SETMELANOTIDE

RM-493-035

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial: Multiple Independent Sub-studies of Setmelanotide in Patients with *POMC*/*PCSK1*, *LEPR*, *NCOA1* (*SRC1)*, or *SH2B1* 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.

[redacted]

EudraCT No. 2021-002873-24

Study Sponsor: Rhythm Pharmaceuticals, Inc.
222 Berkeley Street
12th Floor
Boston, MA 02116

Document Date (Version): 25 September 2023 (Version 7.0)

[redacted]

SUMMARY OF CHANGES TO THE PROTOCOL

The protocol history is below:

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[redacted]	[redacted]

Typographical and administrative changes were also made to improve the clarity of the document (as applicable).

APPROVAL SIGNATURE PAGE

Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial: Multiple Independent Sub-studies of Setmelanotide in Patients with *POMC*/*PCSK1*, *LEPR*, *NCOA1* (*SRC1)*, or *SH2B1* Gene Variants in the Melanocortin-4 Receptor Pathway

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REVIEWED/APPROVED BY:

[redacted]	[redacted] [redacted] this document. Date: Sep 26, 2023 08:34 EDT	26-Sep-2023
[redacted] Rhythm Pharmaceuticals, Inc.	Signature	Date

INVESTIGATOR STATEMENT

Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial: Multiple Independent Sub-studies of Setmelanotide in Patients with *POMC*/*PCSK1*, *LEPR*, *NCOA1* (*SRC1)*, or *SH2B1* 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) 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)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
α-MSH	alpha-melanocyte-stimulating hormone
ACMG	American College of Medical Genetics
ADA	Anti-drug antibody
ADV	Audio data verification
AE	Adverse event
ANCOVA	Analysis of covariance
B	Benign
BBS	Bardet-Biedl syndrome
BMI	Body mass index
BP	Blood pressure
CAP	College of American Pathologists
CDC	Centers for Disease Control and Prevention
CDI-2	Children's Depression Inventory-2
CFR	Code of Federal Regulations
%CHFB	Percent change from baseline
CHFB	Change from baseline
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
COVID-19	Coronavirus Disease 2019
CRA	Clinical research associate
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
% CV	Percent coefficient of variation
DCF	Data clarification form
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
e-diary	Electronic diary

Abbreviation or Specialist Term	Explanation
eGFR	Estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
[redacted]	[redacted]
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive response technology
ISO	International Organization for Standardization
ITT	Intention-to-treat
IUD	Intrauterine device
IWQOL	Impact of Weight on Quality of Life
Kcal	Kilocalorie
LB	Likely benign
LEPR	Leptin receptor
LS	Least square
LTE	Long-Term Extension
MAR	Missing at random
Max	Maximum
MC4R	Melanocortin-4 receptor
MHP	Mental health professional
Min	Minimum
MMRM	Mixed model for repeated measures
[redacted]	[redacted]

Abbreviation or Specialist Term	Explanation
MDRD	Modification of Diet in Renal Disease
NAFLD	Non-alcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NCOA1	Nuclear receptor coactivator 1
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
P/LP	Pathogenic, likely pathogenic
PCSK1	Proprotein convertase subtilisin/kexin type 1
PG	Prevention Genetics
PGIS	Patient Global Impression of Severity
PGIC	Patient Global Impression of Change
PHQ-9	Patient Health Questionnaire-9
PK	Pharmacokinetic
POMC	Pro-opiomelanocortin
PP	Per-Protocol
PPL	POMC, PCSK1, and LEPR
Q	Quarter
QD	Once daily
q.s.	Quantity sufficient
rDV	Remote data verification
rIMV	Remote interim monitoring visits
ROAD	Rare Obesity Advanced Diagnosis
RR	Respiratory rate
rSDM	Remote source data monitoring
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SH2B1	SRC homology 2 B adapter protein 1
SMC	Site monitoring contact
SoA	Schedule of Assessment
SP	Suspected pathogenic

Abbreviation or Specialist Term	Explanation
SRC1	Steroid receptor coactivator-1
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
URO	Uncovering Rare Obesity (genetic panel)
US	United States
VIS	Variant Interpretation Service
VUS	Variant of Uncertain Significance
VUS-SP	Variant of Uncertain Significance Suspected to be Pathogenic
WES	Whole Exome Sequencing
WOCBP	Women of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company:
Rhythm Pharmaceuticals, Inc.

