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Rhythm Pharmaceuticals, Inc.
Protocol #: RM-493-034

A 2-Stage (Open-Label Followed by Randomized Double-Blind, Placebo-Controlled Stage), Phase 2 Trial of Setmelanotide in Patients with Specific Gene Variants in the Melanocortin-4 Receptor Pathway

Statistical Analysis Plan

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ACMG	American College of Medical Genetics
AE	Adverse Event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CDI-2	Children's Depression Inventory-2
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
LP	Likely Pathogenic
MC4R	Melanocortin-4 Receptor
NCOA1	Nuclear Receptor Coactivator 1
P	Pathogenic
P/LP	Pathogenic, Likely Pathogenic
PCSK1	Proprotein Convertase Subtilisin/Kexin Type 1
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PHQ-9	Patient Health Questionnaire-9
PK	Pharmacokinetic
PP	Per-Protocol
QD	Once Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SH2B1	SRC Homology 2 B Adapter Protein 1
SOA	Schedule of Assessments
SRC1	Steroid Receptor Coactivator-1
TEAE	Treatment-Emergent Adverse Event
URO	Uncovering Rare Obesity
VUS	Variant of Uncertain Significance
VUS-SP	Variant of Uncertain Significance Suspected to be Pathogenic

I. Introduction

A. Background

The purpose of this Phase 2 trial is to evaluate the safety and efficacy of once daily (QD) subcutaneous (SC) administration of setmelanotide, a synthetic, cyclic octapeptide (8-amino acid-containing peptide) melanocortin-4 receptor (MC4R) agonist, in patients with obesity and specific gene variants in the MC4R pathway. This Statistical Analysis Plan (SAP) is based on version 2.0, 27JUL2022 of the Protocol RM-493-034.

II. Protocol Objectives and Study Endpoints

	Objectives	Endpoints
Primary	To evaluate the proportion of patients with obesity with genetic variants in a specific gene in the MC4R pathway who achieve a clinically meaningful reduction in body weight in response to setmelanotide at the end of open-label treatment	The proportion of patients by genotype who demonstrate a significant clinically meaningful response (defined below) to setmelanotide at the end of Stage 1(Week 16): – For all patients: achieving a ≥5% reduction in BMI from Baseline
Secondary	To evaluate change in weight parameters and hunger in response to setmelanotide in patients with genetic variants in a specific gene in the MC4R pathway at the end of open-label treatment	• Mean change and percent change in BMI from Baseline to end of Stage 1 in all patients and patients ≥18 years old, per gene cohort • Mean change and percent change in body weight from Baseline to end of Stage 1 in patients ≥18 years old, per gene cohort • Mean change in BMI Z-score from Baseline to end of Stage 1 in patients <18 years old, per gene cohort • Mean percent change in the weekly average of the daily maximal hunger score from Baseline to end of Stage 1 in patients ≥12 years old, per gene cohort • The proportion of patients ≥12 years old, per gene, who achieve a ≥2-point reduction (improvement) from Baseline to end of Stage 1 in the weekly average of the daily maximal hunger score
[redacted]	[redacted]	[redacted]

	Objectives	Endpoints
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

	Objectives	Endpoints
		[redacted]

	Objectives	Endpoints
Safety	To evaluate the safety and tolerability of setmelanotide in patients with genetic variants in the MC4R pathway	Safety and tolerability assessed by the frequency and severity of AEs, changes in vital signs, and changes in laboratory evaluations at the end of Stage 1 and Stage 2

A. Estimand

Attribute	Description
Treatment	Setmelanotide
Population	Patients between ages of 6 and 65 with Specific Gene Variants in the Melanocortin-4 Receptor Pathway
Endpoint	Achieving a ≥5% reduction in BMI from Baseline at the end of Stage 1
Intercurrent Events	For Discontinuation of randomized treatment or use of a rescue medication if any, Treatment policy strategy will be implemented.
Population-level Summary	Proportion of patients achieving a ≥5% reduction in BMI from Baseline at the end of Stage 1

III. Study Design

A. Design Overview

This is a 2-stage (open-label stage followed by a randomized double-blind, placebo-controlled stage) Phase 2 trial of setmelanotide in patients with obesity with specific gene variants in the MC4R pathway. Approximately 100 patients between the ages of 6 and 65 years, inclusive, are planned to be enrolled in Stage 2 of the trial with up to 200 patients enrolled in Stage 1 (open-label).

Stage 1 (Open Label)

Stage 1 of the trial begins with the Enrollment Visit (Study Day 1). During the Enrollment Visit, the patient will have their body weight recorded. This will be the patient's "Baseline Weight" during the Enrollment Visit. During Stage 1, the patient (or caregiver) will administer setmelanotide on a daily basis for 16 weeks. During this period, the patient will have in-person as well as virtual visits using a validated Telehealth platform with the trial center.

To be eligible to enter Stage 2 of the trial, a patient

- ≥18 years old must have achieved a body mass index (BMI) at least 3% less than the Baseline BMI at the end of Stage 1
- <18 years old must have achieved a BMI at least 3% less than the Baseline BMI or a

decrease in BMI Z-score of at least 0.05 at the end of Stage 1

If the patient completed the full 16 weeks of Stage 1 and at the Day 112 visit (Week 16) the patient has not achieved the required change in BMI or BMI Z-score (for patients <18 years) since the Baseline Visit, instead of the Stage 2 Entry Visit, the site will perform the End-of-Treatment (EOT) Visit for this patient. These patients will end treatment with setmelanotide and continue to be monitored for resolution of any ongoing serious adverse events (SAEs) with virtual visits once every 4 weeks until all SAEs have resolved.

Stage 2 (Randomized, Double-Blind, Placebo-Controlled)

Eligible patients who enter Stage 2 will continue in the trial for an additional 24 weeks. Stage 2 of the trial will begin with the Stage 2 Entry Visit. The patient will have a body weight recorded at stage 2 entry visit. This measurement will be their Stage 2 Entry Weight Measurement. At the Stage 2 Entry Visit, all eligible patients will be randomized 2:1 to either continue daily setmelanotide or receive matching placebo. Stratification by gene cohort will occur for specific genes being enrolled into this trial as determined by the Sponsor.

