SETMELANOTIDE (RM-493)

RM-493-037

A Phase 3, Randomized, Double-Blind Trial of Two Formulations of Setmelanotide (Daily and Weekly) with a Crossover to Open-Label Once Weekly Setmelanotide in Patients with Specific Gene Defects in the Melanocortin-4 Receptor Pathway Who Are Currently on a Stable Dose of the Once Daily Formulation

This trial will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

IND No. [redacted]

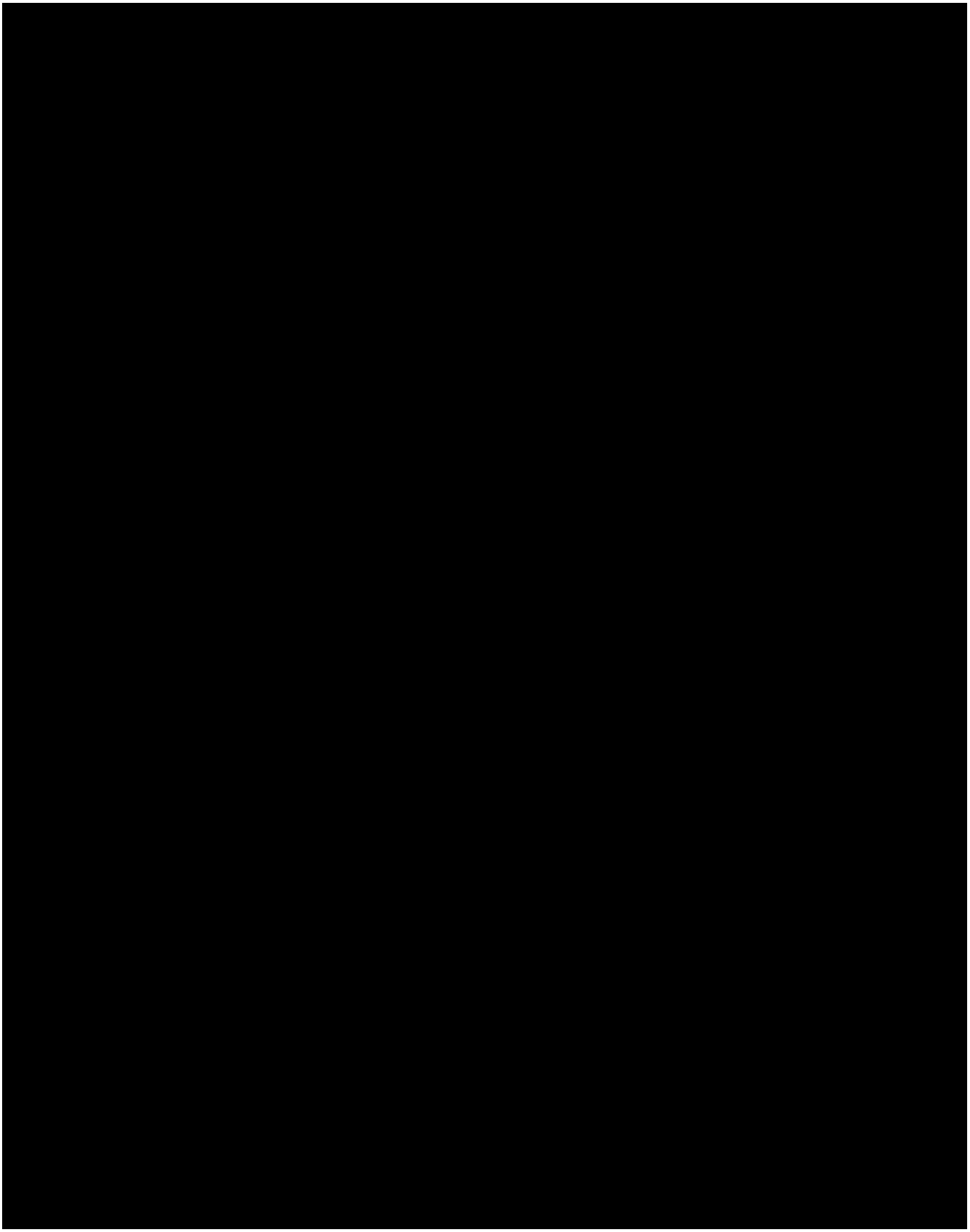
EudraCT 2021-004597-65

Trial Sponsor: Rhythm Pharmaceuticals, Inc.

[redacted]

Document Date (Version): 07 July 2022 (Version 4.0)

[redacted]



APPROVAL SIGNATURE PAGE

Protocol Title:	A Phase 3, Randomized, Double-Blind Trial of Two Formulations of Setmelanotide (Daily and Weekly) with a Crossover to Open-Label Once Weekly Setmelanotide in Patients with Specific Gene Defects in the Melanocortin-4 Receptor Pathway Who Are Currently on a Stable Dose of the Once Daily Formulation
Protocol Number:	RM-493-037
Document Version:	Version 4.0
Document Date:	07 July 2022

REVIEWED/APPROVED BY:

[redacted]

[redacted] Signature Date

[redacted]

Rhythm Pharmaceuticals, Inc.

INVESTIGATOR STATEMENT

Protocol Title:	A Phase 3, Randomized, Double-Blind Trial of Two Formulations of Setmelanotide (Daily and Weekly) with a Crossover to Open-Label Once Weekly Setmelanotide in Patients with Specific Gene Defects in the Melanocortin-4 Receptor Pathway Who Are Currently on a Stable Dose of the Once Daily Formulation
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I understand that all documentation provided to me by Rhythm Pharmaceuticals, Inc. (Rhythm) or its designated representative(s) concerning this trial that has not been published previously will be kept in the strictest confidence. This documentation includes the trial protocol, Investigator's Brochure, case report forms, and other scientific data.

This trial will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB)/Ethics Committee (EC). No changes will be made to the trial protocol without the prior written approval of Rhythm and the IRB/EC, except where necessary to eliminate an immediate hazard to the patient.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

Investigator Name (*printed*)	Investigator Signature	Date

Investigational site or name of institution and location (*printed*)

1. SYNOPSIS

Name of Sponsor/Company:
Rhythm Pharmaceuticals, Inc.

Name of Investigational Product:
Setmelanotide (RM-493): [redacted] for daily administration and [redacted] for weekly administration

Title of Trial:
A Phase 3, Randomized, Double-Blind Trial of Two Formulations of Setmelanotide (Daily and Weekly) with a Crossover to Open-Label Once Weekly Setmelanotide in Patients with Specific Gene Defects in the Melanocortin-4 Receptor Pathway Who Are Currently on a Stable Dose of the Once Daily Formulation

Trial center(s): This trial will be conducted at multiple trial centers located in the United States (US), Canada, and Europe

Phase of development: 3

Objectives:

Primary:

- To compare the pharmacokinetics (PK) of the once daily (QD) and once weekly (QW) formulations of setmelanotide

Secondary:

- To assess the safety of the QW formulation of setmelanotide with up to 6 months (26 weeks) of drug administration

[redacted]

Methodology:

This trial is designed to compare the safety, PK, and [redacted] of the QW and QD formulations of setmelanotide, as well as to evaluate the safety and [redacted] of up to 6 months of QW setmelanotide administration in patients with Bardet-Biedl syndrome (BBS), biallelic PPL (POMC [pro-opiomelanocortin], PCSK1 [proprotein convertase subtilisin/kexin Type 1], LEPR [leptin receptor]), or heterozygous PPL. Eligible patients are those who are currently taking QD setmelanotide in Trial RM-493-022, referred to as the long-term extension (LTE) trial, for at least 6 months with acceptable safety and tolerability, and who wish to continue with setmelanotide treatment, and who otherwise meet all inclusion and exclusion criteria. Approximately 30 patients will be targeted in 3 age groups as follows: approximately 20 patients who are ≥18 years old; approximately 6 patients ≥12 to <18 years old; and approximately 4 patients ≥6 to <12 years old at the time of trial entry.

The trial consists of a Screening Period for transition from the LTE trial, a Run-in Period of up to 1 week of continuation on the patient's current dose level of QD setmelanotide (2, 2.5, or 3 mg), a 13-week

double-blind phase in which the patients will be randomized to either QD or QW setmelanotide, a 13-week non-randomized open-label phase where all patients will receive open-label QW setmelanotide, and a 3-week follow-up period in which all patients will return to their run-in dose of QD setmelanotide to prepare for re-enrollment into Trial RM-493-022 or to resume the QD formulation in some other way.

During the Screening Period, patients will undergo medical evaluation and other trial procedures, [redacted] To ensure continuity of treatment, informed consent for this trial will be obtained and eligibility of the patient will be confirmed before the patient is withdrawn from the LTE trial.

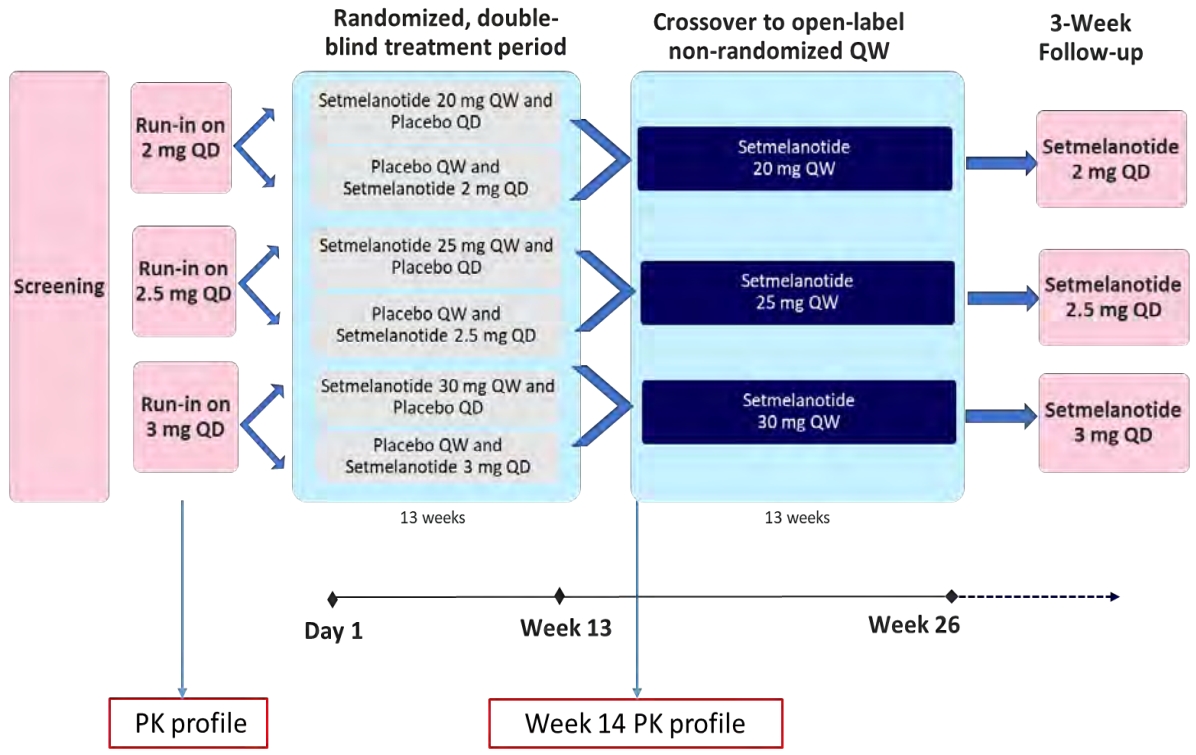
The patient will have a Run-in Period of 1 day to 1 week on QD setmelanotide at the dose they were on in the LTE trial. The first day of the Run-in Period (Visit 2) should coincide with the patient's last visit in the LTE trial to avoid an interruption of treatment. On the first day of the Run-in Period, patients will have serial blood samples taken for measurement of setmelanotide concentrations (QD formulation) and 24-hour PK profiles will be performed.