Name of Investigational Product:
Setmelanotide

Title of Trial: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial: Multiple Independent Sub-studies of Setmelanotide in Patients with *POMC*/*PCSK1*, *LEPR*, *NCOA1* (*SRC1)*, or *SH2B1* Gene Variants in the Melanocortin-4 Receptor Pathway

Study center(s): Up to approximately [redacted] centers in North America, Europe, China, and the Middle East

Studied period (years):
Estimated date first patient enrolled: 2nd Quarter (Q2) 2022
Estimated date last patient completed: Q4 2024

Trial Design, Objectives and Endpoints:
This master protocol describes multiple independent, randomized, double-blind, placebo-controlled, sub-studies of setmelanotide in patients with obesity with specific gene variants in the melanocortin-4 receptor (MC4R) pathway:

- [redacted] (Sub-study 035a)
- [redacted] (Sub-study 035b)
- [redacted] (Sub-study 035c)
- [redacted] (Sub-study 035d)

These sub-studies have a high degree of similarities. The objectives and endpoints are identical for all sub-studies in patients with [redacted] (Sub-study 035a), [redacted] (Sub-study 035b), [redacted] (Sub-study 035c), and [redacted] (Sub-study 035d) gene variants in the MC4R pathway.

Objectives	Endpoints
Primary (Identical for all Sub-studies)	
• To evaluate the efficacy of setmelanotide on changes in body weight	• The difference in mean change in body weight from baseline at [redacted] in patients treated with setmelanotide compared to placebo, assessed as percent change from baseline body mass index (BMI)

Objectives	Endpoints
Secondary (Identical for all Sub-studies)	
Key Secondary:	**Key Secondary:**
• To evaluate the efficacy of setmelanotide based on the portion of patients with a clinically meaningful decrease in body weight defined as ≥5% decrease from baseline	• The proportion of patients who achieve at least 5% reduction in baseline BMI at [redacted], in patients treated with setmelanotide compared to placebo
• To evaluate the efficacy of setmelanotide on changes in body weight in adult patients with obesity	• The difference in mean change in body weight from baseline at [redacted] in adult patients (age ≥18 years at baseline) treated with setmelanotide compared to placebo, assessed as percent change in baseline body weight
• To evaluate changes in hunger score in response to setmelanotide from baseline to [redacted] of treatment	• The difference in mean percent change in the weekly average most hunger score at [redacted] in patients treated with setmelanotide compared to placebo, utilizing the Hunger Questions for Patients ≥12 years of Age©
• To evaluate the efficacy of setmelanotide on the portion of patients with at least 10% decrease in body weight	• The proportion of patients who achieve at least 10% reduction in baseline BMI at [redacted], in patients treated with setmelanotide compared to placebo
Other Secondary:	**Other Secondary:**
• To evaluate the efficacy of setmelanotide on changes in BMI in pediatric patients with obesity	• The difference in mean change in BMI from baseline at [redacted] in pediatric patients (age <18 years at baseline) treated with setmelanotide compared to placebo assessed as change in baseline BMI Z-score • The difference in change from baseline at [redacted] in % of the 95th BMI percentile, as defined by the Centers for Disease Control and Prevention (CDC), in patients <18 years at baseline treated with setmelanotide compared to placebo
• To evaluate change in waist circumference in response to setmelanotide from baseline to [redacted] of treatment	• The difference from baseline at [redacted] in mean change in waist circumference in patients treated with setmelanotide compared to placebo
• To evaluate the safety and tolerability of setmelanotide	• The overall safety and tolerability of setmelanotide in patients with genetic variants in the MC4R pathway
• To evaluate quality of life parameters following treatment with setmelanotide	• The difference in mean change from baseline at [redacted] in physical functioning score

	and total score for Impact of Weight on Quality of Life in adults (IWQOL-Lite) and in children (IWQOL-Kids-Parent Proxy) in patients treated with setmelanotide compared to placebo
• To evaluate the ability of an initial response to setmelanotide (defining a responder population) to predict long-term benefit	• The difference in mean body weight loss, and % body weight loss at [redacted] in setmelanotide responders (defined as patients with ≥5% body weight loss if ≥18 years of age, or a decrease in BMI by ≥3% if <18 years of age, after [redacted] of therapy at [redacted] day or at the maximally tolerated dose) as compared to the placebo group
Exploratory (Identical for all Sub-studies)	
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]

Methodology:

Multiple randomized, double-blind, placebo-controlled independent sub-studies will enroll patients with obesity (6 to 65 years of age) and with *POMC* and/or *PCSK1*, *LEPR*, *NCOA1 (SRC1)*, or *SH2B1* gene variants in the MC4R pathway.

