SETMELANOTIDE

RM-493-034

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

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 No. 2021-002855-12

Trial Sponsor: Rhythm Pharmaceuticals, Inc.
[redacted]

Document Date (Version): V2.0 – 27 July 2022 (Global)

CONFIDENTIALITY NOTE

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APPROVAL SIGNATURE PAGE

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REVIEWED/APPROVED BY:

[redacted] [redacted] 28-Jul-2022

[redacted] Signature Date

[redacted]

INVESTIGATOR STATEMENT

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

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I understand that all documentation provided to me by Rhythm Pharmaceuticals, Inc. (Rhythm, the Sponsor) 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 (IB), 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)/Independent Ethics Committee (IEC). No changes will be made to the trial protocol without the prior written approval of Rhythm and the IRB/IEC, 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	Signature of Investigator	Date

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

1. SYNOPSIS

Name of Sponsor/Company:
Rhythm Pharmaceuticals, Inc.

Name of Investigational Product:
Setmelanotide

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

Trial center(s): Approximately 80 centers in North America, Europe and the Middle East

Studied period (years):
Estimated date first patient enrolled: 4th Quarter (Q4) 2021
Estimated date last patient completed: Q4 2024

Phase of development: 2

Objectives:

Primary:

- To evaluate the proportion of patients with obesity with genetic variants in a specific gene in the melanocortin-4 receptor (MC4R) pathway who achieve a clinically meaningful reduction in body weight in response to setmelanotide at the end of open-label treatment

Secondary:

- To evaluate change in weight parameters and hunger in response to setmelanotide in patients with genetic variants in a specific gene in the MC4R pathway at the end of open-label treatment

[redacted]

Safety:

- To evaluate the safety and tolerability of setmelanotide in patients with genetic variants in the MC4R pathway

Methodology:
This is a 2-stage (open-label stage followed by a randomized double-blind, placebo-controlled stage) Phase 2 trial of setmelanotide in patients with obesity with specific gene variants in the MC4R pathway.

Screening

The Screening Period begins with signing the informed consent/assent form and will last between 2 and 8 weeks. During the Screening Period, patients will undergo all procedures as outlined in the Schedule of Assessments (SoA) Stage 1 (Table 1) to determine if they meet the Inclusion and Exclusion criteria.

During the Screening Period, patients will undergo medical evaluation and they or their caregivers will receive training on injection of trial medication and other trial procedures. Patients (or their caregivers) will be issued an electronic diary to capture daily compliance with injections (post enrollment) and hunger score assessments (starting during Screening).

Stage 1 (Open-Label)

Stage 1 of the trial begins with the enrollment visit (Study Day 1).

During the enrollment visit, patients will undergo all procedures as outlined in the SoA Stage 1 (Table 1), and it will be reconfirmed that the patient continues to meet all Inclusion and no Exclusion criteria.

At the enrollment visit, the trial center must confirm that the patient completed the electronic diary at least 4 of 7 days prior to the enrollment visit. If the diary was not completed, the patient may not enter the trial. The enrollment visit may be re-scheduled if the remaining visit window allows.

During the enrollment visit, the patient will have their body weight recorded. This will be the patient's "Baseline Weight."

During the enrollment visit, the patient (or caregiver) will receive training on injections of trial medication and inject the first dose of setmelanotide under the supervision of the trial staff. In clinic doses of trial medication, including the first dose, will be administered following blood sampling for pharmacokinetic (PK) analysis.

During Stage 1, the patient (or caregiver) will administer setmelanotide on a daily basis for 16 weeks. During this period, the patient will have in-person as well as virtual visits with the trial center using a validated Telehealth platform. During the virtual visits, the patient (or caregiver) will record a body weight measurement and be assessed for compliance with trial procedures and adverse events (AEs). Any visit that is planned as a virtual visit may be converted to an in-person visit at the discretion of the Investigator. If more than 2 virtual visits are to be converted into in-person visits, Sponsor approval is required.

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

- ≥18 years old must have achieved a body mass index (BMI) at least 3% less than the Baseline BMI at the end of Stage 1
- <18 years old must have achieved a BMI at least 3% less than the Baseline BMI or a decrease in BMI Z-score of at least 0.05 at the end of Stage 1

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

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

Patients who enter Stage 2 will continue in the trial for an additional 24 weeks. Stage 2 of the trial will begin with the Stage 2 Entry Visit. During the Stage 2 Entry Visit, the patient will complete all assessments as per the SoA Stage 2 (Table 2). The patient will have a body weight recorded. This

measurement will be their Stage 2 Entry Weight Measurement. In clinic doses of trial medication will be administered following blood sampling for PK analysis.

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

Patients will continue to have virtual visits and in-person clinic visits as per the SoA for Stage 2 (Table 2).

At the Investigator's discretion, either (1) additional virtual or in-person visits may be scheduled or (2) planned virtual visits may be converted to in-person visits. If more than 2 virtual visits are to be converted into in-person visits, Sponsor approval is required.

End of Treatment/End of Trial

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

Switch to Treatment with Setmelanotide

During Stage 2 of the trial, patient weight will be monitored as per the SoA Stage 2 (Table 2). Additional virtual visits may be scheduled at the discretion of the Investigator.

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

To be eligible, a patient must be scheduled for an in-person visit at the clinic. At the visit, the patient's body weight will be recorded. If the visit occurs within 2 weeks of an expected trial visit as per the SoA Stage 2 (Table 2), then the visit may replace that expected trial visit. All procedures as outlined in the SoA Stage 2 for the expected trial visit should occur. At this visit, the patient will return their double-blind trial medication supply. The patient may then be enrolled into the LTE trial or will be issued open-label setmelanotide and will continue in the trial via bridging visits until the LTE trial is available. The patient's initial assignment to either trial medication or placebo will continue to be blinded to all parties.

Ensuring Diversity of Genes

A patient must have a pre-identified genetic variant in an established MC4R pathway gene that contributes to obesity to enroll in this trial. A list of genes that have variants that are eligible for enrollment into the trial is provided in Appendix 1. Gene variant enrollment by gene is at the discretion of the Sponsor.

The trial aims to enroll up to 10 patients with each gene into the trial. Enrollment will be monitored by the Sponsor and further enrollment of patients with a genotype may be paused once approximately 10 patients with that particular gene have been enrolled.

Patient response to setmelanotide by gene will be monitored by the Sponsor during the open-label portion of the trial in 2 ways: the rate of patients qualifying for Stage 2 of the trial and the magnitude of response to setmelanotide. The Sponsor may increase or decrease the target number of patients

enrolled with a particular gene or may close any individual gene cohort after assessment of lack efficacy on 3 or more patients. The total sample size of the trial will not be increased.

Number of patients (planned):

Approximately 100 to 200 patients will be enrolled into this trial.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. Patients must have a pre-identified genetic variant in an established MC4R pathway gene that contributes to obesity.

   Note: Genetic testing requirements and a list of genes which have variants that are eligible for enrollment into the trial are provided in Appendix 1.
2. Patients between the ages of 6 and 65, inclusive, at the time of signing Informed Consent or Assent.
3. Patients with obesity, defined as BMI ≥40 kg/m^2 for patients ≥18 years of age or BMI ≥97th percentile for age and gender for patients 6 to <18 years of age based on the United States (US) Centers for Disease Control and Prevention criteria.
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 (including the once daily [QD] injection regimen and all other trial procedures) and is able to understand and sign the written informed consent/assent. Patients who are unable to comply with all trial procedures due to cognitive limitations or any other reason should not be enrolled.
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 8.9.7:

   - Combined (estrogen and progestin) hormonal contraception associated with inhibition of ovulation (i.e., 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 level in the post-menopausal lab range) and 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 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. Symptoms or behaviors of hyperphagia persistent during the patient's life, including manifestations in childhood, as determined by the Investigator at screening.

Exclusion Criteria:

1. Patients with the following genetic variants: biallelic Bardet-Biedl Syndrome (BBS); biallelic Alström Syndrome 1 (ALMS1); homozygous, heterozygous, or compound heterozygous variants in MC4R, pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), leptin receptor (LEPR), nuclear receptor coactivator 1 (NCOA1; steroid receptor coactivator-1 [SRC1]) or SRC homology 2 B adapter protein 1 (SH2B1) genes as well as 16p11.2 chromosomal deletions that include the SH2B1 gene.
2. Weight loss >2% in the previous 3 months.

   Patients will not be excluded for using regimens for weight maintenance or to prevent weight gain, such as dietary and/or exercise regimens, or medications, supplements or herbal treatments (e.g., orlistat, lorcaserin, phentermine, topiramate, naltrexone, bupropion, glucagon-like peptide-1 [GLP-1] receptor agonists, etc.), provided:

   - the regimen and/or dose has been stable for at least 3 months prior to randomization
   - the patient has not experienced weight loss >2% during the previous 3 months, AND
   - the patient intends to keep the regimen and/or dose stable throughout the course of the trial.
3. Bariatric surgery or procedure (e.g., gastric bypass/band/sleeve, duodenal switch, gastric balloon, intestinal barrier, etc.) within the last 6 months. All patients with a history of bariatric surgery or procedures must be discussed with, and receive approval from, the Sponsor prior to enrollment.
4. Documented diagnosis of current unstable major psychiatric disorder(s) (e.g., major depressive disorder, bipolar disorder, schizophrenia, etc.) or documented worsening psychiatric condition that required changes in treatment regimen within the previous 2 years, or other psychiatric related risks that the Investigator believes may interfere with trial compliance or patient safety.
5. Clinically significant depression or suicidality, as defined by: any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) during Screening, any suicide attempt during the patient's lifetime, any suicidal behavior in the last month, or a Patient Health Questionnaire-9 (PHQ-9) score of ≥15 during Screening process.

