POMC	Pro-opiomelanocortin
PP	Per-Protocol
PPL	POMC, PCSK1, and LEPR
QD	Once Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SH2B1	SRC Homology 2 B Adapter Protein 1
SOA	Schedule of Assessments
SRC1	Steroid Receptor Coactivator-1
TEAE	Treatment-Emergent Adverse Event
URO	Uncovering Rare Obesity
VUS	Variant of Uncertain Significance
VUS-SP	Variant of Uncertain Significance Suspected to be Pathogenic
WES	Whole Exome Sequencing

I. Introduction

A. Background

This is a multiple randomized, double-blind, placebo-controlled, independent sub-studies of setmelanotide in patients with obesity who have pro-opiomelanocortin (POMC) or proprotein convertase subtilisin/kexin type 1 (PCSK1) (sub-study 035a), leptin receptor (sub-study 035b), nuclear receptor coactivator-1 (NCOA1), also referred to as steroid receptor coactivator 1 (SRC1) (sub-study 035c), or SRC homology 2 B adapter protein 1 (SH2B1) (sub-study 035d) gene variants in the MC4R pathway. This analysis plan describes additional detail needed to complete the analysis for all independent sub-studies (sub-study 035a, b, c, and d).

B. Protocol and Amendment History

This Statistical Analysis Plan (SAP) is based on version 7.0 of the Protocol RM-493-035.

[redacted]

C. Changes from Planned Analyses

[redacted]

II. Protocol Objectives and Study Endpoints

	Objectives	Endpoints
Primary	To evaluate the efficacy of setmelanotide on changes in body weight	The difference in mean change in body weight from baseline at 52 weeks in patients treated with setmelanotide compared to placebo, assessed as percent change from baseline BMI
Key Secondary	To evaluate the efficacy of setmelanotide based on the portion of patients with a clinically meaningful decrease in body weight defined as ≥5% decrease from baseline	The proportion of patients who achieve at least 5% reduction in baseline BMI at 52 weeks, in patients treated with setmelanotide compared to placebo
	To evaluate the efficacy of setmelanotide on changes in body weight in adult patients with obesity	The difference in mean change in body weight from baseline at 52 weeks in adult patients (age ≥18 years at baseline) treated with setmelanotide compared to placebo, assessed as percent change in baseline body weight
	To evaluate changes in hunger score in response to setmelanotide from baseline to 52 weeks of treatment	The difference in mean percent change in the weekly average most hunger score at 52 weeks in patients treated with setmelanotide compared to placebo, utilizing the

	Objectives	Endpoints
		Hunger Questions for Patients ≥12 years of Age
	To evaluate the efficacy of setmelanotide on the portion of patients with at least 10% decrease in body weight	The proportion of patients who achieve at least 10% reduction in baseline BMI at 52 weeks, in patients treated with setmelanotide compared to placebo
Other Secondary	To evaluate the efficacy of setmelanotide on changes in BMI in pediatric patients with obesity	The difference in mean change in BMI from baseline at 52 weeks in pediatric patients (age <18 years at baseline) treated with setmelanotide compared to placebo assessed as change in baseline BMI Z-score
		The difference in change from baseline at 52 weeks in % of the 95th BMI percentile, as defined by the Centers for Disease Control and Prevention (CDC), in patients <18 years at baseline treated with setmelanotide compared to placebo
	To evaluate change in waist circumference in response to setmelanotide from baseline to 52 weeks of treatment	The difference from baseline at 52 weeks in mean change in waist circumference in patients treated with setmelanotide compared to placebo
	To evaluate the safety and tolerability of setmelanotide	The overall safety and tolerability of setmelanotide in patients with gene variants in the MC4R pathway

	Objectives	Endpoints
	To evaluate quality of life parameters following treatment with setmelanotide	The difference in mean change from baseline at 52 weeks in physical functioning score and total score for Impact of Weight on Quality of Life in adults (IWQOL-Lite) and in children (IWQOL-Kids-Parent Proxy) in patients treated with setmelanotide compared to placebo
	To evaluate the ability of an initial response to setmelanotide (defining a responder population) to predict long-term benefit	The difference in mean body weight loss, and % body weight loss at 52 weeks in setmelanotide responders (defined as patients with ≥5% body weight loss if ≥18 years of age, or a decrease in BMI by ≥3% if <18 years of age, after 12 weeks of therapy at [redacted]/day or at the maximally tolerated dose) as compared to the placebo group

[redacted]

[redacted]

A. Estimand

The primary estimand to support regulatory decisions are described in the following table:

Attribute	Description
Treatment	Setmelanotide or Placebo
Population	Patients between the ages of 6 and 65 years with obesity who have pro-opiomelanocortin (POMC) or proprotein convertase subtilisin/kexin type 1 (PCSK1)
Endpoint	Percent change from baseline BMI at 52 weeks
Intercurrent Events	For Discontinuation of randomized treatment or use of a rescue medication if any, Treatment policy strategy will be implemented. For Death, the worst observed value amongst all subjects in the primary analysis will be imputed.
Population-level Summary	Difference in mean percent change from baseline BMI at 52 weeks

III. Study Design

A. Design Overview

Approximately [redacted] patients between the ages of 6 and 65 years, inclusive, are planned to be enrolled in individual sub-studies (approximately [redacted] patients per

treatment arm for Sub-studies 035a and 035b, approximately [redacted] patients per treatment arm for Sub-studies 035c and 035d) based on the following gene variants:

- POMC and/or PCSK1 (Sub-study 035a)
- LEPR (Sub-study 035b)
- NCOA1 (SRC1) (Sub-study 035c)
- SH2B1 (Sub-study 035d)

Following randomization, patients will self-inject (or the caregiver will inject the patient) SC trial drug daily for approximately 52 weeks. During the trial, patients will attend either in-person or virtual telehealth visits, as described in the schedule of assessments (SOA). Any visit planned as a virtual visit may be converted to an in-person visit, at the discretion of the Investigator. If more than 2 virtual visits are to be converted into in-person visits, Sponsor approval is required. At every visit, patients will receive individualized counseling in healthy nutrition and physical activity, based on the guidelines of the American College of Cardiology, American Heart Association, and The Obesity Society (ACC, AHA, TOS Guidelines 2013). Counseling will be performed by qualified personnel. Patients will be encouraged to perform 150 minutes of moderate exercise per week.

The end of treatment (EOT) visit will occur as an in-person clinic visit at Week 52, which is the final day of treatment with setmelanotide or placebo. Patients who discontinue treatment prematurely are to attend the Early Termination visit within 14 days (+7 days) after the last dose of trial drug for final trial assessments.

Patients meeting the eligibility criteria may be able to participate in an open-label Long-Term Extension (LTE) trial with setmelanotide treatment. If the LTE is not yet available at the time of the EOT visit, then the eligible patient may receive open-label setmelanotide and attend Bridging visits on an every 12-week basis until either the LTE trial is available or the trial ends. Eligible patients will follow the dose escalation scheme described in Section IV at the beginning of the treatment with open-label setmelanotide. Additional visits may be scheduled at the discretion of the Investigator or the Sponsor.

- Patients who complete treatment and do not enroll into the LTE trial will have the End of Study (EOS) visit conducted via telephone at Week 56. If required by local regulation or if deemed necessary to assess patient safety by physical examination or after a longer follow-up period, the visit may be converted to an in-person visit, and/or can occur up to Week 60.

- Patients who have withdrawn or discontinued trial treatment after at least 6 months of treatment in the current trial, regardless of randomized treatment assignment in this current trial, may be eligible to enroll in the LTE trial (or

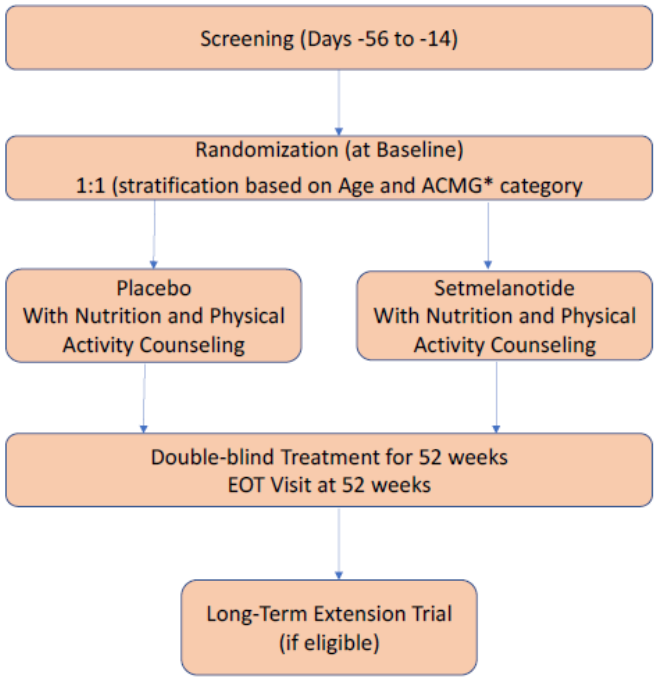
Bridging Visits if LTE is not available) at 1 year (Week 52) from the date of their randomization in the current trial.