Sub-studies 035a and 035b: Patients with heterozygous *POMC* and/or *PCSK1* (Sub-study 035a), and *LEPR* (Sub-study 035b) gene variants, will be stratified based on their American College of Medical Genetics (ACMG) gene variant classification: pathogenic (P), likely pathogenic (LP) or a variant of uncertain significance suspected to be pathogenic (VUS-SP).

Sub-study 035c: Patients with a homozygous, heterozygous, or compound heterozygous *NCOA1 (SRC1)* gene variant will be enrolled in Sub-study 035c.

Sub-study 035d: Patients with a homozygous, heterozygous, or compound heterozygous *SH2B1* gene variant and/or *SH2B1* deletion (16p11.2 deletion encompassing *SH2B1* gene) will be enrolled in Sub-study 035d. Patients will be stratified based on their gene variant: P/LP (including 16p11.2 deletions that encompass *SH2B1*) or VUS. The number of patients with a VUS variant will initially be capped at 50%. At the discretion of the Sponsor, based on the feasibility of enrolling a sufficient number of patients with a P/LP variant, the number of patients enrolled with a VUS variant may be expanded.

The trial schema is in Figure 1.

Screening

The Screening Period begins with the signing of the informed consent/assent form and will last between 2 and 8 weeks (Days -14 to -56). During the Screening Period, patients will undergo all procedures as outlined in the Schedule of Assessment (SoA, Table 1) to determine if they meet the Inclusion and Exclusion criteria of the trial.

During the Screening Period, patients or caregivers will undergo training on injection of trial drug and other trial procedures. Patients (or their caregivers) will be issued an electronic diary (e-diary) to capture daily compliance with injections (post Enrollment) and hunger score assessments (starting at screening).

Baseline

At the Trial Day 1 visit:

- Patients will undergo all procedures as outlined in the SoA (Table 1), and eligibility for the trial will be reconfirmed.
- Patients who meet all eligibility criteria will be randomized 1:1 to receive daily subcutaneous (SC) administration of either setmelanotide or matching placebo.
- All eligible patients will be stratified based on age group:
  - 6 to <12 years of age
  - 12 to <18 years of age
  - 18 to ≤65 years of age
- Patients with *POMC* or *PCSK1* (Sub-study 035a), or *LEPR* (Sub-study 035b) gene variants will also be stratified based on ACMG classification (P/LP or VUS-SP), in addition to the age classification.
- Patients with *NCOA1 (SRC1)* (Sub-study 035c) gene variant will be only stratified based on age.
- Patients with *SH2B1* (Sub-study 035d) gene variants will also be stratified based on ACMG classification (P/LP or VUS, ratio 1:1), in addition to the age classification. P/LP are defined as chromosomal 16p11.2 deletion encompassing the *SH2B1* gene and all *SH2B1* P/LP gene variants. The number of patients with a VUS variant will initially be capped at 50%. At the discretion of the Sponsor, based on the feasibility of enrolling a sufficient number of patients with a P/LP variant, the number of patients enrolled with a VUS variant may be expanded.
- The trial center must confirm that patients completed the e-diary at least 4 of the 7 days prior to the baseline visit. If the e-diary is not appropriately completed, patients may not enter the trial. The baseline visit may be re-scheduled if the remaining visit window allows.
- Patients will have body weight and height assessed; this will be recorded as the patient's baseline weight and height and the basis for baseline BMI-related measures. Patients will be

issued additional required equipment to capture vital sign measurements during virtual telehealth visits.

- Patients or caregivers will inject SC the first dose of trial drug under the supervision of the trial staff.

Treatment Period ([redacted])

Following randomization, patients will self-inject (or the caregiver will inject the patient) SC trial drug daily for approximately [redacted].

During the trial, patients will attend either an in-person or virtual telehealth visits, as described in the SoA (Table 1). Any visit 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.

At every visit, patients will receive individualized counseling in healthy nutrition and physical activity, based on the guidelines of the American College of Cardiology, American Heart Association, and The Obesity Society (ACC, AHA, TOS Guidelines 2013). Counseling will be performed by qualified personnel. Patients will be encouraged to perform 150 minutes of moderate exercise per week.

End of Treatment (EOT)

The EOT visit will occur as an in-person clinic visit at [redacted], which is the final day of treatment with setmelanotide or placebo.

Patients who discontinue treatment prematurely are to attend the Early Termination visit within 14 days (+7 days) after the last dose of trial drug and complete the EOT assessments (SoA).