On Day 1 (Visit 3), patients will be randomized 1:1 to receive either QD or QW setmelanotide. Patients who were on QD setmelanotide at a dose of 2 mg at the time of trial entry will be randomized to receive either QD setmelanotide 2 mg or QW setmelanotide at a dose of 20 mg, whereas patients who were on QD setmelanotide at a dose of 2.5 mg will be randomized to receive either QD setmelanotide 2.5 mg or QW setmelanotide at a dose of 25 mg, and finally patients who were on QD setmelanotide at a dose of 3 mg will be randomized to receive either QD setmelanotide 3 mg or QW setmelanotide at a dose of 30 mg. Study medication will be administered in a double-dummy fashion in order to maintain the double blind. Patients will receive the first QW dose on Day 1 of the randomized treatment period (Visit 3). The randomization will be stratified by age group.

- Patients randomized to QW setmelanotide will receive blinded QW setmelanotide and QD placebo injections until the Week 14 visit (ie, completion of 13 weeks of blinded dose administration). Starting with Week 14, patients will continue with open-label QW injections of setmelanotide during the 13-week non-randomized phase.
- Patients randomized to QD setmelanotide will receive blinded QD setmelanotide and QW placebo injections until the Week 14 visit (ie, completion of 13 weeks of blinded dose administration). Starting with Week 14, patients will continue with open-label QW injections of setmelanotide during the 13-week non-randomized phase.

Prior to the QW dose of study drug at prespecified time points during the double-blind treatment phase, predose blood samples will be collected for trough plasma drug concentrations in all patients. At Week 14, serial blood samples (including a predose blood sample) will be taken for measurement of steady-state setmelanotide concentrations (QD and QW formulations) for a 24-hour PK profile.

For the 3-week Follow-up Period, all patients will return to their run-in dose of QD setmelanotide. The trial design is depicted in the figure below.



Abbreviations: PK = pharmacokinetic, QD = once daily; QW = once weekly.

The safety and tolerability of setmelanotide will be assessed by the frequency and severity of adverse events (AEs)/serious adverse events (SAEs) and injection site reactions (ISRs), as well as changes in physical examination (to include comprehensive skin examination), electrocardiograms (ECGs), vital signs (including resting blood pressure [BP] and heart rate [HR]), routine laboratory evaluations, development of anti-drug antibodies, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

[redacted]

Number of patients (planned):

It is intended that a total of ~30 patients will be enrolled in the trial. Patients will come from 3 targeted age groups: ≥18 years old (~20 patients), ≥12 to <18 years old (~6 patients), and ≥6 to <12 years old (~4 patients).

Diagnosis and main criteria for inclusion:

Patients with BBS, biallelic PPL, and heterozygous PPL who have been on open-label QD setmelanotide treatment for at least 6 months with acceptable safety and tolerability, and the dose level must have been stable at 2, 2.5, or 3 mg of setmelanotide for at least the last 3 months.

Investigational product, dosage and mode of administration:

The setmelanotide QW formulation [redacted] will be provided as a sterile solution at a concentration of 30 mg/mL for administration of dose levels of 20, 25, and 30 mg by subcutaneous (SC) injection.

Setmelanotide QD drug product [redacted] will be provided as a sterile solution at a concentration of 10 mg/mL for administration of dose levels of 2, 2.5 and 3 mg by SC injection. The product will be provided in clear glass vials.

Duration of treatment:

Total duration of treatment with setmelanotide in this trial will be ~30 weeks: a Run-in Period of 1 day to 1 week on QD setmelanotide, 13 weeks on randomized setmelanotide treatment (QD or QW), 13 weeks on non-randomized QW setmelanotide, followed by 3 weeks on the QD formulation.

Reference therapy, dosage and mode of administration:

QD or QW matching placebo for SC injection. Placebo is vehicle only and is identical in appearance to active treatment.

Criteria for evaluation:

Primary Endpoint:

- Comparison of steady-state PK parameters (maximum plasma concentration [C_{max},], time to maximum plasma concentration [T_{max}], trough plasma concentration [C_{trough}], area under the plasma concentration-time curve over the dosing interval [$AUC_{0\text{-}tau}$]) for QW compared with QD setmelanotide

Secondary Endpoint:

- Safety outcomes, including AEs/SAEs, ISRs, and changes in laboratory parameters, vital signs, ECG recordings, and physical examination findings, etc.

[redacted]

Statistical methods:

The primary objective is to assess steady-state PK parameters (C_{max}, T_{max}, C_{trough}, $AUC_{0\text{-}tau}$) for QW compared with QD setmelanotide. The sample size is based on availability of the patients enrolled in the LTE trial and is not driven by formal statistical hypothesis testing on non-inferiority/similarity.

The PK profile of the 2 formulations of setmelanotide will be characterized and the steady-state PK parameters (C_{max}, T_{max}, C_{trough}, and $AUC_{0\text{-}tau}$) will be summarized for QD and QW setmelanotide by dose

level and prior treatment regimen (QW or QD) during the double-blind phase of the trial using descriptive statistics (e.g., n, mean, standard deviation, geometric mean, minimum, median, maximum, % coefficient of variation [CV], geometric mean CV, and confidence intervals [CI]).

[redacted]

AEs/SAEs, including ISRs, as well as discontinuations due to AEs will be summarized descriptively with frequencies and percentages. By-patient AE data listings including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided. Injection site reactions for the QD and QW formulations will be summarized separately.

Safety data including laboratory evaluations, ECGs, physical examinations, and vital signs assessments will be summarized by time of collection. In addition, change from baseline to any postdose values will be summarized for vital signs, ECGs, and clinical laboratory results. Frequency of patients with abnormal safety laboratory results will be tabulated. Continuous outcomes (e.g., vital signs, safety laboratory parameters) will be summarized using n, mean, median, standard deviation, etc.

2. SCHEDULE OF ACTIVITIES

The Schedule of Activities (SoA) to be conducted are depicted in Table 1.

Any patient withdrawing from the trial will complete the Early Termination Visit, if possible.

Screening Period: To ensure continuity of treatment, informed consent for this trial will be obtained and eligibility of the patient will be confirmed before the patient is withdrawn from the long-term extension (LTE) trial. Visit procedures from the last visit of the LTE trial and first visit of this trial are not intended to be duplicated. Thus, any repeat assessments do not need to be conducted and data from the last visit of the LTE trial will be used as Visit 1 data in this trial, as applicable.

Run-in Period: Day 1 of the Run-in Period should coincide with the patient's last visit in the LTE trial to avoid an interruption of treatment. The patient will have a Run-in Period of 1 day to 1 week on QD setmelanotide at the dose they were on in the LTE trial.

Table 1: Schedule of Activities

Trial Period	**Screening*** **(up to 21 days)**	**Run-In$^{\Delta}$ (up to 1 week)**	**Randomized, Double-Blind Treatment (QD and QW)**													**Open-Label Non-Randomized QW Administration**				**Restart QD**	**Follow-up on QD (EoS)**	**Early Termination**
Visit (V) Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V 10**	**V 11**	**V 12**	**V 13**	**V 14**	**V 15**	**V 16**	**V 17**	**V 18**	**V 19**	**V 20**	**V 21**	
Trial Week	**-4**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**16**	**18**	**22**	**27**	**30**	
Trial Day ± Visit Window	**-28 to -8**	**-7 to -1**	**1**	**8 ± 1**	**15 ± 1**	**22 ± 1**	**29 ± 3**	**36 ± 1**	**43 ± 1**	**50 ± 1**	**57 ± 3**	**64 ± 1**	**71 ± 1**	**78 ± 1**	**85 ± 1**	**92 ± 0**	**106 ± 1**	**120 ± 3**	**148 ± 3**	**183 ± 3**	**204 ± 3**	**(n/a)**
In Person Visit	**X**	**X**	**X**				**X**				**X**					**X**		**X**	**X**	**X**	**X**	**X**
Telehealth Visit††				**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**	**X**		**X**					
Informed consent/assent[1]	X																					
Inclusion/exclusion review	X		X																			
Medical history & prior medication review	X		X																			
Fitzpatrick scale	X																			X	X	
Comprehensive skin exam[2]	X																			X	X	X
Randomization			X																			
Pregnancy test[3]	X	X	X†				X†				X†					X†		X†	X†	X†	X†	X†
Study drug: administer[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study drug dispense[4]		X	X				X				X					X		X	X	X		
[redacted]																						

Table 1: Schedule of Activities

Trial Period	Screening* (up to 21 days)	Run-In$^{\Delta}$ (up to 1 week)	Randomized, Double-Blind Treatment (QD and QW)													Open-Label Non-Randomized QW Administration				Restart QD	Follow-up on QD (EoS)	Early Termination
Visit (V) Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V 10**	**V 11**	**V 12**	**V 13**	**V 14**	**V 15**	**V 16**	**V 17**	**V 18**	**V 19**	**V 20**	**V 21**	
Trial Week	**-4**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**16**	**18**	**22**	**27**	**30**	
Trial Day ± Visit Window	**-28 to -8**	**-7 to -1**	**1**	**8 ± 1**	**15 ± 1**	**22 ± 1**	**29 ± 3**	**36 ± 1**	**43 ± 1**	**50 ± 1**	**57 ± 3**	**64 ± 1**	**71 ± 1**	**78 ± 1**	**85 ± 1**	**92 ± 0**	**106 ± 1**	**120 ± 3**	**148 ± 3**	**183 ± 3**	**204 ± 3**	**(n/a)**
In Person Visit	**X**	**X**	**X**				**X**				**X**					**X**		**X**	**X**	**X**	**X**	**X**
Telehealth Visit††				**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**	**X**		**X**					
[redacted]																						
Height[6]	X		X													X				X		X
[redacted]																						
C-SSRS[10]	X	X†	X†				X†				X†					X†		X†	X†	X†	X†	X†
PHQ-9[21]	X	X†	X†				X†				X†					X†		X†	X†	X†	X†	X†
Dosing Diary[11]		X	For each dose administered (QW or QD)																			
[redacted]																						

Table 1: Schedule of Activities

Trial Period	Screening* (up to 21 days)	Run-In$^{\Delta}$ (up to 1 week)	Randomized, Double-Blind Treatment (QD and QW)													Open-Label Non-Randomized QW Administration				Restart QD	Follow-up on QD (EoS)	Early Termination
Visit (V) Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V 10**	**V 11**	**V 12**	**V 13**	**V 14**	**V 15**	**V 16**	**V 17**	**V 18**	**V 19**	**V 20**	**V 21**	
Trial Week	**-4**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**16**	**18**	**22**	**27**	**30**	
Trial Day ± Visit Window	**-28 to -8**	**-7 to -1**	**1**	**8 ± 1**	**15 ± 1**	**22 ± 1**	**29 ± 3**	**36 ± 1**	**43 ± 1**	**50 ± 1**	**57 ± 3**	**64 ± 1**	**71 ± 1**	**78 ± 1**	**85 ± 1**	**92 ± 0**	**106 ± 1**	**120 ± 3**	**148 ± 3**	**183 ± 3**	**204 ± 3**	**(n/a)**
In Person Visit	**X**	**X**	**X**				**X**				**X**					**X**		**X**	**X**	**X**	**X**	**X**
Telehealth Visit††				**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**	**X**		**X**					
PK blood sampling (trough)[13]			X†				X†				X†					X†		X†	X†	X†		
PK profile[14]		X														X†						
Injection site inspection[15]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests[16]	X		X								X					X				X	X	X
Anti-drug antibodies[17]			X								X					X				X		X
[redacted]																						
Vital signs[18]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG (12-lead)[19]	X		X								X					X				X	X	X
Physical exam[20]	X		X				X				X					X		X		X	X	X
Adverse event assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EoS = End of Study; [redacted] HR = heart rate; min = minute; n/a = not applicable; LTE = long-term extension; PHQ-9=Patient Health Questionnaire– 9; PK = pharmacokinetic; QD = once daily; QW = once weekly; V = visit.

