Rhythm Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

Protocol Number RM-493-030 (9 September 2021)

IND# [redacted]

A Phase 2, Open-Label 20-Week Study to Evaluate the Safety and Efficacy of Setmelanotide in Subjects with Hypothalamic Obesity

Rhythm Pharmaceuticals, Inc.
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Version 2.0
26 May 2022

[redacted]

Confidential

APPROVAL SIGNATURE PAGE

Protocol Title: A Phase 2, Open-Label 20-Week Study to Evaluate the Safety and Efficacy of Setmelanotide in Subjects with Hypothalamic Obesity

Sponsor: Rhythm Pharmaceuticals, Inc.
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Protocol Number: RM-493-030

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Author
03 June 2022 8:13 AM -04:00

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:

[redacted]

Signature: [redacted] Digitally signed by [redacted]
Date: 2022.06.03 09:43:57 -04'00'

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1 List of Abbreviations and Definition of Terms

Abbreviation	Description
AE	Adverse Event
ATC-3	Anatomical Therapeutic Chemical 3rd level
ATC-4	Anatomical Therapeutic Chemical 4th level
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
C-SSRS	Columbia-Suicide Severity Rating Scale
DAO	Data as Observed
DXA	Dual-Energy X-Ray
ECG	Electrocardiogram
EOS	End of Study
EQ-5D	EuroQol-Five Dimension
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FCS	Fully Conditional Specification
HO	Hypothalamic Obesity
HR	Heart Rate
ICH	International Conference on Harmonization
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite-Clinical Trials
LOCF	Last Observation Carried Forward
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NCS	Non-clinically Significant
OC	Observed Counts
PHQ	Patient Health Questionnaire
PP	Per-Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneously
SD	Standard Deviation
SF	Short Form

Abbreviation	Description
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-493-030, *A Phase 2, Open-Label 20-Week Study to Evaluate the Safety and Efficacy of Setmelanotide in Patients with Hypothalamic Obesity* and is based on the study protocol Version 2.0 dated 9 September 2021 and study Electronic Case Report Forms (eCRFs) Version 1.0 dated 18 March 2021.

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 change in body weight in response to setmelanotide administered subcutaneously (SC) daily in patients with Hypothalamic Obesity (HO).

3.1.2 Secondary Objective(s)

The secondary objectives of this study are to evaluate changes in parameters of body weight, body mass index (BMI), waist circumference, and hunger in response to setmelanotide in patients with HO and to evaluate the safety and tolerability of setmelanotide in patients with HO.

[redacted]

3.2 Overall Design

This is a Phase 2, multi-center, open-label, proof of concept study designed to assess the effect of setmelanotide on weight loss on a population affected by HO. Approximately 15 patients aged 6 to 40 years, inclusive, are planned to be enrolled across approximately 3-5 clinical sites in the United States.

Patients will first enter the Screening Period, during which they will be assessed for eligibility and complete all screening procedures as described in the Schedule of Activities (SoA) (Section 16.1). Individuals who do not meet the criteria for participation in this study (screen failure) may be eligible for rescreening at a later date, depending on the reason for the initial screen failure and provided enrollment is still open. If a patient is approved for rescreening by the Sponsor, the rescreened patient should be assigned the same Screening number as for the initial screening. Up to 3 screenings per patient are allowed (2 screening failures).

Patients who are determined to be eligible, based on screening assessments, will return to the clinic for the Baseline Visit (Visit 2) and receive their first setmelanotide dose. Patients will return to the study center for Visits 3, 4, and 5 (Weeks 4, 8, and 12, respectively), with each of these visits conducted approximately 4 weeks apart. All patients will return to the study center at Week 16 (Visit 6) and receive the last setmelanotide injection. After completion of Visit 6, participation in the current study will then conclude in one of the following 2 ways:

1. Patients meeting the primary endpoint meeting may be eligible to be enrolled in a separate extension study, Rhythm Study RM-493-022, under which auspices the patient will continue to receive setmelanotide.

2. Patients who do not meet the primary endpoint or elect not to continue setmelanotide are to discontinue setmelanotide at Visit 6 and return for an End-of-Study Visit (Visit 7) 4 weeks thereafter for a final safety review under the auspices of the current study.

3.2.1 Study Patients

The study is planned to enroll ~15 patients affected by HO, with ~5-10 patients aged >12 years, and up to 10 patients between 6 and 12 years.

3.3 Treatments and Assignment to Treatments

All patients will receive setmelanotide in this study. The starting setmelanotide dose is dependent on patient age at the time of Visit 2 (Day 1); however, for all patients, the setmelanotide dose will be titrated to a final dose of 3.0 mg/day (initial titration phase), as follows:

Patients aged 6 to <16 years, inclusive

• Starting at Baseline (Day 1; Visit 2) through approximately Day 14, patients will receive setmelanotide 1.0 mg/day.

• Starting at approximately Day 15 through 28, patients will receive setmelanotide 2.0 mg/day.

• Starting on approximately Day 29 (Visit 3), patients will receive setmelanotide 3.0 mg/day; patients will continue to receive setmelanotide 3.0 mg/day for 12 weeks.

Patients aged ≥16 years, inclusive

• Starting at Baseline (Day 1; Visit 2) through approximately Day 14, patients will receive setmelanotide 2.0 mg/day.

• Starting at approximately Day 15, patients will receive setmelanotide 3.0 mg/day; patients will continue to receive setmelanotide 3.0 mg/day for 14 weeks.

3.4 Determination of Sample Size

The objective of this study is to evaluate safety and preliminary efficacy on weight loss in patients with HO. The primary endpoint is the proportion of patients who achieve at least 5% BMI reduction from baseline at ~16 weeks of treatment with setmelanotide. Given the exploratory nature of the study, the sample size is primarily driven by clinical considerations, with the considerations of statistical testing. It is planned to enroll ~5-10 patients aged >12 years, and up to 10 patients between 6 and 12 years. With 10 patients aged >12 years and up to 10 patients aged 6 to 12 years, at 1-sided 0.05 significance level, the study provides ~90% power to reject the null hypothesis that the true response rate is less than historical control rate of 5%, assuming a 40% target response rate in setmelanotide.