End of Treatment/End of Trial

The EOT Visit will occur as an in-person clinic visit on Study Day 112 for patients who complete only Stage 1 or on Study Day 280, which is the final day of treatment with setmelanotide or placebo for patients who complete Stage 2. A final End of Study (EOS) Visit will occur 4 weeks after the EOT visit. The EOS Visit will be conducted via telephone. At the end of Stage 2, patients may be offered the option of enrolling into a long-term extension (LTE) trial. If required by local regulation or if deemed necessary to assess patient safety by physical examination or after a longer follow-up period, the EOS Visit may be converted to an in-person visit, and/or can occur up to Week 48.

Regardless of treatment assignment, patients will be offered to start open-label treatment with setmelanotide if, during a visit, a patient's BMI has increased by at least 5% from the Stage 2 Entry Weight. Open-label treatment will be offered via enrollment in a separate LTE trial or, if the LTE trial is not available, via bridging visits until the LTE trial is available.

B. Study Population

Approximately 100 patients between the ages of 6 and 65 years, inclusive, are planned to be enrolled in Stage 2 of the trial with up to 200 patients enrolled in Stage 1 (open-label).

C. Sample Size Determination

Sample size is not based on any statistical considerations.

D. Treatment Randomization

At the Stage 2 Entry Visit, all eligible patients will be randomized 2:1 to either continue daily setmelanotide or receive matching placebo. Stratification by gene cohort will occur for specific genes being enrolled into this trial as determined by the Sponsor.

Patients with genetic variants in the following genes that have been categorized by a Clinical Laboratory Improvement Amendment (CLIA)/College of American Pathologists (CAP)/ISO15189 certified laboratory using American College of Medical Genetics (ACMG) criteria as (1) pathogenic, (2) likely pathogenic, or (3) a variant of uncertain significance as potentially causing dysfunction in the melanocortin-4 receptor pathway and leading to obesity are eligible for this trial. The genes eligible for enrollments are as following:

LEP, ISL1, DNMT3A, TRPC5, PLXNA4, NRP1, SEMA3E, SEMA3F, MECP2, SEMA3A, SEMA3C, PHIP, NRP2, MRAP2, MC3R, CPE, SEMA3B, SEMA3D, SIM1, HTR2C, SEMA3G, KSR2, MAGEL2, RPGRIP1L, TBX3, PLXNA1, CREBBP, PLXNA3, PLXNA2, TUB and OTHER.

E. Assessment Schedule

Refer to Appendix XII.

IV. Interventions

A. Treatment Administration

Trial drug will be administered as a subcutaneous (SC) injection once daily (QD).
Patients 12 years of age and older: Setmelanotide 2 mg QD for approximately 2 weeks, then increased to setmelanotide 3 mg QD for the remainder of the trial. Dose escalation should occur at the trial visit planned for Day 14 (±3 days) and should occur on the day of that visit. Note: if the starting dose of setmelanotide is not tolerated reduce to 1 mg QD; the lowest target dose in patients ≥12 years of age is 1.0 mg QD; however, in consultation with the Medical Monitor, the dose may be lowered to 0.5 mg QD if not tolerated.

Patients 6 to <12 years of age: Setmelanotide 1 mg QD for approximately 1 week, then increased to setmelanotide 2 mg QD for approximately 1 week, then increased to setmelanotide 3 mg QD for the remainder of the trial. Dose escalation should occur during the phone call planned for Day 7 (±2 days) and at the trial visit planned for Day 14 (±3 days) and should occur on the day of that visit. Note: if the starting dose of setmelanotide is not tolerated reduce to 0.5 mg QD; the lowest target dose in patients 6 to <12 years of age is 0.5 mg QD.

All changes in dose other than the per-protocol dose titration should be captured as a protocol violation, regardless of the rationale for the dose adjustment. Trial drug administration will be interrupted if certain safety parameter criteria are met, and additional assessments may be implemented.

V. General Analytical Considerations

A. Data Sources

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

B. Blinding Considerations

Due to the nature of the study additional blinding considerations need to be made for Stage 2. The weight and BMI data in Stage 2 are considered blinding and therefore will be populated with dummy data for blinded outputs.

All blinded team members will maintain the blind until the end of the study and the database is locked.

C. Study Stage

This study has two stages, open-label stage followed by a randomized double-blind, placebo-controlled stage.
In general, unless otherwise specified, events or measurements happen before the randomization date are in Stage 1 and happen on or after the randomization date are in Stage 2. For patients who are not randomized, all events or measurements are in Stage 1. All events happening after visit 14 will not be considered as in Stage 2 for patients who enrolled into bridging visit unless otherwise specified.

D. Definition of Baseline

Baseline Definition

Baseline will be defined as the last non-missing measurement taken prior to the start of stage 1 open-label treatment administration. In the case where the last non-missing measurement and the reference start date coincide and time of measurement is not available, that measurement will be considered Baseline unless the assessment was scheduled to be post-study drug administration in the SOA. Change from baseline is defined as the post-baseline value minus the baseline value, unless specified otherwise. Percent change from baseline = (Change from Baseline/Baseline) x 100.

Study Day

Study Day will be calculated from the reference start date within stage and will be used to show start/stop day of assessments and events. Reference start date is defined as the day of first dose (Day 1) in stage1.

Study Day will be computed as follows:

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

E. Missing Data

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

Analysis Window

All measurements recorded at unscheduled or early termination visits will be mapped according to the windowed visits by actual study day. These records then will be used for analysis if the scheduled ones are missing. If more than one visit occurs within a single visit window, then the analysis will take the one closest to and before the target day. All scheduled assessments will be analyzed according to the protocol defined visits, regardless of the study day

Stage	Study Visit	Study Week	Study Day	Study Day Window
1	Enrollment Visit	1	1	1
1	Virtual Visit 2	2	14	Post-dose - 21
1	Virtual Visit 3	4	28	22 - 35
1	Virtual Visit 4	6	42	36 - 49
1	Visit 5	8	56	50 - 70
1	Virtual Visit 6	12	84	71 - 98
1/2	In-Person Clinic Visit 7	16/End of Stage 1	112	Patients enrolling in Stage 2: 99 to first dose of Stage 2 Patients not enrolling in Stage 2: 99 - 117
2	Virtual Visit 8	18	126	Post-dose - 133
2	Virtual Visit 9	20	140	134 - 154
2	In-Person Clinic Visit 10	24	168	155 - 182
2	Virtual Visit 11	28	196	183 - 210
2	In-Person Clinic Visit 12	32	224	211 - 238
2	Virtual Visit 13	36	252	239 - 266
2	End of Treatment Visit 14	40	280	266 - 283

Primary Efficacy Endpoint Missing Data Imputation

For patients who do not have BMI value at the end of Stage 1 (Week 16), the unscheduled or early termination weight measurement mapped into Week 16 per visit window will be used for the primary analysis. If weights are measured in triplicate within a same date, the average of the triplicates will be calculated before the BMI calculation. The latest height value will be used together to derive the missing Week 16 BMI.