- Patients who transfer to the LTE (or Bridging visits before LTE availability) at 1 year from their randomization date are not required to complete a separate EOS visit.

- Eligible patients who have withdrawn or discontinued trial treatment after at least 6 months of treatment in the current trial but who do not wish to participate in the LTE will have an EOS visit at Week 52.

- Patients who withdraw or discontinue treatment prior to completing at least 6 months of treatment in the current trial are not eligible to participate in the LTE trial. Patients who discontinue prior to 6 months will have an in-person EOS visit at Week 52. For these patients, a virtual EOS visit is permissible if they cannot attend in-person.

The trial design schema is identical for all sub-studies and shown as below.



Note: *ACMG stratification applies to Sub-study 035a, Sub-study 035b and Sub-study 035d only.

B. Study Population

Patients between the ages of 6 and 65 years with obesity who have POMC/PCSK1, LEPR, NCOA1 (SRC1), or SH2B1 Gene Variants in the Melanocortin-4 Receptor Pathway will be included in the analysis respectively for each sub-study.

C. Sample Size Determination

The sample size is mainly driven by the primary hypothesis. The data from the previous studies with setmelanotide were referenced to estimate the required sample size.

The primary hypothesis of the trial is to test the difference of the mean percent changes in BMI between the setmelanotide arm and placebo arm. For Sub-studies 035a and 035b, assuming a pooled SD of 10% and a 20% dropout rate, the sub-study with approximately [redacted] patients (approximately [redacted] patients per arm) will provide approximately 90% statistical power to detect at least 8% mean difference of the percent BMI between setmelanotide arm and placebo arm at Week 52, at one-sided 0.025 significance level. For Sub-studies 035c and 035d, assuming a pooled SD of 10% and a 20% dropout rate, the sub-study with approximately [redacted] patients (approximately [redacted] patients per arm) will provide approximately 90% statistical power to rule out at least 7% mean difference of the percent BMI between the setmelanotide arm and placebo arm at Week 52, at a one-sided 0.025 significance level.

D. Treatment Randomization

Patients who are eligible to enter the sub-studies will be randomized in a 1:1 ratio to receive blinded trial medication (either setmelanotide or placebo).

- Patients with *POMC* or *PCSK1* (Sub-study 035a) and *LEPR* (Sub-study 035b) gene variants will be stratified by ACMG classification (P/LP and VUS-SP) and by age group (6 to <12, 12 to <18, and 18 to ≤65 years of age).
- Patients with *NCOA1 (SRC1)* (Sub-study 035c) will be stratified by age group (6 to <12, 12 to <18, and 18 to ≤65 years of age).
- Patients with *SH2B1* (Sub-study 035d) gene variants will be stratified by ACMG classification (P/LP and VUS) and by age group (6 to <12, 12 to <18, and 18 to ≤65 years of age).

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 randomization number for each eligible patient.

Randomization numbers will not be re-used once assigned.

E. Assessment Schedule

Refer to the schedule of assessment (SOA) under section XI.Appendix 1.

IV. Interventions

A. Treatment Administration

Trial drug will be administered as a subcutaneous (SC) injection once daily (QD).

In patients ≥12 years of age, setmelanotide [redacted] QD or placebo equivalent will be administered for approximately the first 2 weeks, then increased to setmelanotide [redacted] QD or placebo equivalent for the remainder of the trial. Dose escalation should occur at the Day 14 trial visit (±3 days) and should occur on the day of that visit.

In patients aged 6 to <12 years old, setmelanotide [redacted] QD or placebo equivalent will be administered for approximately the first week, then increased to setmelanotide [redacted] QD or placebo equivalent for approximately 1 week, then increased to [redacted] QD or placebo equivalent for the remainder of the trial. Dose escalation to [redacted] (or placebo equivalent) should occur at the Day 14 trial visit (±3 days) and should occur on the day of that visit.

Investigators may increase or decrease the dose, if necessary, to treat an AE. However, setmelanotide doses greater than [redacted] QD and less than [redacted] QD (or placebo equivalents) should not be used for patients 6 to <12 years, or doses/equivalents less than [redacted] QD for patients ≥12 years of age should not be used in this trial.

V. General Analytical Considerations

A. Data Sources

All information requested in this protocol will be recorded on the electronic Case Report Forms (eCRFs) provided by the Sponsor or its designee (or via other data collection methods, eg, electronic laboratory data transfer or electronic patient reporting devices).

During the study, some safety questionnaires are collected on paper. These will not be included in the summary.

B. Blinding Considerations

Due to the nature of the study additional blinding considerations need to be made. The weight and BMI data is considered blinding and therefore will be populated with dummy data until database is locked and all study unblinding prerequisites have been met.

C. Study Period

A double-blinded (DB) period consists of visits from screening to end of treatment (V15) or end of study visit (V16) for patients do not enroll into open-label Unless otherwise specified, measurements taken during the open-label (OL) treatment will only be summarized in listing.

D. Definition of Baseline

Baseline will be defined as the last non-missing measurement taken prior to the start of double-blinded treatment administration. In the case where the last non-missing measurement and the reference start date coincide and time of measurement is not available, that measurement will be considered Baseline unless the assessment was scheduled to be post-study drug administration in the SOA. If treatment start date is not available, the last non-missing assessments on or prior to randomization date for randomized but untreated subjects will be considered as baseline assessments.

The percentage change is calculated as $(X_t - X_{BL}) / X_{BL}*100$ where t is any scheduled post baseline visits and X_{BL} is baseline value. [redacted]

E. Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. Reference start date is defined as the day of first dose (Day 1).

Study Day will be computed as follows:

- Study Day = (date of event - date of first dose) + 1 if the date of the event is on or after the date of first dose.
- Study Day = (date of event - date of first dose) if the date of the event is prior to the date of first dose.

F. Analysis Window

All measurements recorded at unscheduled, early termination, or end of study visits will be mapped according to the windowed visits by actual study day . The mapped

visits will be included for the analysis only if measurement from scheduled visits is missing. If more than one mapped visit occurs within a single visit window, then the analysis will take the one closest and prior to the target day if available, else take the latest one. The following analysis visit windows will apply:

Trial Visit	Study Week	Study Day	Visit Days windows
Double Blind Phase			
V2	Week 2	14	Post-dose- 21
V3	Week 4	28	22 - 42
V4	Week 8	56	43 - 70
V5	Week 12	84	71 - 98
V6	Week 16	112	99 - 126
V7	Week 20	140	127 - 154
V8	Week 24	168	155 - 182
V9	Week 28	196	183 - 210
V10	Week 32	224	211 - 238
V11	Week 36	252	239 - 266
V12	Week 40	280	267 - 294
V13	Week 44	308	295 - 322
V14	Week 48	336	323 - 350
V15 (Week 52)	Week 52	364	351 – 378 and before first OL visit.

If there are multiple scheduled visits, the latest available record will be used for analysis purpose.

G. Missing Data

Unless stated otherwise, missing data will not be replaced with imputed values. When relevant, sections below will address how missing data will be handled for the particular analyses.

Missing or Partial Adverse Event and Medication Start or Stop Date:

For partial start dates:

- If the year is unknown, no imputation will occur.
- If the year is known and the month and day is unknown, then:
  - If the year matches the year of the first dose date, then impute the month and the day the same as first dose date.
  - If the year is not the same year of the first dose, then month and day will be imputed as 01 January.