3.5 Patient Assessments

3.5.1 Vital Signs

Vitals signs include:

- Height (cm)
- Weight (kg)
- Waist circumference (cm)
- Temperature (C)
- Heart Rate (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. Patients 18 years or older will only have height measured at screening. Height, weight, heart rate, 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 Body Composition

Patients will have body composition measurements performed by dual-energy X-ray absorptiometry (DXA) at baseline and Visit 6. The following measures will be obtained by DXA scan:

- Total fat mass (g or kg)
- Lean muscle (g or kg)
- Total body mass (g or kg)

- Total body bone mineral density (g, kg, g/cm^2, or kg/m^2)
- Android/gynoid fat ratio

For the purpose of analysis, all applicable body composition measurements will be standardized to the unit of kilograms, or kg/m^2 for total body bone mineral density, using the following formula:

$$Kg = \frac{g}{1000}$$

3.5.3 Physical & Skin Examination

A complete physical examination will be conducted at Visit 1 and at Visit 7. At other visits, an abbreviated examination will be performed. 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. Additionally, changes in sexual function, for both males and females, will be assessed at each visit. Changes in male sexual function include:

- Change in:
    - Erections
        - Ability to achieve
        - Ability to maintain
        - Change in frequency
        - Change in timing
        - Other
    - Ejaculations
        - Early occurring
        - Difficulty
        - Pain
        - Other
    - Sex drive
        - Increased
        - Decreased
    - Other
- If change is still occurring (Yes, No)

Changes in female sexual function include:

- Change in:

  - Vagina engorgement
  - Clitoral sensitivity
  - Sex drive
  - Other
- If change is still occurring (Yes, No)
- If change is:
  - Sexual
  - Non-sexual
  - Painful

For patients that have not reached Tanner Stage V, Tanner staging (Stage I, Stage II, Stage III, Stage IV, Stage V, and Not Applicable) for assessment of pubertal development will also be conducted at each visit.

A comprehensive skin examination will also be performed at Visit 1 and Visit 6. 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.

3.5.4 Electrocardiogram (ECG)

A single 12-lead ECG recording will be done at: Visit 1, Visit 2 (before and after treatment), Visit 3 and Visit 6. The following items will be measured:

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

3.5.5 Clinical Laboratory Tests

Hematology, clinical chemistry, and urine analysis laboratory tests will be performed at every visit. HbA1c is only collected at Visit 1 and Visit 6; [redacted] is only performed at Visits 2, 6, and 7. At each applicable visit, the laboratory tests will be collected prior to study treatment.

3.5.6 Injection Site Examination

At each visit where study treatment is administered (every visit starting at Visit 2) 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)

3.5.7 Global Hunger Questionnaire

[redacted]. Depending on the age of the patient, 1 of 2 versions of the Global Hunger Questionnaire will be administered. For patients less than 12 years of age, the patient's parent/caregiver will complete the questionnaire; for patients 12 years of age or older, the patient will complete the questionnaire themselves.

The Global Hunger Questionnaire will be performed at every visit starting at Visit 2 and will be completed prior to study treatment administration.

3.5.8 Daily Hunger Questionnaire

[redacted]

The Daily Hunger Questionnaire is a questionnaire that will be completed every day, starting at Visit 1, used to assess patient's own hunger. The questionnaire will be completed prior to the morning meal and prior to study treatment each day in the morning.

3.5.9 Impact of Weight on Quality of Life-Lite Clinical Trials (IWQOL-Lite-CT)

The IWQOL-Lite-CT is a validated 20-item self-report measure of obesity-specific quality of life questionnaire. The IWQOL-Lite-CT yields a Total score and 3 composite scores: Physical (7 items), Physical Function (5 items) and Psychosocial (13 items). Each item has 5 possible scaled responses: 1 – Never/Not at all true; 2 – Rarely/A little true; 3 – Sometimes/Moderately true; 4 – Usually/Mostly true; 5 – Always/Completely true,

where lower item scores indicate higher levels of functioning. Only patients 18 years of age or older will complete the IWQOL-Lite-CT. Patients will complete the IWQOL-Lite-CT at: Visits 1, 2, 3, and 6. For each post-baseline visit, the IWQOL-Lite-CT will be completed prior to study treatment administration.

Scoring Methods

- Physical Score: Includes Items 1-5, 16, 17
- Physical Function Score: Includes Items 1-3, 16, 17
- Psychosocial Score: Includes Items 6-15, 18-20
- Total Score: Includes all Items (1-20)

For each score listed above, if the minimum number of items is answered for a composite (see below), the non-missing item responses are averaged to compute the raw composite score. The composite score is then calculated by transforming the raw composite score to the 0 (worst)-to-100 (best) metric using the following formula for every patient at each time point:

$$100\ (5 - C_{avg})/4.$$

where:
C_{avg} is the raw average score of all non-missing item responses in the composite; this average must be a number between 1 and 5, inclusive.

Missing data rules

The 3 composite scores can be computed if a minimum of 50% of the items for each composite are non-missing. The total score requires 75% of all items to be non-missing. This equates to the following:

- Physical: 4 of 7 items non-missing
- Physical function: 3 of 5 items non-missing
- Psychosocial: 7 of 13 items non-missing
- Total: 15 of 20 items non-missing

3.5.10 Patient Health Questionnaire (PHQ)

There are 2 versions of the Patient Health Questionnaire used depending on the age of the patient. Patients age 6 – 10 will not complete any version of the PHQ; patients 11-17 years of age will complete the PHQ-A; patients 18 years of age or older will complete the PHQ-9.

The PHQ-9 is a 9-item depression scale of the Patient Health Questionnaire. The PHQ-9 is a tool for assisting clinicians in diagnosing depression as well as selecting and

monitoring treatment. The PHQ-9 yields a Total Score and consists of 10 items. Each item has 4 possible scaled responses. The PHQ-A is a modification of the PHQ-9 for adolescents. The PHQ-A also yields a Total Score and consists of 13 items. Each item has 4 possible scaled responses (Kroenke et al., 2001).

Patients will complete the PHQ-9/PHQ-A at every study visit. For each post-baseline visit, the PHQ-9/PHQ-A will be completed prior to study treatment administration.

Scoring Methods

- PHQ-9 Total Score: Calculated as the sum of: PHQ1 – PHQ9 (9 items). A higher total score indicates higher risk of depression.
- PHQ-A Total Score: Calculated as the sum of: PHQA1 – PHQA9 (9 items). A higher total score indicates higher risk of depression.

3.5.11 Columbia-Suicide Severity Rating Scale (C-SSRS)

There are 2 types of the C-SSRS used depending on the age of the patient. Patients age 6 – 11 will complete the Children C-SSRS type; patients 11 years of age and older will complete the Adult C-SSRS type.

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. All patients will complete 2 versions of the C-SSRS throughout the study:

1. The Baseline/Screening version of the scale combines the Baseline and Screening forms to assess suicidality in a patient's lifetime and during a predefined time. This version can assess a patient's lifetime suicidality for data collection purposes.

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 one initial C-SSRS assessment and should be used in every subsequent (post-baseline) visit. The 'Since Last Visit' version of the C-SSRS is asking about any suicidal thoughts or behaviors the patient/participant may have had since the last time the C-SSRS was administered.