* Due to the rarity of these patients and difficulty associated with travel to the trial site, the Screening Period may be extended beyond 3 weeks, if necessary, after discussion with the Sponsor.

Δ The patient will have a Run-in Period of 1 day to 1 week on QD setmelanotide at the dose they were on in the LTE trial. The first day of the Run-in Period (V2) should coincide with the patient's last visit in the LTE trial to avoid an interruption of treatment.

† Assessment/sample should be performed/obtained prior to administration of study drug.

†† Any telehealth visit may optionally be converted to an in-person visit.

[1] Patients who reach the age of consent during the trial must be re-consented, as applicable.

[2] A comprehensive skin evaluation will be performed by the Investigator. Any concerning lesions identified during the Screening Period will be biopsied and results known to be benign prior to trial entry. If the pretreatment biopsy results are of concern, the patient will be excluded from the trial.

[3] A urine pregnancy test may be performed in order to expedite availability of results prior to the first dose at Run-in (V2). All other pregnancy tests will be serum; dosing may continue with results pending.

[4] For the QD doses of study drug, patients/caretakers will draw up and self-administer/administer the study drug each morning beginning with the first dose of Run-in (V2) and for the duration of the 13-week double-blind period. In addition, once each week the QW dose of study drug will be prepared and administered at the trial center or self-administered/administered by the patient/caretaker in between visits. A home healthcare provider can optionally be made available at the patient's home to administer or supervise administration of the QW dose. The patient will receive the first QW dose on Day 1 (V3) at the trial center. On the days of in-person clinic visits, the patients/caretakers will self-administer/administer the QD dose of study drug in the clinic in the presence of the clinical staff to assure proper technique. For accountability, patients/caretakers will return all used vials to the clinic when they visit; the trial staff will record the number returned; and both study drug administration at the clinic, as well as outpatient study drug administration will be recorded in a trial diary.

[redacted]

[6] For patients ≥21 years of age, height will be measured only during the Screening Period. 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. All measurements will be done in triplicate at each timepoint and recorded to the nearest half cm. The stadiometer should be calibrated on a daily basis prior to height assessment.

[redacted]

[redacted]

[10] The Baseline/Screening version of the C-SSRS should only be administered to patients who have never completed an initial C-SSRS assessment prior to entering this trial; however, this version is expected to have been completed in the index trial for all patients prior to entry into this trial. The Screening version of the C-SSRS is to be completed at the Screening visit. At all subsequent visits, the Since Last Version is to be completed. If at any time during the trial a patient has suicidal ideation of type 4 or 5, or any suicidal behavior, the patient should be referred to a mental health professional.

[11] The dosing diary will be completed for all QD and QW dose administration.

[redacted]

[13] A blood sample for trough plasma levels of setmelanotide will be drawn within 30 minutes prior to dosing of QD or QW study drug. On the days when PK profiles are done, the predose (trough) PK sample will be drawn within 30 minutes prior to any study drug administration. No visit window is allowed for Week 14, which must occur exactly 7 days after the Week 13 (V15) dose administration. (i.e., if the Week 13 (V15) visit occurs on Day 86, the Week 14 (V16) visit must occur on Day 93). Patients/caretakers will be reminded that there should be NO study drug administration at home on the day of clinic visits; the drug will be administered in the clinic AFTER the predose PK sample is obtained. For the PK sample, the actual collection (clock) time will be recorded, as well as the time of the previous day's study drug injection as reported by the patient/caretaker.

[14] Patients will undergo serial blood samples taken for measurement of steady-state setmelanotide concentrations (both QD and QW) and PK profiles will be performed. On the first day of the Run-in Period, blood samples for the QD PK profile will be drawn within 30 minutes prior to dose administration. Postdose samples will be collected at: 0.5, 1, 2 (±5 mins), 6, 8, 12, and 24 hours (±30 min). At minimum, mandatory postdose samples must be collected at: 6 and 8 hours (±30 min) and at 24 hours (±30 min). At Week 14, blood samples for the PK profiles will be drawn within 30 minutes prior to dose administration. Postdose samples will be collected at: 0.5, 1, 2 (±5 mins), 6, 8, 12, 24, 48, 72, 96, 120, and 168 hours (±30 min). At minimum, mandatory postdose samples must be collected at: 6 and 8 hours (±30 min), 24 hours (±30 min), 48, 72, 96, 120 hours (±30 min), and 168 hours (±30 min) In case of significant challenges with the collection of any PK sample, the investigator should confirm sample prioritization with the sponsor. Patients/caretakers will be reminded that there should be NO study drug administration at home on the day of clinic visits and that the predose (trough) blood draw must occur PRIOR to study drug administration. The blood draws for the Week 14 PK sampling must occur exactly 7 days after the prior visit. The Investigators will adhere to the site-specific blood volume limits for safety laboratory and PK analyses both to ensure minimal distress and reduce the number of venipunctures in pediatric patients. For patients <18 years of age, it may not be possible to collect all labs at every trial visit, though efforts should be made to collect as many PK samples per protocol. Venipuncture reduction is allowed should a patient <18 years of age experience unacceptable discomfort as deemed by the Investigator.

[15] Injection site evaluations and scoring (by the clinical staff) will include identification of areas of erythema, edema, and induration, as well as the presence of localized pain, tenderness, and itching. At in-person trial visits, the clinical staff will also record measurements of areas of erythema, edema, and induration if possible. Unscheduled evaluations may also be recorded as warranted by clinical conditions.

[16] Safety laboratory tests will include: complete blood count with platelet count and standard indices, chemistry panel, coagulation, and urinalysis with microscopic analysis (if positive findings on dipsticks warrant further examination). For patients <18 years of age, it may not be possible to collect all laboratory samples at every trial visit. Screening may be performed over multiple days, to complete the required assessments. After enrollment, if not all lab tests are possible, then the tests should be collected in the following descending order of priority: safety, anti-drug antibodies, trough PK, [redacted]

[17] Any patient with a positive ADA at the end of trial or early termination will be followed every 3 months after the sample analysis until resolution (ie, no measurable ADA response).

[18] All BP and HR 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, BP should be taken in the non-dominant arm throughout the trial, using the same methodology (automated or manual). Body temperature (°C) and respiration rate (breaths/minute) will be obtained in the sitting position following at least 5 minutes of rest. Note that for virtual visits, BP will be collected.

[19] A single 12-lead ECG will be performed with the patient in the supine position following a period of at least 10 minutes of rest.
[20] A complete physical examination will be conducted at Screening and at the end of trial (Week 30). At other time points, an abbreviated examination, noting any changes from baseline will be performed. 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.
[21] If at any time during the trial an individual patient's PHQ-9 score is ≥10, the patient should be referred to a Mental Health Professional.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibodies
ADV	Audio Data Verification
AE	Adverse event
$AUC_{0\text{-}tau}$	Area under the plasma concentration-time curve over the dosing interval
BBS	Bardet-Biedl syndrome
[redacted]	[redacted]
BP	Blood pressure
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum plasma concentration
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CRA	Clinical Research Associate
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough plasma concentration
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
[redacted]	[redacted]
HR	Heart rate

Abbreviation or Specialist Term	Explanation
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IRT	Interactive response technology
ISR	Injection site reaction
IUD	Intrauterine device
LEPR	Leptin receptor
LTE	Long-term extension
MC4R	Melanocortin-4 receptor
MHP	Mental health professional
[redacted]	
MSH	Melanocyte-stimulating hormone
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
PCSK1	Proprotein convertase subtilisin/kexin type 1
PHQ-9	Patient Health Questionnaire-9
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
P/LP	Pathogenic, likely pathogenic
PPL	POMC (pro-opiomelanocortin), PCSK1 (proprotein convertase subtilisin/kexin type 1), LEPR (leptin receptor)
POMC	Pro-opiomelanocortin
QD	Once daily
QW	Once weekly
rDV	Remote Data Verification
RGDO	Rare genetic disorders of obesity
rIMV	Remote Interim Monitoring Visit
rSDM	Remote Source Data Monitoring
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation or Specialist Term	Explanation
SARS-COV-2	Severe acute respiratory syndrome coronavirus-2
SC	Subcutaneous
SMC	Site Monitoring Visit
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reaction
T_{max}	Time to maximum plasma concentration
US	United States
VUS	Variant of uncertain significance

3. INTRODUCTION

3.1. Rationale for the Trial

Obesity is a multifactorial disease caused by various environmental, neurobehavioral, immunological, endocrine, medical, and genetic/epigenetic factors or a complex interplay between 2 or more of these factors (Maes 1997; Schousboe 2003; Silventoinen 2010; Hall 2012; Pigeyre 2016; Sheikh 2017; Thaker 2017). In a subset of individuals with obesity, rare genetic variants may result in severe obesity. The identification of key genetic determinants of the neuronal pathways and signaling molecules (e.g., leptin) regulating appetite and body weight has led to the discovery of multiple rare genetic disorders of obesity (RGDO) (van der Klaauw 2015). A key neuronal pathway, the central melanocortin and melanocortin-4 receptor (MC4R) pathway, plays an important role in appetite, hunger, and energy utilization. The melanocortins are a family of peptide hormones (including adrenocorticotropic hormone, α-melanocyte-stimulating hormone [MSH], β-MSH, and γ-MSH) derived from the common precursor, pro-opiomelanocortin (POMC). Originating in the hypothalamus, the MC4R pathway concertedly modulates appetite (feelings of hunger and satiety), energy intake (as caloric consumption), and energy expenditure (basal metabolism, thermogenesis, and physical activity) to define long-term body weight.

In humans and animal models, genetic defects in the MC4R pathway, such as POMC deficiency, result in severe forms of early-onset obesity and hyperphagia (Farooqi 2008). Patients with rare genetic variants in leptin receptor (LEPR) and patients with Bardet-Biedl syndrome (BBS, a rare pleiotropic autosomal recessive disorder caused by mutations in as many as 24 different genes) also present with unremitting hunger and severe obesity caused in part by a lack of activation of the MC4R pathway. As a result of hyperphagia, individuals with RGDO have increased calorie intake leading to early-onset, severe obesity, and obesity-related comorbidities such as type 2 diabetes. The Sponsor is developing setmelanotide (also known as RM-493), an MC4R agonist, as a treatment for patients with RGDO. Setmelanotide bypasses upstream signaling defects to directly activate MC4R. Setmelanotide binds with high affinity (inhibitory constant = 2.1 nM) to the human MC4R and is efficient in activating MC4R (50% effective concentration = 0.27 nM). Thus, setmelanotide, has the potential to restore reduced activity in the MC4R pathway in patients with these and other genetic defects and may serve as a form of “replacement” therapy to re-establish weight and appetite control in patients with these disorders.