- If the month and year is known and the day in unknown, then:
  - If the month and year match the month and year of the first dose date, then impute the day the same as first dose date.
  - If year and month is not the same as the first dose date, then the day will be imputed as “01”.

For partial end-dates:

- If the year is missing, no imputation will be performed, and the AE/CM will be assumed as ongoing.
- If the year is present and both month and day are missing and the year is not the same as the last study date, then the month and day will be imputed as the last day of the year, 31 December.
- If the year is present and both month and day are missing and the year is the same as the last study date, then the month and day will be imputed as the last study date.
- If the year and month are present and only the day is missing, and the year and month is not the same as the last study day then the day will be imputed as the last day of the month.
- If the year and month are present and only the day is missing, and the year and month is the same as the last study day then the day will be imputed as the last day of the study.

H. Multiple Study Centers

The study is a multicenter trial. Data from all study sites will be pooled for the purpose of analyses. No adjustment for study center is planned.

I. Covariates Adjustment in Primary Analysis

Covariate adjustment will be addressed in relevant sections below, as appropriate.

J. Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will meet periodically (i.e., every 3 months) to review the cumulative safety data from the study and will make a recommendation to continue or modify the study, if needed. The following data will be presented to the DSMB members:

- Demographics
- Disposition
- Adverse Events
- Vital Signs (excluding weight and BMI)

- 12-Lead ECG
- Injection Site Evaluation
- Skin Examination
- Hyperpigmentation
- Fitzpatrick Classification Scale
- Inclusion/Exclusion Criteria
- Sexual Function (Male)
- Sexual Function (Female)
- Safety Laboratory Data
- Columbia-Suicide Severity Rating Scale
- Patient Health Questionnaire-9

K. Multiple Adjustment

No multiplicity adjustments for testing the primary efficacy endpoint are required because each sub-study has only 1 primary efficacy endpoint, and each sub-study will be analyzed separately. This approach controls the overall alpha at 0.025, one-sided for each sub-study.

There are multiple key secondary efficacy endpoints planned in the trial. The key secondary endpoints are presented according to the sponsor-specified hierarchical order in the table of section II Protocol Objectives and Endpoints. If the primary efficacy endpoint is statistically significant, a step-down procedure of a hierarchical order of testing for the key secondary efficacy endpoints will be applied to control Type-1 error, if needed for any purpose.

L. Analysis Sets

- **Screened Population**
  All patients who are screened (including screen failed) for this study.

- **Safety Analysis Set**
  All patients who received at least 1 dose of trial drug (placebo or setmelanotide). They will be summarized by treatment actually received.

- **Intent-to-treat (ITT) Analysis Set**
  All randomized patients regardless of treatment adherence and availability of baseline data. They will be summarized by randomized treatment group.

- **Modified Intent-to-treat (mITT) Analysis Set**
  All randomized patients who received at least 1 dose of trial drug (placebo or setmelanotide). They will be summarized by randomized treatment group.

- **Per-protocol (PP) Analysis Set**
  All patients in ITT set without any major protocol violations that will result in exclusion of the patients from the primary efficacy analyses. This analysis will only include patients whose gene variants and respective sub-study cohort assignment are re-confirmed based on the PreventionGenetics (PG) Uncovering Rare Obesity (URO) 3.0 genetic panel.

M. Subgroup of Analysis Population

Data from subgroups of subjects in the defined analysis populations will be analyzed for the primary endpoint as specified below.

- Pediatric sub-population (<18 years of age) and in the adult sub-population (≥18 years of age) will be conducted.

N. Special Distribution Schedule

[redacted]

For continuous outcome measure analyses, a weekly average score will be calculated as an arithmetic mean. The baseline score will still be arithmetic mean of the available scores within 7 days before or on the first date of dosing. For visits in (2), (3) and (4), arithmetic mean of the available scores in 7 days before or on the last visit date within the analysis visit window will be calculated.

If there are multiple records with exact same value and date time within a parameter, they will be deduplicated. For the remaining multiple records that have the same date within a parameter, the average will be calculated and this average will be used in the analysis.

O. Data Display Characteristics

Data displays produced for this study will include three types—summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables will be produced as specified in following sections. Additional data listings will be produced for outcome measures that involve

extensive procedures to derive the analyzed outcomes. Figures will be produced when specified in sections to follow.

Data listings will simply list the data recorded on the CRF or derived for each subject. They will be ordered by treatment, site, subject number, and time of assessment. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within subject. Data listings will not display subject initials.

Summary tables will display summary statistics calculated for each of the treatment groups, unless described otherwise in following sections. Tables may have either of two general layouts. When the greatest interest is in direct comparison of one treatment group with the other at particular times, different columns of a summary table will display the statistics for the different treatment groups. The placebo group statistics will be displayed to the left of the treatment group statistics. When the evolution of statistics over time is of greater concern than comparison at particular moments, a group of rows may be designated for the placebo group; the table columns would be designated for different summary statistics of interest. A subsequent group of rows would then be used for the treatment group. In this layout, a group of rows that represent a treatment group would generally be ordered chronologically.

The summary statistics displayed will be a function of the type of data associated with the summarized assessment. Unless stated otherwise in relevant sections to follow, continuous data will be summarized with the number of nonmissing values, mean, standard deviation, minimum, median, and maximum. Categorical data will be summarized with the number of nonmissing values and the numbers of values equal to each of the possible values. Percentages of subjects with each of the possible values will be calculated from the number of subjects in the corresponding analysis population, unless stated otherwise. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables.

P. Blinded Review of Data

After all study data have been collected but prior to examining any study outcome data by treatment group, the data will be reviewed by the study statistician to determine whether any clarifications or changes to the analysis plan are needed. Any revisions made to the analysis plan as a result of the blinded review of the data will be documented.

Q. Software Version

All analyses will be conducted using SAS Enterprise Guide 7.1 (64-bit) or SAS version 9.4 (64-bit).

VI. Patient Accountability

All patients in ITT analysis set will be used for below analyses unless otherwise specified.

A. Patient Demographic and Baseline Characteristics

Patient demographic and baseline characteristics will include the patient's age [6 to <12, 12 to <18, 18 to ≤65 years of age], sex [Child-bearing potential if female], ethnicity, race, weight at baseline, height at baseline, BMI at baseline, waist circumference at baseline, American College of Medical Genetics (ACMG) gene variant classification, skin type from Fitzpatrick Classification Scale assessment.

B. Disposition

All screened patients will be included in this analysis. Patient disposition will include the number of patients screened, patients screen failed, number and percentage of patients in each analysis set, number and percentage of completion status at end of treatment (with discontinuation reason), and at end of study (with discontinuation reason).

C. Protocol Deviations and Violation

Protocol deviations will be classified as major and minor. Some of major deivations will then be determined as protocol violcation. The number and percentage of patients with a major violation will be tabulated by categories of the deviation.

All protocol deviations will be listed.

D. Historic Measurements and Interventions

D.1. Medical History Weight Loss Interventions

A listing will be included to provide information about weight loss intervention program and its start date, end date and outcome of the interventions collected on the "Medical History Weight Loss Interventions" form.

D.2. Historic Height and Weight

The 10 most recent height and weight measurements for each patient are recorded and will be listed.

D.3. Weight History

All weight history data collected on “Weight History” form will be listed.

D.4. Prior Weight Loss Medication History

All prior weight loss medication history data will be listed.

D.5. Prior Surgery Weight Loss Intervention

All prior surgeries intended to treat weight or hunger are recorded and will be listed.

D.6. Prior Weight Loss Programs

All prior treatments (dietary or exercise) intended to treat weight or hunger are recorded on the “Prior Weight Loss Medication History” eCRF page and will be listed.

E. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 or higher. Medical history will be tabulated by system organ class and preferred term. A listing of medical history will be provided.

VII. Efficacy Analyses

A. Efficacy Assessments

A.1 Weight

Weight should be measured after patients have attempted to empty their bladders and after fasting for at least 8 hours. 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 recorded to the nearest 10^{th} of a kg if reported with a digital scale, or half kg with a mechanical scale.

A.2 Waist Circumference

All waist measurements will be done in triplicate at each time point, and recorded to the nearest half centimeter. Waist circumference should be measured when patients are fasted for at least 8 hours and at approximately the same time at each visit.

