Rhythm Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

Protocol Number RM-493-033 (22 Jun 2023)

[redacted]

A Phase 3 Multi-Center, One-Year, Open-Label Study of Setmelanotide in Pediatric Patients Aged 2 to <6 Years of Age with Rare Genetic Causes of Obesity

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Version 4.0
21 August 2023

Prepared By:

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APPROVAL SIGNATURE PAGE

Protocol Title: A Phase 3 Multi-Center, One-Year, Open-Label Study of Setmelanotide in Pediatric Patients Aged 2 to <6 Years of Age with Rare Genetic Causes of Obesity

Sponsor: Rhythm Pharmaceuticals, Inc.
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[redacted]

[redacted]

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.

Sponsor Signatory:

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1 List of Abbreviations and Definition of Terms

Abbreviation	Description
AE	Adverse Event
ASQ®-3	Ages & Stages Questionnaires®, Third Edition
ATC-3	Anatomical Therapeutic Chemical 3rd level
ATC-4	Anatomical Therapeutic Chemical 4th level
BBS	Bardet-Biedl Syndrome
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CSR	Clinical Study Report
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
DAO	Data As Observed
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
HR	Heart Rate
ICH	International Conference on Harmonization
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
PI	Principal Investigator
PT	Preferred Term
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneously
SD	Standard Deviation
SoA	Schedule of Activities
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

2 Introduction

This statistical analysis plan (SAP) describes the efficacy and safety summaries and analyses that will be performed for Study RM-493-033, *A Phase 3 Multi-Center, One-Year, Open-Label Study of Setmelanotide in Pediatric Patients Aged 2 to <6 Years of Age with Rare Genetic Causes of Obesity* and is based on the study protocol Version 5.0 dated 22 June 2023 and study Electronic Case Report Forms (eCRFs) Version 04.000 dated 21 March 2023.

3 Study Objectives and Overall Design

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of this study is to evaluate the effect of setmelanotide on weight-related parameters in pediatric patients aged 2 to <6 years with obesity due to either (1) biallelic variants of the *POMC*, *PCSK1* or *LEPR* genes or (2) Bardet-Biedl Syndrome (BBS).

3.1.2 Secondary Objective(s)

The secondary objectives of this study are to evaluate the effect of setmelanotide on additional weight-related parameters, as well as safety and tolerability in pediatric patients aged 2 to <6 years with obesity due to either (1) biallelic variants of the *POMC*, *PCSK1* or *LEPR* genes or (2) BBS.

3.2 Overall Design

This is a Phase 3 multi-center, open-label study of setmelanotide in pediatric patients aged 2 to <6 years of age with rare genetic causes of obesity. The study is designed to evaluate safety and tolerability of setmelanotide as well as its efficacy on weight-related parameters in pediatric patients.

The Screening Period begins with obtaining informed consent from the parent or guardian and will last between 1 and 8 weeks. During the Screening Period, patients will undergo all procedures as outlined in the Schedule of Activities (SoA; Section 16.1) to determine if they meet the all of the Inclusion (Section 6.1 of the protocol) and none of the Exclusion criteria (Section 6.2 of the protocol) for study eligibility.

During the Screening Period, patients will undergo medical evaluation; and caregivers will receive training on injection of study medication and other study procedures.

At the enrollment visit (Day 1), the patient will have height and body weight recorded. This will be the baseline height and weight. To be eligible for the study, a patient's baseline weight must be at least 15 kg. Height and weight will be monitored closely during the study.

During the enrollment visit, the caregiver will inject the patient's first dose of setmelanotide via subcutaneous (SC) injection under the supervision of the study staff. Patients' caregivers will be issued an electronic diary to capture daily compliance with injections.

Patients will have study visits approximately every 4 weeks through Week 20 and then approximately every 8 weeks through Week 52 and assessments will be performed as per the SoA. Due to the young age of the patients, it may not be possible to perform all planned assessments at each visit. Thus, as described in the SoA, the Investigator will be given latitude to adjust the planned assessments and blood draws as appropriate for the optimal medical care of their patients.

The End of Treatment (EOT) visit will occur on Study Day 365, which is the final day of treatment with setmelanotide. A final End of Study (EOS) visit will occur on Study Day 393 and will be conducted via telephone. Patients may be eligible to enroll into a long-term extension study.

3.2.1 Study Patients

The study plans to enroll approximately 10-15 pediatric patients (approximately 5 or more with biallelic mutations of the *POMC*, *PCSK1* or *LEPR* genes and approximately 5 or more with BBS) in a pivotal cohort. At the direction of the Sponsor, if additional potential patients are identified, a supplemental cohort may be added to gain additional experience.

3.3 Treatments and Assignment to Treatments

All patients will begin treatment at a dose of 0.5 mg of setmelanotide per day administered as a SC injection. Patients will then increase their dose by 0.5 mg increments, every 2 weeks, as described in the SoA (Section 16.1). The maximum dose level of setmelanotide used in this study will be based on the weight bands for the 2- to <6-year-old patients to support an exposure similar to that observed for adults dosed at 2 to 3 mg setmelanotide QD. The maximum dose level in this study for patients who weigh [redacted] will be 0.5 mg, 1.0 mg, 1.5 mg and 2.0 mg QD, respectively.

If a patient's weight decreases to below 15 kg during the study, the Investigator and Sponsor will discuss the patient's status and will jointly determine if a patient should continue the current dose, decrease the dose or discontinue treatment with setmelanotide temporarily or permanently.

A dose reduction to 0.25 mg can be considered in such scenarios or in case of safety or tolerability concerns, including for example, the occurrence of severe renal impairment. These dose adjustments are considered adequate for the pediatric patients to grow in height at a normal rate and support attaining and maintaining an appropriate body weight.

At the discretion of the Investigator, a patient may temporarily pause the dose escalation at any step prior to reaching their final maintenance dose, for safety or tolerability reasons, or due to achieving adequate weight loss. The dose may continue to be evaluated and adjusted, at the discretion of the Investigator, so long as the daily dose is kept between [redacted] and 2.0 mg QD, according to their respective weight.