Patients will complete the C-SSRS at every study visit. For each post-baseline visit, the C-SSRS will be completed prior to study treatment administration.

3.5.12 Short Form (SF)

There are 2 versions of the Short Form Questionnaire used depending on the age of the patient. Patients less than 18 years of age will not complete the SF-10; rather their parent/caregiver will complete the questionnaire; patients 18 years of age or older will complete the SF-12.

The SF-12 is a self-reported outcome measure assessing the impact of health on an individual's everyday life that is often used as a quality of life measure. It is a 12-item shortened form of the 36-item SF-36 that can be completed either by the patient or through interview. The SF-10 is a modified 10-item questionnaire that is to be completed by caregivers rather than the patient. The scoring method yields two summary measures: a physical summary score and a psychosocial summary score.

Patients/caregivers will complete the SF-12/SF-10 at Visits 1, 2, 3, and 6. For each post-baseline visit, the SF-10/SF-12 will be completed prior to study treatment administration.

The SF-10 and SF-12 summary scores will be calculated following the manuals for the handling of the data (scoring, transformations, missing values, etc.).

3.5.13 EuroQol- Five Dimension (EQ-5D)

There are 2 versions of the EQ-5D used depending on the age of the patient. Patients between 6 and 8 years of age will not complete any version of the EQ-5D; patients 8 -16 years of age will complete the EQ-5D-Y; patients 16 years of age or older will complete the EQ-5D-5L.

The EQ-5D-Y is a standardized instrument to measure health-related quality of life that can be used in a wide range of health conditions and treatments. It is the child-friendly version of the EQ-5D. The EQ-5D-Y consists of a descriptive system and the EQ VAS. The EQ-5D-Y descriptive system comprises the following five dimensions: mobility, looking after myself, doing usual activities, having pain or discomfort and feeling worried, sad or unhappy. Each dimension is rated on a 3-point response scale indicating: 1 - no problems, 2 - some problems, and 3 - a lot of problems. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale where the endpoints are labelled "The best health you can imagine" and "The worst health you can imagine". The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgement (EuroQol, 2021).

The EQ-5D-5L is a standardized measure of health status comprised of a descriptive system including five health-related quality of life states (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a VAS of overall health. Each dimension is rated on a 5-point response scale indicating severity of problems, where 1 is "no problems" and 5 is "extreme problems". The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement (EuroQol, 2021).

Patients will complete the EQ-5D-Y/EQ-5D-5L at Visits 1, 2, 3, and 6. For each post-baseline visit, the EQ-5D-Y/EQ-5D-5L will be completed prior to study treatment administration.

4 General Analysis Conventions

All tables, listings, and figures will be programmed using SAS Version 9.4 or higher. Data collected in this study will be documented using summary tables and patient data listings created by using the SAS® system. Confidence intervals (CI) will be performed at a significance level of 5%, unless otherwise specified. 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.

Adverse events, 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 Baseline Visit (Visit 2). Can range between 56 – 14 days prior to Visit 2.
- Treatment Period - From the Baseline Visit (Visit 2) to End of Study (Visit 7, or date of withdrawal).

Of note, patients that receive the last planned setmelanotide dose at Week 16 (Visit 6) and meet the primary endpoint, can elect to enroll in a separate extension study, Rhythm Study RM-493-022, under which auspices the patient will continue to receive setmelanotide.

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.

Table 1 Analysis Visit Windows

Analysis Visit	Target Study Day	Analysis Visit Window
(Intentionally left blank)	-56 - -1	<1*
Baseline	1	1
Week 4	29	2 - 43
Week 8	57	44 – 71
Week 12	85	72 – 99
Week 16	113	100 - 127
Week 20	141	≥ 128

*The exception to this windowing is the height assessment completed prior to Baseline, as height assessments are not completed at Baseline visit. Visit 1 height assessments should be included in the Baseline analysis visit window.

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 rules 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 rules will be applied for determining the values to be used for the summaries and analyses in tables:

- Safety assessments, excluding clinical laboratory tests: the scheduled visit will be used over any unscheduled visits conducted within window; otherwise, the assessment taken closest to the target study day will be used for the summaries and analyses
- 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 (Visit 1),

Unscheduled visits conducted prior to study treatment, and pre-treatment assessments done at the Baseline visit (Visit 2).

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 Full Analysis Set Population

The Full Analysis Set (FAS) population will include all patients who received at least 1 dose of setmelanotide and have baseline data.

5.2 Per-Protocol Population

The Per-Protocol Set (PP) population will include all patients in FAS without any major protocol violations that will result in exclusion of the patients from the analysis.

5.3 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 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 FAS population
- Number of patients in the PP population
- 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 for the number of patients enrolled will be based on the number of patients screened; all other percentages will be based on the number of patients enrolled. 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. Depending on the seriousness of the deviation, the patient might be excluded from the PP analysis. For this study, the protocol deviations that will exclude patients from PP are identified (but not limited to) in Table 2 below.

Table 2 Protocol deviations

Deviation
Any patient that does not have a body weight measurement at the primary endpoint visit (Visit 6)
Any patient that does not have an available screening or baseline body weight measurement
Any enrolled patient that reports an eligibility-related protocol deviation.
Any patient with prohibited concomitant treatments/procedures prior to Visit 6 considered to have a substantial impact on the primary efficacy outcome.
Any patient with a prohibited medical history, unstable medical history condition, or medical history condition that worsens prior to Visit 6 considered to have a substantial impact on the primary efficacy outcome.

All protocol deviations will be presented by patient in a data listing. Patients who are excluded from the PP population will also be presented in a data listing, along with their reason(s) for exclusion. Protocol deviation listings will be reviewed, and each patient will be classified as belonging to the per-protocol set or not. Exclusions from the per-protocol set will be identified and documented prior to database lock.

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 Characteristics

Demographic assessments for this study include:

- Age (years)
- Age categories
- Gender
- Ethnicity
- Race
- Weight at Baseline (kg)
- Height at Baseline (cm)
- Body Mass Index at Baseline (kg/m^2)
- Waist Circumference at Baseline (cm)

Baseline FST Patient demographic data will be summarized for the FAS population. Age will be analyzed as a continuous variable. Age categories, gender, ethnicity, race, and baseline FST will be analyzed as categorical variables.

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

8.2 Medical History

All summaries will be done based on the FAS population. 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). System organ class 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).

8.3 Concomitant Procedures

All summaries will be done based on the FAS population. 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

All summaries will be done based on the FAS population. 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 Body Composition

Dual-energy X-ray absorptiometry measurements (described in Section 3.5.2) at baseline, Visit 6, and the changes from baseline to Visit 6 will be summarized using descriptive statistics.