   Note: Patients who are unable to complete the PHQ-9 or C-SSRS due to significant neurocognitive impairment may be enrolled in the trial provided that there are no clinical signs or symptoms of significant depression or suicidal behavior in the opinion of the Investigator.
6. Current, clinically significant pulmonary, cardiac, endocrine/metabolic, hepatic, or oncologic disease considered severe enough to interfere with the trial and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor to determine eligibility.
7. Significant features of, or meeting the diagnostic criteria for, a genetic syndrome that is associated with obesity.

   Note: Although some of the genetic variants that are eligible to be enrolled into this trial are associated with specific syndromes, the intent of this trial is not to enroll children with significant cognitive impairment or other significant co-morbidities. Patients with eligible genetic variants, but who otherwise do not exhibit the syndrome, are eligible for enrollment.
8. Glycated hemoglobin (HbA_{1C}) >10.0% at Screening.

9. History of significant liver disease other than non-alcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). Patients with NAFLD or NASH will not be excluded based on this criterion
10. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 at Screening. In patients ≥18 years of age the Modification of Diet in Renal Disease (MDRD) Equation should be used to calculate eGFR. In patients <18 years of age, the Bedside Schwartz Equation should be used for calculation of GFR.
11. History or close family history (parents or siblings) of melanoma, or patient history of oculocutaneous albinism.

    Note: If the type of skin cancer in patient's or close family history is not known, then the patient should not be enrolled into the trial.
12. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a comprehensive skin evaluation performed by the Investigator during Screening. If any concerning lesions are identified during Screening, the patient should be referred to a dermatologist. Any concerning lesions identified during Screening will be biopsied and results known to be benign prior to enrollment. If the pre-treatment biopsy results are of concern, the patient may need to be excluded from the trial.
13. Patient is, in the opinion of the Investigator, not suitable to participate in the trial.
14. Participation in any clinical trial with an investigational drug/device within 3 months or 5 half-lives, whichever is longer, prior to the first day of dosing.
15. Patients previously enrolled in a clinical trial involving setmelanotide or any previous exposure to setmelanotide.
16. Hypersensitivity to the active substance or to any of the excipients of the investigational medicinal products (active and placebo).
17. Females who are pregnant or breastfeeding, or planning or desiring to become pregnant during the duration of the trial.
18. Legally protected persons per local regulations (e.g., those that fall under the L1121-6 article of the Public Health code in France).
19. For France only: patient is <18 years of age.

Investigational product, dosage and mode of administration:

Investigational product: Setmelanotide, 10 mg/mL in a sterile solution for injection.

Dosage:

Patients 12 years of age and older: Setmelanotide 2 mg QD for approximately 2 weeks, then increased to setmelanotide 3 mg QD for the remainder of the trial. Note: if the starting dose of setmelanotide is not tolerated reduce to 1 mg QD; the lowest target dose in patients ≥12 years of age is 1.0 mg QD; however, in consultation with the Medical Monitor, the dose may be lowered to 0.5 mg QD if not tolerated.

Patients 6 to <12 years of age: Setmelanotide 1 mg QD for approximately 1 week, then increased to setmelanotide 2 mg QD for approximately 1 week, then increased to setmelanotide 3 mg QD for the remainder of the trial. Note: if the starting dose of setmelanotide is not tolerated reduce to 0.5 mg QD; the lowest target dose in patients 6 to <12 years of age is 0.5 mg QD.

Mode of administration: Subcutaneous (SC) injection

Duration of treatment:

Total treatment with trial medication will be up to 40 weeks. Total participation in the trial will last up to 52 weeks, including the Screening Period and the EOS Visit.

Reference therapy, dosage, and mode of administration:

Reference product: Placebo (vehicle) in a sterile solution for injection.

Dosage: Placebo QD (titrated in the same manner as active treatment)

Mode of administration: SC injection

Criteria for evaluation:

Primary Endpoint:

- The proportion of patients by genotype who demonstrate a significant clinically meaningful response (defined below) to setmelanotide at the end of Stage 1:
  - For all patients: achieving a ≥5% reduction in BMI from Baseline

Secondary Endpoints:

- Mean change and percent change in BMI from Baseline to end of Stage 1 in all patients and patients ≥18 years old, per gene
- Mean change and percent change in body weight from Baseline to end of Stage 1 in patients ≥18 years old, per gene
- Mean change in BMI Z-score from Baseline to end of Stage 1 in patients <18 years old, per gene
- Mean percent change in the weekly average of the daily maximal hunger score from Baseline to end of Stage 1 in patients ≥12 years old, per gene
- The proportion of patients ≥12 years old, per gene, who achieve a ≥2-point reduction (improvement) from Baseline to end of Stage 1 in the weekly average of the daily maximal hunger score.

[redacted]

[redacted]

Statistical methods:

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

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

The trial is a 2-stage design: Stage 1 is open-label treatment, and Stage 2 is randomized, double-blind, placebo-controlled.

The 95% exact confidence interval will be provided for the primary efficacy endpoint. The analyses of the efficacy endpoints in Stage 1 will be performed based on the safety analysis set, and the analyses of the efficacy endpoints in Stage 2 will be performed based on the full analysis set (FAS).

AEs/SAEs will be summarized with frequencies and percentages. A by-patient AE data listing including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided.

Safety data including laboratory evaluations and vital signs assessments will be summarized by time of collection. In addition, change from baseline to any post-dose values will be summarized for vital signs and clinical laboratory results. Frequency of patients with abnormal safety laboratory results will be tabulated.

All safety analyses and summary tables will be based on the safety analysis set.

2. SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments – Stage 1

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

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Study Day	**-56 to -14**	**1**	**7**	**14*, 28, 42, 84**	**56, 112**	
Window			**+/-2**	**+/-3**	**+/-5**	**+/-5**
[redacted]						
Global Hunger Questions (15)		X		X (14)	X	X
C-SSRS (16)	X	X		X	X	X
PHQ-9 (23)	X	X		X	X	X
CDI-2 (24)	X	X		X	X	X
[redacted]						
Adverse Events	X	X	X	X	X	X
Injection Site Inspection		X		X	X	X
Concomitant Medication Review	X	X	X	X	X	X
Safety Laboratory Tests (17)	X				X	X
[redacted]						
Trough PK (18)		X			X	X
Anti-Drug Antibodies (19)	X				X	X
Biomarkers (20)		X			X	X
Daily Drug Compliance (21)		X		X	X	

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Visit Number		**V1**	**V1c**	**V2, V3, V4, V6**	**V5, V7**	
Study Week			**1**	**2, 4, 6, 12,**	**8, 16**	
Study Day	**-56 to -14**	**1**	**7**	**14*, 28, 42, 84**	**56, 112**	
Window			**+/-2**	**+/-3**	**+/-5**	**+/-5**
Dispense/Return Trial medication (22)		X		X	X	X

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

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

* Dose escalation (from 2 mg QD to 3 mg QD) should occur at the trial visit planned for Day 14 (±3 days) and should occur on the day of that visit.

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

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

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

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

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

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

[6] Weight (kg) is to be measured at the clinic using the same scale throughout the trial or at home (during virtual visits) using the same scale provided to the patient as part of the clinical trial. Weight should be measured after patients have attempted to empty their bladders and after fasting for at least 8 hours. Patients are to wear light clothing or underwear and no shoes, with empty pockets and will be weighed at approximately the same time of day. All

measurements will be recorded to the nearest 10th of a Kg if reported with a digital scale, or half Kg with a mechanical scale. Whenever possible, the scale should be calibrated on a regular basis per manufacturer's specifications.

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

[redacted]

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

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

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

[redacted]

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

[redacted]

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

17 Safety laboratory tests will include: Complete blood count (CBC) with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, CO_2, albumin, total protein, glucose, blood urea nitrogen [BUN], creatinine (including eGFR), uric acid, aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transferase [GGT], creatine phosphokinase [CPK], alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase [LDH], calcium, phosphorus), and urinalysis with microscopic analysis if positive findings on dipsticks warrant further examination. Safety

laboratories will also include a coagulation profile (prothrombin time [PT] or international normalized ratio [INR], and partial thromboplastin time [PTT] also referred to as activated PTT [aPTT]).