3.4 Determination of Sample Size

No formal sample size determination was made based on statistical inference. The sample size is not driven by statistical power consideration but is primarily driven by clinical and practical considerations. Given the rare patient population, the study plans to enroll approximately 10-15 patients (approximately 5 or more pediatric patients with biallelic mutations of the *POMC*, *PCSK1* or *LEPR* genes and approximately 5 or more pediatric patients with BBS).

3.5 Patient Assessments

3.5.1 Vital Signs

Vitals signs include:

- Height (cm)
- Weight (kg)
- [redacted]
- Temperature (C)
- Heart Rate (HR) (beats/min)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Respiratory Rate

Vital signs will be assessed from screening and at every post-baseline visit. Height, weight, HR, systolic blood pressure, and diastolic blood pressure will be measured in triplicates at each visit. In addition to the individual measurements the above items will be aggregated into a mean value per visit (i.e. mean of all height measurements).

3.5.2 Bone Age

Bone age will be assessed at the enrollment (baseline) and EOT visits by X-ray.

3.5.3 Physical Examination

A complete physical examination will be conducted at screening and at the EOT Visit. At other timepoints, an abbreviated examination will be performed. The abbreviated examination should focus on heart, lungs, skin, neurologic exam, and any areas of previous abnormal findings, noting any changes from baseline. Tanner staging should be performed at Screening and at the EOT (Week 52) visit. It may be done at additional visits, at the discretion of the PI. While the findings from the physical examination will not be captured on the eCRF, nor analyzed directly, changes from baseline in any physical examination findings identified by the Investigator as clinically significant (CS) will be recorded as an adverse event (AE).

3.5.4 Comprehensive Skin Examination

Comprehensive skin examinations will also be performed per the SOA. Normal and abnormal findings regarding skin lesions will be assessed. At each visit skin hyperpigmentation, changes in skin tone, new mole development, and changes in existing moles will be assessed.

3.5.5 Electrocardiogram (ECG)

A single 12-lead ECG recording will be performed as specified in the SOA. If an ECG is not practical in a young patient, it may be replaced by a rhythm strip and only HR and PR interval will be collected.The following items will be measured:

- HR (beast/min)
- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- QTcF interval (msec)
- Overall Interpretation (Normal, Abnormal – Not Clinically Significant (NCS), Abnormal – CS)

3.5.6 Clinical Laboratory Tests

Hematology, clinical chemistry, and urine analysis laboratory tests will be performed as specified in the SOA. At each applicable visit, the laboratory tests will be collected prior to study treatment. Due to the age of the children, it may not be possible to collect all labs at every study visit. Screening may be performed over multiple days, to complete the required assessments. After enrollment, if all lab tests are not possible, then the tests

should be collected in the following descending order of priority: safety, anti-drug antibodies, trough PK, hemoglobin A1c and then lipid panel.

3.5.7 Injection Site Examination

At each visit where study treatment is administered, the injection site will be evaluated. The injection site evaluation will include:

- Reaction (Erythema, Edema, Induration, Itching, Pain or Tenderness, Other)
    - Length (Erythema, Edema, Induration only)
    - Width (Erythema, Edema, Induration only)
- Finding (None, Mild, Moderate, Severe)
- Clinically significant (Yes, No)

3.5.9 Ages & Stages Questionnaires®, Third Edition (ASQ®-3)

The ASQ®-3 is a developmental screening tool that assesses developmental progress in children between one month to 5 ½ years. The ASQ®-3 is intended for use at six-month intervals between 6 months and 3 years of age, and then at one-year intervals through age 5. Thus, for patients who enter the study at ages between 2 years and 3 years, the ASQ-3 will be administered at the Enrollment (Baseline) Visit, Week 28 visit and EOT Visit. For patients who enter the study between the ages of 3 and 6 years old, the ASQ-3 will only be administered at the Enrollment (Baseline) Visit and EOT Visit.

The ASQ-3 consists of five areas: communication, gross motor, fine motor, problem solving, and personal-social. Each area consists of six questions that are scored Yes = 10 points, Sometimes = 5 points, and Not yet = 0 points. The 10 free-response items will not be analyzed.

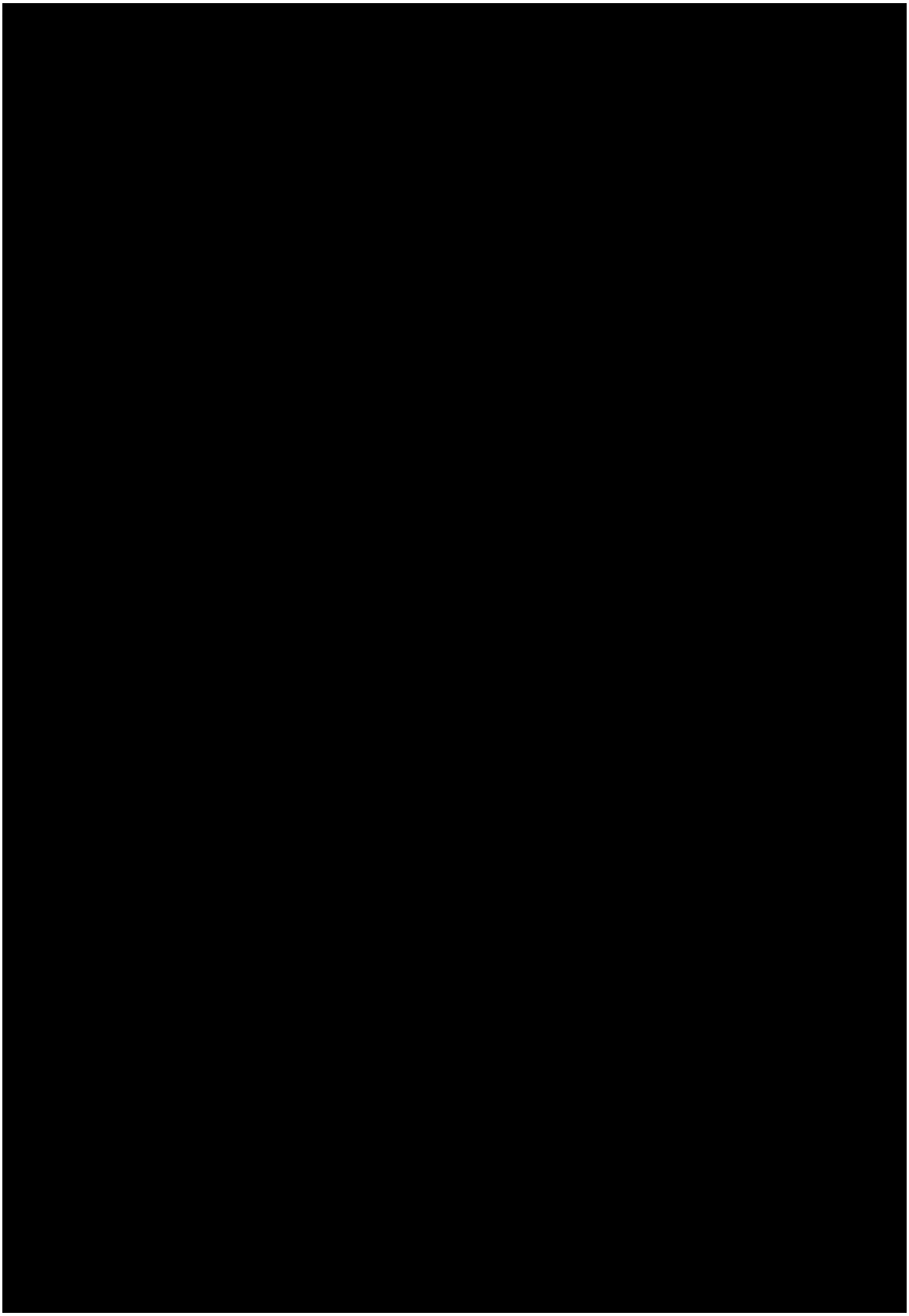
The total area score is calculated by first adding up the questions within each area and then comparing the total area score to the respective cutoff score on the ASQ-3 scoring sheet to be normalized to one of three categories, which indicate whether the child's development appears to be on schedule.