For patients who still do not have BMI value after above imputation at Week 16, they are treated as non-responder for the primary.

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

For partial start dates:

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

For partial end-dates:

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

If the year and month are present and only the day is missing, and the year and month is the same as the last study day then the day will be imputed as the last day of the study.

F. Genetic Diversity

It is possible that a patient may enter the trial with more than one eligible gene. In this situation, all eligible genes will be captured in the database. For analysis purposes, a single gene will be considered the “primary gene” for that patient, and the patient will be analyzed within that gene cohort. The primary gene will be defined as the eligible gene with the most

significant American College of Medical Genetics (ACMG) categorization (e.g., Pathogenic>Likely Pathogenic>Variant of Uncertain Significance [VUS]). If two or more eligible genes share the same most significant ACMG categorization, then the "primary gene" will be defined as the least prevalent gene and the patient will be analyzed within that gene cohort.

G. Multiple Study Centers

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

H. Covariate Adjustment in Primary Analysis

Covariate adjustment is not applicable for this study as there is not statistical testing for the primary analysis.

I. Data Safety Monitoring Board

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

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

J. Interim Analysis

An interim analysis will be performed when all patients have completed Stage 1 or terminated before Stage 1. All Stage 1 related analyses on this SAP will be summarized.

To avoid any potential bias due to patients still enrolled in the study at the time of the interim analysis, an unblinded team member at [redacted] will be involved in ensuring that any data of the Stage 2 are not included in the interim analysis.

K. Multiple Comparisons

There is no statistical testing planned in this study.

L. Analysis Set

- **Screened Population**

  All patients who are screened (including screen failed).

- **Safety Analysis Set**

  All patients who received at least one dose of trial medication.

  - **Safety Analysis Set Enrolled in Stage 2**

    All patients from Safety Analysis Set who enrolled in stage 2 and received at least one dose of trial medication in stage 2.

- **Full Analysis Set (FAS)**

  All patients randomized in Stage 2 who received at least one dose of trial medication (placebo or setmelanotide) after randomization in Stage 2 and have baseline weight data. Analyses performed on the FAS will be based on patients as randomized.

- **Supplemental Analysis Set (SAS)**

  All patients who are eligible after the re-confirmatory genetic diagnosis.

M. Special Distribution Schedule

Hunger Questions and [redacted] will be recorded as:

Stage 1

Daily [Scenario 1] during the Screening Period, [Scenario 2] for 7 consecutive dates after the enrollment visit, [Scenario 3] for 7 consecutive days starting at Study Days 28, 56, and 84, and [Scenario 4] up to 14 consecutive days starting at Study Day 98. These questionnaires should be completed prior to the morning meal (after an 8-hour fast) and prior to dosing in the morning. During the Screening Period, the patient must complete these questionnaires at least 4 of the 7 days prior to V1 (enrollment visit). If a patient completes V7 (Week 16), and is not continuing into Stage 2 of the trial, the patient will stop completing these questionnaires after completing V7 (and return the electronic diary, if applicable).

Stage 2

[Scenario 2] for 7 consecutive days starting at Study Days 140, 168, 196, 224, and 252, and [Scenario 4] up to 14 consecutive days starting at Study Day 266 (Week 38). These

questionnaires should be completed prior to the morning meal (after an 8-hour fast) and prior to dosing in the morning. All patients will stop completing these questionnaires after Visit 14 (Study Day 280), regardless of whether they have completed the full 14 days of data entry (and return the e-diary, if applicable) or at their Early Termination Visit (if applicable).

For continuous outcome measure analyses, a weekly average score will be calculated as an arithmetic mean. The baseline score for Stage 1 will still be arithmetic mean of the available score values within 7 days before or on the first dosing (Day 1). For visits in [Scenario 2], [Scenario 3] and [Scenario 4], arithmetic mean of up to 7 measurements that are closest to and before the scheduled visit date will be calculated. For example, measurements taken between Day 1 (V1) to Day 14 (V2) will be labeled as Day 14 (V2) measurement on the table display.

N. Data Display Characteristics

Data displays produced for this study will include three types—summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables will be produced as specified in following sections. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes. Figures will be produced when specified in sections to follow.

Listings in general will be presented by gene cohort, stage, then treatment (active and placebo) unless otherwise specified.

Data listings will simply list the data recorded on the CRF or derived for each patient. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within patient. Data listings will not display patient initials.

Tables in general will be presented by stage unless otherwise specified. In which stage 1 will be presented by overall, each gene in SEMA 3 gene cohort, and gene cohort, stage 2 will be present by overall, each gene in SEMA 3 gene cohort, gene cohort, and treatment (active and placebo).

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

The summary statistics displayed will be a function of the type of data associated with the summarized assessment. Unless stated otherwise in relevant sections to follow, continuous data will be summarized with the number of nonmissing values, mean, standard deviation, minimum, first quartile (Q1), median, and maximum, third quartile (Q3). Categorical data will

be summarized with the number of nonmissing values and the numbers of values equal to each of the possible values. Percentages of patients with each of the possible values will be calculated from the number of patients in the corresponding analysis population, unless stated otherwise. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables.