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

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

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

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

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

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

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

Table 2: Schedule of Assessments – Stage 2

Assessment	Stage 2 Entry Visit† (In-Person)	Virtual Trial Visits	In-Person Clinic Visits	End of Treatment Visit (In-Person)	End-of-Study Visit (Telephone) [22]	Early Termination Visit (In-Person)	Bridging Visits (if needed) (In-Person)
Visit Number	**V7**	**V8, V9, V11, V13**	**V10, V12**	**V14**	**V15**		
Study Week	**16**	**18, 20, 28, 36**	**24, 32**	**40**	**44**		**Q12 weeks**
Study Day	**112**	**126, 140, 196, 252**	**168, 224**	**280**			
Window (1)		**+/-3**	**+/- 5**	**+/- 5**	**+/-3**		**+/- 5**
Nutrition and physical activity counseling and follow-up	X	X	X	X			X
Physical Exam (2)	X			X	X	X	X
Comprehensive Skin Exam (3)	X			X	X	X	X
[redacted]							
Vital Signs (7)	X	X	X	X		X	X
ECG (8)	X			X		X	X
Pregnancy (9)	X	X	X	X		X	X
[redacted]							
C-SSRS (14)	X	X	X	X	X	X	X
PHQ-9 (21)	X	X	X	X	X	X	X
CDI-2 (23)	X	X	X	X	X	X	X

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Visit Number	**V7**	**V8, V9, V11, V13**	**V10, V12**	**V14**	**V15**		
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Study Day	**112**	**126, 140, 196, 252**	**168, 224**	**280**			
Window (1)		**+/-3**	**+/- 5**	**+/- 5**	**+/-3**		**+/- 5**
[redacted]							
Randomization	X						
[redacted]							
Adverse events	X	X	X	X	X	X	X
Injection site inspection	X	X	X	X		X	X
Concomitant medication Review	X	X	X	X	X	X	X
Safety Laboratory Tests (15)	X		X	X		X	X
[redacted]							
Trough PK (16)	X		X	X		X	X
Anti-Drug Antibodies (17)	X			X		X	X
Biomarkers (18)	X			X		X	X
Daily drug compliance (19)	X	X	X	X			X
Dispense/Return Trial medication (20)	X		X	X		X	X

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

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

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

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

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

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

[redacted]

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

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

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

[redacted]

[redacted]

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

[redacted]

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

[15] Safety laboratory tests will include: Complete blood count (CBC) with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, CO_2, albumin, total protein, glucose, blood urea nitrogen [BUN], creatinine (including eGFR), uric acid, aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transferase [GGT], creatine phosphokinase [CPK], alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase [LDH], calcium, phosphorus), and urinalysis with microscopic analysis if positive findings on dipsticks warrant further examination. Safety laboratories will also include a coagulation profile (prothrombin time [PT] or international normalized ratio [INR], and partial thromboplastin time [PTT] also referred to as activated PTT [aPTT]).

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

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

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

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

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

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

[22] If required by local regulation or if deemed necessary to assess patient safety by physical examination or after a longer follow-up period, the visit may be converted to an in-person visit and/or can occur up to Day 336 (Week 48). If the EOS visit is converted to an in-person visit, a physical examination and a comprehensive skin examination should be completed at that in-person visit. Patients who enroll in the long-term extension trial will have the EOS visit at the same time as the EOT visit.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
α-MSH	alpha-melanocyte-stimulating hormone
ACC	American College of Cardiology
ACMG	American College of Medical Genetics
ADA	Anti-drug antibodies
ADV	Audio data verification
AE	Adverse event
AHA	American Heart Association
ALMS1	Alström syndrome 1
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AS	Alström Syndrome
AST	Aspartate aminotransferase
BBS	Bardet-Biedl Syndrome
BMI	Body mass index
BP	Blood pressure
Bpm	Beats per minute
BUN	Blood urea nitrogen
CAP	College of American Pathologists
CBC	Complete blood count
CDI-2	Children's Depression Inventory-2
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CRF	Case report form
CRA	Clinical research associate
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
% CV	Percent coefficient of variation

Abbreviation or Specialist Term	Explanation
DCF	Data clarification form
DIO	Diet-induced obesity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
[redacted]	[redacted]
[redacted]	[redacted]
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GB	Great Britain
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GFR	Glomerular filtration rate
GLP-1	Glucagon-like peptide-1
HbA_{1C}	Glycated hemoglobin
HDL	High-density lipoprotein
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IP	In-person
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
[redacted]	[redacted]
Kcal	Kilocalories

Abbreviation or Specialist Term	Explanation
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LEPR	Leptin receptor
LTE	Long-term extension
Max	Maximum
MC4R	Melanocortin-4 receptor
MDRD	Modification of Diet in Renal Disease
MHP	Mental health professional
Min	Minimum
mPEG/DSPE	N-[carbonyl-methoxypolyethylene glycol 2000]-1,2-distearoyl-glycero-3-phosphoethanolamine sodium salt
NAFLD	Non-alcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NCOA1	Nuclear receptor coactivator 1
NHLBI	National Heart, Lung, and Blood Institute
PCSK1	Proprotein convertase subtilisin/kexin type 1
PG	PreventionGenetics
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9
PK	Pharmacokinetic
POMC	Pro-opiomelanocortin
PP	Per-Protocol
PPL	POMC, PCKS1, LEPR
PT	Prothrombin time
PTT	Partial thromboplastin time
Q4	4th quarter
QD	Once daily
q.s.	Quantity sufficient
QW	Once weekly
rDV	Remote data verification
RGDO	Rare genetic diseases of obesity
Rhythm	Rhythm Pharmaceuticals, Inc., the Sponsor

Abbreviation or Specialist Term	Explanation
rIMV	Remote Interim Monitoring Visit
RR	Respiratory rate
rSDM	Remote source data monitoring
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SDM	Source data monitoring
SH2B1	SRC homology 2 B adapter protein 1
SMC	Site monitoring contact
SoA	Schedule of Assessments
SRC1	Steroid receptor coactivator-1
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TOS	The Obesity Society (2013 Guideline)
URO	Uncovering Rare Obesity
US	United States
UV	Ultraviolet
VIS	Variant Interpretation Service
VUS	Variant of Uncertain Significance
WES	Whole Exome Sequencing

3. INTRODUCTION

The purpose of this Phase 2 trial is to evaluate the safety and efficacy of once daily (QD) subcutaneous (SC) administration of setmelanotide, a synthetic, cyclic octapeptide (8-amino acid-containing peptide) melanocortin-4 receptor (MC4R) agonist, in patients with obesity and specific gene variants in the MC4R pathway.

The MC4R pathway is the principal regulator of mammalian energy balance and body weight. Originating in the hypothalamus, it concertedly modulates appetite (feelings of hunger and satiety and the drive to eat), 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 variants or acquired disruptions in this pathway result in insufficient activation of MC4Rs leading to overconsumption of food (hyperphagia) and a reduction in energy utilization (Farooqi 2008).

Setmelanotide is authorized for marketing in the United States (US), Great Britain (GB), and the European Union (EU) in adult and pediatric patients 6 years of age and older with obesity due to pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency (USPI 2022, EU SmPC 2021, MHRA SmPC 2021). Setmelanotide is also authorized for marketing in the US in adult and pediatric patients 6 years of age and older with obesity due to Bardet-Biedl Syndrome (BBS) (USPI 2022).

Setmelanotide is under continued clinical investigation globally for the treatment of various rare genetic diseases of obesity (RGDO) as well as acquired diseases resulting in obesity (e.g., hypothalamic obesity) arising from variants demonstrated or hypothesized to impact signaling in the hypothalamic MC4R pathway. Based on accruing genetic and clinical insights, other genetic or acquired forms of early-onset, severe obesity and hyperphagia may also be evaluated in setmelanotide clinical studies. It is expected that setmelanotide would be indicated to treat the obesity and hyperphagia in these patient populations.

3.1. Setmelanotide

Setmelanotide is a synthetic, cyclic octapeptide (8-amino acid-containing peptide) that functions as a potent MC4R agonist. 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). While not an analog, it retains the specificity and functionality of the naturally occurring POMC-derived neuropeptide, alpha-melanocyte-stimulating hormone (α-MSH), which is the endogenous ligand for the MC4R. Setmelanotide is more potent and has a much longer half-life (~10-12 hours in humans) than the short-lived α-MSH ligand.

The setmelanotide peptide was initially selected for clinical development based on its acceptable circulating half-life as a saline formulation administered as a continuous SC infusion (2.8 to 3.5 hours in non-human primates) and the ability to decrease body weight gain and suppress food intake in normal rats. Additional studies demonstrated the efficacy of setmelanotide in suppressing food intake and body weight gain in diet-induced obese (DIO) mice, rats, dogs, and monkeys, as well as in genetic models of obesity, including leptin-deficient ob/ob mice and leptin receptor deficient obese Zucker rats. Later studies in obese monkeys showed that setmelanotide did not increase blood pressure (BP) or heart rate (HR), a potential concern observed with other MC4R agonist compounds.

To support clinical studies, the toxicological profile of setmelanotide formulations has been evaluated in repeat-dose continuous SC infusion toxicity studies up to 13 weeks in duration in rats and monkeys. [redacted]

In addition, safety data from more than 700 clinical trial participants through a cutoff date of 10 November 2021 demonstrate an acceptable safety profile across the populations studied, which include otherwise healthy subjects with obesity, patients with RGDO, and patients with acquired diseases resulting in obesity (e.g., hypothalamic obesity) arising from variants demonstrated or hypothesized to impact the hypothalamic MC4R signaling pathway. In these clinical studies, setmelanotide was administered QD at doses ranging from 0.5 to 5 mg and once weekly (QW) at doses ranging from 2.5 to 30 mg. Across the studies, the most common types of treatment-emergent adverse events (TEAEs) reported among setmelanotide-treated participants by Preferred Term included skin hyperpigmentation, nausea, and headache. Also common were TEAEs related to the injection site including injection site erythema, injection site pruritus, injection site induration, and injection site pain, each occurring in >10% of participants.

Data obtained to date in the setmelanotide clinical program demonstrate robust weight reduction and hunger suppression in patients with RGDO in which the leptin-melanocortin pathway upstream from MC4R is involved. In Phase 3 clinical studies of patients with POMC/PCSK1 and LEPR (PPL) deficiency obesity, setmelanotide demonstrated clinically meaningful and statistically significant body weight loss and hunger score reductions and was well tolerated. Similarly, in a Phase 3 trial of patients with BBS and Alström syndrome (AS), setmelanotide significantly reduced body weight and hunger and was well tolerated, with a predictable and therefore manageable safety profile.

In summary, setmelanotide's unique mechanism of action as a MC4R agonist enables a safe and highly targeted approach to treat patients with severe obesity due to genetic or acquired variants in the MC4R signaling pathway. By restoring impaired signaling in this pathway, setmelanotide can serve as an indirect form of replacement therapy, with the potential for significant improvements in hyperphagia and body weight and related measures.