A data listing will be created to present all DXA assessments. The listing will show the assessment date, DXA assessment, indicator measurement was not done (if applicable), measurement value, and the change from baseline.

8.6 Physical and Skin Examination

Changes in sexual function (described in Section 3.5.3) will be summarized by visit, separately for males and females, using descriptive statistics. The number of patients that experienced a change in sexual function will also be summarized. Skin examination results (described in Section 3.5.3) at Visit 1 and Visit 6 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.

Physical and skin 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). A listing displaying the details of the changes in sexual function, duration of change, and frequency of changes will be created, separately for males and females. 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.

9 Efficacy Analysis

The primary efficacy analysis will be analyzed based on the FAS population. A supportive analysis based on PP will be performed as needed. All secondary efficacy and exploratory efficacy endpoints will be analyzed based on the FAS population, unless otherwise specified below.

9.1 Primary Efficacy Endpoint

The primary endpoint is defined as the proportion of patients who achieve at least 5% BMI reduction from baseline, at ~16 weeks of treatment with setmelanotide. BMI will be calculated using patient's weight and height assessments, using the following formula:

$$BMI = \frac{kg}{m^2}$$

If needed, weight and height will first be converted into kilograms and meters, respectively. Given that body weight is collected in triplicates at each visit, weight (kg) will first be aggregated into one averaged weight per visit. Visits will then be compared against the analysis visit window (described in Section 4.2) to select the Week 16 averaged weight prior to calculating BMI and change in BMI. Patients who are ≥ 18 years of age will only have height measurement done at screening; the averaged triplicate

screening height will be used for the height component of the BMI calculation at each visit. Patients who are < 18 years of age will have their height measured in triplicates at most study visits. As with body weight, height will first be aggregated into one averaged height per visit and compared against the analysis visit window to select the Week 16 averaged height. Regardless of reason, if height is missing for an analysis visit, then height will be imputed using last observation carried forward (LOCF). Change (Δ) in BMI (%) from baseline at 16 weeks of treatment will be calculated as follows:

$$\Delta\ BMI\ (\%) = \left(\frac{Week\ 16\ BMI - Baseline\ BMI}{Baseline\ BMI}\right) * 100$$

An indicator variable will then be created to identify patients that have a decrease in BMI from baseline to Week 16 of 5% or more, allowing for the analysis of proportion of patients who achieve at least 5% BMI reduction.

The primary endpoint will be assessed using an exact binomial test at a 1-sided 0.05 significant level, compared to the null hypothesis proportion of 0.05 (which comes from a historical control rate of 5%). The number of and the binomial proportion of patients who achieve at least 5% BMI reduction from baseline at 16 weeks, the corresponding 2-sided 90% CI, and one-sided binomial test p-value will be presented. The Clopper-Pearson method will be used to calculate the CI. A scatter plot figure will also be created plotting each patient's percent BMI reduction from baseline to Week 16.

The primary analysis will be repeated on the FAS population using LOCF as the primary imputation method, further described in Section 11.1.

9.1.1 Sensitivity Analysis of Primary Endpoint

To assess the robustness of the primary efficacy results, the following additional sensitivity analyses will be conducted:

- Analysis of proportion of patients who achieve at least 5% BMI reduction from baseline, at ~16 weeks of treatment with setmelanotide will be repeated on the PP population, as needed.

9.2 Secondary Efficacy Endpoints

All secondary efficacy endpoints will be analyzed using the FAS population and using data as observed (DAO). In addition, all key secondary efficacy endpoints will impute missing data using LOCF (detailed in Section 11.1)

9.2.1 Composite Reduction in BMI Z-score and Change in Body Weight

One key secondary endpoint is the proportion of patients, aged ≥ 6 to < 18 years, with ≥ 0.2 reduction of BMI z-score along with the proportion of patients aged ≥ 18 years with 5% reduction of body weight from baseline after 16 weeks of setmelanotide treatment.

Body mass index z-score is a measure of relative weight adjusted for child age and sex. Given a child's age, sex, BMI, and an appropriate reference standard, a BMI z-score can be determined. Body mass index z-scores are calculated relative to an external reference (whether national or international), and to ensure alignment with global data, the WHO 2007 reference standard growth card will be used to calculate a patient's BMI z-score for this study (Must et al., 2006). By comparing a patient's BMI at a given visit to the standard WHO 2007 reference BMI for the patient's corresponding age and sex, a BMI z-score can be calculated (WHO, 2021). After a patient's BMI z-score is calculated for each visit, change in BMI z-score at each visit will be calculated using the formula specified in Section 4.3. Patients aged ≥6 to < 18 years with a decrease in BMI z-score from baseline to Week 16 of 0.2 or more will then be identified.

Given that body weight is collected in triplicates at each visit, weight will first be aggregated into one averaged weight per visit. Visits will then be compared against the analysis visit window (described in Section 4.2) to select the Week 16 averaged weight prior to calculating change in body weight. Change (Δ) in body weight (%), in kg, from baseline at 16 weeks of treatment will be calculated as follows:

$$\Delta\ Weight\ (\%) = \left(\frac{Week\ 16\ Weight - Baseline\ Weight}{Baseline\ Weight}\right) * 100$$

Patients aged ≥ 18 years that have a decrease in body weight from baseline to Week 16 of 5% or more will then be identified.

An indicator variable will then be created to identify both patients aged ≥ 6 to <18 years with a decrease in BMI z-score from baseline to Week 16 of 0.2 or more and patients aged ≥ 18 years that have a decrease in body weight from baseline to Week 16 of 5% or more, allowing for the analysis of the composite proportion of patients. The number of and the proportion of patients aged ≥ 6 to < 18 years with ≥ 0.2 reduction of BMI z-score and patients aged ≥18 years with 5% reduction of body weight from baseline after 16 weeks of setmelanotide treatment will be presented.

9.2.2 Reduction in BMI Z-score for Patients aged ≥ 6 to < 18 years

Another key secondary endpoint is the proportion of patients aged ≥ 6 to < 18 years with ≥ 0.2 reduction of BMI z-score from baseline after 16 weeks of setmelanotide treatment. BMI z-score and change from baseline in BMI z-score will be calculated following methods described in Section 9.2.1. The number of and the proportion of patients aged ≥ 6 to < 18 years with ≥ 0.2 reduction of BMI z-score from baseline after 16 weeks of setmelanotide treatment will be presented.

Patients' BMI z-score at each visit, and change from baseline will be presented in a data listing.

9.2.3 Reduction of Body Weight for Patients aged ≥18 years

The last key secondary endpoint is the proportion of patients aged ≥ 18 years with ≥ 5% reduction of body weight from baseline after 16 weeks of setmelanotide treatment. Body weight reduction will be calculated following methods described in Section 9.2.1. The number of and the proportion of patients aged ≥ 18 years with ≥ 5% reduction of body weight from baseline after 16 weeks of setmelanotide treatment will be presented.