The purpose of this trial is to compare the QW and QD formulations of setmelanotide in patients with biallelic PPL, heterozygous PPL, and patients with BBS. QW dosing is expected to provide a more convenient dosing regimen for these patients and would be more suitable for younger patients than QD dosing. In addition, QW dosing would be expected to improve compliance, especially given the long-term requirement for continued dose administration in order to achieve sustained benefits.

3.2. Setmelanotide Benefit/Risk Assessment

In patients with RGDO, setmelanotide has been associated with clinically meaningful reductions in weight and improvement in hunger. In particular, in patients with POMC or LEPR deficiency obesity, who are characterized by early-onset obesity, severe hunger and progressive weight gain, setmelanotide has demonstrated clinically meaningful and statistically significant weight reduction, often bringing patients with very high morbid obesity body mass index (BMI) (>40 kg/m^2) to BMI ranges in the overweight or normal range (<30 kg/m^2). In addition to weight loss, setmelanotide has demonstrated clinically meaningful and statistically significant decreases in hunger. Both the decreased hunger and the weight loss continued over 52 weeks of treatment and are maintained with continued setmelanotide treatment. Furthermore, following the significant weight loss with setmelanotide treatment, there were improvements in lipids and

other parameters, as well as body composition with decreased fat mass and decreased waist circumference. These weight loss changes were accompanied by improvements in quality of life.

Setmelanotide is well tolerated. Side effects of setmelanotide are predictable, well understood, and do not present significant safety concerns. Collectively, safety data obtained to date show that adverse events (AEs) commonly associated with setmelanotide include injection site reactions (ISRs) and skin hyperpigmentation. Less commonly, nausea and vomiting were reported and rarely, sexual AEs have been observed. Potential mechanistic-based events such as hypertension have been assessed throughout the setmelanotide clinical development program and have not been observed. Events associated with severe obesity such as depression and suicidal ideation occurred infrequently and were assessed as not related to setmelanotide.

Specifically, regarding children less than 12 years old, the AEs reported in this population were consistent with those reported in other studies of setmelanotide. Adverse events reported as related to setmelanotide treatment were consistent with the known safety profile. No evidence for concern regarding bone development has been observed.

Daily injection of setmelanotide is technically challenging for pediatric patients and patients with poor coordination/vision or other physical challenges, thus, the Sponsor is developing the weekly formulation to improve compliance and to address user limitations, with the hypothesis that safety and [redacted] between the two formulations will be comparable.

In summary, the QD setmelanotide formulation has a positive benefit-risk profile in patients with genetic defects upstream of the MC4R pathway and the QW formulation may have the added advantage of a more convenient dosing regimen.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of setmelanotide may be found in the Investigator's Brochure.

4. OBJECTIVES AND ENDPOINTS

The objectives and endpoints are described in Table 2.

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the PK of the QD and QW formulations of setmelanotide	• Comparison of steady-state PK parameters (C_{max}, T_{max}, C_{trough}, $AUC_{0\text{-}tau}$) for QW compared with QD setmelanotide
Secondary	
• To assess the safety of the QW formulation of setmelanotide with up to 6 months (26 weeks) of drug administration	• Safety outcomes, including AEs/SAEs, ISRs, and changes in laboratory parameters, vital signs, ECG recordings, and physical examination findings, etc.
[redacted]	

Abbreviations: AE = adverse event; $AUC_{0\text{-}tau}$ = area under the plasma concentration-time curve over the dosing interval; [redacted]; C_{max} = maximum plasma concentration; C_{trough} = trough plasma concentration; ECG = electrocardiogram; [redacted] ISR = injection site reaction; PK = pharmacokinetic; QD = once daily; QW = once weekly; SAE = serious adverse event; T_{max} = time to maximum plasma concentration.

5. INVESTIGATIONAL PLAN

5.1. Overall Trial Design

This trial is designed to compare the safety, pharmacokinetics (PK), and [redacted] of the QW and QD formulations of setmelanotide, as well as to evaluate the safety and [redacted] of up to 6 months of QW setmelanotide administration in patients with BBS, biallelic PPL, or heterozygous PPL. Eligible patients are those who are currently taking QD setmelanotide in Trial RM-493-022, referred to as the long-term extension (LTE) trial, for at least 6 months with acceptable safety and tolerability, and who wish to continue with setmelanotide treatment, and who otherwise meet all inclusion and exclusion criteria. Approximately 30 patients will be targeted in 3 age groups as follows: approximately 20 patients ≥18 years old; approximately 6 patients ≥12 to <18 years old; and approximately 4 patients ≥6 to <12 years old at the time of trial entry.

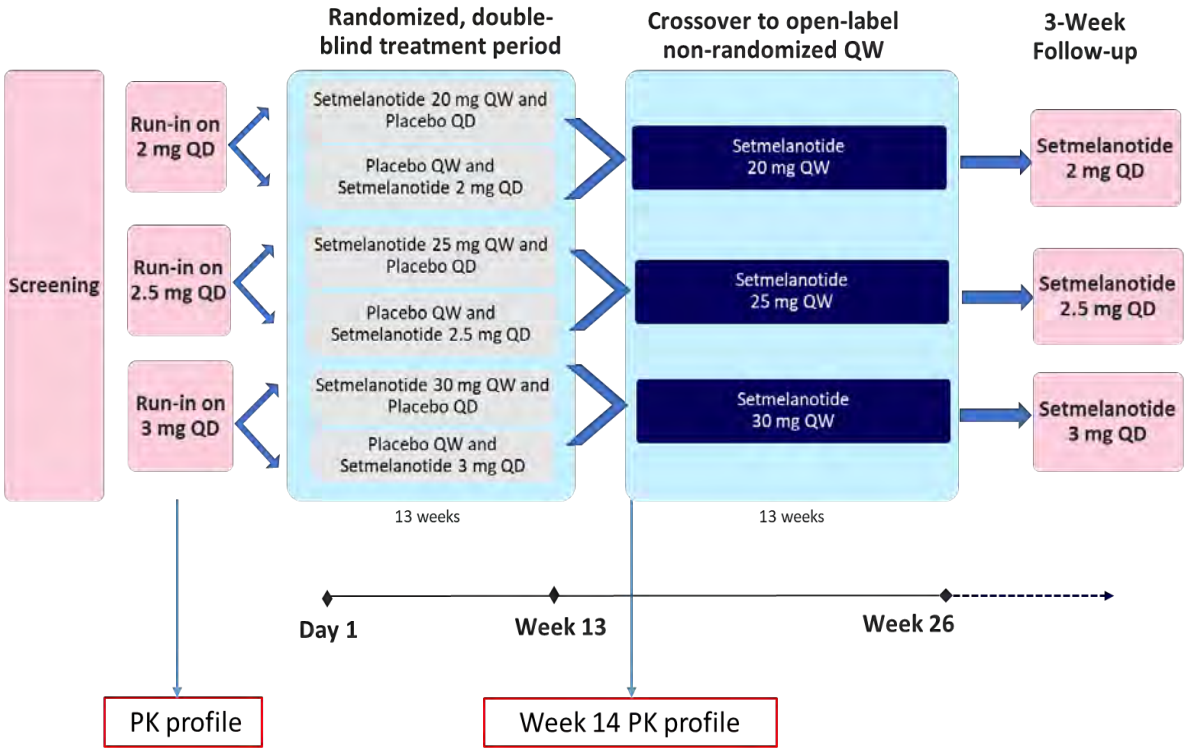
The trial consists of a Screening Period for transition from the LTE trial, a Run-in Period of up to 1 week of continuation on the patient's current dose level of QD setmelanotide (2, 2.5, or 3 mg), a 13-week double-blind phase in which the patients will be randomized to either QD or QW setmelanotide, a 13-week non-randomized open-label phase where all patients will receive open-label QW setmelanotide, and a 3-week follow-up period in which all patients will return to their run-in dose level of QD setmelanotide to prepare for re-enrollment into Trial RM-493-022 or to resume the QD formulation in some other way.

The safety and tolerability of setmelanotide will be assessed by the frequency and severity of AEs/serious adverse events (SAEs) and ISRs, as well as changes in physical examinations (to include comprehensive skin examinations), electrocardiograms (ECGs), vital signs (including resting blood pressure [BP] and heart rate [HR]), routine laboratory evaluations, development of anti-drug antibodies (ADA), and the Columbia-Suicide Severity Rating Scale (C-SSRS).

[redacted]

The trial design is depicted graphically in Figure 1.

Figure 1: Trial Design



Abbreviations: PK = pharmacokinetic; QD = once daily; QW = once weekly.

5.1.1. Screening Period

Upon providing informed consent, patients will 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 2). During the Screening Period, patients will undergo medical evaluation and other trial procedures, [redacted] To ensure continuity of treatment, informed consent for this trial will be obtained and eligibility of the patient will be confirmed before the patient is withdrawn from the LTE trial.

5.1.2. Run-In Period

The patient will have a Run-in Period of 1 day to 1 week on QD setmelanotide at the dose they were on in the LTE trial. The first day of the Run-in Period (Visit 2) should coincide with the patient's last visit in the LTE trial to avoid an interruption of treatment. The first dose of QD setmelanotide as part of the RM-493-037 trial will occur in clinic on the first day of the run-in period.

On the first day of the Run-in Period, patients will have serial blood samples taken for measurement of setmelanotide concentrations (QD formulation) and 24-hour PK profiles will be performed.

5.1.3. Double-Blind and Open-Label Treatment Periods

On Day 1 (Visit 3) patients will be randomized 1:1 to receive either QD or QW setmelanotide. Patients who were on QD setmelanotide at a dose of 2 mg at the time of trial entry will be randomized to receive either QD setmelanotide 2 mg or QW setmelanotide at a dose of 20 mg, whereas patients who were on QD setmelanotide at a dose of 2.5 mg will be randomized to receive either QD setmelanotide 2.5 or QW setmelanotide at a dose of 25 mg, and finally patients who were on QD setmelanotide at a dose of 3 mg will be randomized to receive either QD setmelanotide 3 mg or QW setmelanotide at a dose of 30 mg. Study medication will be administered in a double-dummy fashion in order to maintain the double blind. Patients will receive the first QW dose on Day 1 of the randomized treatment period (Visit 3). The randomization will be stratified by age group.

- Patients randomized to QW setmelanotide will receive blinded QW setmelanotide and QD placebo injections until the Week 14 visit (ie, completion of 13 weeks of blinded dose administration). Starting with Week 14, patients will continue with open-label QW injections of setmelanotide during the 13-week non-randomized phase.
- Patients randomized to QD setmelanotide will receive blinded QD setmelanotide and QW placebo injections until the Week 14 visit (ie, completion of 13 weeks of blinded dose administration). Starting with Week 14, patients will continue with open-label QW injections of setmelanotide during the 13-week non-randomized phase.