O. Blinded Review of Data

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

P. Software Version

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

Q. Gene Cohort Analysis

Gene cohort in this SAP is defined as group of patients with specified primary gene(s). In details, please see below for the grouping:

Gene Cohort	Genotype
SEMA3 Pathway	NRP1, NRP2, PLXNA1, PLXNA2, PLXNA3, PLXNA4, SEMA3A, SEMA3B, SEMA3C, SEMA3D, SEMA3E, SEMA3F, SEMA3G
PHIP	PHIP
SIM1	SIM1
MAGEL2	MAGEL2
Other	TRPC5, MRAP2, HTR2C, KSR2, TBX3, LEP, ISL1, DNMT3A, MECP2, MC3R, CPE, RPGRIP1L, CREBBP, TUB

After a patient enrolls in the trial, the pre-identified primary gene is reconfirmed or may be reclassified with the [redacted] and manual blind review during the trial. A supplemental analysis with the re-confirmative classification of genes will be conducted.

VI. Patient Accountability

All patients in safety analysis set will be used for below analyses unless otherwise specified. The table and listing display for all analyses below will follow section V.N unless otherwise specified.

A. Patient Demographic and Baseline Characteristics

Patient demographic and baseline characteristics will include the patient's age [6 to <12, 12 to <18, and 18 to ≤65 years of age], sex [Child-bearing potential if female], ethnicity, race, weight

at baseline, height at baseline, BMI at baseline, waist circumference at baseline, genotype, skin type from Fitzpatrick Classification Scale assessment.

Demographic and baseline characteristics will be tabulated for stage 1 and stage 2 separately, and listing will be included for all patients.

B. Disposition

Stage 1

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

Stage 2

All patients randomized into stage 2 will be included in this analysis. Patient disposition will include number of patients in FAS, number and percentage of completion status at end of treatment (with discontinuation reason), at end of study (with discontinuation reason). Patients who have finished visit 14 and enrolled into bridging visit will be considered as Competed in the end of treatment in stage 2.

Disposition listing will be included for all patients.

C. Protocol Deviations

Protocol deviations will be classified as major and minor.

All protocol deviations will be listed for all patients.

D. Historic Measurements and Interventions

D.1. Medical History Weight Loss Interventions

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

D.2. Historic Height and Weight

The records of historic height and weight measurements for each patient will be listed.

D.3. Weight History

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

D.4. Prior Weight Loss Medication History

All prior weight loss medication history data will be listed.

D.5. Prior Surgery Weight Loss Intervention

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

D.6. Prior Weight Loss Programs

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

E. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 Medical history will be tabulated by system organ class and preferred term. A listing of medical history will be provided.

VII. Efficacy Analyses

The analysis of the efficacy endpoints in Stage 1 will be performed based on the safety analysis set, and the analyses of the efficacy endpoints in Stage 2 will be performed based on the full analysis set (FAS). End of Stage 1 in below section will refer to the measurement collected at Week 16 and end of Stage 2 will refer to Week 40, unless otherwise specified. The tabulation and listing formats for all analyses below will follow section V.N unless otherwise specified.

A. Efficacy Assessments

A.1 Weight

Weight should be measured after patients have attempted to empty their bladders and after fasting for at least 8 hours. Patients are to wear light clothing or underwear and no shoes, with empty pockets and will be weighed at approximately the same time of day. All measurements will be recorded to the nearest 10th of a kg if reported with a digital scale, or half kg with a mechanical scale. Weight measurements will be collected in triplicate. Only in-person visits measurements will be summarized in tables.

[redacted]

[redacted]

A.3 Height

For patients ≥21 years of age, height is to be measured at Screening only. For patients aged <21 years, height is to be measured at the time points listed in the SoA. Only in-person visits measurements will be summarized in tables.

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.

A.4 BMI and BMI Z-score calculation

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

BMI z-score for patients < 18 years will be calculated according to the Centers for Disease Control and Prevention (CDC) Growth Charts. The LMS-based BMI z-score is calculated as:

BMI z-score = ((value / M)**L) – 1] / (S * L)

where L, M, S are given in XII. Appendix 1 according to patients' gender and age at screening.

Only in-person visits measurements will be summarized in tables.

B. Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of patients by gene cohort who demonstrate a significant clinically meaningful response (defined below) to setmelanotide at the end of Stage 1:

- For all patients: ≥5% reduction in BMI from Baseline

A table with frequency count and percentage of patients who have met the meaningful response will be tabulated. The 95% exact confidence interval will also be included.

C. Secondary Efficacy Analyses

For the below list of secondary endpoints, summary statistics will be provided for the continuous endpoints while proportion and percentage will be provided for the categorical endpoint. The analyses of the continuous endpoints are presented by gene cohort and by visit unless otherwise specified.

- Mean change and percent change in BMI from Baseline to end of Stage 1 in all patients and patients ≥18 years old, per gene cohort
    - The 95% confidence interval with Student *t*-distribution will also be provided for the mean percent change in BMI from Baseline
- Mean change and percent change in body weight from Baseline to end of Stage 1 in patients ≥18 years old, per gene cohort
- Mean change in BMI Z-score from Baseline to end of Stage 1 in patients <18 years old, per gene cohort
- Mean percent change in the weekly average of the daily maximal hunger score from Baseline to end of Stage 1 in patients ≥12 years old, per gene cohort
- The proportion of patients ≥12 years old, per gene cohort, who achieve a ≥2-point reduction (improvement) from Baseline to end of Stage 1 in the weekly average of the daily maximal hunger score
    - Patients ≥12 years old with no measurement at the end of Stage 1 will be treated as a non-responder.

[redacted]

[redacted]

VIII. Questionnaires

All patients in safety analysis set will be used for below analyses in Stage 1 and FAS in Stage 2 unless otherwise specified. The tabulation and listing formats for all analyses below will follow section V.N unless otherwise specified.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]e eating from others?

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

G. Nutrition and Exercise Counseling

All nutrition and exercise counseling will be listed for all patients in Safety analysis set.

IX. Safety Analyses

All patients in safety analysis set will be used for below analyses in Stage 1 and in Stage 2 unless otherwise specified. The tabulation and listing formats for all analyses below will follow section V.N unless otherwise specified.

A. Exposure

A.1 Study Treatment Exposure

Duration of study treatment (days) will be calculated within each of the two study stages (stages are defined in section V.C) based on below formula:

Duration = Date of last administration – Date of first administration + 1

Summary statistics will be provided. For patient enrolled in Stage 2, the date of last administration will be the latest record before randomization date in Stage 1 analysis. And the date of first administration will be the first record on or after randomization date in Stage 2 analysis. The date of last administration in Stage 2 will be the record on visit 14 or last administration record before the first bridging visit (if visit 14 record is not available) for patients enrolled into bridging visit.