Patients' body weight at each visit, including the individual measurements as well as the aggregate, and change from baseline will be presented in a data listing.

9.2.4 Change in Waist Circumference

The change from baseline in waist circumference (cm) in patients aged ≥ 18 years after 16 weeks of setmelanotide treatment will be summarized by descriptive statistics. Given that waist circumference is collected in triplicates at each visit, waist circumference will first be aggregated into one averaged waist circumference per visit. Visits will then be compared against the analysis visit window (described in Section 4.2) to select the Week 16 averaged waist circumference prior to calculating change in waist circumference. For patients aged ≥ 18 years, the change in waist circumference (cm) from baseline after 16 weeks of treatment will be calculated using the formula specified in Section 4.3. In addition to change from baseline in waist circumference, percent change from baseline will be presented at the Week 16 visit. Percent change from baseline will be calculated as follows

$$\Delta\ Waist\ Circumference\ (\%) = \left(\frac{Week\ 16\ Waist\ Circumference - Baseline\ Waist\ Circumference}{Baseline\ Waist\ Circumference}\right) * 100$$

Patients' waist circumference at each visit, including the individual measurements as well as the aggregate, change from baseline, and percent change from baseline will be presented in a data listing.

9.2.5 Hunger Response

Hunger in response to 16 weeks of setmelanotide treatment will be measured by change from baseline in daily (described in Section 3.5.8) and global hunger scores (described in Section 3.5.7) in obese patients with hypothalamic injury. Hunger response will be performed using DAO that is, no imputation will be done.

During the screening period, the patient must complete the daily hunger questionnaire in the electronic diary at least 4 of the 7 days prior to the day of first study drug administration. As such, for each daily hunger questionnaire item(s), Baseline daily hunger score(s) will be calculated as the average of these 7 days prior to the day of first study drug administration. In addition, for the purpose of analysis, the daily hunger score(s) will be averaged on a weekly basis. For each daily hunger questionnaire item(s), the average of the diary entries specified in Table 3 will be averaged together to create a weekly diary item average. If the Baseline study week cannot be computed using the

diary days specified in Table 3, then Diary Day 1 will be used for Baseline score, and then study Week 1 will only include diary days 2 – 7.

Table 3 Daily Hunger Questionnaire Weekly Grouping

Diary Days	Study Week
-7 to -1*	Baseline
1 to 7*	Week 1
8 to 14	Week 2
15 to 21	Week 3
22 to 28	Week 4
29 to 35	Week 5
36 to 42	Week 6
43 to 49	Week 7
50 to 56	Week 8
57 to 62	Week 9
63 to 70	Week 10
71 to 77	Week 11
78 to 84	Week 12
85 to 91	Week 13
92 to 98	Week 14
99 to 105	Week 15
106 to 112	Week 16
113 to 119	Week 17
120 to 126	Week 18
127 to 132	Week 19
133 to End of Study	Week 20

*If Baseline study week cannot be computed as specified in the table, then Diary Day 1 will be used for Baseline score; study Week 1 will then only include diary days 2 – 7.

To assess daily hunger, the weekly averaged questionnaire items, change from baseline, and percent change from baseline for the weekly averaged questionnaire item(s) will be presented descriptively at Baseline and Week 16 . The weekly averaged individual responses will be presented in frequency tables, whereas the change from baseline and percent change from baseline will be presented using descriptive statistics. Daily hunger results will be stratified by age (< 12 years of age and ≥ 12 years of age) given that patients under the age 12 are given a different questionnaire version.

To assess global hunger, a shift table of the first questionnaire item will be created to present any change from baseline in item 1 response To 16 weeks of treatment. The table will show the number and percentage of patients who had values that shifted from baseline item 1 response to Week 16 item 1 response. 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. Global hunger results will be stratified by age (< 12 years of age and ≥ 12 years of age) given that patients under the age 12 are given a different questionnaire version.

Daily and global hunger will be presented by patient in data listings. The listings will include study visit and/or study day, item responses, and change from baseline.

[redacted]

[redacted].

9.3.1 Body Weight Loss

The proportion of patients (all ages) who achieve at least 5% body weight reduction from baseline, at ~16 weeks of treatment with setmelanotide will assessed following similar methods as for the primary endpoint. Given that body weight is collected in triplicates at each visit, weight will first be aggregated into one averaged weight per visit. Visits will then be compared against the analysis visit window (described in Section 4.2) to select the Week 16 averaged weight prior to calculating change in body weight. Change (Δ) in body weight (%), in kg, from baseline at 16 weeks of treatment will be calculated as follows:

$$\Delta\ Weight\ (\%) = \left(\frac{Week\ 16\ weight - Baseline\ weight)}{Baseline\ weight}\right) * 100$$

An indicator variable will then be created to identify all patients that have a decrease in body weight from baseline to Week 16 of 5% or more, allowing for the analysis of proportion of all patients who achieve at least 5% body weight reduction.

Proportion of all patients who achieve at least 5% body weight reduction will be assessed using an exact binomial test at a 1-sided 0.05 significant level, compared to the null hypothesis proportion of 0.05. The number of and the binomial proportion of all patients who achieve at least 5% body weight reduction from baseline at 16 weeks, the corresponding 2-sided 90% CI, and one-sided binomial test p-value will be presented. The Clopper-Pearson method will be used to calculate the CI.

9.3.2 Change in BMI, Weight, and Waist Circumference (all ages)

The change from baseline in BMI, body weight, and waist circumference in all patients after 16 weeks of setmelanotide treatment will be summarized by descriptive statistics. Calculations for change from baseline and percent change from baseline for all parameters will follow the same methods specified in Section 9.1 for BMI, Section 9.2.4 for waist circumference, and Section 9.2.1 for body weight.

Individual patient figures will be created for each weight-related parameter of interest (BMI, body weight, waist circumference) to present a patient's change over time

throughout the study; patient information, such as age, sex, baseline weight, and baseline BMI will also be presented in the figures. Change from baseline to each analysis visit for each parameter will be calculated following the same methods as for calculating the Week 16 change from baseline, as specified above in the respective sections.

9.3.3 BMI Z-Score

The change from baseline in BMI z-score in patients aged 6 to 12 years and in those aged 6 to < 18 years will be summarized, separately, by descriptive statistics at each visit. BMI z-score and change from baseline in BMI z-score will be calculated using the methods specified in Section 9.2.1.

Patients' BMI z-score at each visit and change from baseline will be presented in a data listing.