- Below the cut-off = Further assessment with a professional may be needed.
- Close to the cut-off = Providing learning activities and monitor.

- Above the cut-off = The child's development appears to be on schedule.

The following table presents ASQ-3 Referral cutoff scores and monitoring zone cutoff scores used in the analysis:

PARCAT2	PARAM	Referral Cutoff	Monitoring zone Cutoff
30 Month Questionnaire	Communication - 30	33.30	43.56
36 Month Questionnaire	Communication - 36	30.99	41.43
42 Month Questionnaire	Communication - 42	27.06	38.54
48 Month Questionnaire	Communication - 48	30.72	41.82
54 Month Questionnaire	Communication - 54	31.85	42.82
60 Month Questionnaire	Communication - 60	33.19	42.80
30 Month Questionnaire	Gross Motor - 30	36.14	44.84
36 Month Questionnaire	Gross Motor - 36	36.99	45.84
42 Month Questionnaire	Gross Motor - 42	36.27	45.15
48 Month Questionnaire	Gross Motor - 48	32.78	42.74
54 Month Questionnaire	Gross Motor - 54	35.18	44.58
60 Month Questionnaire	Gross Motor - 60	31.28	41.72
30 Month Questionnaire	Fine Motor - 30	19.25	33.02
36 Month Questionnaire	Fine Motor - 36	18.07	32.57
42 Month Questionnaire	Fine Motor - 42	19.82	33.68
48 Month Questionnaire	Fine Motor - 48	15.81	30.58
54 Month Questionnaire	Fine Motor - 54	17.32	31.72
60 Month Questionnaire	Fine Motor - 60	26.54	39.05
30 Month Questionnaire	Problem Solving - 30	27.08	38.63
36 Month Questionnaire	Problem Solving - 36	30.29	41.13
42 Month Questionnaire	Problem Solving - 42	28.11	39.82
48 Month Questionnaire	Problem Solving - 48	31.3	42.04
54 Month Questionnaire	Problem Solving - 54	28.12	39.68
60 Month Questionnaire	Problem Solving - 60	29.99	41.29
30 Month Questionnaire	Personal - Social - 30	32.01	41.94
36 Month Questionnaire	Personal - Social - 36	35.33	44.07
42 Month Questionnaire	Personal - Social - 42	31.12	41.25
48 Month Questionnaire	Personal - Social - 48	26.6	38.47
54 Month Questionnaire	Personal - Social - 54	32.33	42.55
60 Month Questionnaire	Personal - Social - 60	39.07	46.96



[redacted]

4 General Analysis Conventions

[redacted] Data for all patients in the clinical database will be included in the data listings. Calculated (derived) variables will be listed as appropriate.

All efficacy, safety and baseline characteristics variables will be presented using descriptive statistics and figures as appropriate. Continuous variables will be summarized using descriptive statistics (number of observations, mean, standard deviation (SD), median, minimum, and maximum). Categorical variables will be presented in frequency tables with number and percent of observations for each level. Missing counts for all variables will be presented for informational purposes only and will not be included in percentage calculations.

Study days will be calculated relative to the first injection of study drug. Day 1 will be the first day of study drug administration in the study. In data listings, the relative study day (in relation to date of first study drug administration) of all dates will be presented.

AEs, medical history events, and concomitant treatments/procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 24.0 or higher. Prior/concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Global B3, March 2021 or higher.

Any changes from the SAP will be detailed in the Clinical Study Report (CSR).

4.1 Study Periods

The study has two periods: Screening and Treatment.

- Screening Period – From providing informed consent to just before the Enrollment (Baseline) Visit (Day 1). Can range between 56 – 1 day(s) prior to the Enrollment (Baseline) Visit.
- Treatment Period - From the Enrollment (Baseline) Visit to EOT (Day 365, or date of withdrawal).

A final EOS visit will occur on Study Day 393 and will be conducted via telephone. Patients may be eligible to enroll into a long-term extension study.

4.2 Visit Windows

Study visits are expected to occur according to the protocol schedule (Section 16.1). Efficacy by-visit summaries and analyses will use analysis visits. Both scheduled and unscheduled visits (including early termination visit) will be windowed based on the following analysis visit windows.