3.2. Benefit/Risk Assessment

In patients with rare genetic forms of obesity, setmelanotide has been associated with clinically meaningful reductions in weight and improvement in hunger. In particular, in patients with POMC or LEPR deficiency obesity or BBS, who are characterized by early onset obesity, severe hunger and progressive weight gain, setmelanotide has demonstrated clinically meaningful and statistically significant weight reduction. In addition to weight loss, setmelanotide has

demonstrated clinically meaningful and statistically significant decreases in hunger. Both the decreased hunger and the weight loss are maintained with continued setmelanotide treatment. Furthermore, following the significant weight loss with setmelanotide treatment, there were improvements in glycated hemoglobin (HbA_{1C}), glucose and lipids, 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 and skin hyperpigmentation. Less commonly, nausea and vomiting were reported and rarely, sexual events 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.

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 (IB).

4. OBJECTIVES AND ENDPOINTS

The objectives and endpoints are described in Table 3.

Table 3: Objectives and Endpoints

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

Table 3: Objectives and Endpoints

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

Table 3: Objectives and Endpoints

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

AE = adverse event; BMI = body mass index; ECG = electrocardiogram; [redacted]; MC4R = melanocortin 4 receptor.

5. INVESTIGATIONAL PLAN

5.1. Overall Trial Design

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

5.1.1. Screening Period

Upon providing informed consent/assent, 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 Assessments (SoA) Stage 1 (Table 1). During the Screening Period, patients will undergo medical evaluation and they or their caregivers will receive training on injection of trial medication and other trial procedures. Patients (or their caregivers) will be issued an electronic diary to capture daily compliance with injections (post enrollment) and hunger score assessments (starting during Screening).

5.1.2. Stage 1 (Open-Label)

Stage 1 of the trial begins with the Enrollment Visit (Study Day 1). During the Enrollment Visit, patients will undergo all procedures as outlined in the SoA Stage 1 (Table 1) and it will be reconfirmed that the patient continues to meet the Inclusion and Exclusion criteria. At the Enrollment Visit, the trial center must confirm that the patient completed the electronic diary at least 4 of 7 days prior to the Enrollment Visit. If the diary was not appropriately completed, the patient may not enter the trial. The Enrollment Visit may be re-scheduled if the remaining visit window allows.

During the Enrollment Visit, the patient will have their body weight recorded. This will be the patient's "Baseline Weight." During the Enrollment Visit, the patient (or caregiver) will receive training on injections of trial medication and will administer the first dose of setmelanotide under the supervision of the trial staff. In-clinic doses of trial medication, including the first dose, will be administered following blood sampling for pharmacokinetic (PK) analysis.

During Stage 1, the patient (or caregiver) will administer setmelanotide on a daily basis for 16 weeks. During this period, the patient will have in-person as well as virtual visits using a validated Telehealth platform with the trial center. During the virtual visits, the patient (or caregiver) will record a body weight measurement and be assessed for compliance with trial procedures and AEs. Any visit that is planned as a virtual visit may be converted to an in-person visit at the discretion of the Investigator. If more than 2 virtual visits are to be converted into in-person visits, Sponsor approval is required.

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

- ≥18 years old must have achieved a body mass index (BMI) at least 3% less than the Baseline BMI at the end of Stage 1
- <18 years old must have achieved a BMI at least 3% less than the Baseline BMI or a decrease in BMI Z-score of at least 0.05 at the end of Stage 1

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

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

Eligible patients who enter Stage 2 (see Section 5.1.2) will continue in the trial for an additional 24 weeks. Stage 2 of the trial will begin with the Stage 2 Entry Visit. During the Stage 2 Entry Visit, the patient will complete all assessments as per the SoA Stage 2 (Table 2). The patient will have a body weight recorded. This measurement will be their Stage 2 Entry Weight Measurement. In clinic doses of trial medication will be administered following blood sampling for pharmacokinetic (PK) analysis.

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

stratified will be provided in a separate document. Patients will have either virtual or in-person visits as indicated in the SoA for Stage 2 (Table 2) and depicted in Figure 1. At the Investigator's discretion, either (1) additional virtual or in-person visits may be scheduled or (2) planned virtual visits may be converted to in-person visits. If more than 2 virtual visits are to be converted into in-person visits, Sponsor approval is required.

5.1.3.1. End of Treatment and End of Study

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

5.1.3.2. Switch to Treatment with Setmelanotide

During Stage 2 of the trial, patient weight will be monitored as per the SoA Stage 2 (Table 2). Additional virtual visits may be scheduled at the discretion of the Investigator.

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

To be eligible, the patient must be scheduled for an in-person visit at the clinic. At the visit, the patient's body weight will be recorded. If the visit occurs within 2 weeks of an expected trial visit as per the SoA Stage 2 (Table 2), then the visit may replace that expected trial visit. All procedures as outlined in the SoA Stage 2 for the expected trial visit should occur. At this visit, the patient will return their double-blind trial medication supply. The patient may then be enrolled into the LTE trial or will be issued open-label setmelanotide and will continue in the trial via bridging visits until the LTE trial is available. The patient's initial assignment to either trial medication or placebo will continue to be blinded to all parties.

5.1.3.3. Trial, Site, or Cohort Suspension or Termination

This trial, any site, or any cohort of patients (for a gene, gene variants, or subset of variants) may be suspended or terminated, if in the opinion of the Sponsor, there is sufficiently reasonable cause. The Sponsor may also prioritize cohorts for enrollment at its discretion. The Sponsor will provide written notification documenting the reason for cohort/site/trial termination to the Investigator.

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

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enroll patients at an acceptable rate
- Insufficient adherence to protocol requirements

- Insufficiently complete and/or evaluable data
- Plans to modify, suspend or discontinue the cohort or the development of the trial medication

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

5.1.4. Genetic Diversity

To enroll in this trial, a patient must have a pre-identified genetic variant in an established MC4R pathway gene that contributes to obesity. A list of genes that have variants that are eligible for enrollment into the trial is provided in Appendix 1. Gene variant enrollment by gene is at the discretion of the Sponsor.

This trial aims to enroll up to 10 patients with each gene into the trial. Enrollment will be monitored by the Sponsor and further enrollment of patients with a genotype may be paused once 10 patients with that particular gene have been enrolled into the trial.

Patient response to setmelanotide by gene will be monitored by the Sponsor during the open-label portion of the trial in 2 ways: the rate of patients qualifying for Stage 2 of the trial and the magnitude of response to setmelanotide. The Sponsor may increase or decrease the target number of patients enrolled with a particular gene or may close any individual gene cohort after assessment of lack of efficacy on 3 or more patients. The total sample size of the trial will not be increased.

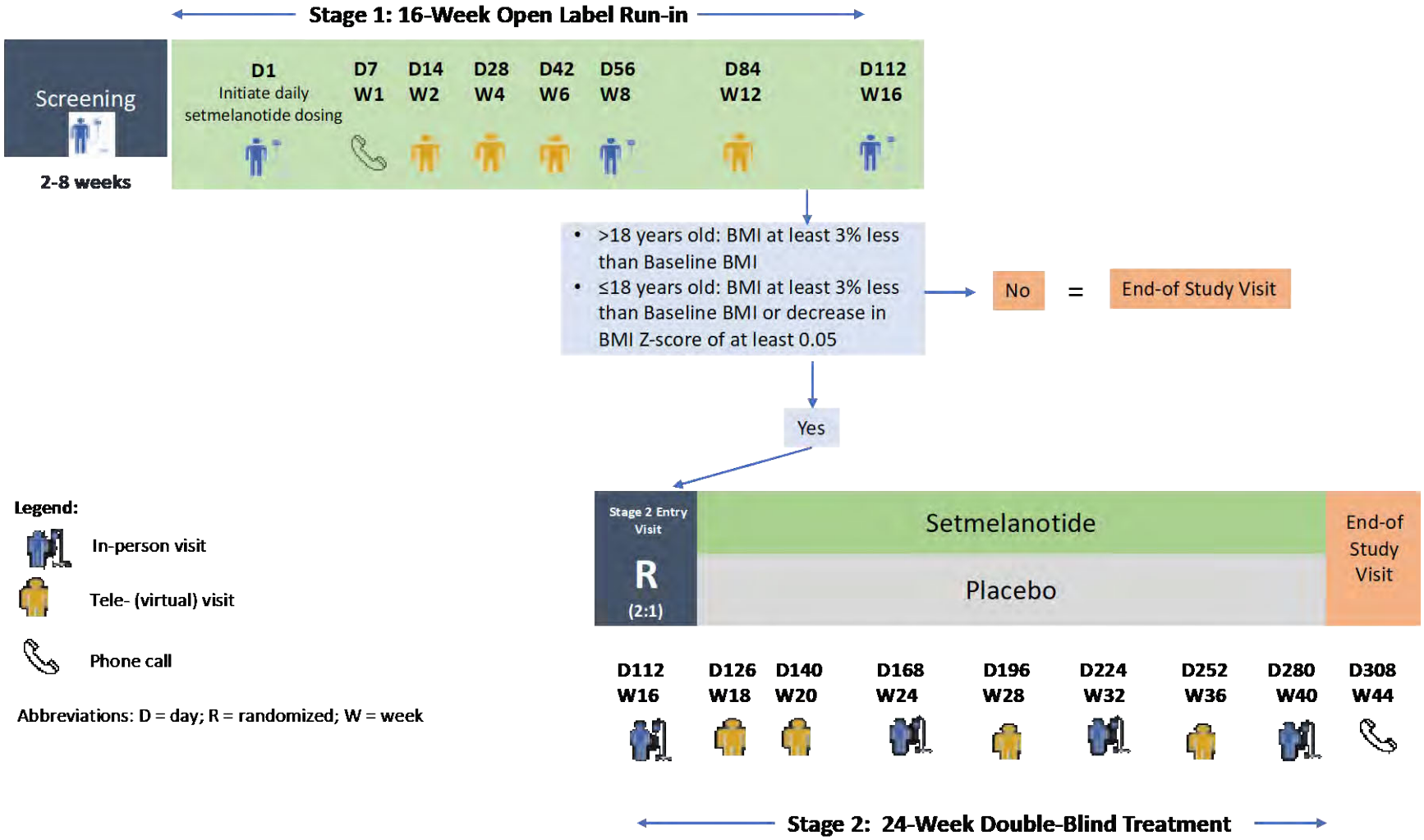
It is possible that a patient may enter the trial with more than 1 eligible gene. In this situation, all eligible genes will be captured in the database. For analysis purposes, a single gene will be considered the "primary gene" for that patient, and the patient will be analyzed within that gene cohort. The primary gene will be defined as the eligible gene with the most significant American College of Medical Genetics (ACMG) categorization (e.g., Pathogenic>Likely Pathogenic>Variant of Uncertain Significance [VUS]). If 2 or more eligible genes share the same most significant ACMG categorization, then the "primary gene" will be defined as the least prevalent gene and the patient will be analyzed within that gene cohort. Additional sensitivity analyses may be conducted. The expected prevalence of the genes being enrolled into this trial will be provided in a separate document.