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)

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:

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

Patient compliance with study drug will be summarized descriptively in a table. The number of patients who experienced at least one dose interruptions 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 clinically significant, 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 Adverse Event (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. Adverse events, including SAEs, will be collected from the provision of informed consent until the End of Study (EOS) visit (Visit 7). 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 AE
- 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 AE (SAE)
- Patients with at least one serious TEAE (SAE) related to study drug
- Patients with at least one serious TEAE
- Patients with AE resulting in death on study
- Patients who did not have an AE

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:

- All TEAEs by MedDRA SOC and PT
- Treatment-emergent SAE 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. System organ class 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

Treatment-emergent AEs will also be summarized by 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

Treatment-emergent AEs 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).

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, serious adverse events, and adverse events 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 – Non-clinically Significant (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.

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

[redacted]

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 measurements (described in Section 3.5.4) at Visit 2 (pre and post-dose), Visit 3, Visit 6, 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 Other Safety Endpoints

10.7.1 IWQOL-Lite-CT

The four composite scores (described in Section 3.5.9), and change from baseline to 16 weeks of treatment in the four composite scores will be presented descriptively. The composite scores and change from baseline composite scores will be presented using mean, SD, minimum, maximum, and median statistics.

The IWQOL-Lite-CT will be presented by patient in data listings. The listings will include study visit and/or study day, the individual item responses, the four composite scores, and change from baseline for the four composite scores.

10.7.2 PHQ

The total score (described in Section 3.5.10) and change from baseline to 16 weeks of treatment in total score will be presented descriptively.The total score and change from baseline total score will be presented using mean, SD, minimum, maximum, and median statistics.

The PHQ will be presented by patient in data listings. The listings will include study visit and/or study day, the individual item responses, total score, and change from baseline for the total score.

10.7.3 C-SSRS

The individual questionnaire items (described in Section 3.5.11) will be presented descriptively at each visit. The individual responses will be presented in frequency tables. Additionally, a shift table of individual questionnaire items will be created to present any change from baseline in item responses across all post-baseline visits. The table will show the number and percentage of patients who had values that shifted from baseline item responses to each post-baseline visit item response. 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.

The C-SSRS will be presented by patient in data listings. The listings will include study visit and/or study day and item responses.

10.7.4 SF

The two summary scores (described in Section 3.5.12), and change from baseline to 16 weeks of treatment in the two summary scores will be presented descriptively. The

summary scores and change from baseline summary scores will be presented using mean, SD, minimum, maximum, and median statistics.

The SF will be presented by patient in data listings. The listings will include study visit and/or study day, the individual item responses, the two summary scores, and change from baseline for the two summary scores.

10.7.5 EQ-5D

The VAS (described in Section 3.5.13) and change from baseline to 16 weeks of treatment in the VAS score will be presented descriptively. The VAS score and change from baseline in VAS score will be presented using mean, SD, minimum, maximum, and median statistics.

The EQ-5D will be presented by patient in data listings. The listings will include study visit and/or study day, the individual item response, VAS, and change from baseline for the VAS score.

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. Calculations for all questionnaires will follow the methods specified in the specific sections of this SAP for the handling of the data.

For primary and key secondary analyses, missing data for Week 16 body weight and BMI will be imputed using LOCF. With the LOCF imputation method, if a patient is missing their Week 16 assessment, their last non-missing assessment will be used. Given that BMI will be calculated using patient's weight and height measurements, if height is missing for any analysis visit, height will be imputed using LOCF.

The primary analysis may be repeated using multiple imputation (MI) as a sensitivity analysis as needed. If performed, MI methods are specified in Section 16.5.

11.2 Handling of Missing/Partial Dates

While every effort will be made to obtain full, complete information on all data collected Table 4 outlines the imputation rules to be followed for any missing dates. Dates will be presented as collected in the listings.

Table 4 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
Adverse Event/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
Adverse Event/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

To evaluate the consistency of the results of the primary and secondary efficacy analysis across different subgroups of interest, the primary analysis specified above (Section 9.1) will be repeated, stratifying for each of the following subgroups specified below:

- Age (< 18 years, 18+ years)

Additionally, to evaluate the exploratory objectives of this study in patients of different age groups, body weight loss, change from baseline in BMI, weight, and waist circumference (described in Sections 9.3.2 and 9.3.3) will be stratified by:

- Age (6 - < 18 years, 18+ years)
- Pediatric age (6 - < 12 years, 12 – < 18 years)

12 Interim Analysis and Data Monitoring

There is no planned interim analysis 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). Advanced Clinical 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

EuroQol. (2021). *EQ-5D-5L | EQ-5D-5L User Guide*. EQ-5D. https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/.

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16 Appendices

16.1 Schedule of Assessments

Table 1: Schedule of Activities

Study Period/Procedure	Screening	Study Treatment						EOS Visit	Treatment Discontinuation Visit
Clinic Visit Number	V1	V2	-	V3 [1]	V4	V5	V6 [2]	V7 [2]	
Study Day	-56 to -14	1	15	29	57	85	113	141	
Visit Window (days)	-	-	+3d	± 4 d	± 4 d	± 4 d	± 4 d	± 4 d	± 4 d
Informed consent/assent [3]	X								
Inclusion/exclusion criteria review	X	X							
Medical history review	X								
Physical examination [4]	X	X		X	X	X	X	X	X
Comprehensive skin examination [5]	X						X		X
Fitzpatrick classification scale	X						X	X	X
Weight [6]	X	X		X	X	X	X	X	X
Waist circumference [7]	X	X		X	X	X	X	X	X
Height [8]	X			X	X	X	X	X	X
Body composition assessment by DXA [9]	X						X		X
Vital signs [10]	X	X		X	X	X	X	X	X
ECG (12-lead) [11]	X	X [11]		X [11]			X [11]		X
Pregnancy test [12]	X	X[13]		X	X[13]	X[13]	X[13]		X
Daily hunger questionnaires [14, 15]	X	Daily							X
Global hunger assessment [15]		X[13]		X[13]	X[13]	X[13]	X[13]	X	X
PHQ-A or PHQ-9 [16, 17]	X	X[13]		X[13]	X[13]	X[13]	X[13]	X	X
C-SSRS [18]	X	X[13]		X[13]	X[13]	X[13]	X[13]	X	X
SF-12 or SF-10 [19]	X	X[13]		X[13]			X[13]		X
IWQOL-Lite-CT [20]	X	X[13]		X[13]			X[13]		X

Study Period/Procedure	Screening	Study Treatment						EOS Visit	Treatment Discontinuation Visit
Clinic Visit Number	V1	V2	-	V3 [1]	V4	V5	V6 [2]	V7 [2]	
Study Day	-56 to -14	1	15	29	57	85	113	141	
Visit Window (days)	-	-	+3d	± 4 d	± 4 d	± 4 d	± 4 d	± 4 d	± 4 d
EQ-5D-5L or Y [21]	X	X[13]		X[13]			X[13]		X
Safety laboratory tests [22]	X	X		X[13]	X[13]	X[13]	X[13]	X	X
FSH*	X								
[redacted]									
Injection site inspection [24]		X		X	X	X	X		X
Telephone call [25]			X						
Review of type of lesion on MRI [26]	X								
Study drug administration [27]		Daily dosing							
Dispense/Return study drug [28]		X		X	X	X	X		
Adverse event assessment [29]	X	X	X	X	X	X	X	X	X
Concomitant medications review	X	X	X	X	X	X	X	X	X

D = Days; EOS = End of Study; PK = Pharmacokinetics; V = Study Visit Number.