A.2 Study Treatment Compliance

Compliance to dosing will be monitored throughout the trial by having the patient/caregiver complete a daily dosing log.

Compliance will be calculated within each of the two study stages as:

Compliance (%) = # of actual administration / # of expected administration*100

Where:

# of actual administration = number of administrations from daily dosing diary
# of expected administration = (Date of last administration – date of first administration +1) = Duration

For patient enrolled in Stage 2, the number of dose administration will be derived from the records before randomization date in Stage 1 analysis. And the number of dose administration will be derived from the records on or after randomization date in Stage 2 analysis. The number of dose administration in Stage 2 or last administration record before the first bridging visit (if visit 14 record is not available) will be derived from the records before and on visit 14 for patients enrolled into bridging visit.

A.3 Dose Level Changes

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

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

B. Adverse Events

All adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version MedDRA24.1.

A treatment-emergent adverse event (TEAE) is defined as following:

Stage 1

An adverse event will be considered as treatment-emergent adverse event in Stage 1 period as following:

- If the start date is completely missing and end date is on or after Stage 1 treatment administration and before Stage 2 treatment administration and it is not ongoing.
- Or the event start date is on or after the Stage 1 treatment administration but before the first Stage 2 treatment administration.

Stage 2

An adverse event will be considered as treatment-emergent adverse event in Stage 2 period as following:

- If the start date is completely missing and end date is after Stage 2 treatment administration or ongoing.
- Or the event start date is on or after the Stage 2 treatment administration.
- Any events happening 30 days after the dosing date at visit 14 will not be considered as TEAE in stage 2

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

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

An overall summary will be prepared for the following type of AEs :

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

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

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

All AE data will be listed in one listing by cohort and treatment and a column to indicate the period of the AE occurs. Separate AE listings will be created for SAE, AE with CTCAE Grade 3 or higher and AE leading to Drug Permanently Discontinued.

C. Injection Site Evaluation

Frequency and percentage of injection site reaction (including Erythema, Edema, Induration, Itching, Pain or Tenderness, Other) will be tabulated by no reaction or severity (mild, moderate, and serve) by stage and visit. Percentage is based on the number of patients with assessment performed within each visit.

Injection site reaction data will be presented in listing by stage.

D. Clinical Laboratory Results

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

Blood samples for a fasting glucose, [redacted] measurements will be obtained at the time points designated in the

SOA. They will follow the analysis in section VII.D and will be analyzed separately from laboratory data.

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

Summaries of actual values and changes from baseline within stage will be presented by stage and visit according to SOA. Similarly, summary statistics for the eGFR will be provided.

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

Laboratory test results will be presented in data listings.

Pregnancy test will be presented in data listings.

E. Vital Signs

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

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

Summary statistics for actual values and changes from baseline within stage will be presented. Only in-person visits measurements will be summarized in table.

Vital sign data will also be presented in listing.

F. Physical Examination

Tanner staging data will be presented in listing.

G. Prior and Concomitant Medications

Prior and concomitant medications (CMs) will be coded using WHO-DD version September 2021.

G.1 Prior Medications

Prior medications are defined as medications with an end date prior to the first dose of study drug in Stage 1. Prior medications will be tabulated by Anatomic Therapeutic Chemical (ATC) Level 2 classification and Preferred Term (PT) by treatment group and overall. A patient having more than one medication within the same ATC Level 2 or preferred term will be counted only once for that ATC Level 2 or preferred term.

G.2 Concomitant Medications

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

Stage 1
A medication will be considered a concomitant medication in Stage 1 as following:

- If the end date is completely missing and the medication start date is before the Stage 2.
- Or the medication start date is before the Stage 2 treatment administration and end date is on or after Stage 1 treatment administration or it is ongoing.

Stage 2
A medication will be considered a concomitant medication in Stage 2 as following:

- If the end date is completely missing
- Or the medication is either ongoing or end date is on or after Stage 2 treatment administration.
- Any medications happening after the dosing date at visit 14 will not be considered as concomitant medication in stage 2

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

A listing of prior and concomitant medications will be provided.

H. Concomitant Procedures

Concomitant procedures data will be listed by stage. The definition of stage will follow adverse events in IX.B.

I. Skin Examination

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

The skin examination should include a full body (head-to-toe skin examination).

Frequency count of most severe outcome across all skin regions within patients will - be provided by stage and visit. The severity of the outcome is rated as Abnormal, CS > Anormal, Not CS > Normal > Not Done.

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

All skin examination data will be presented in listing.

J. Hyperpigmentation

Hyperpigmentation form will be administrated at postbaseline visits.

All hyperpigmentation data will be presented in listing.

K. Sexual Function

Sexual function forms have different versions between male and female.
All sexual function data will be presented in listing by version.

L. Electrocardiogram

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

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

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

ECG data will be presented in listing.

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

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

There are two versions of the C-SSRS forms:

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

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

A frequency and percentage table and a shift from baseline by visit will be provided to display the number of patients who have answered at least one 'Yes' to: Suicidal Ideation (1-5),

Suicidal behavior (6-10), either have suicidal ideation or suicidal behavior (1-10), and the question "Non-Suicidal Self-Injurious Behavior".

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

Suicidal Ideation (1-5)

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

Suicidal behavior (6-10)

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

All C-SSRS data will be listed.

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

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

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

All PHQ-9 data will be listed.

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

The CDI-2 has both a self-report and a parent version.

The CDI-2: Self-Report Short version is an efficient screening measure that contains 12 items and will be administered to patients <12 years of age according to the SoA.

Items on the CDI-2 Parent form correspond to items on the self-report version and are suitably rephrased. Item selection for the parent forms was guided to maximize validity, and thus focused on observable manifestations of depression. The CDI-2 parent form consists of 17 items and the 4 choices provided for each item correspond to 4 levels of symptomatology: 0 (not at all), 1 (some of the time), 2 (often), or 3 (most of the time). The CDI-2 parent version will be administered to caregivers of patients <12 years of age according to the SoA. Any patient with a CDI-2 score >20 during the trial will be referred to an MHP.