5.1.5. Trial Conduct During the COVID-19 (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, maintain compliance with Good Clinical Practice (GCP), and 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 6.

Figure 1: Trial Design



Note: if required by local regulation or if deemed necessary to assess patient safety by physical examination or after a longer follow-up period, the EOS visit may be converted to an in-person visit, and/or can occur up to Week 48.

5.2. Patient and Trial Completion

A patient is considered to have completed the trial if he/she has received the last planned dose of trial medication on Study Day 280 and completed the EOS telephone visit on Day 308.

Patients who discontinue before completing the Study Day 280 EOT visit are to attend an Early Termination visit within 14 days (±7 days) after the last dose of trial 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.

6. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective approval of protocol deviations to recruitment and enrollment criteria (i.e., protocol waivers or exemptions) is not permitted.

6.1. Patient Inclusion Criteria

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

1. Patients must have a pre-identified genetic variant in an established MC4R pathway gene that contributes to obesity

   Note: Genetic testing requirements and a list of genes which have variants that are eligible for enrollment into the trial are provided in Appendix 1.

2. Patients between the ages of 6 and 65, inclusive, at the time of signing Informed Consent or Assent.
3. Patients with obesity, defined as BMI ≥40 kg/m^2 for patients ≥18 years of age or BMI ≥97th percentile for age and gender for patients 6 to <18 years of age based on the US Centers for Disease Control and Prevention criteria.
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 (including the QD injection regimen and all other trial procedures) and is able to understand and sign the written informed consent/assent. Patients who are unable to comply with all trial procedures due to cognitive limitations or any other reason should not be enrolled.
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 8.9.7:

- Combined (estrogen and progestin) hormonal contraception associated with inhibition of ovulation (i.e., 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 level in the post-menopausal lab range) and 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 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. Symptoms or behaviors of hyperphagia persistent during the patient's life, including manifestations in childhood, as determined by the Investigator at screening.

6.2. Patient Exclusion Criteria

Patients meeting any of the following criteria are not eligible for trial participation:

1. Patients with the following genetic variants: biallelic Bardet-Biedl Syndrome (BBS); biallelic Alström Syndrome 1 (ALMS1); homozygous, heterozygous, or compound heterozygous variants in MC4R, POMC, PCSK1, LEPR, nuclear receptor coactivator 1 (NCOA1; steroid receptor coactivator-1 [SRC1]) or SRC homology 2 B adapter protein 1 (SH2B1) genes as well as 16p11.2 chromosomal deletions that include the SH2B1 gene.
2. Weight loss >2% in the previous 3 months.

   Patients will not be excluded for using regimens for weight maintenance or to prevent weight gain, such as dietary and/or exercise regimens, or medications, supplements or herbal treatments (e.g., orlistat, lorcaserin, phentermine, topiramate, naltrexone, bupropion, glucagon-like peptide-1 [GLP-1] receptor agonists, etc.), provided:

   - the regimen and/or dose has been stable for at least 3 months prior to randomization

- the patient has not experienced weight loss >2% during the previous 3 months, AND
- the patient intends to keep the regimen and/or dose stable throughout the course of the trial.

3. Bariatric surgery or procedure (e.g., gastric bypass/band/sleeve, duodenal switch, gastric balloon, intestinal barrier, etc.) within the last 6 months. All patients with a history of bariatric surgery or procedures must be discussed with, and receive approval from, the Sponsor prior to enrollment.
4. Documented diagnosis of current unstable major psychiatric disorder(s) (e.g., major depressive disorder, bipolar disorder, schizophrenia, etc.) or documented worsening psychiatric condition that required changes in treatment regimen within the previous 2 years, or other psychiatric related risks that the Investigator believes may interfere with trial compliance or patient safety.
5. Clinically significant depression or suicidality, as defined by: any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) during Screening, any suicide attempt during the patient's lifetime, any suicidal behavior in the last month, or a Patient Health Questionnaire-9 (PHQ-9) score of ≥15 during Screening process.

   Note: Patients who are unable to complete the PHQ-9 or C-SSRS due to significant neurocognitive impairment may be enrolled in the trial provided that there are no clinical signs or symptoms of significant depression or suicidal behavior in the opinion of the Investigator.
6. Current, clinically significant pulmonary, cardiac, endocrine/metabolic, hepatic, or oncologic disease considered severe enough to interfere with the trial and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor to determine eligibility.
7. Significant features of, or meeting the diagnostic criteria for, a genetic syndrome that is associated with obesity.

   Note: Although some of the genetic variants that are eligible to be enrolled into this trial are associated with specific syndromes, the intent of this trial is not to enroll children with significant cognitive impairment or other significant co-morbidities. Patients with eligible genetic variants, but who otherwise do not exhibit the syndrome, are eligible for enrollment.
8. HbA_{1C} >10.0% at Screening.
9. History of significant liver disease other than non-alcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). Patients with NAFLD or NASH will not be excluded based on this criterion
10. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 at Screening. In patients ≥18 years of age the Modification of Diet in Renal Disease (MDRD) Equation should be used to calculate eGFR. In patients <18 years of age, the Bedside Schwartz Equation should be used for calculation of GFR.
11. History or close family history (parents or siblings) of melanoma, or patient history of oculocutaneous albinism.

Note: If the type of skin cancer in patient's or close family history is not known, then the patient should not be enrolled into the trial.

12. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a comprehensive skin evaluation performed by the Investigator during Screening. If any concerning lesions are identified during Screening, the patient should be referred to a dermatologist. Any concerning lesions identified during Screening will be biopsied and results known to be benign prior to enrollment. If the pre-treatment biopsy results are of concern, the patient may need to be excluded from the trial.
13. Patient is, in the opinion of the Investigator, not suitable to participate in the trial.
14. Participation in any clinical trial with an investigational drug/device within 3 months or 5 half-lives, whichever is longer, prior to the first day of dosing.
15. Patients previously enrolled in a clinical trial involving setmelanotide or any previous exposure to setmelanotide.
16. Hypersensitivity to the active substance or to any of the excipients of the investigational medicinal products (active and placebo).
17. Females who are pregnant or breastfeeding, or planning or desiring to become pregnant during the duration of the trial.
18. Legally protected persons per local regulations (e.g., those that fall under the L1121-6 article of the Public Health code in France).
19. For France only: patient is <18 years of age.

6.3. Treatment Discontinuation and Withdrawal from the Trial

Given this rare patient population, every effort should be made to encourage and keep patients enrolled in the trial until completion, 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 and completion of trial participation.

Discontinuation of trial treatment or skipped visits/injections may be allowed without withdrawal from the trial.

Some patients' reason for discontinuation may be related to injection site reactions and burdensome laboratory/visits. Patients can be offered the option to discontinue trial medication but remain in the trial. These patients who stop therapy will be counted as a non-responder, irrespective of treatment assignment. However, they will be followed and have weight assessments at each visit, particularly at the final visit to determine weight trajectory for all patients. Patients who withdraw before completing Visit 14 are to attend an Early Termination visit within 14 days (±7 days) after the last dose of trial medication for final trial assessments. If possible, patients will be asked to determine weight assessment at the expected time of their EOT visit.

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 opinion of Investigator justifies treatment or trial withdrawal. For specific predefined events, additional monitoring and guidance for the Investigator is provided in Appendix 5.
- Non-adherence to trial medication regimen or protocol requirements.
- Non-compliance with instructions or failure to return for follow-up.
- Note: The Sponsor may choose to discontinue investigation of a particular genetic cohort/variant at any time; therefore, continued participation of patients for that genetic cohort/variant will be addressed at that time

All patients withdrawn prior to completing the treatment period should be strongly encouraged to complete the Early Termination visit as outlined in the SoA (Table 1 and Table 2), even if they are no longer receiving trial medication.

6.4. Lost to Follow-up

Patients are considered as being lost to follow-up if they fail to return for scheduled evaluations and cannot be contacted by the site. The following actions must be taken if the patient fails to return to the clinic for a required trial evaluation:

- The trial site must attempt to contact the patient and reschedule the missed evaluation as soon as possible and counsel the patient on the importance of maintaining the assigned evaluation schedule.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with them or next of kin by, for example, repeat telephone calls, certified letter to the patient's last known mailing address, or local equivalent methods. At least 3 unique documented contact attempts to follow-up over a period of weeks to months should be made, including at least 1 in relation to the final visit on Day 308. The patient should only be permanently recorded as lost to follow-up if they did not respond to any contact attempts by Day 308. These contact attempts should be documented in the patient's medical records.