Post-treatment Follow-up

Patients meeting the eligibility criteria may be able to participate in an open-label Long-Term Extension (LTE) trial with setmelanotide treatment. If the LTE is not yet available at the time of the EOT visit, then an eligible patient may receive open-label setmelanotide and attend Bridging visits on an every [redacted] basis until either the LTE trial is available or the trial ends. Eligible patients will follow the dose escalation scheme described in Section 6.3 at the beginning of the treatment with open-label setmelanotide. Additional visits may be scheduled at the discretion of the Investigator or the Sponsor.

- Patients who complete treatment and do not enroll into the LTE trial will have an End of Study (EOS) visit conducted via telephone at [redacted]. 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 [redacted].
- Patients who have withdrawn or discontinued trial treatment after at least [redacted] of treatment in the current trial, regardless of randomized treatment assignment in this current trial may be eligible to enroll in the LTE trial (or Bridging Visits if LTE is not available) at [redacted] (Week [redacted]) from the date of their randomization in the current trial. Patients who transfer to the LTE (or Bridging visits) at [redacted] from the date of randomization are not required to complete a separate EOS visit.
- Patients who have withdrawn or discontinued trial treatment after at least [redacted] of treatment in the current trial but who do not wish to participate in the LTE will have an EOS visit at [redacted]
- Patients who withdraw or discontinue treatment prior to completing at least [redacted] of treatment in the current trial are not eligible to participate in the LTE trial. Patients who

discontinue prior to [redacted] will have an in-person EOS visit at [redacted]. For these patients, a virtual EOS visit is permissible if they cannot attend in-person.

[redacted]

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. Patients must have a pre-identified:
   - Heterozygous gene variant in the *POMC* gene or *PCSK1* gene (Sub-study 035a),
   - Heterozygous gene variant in the *LEPR* gene (Sub-study 035b),
   - Homozygous, heterozygous, or compound heterozygous variant in the *NCOA1 (SRC1)* gene (Sub-study 035c),
   - Homozygous, heterozygous, or compound heterozygous variant in the *SH2B1* gene, or chromosomal 16p11.2 deletion encompassing the *SH2B1* gene (Sub-study 035d),

   For *POMC*, *PCSK1*, *LEPR*, *NCOA1 (SRC1)*, and *SH2B1* gene variants, to be considered for inclusion, the variant must either:
   - Be categorized by a Clinical Laboratory Improvement Amendments (CLIA)/College of American Pathologists (CAP)/International Organisation for Standardization (ISO) 15189-certified laboratory using ACMG criteria as
     a) Pathogenic (P); or
     b) Likely pathogenic (LP); or
     c) Variant of uncertain significance (VUS); or
     d) For *POMC*, *PCSK1*, and *LEPR,* in addition to P/LP, only the sub-category of VUS variants that are suspected to be pathogenic (VUS-SP) will be eligible for inclusion.

   If a patient has 2 or more variants eligible for the trial, she/he will be assigned to a sub-study according to the following 2 rules:

   1) To the highest ACMG pathogenicity category according to the following hierarchy: P > LP > VUS-SP > VUS (see Appendix 1 for further examples).
      - For example, if a patient carries both a *POMC* Pathogenic (P) variant and a *LEPR* VUS-SP variant, the patient will be assigned as a *POMC* Pathogenic (P) patient (Sub-study 035a).
   2) If the 2 variants have the same ACMG classification, the patient will be assigned to the sub-study with lower overall frequency of gene variants according to the following hierarchy (least frequent to most frequent): *LEPR* > *POMC/PCSK1* > *NCOA1 (SRC1)* > *SH2B1* (see Appendix 2 for further examples).
      - For example, if a patient carries both a *LEPR* Pathogenic (P) variant and a *SH2B1* Pathogenic (P) variant, the patient will be assigned as a *LEPR* Pathogenic (P) patient (Sub-study 035b).

   [redacted]
2. Between 6 and 65 years of age at the time of provision of informed consent/assent.
3. Obesity, with reported onset in childhood, and BMI ≥30 kg/m^2 for patients ≥18 years of age or BMI ≥95th percentile for age and gender for patients 6 to 17 years of age, based on the United States (US) CDC criteria, at screening.

4. Patient and/or parent or guardian is able to communicate well with the Investigator, understand and comply with the requirements of the trial (including 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 into the trial.
5. Patient and/or parent or guardian reports that the patient experienced childhood obesity, defined as the patient and/or parent or guardian reporting that the patient had obesity or was significantly overweight prior to the age of 6 years old.
6. 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 7.2.6:

   - 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) do not require contraception during the trial.