Analysis Visit	Target Study Day	Analysis Visit Window
Baseline	1	≤ 1
Week 2	15	2 – 22
Week 4	29	23 – 36
Week 6	43	37 – 50
Week 8	57	51 – 71
Week 12	85	72 – 99

Week 16	113	100 – 127
Week 20	141	128 – 169
Week 28	197	170 – 225
Week 36	253	226 – 281
Week 44	309	282 – 337
Week 52	365	338 – 379
Week 56	393	≥ 380

If two or more assessments (include both scheduled and unscheduled assessments) are available for the analysis visits, then all assessments will be included in data listings and the following rule will be applied for determining the values to be used for the summaries and analyses in tables:

- Efficacy assessments: the assessment taken closest to the target study day will be used for the summaries and analyses; if two visits are equally distant to the target study day, then the more recently occurring visit will be chosen (i.e. If the target study day was 01 JAN 2021 and Visit A occurred on 27 DEC 2020 and Visit B occurred on 06 JAN 2021 (both 5 days apart from the target study day), then Visit B will be chosen).

Safety by-visit summaries and analyses will use the nominal evaluation visit, as recorded on the eCRF. Both scheduled and unscheduled visits (including early termination visit) will be windowed based on the protocol-specified windows outlined in Section 16.1. If two or more assessments (include both scheduled and unscheduled assessments) are available for the visits, then all assessments will be included in data listings and the following rule will be applied for determining the values to be used for the summaries and analyses in tables:

- Safety assessments, including clinical laboratory tests: the scheduled visit will be used over any unscheduled visits conducted within window; otherwise, the latest assessment will be used for the summaries and analyses.

4.3 Baseline Definitions

For all analyses, baseline will be defined as the most recent measurement prior to the first administration of study drug, including assessments done at the Screening visit, Unscheduled visits conducted prior to study treatment, and pre-treatment assessments done at the Enrollment (Baseline) visit.

In general, change from baseline (Δ) will be calculated as the value at a given time point, *X*, minus the baseline value:

$$\Delta = X\ Value - Baseline\ Value$$

5 Analysis Populations

5.1 Safety Population

The Safety Analysis Set population will include all patients who received at least 1 dose of study drug.

6 Patient Disposition

The disposition of patients will be presented in total, including:

- Number of patients screened, including screen failures
- Number of patients enrolled into the study
- Number of patients who completed the treatment
- Number of patients who early withdrew/discontinued from the treatment
- Number of patients who completed the study
- Number of patients who early withdrew/discontinued from the study
- Number of patients that continued onto the extension study (RM-493-022)
- Number of patients in the Safety population

Specifically, the number and percentage of patients in each of the specified categories above will be presented. Percentages will not be presented for the number of patients enrolled or screened; all other percentages will be based on the number of patients in the safety population. The discontinuation reason as specified on the eCRFs will also be summarized by number and percent under 'Early withdrawals/discontinuations' section.

All patients' disposition information (date of study completion/discontinuation, reason for discontinuation, date of last dose, reason for treatment discontinuation, and COVID-19 impact) will be presented in a data listing. Inclusion/exclusion data will also be presented by patients in a data listing.

7 Protocol Deviations

A protocol deviation occurs when a patient deviates from the protocol procedures. All protocol deviations will be presented by patient in a data listing.

COVID-19 Impact

As the study started during the COVID-19 pandemic, missed/modified study visits, study procedures, and study dosing due to COVID-19 will be collected. A data listing will present any study visit, study procedure, and/or study assessment that due to COVID-19 were:

- Conducted remotely
- Modified or missed
- Out of window
- Resulted in study discontinuation
- Resulted in site closure

8 Demographic and Baseline Characteristics

8.1 Demographic and Baseline Characteristics

Demographic assessments for this study include:

- Age (years)
- Gender
- Ethnicity
- Race
- Weight at Baseline (kg)
- Height at Baseline (cm)
- Body Mass Index (BMI) at Baseline (kg/m^2)
- BMI Z-score at Baseline
- Waist Circumference at Baseline (cm)
- Gene Type (*POMC*, *PCSK1*, *LEPR*, and BBS)
- Fitzpatrick Skin Type (FST) at Baseline

Age, baseline weight, baseline height, baseline BMI, baseline BMI Z-score, and baseline waist circumference will be analyzed as a continuous variable. Gender, ethnicity, race, gene type, and baseline FST will be analyzed as categorical variables.

Demographics characteristics will be presented by patient in a data listing.

8.2 Medical History

History of relevant surgical events and medical conditions will be collected. Medical History will be coded according to MedDRA; the version used will be noted as a footnote in the tables and listings.

The number and percentage of patients reporting medical history will be summarized by system organ class (SOC) and preferred term (PT). SOC and PTs will be presented in descending frequency first and then alphabetically if there are ties. Each patient will contribute at most one count per summarization category. In other words, if a patient has more than one medical history event with same PT, the patient will be counted only once for that PT. Similarly, if a patient has more than one medical history event for a SOC, the patient will be counted only once in that SOC.

Medical history information will be reported by patient in a data listing. The listing will show the verbatim term (i.e., term reported by the site), the MedDRA SOC, MedDRA PT, event start date, and event end date (or ongoing). Medical history of weight loss interventions (type of intervention, start and end dates, and a summary of the outcome), historic height and weight (the 10 most recent height and weight measurements along with the date of assessment), and nutritional counseling (whether the patient completed nutritional counseling, and if so, the date and outcome) will be reported by patient in a data listing.

8.3 Concomitant Procedures

Concomitant procedures for this study are defined as any surgical, therapeutic, or diagnostic procedure that a patient has performed on or after the date of enrollment. Procedures will be coded using the MedDRA. The versions used for the coding will be noted as a footnote in the tables and listings.

Concomitant procedures will be summarized in a table and will follow the same methods specified for medical history (Section 8.2). Concomitant procedure information will be reported by patient in a data listing. The listing will show the verbatim term, the MedDRA SOC, MedDRA PT, indication, event start date, and event end date (or ongoing).

8.4 Prior and Concomitant Medications

Concomitant medications for this study are defined as any medication the patient is receiving at the time of enrollment, or any new medication received by the patient after the date of enrollment. Prior medications are medications with a stop date prior to date of study enrollment. Medications will be coded using the WHO Drug Dictionary. The versions used for the coding will be noted as a footnote in the tables and listings.

The number and percentage of patients who receive prior and concomitant medications will be summarized, separately, by the WHO Drug Dictionary Anatomical Therapeutic Chemical 4th level (ATC-4) and the preferred name. If the 4th level term is not available, the next available level (e.g., ATC-3) will be used.