Patients should be in standing position, in light clothing and have attempted to empty their bladder.

A.3 Height

For patients ≥21 years of age, height should be measured at screening only. For patients aged <21 years, height is to be measured at the time points designated in the SOA.

Height (cm) will be measured, without shoes, socks, or hats, using a wall-mounted stadiometer. All measurements will be done in triplicate at each time point and recorded to the nearest half centimeter.

A.4 BMI and BMI Z-score calculation

The Body Mass Index will be calculated as Weight (kg) / [Height (m)]^2. In the case where there are measurements in triplicate, the average of the triplicates will be calculated before the BMI calculation.

BMI z-score for patients < 18 years at baseline will be calculated according to the Centers for Disease Control and Prevention (CDC) Growth Charts. The BMI z-score derivaiton will incorprate the SAS program and dataset from CDC Growth Charts (Ages 0-20 Years).

The change from baseline at 52 weeks in percentage of the 95th BMI percentile for each patient will be calculated as:

- Change in Percentage = (BMI_{W52} / P_{95} – BMI_{BL} / P_{95}) * 100

where P_{95} is calculated from the above mentioned SAS program.

B. Primary Efficacy Analysis

The primary efficacy variable is the percent change of BMI from baseline at Week 52 based on the ITT analysis set and mITT analysis set using multiple imputation.

The null and alternative hypothesis for this efficacy variable is:

- The null hypothesis is that the mean percent change of BMI from baseline for patients who have 52 weeks of setmelanotide treatment is larger or equal to the mean percent change of BMI from baseline for patients who have 52 weeks of placebo treatment.
- The alternative hypothesis is that the mean percent change of BMI from baseline for patients who have 52 weeks of setmelanotide treatment is less

than the mean percent change of BMI from baseline for patients who have 52 weeks of placebo treatment.

An ANCOVA (analysis of covariance) model will be used to determine whether there exist any significant mean differences in percent BMI change between the setmelanotide arm and placebo arm at Week 52, adjusted by stratification factors and baseline BMI as a covariate. The p-value, LS means, and 2-sided 95% CI for the difference of least square-means of the percent BMI change from baseline at Week 52 will be provided from the ANCOVA model.

The stratification factors will be:

- Sub-study a and b: Age group [6 to <12, 12 to <18, 18 to ≤65 years of age] and ACMG [P/LP, VUS-SP]
- Sub-study c: Age group [6 to <12, 12 to <18, 18 to ≤65 years of age]
- Sub-study d: Age group [6 to <12, 12 to <18, 18 to ≤65 years of age] and ACMG [P/LP, VUS]

In the event of missing BMI data at Week 52, the missing measurements of non-retrieved dropouts will be imputed based on known measurements from retrieved dropouts in the same treatment group. This imputation is only used in primary endpoint.

Retrieved dropout is defined as a treatment discontinued patient before Week 52 who has the measurement value from EOS visit at Week 52 or that is mapped to the Week 52 per visit window. A non-retrieved dropout is defined as a treatment discontinued patient without such measurement

In case there are not enough retrieved dropouts to provide a reliable multiple imputation model, a multiple imputation method based on observed data from the placebo group will be applied. In this approach, intermittent data collected while on active treatment will not be used for imputation.

Multiple Imputation

Primary analysis will be performed with missing BMI data imputed with multiple imputation (MI) method under Missing Not At Random (MNAR) assumption. MI method is described as following:

Step A. A regression model will be used to impute values of non-retrieved dropout from retrieved dropout values at EOS visit at Week 52 within each treatment group. The model will use stratification factors, and baseline BMI value of the outcome variable. 50 imputations will be the initial setting.

Step B. A regression model will be used to impute missing values at Week 52 from values of placebo treatment group only for either treatment group. The model will use stratification factors, and baseline BMI value of the outcome variable. 50 imputations will be the initial setting.

The choice between Step A and B depends on whether A will converge. Only if A does not converge then B will be used. Convergence of the process will be assessed after unblinding. Seed is set to be 220704 for reproduction of the results if necessary. The results of the 50 analyses will then be combined into a single analysis using PROC MIANALYSE.

As supportive analyses for the primary efficacy endpoint, by-visit analyses will be provided with descriptive statistics of observed values (including retrieved dropout values), change from baseline (CHFB), and percent change from baseline (%CHFB) for BMI. For mean CHFB and mean %CHFB of BMI at each visit, the 2-sided 95% CI from Student's t-distribution will be provided for each treatment arm.

B.1Sensitivity Analyses

The following sensitivity analyses based on the ITT analysis set will be performed to examine the robustness of the primary efficacy analysis.

- Mixed model for repeated measures (MMRM) approach which will take account of the missing data under the assumption of missing at random (MAR)

  The percent change from baseline to each postbaseline visits (V2 to V15) in BMI will be analyzed using observed data (with retrieved dropouts measurements included). The MMRM will use restricted maximum likelihood based mixed model for repeated measures with fixed effect for treatment, visits, baseline BMI value, stratification factors and treatment by visit interaction. Patients will be the random effect. Unstructured covariance structure will be used. If this covariance structure fails to converge, a simplier covariance structure will be used. A contrast will be written within the MMRM model to get each visit-specific treatment difference (least squares treatment means, treatment difference estimates and 95% CIs). Convergence of the model will be assessed after unblinding, and covariates may be removed.

- Separately, subgroup analyses of the primary endpoint in the pediatric sub-population (<18 years of age) and in the adult sub-population (≥18 years of age) will be conducted.

An ANCOVA model by sub-population with BMI percent change from baseline as dependent variable and ACMG, and treatment as independent variables. The LS means, difference of LS means, CI for the difference of LS means and the p-value for the treatment term will be presented. The MI data from primary analysis will be used if there is any missing data and PROC MIANALYZE will be used to combine the results. The data used in this subgroup analysis will be the same data used in the primary analysis.

- Completer Analysis: with patients who completed the primary assessment at Week 52.

  Follow the same analysis method as primary but only include observed data (no imputation or retrieved dropout records) of patients that completed the treatment.

- PP Analysis: with per-protocol analysis set.

  Follow the same analysis method as primary analysis but with PP analysis set of patients.

C. Secondary Efficacy Analysis

For all the key secondary efficacy analyses, the two methods below will be used to analyze the corresponding types of endpoints (dichotomous or continuous). Data with retrieved dropout measurements will be used for all secondary efficacy analyses.

Analysis of Dichotomous Endpoints with Proportion of Patients

For the key secondary efficacy endpoints at Week 52, the Cochran-Mantel-Haenszel test (raw mean score difference) will be conducted at 1-sided 0.025 level on comparison of setmelanotide arm versus placebo arm controlling for stratification variables as defined in the primary analysis. The 2-sided 95% CI for the proportion of patients at Week 52 will be provided based on Wilson score for proportions for each group, and the strata-adjusted proportion difference between the groups will be also provided based on Mantel-Haenszel method. Patients with missing value are considered as non-responder.

As supportive analyses, by-visit analysis will be performed. The proportion of patients at each visit including the End of Treatment visit will be provided with 2-sided 95% CI based on Wilson score for proportions for each group.

Analysis of Continuous Endpoints

For the key secondary efficacy endpoints at 52 weeks, the ANCOVA controlling for stratification variables as defined for the primary analysis will be performed.

As supportive analyses, by-visit analyses will be provided with descriptive statistics of observed values, CHFB, and %CHFB. For mean CHFB and mean %CHFB at each visit, the 2-sided 95% CI from Student's t-distribution will be provided for each treatment arm.

C.1 Key Secondary

All patients in the mITT analysis set will be used for the key secondary endpoints.

Below is a list of the key secondary endpoints:

1. The proportion of patients who achieve at least 5% reduction in baseline BMI at 52 weeks, in patients treated with setmelanotide compared to placebo. Analyzed as a dichotomized endpoint.

2. The difference in mean change in body weight from baseline at 52 weeks in adult patients (age ≥18 years at baseline) treated with setmelanotide compared to placebo, assessed as percent change in baseline body weight. The body weight at baseline will be included as one of the covariates. Analyzed as a continuous endpoint.

3. The difference in mean percent change from baseline in the weekly average most hunger score ("In the last 24 hours, how hungry did you feel when you were the most hungry?") at 52 weeks in patients treated with setmelanotide compared to placebo, utilizing the Hunger Questions for Patients ≥12 years of Age. The weekly average most hunger score at baseline will be included as one of the covariates. Analyzed as a continuous endpoint.