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

All CDI-2 data will be listed by version.

X. Supplemental Analysis

A supplemental analysis deriving from re-confirmatory genetic diagnosis is conducted for Primary endpoint, and Secondary endpoints of efficacy for patients in Supplemental Analysis Set.

Patients who become ineligible for the trial after the re-confirmatory genetic diagnosis will be excluded from the supplemental analysis.

XI. Pharmacokinetic Analysis

The trough concentration values will be reported descriptively as mean, standard deviation (SD), maximum (Max), minimum (Min), median, and percent coefficient of variation (% CV) based on dose and visit.

The PK concentration and ADA will be listed.

XII. References

Altman DG, Dore CJ. Randomisation and baseline comparisons in clinical trials. *Lancet* 1990; 335(8682): 149-53.

Senn S. Testing for baseline balance in clinical trials. *Stat Med* 1994; 13(17): 1715-26.

XIII. Appendix 1: BMI-for-age charts, 2 to 20 years, LMS parameters and selected smoothed BMI (kilograms/meters squared) percentiles, by sex and age

Sex	Age (months)	L	M	S	P95	Age at Screen
M	24	-2.01118	16.57503	0.080592	19.33801	2
M	36.5	-1.41999	16.0003	0.072634	18.23842	3
M	48.5	-1.71487	15.62817	0.071889	17.83614	4
M	60.5	-2.61517	15.41914	0.075992	17.93893	5
M	72.5	-3.21171	15.38353	0.083048	18.41421	6
M	84.5	-3.32319	15.51287	0.092131	19.15236	7
M	96.5	-3.18306	15.78231	0.102091	20.06793	8
M	108.5	-2.97115	16.16712	0.111721	21.08893	9
M	120.5	-2.76565	16.64614	0.120112	22.15409	10
M	132.5	-2.59056	17.20089	0.126735	23.21358	11
M	144.5	-2.44743	17.81463	0.131389	24.22985	12
M	156.5	-2.32946	18.4718	0.134141	25.17811	13
M	168.5	-2.22736	19.15759	0.135251	26.04662	14
M	180.5	-2.13234	19.85766	0.13511	26.83688	15
M	192.5	-2.03902	20.55765	0.134198	27.56393	16
M	204.5	-1.94913	21.24248	0.133057	28.25676	17
M	216.5	-1.87467	21.89587	0.132286	28.95862	18
M	228.5	-1.83514	22.50072	0.132566	29.72674	19
M	240	-1.84233	23.02029	0.134539	30.58964	20
Sex	Age (months)	L	M	S	P95	Age at Screen
F	24	-0.98661	16.4234	0.085452	19.10624	2
F	36.5	-2.09683	15.69924	0.078605	18.25475	3
F	48.5	-3.01852	15.29855	0.078713	18.02851	4
F	60.5	-3.35008	15.15188	0.0843	18.25738	5
F	72.5	-3.22561	15.2169	0.093803	18.83778	6
F	84.5	-2.92619	15.45357	0.105325	19.67794	7
F	96.5	-2.61719	15.827	0.117159	20.69525	8
F	108.5	-2.36092	16.30609	0.128014	21.81725	9
F	120.5	-2.1713	16.86231	0.137057	22.98258	10
F	132.5	-2.04524	17.46907	0.143868	24.14141	11
F	144.5	-1.97552	18.10149	0.148361	25.25564	12
F	156.5	-1.95498	18.73643	0.150705	26.2988	13
F	168.5	-1.97707	19.35257	0.151256	27.25597	14
F	180.5	-2.03489	19.93057	0.150512	28.12369	15
F	192.5	-2.11916	20.45326	0.14909	28.90981	16
F	204.5	-2.21574	20.90576	0.147723	29.6335	17
F	216.5	-2.30369	21.27532	0.147269	30.32554	18
F	228.5	-2.35568	21.55082	0.148724	31.0288	19
F	240	-2.34496	21.717	0.152975	31.76474	20

XIV. Appendix 2: Schedule of Assessments

Table 1: Schedule of Assessments – Stage 1

Assessment	Screening (In-Person)	Enrollment Visit (IP)	Phone Call†	Virtual Trial Visits	In-Person Trial Visits	Early Termination Visit (In-Person)
Visit Number		**V1**	**V1c**	**V2, V3, V4, V6**	**V5, V7**	
Study Week			**1**	**2, 4, 6, 12,**	**8, 16**	
Study Day	**-56 to -14**	**1**	**7**	**14*, 28, 42, 84**	**56, 112**	
Window			**+/-2**	**+/-3**	**+/-5**	**+/-5**
Informed Consent/Assent (1)	X					
Inclusion/Exclusion	X	X				
Genetic Sample (2)	X	X				
Optional WES (3)	X	X				
Medical History	X	X				
Nutrition and physical activity counseling and follow-up		X	X	X	X	
Physical Exam (4)	X	X			X	X
Fitzpatrick Classification Scale	X					
Comprehensive Skin Exam (5)	X				X	X
Weight (6)	X	X		X	X	X
Height (7)	X	X			X	X
[redacted]						
Vital Signs (9)	X	X		X	X	X
ECG (10)	X				X	X
Pregnancy (11)	X	X		X	X	X
Hunger Questions (12)	X	X		X	X	X

Assessment	Screening (In-Person)	Enrollment Visit (IP)	Phone Call†	Virtual Trial Visits	In-Person Trial Visits	Early Termination Visit (In-Person)
Visit Number		**V1**	**V1c**	**V2, V3, V4, V6**	**V5, V7**	
Study Week			**1**	**2, 4, 6, 12,**	**8, 16**	
Study Day	**-56 to -14**	**1**	**7**	**14*, 28, 42, 84**	**56, 112**	
Window			**+/-2**	**+/-3**	**+/-5**	**+/-5**
[redacted]						
C-SSRS (16)	X	X		X	X	X
PHQ-9 (23)	X	X		X	X	X
CDI-2 (24)	X	X		X	X	X
[redacted]						
[redacted]						
Adverse Events	X	X	X	X	X	X
Injection Site Inspection		X		X	X	X
Concomitant Medication Review	X	X	X	X	X	X
Safety Laboratory Tests (17)	X				X	X
[redacted]						

Trough PK (18)		X			X	X
Anti-Drug Antibodies (19)	X				X	X
Biomarkers (20)		X			X	X
Daily Drug Compliance (21)		X		X	X	
Dispense/Return Trial medication (22)		X		X	X	X

Abbreviations: ADA = anti-drug antibodies; CDI-2 = Children's Depression Inventory -2; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted]; IP = In Person; [redacted]; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetic; QoL = quality of life; WES = Whole Exome Sequencing.