ATC-4 and preferred name will be presented in descending frequency first and then alphabetically if there are ties. Each patient will contribute at most one count per summarization category. In other words, if a patient has more than one medication with same preferred name, the patient will be counted only once for that preferred name. Similarly, if a patient has more than one medication for an ATC-4 level, the patient will be counted only once in that ATC-4 level and preferred name.

Prior and concomitant medications will be presented by patient in a data listing. The listing will show the verbatim medication/therapy, the ATC-4 term, preferred name, indication, medication start date, medication end date (or ongoing), dose, dose unit, frequency, and route.

8.5 Physical Examination

Physical examination assessments will be presented by patient in data listings. The physical examination listing will show the date of examination, indicator examination was not done (if applicable), reason examination was not done, and Tanner Staging results (if applicable).

9 Efficacy Analysis

Efficacy analyses of weight, waist circumference, BMI, and BMI z-scores will be conducted using the data as observed (DAO) with no imputation for missing data. Additional analyses will be conducted using the last observation carried forward (LOCF) to impute any missing data.

If needed, weight and height will first be converted into kilograms and meters, respectively. Given that height and body weight are collected in triplicates at each visit, these will first be aggregated into one averaged value per visit. Visits will then be compared against the analysis visit window (described in Section 4.2) to select the appropriate averaged values prior to calculating weight, BMI, BMI z-score, and changes. If height is missing for an analysis visit, then height will be imputed using LOCF.

9.1 Primary Efficacy Endpoints

9.1.1 Proportion of Patients with a Decrease from Baseline to 52 Weeks in BMI Z-score ≥ 0.2

A "responder" is defined as a decrease from baseline to 52 weeks in the patient's BMI z-score of ≥0.2. The WHO Child Growth Standards 2007 will be used for BMI z-score. At each visit, an indicator variable will be created to identify patients that have a decrease in BMI z-score from baseline of 0.2 or more, allowing for the analysis of proportion of patients who meet the "responder" definition. The proportion and the corresponding 2-sided 95% CI using the Clopper-Pearson method will be reported for each visit. Sample SAS code to calculate the BMI z-score can be found at https://www.who.int/tools/child-growth-standards/software.

9.1.2 Mean Percent Change in BMI from Baseline to Week 52

For the analysis of Mean percent change in BMI from baseline, percent changes in BMI from baseline over time will be summarized using descriptive statistics. Mean percent change in BMI from baseline over time will also be provided graphically. A 2-sided 95% CI with Student's *t*-distribution will be provided for Mean percent change in BMI from baseline. In addition, patient figures showing the percent change in BMI from baseline will be created. Information on the patient's baseline BMI will be included in the figure.

9.2 Secondary Efficacy Endpoints

9.2.1 Change in BMI Percentage of the 95th Percentile

For each patient and visit, the BMI for that patient relative to the 95th percentile for the corresponding age and gender will be calculated. The actual relative value, change from baseline in the relative value, and percent change in relative value from baseline will be summarized using descriptive statistics at each visit.

9.2.2 Change in Weight

Weight, change in weight from baseline, and percent change in weight from baseline will be summarized using descriptive statistics at each visit. This information will also be provided graphically for change in weight from baseline and percent change in weight from baseline. In addition, for each patient figures showing change in weight and percent change in weight from baseline over time will be created. Information on the patient's baseline weight, BMI, and BMI z-score will be included in the figure.

9.2.3 Change in BMI and BMI z-scores

BMI, change in BMI from baseline, BMI z-score, change in BMI z-score from baseline, and percent change in BMI z-score from baseline will be summarized using descriptive statistics. This information will also be provided graphically for change in BMI from baseline, and change in BMI z-score from baseline. In addition, for each patient figures showing the change in BMI, and the change in BMI z-scores from baseline will be created. Information on the patient's baseline weight, BMI, and BMI z-score will be included in the figure.

9.2.4 Ages and Stages Questionnaire, Third Edition

The normalized categories in the five areas (see Section 3.5.9) and their shift from baseline will be tabulated at each visit. A listing of these data will also be provided.

10 Safety Analysis

10.1 Safety Endpoints

All safety endpoints will be based on the Safety Population. Safety endpoints include:

- Safety and tolerability assessed by the frequency and severity of AEs (see Section 10.3 for more details)
- Safety and tolerability assessed by vital signs (see Section 10.5 for more details)
- Safety and tolerability assessed by laboratory evaluations (see Section 10.4 for more details)
- Change from baseline in metabolic parameters following treatment with setmelanotide, including fasting glucose, HbA1c, lipid profiles (total-, high-density lipoprotein [HDL]-, and low-density lipoprotein [LDL]-cholesterol, triglycerides).

10.2 Study Treatment

10.2.1 Study Drug Exposure

Dosing of study treatment will be monitored throughout the study by having the patient complete a daily dosing log that records daily dosing information, including:

- The time of dosing

- If the injection occurred (Yes/No)
- Reason for not injecting (Forgot, Trouble with injection, Ran out/misplaced drug, Other)

Study treatment duration, in weeks, will be calculated as the number of weeks patients were administered study drug and will be summarized using descriptive statistics. Study treatment duration will be calculated using the following formula:

$$Treatment\ Duration\ (weeks) = \frac{(Date\ of\ last\ injection - Date\ of first\ injection) + 1}{7}$$

For each patient, total exposure (mg) will be summarized descriptively in a table as the total sum of all dose mg that a patient receives throughout the study.

For each patient, study drug compliance will be calculated using the following formula:

$$\text{Compliance (\%)} = \left(\frac{\text{Number of daily dosing logs where injection occurred}}{\text{Date of last injection} - \text{Date of first injection} + 1}\right) \times 100\%$$

Patient compliance with study drug will be summarized descriptively in a table. The number of patients who experienced at least one dose interruption will also be presented, as well as the reason for the interruption.

Study drug compliance will be presented by patient in a data listing. The listing will show the daily dosing study day, date of the daily dosing log, indicator if patient was injected, reason for not injecting, treatment duration, and compliance percentage.