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

   Male participants with female partners of childbearing potential must agree to use a highly effective method of contraception if they become sexually active during the trial or within 90 days following their participation in the trial. Male patients must also not donate sperm during and for 90 days following their participation in the trial.
7. Reported history of lifestyle intervention with diet and exercise.
8. 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. 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.
2. Weight loss >2% in the previous 3 months.

   Patients will <u>not</u> 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. 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.
4. 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, or any suicidal behavior in the last month, or a Patient Health Questionnaire-9 (PHQ-9) score of ≥15 during screening.
5. 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.
6. HbA1c >10% at screening.
7. 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.)
8. 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 to calculate eGFR (see Section 7.2.5).
9. History or close family history (parents or siblings) of melanoma, or patient history of oculocutaneous albinism.
10. 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. 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.
11. Patient is, in the opinion of the Investigator, not suitable to participate in the trial.
12. 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.
13. Previously enrolled in a clinical trial involving setmelanotide or any previous exposure to setmelanotide.
14. Hypersensitivity to the active substance or to any of the excipients of the investigational medicinal products (active and placebo).
15. Females who are pregnant or breastfeeding, or planning or desiring to become pregnant during the duration of the trial.
16. Patients with the following gene variants: [redacted] (and/or clinical diagnosis of Bardet-Biedl syndrome [BBS]), [redacted], or any [redacted]

17. Legally protected persons per local regulations (e.g., those that fall under the L1121-6 article of the Public Health code in France) or other applicable local laws.

Investigational product, dosage and mode of administration:

Investigational product: Setmelanotide, [redacted]/mL in a sterile solution for injection.

Dosage for every sub-study:

- Patients 6 to <12 years old will start at a dose of [redacted]/day for [redacted] escalate to [redacted]/day for [redacted] and then to [redacted]/day for the remaining [redacted] of treatment. *Note:* if the starting dose of setmelanotide is not tolerated, then reduce the dose to [redacted]; the minimum acceptable dose in patients 6 to <12 years of age is [redacted], unless discussed with Sponsor for safety considerations.
- Patient's ≥12 years old will start at a dose of [redacted]/day for [redacted] and then escalate to [redacted]/day for the remaining [redacted] of treatment. *Note:* if the starting dose of setmelanotide is not tolerated, then reduce the dose to [redacted]; the minimum acceptable dose in patients ≥12 years of age is [redacted], unless discussed with Sponsor for safety considerations.

Mode of administration: Subcutaneous (SC) injection.

Duration of treatment:

Total treatment with either setmelanotide or matching placebo will be approximately [redacted]. Total participation in the trial will last up to [redacted], 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.

Statistical methods (Identical for all sub-studies):

The primary objective is to independently evaluate for each sub-study the mean change in body weight (assessed as percent change in BMI) in response to setmelanotide from baseline to [redacted] in patients with [redacted] (Sub-study 035a), [redacted] (Sub-study 035b), [redacted] (Sub-study 035c), or [redacted] (Sub-study 035d) gene variants in the MC4R pathway.

The primary hypothesis of the trial is to test the difference of the mean percent changes in BMI between the setmelanotide arm and placebo arm.

For Sub-studies 035a and 035b, assuming a pooled standard deviation (SD) of 10% and a 20% dropout rate, the sub-study with approximately [redacted] patients (approximately [redacted] patients per arm) will provide approximately 90% statistical power to rule out at least -8% mean difference of the percent BMI between the setmelanotide arm and placebo arm at [redacted], at one-sided 0.025 significance level.

For Sub-studies 035c and 035d, assuming a pooled SD of 10% and a 20% dropout rate, the sub-study with approximately [redacted] patients (approximately [redacted] patients per arm) will provide approximately 90% statistical power to rule out at least -7% mean difference of the percent BMI between the setmelanotide arm and placebo arm at [redacted], at a one-sided 0.025 significance level.

The overall randomization ratio of setmelanotide-treated patients to placebo-treated patients is 1:1, stratified by:

- ACMG classification (P/LP or VUS-SP) and age group (6 to <12, 12 to <18, and 18 to ≤65 years of age) for [redacted] (Sub-study 035a), [redacted] (Sub-study 035b)
- Age group (6 to <12, 12 to <18, and 18 to ≤65 years of age) only for [redacted] (Sub-study 035c).