6.5. Lifestyle Counseling

6.5.1. Physical Activity

During the trial, patients will receive physical activity counseling by qualified site personnel and will be encouraged to perform aerobic physical activity for a duration of at least 150 minutes per week, maintaining an average target HR of 70% of their maximum HR. Aerobic physical activity includes repetitive motions of large muscle groups, such as brisk walking, swimming, mowing

the lawn, running, dancing, etc. Maximum HR is calculated as 220 beats per minute (bpm) minus patient's age in years.

Example: if a patient is 50 years old, the maximal HR is calculated as 220 bpm –50 years of age = 170 bpm. For this patient, 70% of the maximal HR (0.70 × 170 bpm) is 119 bpm. Therefore, this patient will be encouraged to perform 150 min of aerobic physical activity per week targeting an average HR of 119 bpm.

Each patient will be provided with an electronic tracker to monitor HR and physical activity to inform whether the target level of physical activity was fulfilled. At every virtual and in-person visit, each patient will be asked if they performed the target level of activity.

6.5.2. Nutrition

During the trial, patients will receive dietary counseling by qualified site personnel and will be encouraged to follow a diet with a reduction of 500-750 kilocalories (Kcal) per day as advised by the American College of Cardiology (ACC), American Heart Association (AHA), The Obesity Society (TOS) 2013 guidelines (Jensen 2014). At each visit (virtual and in-person) patients will be counselled on nutrition and compliance will be assessed by on-site personnel.

6.5.3. Skin Protection

Skin hyperpigmentation, or tanning, was observed in the cynomolgus monkey toxicology studies and the human studies. These events were reversible upon cessation of trial medication. However, it is still uncertain if exposure to sunlight might exacerbate the tanning effects of setmelanotide. Therefore, patients will be advised to use sunscreen and/or to wear protective clothing to avoid excessive exposure of their skin to sunlight and to avoid sun-tanning.

It is also important that patients do not participate in any activities that will intentionally cause their skin to tan (e.g., visit ultraviolet [UV] tanning salons, use spray tanners, self-tanning lotions, etc.).

7. TREATMENT OF PATIENTS

7.1. Description of Trial Medication

All trial medication is for investigational use only and is to be used only within the context of this protocol. All investigational trial medication (setmelanotide and placebo) will be supplied by the Sponsor.

[redacted]

The reference therapy for the double-blind period of this trial is a placebo vehicle. [redacted]

[redacted]

Setmelanotide and placebo are clear, colorless to slightly opalescent solutions essentially free of visible particulates and are suitable for a double-blind trial.

7.2. Randomization, Blinding, and Unblinding

7.2.1. Stage 1

Stage 1 of the trial is open-label, and all patients will receive setmelanotide.

7.2.2. Stage 2

Patients who are eligible to enter Stage 2 of the trial will be randomized in a blinded manner on Day 112 (Stage 2 Entry Visit) in a 2:1 ratio to receive either setmelanotide (2) or placebo (1). The randomization schedule will be generated by the Sponsor or its designee, and trial personnel will use a web-based interactive response technology (IRT) system to obtain the randomization number for each eligible patient.

Stage 2 of this trial is double-blinded. The patient, Investigator, and Sponsor will be blinded to trial treatment.

7.2.3. Blinding and Unblinding

Full details for the blinding and unblinding are provided in the separate Blinding and Unblinding Plan.

Blinded randomization will occur via an IRT.

Emergency unblinding for AEs may be performed through an IRT. The IRT 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 treatment 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 treatment 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 treatment 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, Independent Ethics Committees (IECs), and/or Institutional Review Boards (IRBs). Investigators will receive only blinded information unless unblinded information is judged necessary for safety reasons.

7.3. Administration

Trial medication will be administered as a SC injection QD.

Patients 12 years of age and older: trial medication (setmelanotide or matching placebo) 2 mg QD for approximately 2 weeks, then increased to 3 mg QD. Dose escalation should occur at the trial visit planned for Day 14 (±3 days) and should occur on the day of that visit.

Note: if the starting dose of trial medication is not tolerated reduce to 1 mg QD; the lowest target dose in patients ≥12 years of age is 1.0 mg QD; however, in consultation with the medical monitor, the dose may be lowered to 0.5 mg QD if not tolerated.

Patients 6 to <12 years of age: trial medication 1 mg QD for approximately 1 week, then increased to 2 mg QD for approximately 1 week, then increased to 3 mg QD. Dose escalation should occur during the phone call planned for Day 7 (±2 days) and at the trial visit planned for Day 14 (±3 days) and should occur on the day of that visit.

Note: if the starting dose of trial medication is not tolerated reduce to 0.5 mg QD; the lowest target dose in patients 6 to <12 years of age is 0.5 mg QD.

Note that the above dosing and titration scheme is based on the same dosing and titration scheme employed in the completed RM-493-023 Phase 3 trial in patients with BBS and AS, which included patients as young as 6 years of age. Review of the AEs in the overall trial population or the pediatric population within Trial RM-493-023 did not show an increase in the frequency or severity of AEs such as nausea during the titration period, despite the shorter titration period of setmelanotide compared to previous studies. Based on these data, the dosing and titration scheme above, including duration, is expected to be safe and well tolerated, and it allows patients to reach a targeted therapeutic and efficacious dose of setmelanotide in a more timely manner. Investigators may increase or decrease the dose, if necessary, to treat an AE, although a setmelanotide dose greater than 3 mg QD should not be used in this trial. If an Investigator feels that a dose adjustment is required for a reason other than an AE (e.g., exaggerated weight loss), the decision should be discussed with the Sponsor prior to changing the dose.

All changes in dose other than the per-protocol dose titration should be captured as a protocol violation, regardless of the rationale for the dose adjustment.

There will be extensive training of patients and caregivers (as applicable) in drug administration including educational materials. Trial-specific training materials will be provided to both the investigative staff and trial participants and caregivers.

Patients will be reminded to bring their trial medication to in person visits and that there should be no trial medication administration at home on the day of clinic visits. Blood sampling for PK analysis will be performed prior to administration of trial medication on the day of in clinic visits.

7.4. Drug Interruption and Stopping Rules

Safety parameters will be monitored during the trial. Trial drug administration will be interrupted if certain safety parameter criteria are met, and additional assessments may be implemented. The Medical Monitoring plan provides for detailed instructions.

7.5. Treatment Compliance

Accountability for the trial medication at the trial site is the responsibility of the Investigator. The Investigator will ensure that the trial medication 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/unused trial medication to the trial center, and return to the Sponsor or Sponsor's designee (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 complete a daily dosing log, and by accounting for trial medication dispensed and returned (used and partially used).

7.6. Preparation/Handling/Storage/Accountability

Only patients enrolled in the trial may receive trial medication and only authorized site staff may supply or administer trial medication. All trial medication must be stored 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 trial medication accountability, reconciliation, and record maintenance (ie. receipt, reconciliation, and final disposition records).

All unopened trial medication must be kept at a temperature between 2°C to 8°C. Setmelanotide is stable at room temperature for a short time period that will allow patients to transport trial medication home; ice packs and cooler bags will be provided for patients and caregivers who will travel long distances from the clinic. Once at home, the unopened trial medication must be stored in the patient's refrigerator. Opened trial medication may be stored at room temperature for up to 30 days.

For accountability, patients/caregivers will return all used trial medication kits to the clinic when they visit. The trial staff will record the number returned, and both clinic administered trial medication, as well as outpatient trial medication administration will be recorded in a trial diary.

7.7. Concomitant Medications

Medication that is considered necessary for the patient's safety and wellbeing may be given during the trial at the discretion of the treating physician after discussion with the Medical Monitor.

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

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 and anti-obesity medications may be used as long as:

- the regimen and/or dose has been stable for at least 3 months prior to randomization
- the patient has not experienced weight loss ≥2% during the previous 3 months, AND
- the patient intends to keep the regimen and/or dose stable throughout the course of the trial.

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

8. ASSESSMENTS

Trial procedures and their timing are summarized in the SoA (Table 1 and Table 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 electrocardiogram (ECG), and perform blood draws (at the specified time point, if applicable). In-clinic dosing should follow PK draws. Adjustments may be made depending upon specific circumstances and in consultation with the Sponsor.

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

Note that additional assessments may be performed at the Investigator's discretion as needed to ensure patient safety.

8.1. Informed Consent / Assent

A complete description of the trial is to be presented to each potential patient and parent or legal guardian/representative and signed and dated informed consent and/or assent 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 informed consent form(s) (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.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) 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.

8.2. Inclusion/Exclusion Review

Inclusion and exclusion criteria are to be reviewed per the SoA (Table 1) 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 (Table 1). 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 prior to first dose of trial medication, to assess continued trial eligibility and adherence to final inclusion/exclusion criteria. This medical history update includes a review for changes from Screening as well as 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 is to be measured at Screening only. For patients aged <21 years, height is to be measured at the time points listed in the SoA (Table 1 and Table 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 cm.

8.5. Fitzpatrick Scale

Each patient is to be categorized for skin type according to the Fitzpatrick scale. The Fitzpatrick scale is presented in Appendix 3.