1. Patients who are <16 years of age will receive first daily dose of 3.0 mg at V3, at the clinic.
2. Study endpoints are analyzed at V6. After completing V6. Patients meeting the primary endpoint may be eligible to be enrolled in a separate extension study, Rhythm Study RM-493-022, under which auspices the patient will continue to receive setmelanotide. Patients who do not meet the primary endpoint or elect not to continue setmelanotide are to discontinue setmelanotide at Visit 6 and return for an End-of-Study Visit (Visit 7) 4 weeks thereafter for a final safety review under the auspices of the current study.
3. Although the study procedures and assessments required per protocol are classified as "No or Minimal Risk" (with the exception of DXA which may be classified as "Minor Increase over 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 Appendix 2.
4. A complete physical examination will be conducted at Screening and at the EOS V7. At other time points, 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. In addition, Tanner Staging for assessment of pubertal development will be conducted for those patients who have yet to reach Tanner Stage V. Whenever possible, the same trained health care professional will conduct the exam and Tanner Staging.
5. A comprehensive skin examination will be performed by the Investigator. The skin examination should include a full body (head-to-toe skin examination). If any concerning lesions are identified during Screening, the patient should be referred to a dermatologist. Any concerning lesions will be biopsied by the dermatologist and results must be benign prior to the first dose of setmelanotide. If the pre-treatment biopsy results are of concern, the patient will be excluded from the study. Additionally, any concerning lesion or change in an existing lesion during the course of the study must be evaluated by the dermatologist and biopsied, if clinically indicated in the opinion of the dermatologist.
6. Weight (kg) is to be measured at the clinic using the same scale throughout the study, including the Screening Visit, after patients have emptied their bladders and pockets and after fasting for at least 8 hours. Patients are to wear light clothing or underwear and no shoes, and will be weighed at approximately the same time of day. Weight should be recorded to the nearest 10^{th} of a decimal place if reported by a digital scale or to the nearest half of a Kg if reported by a mechanical scale.
7. Waist circumference (cm) will be done 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. Patients should be standing and in light clothing and have emptied their bladder. Whenever possible, the same study staff member should perform the measurement for a given patient to minimize variability.
8. For patients ≥18 years of age, height needs to be measured at Screening only. 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 cm.
9. Body composition assessment will be performed using DXA. If DXA is not available at the clinic, this procedure may be skipped, with prior approval of the Sponsor.
10. All blood pressure (BP) and heart rate (HR) measurements are to be obtained with the patient in the sitting position following at least 5 minutes of rest. All measurements will be taken in triplicate, approximately 2 minutes apart. When possible, BP should be taken in the non-dominant arm throughout the study, using the same methodology (automated or manual). Body temperature (°C) and respiration rate (breaths/minute) will be obtained in the sitting position following at least 5 minutes of rest.
11. A single 12-lead ECG will be performed in the supine position following a period of at least 10 minutes of rest. At V2, the ECG will be performed before and 4 hours after dosing, and at V3 and V6, the ECG is to be performed at 4 hours after dosing.
12. A urine pregnancy test may be performed to expedite availability of results prior to dosing on Day 1. All other pregnancy tests will be serum tests; dosing may continue with results pending.
13. Collected prior to study drug administration.
14. Daily hunger questionnaire scores will be recorded prior to the patient's morning meal. During Screening, the patient must complete the daily hunger questionnaire in the electronic diary at least 4 of the 7 days prior to V2, paper version can be used if required. Patients who do not meet this requirement should not be enrolled into the study. V2 may be rescheduled if needed to fulfill this requirement with Sponsor approval.

[redacted]

16. In order to be eligible for the study, an individual patient's PHQ-A or PHQ-9 score must be <15 at Screening. If at any time during the study an individual patient's PHQ-A or PHQ-9 score is ≥10, the patient should be referred to a Mental Health Professional (MHP).
17. The PHQ-A will be administered to patients 11-17 years old and the PHQ-9 will be administered to patients ≥18.
18. In order to be eligible for the study, a patient at Screening cannot have a suicidal ideation of type 4 or 5, any lifetime history of a suicide attempt, or any suicidal behavior in the last month. If at any time during the study a patient has a suicidal ideation of type 4 or 5, or any suicidal behavior, the patient should be referred to an MHP.
19. The SF-12 will be administered to patients ≥18 years of age and the SF-10 will be administered to the parents/caregivers of patients <18 years of age.