- ACMG classification (P/LP or VUS) and age group (6 to <12, 12 to <18, and 18 to ≤65 years of age) for [redacted] (Sub-study 035d),

The analysis of the primary efficacy endpoint will include all available data, including all post-discontinuation data. The treatment effect based on the intention-to-treat (ITT) estimand will be estimated, which considers the actual measurements of patients regardless of adherence to treatment. An analysis of covariance (ANCOVA) model will be used to determine whether there exist any significant mean differences in percent BMI reduction between the setmelanotide arm and placebo arm at [redacted], adjusted by stratification factor(s) and baseline as covariate(s). In the event of missing data, the primary analysis will model the missing measurements of non-retrieved dropouts based on known measurements from retrieved dropouts in the same treatment group. In case there are not enough retrieved dropouts to provide a reliable multiple imputation model, a multiple imputation method based on observed data from the placebo group will be applied. In this approach, intermittent data collected while on active treatment will not be used for imputation. The p-value and 2-sided 95% confidence interval (CI) for the difference of least square (LS)-means of the percent BMI loss at [redacted] will be provided from the ANCOVA model. Separately, subgroup analyses of the primary endpoint in the pediatric sub-population (<18 years of age) and in the adult sub-population (≥18 years of age) will be conducted.

For each sub-study, there are multiple key secondary efficacy endpoints planned. The key secondary endpoints will be analyzed according to the pre-specified hierarchical order. If the primary efficacy endpoint is statistically significant, a step-down procedure of a hierarchical order of testing for the key secondary efficacy endpoints will be applied to control Type 1 error, if needed for any purpose.

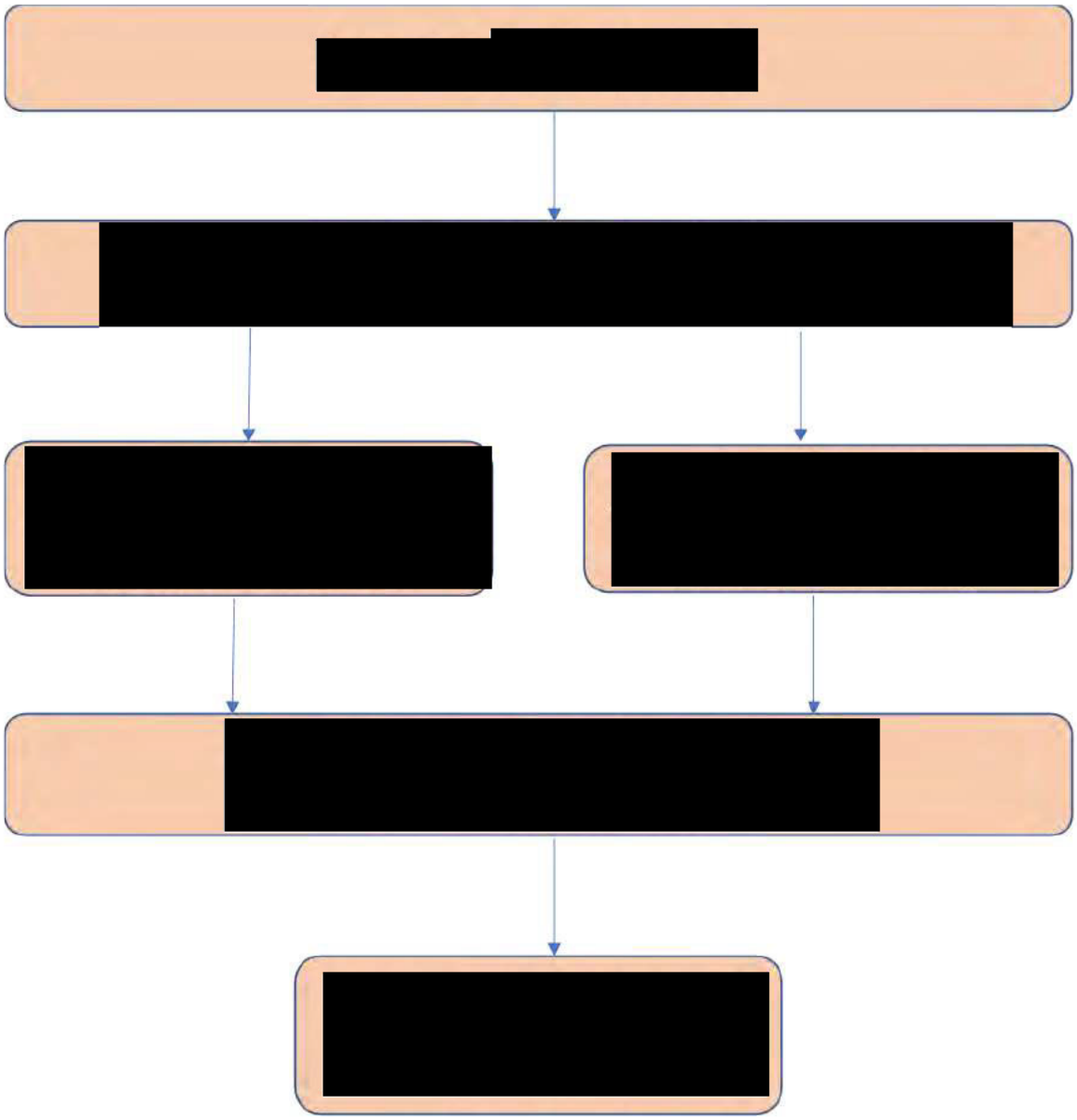
The efficacy analyses will be performed based on an ITT set, which includes all randomized patients, regardless of treatment adherence and availability of baseline data.