Prior to the QW dose of study drug at prespecified time points during the double-blind treatment phase, predose blood samples will be collected for trough plasma drug concentrations in all patients. At Week 14, serial blood samples (including a predose blood sample) will be taken for measurement of steady state setmelanotide concentrations (QD and QW formulations) for 24-hour PK profiles.

5.1.4. Follow-up Period

For the 3-week Follow-up Period, all patients will return to their run-in dose of QD setmelanotide to prepare for re-enrollment into Trial RM-493-022 or to resume the QD formulation in some other way.

5.1.5. Patient and Trial Completion

A patient is considered to have completed the trial if he/she has completed the trial through the 3-week follow-up period.

A patient who discontinues before completing all planned visits is to attend an Early Termination visit within 14 days (±7 days) after their last dose of study medication for final trial assessments.

The end of the trial is defined as the date of the last visit of the last patient under the auspices of the current trial.

5.2. Discussion of Trial Design

Patients to be enrolled in this trial will be those who have been on open-label QD setmelanotide treatment in the LTE trial for at least 6 months with acceptable safety and tolerability, and the dose level must have been stable at 2, 2.5, or 3 mg of setmelanotide for at least the last 3 months.

Switching these patients from the daily to the weekly formulation will allow intra-patient comparison of the PK profiles of the 2 formulations as well as comparisons of safety and [redacted] between the 2 formulations.

For patients randomized to QW setmelanotide, this trial design will allow the pattern of [redacted] to be observed for 6 months on the QW formulation as a patient switches from the daily formulation during the Run-in Period to the weekly formulation of setmelanotide.

To maintain the blind during the randomized treatment period, all patients will receive placebo injections [redacted] from the QD formulation or [redacted] from the QW formulation) in addition to the setmelanotide injections in a double-dummy fashion. Placebo and active study drug will be visually indistinguishable.

A formal non-inferiority trial design for the QD vs QW formulation is not feasible because a large sample size would be required, which is unachievable in RGDO. Therefore, the sample size is primarily driven by availability of patients on stable doses of setmelanotide and by other clinical considerations.

5.3. Dosing Rationale

Patients to be enrolled in this trial will be those who are on open-label QD setmelanotide treatment at a dose level of 2, 2.5, or 3 mg. Given the PK, safety, and [redacted] results for otherwise healthy patients with obesity in Trial RM-493-026, it is anticipated that 30 mg QW setmelanotide will provide PK, safety, and [redacted] comparable to the 3 mg QD setmelanotide dose.

Likewise, it is anticipated that 25 mg QW setmelanotide will provide PK, safety, and [redacted] comparable to the 2.5 mg QD setmelanotide dose and that 20 mg QW setmelanotide will provide PK, safety, and [redacted] comparable to the 2 mg QD setmelanotide dose.

5.4. Trial Termination

This trial may be terminated, if in the opinion of the Investigator (at a participating site) or the Sponsor, there is sufficiently reasonable cause. The terminating party will provide written notification documenting the reason for termination to either the Investigator(s) or Sponsor.

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

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend, or discontinue the development of the study drug

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

5.5. Trial Conduct During the Coronavirus Pandemic

The worldwide coronavirus disease 2019 (COVID-19) pandemic may impact the conduct of clinical studies due to the challenges from quarantines, site closures, travel limitations, and other considerations if site personnel or trial participants become potentially exposed to or infected with COVID-19. To assure the safety of trial participants, to maintain compliance with Good Clinical Practice (GCP), and to minimize risks to trial integrity, if necessary, in consultation with the Sponsor, the method of assessment may be changed (e.g., paper assessments replaced by electronic assessments). In addition, site visits may be replaced with telephone, internet-based video-conferencing applications, or home visits by qualified health care professionals. Normal procedures, as detailed in this protocol, will be resumed as soon as possible thereafter.

More detailed guidance on trial conduct during the COVID-19 pandemic is provided in Appendix 1.

6. SELECTION AND WITHDRAWAL OF PATIENTS

6.1. Patient Inclusion Criteria

Patients must meet all of the following criteria to be eligible for trial participation:

1. All patients must have met the criteria for diagnosis of a gene defect in the MC4R pathway (BBS, biallelic PPL, heterozygous PPL), for which they are being treated with QD setmelanotide.
2. Patients must be ≥6 years old at screening.
3. Patients must have been taking the setmelanotide QD formulation for at least 6 months in the LTE trial with acceptable safety and tolerability, and the dose level must have been stable at 2, 2.5 or 3 mg of setmelanotide for at least the last 3 months prior to starting the Run-in Period.
4. Patient and/or parent or guardian is able to communicate well with the Investigator, to understand and comply with the requirements of the trial and is able to understand and sign the written informed consent/assent.
5. Patient must meet one of the following requirements:

   Female participants of childbearing potential, defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), must be confirmed non-pregnant and agree to use a highly effective form of contraception throughout the trial and for 90 days following the trial. Highly effective forms of contraception are detailed below and in Section 8.8.7:

   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
   - Progestin-only hormonal contraception associated with inhibition of ovulation (oral, implantable, or injectable)
   - Intrauterine device (IUD)

- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomy/vasectomized partner (provided that the vasectomized partner is the sole sexual partner of the female participant, and the vasectomized partner has received medical assessment of surgical success)
- Sexual abstinence, only if it is the preferred and usual lifestyle of the patient

Female participants of non-childbearing potential, defined as: permanently sterile (status post hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or post-menopausal for at least 12 months (and confirmed with a screening follicle-stimulating hormone (FSH) level in the post-menopausal lab range) do not require contraception during the trial.

Younger female patients who have not achieved sexual maturity at trial entry will be assessed for Tanner staging and required to comply with contraception requirements at first menarche.

Male participants with female partners of childbearing potential must agree to use a highly effective method of contraception if they become sexually active during the trial or within 90 days following their participation in the trial. Male patients must also not donate sperm during and for 90 days following their participation in the trial.

6.2. Patient Exclusion Criteria

A patient who meets any of the following criteria will be excluded from this trial.

1. HbA_{1C} >9.0% at screening.
2. Has taken a medication that is approved to treat obesity (e.g., orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion) within 3 months prior to starting the Run-in Period. Glucagon-like peptide-1 (GLP-1) receptor agonists being prescribed for the treatment of obesity are not allowed.
3. History of significant liver disease or liver injury, or a current liver assessment due to abnormal liver tests for an etiology other than nonalcoholic fatty liver disease (NAFLD). Thus, any underlying etiology besides NAFLD, including diagnosed nonalcoholic steatohepatitis (NASH), other causes of hepatitis, or history of hepatic cirrhosis is exclusionary, but the presence of NAFLD is not exclusionary.
4. Moderate to severe renal dysfunction as defined by a glomerular filtration rate <30 mL/min (based upon the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine equation 2021 from the National Kidney Foundation). In patients <18 years of age the Bedside Schwartz Equation should be used to calculate estimated glomerular filtration rate (eGFR).
5. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of comprehensive skin evaluation performed by the Investigator during screening. Any concerning lesions identified during the Screening Period will be biopsied and results

must be known to be benign prior to enrollment. If the pretreatment biopsy results are of concern, the patient should be excluded from the trial.

6. Diagnosis of schizophrenia, bipolar disorder, personality disorder, or other psychiatric disorders that the Investigator believes will interfere significantly with trial compliance. Neurocognitive disorders affecting ability to consent will not be disqualifying as long as an appropriate guardian able to give consent has been appointed.
7. Clinically significant depression or suicidality as defined by: any suicidal ideation of type 4 or 5 on the C-SSRS, any lifetime history of a suicide attempt, or any suicidal behavior in the last month or a Patient Health Questionnaire-9 (PHQ-9) score of ≥15 during Screening in patients with no significant neurocognitive deficits.
8. Patient is not suitable, in the opinion of the Investigator, to participate in the trial.
9. Hypersensitivity to the active substance or to any of the excipients of the investigational products (active or placebo).
10. Inability to comply with the QW and QD injection regimens.
11. Participation in any clinical trial with an investigational drug/device within 3 months prior to the first day of dosing, with the exception of a setmelanotide clinical trial.
12. Legally protected persons per local regulations (e.g., those that fall under the L1121-6 article of the Public Health code in France) or other applicable local laws.
13. The patient or a relative of the patient is the investigator or a sub-investigator, research assistant, pharmacist, trial coordinator, or other staff directly involved with the conduct of the trial.

6.3. Re-Screening

Patients may be re-screened once if the screen failure is due to an entry criterion result that may change over time (e.g., HbA1c >9.0%). In this situation, the patient may be re-screened after at least 1 month and no more than 6 months. Re-screening of a patient is up to the discretion of the Sponsor and must be approved by the Sponsor prior to any re-screening procedures. Re-screened participants must be informed and provide consent again at re-screening. All screening procedures and assessments must be performed at re-screen.

6.4. Patient Withdrawal Criteria

Given this rare patient population, every effort will be made to encourage and keep patients enrolled in the trial until completion, regardless of premature study drug discontinuation, unless there are any safety concerns necessitating withdrawal of the patient. The Sponsor will provide assistance for patient and caregiver travel and will provide other necessary logistical support to ease the burden on the patient in order to facilitate compliance.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site trial records.

Patients will be informed that they have the right to withdraw from the trial at any time for any reason, without prejudice to their medical care. The Investigator also has the right to withdraw patients from the trial for reasons such as:

- AEs, which in the opinion of the Investigator, justifies treatment or trial withdrawal. Appendix 3
- Non-adherence to the study drug regimen or protocol requirements.
- Non-compliance with instructions or failure to return for follow-up.

7. TREATMENT OF PATIENTS

7.1. Description of Study Medication

All study medication is for investigational use only and is to be used only within the context of this protocol. All investigational study medication (setmelanotide QW formulation, QD formulation, and vehicle placebos) will be supplied by the Sponsor.

Setmelanotide QW formulation will be provided as a sterile solution at a concentration of 30 mg/mL for administration at dose levels of 20, 25, and 30 mg by SC injection. Setmelanotide QW drug product consists of setmelanotide dissolved in a liquid lipid phase consisting of key excipients, soy phosphatidylcholine and glycerol dioleate. The solution is a clear, pale yellow to yellow solution, practically free from particles. The placebo for the QW formulation will consist of the vehicle only (no active ingredient) and will be visually indistinguishable from the QW drug product.

Setmelanotide QD drug product ([redacted]) will be provided as a sterile solution at a concentration of 10 mg/mL for administration at dose levels of 2, 2.5, and 3 mg by SC injection. Setmelanotide is a clear to slightly opalescent, colorless to pale yellow solution essentially free of visible particulates. The QD formulation will be provided in clear glass vials. The placebo for the QD formulation will consist of the vehicle only (no active ingredient), will be visually indistinguishable from the drug product, and will be provided in clear glass vials.

7.2. Randomization and Blinding

Patients will be randomized on Day 1 (Visit 3) to treatment with either QD or QW setmelanotide. The trial staff will utilize an interactive response technology (IRT) system to obtain the randomization number for each patient.

No randomization or blinding will be done for the 13-week open-label phase or for the 3-week QD follow-up phase.

7.2.1. Blinding and Unblinding

To maintain the blind during the 13-week randomized treatment period, all patients will receive placebo injections [redacted] from the QD formulation or [redacted] from the QW formulation) in addition to the setmelanotide injections in a double-dummy fashion.