8.6. Pharmacokinetic Assessments

Blood samples for determination of setmelanotide levels in plasma will be collected as indicated in the SoA in Table 1 and Table 2. For all blood samples for PK analysis, the actual (clock) time each PK blood sample is collected will be recorded in the source documents and electronic case report form (eCRF). Plasma will be harvested from each blood sample collected for PK analysis and the plasma will be frozen, shipped to a bioanalytical laboratory designated by the Sponsor, and analyzed for setmelanotide concentrations.

Setmelanotide plasma PK will be assessed in all patients by trough (pre-dose) concentrations measured prior to dose administration in the clinic as per the SoA.

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

8.7. Efficacy Assessments

8.7.1. Weight

Weight (kg) will be recorded at the time points designated in the SoA (Table 1 and Table 2). Whenever possible, the same scale at the site should be used throughout the trial, including the Screening Visit, and should be calibrated on a regular basis per the manufacturer's instructions. Patients will be provided a trial-specific scale to be used at home for all virtual visits under direct visual observation by site personnel.

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

[redacted]

[redacted]

[redacted]

[redacted]

8.7.6. Biomarkers

A blood sample will be collected for metabolic, inflammation, metabolomic and/or proteomic biomarker analysis at the time points specified in the SoA (Table 1 and Table 2). This sample may or may not be analyzed. All samples are sent to a central laboratory and may be sent to other laboratories for further analyses. Additional details are described in the laboratory manual.

8.8. Nutrition and Physical Activity Counseling and Follow-Up

Patients will be asked at every visit per the SoA (Table 1 and Table 2) if they are achieving nutrition and physical activity counseling target recommendations.

8.9. Safety Assessments

Safety will be assessed as described in the sections below.

8.9.1. Vital Signs

Vital signs include systolic and diastolic BP, HR, respiration rate (RR), and body temperature (°C). Vital signs will be obtained in the sitting position following at least 5 minutes of rest at each time point designated in the SoA (Table 1 and Table 2).

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) and ensuring that an appropriately sized cuff is used.

Repeat measures and more frequent monitoring can be implemented for significant increases in BP or HR.

Participants will be instructed on the proper use of and will be provided with WiFi/Bluetooth connected devices for measuring and transmitting data on blood pressure and temperature during virtual trial visits. The data are stored and automatically transferred when connected to WiFi. Refer to Appendix 8 for additional details.

8.9.2. Physical Examination

A complete physical examination will be conducted at Screening and at the EOT visit. At other time points, as designated in the SoA (Table 1 and Table 2), an abbreviated examination will be performed.

- 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 a neurologic examination.
- 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 physical examinations and Tanner Staging.

All physical examinations are to be conducted in adequate light.

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.

8.9.3. Comprehensive Skin Examination

A comprehensive skin examination will be performed by the Investigator at the time points designated in the SoA (Table 1 and Table 2).

The skin examination should include a full body (head-to-toe skin examination). If any concerning lesions are identified during Screening, the patient should be referred to a dermatologist. Any concerning lesions will be biopsied by the dermatologist and results must be benign prior to the first dose of setmelanotide. If the pre-treatment biopsy results are of concern, the patient may be excluded from the trial. Additionally, any concerning lesion or change in an existing lesion during the course of the trial must be evaluated by the dermatologist and biopsied, if clinically indicated in the opinion of the dermatologist.

8.9.4. Electrocardiogram

A single 12-lead ECG will be performed at the time points designated in the SoA (Table 1 and Table 2). ECGs are to be performed with the patient in the supine position following a period of at least 10 minutes of rest.

8.9.5. Laboratory Assessments

Blood and urine samples for clinical laboratory tests are to be collected at the time points designated in the SoA (Table 1 and Table 2). Clinical safety laboratory tests are to be performed after patients have been fasting for 8 hours. Samples are to be collected prior to setmelanotide administration.

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

Clinical laboratory parameters to be evaluated, including hematology, clinical chemistry, coagulation studies, [redacted] as well as urine analysis, are identified in the SoA (Table 1 and Table 2).

GFR will be calculated in patients ≥18 years of age using the MDRD Equation: glomerular filtration rate (GFR) = 175 × (creatinine in mg/dL)-1.154 × (age in years)-0.203 × (0.742 if female) × (1.210 if African American). GFR will be calculated in patients <18 years of age using the Bedside Schwartz Equation: GFR (mL/min/1.73 m²) = (0.41 × height in centimeters)/creatinine in mg/dL).

8.9.6. Anti-Drug Antibodies (ADA)

Blood samples for analysis of anti-drug antibodies (ADA) will be collected at the time points specified in the SoA (Table 1 and Table 2). If a patient has a positive ADA titer, they will be followed every 3 months after the ADA sample analysis until resolution of the ADA titer.

8.9.7. Pregnancy and Contraception

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

It is imperative all trial patients adhere to the contraception and pregnancy testing requirements as outlined below.

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 during the trial at the time points specified in the SoA (Table 1 and Table 2); however, setmelanotide dosing may continue with results pending. At Visit 1 and Visit 7, for sites where pregnancy tests are required for virtual visits, females of childbearing potential will be given urine pregnancy test kits for use at each of the virtual visits in Stage 1 and Stage 2, respectively.

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 follicle stimulating 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 whether 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 with medical assessment of surgical success 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. Sexual 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 by completing the Pregnancy Reporting Form and following the Sponsor reporting procedures outlined in Appendix 5.

Details of all pregnancies in female patients and female partners of male patients will be collected after the start of trial 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.

8.9.8. Injection Site Examination

Injection sites will be carefully inspected, evaluated, and scored at the time points outlined in the SoA (Table 1 and Table 2) during the trial period. The injection site evaluation will include identification and measurement of areas of erythema, edema, and induration, as well as the presence of localized pain, tenderness, and itching. A sample injection site evaluation form is included in Appendix 4.

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

8.9.9. Suicidal Ideation and Depression Monitoring

As setmelanotide is considered to act through the central nervous system (CNS), suicidal ideation and risk will be assessed using the C-SSRS scale (Section 8.9.9.1) and depression will be assessed using the PHQ-9 or the Children's Depressive Inventory-2 (CDI-2) (Section 8.9.9.2 and 8.9.9.3).

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 of ≥10
- A CDI-2 score of >20

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 condition can be adequately treated with psychotherapy and/or pharmacotherapy, then the patient, at the discretion of the MHP, may be continued in the trial.

In patients with cognitive impairment or pediatric patients, the ability to complete the C-SSRS or PHQ-9 may be limited. If in the clinical opinion of the Investigator a specific patient cannot complete the instrument(s), 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 PHQ-9 and C-SSRS are not administered, the Investigator should document that the issues of depression and suicidality were assessed clinically (e.g., discussion with caregivers).

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

Patients ≥6 years of age

As required in the US by the Food and Drug Administration (FDA), for clinical trials of CNS-acting medications, changes in 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 MPH). There are 2 versions of the C-SSRS that will be administered according to the SoA (Table 1 and Table 2):

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

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

To be eligible for the trial, a patient cannot have a suicidal ideation of type 4 or 5, a suicide attempt during the patient's lifetime, or any suicidal behavior in the last month.

Any patient with a suicidal behavior or a suicidal ideation of type 4 or 5 on the CSSRS will be referred to a mental health professional.

8.9.9.2. Patient Health Questionnaire -9 (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. The PHQ-9 will be administered in patients ≥12 years of age or according to the SoA (Table 1 and Table 2).

Any patient with a PHQ-9 score ≥10 will be referred to a mental health professional.

8.9.9.3. Children's Depression Inventory-2

The CDI-2 has both a self-report and a parent version. The CDI-2: Self-Report Short version is an efficient screening measure that contains 12 items and takes about 5-10 minutes to administer. The self-report short version will be administered to patients <12 years of age according to the SoA (Table 1 and Table 2).

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

Any patient with a CDI-2 score >20 will be referred to a mental health professional.

8.9.10. Overdose

One accidental overdose has been reported in the clinical program in a pediatric patient receiving a 5-mg dose instead of a 0.5-mg dose. The patient had mild symptoms that resolved.

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 as well as 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 Sponsor based on the clinical evaluation of the patient.

8.9.11. Adverse and Serious Adverse Events

Adverse events 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 trial treatment or trial procedures, or that caused the patient to discontinue trial treatment (see Section 6.3).

Details on recording AEs and SAEs, including definitions, are provided in Appendix 5.

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

All AEs, including SAEs, will be collected from the time informed consent is signed until the EOS visit at the time points designated in the SoA (Table 1 and Table 2). AEs reported after dosing on Day 1 will be considered TEAEs.

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

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours without undue delay but no later than within 24 hours, as indicated in Appendix 5. The Investigator will submit any updated SAE data to the Sponsor without undue delay but no later than within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information from 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 AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 5.

8.9.11.2. 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.

8.9.11.3. 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 5.

8.9.11.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that regulatory obligations and ethical responsibilities towards the safety of patients and the safety of a trial 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 trial treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, IECs, 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 Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9. SAFETY DATA MONITORING

The Investigators will be responsible to review and evaluate safety data from their patients in a continuous manner. Cumulative safety data from the trial will be reviewed by the Sponsor on an ongoing basis for any safety signals or tolerability concerns. Additionally, this trial will be monitored by an independent Data Safety Monitoring Board (DSMB). The DSMB will operate under a separate charter and will meet periodically (e.g., every 3 months) to review the cumulative safety data from the trial and will make a recommendation to continue or modify the trial, if needed.

10. STATISTICS

This section describes the plans for analysis of the trial data. 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 study report for the trial, as appropriate.

10.1. Sample Size Determination

The trial is a 2-stage design: Stage 1 is open-label treatment part, and Stage 2 is randomized, double blind, placebo-controlled part. It is planned to enroll 100-200 patients in the trial. Sample size is not based on any statistical considerations.