Adverse events (AEs)/serious 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. The safety analyses will be performed based on a Safety Analysis Set, which is defined as all patients who received at least 1 dose of trial treatment (placebo or setmelanotide).

1.2. [redacted]

Figure 1: [redacted]



Note: [redacted].

1.3. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2. INTRODUCTION

2.1. [redacted]

[redacted]

2.2. [redacted]

[redacted]

2.2.1. [redacted]

[redacted]

melanocyte stimulating hormone (α

lived α

[redacted]

[redacted]

2.2.2. [redacted]

[redacted]

2.3. [redacted]

[redacted]

[redacted]

3. OBJECTIVES AND ENDPOINTS

The objectives and endpoints are identical for all sub-studies in patients with *POMC* and/or *PCSK1* (Sub-study 035a), *LEPR* (Sub-study 035b), *NCOA1 (SRC1)* (Sub-study 035c), and *SH2B1* (Sub-study 035d) gene variants in the MC4R pathway. The objectives and endpoints are described in Table 2.

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary (Identical for all Sub-studies)	
• To evaluate the efficacy of setmelanotide on changes in body weight	• The difference in mean change in body weight from baseline at [redacted] in patients treated with setmelanotide compared to placebo, assessed as percent change from baseline BMI
Secondary (Identical for all Sub-studies)	
Key Secondary: • To evaluate the efficacy of setmelanotide based on the portion of patients with a clinically meaningful decrease in body weight defined as ≥5% decrease from baseline	**Key Secondary:** • The proportion of patients who achieve at least 5% reduction in baseline BMI at [redacted], in patients treated with setmelanotide compared to placebo
• To evaluate the efficacy of setmelanotide on changes in body weight in adult patients with obesity	• The difference in mean change in body weight from baseline at [redacted] in adult patients (age ≥18 years at baseline) treated with setmelanotide compared to placebo, assessed as percent change in baseline body weight
• To evaluate changes in hunger score in response to setmelanotide from baseline to [redacted] of treatment	• The difference in mean percent change in the weekly average most hunger score at [redacted] in patients treated with setmelanotide compared to placebo, utilizing the Hunger Questions for Patients ≥12 years of Age©
• To evaluate the efficacy of setmelanotide on the portion of patients with at least 10% decrease in body weight	• The proportion of patients who achieve at least 10% reduction in baseline BMI at [redacted], in patients treated with setmelanotide compared to placebo

Table 2: Objectives and Endpoints

Objectives	Endpoints
Other Secondary	**Other Secondary**
• To evaluate the efficacy of setmelanotide on changes in BMI in pediatric patients with obesity	• The difference in mean change in BMI from baseline at [redacted] in pediatric patients (age <18 years at baseline) treated with setmelanotide compared to placebo assessed as change in baseline BMI Z-score • The difference in change from baseline at [redacted] in % of the 95th BMI percentile, as defined by the Centers for Disease Control and Prevention (CDC), in patients <18 years at baseline treated with setmelanotide compared to placebo
• To evaluate change in waist circumference in response to setmelanotide from baseline to [redacted] of treatment	• The difference from baseline at [redacted] in mean change in waist circumference in patients treated with setmelanotide compared to placebo
• To evaluate the safety and tolerability of setmelanotide	• The overall safety and tolerability of setmelanotide in patients with gene variants in the MC4R pathway
• To evaluate quality of life parameters following treatment with setmelanotide	• The difference in mean change from baseline at [redacted] in physical functioning score and total score for Impact of Weight on Quality of Life in adults (IWQOL-Lite) and in children (IWQOL-Kids-Parent Proxy) in patients treated with setmelanotide compared to placebo
• To evaluate the ability of an initial response to setmelanotide (defining a responder population) to predict long-term benefit	• The difference in mean body weight loss, and % body weight loss at [redacted] in setmelanotide responders (defined as patients with ≥5% body weight loss if ≥18 years of age, or a decrease in BMI by ≥3% if <18 years of age, after [redacted] of therapy at [redacted] or at the maximally tolerated dose) as compared to the placebo group