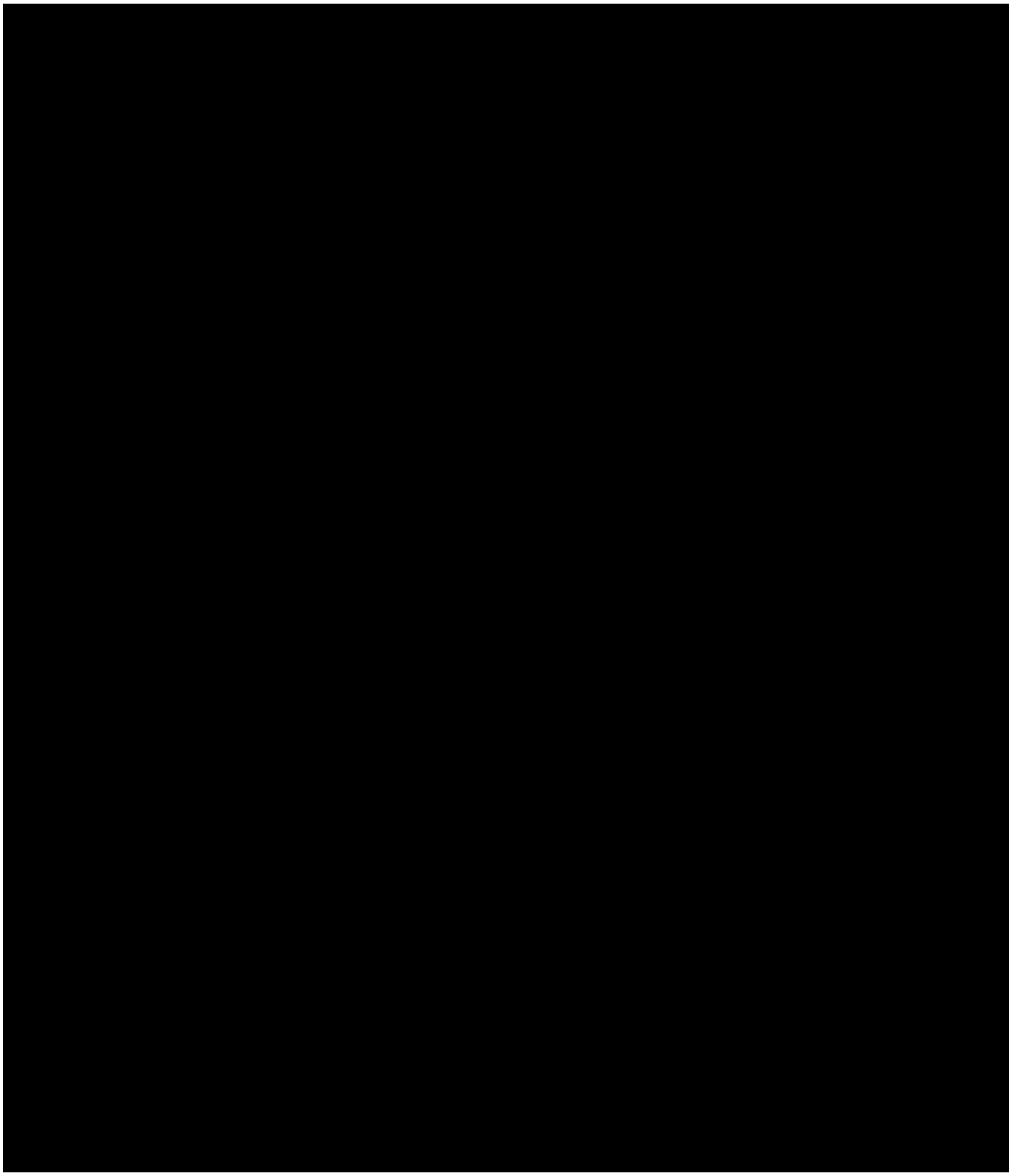
20. IWQOL-Lite-CT will be administered to patients ≥18 years of age.
21. The EQ-5D-5L will be administered to patients ≥16 years of age. The EQ-5D-Y will be administered to patients >8 up to <16 years of age. In patients under the age of 8 years of age will not complete the EQ-measures.
22. Safety laboratory tests will include: complete blood count with differential (platelet count, red blood cell [RBC] count, hemoglobin, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, basophils) and standard indices (mean corpuscular volume, mean corpuscular hemoglobin, %reticulocytes), chemistry panel (includes sodium, potassium, chloride, CO_2, albumin, total protein, glucose, BUN, creatinine, uric acid, AST, ALT, GGT, CPK, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, calcium, phosphorus), and urinalysis with microscopic analysis if positive findings on dipsticks warrant further examination.
23. Blood samples will be collected prior to dose administration in the fasting state for total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides.
24. Injection site evaluations and scoring (by the clinical staff) will include identification and measurement of areas of erythema, edema, and induration, as well as the presence of localized pain, tenderness, and itching. Additional evaluation data can be collected at any visit in which there are injection site reactions, even if not a time point for formal assessment.
25. Site personnel will call the patient on Day 15 to confirm the proper dose escalation has occurred and to collect AEs.
26. All patients must have evidence of hypothalamic injury on MRI completed within 8 months of Screening. If no MRI is available, then it may be repeated during the Screening Period.
27. Patients/caretakers will draw up and self-administer/administer the drug once daily in the morning beginning the morning of Day 1 and for the duration of dosing. On days with clinic visits, the patients/caretakers will administer the drug in the clinic in the presence of the clinical staff to assure proper technique.
28. Patients/caretakers will return all (the number recorded) used vials to the clinic when they visit, and both clinic-administered study drug as well as outpatient study drug administration will be recorded in a study diary.
29. AEs will be recorded from the time a patient provides informed consent. AEs reported after dosing on Day 1 will be considered TEAEs.

* FSH should be measured in women who have been post-menopausal >12 months and should be in post-menopausal range.

16.2 Changes in Analysis Planned in the Protocol

Table 5 Changes in Analysis Planned in the Protocol

CSP Section	SAP section	Description/Rationale of Change



16.5 Multiple Imputation Methods

As stated in Section 11.1, the MI procedure may be performed as needed as a sensitivity analysis. If performed, the following methods will be used:

Missing data for Week 16 will be imputed using MI under the Missing at Random (MAR) assumption. Change from baseline in BMI will be derived from the corresponding imputed values. The following steps will be followed to create the imputations:

1.1. Regardless of the actual pattern of missing data, the Markov Chain Monte Carlo (MCMC) method of the SAS PROC MI procedure will first be used to make it monotone. The single chain method will be used. The minimum values for imputed variables will be set to 0, in order to force PROC MI to redraw another value for imputation when an intended imputed value is less than the 0. Imputed values will be rounded to the nearest integer. The seed number will be set to 112595 and 5 imputations will be created.

1.2. The SAS PROC MI will be used for imputing missing values of data with monotone missing pattern. One imputation will be made using each of the 5 MCMC-imputed datasets. A linear regression model will be used with covariates for non-missing BMI from earlier scheduled time points including baseline as well as age. The minimum values for imputed variables will be set to 0, in order to force PROC MI to redraw another value for imputation when an intended imputed value is less than the 0. Imputed values will be rounded to the nearest integer. Change from baseline in BMI will be derived from the corresponding imputed values.

1.3. If the monotone pattern does not converge, the imputations will be created with an arbitrary missing data pattern. The seed number will still be set to 112595 and 5 imputed datasets will be created by fully conditional specification (FCS). One imputation will be made using each of the 5 imputed datasets. A linear regression model will be used with covariates for non-missing data from earlier scheduled time points including baseline as well as age. The minimum values for imputed variables will be set to 0, in order to force PROC MI to redraw another value for imputation when an intended imputed value is less than the 0. Imputed values will be rounded to the nearest integer. Change from baseline will be derived from the corresponding imputed values.

2. The imputed datasets will be analyzed as specified in the respective Section 9.

3. The resulting analysis on the imputed datasets will then be combined to produce a single set of statistics as follows.

3.1. For any binary outcome, the results from the exact binomial test will be combined to produce a pooled proportion, 95% CI, and p-value using the SAS PROC MIANALYZE procedure.

3.2. For any continuous outcome, the results from the ANCOVA analysis will be combined using SAS PROC MIANALYZE.