10.2.2 Treatment Administration

Study treatment administration will be presented by patient in a data listing. The listing will show the date study drug was dispensed, items dispensed, treatment administration date, indicator if patient was injected, reason for not injecting, dose (mg), injection location, and kit number. A listing containing the patient supply accountability log will also be created. This listing will contain the article name, item number, expiry date, lot ID, item type, unit, quantity dispensed, item status, date returned/reported, item condition, quantity returned, amount returned, and any comments.

10.2.3 Injection Site Evaluation

Injection site evaluation (described in Section 3.5.6) at each visit will be summarized using descriptive statistics.

Injection site evaluation will be presented by patient in a data listing. The listing will show the date of evaluation, indicator if patient was evaluated, reason evaluation was not performed, reaction, finding, indicator if CS, length (mm), and width (mm).

10.2.4 Dose Level Changes

Any dose level changes that occur throughout the study will be captured in a data listing. For each patient, the visit, reason for dose level change, date of new dose, new dose level (mg), and planned location for injection will be presented.

10.3 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study treatment, whether or not considered related to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment. AEs, including Serious Adverse Events (SAE), will be collected from the provision of informed consent until the EOS visit. All AEs reported will be coded using the MedDRA version in force at the time of database freeze) and classified by MedDRA SOC and PT. The MedDRA version used for the coding will be noted as a footnote in the tables and listings.

All AEs will be presented by patient in a data listing. The listing will show the verbatim term, MedDRA SOC, MedDRA PT, event start date, event end date (or ongoing), SAE indicator, severity, relationship to study drug, action taken with study drug, action taken, and outcome.

10.3.1 Overview of Adverse Events

An overview summary table of AEs will be provided, including the number and percentage of patients reporting an AE for the following categories:

- Patients with at least one treatment-emergent AE (TEAE)
- Patients with at least one TEAE related to study drug
- Patients with at least one TEAE leading to drug discontinuation
- Patients with at least one TEAE leading to study discontinuation
- Patients with at least one serious TEAE
- Patients with at least one serious TEAE related to study drug
- Patients with AE resulting in death on study

10.3.2 Treatment-Emergent Adverse Events

A TEAE is any AE that begins or worsens in intensity on or after the date of the first administration of study drug. Summaries of TEAEs (including number and percentage of patients) will be displayed by the following:

- TEAEs by MedDRA SOC and PT
- TEAEs related to study drug by MedDRA SOC and PT

- TEAEs leading to drug discontinuation by MedDRA SOC and PT
- TEAEs leading to study discontinuation by MedDRA SOC and PT
- Serious TEAEs by MedDRA SOC and PT
- Serious TEAEs related to study drug by MedDRA SOC and PT
- AEs resulting in death on study by MedDRA SOC and PT

The number and percentage of patients who experienced at least one of the events listed above will be summarized overall and for each SOC and each PT. SOC and PTs will be presented in descending frequency first and then alphabetically if there are ties. Each patient will contribute at most one count per summarization category. In other words, if a patient has more than one TEAE with same PT, the patient will be counted only once for that PT. Similarly, if a patient has more than one TEAE for a SOC, the patient will be counted only once in that SOC and PT.

10.3.3 Severity of the Adverse Event

TEAEs will also be summarized by maximum severity and will follow the same methods specified in Section 10.3.2. The severity of the TEAE is classified into the five Common Terminology Criteria for Adverse Events (CTCAE) categories of Mild, Moderate, Severe, Life Threatening or Disabling, and Death. If a patient has multiple occurrences of the same MedDRA SOC or PT, then only the most severe event will be summarized in the tables for that SOC and PT. If the severity assessment is missing, the severity of 'Severe' will be assumed.

10.3.4 Relationship to Study Drug

TEAEs will also be summarized by relationship to study drug and will follow the same methods specified in Section 10.3.2. The relationship of the TEAE is classified into two categories of Related and Not Related. If the relationship assessment is missing, the relationship will be considered related. Related TEAEs will also be summarized by MedDRA SOC, PT and maximum severity (defined in Section 10.3.3). If the patient experiences both a related and not related TEAE within a particular SOC or PT, only the related TEAE will be summarized in the table.

10.3.5 Death, Serious Adverse Events, Adverse Events Leading to Discontinuation

Serious TEAEs, TEAEs leading to death, and TEAEs leading to study drug discontinuation will be summarized, in separate summary tables, by MedDRA SOC and PT, following the same methods specified in Section 10.3.2. Furthermore, serious TEAEs will also be summarized, separately, by MedDRA SOC, PT, maximum severity/relationship/ relationship and maximum severity (defined in Section 10.3.3 and 10.3.4).

Additionally, separate patient listings also will be provided for the following: patient deaths, SAEs, and AEs leading to study discontinuation and drug discontinuation.

The patient death listing will include any AEs that lead to an outcome of death, and will show the verbatim term, MedDRA SOC, MedDRA PT, event start date, date of death, severity, relationship to study drug, action taken with study drug, action taken, and outcome.

The SAE listing will include any AEs that are classified as an SAE, and will show the verbatim term, MedDRA SOC, MedDRA PT, event start date, event end date (or ongoing), SAE category, severity, relationship to study drug, action taken with study drug, action taken, and outcome.

The AEs leading to discontinuation listing in will include any AEs that lead to an outcome of discontinuation or study drug withdrawn, and will show the verbatim term, MedDRA SOC, MedDRA PT, event start date, event end date (or ongoing), SAE indicator, severity, relationship to study drug, and outcome.

10.4 Clinical Laboratory Data

Hematology, clinical chemistry, and urine analysis laboratory assessments, not discussed below in Section 10.4.1, collected at each study visit and the changes from baseline to any post-baseline visit will be summarized by descriptive statistics. All laboratory tests will be compared to their laboratory normal range. Values outside of the normal range will be further classified as: Low – CS, High – CS, Low – NCS, High – NCS. Additionally, a shift table will be created to present any change from baseline in normal ranges in all laboratory tests across all post-baseline visits. This table will show the number and percentage of patients who had values that shifted from low - CS, low-NCS, normal, high – NCS, or high-CS at baseline to low - CS, low-NCS, normal, high – NCS, or high-CS at each post-baseline visit. Percentage of patients will be calculated using the number of patients with a baseline value and a non-missing value at the specified post-baseline visit as the denominator.