4. The proportion of patients who achieve at least 10% reduction in baseline BMI at 52 weeks, in patients treated with setmelanotide compared to placebo. Analyzed as a dichotomized endpoint.

Supportive analyses will be tabulated for each of the 4 endpoints separately.

C.2 Other Secondary

All patients in the mITT analysis set will be used for the other secondary endpoints. Below is a list of other secondary endpoints:

- The difference in mean change in BMI from baseline at 52 weeks in pediatric patients (age <18 years at baseline) treated with setmelanotide compared to placebo assessed as change in baseline BMI Z-score (refer to section VII.A.4).

- The difference in change from baseline at 52 weeks in percentage of the 95th BMI percentile (refer to section VII.A.4), as defined by the Centers for Disease Control and Prevention (CDC), in patients <18 years at baseline treated with setmelanotide compared to placebo.

- The difference from baseline at 52 weeks in mean change in waist circumference in patients treated with setmelanotide compared to placebo.

  The average of the triplicate waist circumference measurements will be calculated at each time point before being used for this analysis purpose.

- The difference between patients treated with setmelanotide and placebo in mean change from baseline at 52 weeks in
  - physical functioning score or physical comfort score
  - total score for Impact of Weight on Quality of Life in adults (IWQOL-Lite)
  - total score for Impact of Weight on Quality of Life in children (IWQOL-Kids-Parent Proxy)

  Refer to the analysis in section VIII.F.

- Body weight loss at Week 52:
  - The difference in mean body weight loss between setmelanotide responders and placebo group.
  - % body weight loss in setmelanotide responders as compared to the placebo group.

  Initial setmelanotide responders are defined as Setmelanotide treated patients with ≥5% body weight loss if ≥18 years of age, or a decrease in BMI by ≥3% if <18 years of age, at the time of consecutive 12 weeks with the increased [redacted] day or with final increased dose level. Table will be presented by Initial Non-responder of Setmelanotide, Initial Responder of Setmelanotide and Placebo.

A table will include the by-visit supportive analysis (section VII.C) without statistical testing for each of the other secondary endpoints above.

D. [redacted]

[redacted]

[redacted]

E. Supplemental Analysis

For Sub-study 035d, a subgroup analysis of PL/P vs VUS using Prevention Genetics (PG)'s re-confirmatory genetic diagnosis will be conducted for the primary efficacy endpoint by visit.

VIII. Questionnaires

A. Hunger Questions

All patients in mITT analysis set will be used for below analyses.

Hunger questions have two different versions and will be analyzed separately. These questionnaires should be completed in the morning prior to the morning meal (after an 8-hour fast) and prior to dosing. This questionnaire will be distributed as per section V.N.

Hunger Questions for Patients ≥12 Years of Age

Patients ≥12 years of age who are able to validly and reliably self-report will be administered "Hunger Questions for Patients ≥12 Years of Age." This questionnaire comprises three items (listed below) that are designed to be evaluated separately (rather than as a composite score). Each item asks patients to rate their hunger on an 11-point numeric rating scale ranging from 0 to 10 (0 = not hungry at all, and 10 = hungriest possible).

- In the last 24 hours, on average, how hungry did you feel?
- In the last 24 hours, how hungry did you feel when you were the most hungry?
- This morning when you woke up for the day, how hungry did you feel?

Refer to section V.N for weekly average score calculation. Descriptive summaries of weekly average score, changes from baseline and percent change from baseline for each of above three items will be separately presented by treatment group and visit.

The score from "In the last 24 hours, how hungry did you feel when you were the most hungry?" will follow section VII.C.1 and will also present the supportive analysis (section VII.C.). In addition to evaluation of the continuous endpoint based on change in peak (most) hunger, a responder analysis comparing treatment groups will also be conducted and summary statistics will be presented by responder/non-responder within each treatment group. A repsonder is defined as below:

- Patients who achieve at least 5% reduction in baseline BMI at 52 weeks (retrieved dropout values included)

Hunger Questions for Patients 6 to <12 Years of Age

Patients 6 to <12 years of age will be administered "Hunger Questions for Patients 6 to <12 Years of Age". This questionnaire (listed below) assesses hunger using a pictorial (smiley face) version of the Likert rating scale with scores from 0 to 4 (0 = not hungry at all, 1 = a little hungry, 2 = somewhat hungry, 3 = very hungry, and 4 = hungriest possible).

- How hungry do you feel right now?

Refer to section V.N for the weekly average score calculation. Descriptive summaries of weekly average score, changes from baseline and percent change from baseline will be presented by treatment group and visit.

All hunger questions data will be listed by version and treatment group.

B. Global Hunger

All patients in mITT analysis set will be used for below analyses.

Two global hunger questions will be administered: the Patient Global Impression of Severity (PGIS) and the Patient Global Impression of Change (PGIC). The PGIS is administered at baseline and both questions (listed below) are administered thereafter, according to the schedule in the SOA. Both questions have a recall period of 7 days, and there are two versions of each question: one for patients ≥12 years of age who can self-report and one for caregivers of patients <12 years of age and/or patients who have cognitive impairment and cannot self-report. These two versions will be analyzed separately.

Patients ≥12 years of age who can self-report

- PGIS: Overall, how would you rate the hunger you experience now?
  - Response items: No hunger=1, Mild hunger=2, Moderate hunger=3, Severe hunger=4
- PGIC: Overall, how does the hunger you experience now compare to your hunger before you started this study?
  - Response items: Much less hungry=1, Somewhat less hungry=2, No change in hunger=3, Somewhat hungrier=4, Much hungrier=5

Caregivers of patients <12 years of age and/or patients who have cognitive impairment and cannot self-report

- PGIS: How hungry is your child acting now?
  - Response items: Not hungry at all=1, A little hungry=2, Moderately hungry=3, Extremely hungry=4
- PGIC: How hungry does your child act now compared to before starting this study?
  - Response items: Much less hungry=1, Somewhat less hungry=2, No change in hunger-related behavior=3, Somewhat more hungry=4, Much more hungry=5

For PGIS from both versions, frequency for change from baseline for categorical items will be tabulated by version, treatment group and visit. Summary statistics will also be proivded.

For PGIC from both versions, frequency and percentage of the five response items will be tabulated by version, treatment group and visit.

All global hunger data will be listed by version and treatment group.

C. [redacted]

[redacted]

[redacted]

D. [redacted]

[redacted]

[redacted]

[redacted]

E. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

F. Impact of Weight on Quality of Life (IWQOL)

All patients in mITT analysis set will be used for below analyses.

IWQOL has two different versions and will be analyzed separately. The IWQOL questionaries will be administered according to the SOA.

IWQOL-Lite

The IWQOL-Lite will be administered to patients ≥18 years of age. The questionnaire is responsive to weight loss and gain, sensitive to treatment-seeking status as well as to the degree of obesity.

The IWQOL-Lite is a validated 31-item self-reported measure of obesity-specific quality of life questionnaire. Each question has 5 response items: Always True=5, Usually True=4, Sometimes True=3, Rarely True=2, Never True=1. The IWQOL-Lite provides a total score inclusive of 5 domains:

Domain	Total Number of Items	Minimum Required Number of Responses	Max Score	Min Score
Physical Function	11	6	55	11
Self-esteem	7	4	35	7
Sexual Life	4	2	20	4
Distress	5	3	25	5
Work	4	2	20	4
Total	31	24	155	31

The raw score will first be calculated by using formula below for each domain or all domains combined before being analyzed. The raw score will be rounded to the nearest whole integer. The raw score will only be calculated if the required number of minimum responses is met.

> Raw score = round[total number of items x (sum of valid scales from non-missing items/number of non-missing items)]

Raw scores for each domain are computed for each of the five scales only if a minimum of 50% of the items for that scale are answered, and for the total score only if all raw scores are available and 75% of the answers for all items are completed. (The required number of minimum responses is: Physical Function=6 of 11; Self-Esteem =4 of 7; Sexual Life=2 of 4; Public Distress=3 of 5; Work=2 of 4; Total=24 of 31.)

The transformed score is on a scale of 0 to 100, where 100 represents the best quality of life.