† A phone visit should occur on Day 7 (±2 days) for all patients <12 years of age; at this visit dose escalation should occur from 1 to 2 mg once daily (QD).

* Dose escalation (from 2 mg QD to 3 mg QD) should occur at the trial visit planned for Day 14 (±3 days) and should occur on the day of that visit. NOTE: Additional assessments may be performed at the Investigator's discretion as needed to ensure patient safety.

1 Although the trial procedures and assessments required per protocol are classified as "No or Minimal Risk" according to the 2008 Guidance Document "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population," considerations for reducing pain and distress in patients younger than 18 years of age are included in Appendix 2.

2 Patients will have a sample collected for confirmatory genetic testing either during Screening or at the Enrollment visit; this only needs to be completed 1 time. The Sponsor may waive this requirement for individual patients who have a genetic sample analysis from certain testing laboratories.

3 All patients will be offered the opportunity to opt-in to having WES performed; a separate blood sample is not required (testing to be completed from confirmatory genetic sample collected either during Screening or at the Enrollment visit).

4 A complete physical examination will be conducted at Screening and at Visit 7 or the early termination (ET) visit and include review of peripheral lymph nodes, head, eyes (including conjunctiva), ears, nose, mouth and oropharynx, neck, heart, lungs, abdomen, musculoskeletal including back, extremities and neurologic. At other time points, an abbreviated examination will be performed. The abbreviated examination should focus on heart, lungs, skin, neurologic examination, and any areas of previous abnormal findings, noting any changes from baseline. In addition, Tanner Staging for assessment of pubertal development will be conducted for those patients who have yet to reach Tanner Stage V. Whenever possible, the same trained health care professional will conduct the examination and Tanner Staging.

5 A comprehensive skin evaluation will be performed by the Investigator or designee. The skin examination should include a full body skin examination (head- to-toe skin examination). If any concerning lesions are identified during Screening, the patient should be referred to a dermatologist. Any concerning lesions identified during 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 may be excluded from the trial. Additionally, any lesion or significant change in an existing lesion during the course of the trial must be evaluated by a dermatologist and biopsied, if clinically indicated in the opinion of the dermatologist.

6 Weight (kg) is to be measured at the clinic using the same scale throughout the trial or at home (during virtual visits) using the same scale provided to the patient as part of the clinical trial. Weight should be measured after patients have attempted to empty their bladders and after fasting for at least 8 hours. Patients are to wear light clothing or underwear and no shoes, with empty pockets and will be weighed at approximately the same time of day. All measurements will be recorded to the nearest 10th of a Kg if reported with a digital scale, or half Kg with a mechanical scale. Whenever possible, the scale should be calibrated on a regular basis per manufacturer's specifications.

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

8 [redacted]

[redacted]

[9] All vital signs measurements are to be obtained in the sitting position following at least 5 minutes of rest. All measurements will be taken in triplicate, approximately 2 minutes apart. When possible, blood pressure (BP) should be taken in the non-dominant arm throughout the trial, using the same methodology (automated or manual) and ensuring that an appropriately sized cuff is used. For virtual visits, patients will be instructed on the proper use of and will be provided with WiFi/Bluetooth connected devices for measuring and transmitting data on blood pressure, and temperature during virtual trial visits. The data are stored and automatically transferred when connected to WiFi.

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

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

[redacted]

[14] Assessments will only be performed at Study Weeks 4, 8, and 12.

[redacted]

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

[17] Safety laboratory tests will include: Complete blood count (CBC) with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, CO_2, albumin, total protein, glucose, blood urea nitrogen [BUN], creatinine (including eGFR), 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), and urinalysis with microscopic analysis if positive findings on dipsticks warrant further examination. Safety laboratories will also include a coagulation profile (prothrombin time [PT] or international normalized ratio [INR], and partial thromboplastin time [PTT] also referred to as activated PTT [aPTT]).

[18] A blood sample for PK will be drawn at the time points indicated before dosing, with dosing performed at the clinic. PK samples will be drawn with patients/caregivers being reminded there should be NO trial medication administration at home on the day of clinic visits; the drug will be administered in the clinic by the patient AFTER the PK sample is obtained. For the PK sample, the actual collection (clock) time will be recorded.

[19] Any patient with a positive ADA will be followed every 3 months after the ADA sample analysis until resolution of the ADA.
[20] A biomarker blood sample will be collected for metabolic, inflammation, metabolomic and/or proteomic biomarker analysis. This sample may not be analyzed. All samples are sent to a central laboratory. Additional details are described in the laboratory manual.
[21] A daily question querying whether the patient completed their daily injection will be asked via electronic diary. Paper versions can be used, if needed.
[22] Dispensing will be made by site staff, using the dispensation function in the Interactive Response Technology (IRT) system, as outlined in the SoA. Dispensing may also be made directly to the patient if required and allowed by local regulations. At the Early Termination visit, only drug return will apply.
[23] If at any time during the trial an individual patient's PHQ9 score is ≥10, the patient should be referred to a Mental Health Professional.
[24] The CDI-2 will be administered to patients <12 years of age (self-report short form) and to caregivers of patients <12 years of age (parent version).