Blinded randomization will occur via an IRT system.

Emergency unblinding for AEs may be performed through an IRT system. The IRT system will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's intervention assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor before unblinding a patient's intervention assignment unless this could delay emergency treatment for the patient. The date and reason for the unblinding by the Investigator must be recorded. If a patient's intervention assignment is unblinded, the Sponsor must be notified by the Investigator within 24 hours that an unblinding occurred. The Investigator should not reveal to the Sponsor the patient's treatment allocation unless the Sponsor requests this information for safety purposes.

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

7.3. Administration

Details on preparation and administration of setmelanotide for dosing are provided in the Pharmacy Manual. Extensive training on drug administration, including educational materials, will be provided to the patients/caregivers. Trial-specific training materials will be provided to both the investigative staff and trial participants and caregivers. Both the QW and QD formulations of setmelanotide will be administered by SC injection. A home healthcare provider may be contracted to observe or perform the administration of injections of the QW study drug to the patient at the patient's home.

All patients will receive QD setmelanotide injections during the Screening (supplied by the LTE trial) and during the Run-in Periods (supplied under this protocol). For the QD doses of study drug supplied under this protocol, patients/caretakers will draw up and self-administer/administer the study drug each morning during the Run-in Period.

Starting on Day 1 (Visit 3) of the trial and throughout the duration of the double-blind period, study medication will be administered in a double-dummy fashion. Patients randomized to QW setmelanotide will concurrently receive QD injections of placebo [redacted] Patients randomized to QD setmelanotide will concurrently receive QW injections of placebo [redacted] For the QD doses of study drug, patients/caretakers will draw up and self-administer/administer the study drug each morning during the double-blind period. On the days of in-person clinic visits, the patients/caretakers will administer the QD dose of study drug in the clinic in the presence of the clinical staff to assure proper technique. In addition, once each week, the QW dose of study drug will be prepared and administered by the trial staff at the trial center or by the patient, caretaker, or home healthcare provider, if applicable, at the patient's home. The patient will receive the first QW dose on Day 1 (Visit 3) at the trial center. The QD study drug and QW study drug should not be administered in the same location. The location of each

injection will be documented so that any ISRs resulting from QD study drug will be differentiated from those resulting from QW study drug.

During the non-randomized phase, all patients will receive open-label QW setmelanotide prepared and administered by the trial staff at the trial center or by the patient, caretaker, or health home care provider, as applicable, at the patient's home. During the follow-up period, all patients will return to QD setmelanotide (self-administered or administered by the patient's caretaker) at the dose they were on at the time of trial entry.

Dose adjustment is not permitted during the trial. Any change in dose must be captured as a protocol violation, regardless of the rationale for the dose adjustment.

7.4. Treatment Compliance

Accountability for the study drug (including placebo) at the trial site is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the delivery date to the site, inventory at the site, use by each patient, return of all used study drug to the trial center, and return to the Sponsor (or disposal of the drug, if approved by the Sponsor) will be maintained by the clinical site. Reasons for departure from the expected dispensing regimen must also be recorded. The Sponsor or its designee will review drug accountability at the site during monitoring visits.

Compliance with dosing will be monitored throughout the trial by having the patient/caregiver capture dosing in an electronic diary, and by accounting for vials dispensed and returned (used and partially used).

7.5. Preparation/Handling/Storage/Accountability

Only patients enrolled in the trial may receive study medication and only authorized site staff may supply study medication. All study medication must be stored at the trial center in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff. The Investigator is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

All study medication must be kept at a temperature between 2°C to 8°C. Both formulations are stable at room temperature for a short time period that will allow patients to transport study drug home; ice packs and cooler bags will be provided for patients and caretakers who have to travel a long distance from the clinic. Once at home, the unopened study medication must be stored in the patient's refrigerator.

For accountability, patients/caretakers will return all used vials to the clinic when they visit, the trial staff will record the number returned, and both study drug administration in the clinic and outpatient study drug administration will be recorded in a trial diary.

7.6. Concomitant Medications

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the trial must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

GLP-1 receptor agonists may be used up to the dose approved for the treatment of diabetes mellitus (e.g., liraglutide up to a daily dose of 1.8 mg) as long as (1) it is not being prescribed for the treatment of obesity, (2) the dose has been stable for at least 3 months prior to enrollment, (3) the patient has not experienced weight loss during the previous 3 months, AND (4) the patient intends to keep the dose stable throughout the course of the trial.

All concomitant medications should be kept at a stable dose throughout the course of the trial, unless a dose change is necessary to treat an AE.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Patients should not make significant changes to their diet or exercise routines during the course of the trial.

7.6.1. Prohibited Medications

Medications that are approved to treat obesity (e.g., orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion) are not allowed within 3 months prior to the first dose of study medication (e.g., enrollment) and are prohibited during the course of the trial. GLP-1 receptor agonists being prescribed for the treatment of obesity are not allowed.

8. ASSESSMENTS

Trial procedures and their timing are summarized in the SoA (Section 2). Adherence to the trial design requirements, including those specified in the SoA is essential and required for trial conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

When scheduled at the same time point, the order of procedures should be as follows: obtain vital signs, perform 12-lead ECG, and perform blood draws (at the specified time point, if applicable). Adjustments may be made depending upon specific circumstances and in consultation with the Sponsor.

For patients <18 years of age, it may not be possible to perform all planned assessments at each visit. Thus, as described in the SoA (Section 2), the Investigator will be given latitude to adjust

the planned assessments and blood draws as appropriate for the optimal medical care of the patients.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

8.1. Informed Consent/Assent

The method of obtaining and documenting the informed consent and assent (if applicable) and the contents of the consent will comply with current International Council for Harmonisation (ICH) E6 GCP Guidelines and all applicable laws and regulations. A complete description of the trial is to be presented to each potential patient or parent/legal guardian and a signed and dated informed consent form (ICF) and/or assent form is to be obtained before any trial-specific procedures are performed. Patients must be informed of and provide consent/assent to the most current version of the ICFs during their participation in the trial, and a copy of the ICF(s) must be provided to the patient or their legally authorized representative. Patients who reach the age of consent during the trial must be re-consented, as applicable, per local laws.

Procedures conducted as part of the LTE trial or patient's routine clinical management (e.g., laboratory tests) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 2).

8.2. Inclusion/Exclusion Review

Inclusion and exclusion criteria must be carefully reviewed to ensure the patient is eligible for the trial.

8.3. Demographics, Concomitant Medications and Medical History

Medical history and demographic data including the patient's gender, race, date of birth, and concomitant medication use will be obtained for all patients during the Screening Period. Additionally, the patient's history of childhood obesity and previous weight loss efforts will be collected.

The medical history should be updated on Day 1 (Visit 3) prior to the first dose of randomized study drug, to assess continued trial eligibility and adherence to final inclusion/exclusion criteria. This medical history update includes a review for changes from screening and a review of the patient's recent medication use to assess whether any changes have occurred since the previous visit.

8.4. Height

For patients ≥21 years of age, height should be measured at Screening only. For patients aged <21 years, height is to be measured at the time points designated in the SoA (Section 2).

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 centimeter.

8.5. Fitzpatrick Classification Scale

Each patient is to be categorized for skin type according to the Fitzpatrick classification scale (Table 3).

Table 3: Fitzpatrick Classification Scale

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

Source: Fitzpatrick TB. Soleil et peau. J Med Esthet. 1975;2:33034.

8.6. Pharmacokinetic Assessments

For all blood samples collected for PK analysis, the actual (clock) time the blood sample is drawn will be recorded in the source documents and electronic case report form (eCRF). Plasma will be harvested from each blood sample and the plasma will be frozen, shipped to a bioanalytical laboratory designated by the Sponsor, and analyzed for setmelanotide concentrations. A temporary indwelling catheter may be placed to obtain serial blood samples for the PK profiles.

Patients/caretakers will be reminded that there should be no study drug administration at home on the day of clinic visits so that samples for trough (predose) concentrations can be drawn within 30 minutes prior to dosing at the clinic.

8.6.1. Blood sampling

Blood samples will be collected from all patients according to the SoA (Table 1) instructions for PK sampling. All efforts will be made to obtain all PK samples relative to dosing. The exact time of sample collection will be noted.

In case of significant challenges with the collection of any PK sample, the investigator should confirm sample prioritization with the sponsor.

[redacted]

[redacted]

[redacted]

8.8. Safety Assessments

8.8.1. Vital Signs

Vital signs include systolic and diastolic BP, HR, respiration rate, and body temperature (°C). Vital signs will be obtained in the sitting position following at least 5 minutes of rest. Note that for virtual visits, BP will be collected.

All BP and HR measurements will be taken in triplicate, approximately 2 minutes apart. When possible, BP should be taken in the non-dominant arm throughout the trial, using the same methodology (automated or manual).

Repeat measures and more frequent monitoring can be implemented for significant increases in BP or HR. In addition, if results from outpatient measurement of vital signs indicate clinically significant abnormalities, these results should be re-checked either by the patient's primary care physician or at the investigative site.

8.8.2. Physical Examination

A complete physical examination will be conducted at screening and at the end of trial visit (Week 30). At other time points, an abbreviated examination will be performed. All physical examinations are to be conducted in adequate lighting.

- A complete physical examination will 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.
- The abbreviated examination should focus on heart, lungs, skin, neurologic examination, and any areas of previous abnormal findings, noting any changes from baseline.
- 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.

Changes from baseline in any physical examination findings identified by the Investigator as clinically significant must be recorded as an AE on the appropriate eCRF.

8.8.3. Comprehensive Skin Examination

A comprehensive skin examination will be performed by the Investigator or qualified designee. The skin examination should include a full body (head-to-toe) 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 classified as benign prior to the first dose of setmelanotide. If the pretreatment biopsy results are of concern, the patient will be excluded from the trial.

During the course of the trial, any concerning lesion or change in an existing lesion must be evaluated by the dermatologist and biopsied, if clinically indicated in the opinion of the dermatologist. The decision to continue the patient on setmelanotide treatment or to discontinue treatment will be decided by the Investigator after discussion with the Medical Monitor.

8.8.4. Electrocardiogram

Single 12-lead ECGs will be performed with the patient in the supine position following a period of at least 10 minutes of rest.

8.8.5. Laboratory Assessments

Blood and urine samples for clinical laboratory tests are to be collected after patients have been fasting for 8 hours. Samples are to be collected prior to setmelanotide administration.

The Investigators will adhere to the site-specific blood volume limits for safety laboratory and PK analyses to ensure minimal distress to pediatric patients. Due to the age of the children potentially eligible for participation in this trial, it may not be possible to collect all labs at every trial visit in this patient population, though efforts should be made to collect as many PK samples per protocol. Screening may be completed over multiple days to complete the required assessments. Venipuncture reduction is allowed should a patient experience unacceptable discomfort as deemed by the Investigator. After enrollment, if not all lab tests are possible, then the tests should be collected in the following descending order of priority: safety, anti-drug antibodies, trough PK, hemoglobin A1c, and then lipid panel.

All clinically significant laboratory abnormalities will be followed-up by repeat testing and further investigated according to the judgment of the Investigator.

The routine clinical laboratory parameters to be evaluated are as follows:

<u>Hematology</u>

Complete blood count with platelet count and standard indices will be obtained.