10.2. Populations for Analyses

There are 2 analysis populations defined in the protocol:

- Full Analysis Set (FAS): all patients randomized in Stage 2 who received at least 1 dose of trial medication (placebo or setmelanotide) in Stage 2 and have baseline data. Analyses performed on the FAS will be based on patients as randomized.
- Safety Analysis Set: All patients who received at least 1 dose of trial medication.

10.3. Statistical Analyses

A separate SAP will be developed, which will include a more technical and detailed description of the statistical analyses described in this section.

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

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

The 95% exact confidence interval will be provided for the primary efficacy endpoint. The analyses of the efficacy endpoints in Stage 1 will be performed based on the safety analysis set, and the analyses of the efficacy endpoints in Stage 2 will be performed based on the FAS, which is defined as all patients randomized in Stage 2 who received at least 1 dose of trial medication (placebo or setmelanotide) in Stage 2 and have baseline data.

AEs/SAEs will be summarized with frequencies and percentages. A by-patient AE data listing including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided.

Safety data including laboratory evaluations and vital signs assessments will be summarized by time of collection. In addition, change from baseline to any post-dose values will be summarized for vital signs and clinical laboratory results. Frequency of patients with abnormal safety laboratory results will be tabulated.

All safety analyses and summary tables will be based on the safety analysis set.

10.3.1. Interim Analyses

There are no planned interim analyses.

11. LIST OF REFERENCES

Farooqi IS, O'Rahilly S. Mutations in ligands and receptors of the leptin-melanocortin pathway that lead to obesity. Nat Clin Pract Endocrinol Metab. 2008;4(10):569-77.

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

Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129(25 Suppl 2):S102-38.

National Institutes of Health (NIH), National Heart Lung and Blood Institute (NHLBI). The Practical Guide. Identification, evaluation, and treatment of overweight and obesity in adults. NIH Publication No. 00-4084, October 2000.

Rhythm Pharmaceuticals. IMCIVREE (setmelanotide) Package Insert. U.S. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213793s001lbl.pdf. Revised June 2022. Accessed 23 June 2022.

Rhythm Pharmaceuticals. IMCIVREE (setmelanotide) Summary of Product Characteristics. European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/imcivree-epar-product-information_en.pdf. Revised November 2021. Accessed 22 July 2022.

Rhythm Pharmaceuticals. IMCIVREE (setmelanotide) Summary of Product Characteristics. Medicines and Healthcare Products Regulatory Agency. https://mhraproducts4853.blob.core.windows.net/docs/f22032c92d5504e9a5c3270ba2dacde0cc17819b. Revised December 2021. Accessed 22 July 2022.

12. APPENDICES

APPENDIX 1. LIST OF GENES ELIGIBLE FOR ENROLLMENT AND GENETIC TESTING REQUIREMENTS

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

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

GENETIC TESTING REQUIRMENTS:

Eligibility per Inclusion Criterion #1 and assignment to the appropriate sub-study cohort will be based on either:

a. genetic diagnosis made by a CLIA/CAP/ISO15189 laboratory, or

b. genetic report available at screening from a non-CLIA/CAP/ISO15189 laboratory, sent for review and adjudication via Variant Interpretation Service (VIS) conducted by PreventionGenetics (PG), a CLIA/CAP/ISO15189 certified laboratory.

In addition to the eligibility testing described above, all patients will have confirmatory diagnosis made based on the PG Uncovering Rare Obesity (URO) 3.0 panel (79 genes +1 chromosomal region).

All randomized patients will be included in the safety and Full Analysis Set (FAS) analyses. The Per-Protocol (PP) analysis will only include patients whose confirmatory diagnosis testing matches the respective sub-study cohort assignment. There are 3 potential scenarios for sub-study cohort assignment:

- If at Screening the genetic diagnosis is derived from PG, a CLIA/CAP/ISO15189 certified laboratory (URO 3.0 panel), the patient will be assigned to the cohort reported in the PG URO 3.0 genetic report. A genetic sample will be taken for confirmatory testing, unless waived by the Sponsor.
- If the genetic diagnosis is derived from a non-CLIA/CAP/ISO15189 laboratory (such as a research academic center laboratory), the genetic report will be reviewed and adjudicated by PG for VIS before the patient enters Screening. The VIS result will be utilized for cohort assignment. A genetic sample will be taken either at the time of screening or at Study Visit 1 (V1) and confirmatory testing will be run using the PG laboratory. If the confirmatory genetic report does not confirm the initial genetic diagnosis and sub-study cohort assignment, then patients will be included in the safety and FAS analyses only, and not in the PP analysis.
- If the genetic diagnosis is derived from a CLIA/CAP/ISO15189 laboratory, other than PG, no PG VIS review is required. A genetic sample will be taken either at the time of screening or at V1 and confirmatory testing will be run using the PG laboratory.

All patients will have genetic samples processed for confirmatory genetic testing. Where permitted by law, all patients may provide additional informed consent to have genetic samples stored for future research purposes.

APPENDIX 2. 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" 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 participants <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.
- 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.
- Trial medication injections should only be performed by caregiver (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 examination 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 representative examples of rare genetic diseases of obesity impacting the MC4R pathway, there is the possibility of major benefit.

APPENDIX 3. FITZPATRICK 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

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

APPENDIX 4. INJECTION SITE EVALUATIONS

Injection sites will be assessed at the time points outlined in the Schedule of Assessments (Table 1 and Table 2), and in the setting of any injection site reaction adverse experience. This assessment will consider severity and measurement (length and width if applicable) of any instance of erythema, edema, induration, itching, pain/tenderness or other relevant findings.

Local Skin Tolerability Assessment

Reaction	NONE	Mild	Moderate	Severe	Measurement (if applicable)
Erythema* [1]	☐	☐	☐	☐	
Edema*	☐	☐	☐	☐	
Induration* [1]	☐	☐	☐	☐	
Itching	☐	☐	☐	☐	
Pain or Tenderness	☐	☐	☐	☐	
Other: _____	☐	☐	☐	☐	

* If present, region will be measured, length and width as appropriate.

[1] In the event of severe erythema, defined as ≥10 cm, and/or induration of the injection area of the size of ≥10 cm and in the presence of fever defined as ≥38°C, or based on the Investigator's clinical judgement, the Investigator should contact the Sponsor and discuss therapeutic management of the patient and potential temporary drug discontinuation.

Initials:_____

APPENDIX 5. 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 trial treatment, whether or not considered related to the trial 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 trial 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 trial 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 trial 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. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil 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 study, 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

A SAE is defined as any untoward medical occurrence that, at any dose:
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 CRF 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 1 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 trial 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 trial treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) 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.**
- 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 trial medication, 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 trial medication exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of the trial medication.
- The AE resolved or improved with decreasing the dose or stopping use of the trial medication (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between the trial medication 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 trial medication); 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 trial medication);

Assessment of Causality
– 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 trial medication).

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 post-mortem 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 without undue delay but no later than within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the trial is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a trial patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or by telephone.

SAE Reporting via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting will be provided to sites.

APPENDIX 6. GUIDANCE ON TRIAL CONDUCT DURING THE COVID-19 (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 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 Assessments 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 efficacy 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 caregiver 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 case report form (CRF).
- If a patient is unable to attend a site visit, investigational product may be shipped to directly to the patient.

Note that remote monitoring for COVID-19 will include source data verification.

<u>COVID-19 Infection in Trial Patients:</u>

There are 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 SARS-COV-2 should have this recorded as an AE, and if hospitalized, this should be reported as a serious AE (SAE).

APPENDIX 7. 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), IB, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the trial is initiated.
- Any amendments to the protocol will require IRB/IEC 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/IEC
  - Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC 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/IEC, 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/IEC 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.
- 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 and will retain their unique identifier.

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/IEC 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 forms (eCRF) unless transmitted to the Sponsor electronically (e.g., electronic 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/IEC 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, 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 of patients and integrity of the patient data. Each individual rIMV 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 the CRA asks Investigator site staff member to read patient source documents during a telephone call while reviewing the electronic Case Report Form (eCRF) 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 regulations, 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, Site, or Cohort Closure

The Sponsor reserves the right to close a trial cohort or site or terminate the trial at any time for any reason at the sole discretion of the Sponsor. 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:

- Determination of unexpected, significant, or unacceptable risk to patients
- 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 participants by the Investigator.
- Total number of participants enrolled earlier than expected.
- Insufficiently complete and/or evaluable data

For cohort termination:

- Plans to modify, suspend or discontinue the cohort

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

APPENDIX 8. DEVICES USED FOR VIRTUAL VISITS

Detailed information pertaining to each device used, including manufacturer and model number, are maintained within in the following trial documents:

- Connected Device Operations Plan.
- Investigator Manual for Weight Scale, Blood Pressure and Temperature Data Monitoring.
- Subject Reference Guide for each device (adult and pediatric versions).

All devices (including any new devices) outlined in trial documents will meet the same standards and requirements in accordance with the Food and Drug Administration's (FDA's) guidance for industry, *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations*. If new devices are added due to regional considerations, the trial documents will be updated accordingly.

Devices may vary by region and age of the participant; however, all devices are either calibrated at the time of manufacture or are self-calibrating with every use (weight scales). All trial participants will receive a device and a hot spot for data transmission. Devices are assigned by site to each participant using non-identifying trial participant information (date of birth, gender and Subject ID number). Data are transmitted to a dedicated and secure Carematix portal and are password protected for site access. Transmitted data are entered into the eCRF by delegated site staff, and are100% verified by clinical research associates (CRAs) during monitoring. Out-of-range values are flagged to the site for follow-up and any queries are documented through a written data clarification form (DCF) process.