Table 2: Schedule of Assessments – Stage 2

Assessment	Stage 2 Entry Visit† (In-Person)	Virtual Trial Visits	In-Person Clinic Visits	End of Treatment Visit (In-Person)	End-of-Study Visit (Telephone) [22]	Early Termination Visit (In-Person)	Bridging Visits (if needed) (In-Person)
Visit Number	**V7**	**V8, V9, V11, V13**	**V10, V12**	**V14**	**V15**		
Study Week	**16**	**18, 20, 28, 36**	**24, 32**	**40**	**44**		**Q12 weeks**
Study Day	**112**	**126, 140, 196, 252**	**168, 224**	**280**			
Window (1)		**+/-3**	**+/- 5**	**+/- 5**	**+/-3**		**+/- 5**
Nutrition and physical activity counseling and follow-up	X	X	X	X			X
Physical Exam (2)	X			X	X	X	X
Comprehensive Skin Exam (3)	X			X	X	X	X
[redacted]							
Vital Signs (7)	X	X	X	X		X	X
ECG (8)	X			X		X	X
Pregnancy (9)	X	X	X	X		X	X
[redacted]							
C-SSRS (14)	X	X	X	X	X	X	X
PHQ-9 (21)	X	X	X	X	X	X	X

CDI-2 (23)	X	X	X	X	X	X	X

Assessment	Stage 2 Entry Visit[†] (In-Person)	Virtual Trial Visits	In-Person Clinic Visits	End of Treatment Visit (In-Person)	End-of-Study Visit (Telephone) [22]	Early Termination Visit (In-Person)	Bridging Visits (if needed) (In-Person)
Visit Number	**V7**	**V8, V9, V11, V13**	**V10, V12**	**V14**	**V15**		
Study Week	**16**	**18, 20, 28, 36**	**24, 32**	**40**	**44**		**Q12 weeks**
Study Day	**112**	**126, 140, 196, 252**	**168, 224**	**280**			
Window (1)		**+/-3**	**+/- 5**	**+/- 5**	**+/-3**		**+/- 5**
[redacted]							
Randomization	X						
[redacted]							
Adverse events	X	X	X	X	X	X	X
Injection site inspection	X	X	X	X		X	X
Concomitant medication Review	X	X	X	X	X	X	X
Safety Laboratory Tests (15)	X		X	X		X	X
[redacted]							
Trough PK (16)	X		X	X		X	X
Anti-Drug Antibodies (17)	X			X		X	X
Biomarkers (18)	X			X		X	X
Daily drug compliance (19)	X	X	X	X			X
Dispense/Return Trial medication (20)	X		X	X		X	X

Abbreviations: ADA = anti-drug antibodies; CDI-2 = Children's Depression Inventory -2; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; [redacted]; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetic; Q = every.

† The Stage 2 Entry visit is the same visit as the final visit from Stage 1.

NOTE: Additional assessments may be performed at the Investigator's discretion as needed to ensure patient safety.

1 For patients who qualify for Stage 2 at the Week 16 visit in Stage 1, the Stage 2 Baseline Visit (B1) is the same as Week 16 in Stage 1.

2 A complete physical examination will be conducted at the Stage 2 entry visit and at the End-of-Treatment Visit. At other time points, an abbreviated examination will be performed. The abbreviated examination should focus on heart, lungs, skin, neurologic examination, and any areas of previous abnormal findings, noting any changes from baseline. In addition, Tanner Staging for assessment of pubertal development will be conducted for those patients who have yet to reach Tanner Stage V. Whenever possible, the same trained health care professional will conduct the examination and Tanner Staging. Assessment to be performed at Visit 15 only if that is an in-person visit.

3 A comprehensive skin evaluation will be performed by the Investigator or designee. The skin examination should include a full body skin examination (head- to-toe skin examination). Any lesion or significant change in an existing lesion during the course of the trial must be evaluated by a dermatologist and biopsied, if clinically indicated in the opinion of the dermatologist. Assessment to be performed at Visit 15 only if that is an in-person visit.

[redacted]

7 All vital signs measurements are to be obtained in the sitting position following at least 5 minutes of rest. All measurements will be taken in triplicate, approximately 2 minutes apart. When possible, blood pressure (BP) should be taken in the non-dominant arm throughout the trial, using the same methodology (automated or manual) and ensuring that an appropriately sized cuff is used. For virtual visits, patients will be instructed on the proper use of and will be provided with WiFi/Bluetooth connected devices for measuring and transmitting data on blood pressure, and temperature during virtual trial visits. The data are stored and automatically transferred when connected to WiFi.

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

9 Except for virtual visits, all other pregnancy tests will be serum tests; dosing may continue with results pending. At sites where pregnancy tests are required for virtual visits, at Visit 7 women of child-bearing potential will be given urine pregnancy kits for use at each of the virtual visits.

[redacted]

[12] Assessments will only be performed at Study Weeks 20, 28, and 36.

[redacted]

[14] The 'Since Last Visit' version of the scale will be used to assess suicidality since the last time the C-SSRS was administered. If at any time during the trial a patient has a suicidal ideation of type 4 or 5, or any suicidal behavior, the patient should be referred to a mental health professional (MHP).

[15] Safety laboratory tests will include: Complete blood count (CBC) with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, CO_2, albumin, total protein, glucose, blood urea nitrogen [BUN], creatinine (including eGFR), 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), and urinalysis with microscopic analysis if positive findings on dipsticks warrant further examination. Safety laboratories will also include a coagulation profile (prothrombin time [PT] or international normalized ratio [INR], and partial thromboplastin time [PTT] also referred to as activated PTT [aPTT]).

[16] A blood sample for PK will be drawn at the time points indicated before dosing, with dosing performed at the clinic. PK samples will be drawn with patients/caregivers being reminded there should be NO trial medication administration at home on the day of clinic visits; the drug will be administered in the clinic by the patient AFTER the PK sample is obtained. For the PK sample, the actual collection (clock) time will be recorded.

[17] Any patient with a positive ADA will be followed every 3 months after the ADA sample analysis until resolution of the ADA.

[18] A biomarker blood sample will be collected for metabolic, inflammation, metabolomic and/or proteomic biomarker analysis. This sample may not be analyzed. All samples are sent to a central laboratory. Additional details are described in the laboratory manual.

[19] A daily question querying whether the patient completed their daily injection will be asked via electronic diary. Paper versions can be used, if needed.

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

[21] If at any time during the trial an individual patient's PHQ9 score is ≥10, the patient should be referred to a Mental Health Professional.

[22] If required by local regulation or if deemed necessary to assess patient safety by physical examination or after a longer follow-up period, the visit may be converted to an in-person visit and/or can occur up to Day 336 (Week 48). If the EOS visit is converted to an in-person visit, a

physical examination and a comprehensive skin examination should be completed at that in-person visit. Patients who enroll in the long-term extension trial will have the EOS visit at the same time as the EOT visit.

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