All laboratory data will be presented in data listings as collected. The listings will show the sample date, laboratory test, indicator test was not done (if applicable), reason test was not done (if applicable), laboratory value, and the change from baseline. Values outside of the reference range will be flagged with ‘H’ for high and ‘L’ for low, respectively.

10.5 Vital Signs

The aggregated vital signs (described in Section 3.5.1 and 3.5.2) at each study visit and the changes from baseline to any post-baseline visit will be summarized using descriptive statistics.

Vital signs will be presented in a listing. The listing will show the assessment date, vital sign, indicator measurement was not done (if applicable), measurement value, and the change from baseline. Values will include both the triplicate measurements and their aggregated value, where applicable.

10.6 Electrocardiograms

The ECG and the changes from pre-dose baseline will be summarized descriptively at each visit. In addition, a shift table will be created to show any change from pre-dose baseline to each visit in the overall ECG interpretation.

QTcF interval prolongation will be presented separately as well. The number and percentage of patients with a QTcF interval of >450 msec, >480 msec, and >500 msec will be summarized by visit, along with the number and percentage of patients with a change from pre-dose baseline in QTcF interval of 30 - < 60 msec and ≥60 msec.

All ECG results will be presented in a data listing. The listing will show the assessment date, ECG measurement, indicator ECG was not done (if applicable), reason ECG was not done (if applicable) ECG value, the change from baseline.

10.7 Hyperpigmentation

Skin examination results (described in Section 3.5.4) at each visit will be summarized by skin region using descriptive statistics. Results from the hyperpigmentation assessment will be summarized by visit descriptively, including the number of patients that experienced a hyperpigmentation or skin change event. The skin examination listing will show the date of examination, indicator examination was not done (if applicable), reason examination was not done, skin region, result of exam, and any noted findings. A listing displaying the details of skin hyperpigmentation, changes in skin tone, development of new moles, changes in existing moles, and AE relatedness will be created.

10.8 Bone Age

Bone age will be collected at the enrollment visit (baseline) and the EOT visit. Bone age and the change from baseline to EOT will be summarized using descriptive statistics.

A listing of the date of x-ray, date of bone age assessment, and the result, and the change from baseline will be provided.

[redacted]

11 Statistical/Analytical Issues

11.1 Handling of Missing Data

In general, the number of patients with missing values will be summarized and reported as appropriate in all outputs. Unless otherwise specified in the SAP, missing data will not be imputed.

11.2 Handling of Missing/Partial Dates

While every effort will be made to obtain full, complete information on all data collected the table below outlines the imputation rules to be followed for any missing dates. Dates will be presented as collected in the listings.

Imputation Criteria for Missing/Partial Dates

Variable	**Missing Day**	**Missing Month or Day and Month**	**Missing Year, Month and Year, or Day and Year**	**Missing Day, Month, Year**

AE/Medication Start Date	Assign to the first of the month (i.e. UNK-JAN-2019 becomes 01-JAN-2019)	Assign to the month of 'June' (i.e. 01-UNK-2019 becomes 01-JUN-2019), provided the imputed date is on or after the patient's baseline study treatment date; otherwise, the subsequent month after study treatment will be used.	Assign to year of study treatment will be used (i.e. 01-JAN-UNK becomes 01-JAN-2019), provided the imputed date is on or after the patient's study treatment date; otherwise, the subsequent year after treatment will be used.	Assign to baseline study treatment date
AE/Medication End Date	Assign the last day of the month (i.e. UNK-JAN-2019 becomes 31-JAN-2019).	Assign to the subsequent month after the start date.	Assign to the year of baseline study treatment (i.e. 01-JAN-UNK becomes 01-JAN-2019), provided the imputed date is after the start date; otherwise, the subsequent year after start date will be used.	Assumed medication is ongoing; no imputation

11.3 Pooling of Centers in Multi-Center Studies

As no site-level analyses are planned, there will be no pooling of centers.

11.4 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons or multiplicity will be made.

11.5 Examination of Subgroups

Analyses by genotype may be provided.

12 Interim Analysis and Data Monitoring

An interim analysis is planned for 23 August 2023, the last day study day prior to the first scheduled Bridging Visit (see protocol for more information). The purpose of this analysis is to support a regulatory submission to the European Medicines Agency (EMA).

All efficacy analyses, demographics, medical history, concomitant procedures, prior medications, and concomitant medications will be created for this analysis but will only include patients that have completed or early discontinued from the study as of 23 August 2023. The results of this analysis will not be considered for the purposes of modifying the study.

13 Quality Control

All data displays and analyses will adhere to the International Conference on Harmonization (ICH) *Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports (ICH Topic E3).*

All analyses will be performed using SAS® Version 9.4 (or later). [redacted] will follow its standard operating procedures in the creation and quality control of all tables, listings, figures, and analyses. Sponsor or its designee will review all tables, listings, and figures prior to final database lock. All final SAS programs and associated output files will be transferred to Sponsor in agreed-upon format at project completion.

14 Tables and Listings Conventions

Mock-ups for statistical tables and listings will be provided. Final formats for the statistical tables and listings may deviate from these mock-ups upon agreement with the Sponsor. Footnotes will be used as needed to clarify the information that is presented in the tables and listings. Unless otherwise requested by the Sponsor, the term 'patient' will be used in all tables and listings, in accordance with Clinical Data Interchange Standards Consortium (CDISC) standards.

The table and listing mock shells, along with their programming convention, will be provided in a separate document.