> Transformed score = (maximum score – raw score) / (maximum score – minimum score) *100

For the transformed composite total score of the five domains, summary statistics for total score of items and changes from baseline will be provided by visits.

For the transformed score of within each five domains, summary statistics for the score and changes from baseline will be provided by visits.

IWQOL-Kids-Parent Proxy

The IWQOL-Kids-Parent Proxy version will be used for patients who are between the ages of 11 to 17 years. Parents or parent proxies of patients 11 to 17 years will complete the IWQOL-Kids-Parent Proxy version.

The IWQOL-Kids-Parent Proxy version has been evaluated psychometrically. It has 27 items and includes 4 domains ("Physical Comfort", "Body Esteem", "Social Life", and "Family Relations") to measure the impact of weight on kids' quality of life. The instrument uses a 5-point Likert scale (Always True=1, Usually True=2, Sometimes True=3, Rarely True=4, Never True=5).

Domain	Total Number of Items	Minimum Required Number of Responses	Max Score	Min Score
Physical Comfort	6	3	30	6
Body Esteem	9	5	45	9
Social Life	6	3	30	6
Family Relations	6	3	30	6
Total	27	21	135	27

The raw score will first be calculated by using formula below for each domain or all domains combined before being analyzed. The raw score will be rounded to the nearest whole integer. The raw score will only be calculated if the required number of minimum responses is met.

> Raw score = round[total number of items x (sum of valid scales from non-missing items/number of non-missing items)]

Raw scores for each domain are computed for each of the five scales only if a minimum of 50% of the items for that scale are answered, and for the total score only if all raw scores are available and 75% of the answers for all items are completed. (The required number of minimum responses is: Physical Comfort =3 of 6; Body Esteem =5 of 9; Social Life =3 of 6; Family Relations = 3 of 6; Total =21 of 27)

The transformed score is on a scale of 0 to 100, where 100 represents the best quality of life.

> Transformed score = (raw score – total number of items) / (maximum score – minimum score) *100

For the transformed composite total score of the four domains, summary statistics for total score of items and changes from baseline will be provided by visits.

For the transformed score of within each four domains, summary statistics for the score and changes from baseline will be provided by visits.

All IWQOL data will be listed by version and treatment group.

G. Nutrition and Exercise Counseling

All nutrition and exercise counseling will be listed.

IX. Safety Analyses

All patients in Safety analysis set will be used for below analyses unless otherwise specified.

A. Exposure

A.1 Study Treatment Exposure

Duration of study treatment (days) will be calculated based on below formula:

> Duration = Date of last DB adminitration – Date of first DB administration + 1

Summary statistics will be provided by treatment group.

A.2 Study Treatment Compliance

Compliance to dosing will be monitored throughout the trial by having the patient/caregiver complete a daily dosing log, and by the on site visit Study Treatment Administration forms.

Compliance will be calculated as:

> Compliance (%) = # of actual administration during DB period / # of expected administration*100

[redacted]

Where:

# of actual administration = Duration minus total number of missed doses during DB period
# of expected administration = Duration

A.3 Dose Level Changes

The frequency and percentage of reasons for dose level change will be provided (excluding reason 'Per Protocol Planned') by treatment group. A patient could have more than one dose level changes.

All study treatment administration and dose level changes data will be listed.

B. Adverse Events

All adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version MedDRA27.0 or higher. Intensity of all AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE grade refers to the severity of the AE and ranges from Grade 1 (mild AE), Grade 2 (moderate AE), Grade 3 (severe AE), and Grade 4 (life-threatening or disabling AE) to Grade 5 (death related to AE).

A treatment-emergent adverse event (TEAE) is defined as any events happen on or after the date of the first study treatment administration. A detailed definition will be as following:

An adverse event will be considered as treatment-emergent adverse event in double-blinded period as following:

- If the start date is completely missing.
- or the event start date is on or after the double-blinded treatment administration but (1) before the EOT date +30 days or Date of first open-label setmelanotide, whichever date comes first, for patients who started to take the treatment with open-label setmelanotide for bridging visits, and (2) before the EOT date + 30 days for all other patients.

The number and percent of patients experiencing a treatment-emergent adverse event will be summarized by period. Patient who reports multiple treatment-emergent AEs within the same System Organ Class (SOC) and/or Preferred Term (PT) is counted only once for that System Organ Class and/or Preferred Term. The most severe PT will be counted if patient has different severities within same PT. The maximum CTCAE grade PT will be counted if patient has different grades within

the same PT. AE missing relationship will be imputed as 'Related'. AE missing CTCAE grade will be imputed as 'Grade 3 - Severe'.

An overall summary will be prepared for the following type of AEs by treatment group and overall:

- Any AE
- Any TEAE
- Any TEAE related to study drug
- Any serious TEAE
- Any serious TEAE related to study drug
- Any TEAE with CTCAE grade 3 or higher
- Any TEAE leading to drug permanently discontinued
- Any TEAE leading to drug permanently discontinued and related to study drug

Separate summaries will be prepared for the following types of treatment-emergent AEs by treatment group and overall:

- By SOC and PT
- By SOC and PT for study drug related events
- By SOC and PT for serious events
  - By SOC and PT for treatment related serious events
- By SOC, PT and maximum CTCAE grade
  - By SOC, PT and maximum CTCAE grade for study drug related events
- By SOC and PT for event with CTCAE grade 3 or higher
- By SOC and PT for events leading to drug permanently discontinued
  - By SOC and PT for study drug related events leading to drug permanently discontinued

All AE data will be listed. Separate AE listings will be created for SAE, AE with CTCAE Grade 3 or higher, AE leading to Drug Permanently Discontinued.

C. Injection Site Evaluation

Frequency and percentage of injection site reaction (including Erythema, Edema, Induration, Itching, Pain or Tenderness, Other) will be tabulated by no reaction or severity (mild, moderate, and serve) by visit. Percentage is based on the number of patients with assessment performed within each visit. In addition, a by-visit table of number of patiets with at least one injection site reaction will be summerzied.

Injection site reaction data will be presented in listings.

D. Clinical Laboratory Results

Laboratory test results include hematology, coagulation, clinical chemistry, and urinalysis.

[redacted]

Antidrug antibody will be summarized by visit and be listed separately from laboratory data.

For hematology, coagulation and clinical chemistry, summaries of actual values and changes from baseline will be presented by treatment group for each visit according to SOA. Similarly, summary statistics for the eGFR will be provided. For the purpose of the summary statistics, values below the lower limit of quantification will be imputed as half of the lower limit value.

Low/Normal/High shift from baseline tables will also be provided for hematology, coagulation, and clinical chemistry. Normal/Abnormal shift from baseline tables will be provided for urinalysis.

Laboratory test results will be presented in data listings.

Pregnancy test will be presented in data listings.

E. Vital Signs

Vital signs include systolic and diastolic blood pressure (mmHg), heart rate (beats/min), respiration rate (breaths/min), and body temperature (°C). Vital signs will be obtained in the sitting position following at least 5 minutes of rest at each time point designated in the SOA.

All blood pressure and heart rate measurements will be taken in triplicate, approximately 2 minutes apart. The average of triplicate measurements will first be calculated within each patient then used in the summary statistics.

Summary statistics for actual values and changes from baseline for heart rate, respiratory rate and body temperature will be presented by treatment group for each visit.

The blood pressure measurements will follow the analysis in section VII.D and will be analyzed separately from other vital signs.

Vital sign data will also be presented in listings.

F. Physical Examination

Tanner staging data will be presented in listings.

G. Prior and Concomitant Medications

Prior and concomitant medications (CMs) will be coded using WHO-DD version 202403 or higher.

G.1 Prior Medications

Prior medications are defined as medications with an end date prior to the first dose of study drug. Prior medications will be tabulated by Anatomic Therapeutic Chemical (ATC) Level 2 classification and Preferred Term (PT) by treatment group and overall. A patient having more than one medication within the same ATC Level 2 or preferred term will be counted only once for that ATC Level 2 or preferred term.

G.2 Concomitant Medications

Concomitant medications are defined as medications which are taken during the course of study treatment. A detailed definition will be as following:

A medication will be considered a concomitant medication in double-blinded period as following:

- If the end date is completely missing
- or the medication start date is on or before the EOT date and end date is on or after double-blinded treatment administration or it is ongoing.