<u>Chemistry</u>

Sodium, potassium, chloride, carbon dioxide, albumin, total protein, glucose, blood urea nitrogen, creatinine, uric acid, aspartate aminotransferase, alanine aminotransferase, gamma-

glutamyltranspeptidase, creatine phosphokinase, alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase, calcium and phosphorus.

Coagulation Profile

Prothrombin time or international normalized ratio, and partial thromboplastin time, also referred to as activated partial thromboplastin time.

Urinalysis

Urine pH, glucose, protein, ketones, bilirubin, blood, urobilinogen, specific gravity, nitrite, and leukocytes by dipstick analysis or machine urinalysis. Urine microscopic examination will be performed if positive findings on dipsticks warrant further examination.

8.8.6. Anti-Drug Antibodies

Blood samples for measurement of ADA will be collected according to the SoA in Table 1. Any patient with a positive titer will be followed until resolution.

8.8.7. Pregnancy and Contraception

In animal reproduction studies, setmelanotide was not teratogenic at doses >10 times the maximum recommended human dose of 3 mg. No evidence of embryo-fetal toxicity was observed. Pre-and post-natal development studies in rats showed no adverse setmelanotide-related effects. Please refer to the Investigator's Brochure for additional information.

Females of childbearing potential, defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) must not be pregnant and must have a negative serum pregnancy test result at the Screening Visit. A urine pregnancy test may be performed to expedite availability of results prior to dosing on Day 1. Serum pregnancy testing will also be performed; however, setmelanotide dosing may continue with results pending. For females of childbearing potential, a highly effective form of contraception (as defined in the Inclusion Criteria, Section 6.1) must be used/practiced throughout the trial and for 90 days following the trial.

Highly effective forms of contraception include:

- Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomy/vasectomized partner (provided that the vasectomized partner is the sole sexual partner of the female participant, and the vasectomized partner has received medical assessment of surgical success)
- Sexual abstinence, only if it is the preferred and usual lifestyle of the patient.

Females of non-childbearing potential, defined as permanently sterile (status post hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or post-menopausal for at least 12 months (and confirmed with a screening FSH hormone level in the post-menopausal range) do not require contraception during the trial.

Younger female patients who have not reached sexual maturity at trial entry will be assessed for Tanner Staging, and upon reaching Tanner Stage V or menarche, will be counseled on pregnancy and required to comply with contraception requirements and pregnancy tests at all visits for the remainder of the trial.

It is not known if this treatment will affect spermatogenesis. Therefore, males with female partners of childbearing potential must agree to use contraception (e.g., if they have not had a vasectomy then should either (a) abstain from reproductive sexual intercourse or (b) use a double barrier method [i.e., condom and diaphragm with spermicide] during intercourse) if they become sexually active during the trial and for 90 days following the trial. True abstinence is acceptable only if it is the preferred and usual lifestyle of the patient. Male patients must not donate sperm for 90 days following their participation in the trial.

In the event of pregnancy during setmelanotide treatment, setmelanotide is to be permanently discontinued.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the SAE reporting procedures outlined in Appendix 3.

Details of all pregnancies in female patients and female partners of male patients will be collected after the start of study treatment through 30 days after the last dose of setmelanotide in the trial.

Note that pregnancy itself is not considered a SAE. However, abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.8.8. Injection Site Examination

Injection sites will be carefully inspected, evaluated, and scored by the clinical staff during each in-person and telehealth trial visit. It is important to distinguish injection sites for the QW formulation from those with the QD formulation. It is recommended to use a dedicated part of the body (such as a single quadrant of the abdomen) for the QW injections to facilitate this process.

The injection site evaluation will include identification of areas of erythema, edema, and induration, as well as the presence of localized pain, tenderness, and itching. At in-person trial visits, the clinical staff will also record measurements of areas of erythema, edema, and induration. A sample injection site evaluation form is included in Appendix 2.

In addition, unscheduled evaluations may also be recorded as warranted by clinical conditions.

8.8.9. Suicidal Ideation and Depression Monitoring

As setmelanotide is considered to act through the central nervous system (CNS), a patient should be referred to a mental health professional (MHP) if he/she has:

- Any suicidal behavior
- Any suicidal ideation of type 4 or 5 on the C-SSRS
- A PHQ-9 score ≥10

A referral to a MHP should also be made if in the opinion of the Investigator it is necessary for the safety of the patient. If a patient's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the patient, at the discretion of the MHP, should be continued in the trial.

In cognitively impaired patients or pediatric patients, the ability to complete the following Mental Health Assessment instruments as intended may be limited. If in the clinical opinion of the Investigator a specific patient cannot complete the instrument, the following strategies may be employed:

- Site staff may administer the questions directly to the patient or may ask for the information from a third party, such as a caregiver or family members, as appropriate.
- The Investigator may use his/her clinical judgment to skip any questionnaires that he/she feels are not appropriate for a specific patient.

Any deviation from the intended use of an instrument should be documented by the Investigator, along with the reason for the deviation. If the C-SSRS is not administered, the Investigator should document that the issue of suicidality was assessed clinically (e.g., discussion with caregivers).

8.8.9.1. Columbia-Suicide Severity Rating Scale

As required in the US by the Food and Drug Administration (FDA), for clinical trials of CNS-acting medications, changes in depression/suicidality as assessed by the C-SSRS will be monitored over the course of the trial to ensure patient safety.

The C-SSRS is a tool used not only to predict suicide attempts but to assess the full range of evidence-based ideation and behavior items, with criteria for next steps (e.g., referral to a MHP). There are 2 versions of the C-SSRS that will be administered:

- The **Screening** version of the scale documents recent (within the past month) scores from the screening C-SSRS scale. This version can assess a patient's eligibility based on inclusion/exclusion criteria.

  [Note that patients will have completed the Baseline/Screening version of the C-SSRS scale during the index trial and are therefore not expected to complete this version in the current trial. **Thus, the baseline assessment that was collected at the beginning of the index trial should continue to be used as the baseline for this trial.** (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 period. This version can assess a patient's lifetime suicidality for data collection

purposes as well as eligibility, based on inclusion/exclusion criteria, for the index trial.)]

- 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 every subsequent 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 you have administered the C-SSRS.

To be eligible for the trial, a patient cannot have suicidal ideation of type 4 or 5, any lifetime history of suicide attempt, or any suicidal behavior in the last month in patients with no significant neurocognitive deficits.

Pediatric patients may not be able to complete the C-SSRS as intended. If in the clinical opinion of the Investigator a specific patient cannot complete the instrument, the following strategies may be employed:

- Site staff may administer the questions directly to the patient or may ask for the information from a third party, such as a caregiver or family members, as appropriate.
- The Investigator may use his/her clinical judgment to skip any questionnaires that he/she feels are not appropriate for a specific patient.

Any deviation from the intended use of an instrument should be documented by the Investigator, along with the reason for the deviation. If the C-SSRS is not administered, the Investigator should document that the issue of suicidality was assessed clinically (e.g., discussion with caregivers).

A patient should be referred to an MHP if he/she has:

- Any suicidal behavior.
- Any suicidal ideation of type 4 or 5 on the C-SSRS.

A referral to a MHP should also be made if, in the opinion of the Investigator, it is necessary for the safety of the patient. If a patient's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the patient, at the discretion of the MHP, should be continued in the trial.

8.8.9.2. 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. After the patient has completed the PHQ-9 questionnaire, it is scored by the trial staff.

8.8.10. Overdose

In the event of an overdose, the Investigator should contact the Medical Monitor immediately. Appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

The quantity of the excess dose and the duration of the overdose are to be documented in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

8.8.11. Adverse and Serious Adverse Events

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or trial procedures, or that caused the patient to discontinue study treatment (see Section 6.4).

Details on recording AEs and SAEs, including definitions, are provided in Appendix 3.

8.8.11.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs, including SAEs, will be collected from the start of the Run-in Period to the end-of-trial visit (Week 30). AEs reported after starting the Run-in Period will be considered treatment-emergent AEs.

Medical occurrences that begin before the start of the Run-in Period but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours from the point in time when the Investigator becomes aware of the SAE. All SAEs must be reported whether or not considered causally related to the study drug. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs in former trial patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the trial, and he/she considers the event to be reasonably related to the trial treatment or trial participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.8.11.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.8.11.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up. Further information on follow-up procedures is given in Appendix 3.

8.8.11.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that regulatory obligations and ethical responsibilities toward the safety of patients and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.
- An Investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

9. STATISTICS

This section describes the plans for analysis. Details of the statistical methodology for summaries and statistical analyses will be provided in a separate statistical analysis plan (SAP), which will be maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. If, after the trial has completed, changes are made to the SAP, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the clinical trial report for the trial, as appropriate.

9.1. Sample Size Determination

The primary objective is to assess steady-state PK parameters (maximum plasma concentration [C_{max},], time to maximum plasma concentration [T_{max}], trough plasma concentration [C_{trough}], area under the plasma concentration-time curve over the dosing interval [$AUC_{0\text{-}tau}$]) for QW compared with QD setmelanotide. The sample size is based on availability of the patients enrolled in the LTE trial and is not driven by formal statistical hypothesis testing on non-inferiority/similarity.

9.2. Populations for Analyses

The analysis populations are defined as follows:

- Pharmacokinetic Analysis Set (PKAS): All patients who receive at least 1 dose of setmelanotide and who have a sufficient number of measurable plasma concentrations to permit assessment of noncompartmental parameters.
- Full Analysis Set (FAS): All patients who receive at least 1 dose of setmelanotide. Patients will be analyzed according to their randomly assigned treatment.

- Per Protocol Set: All patients in FAS without any major protocol violations that would result in exclusion of the patients from the analysis. Patients will be analyzed according to their randomly assigned treatment.
- Safety Analysis Set: All patients who are randomized and receive at least 1 dose of protocol-specified study drug. Patients will be analyzed according to the treatment they actually received.

9.3. Statistical Analyses

9.3.1. Primary Analysis of PK Parameters

The PK profile of the 2 formulations of setmelanotide will be characterized and the steady-state PK parameters (C_{max}, T_{max}, C_{trough}, and $AUC_{0\text{-}tau}$) will be summarized for QD and QW setmelanotide by dose level and prior treatment regimen (QW or QD) during the double-blind phase of the trial using descriptive statistics (e.g., n, mean, standard deviation, geometric mean, minimum, median, maximum, % coefficient of variation [CV], geometric mean CV, and confidence interval [CI]).

[redacted]

9.3.3. Safety Analyses

AEs/SAEs including ISRs, as well as discontinuations due to AEs will be summarized with frequencies and percentages. By-patient AE data listings including onset and resolution dates,

verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided. Injection site reactions for the QD and QW formulations will be summarized separately.

Safety data including laboratory evaluations, ECGs, physical examinations, and vital signs assessments will be summarized by time of collection. In addition, change from baseline to any postdose values will be summarized for vital signs, ECGs, and clinical laboratory results. Frequency of patients with abnormal safety laboratory results will be tabulated. Continuous outcomes (e.g., vital signs, safety laboratory parameters) will be summarized using n, mean, median, standard deviation, etc.

All safety analyses and summary tables will be based on Safety Analysis Set.

9.3.4. Interim Analysis

No unblinded interim analysis is planned. Blinded interim analyses may be conducted during the course of the trial to facilitate scientific monitoring and business needs.