15 References

16 Appendices

16.1 Schedule of Assessments

Assessment	Screening	Enrollment Visit (Baseline)	Dose Escalation Visits[19]	Study Visits	End of Treatment Visit	End of Study Visit (Telephone)	Early Termination Visit
Study Week	-8 to -1		2, 4, 6	8, 12, 16, 20, 28, 36, 44[17]	52	56	
Study Day	-56 to -1	1	15, 29, 43	57, 85, 113, 141, 197, 253, 309	365	393	
Window			+/-3	+/-5	+/- 5	+/-3	
Informed Consent	X						
Inclusion/ Exclusion	X	X					
Genetic Sample[9, 18]		X					
Medical History	X						
Physical Exam[1]	X	X*	X	X	X		X
Fitzpatrick classification scale		X			X		X
Comprehensive Skin Exam[2]	X	X		X	X		X
Weight[3]	X	X	X	X	X		X
Height[4]	X	X	X	X	X		X
Waist circumference[5]	X	X	X	X	X		X
Vital Signs[6]	X	X	X	X	X		X
ECG[7]	X	X	X	X[12]	X		X
Daily drug compliance[8]		X	X	X	X		
[redacted]							
Adverse events	X	X	X	X	X	X	X
Injection site inspection		X	X	X	X		X
Concomitant medication Review	X	X	X	X	X	X	X
Optional Nutritional Counseling[14]		X	X	X	X		
Bone Age[15]		X			X		
Ages & Stages Questionnaires, Third Edition (ASQ- 3)[16]		X		X	X		

Assessment	Screening	Enrollment Visit (Baseline)	Dose Escalation Visits[19]	Study Visits	End of Treatment Visit	End of Study Visit (Telephone)	Early Termination Visit
Study Week	**-8 to -1**		**2, 4, 6**	**8, 12, 16, 20, 28, 36, 44[17]**	**52**	**56**	
Study Day	**-56 to -1**	**1**	**15, 29, 43**	**57, 85, 113, 141, 197, 253, 309**	**365**	**393**	
Window			+/-3	+/-5	+/- 5	+/-3	
Safety Lab Tests[9]	X	X	X	X[12]	X		X
[redacted]							
Anti-Drug Antibodies[9]	X			X[12]	X		X
PK profile[9]		X[12]		X[12]			X
Trough PK[9]			X	X[13]	X		
Dispense Study Drug		X	X	X			
Return Study Drug			X	X	X		
Optional Informed Consent for Exit Interviews					X		

Abbreviations: ECG=Electrocardiogram [redacted]

Note: If there are <2 weeks between screening and enrollment, the enrollment visit physical examination may be waived.

1. A complete physical examination will be conducted at screening and at the End of Treatment (EOT) Visit. At other timepoints, an abbreviated examination will be performed. The abbreviated examination should focus on heart, lungs, skin, neurologic exam, and any areas of previous abnormal findings, noting any changes from baseline. Tanner staging should be performed at Screening and at the EOT (Week 52) visit. It may be done at additional visits, at the discretion of the Investigator
2. A comprehensive skin evaluation will be performed by the Investigator or qualified designee. The skin exam should include a full body skin exam (head-to-toe skinexamination). Any concerning lesions identified during the Screening Period will be biopsied and results known to be benign prior to first dose of setmelanotide. If the pre-treatment biopsy results are of concern, the patient will be excluded from the study. Additionally, any new lesion or change in an existing lesion identified during the course of the study must be evaluated by a dermatologist and biopsied, if clinically indicated in the opinion of the dermatologist.
3. Weight (kg) is to be measured at the clinic using the same scale throughout the study or at home (during virtual visits or visiting nurse visits) using the same scale provided to the patient as part of the clinical study. 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 tenth kg if reported with a digital scale, or half Kg with a mechanical scale.
4. 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.
5. [redacted]
6. All blood pressure (BP) and heart rate (HR) measurements are to be obtained in a 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 using the same methodology (automated or manual) throughout the study.
7. A single 12-lead ECG will be performed. If an ECG is not practical in a young patient, it may be replaced by a rhythm strip and HR and PR interval should be documented.
8. A daily question querying whether the patient completed their daily injection will be asked via electronic diary. Paper versions can be used, if required.
9. Safety laboratory tests will include CBC with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, CO2, albumin, total protein, glucose, BUN, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), creatine phosphokinase (CPK), alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), calcium, phosphorus), thyroid-stimulating hormone (TSH) and urinalysis with microscopic analysis if positive findings on dipsticks warrant further examination. If there is a marginal value close to the exclusion range, it is suggested to repeat the laboratory analyses at Investigator's discretion. To allow for pre- and post-dose sampling, patients will attend the site visit having fasted for an 8-hour time period without injecting the trial product. On the day of the site visit, dosing will be conducted on site. The Investigator's will adhere to the site-specific blood volume limits for safety laboratory and PK analyses to ensure minimal distress to the pediatric patients. Due to the age of the children, it may not be possible to collect all labs at every study visit. Screening may be performed over multiple days, to complete the required assessments. After enrollment, if all lab tests are not possible, then the tests should be collected in the following descending order of priority: safety, anti-drug antibodies, trough PK, hemoglobin A1c and then lipid panel. If it is not possible to collect the safety labs on two consecutive visits, the patient should be discussed with the Sponsor. If the geneticsample cannot be collected at the enrollment visit, it may be collected during a later study visit. Anti-drug antibody samples are to be collected prior to dosing with setmelanotide. If PK profile cannot be obtained due to logistical challenges, the Investigator should aim to at least obtain sample trough PK.
10. [redacted]
11. [redacted]

12. [redacted]
13. [redacted]
14. Based on the age and status of the patient, optional nutritional counseling may be requested by the Investigator, either during the enrollment visit or at any other timeduring the study. For pediatric patients, nutritional counseling will be performed by an appropriate dietician or nutritionist (or equivalent) to ensure that pediatric patients have adequate nutritional intake to maintain proper growth and development.
15. Bone age may be read locally initially, but the Sponsor may request central reading of images. A standard bone age measurement (of the hand/wrist area) will be obtained at the beginning and the end of the study to monitor for growth related safety concerns.
16. The ASQ-3 is intended for use at six-month intervals between 6 months and 3 years of age, and then at one-year intervals through age 5. Thus, for patients who enter the study at ages between 2 years and 3 years, the ASQ-3 should be administered at the Baseline Visit, Week 28 visit and End-of-Treatment Visit. For patients who enter the study between the ages of 3 and 6 years old, the ASQ-3 should only be administered at the Baseline Visit and End-of-Treatment Visit.
17. The dose may continue to be evaluated and adjusted, at the discretion of the Investigator, in 0.5 mg increments, so long as the daily dose is kept between 0.5 mg and the weight-based maximum for the patient (see Table 3)

[redacted]

16.2 Changes in Analysis Planned in the Protocol

Changes in Analysis Planned in the Protocol

CSP Section	SAP section	Description/Rationale of Change

16.3 Change History

The table below outlines the changes made to the SAP since the previous version.

[redacted]