Concomitant medications will be tabulated by ATC Level 2 classification and PT by treatment group and overall. A patient having more than one medication within the same ATC Level 2 or preferred term will be counted only once for that ATC Level 2 or preferred term.

A listing of prior and concomitant medications will be provided.

H. Concomitant Procedures

Concomitant procedures data will be listed.

I. Skin Examination

A comprehensive skin examination will be performed by the Investigator at the time points designated in the SOA.

The skin examination should include a full body (head-to-toe skin examination). Frequency count of most severe outcome across all skin regions within patients will - be provided by visit. The severity of the outcome is rated as Abnormal, CS > Anormal, Not CS > Normal > Not Done.

Also, the frequency count by skin region with abnormal clinical significant result will be provided by visits.

All skin examination data will be presented in listing.

J. Hyperpigmentation

Skin hyperpigmentation is one of the most common adverse reactions in setmelanotide studies. Hyperpigmentation form will be administrated at postbaseline visits.

All hyperpigmentation data will be presented in listing.

K. Sexual Function

Disturbance in sexual arousal in males and sexual adverse reactions in females will be monitored closely. Sexual function forms have different versions between male and female and will be analyzed separately. Sexual function form will be administrated at postbaseline visits.

All sexual function data will be presented in listing by version.

L. Electrocardiogram

A single 12-lead electrocardiogram (ECG) is performed at the visits designated in the SOA.

ECG measurements include PR interval (msec), RR interval (msec), QRS interval (msec), QT uncorrected (msec), QT corrected with Bazzett's formula (msec), QT corrected with Fridericia formula (msec). Summaries of actual values and changes from baseline of these measurements will be presented by treatment group and visit.

A frequency and percentage table of normal, abnormal not clinically significant and abnormal clinically significant for overall ECG evaluation will be tabulated by treatment group and visit.

ECG data will be presented in listing.

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

The C-SSRS that will be administered to patients ≥6 years of age according to the SOA.

There are two versions of the C-SSRS forms:

1. The Baseline/Screening version of the scale is the initial form of the instrument to assess suicidality in a patient's lifetime. This version can assess a patient's lifetime suicidality for data collection purposes as well as eligibility based on inclusion/exclusion criteria.

2. The 'Since Last Visit' version of the scale assesses suicidality since the patient's last visit. This version is meant to assess patients who have completed at least 1 initial C-SSRS assessment and should be used in subsequent visits. The 'Since Last Visit' version of the C-SSRS is inquiries about any suicidal thoughts or behaviors the patient/participant may have had since the last time the C-SSRS was administered.

A frequency and percentage table and a shift from baseline by visit will be provided to display the number of patients who have answered at least one 'Yes' to: Suicidal Ideation (1-5), Suicidal behavior (6-10), either have suicidal ideation or suicidal behavior (1-10), and the question "Non-Suicidal Self-Injurious Behavior".

In details, the Suicidal Ideation and Suicidal behavior will include questions as below:

Suicidal Ideation (1-5)

1. Wish to be dead
2. Non-Specific thoughts
3. Ideation without intent to act
4. Ideation with some intent to act
5. Ideation with specific plan

Suicidal behavior (6-10)

6. Preparatory acts or behavior
7. Aborted attempt
8. Interrupted attempt
9. Actual attempt
10. Completed suicide

All C-SSRS data will be listed.

N. Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a 9-item depression scale of the Patient Health Questionnaire and will be used for patients ≥12 years of age. After the patient has completed the PHQ-9 questionnaire, it is scored by the trial staff. Any patient with a PHQ-9 score ≥10 will be referred to a mental health professional (MHP). The PHQ-9 will be administered according to the SOA.

Summary statistics for the score of summation of the 9 items and changes from baseline will be provided by visits. Frequency count and percentage of number of patients with score ≥10 will also be included. Only scores with all 9 items answered will be summarized.

All PHQ-9 data will be listed.

O. 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 and will be administered to patients <12 years of age according to the SoA.

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 <12 years of age according to the SoA. Any patient with a CDI-2 score >20 during the trial will be referred to an MHP.

Summary statistics for the score of summation of the items and changes from baseline will be provided by version, treatmentgroup and visit. Frequency count and percentage of number of patients with score > 20 will also be included. Only scores with all items answered will be summarized.

All CDI-2 data will be listed by version.

X. References

Centers for Disease Control and Prevention. (2022, February 18). SAS program (ages 0 to < 20 years). Centers for Disease Control and Prevention. Retrieved July 4, 2022, from https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

XI. Appendix 1: Schedule of Assessment

Assessment	Screening (In-Person)	Baseline Visit (In-Person)	Virtual Trial Visits	In-Person Clinic	End of Treatment Visit (In-Person)[1]	End of Study Visit[1]	Bridging Visit[2](In-Person)	Early Termination Visit (In-Person)
Trial Days	**-56 to -14**	**1**	**14, 28, 84, 112, 168, 196, 252, 336**	**56, 140, 224, 280, 308**	**364**	**392 (or 420)**	**Every 12 weeks**	**-**
Trial Visit	**-**	**V1**	**V2, V3, V5, V6, V8, V9, V11, V14**	**V4, V7, V10, , V12, V13**	**V15 (Week 52)**	**V16**	**-**	**-**
Window (Days)	**-**		**±3**	**±5**	**±5**	**±3**	**+7**	**+14**
Informed Consent/Assent[3]	X							
Inclusion/Exclusion	X	X						
Randomization		X						
Sample for genetic confirmation by URO 3.0 panel[4]	X							
Optional WES testing[5]	X							
Optional saliva collection[6]	X							
Nutrition and physical activity counseling and follow-up		X	X	X	X		X	
Physical examination[7]	X	X		X	X	X	X	X
Fitzpatrick Scale		X						

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Trial Days	**-56 to -14**	**1**	**14, 28, 84, 112, 168, 196, 252, 336**	**56, 140, 224, 280, 308**	**364**	**392 (or 420)**	**Every 12 weeks**	**-**
Trial Visit	**-**	**V1**	**V2, V3, V5, V6, V8, V9, V11, V14**	**V4, V7, V10, , V12, V13**	**V15 (Week 52)**	**V16**	**-**	**-**
Window (Days)	**-**		**±3**	**±5**	**±5**	**±3**	**+7**	**+14**
Comprehensive skin examination[8]	X			X[8] (V10)	X		X	X
Weight[9]	X	X		X	X		X	X
Height[10]	X	X		X	X		X	X
Waist circumference[11]	X	X		X	X		X	X
Vital signs[12]	X	X	X	X	X		X	X
ECG[13]	X	X			X		X	X
Pregnancy testing[14]	X	X	X	X	X		X	X
Hunger Questions[15,16]	X	X	X	X	X		X	X
Global Hunger Questions[15]		X	X	X	X		X	X
[redacted]								
C-SSRS[17]	X	X	X	X	X	X	X	X
PHQ-9[18]	X	X	X	X	X	X	X	X
CDI-2[19]	X	X	X	X	X	X	X	X

Assessment	Screening (In-Person)	Baseline Visit (In-Person)	Virtual Trial Visits	In-Person Clinic	End of Treatment Visit (In-Person)[1]	End of Study Visit[1]	Bridging Visit[2](In-Person)	Early Termination Visit (In-Person)
Trial Days	**-56 to -14**	**1**	**14, 28, 84, 112, 168, 196, 252, 336**	**56, 140, 224, 280, 308**	**364**	**392 (or 420)**	**Every 12 weeks**	**-**
Trial Visit	**-**	**V1**	**V2, V3, V5, V6, V8, V9, V11, V14**	**V4, V7, V10, , V12, V13**	**V15 (Week 52)**	**V16**	**-**	**-**
Window (Days)	**-**		**±3**	**±5**	**±5**	**±3**	**+7**	**+14**
[redacted]								
Adverse events	X	X	X	X	X	X	X	X
Injection site inspection		X	X	X	X		X	X
Concomitant medication review	X	X	X	X	X	X	X	X