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11. APPENDICES

APPENDIX 1. GUIDANCE ON TRIAL CONDUCT DURING THE CORONAVIRUS PANDEMIC

The coronavirus disease 2019 (COVID-19) pandemic could impact the conduct of this clinical trial for several reasons, including: self-isolation/quarantine by patients and trial site personnel; travel restrictions/limited access to public places, including hospitals; and reassignment of site personnel to critical tasks.

In accordance with recent health authority guidance, the Sponsor is providing temporary considerations for trial conduct in the event of disruption of the trial. This guidance does not supersede any local or government requirements or the clinical judgment of the Investigator. If at any time a patient's safety is considered to be at risk, trial intervention will be discontinued, and trial follow-up will be conducted.

If COVID-19 restrictions are imposed on or by the trial site and the site cannot fully carry out normal operations, the following measures are recommended on a temporary basis during the COVID-19 pandemic:

- Where possible, every effort should be made to complete all protocol-required assessments. In place of a required site visit, a qualified healthcare provider could perform trial-related procedures as per the Schedule of Activities (Section 2) via a home visit, including but not limited to collection of body weight, vital signs, physical examinations, electrocardiograms (ECGs), recording of adverse events (AEs), collection of blood and urine samples. Most [redacted] assessments could potentially be done off site. Investigators should use their clinical judgment to determine whether a patient can continue trial treatment in the absence of on-site clinic visits or consider alternatives such as temporary treatment interruption or trial discontinuation.
- All protocol-required assessments missed due to COVID restrictions should be documented in detail within the patients' source documents and should be clearly designated as "COVID-19 RELATED". It must be documented if a site visit is instead conducted remotely. Source documentation should detail how each assessment was collected (e.g., remote vs. on-site, central vs. local laboratory, vital signs taken at home by caretaker vs. delegated in-home nursing, etc.).
- If applicable, discontinuations of trial interventions and withdrawal from the trial due to disruption of trial conduct by the pandemic should be documented with the prefix "COVID-19 RELATED" in the electronic case report form (eCRF).
- If a patient is unable to attend a site visit, investigational product may be shipped directly to the patient.

COVID-19 Infection in Trial Patients:

There is currently no available data suggesting that patients treated with setmelanotide should have treatment interrupted during the COVID-19 pandemic. If a patient develops symptoms associated with coronavirus infection, it is recommended to confirm the diagnosis using locally approved laboratory kits and report it to the local health authorities, as required. Patients with positive test results for severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) should

have this recorded as an AE, and if hospitalized, this should be reported as a serious adverse event (SAE).

APPENDIX 2. INJECTION SITE EVALUATIONS

Injection sites will be assessed (by the clinical staff) using a form similar to the depiction below at the time points outlined in the Schedule of Activities (Section 2), and in the setting of any injection site reaction adverse experience.

Local Skin Tolerability Assessment

Reaction	**NONE**	**Mild**	**Moderate**	**Severe**	**Measurement (if applicable)**
Erythema*	□	□	□	□	
Edema*	□	□	□	□	
Induration*	□	□	□	□	
Itching	□	□	□	□	
Pain or Tenderness	□	□	□	□	
Other: _____	□	□	□	□	

* If present, region will be measured, length and width as appropriate during in-clinic visits and if possible during telehealth visits.
Initials:_____

APPENDIX 3. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of Adverse Event (AE)

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical trial patient, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: 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.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the trial. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • [redacted] or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the [redacted] assessments. However, the signs, symptoms, and/or clinical sequelae resulting from [redacted] will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.

Definition of Serious Adverse Event (SAE)

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under trial, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Important medical event • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the patient's medical records in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

Intensity of all AEs including clinically significant treatment-emergent laboratory abnormalities, injection site reactions and potential systemic reactions will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE grade refers to the severity of the AE and ranges from Grade 1 (mild AE), Grade 2 (moderate AE), Grade 3 (severe AE), and Grade 4 (life-threatening or disabling AE) to Grade 5 (death related to AE).

Adverse events not listed by the CTCAE will be graded as follows:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data.**

Assessment of Causality

- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the study drug, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
- The temporal association between study drug exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of the study drug.
- The AE resolved or improved with decreasing the dose or stopping use of the study drug (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between the study drug and the AE will be assessed using one of the following categories:

- **Not Related:** Factors consistent with an assessment of Not Related include:
  - Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of the study drug); or
  - Other causative factors more likely explain the event (e.g., a pre-existing condition, other concomitant treatments).
- **Related**: Factors consistent with an assessment of Related include:
  - There is a "reasonable possibility" of a relationship, i.e., there are facts, evidence, and/or arguments to suggest a causal relationship (not just that “a relationship cannot be ruled out”);
  - There is a positive temporal relationship (e.g., the event occurred within a reasonable time frame following administration of study drug);
  - The AE is more likely explained by the investigational product than by another cause (i.e., the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the study drug).

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the trial or during a recognized follow-up period, the Investigator will provide a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours from the point in time when the investigator becomes aware of the SAE. All SAEs must be reported whether or not considered causally related to the study drug.

SAE & Pregnancy Reporting to Sponsor
• All SAEs will be reported via the SAE Report Form within 24 hours of the Investigators awareness to RhythmSafety.SM@ppdi.com or via fax [redacted] • If a pregnancy is reported by a patient or patient partner, the Investigator should inform the Sponsor by completing a Pregnancy Reporting Form within 24 hours and sending via RhythmSafety.SM@ppdi.com or via fax [redacted] • The site will also enter the SAE data into the electronic data collection system as soon as it becomes available.

APPENDIX 4. CONSIDERATIONS FOR REDUCING PAIN AND DISTRESS IN THE PEDIATRIC POPULATION

Although the trial procedures and assessments required per protocol are classified as "No or Minimal Risk", 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 Paediatric Population", considerations for reducing pain and distress in patients <18 years of age are suggested below.

- The clinical trial may only be conducted if it exposes the person concerned to as little burden and other foreseeable risks as possible.
- Physical and emotional pain should be prevented as much as possible, and effectively treated when unavoidable. This includes adherence to site-specific blood volume limits for safety laboratory and PK analyses (as applicable) to ensure minimal distress and reduce the number of excessive venipunctures in pediatric patients.
- In order to minimize pain, distress, and fear, facilities should be appropriate to childcare, and the personnel should be trained to look after children and supervised by experienced health care professionals. Staff should be trained to communicate with both parents (or legal representative) and children. Generally, this would assume non-adult patients are being studied at experienced pediatric centers.
- For most procedures, the child should always be accompanied by a trial-related staff member who could provide reassurance. At the sign of distress and/or dissent, the procedure should be stopped. A short pause to allow the child to feel in control, further explanation, and an assessment of the situation may be needed to reassure the child, or to decide to definitely abandon the procedure at the discretion of the Investigator.
- In all situations, investigations/interventions should be limited to the minimum required for obtaining valid data and performed using size-/age-appropriate material and devices, including limiting in advance the number of attempts for sampling.
- Study drug injections should only be performed by parents (or home health care professionals), unless the child is of suitable age and competency, and desires the ability to do so.
- Although almost all trial procedures are classified as low risk, risk should be continuously monitored and assessed by appropriate personnel.
- For assessments in which there is a psychological component, measures should be taken to minimize distress. For example, Tanner Staging assessments could utilize a diagram for the child to point to and indicate what stage they currently are, vs. having to have an exam without clothes.

A comment on benefit risk: Risk is very low, from procedures and/or known safety profile of the drug (both clinically and toxicologically, where large margins and preliminary data from juvenile toxicology studies have not identified any new or concerning safety concerns) and based on one representative example of rare genetic disorder of obesity impacting the MC4R pathway, there is the possibility of major benefit.

APPENDIX 5. TRIAL GOVERNANCE CONSIDERATIONS

Regulatory and Ethical Considerations

- This trial will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB) by the Investigator and reviewed and approved by the IRB before the trial is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial patients.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the trial to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of serious adverse events (SAEs) or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the trial to the patient or his/her legally authorized representative and answer all questions regarding the trial.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that

meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB or trial center.

- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the trial.
- Patients who reach the age of consent during the trial must be re-consented, as applicable, per local laws.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.
- Patients who are rescreened are required to sign a new ICF.

Data Protection

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal trial-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Data Quality Assurance

All patient data relating to the trial will be recorded on printed or electronic case report form (eCRF) unless transmitted to the Sponsor electronically (e.g., e-diary). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit trial-related monitoring, audits, IRB review and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this trial including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

In an exceptional case where a local restriction for the on-site Monitoring Visit at the investigator site is implemented (e.g., due to COVID-19), the Clinical Research Associate (CRA) will perform routine scheduled Remote Interim Monitoring Visits (rIMV) for active sites. The aim of the remote activities is to ensure adequate ongoing oversight of trial activities to identify and eliminate any immediate risk to the safety and integrity of the patients. Each individual RMV should be approved by the Sponsor on a case-by-case basis.

There are 5 types of rIMV that may be performed, where approved by the relevant local authorities, which include:

- Remote Source Data Monitoring (rSDM) visits
- Remote Data Verification (rDV) visits
- Audio Data Verification (ADV) visits: An alternative approach for remote data verification of critical patient data, when Monitor asks Investigator site staff member to read patient source documents during a telephone call while reviewing the Case Report Form (CRF) to verify patient safety is protected and the data reported by Investigator (e.g., in the CRF) is accurate and complete
- Video Source Data Monitoring visits: Process for conducting SDM during a video call/conference between the Monitor and Investigator site staff member, when the Investigator site staff member shares the patient source documents with the Monitor via camera so that the Monitor can perform Source Data Review and Source Data Verification as per the project-specific instructions.
- Remote Site Monitoring Contact (SMC) visits

Depending on the local regulation, some of these types of rIMV may be allowed or not.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the Investigator for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified immediately by telephone or e-mail and the notification confirmed in writing if a custodial change occurs.

Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

Any electronic trial data are to be entered into a secure, validated data processing system and a backup maintained. Any changes to electronic trial data will be documented.

Trial and Site Closure

The trial is to be discontinued if the required approval or favorable approval is revoked. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

The Investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the Sponsor or investigator may include but are not limited to:

For trial termination:

- Discontinuation of further trial intervention development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines.

Inadequate or no recruitment (evaluated after a reasonable amount of time) of patients by the Investigator.

- Total number of patients included earlier than expected.

If the trial is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

Publication Policy

All information regarding setmelanotide supplied by the Sponsor to the Investigator or generated as a result of any clinical studies is privileged and confidential information belonging to the Sponsor. The Investigator agrees to use the Sponsor's confidential information solely to accomplish the trial and will not use such information for any other purposes without the prior written consent of the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete and accurate data obtained during the trial. The information obtained from the clinical trial will be used towards the development of setmelanotide and may be disclosed by the

Sponsor to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

It is anticipated that the results of this trial may be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. The Sponsor generally supports publication of multicenter studies initially in their entirety and not as individual site data. A coordinating investigator will be designated.

Subsequently, individual Investigators may publish results from the trial in compliance with their agreement with the Sponsor.

A pre-publication manuscript is to be provided to the Sponsor at least 30 days prior to the submission of the manuscript to a publisher. Similarly, the Sponsor will provide any company-prepared manuscript to the Investigators for review at least 30 days prior to submission to a publisher. All publications and presentations must be approved in writing by the Sponsor before public disclosure.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.