Assessment	Screening (In-Person)	Baseline Visit (In-Person)	Virtual Trial Visits	In-Person Clinic	End of Treatment Visit (In-Person)[1]	End of Study Visit[1]	Bridging Visit[2](In-Person)	Early Termination Visit (In-Person)
Trial Days	**-56 to -14**	**1**	**14, 28, 84, 112, 168, 196, 252, 336**	**56, 140, 224, 280, 308**	**364**	**392 (or 420)**	**Every 12 weeks**	**-**
Trial Visit	**-**	**V1**	**V2, V3, V5, V6, V8, V9, V11, V14**	**V4, V7, V10, , V12, V13**	**V15 (Week 52)**	**V16**	**-**	**-**
Window (Days)	**-**		**±3**	**±5**	**±5**	**±3**	**+7**	**+14**
Safety laboratory tests[21]	X	X		X	X		X	X
[redacted]								
Trough PK		X		X	X			X
Anti-drug antibodies[22]		X		X	X	X	X	X
Biomarkers[23]		X			X			X
Daily drug compliance[24]		X	X	X	X		X	
Dispense/return trial drug[25]		X		X	X (return only)			X (return only)
Optional Informed Consent for Exit Interview					X			X

Abbreviations: CDI-2 = Children's Depression Inventory-2; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; [redacted] IWQOL = Impact of Weight on Quality of Life; QoL = quality of life; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetic; QoL = quality of life; URO = uncovering rare obesity; V = visit; WES = Whole Exome Sequencing.

[1] End of Treatment (EOT) is described in Section **Error! Reference source not found.** in the protocol. The End of Study (EOS) visit requirements are described in Section 4.1.5 in the protocol. The EOS visit is not required for eligible patients who transfer to the LTE (or Bridging Visit before LTE availability). The EOS Visit can be conducted by telephones for patients who either complete treatment and who do not enroll in the LTE or for patients who discontinue prior to completing 6 months but remain enrolled; if required by local regulation or if deemed necessary to assess patient safety by physical examination or after a longer follow-up period, the visit may be converted to an in-person visit and/or can occur up to Day 420 (Week 60). The EOS visit is separate from the last visit or contact for each patient which may occur at an unscheduled visit, the ET visit, the EOT visit, the EOS visit, or a scheduled Bridging Visit.

[2.] Patients who complete the treatment period (or patients who complete at least 6 months of treatment and remain enrolled) and have reached 1 year from the date of their randomization may be eligible for the LTE. If the LTE is not available, eligible patients may receive open-label setmelanotide by attending Bridging visits on an every 12-week basis until either the LTE trial is available or the trial ends. Additional visits may be scheduled at the discretion of the Investigator or the Sponsor.

[3] Although the trial procedures and assessments required per protocol are classified as “No or Minimal Risk” according to the 2008 Guidance Document “Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population,” considerations for reducing pain in distress in patients younger than 18 years of age are included in the protocol (**Error! Reference source not found.**).

[4] Patients will have a blood sample obtained either during screening or at the baseline visit for confirmatory genetic testing; this only needs to be completed 1 time. The Sponsor may waive this requirement for individual patients who have an existing genetic sample analysis from certain testing laboratories. If allowed by local regulation, excess blood may be stored and used for the development and validation of a companion diagnostic assay.

[5] All patients will be offered the opportunity to opt-in to having WES performed. This test could be performed on the same blood sample as the confirmatory genetic test.

[6] An optional saliva sample may be collected, and where permitted by local regulation, the sample may be stored and used for the development and validation of a companion diagnostic assay.

[7] A complete physical examination will be conducted at screening and at the EOT visit and include review of peripheral lymph nodes, head, eyes (including conjunctiva), ears, nose, mouth and oropharynx, neck, heart, lungs, abdomen, musculoskeletal including back, extremities, and a neurologic examination. At other time points, an abbreviated examination will be performed. The abbreviated examination should focus on heart, lungs, skin, neurologic examination, 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 examination and Tanner Staging. *Note:* the physical examination at the EOS visit will only be performed if this visit is converted to an in-person visit.

[8] A comprehensive skin evaluation will be performed by the Investigator or designee. The skin examination should include a full body skin examination (head-to-toe skin examination). If any concerning lesions are identified during screening, the patient should be referred to a dermatologist. Any concerning lesions identified during screening will be biopsied and results must be benign prior to first dose of setmelanotide. If the pre-treatment biopsy results are of concern, the patient may be excluded from the trial. Additionally, any concerning lesion or significant change in an existing lesion during the course of the trial must be evaluated by a dermatologist and biopsied, if clinically indicated in the opinion of the dermatologist. An additional comprehensive skin examination will be performed at Visit 10.

[9] 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 fasting for at least 8 hours. Patients are to wear light clothing or underwear and no shoes, with empty pockets,

[redacted]

and will be weighed at approximately the same time of day. All measurements will be recorded to the nearest 10th of a kg if reported with a digital scale, or half kg with a mechanical scale.

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

[11] Waist circumference (cm) will be measured in triplicate and recorded to the nearest half cm. Waist circumference should be measured after patients have fasted for at least 8 hours and at approximately the same time at each visit. Whenever possible, the same trial staff member should perform the measurement for a given patient to minimize variability. Patients should be in standing position, in light clothing and have attempted to empty their bladder.

[12] All vital signs measurements are to be obtained in the sitting position following at least 5 minutes of rest. Blood pressure and heart rate will be taken in triplicate, approximately 2 minutes apart. When possible, blood pressure should be taken in the non-dominant arm using the same methodology (automated or manual) throughout the trial. Patients and, as applicable, caregivers will be instructed on the proper use of and will be provided with WiFi/Bluetooth connected devices for measuring and transmitting data on blood pressure and temperature during virtual trial visits. The data are stored and automatically transferred when connected to Wi-Fi.

[13] A single 12-lead ECG will be performed in the supine position following a period of at least 10 minutes of rest.

[14] A urine pregnancy test may be performed to expedite availability of results prior to dosing on Day 1. With the exception of virtual visits, at all other designated time points, serum pregnancy testing will be performed; however, setmelanotide dosing may continue with results pending. At sites where pregnancy tests are required for virtual visits, at Visit 1 women of child-bearing potential will be given urine pregnancy kits for use at each of the virtual visits.

[15] [redacted] In addition, 2 global hunger questions will be administered: the Patient Global Impression of Severity (PGIS) and the Patient Global Impression of Change (PGIC). The PGIS is administered at baseline and both questions are administered thereafter, according to the schedule in the SoA. Both questions have a recall period of 7 days, and there are 2 versions of each question: one for caregivers of patients ≤12 years of age and/or who have cognitive impairment and cannot self-report and one for patients ≥12 years who can self-report.

[16] [redacted]

[17] The C-SSRS is a tool used not only to predict suicide attempts but to assess the full range of evidence-based ideation and behavior items, with criteria for next steps (e.g., a Mental Health Professional [MHP]) that can be completed in patients ≥6 years of age. The Baseline/Screening version of the scale is the initial form of the instrument to assess suicidality in a patient's lifetime and is administered at screening. 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

[redacted]

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.

[18] The PHQ-9 will be used for patients ≥12 years of age. If at any time during the trial an individual patient's PHQ-9 score is ≥10, the patient should be referred to a MHP.

[19] The CDI-2 will be administered to patients <12 years of age (self-report short form) and to caregivers of patients <12 years of age (parent version).

[20] [redacted]

[21] Safety laboratory tests will include: complete blood count with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, carbon dioxide, albumin, total protein, glucose, blood urea nitrogen, creatinine (including eGFR, uric acid, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, creatine phosphokinase, alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase, calcium, phosphorus), and urinalysis with microscopic analysis if positive findings on dipsticks warrant further examination. Safety laboratories will also include a coagulation profile (prothrombin time or international normalized ratio, and partial thromboplastin time also referred to as activated partial thromboplastin time).

[22] A positive anti-drug antibody (ADA) will be followed every 3 months after the ADA sample analysis until resolution of the ADA.

[23] A biomarker blood sample will be collected for metabolic, inflammation, metabolomic and/or proteomic biomarker analysis. This sample may not be analyzed.

[24] A daily question querying whether the patient completed their daily injection will be asked via an e-diary. This is not required during Bridging Visits.

[25] Dispensing will be made by site staff, using the dispensation function in the interactive response technology (IRT) system as outlined in the SoA. Dispensing may also be made directly to the patient if required and allowed by local regulations. At the Early Termination visit and V15, only drug return will apply.