Table 2: [redacted]

[redacted]	[redacted]
[redacted]	
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]

Abbreviations: AE = adverse event; BMI = body mass index; [redacted]; IWQOL = Impact of Weight on Quality of Life; MC4R = melanocortin-4 receptor.

4. TRIAL DESIGN

4.1. [redacted]

[redacted]

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

[redacted]

4.1.1. Screening Period

The Screening Period is identical for the sub-studies and it begins with signing the informed consent/assent form and will last between 2 and 8 weeks (Days -14 to -56). During the Screening Period, patients will undergo all procedures as outlined in the Schedule of Assessment (SoA; Table 1) to determine if they meet the Inclusion and Exclusion criteria of the trial.

During the Screening Period, patients or caregivers will undergo training on injection of trial drug and other trial procedures. Patients (or their caregivers) will be issued an electronic diary (e-diary) to capture daily compliance with injections (post Enrollment) and hunger score assessments (starting at screening).

4.1.2. Baseline

At baseline (Trial Day 1 Visit):

- Patients will undergo all procedures as outlined in the SoA (Table 1), and eligibility for the trial will be reconfirmed.
- Patients who meet all eligibility criteria will be randomized 1:1 to receive daily SC administration of either setmelanotide or matching placebo.
- All eligible patients will be stratified based on age group:
  - 6 to <12 years of age
  - 12 to <18 years of age
  - 18 to ≤65 years of age

- Patients with *POMC* or *PCSK1* (Sub-study 035a), or *LEPR* (Sub-study 035b) gene variants will also be stratified based on American College of Medical Genetics (ACMG) classification (P/LP or VUS-SP,), in addition to the age classification.
- Patients with *NCOA1 (SRC1)* (Sub-study 035c) gene variants will be only stratified based on age.
- Patients with *SH2B1* (Sub-study 035d) gene variants will also be stratified based on ACMG classification (P/LP or VUS, ratio 1:1), in addition to the age classification. P/LP are defined as chromosomal 16p11.2 deletion encompassing the *SH2B1* gene and all *SH2B1* P/LP gene variants. The number of patients with a VUS variant will initially be capped at 50%. At the discretion of the Sponsor, based on the feasibility of enrolling a sufficient number of patients with a P/LP variant, the number of patients enrolled with a VUS variant may be expanded.
- The trial center must confirm that patients completed the e-diary at least 4 of the 7 days prior to the baseline visit. If the e-diary is not appropriately completed, patients may not enter the trial. The baseline visit may be re-scheduled if the remaining visit window allows.
- Patients will have body weight and height assessed; this will be recorded as the patient's baseline weight and height and the basis for baseline BMI-related measures.
- Patients or caregivers will inject SC the first dose of trial drug under the supervision of the trial staff.

4.1.3. Treatment Period

Following randomization, patients will self-inject (or the caregiver will inject the patient) SC trial drug daily for approximately [redacted].

During the trial, patients will attend either in-person or virtual telehealth visits, as described in the SoA (Table 1). Any visit 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.

At every visit, patients will receive individualized counseling in healthy nutrition and physical activity, based on the guidelines of the American College of Cardiology, American Heart Association, and The Obesity Society (ACC, AHA, TOS Guidelines 2013). Counseling will be performed by qualified personnel. Patients will be encouraged to perform 150 minutes of moderate exercise per week.

4.1.4. End of Treatment (EOT)

The End of Treatment (EOT) visit will occur as an in-person clinic visit at [redacted] which is the final day of treatment with setmelanotide or placebo.

Patients who discontinue treatment prematurely are to attend the Early Termination visit within 14 days (+7 days) after the last dose and complete the EOT assessments (SoA).

4.1.5. Post-treatment Follow-up

Patients meeting the eligibility criteria may be able to participate in an open-label Long-Term Extension (LTE) trial with setmelanotide treatment. If the LTE is not yet available at the time of EOT visit, then the eligible patient may receive open-label setmelanotide and attend Bridging visits on an every [redacted] basis until either the LTE trial is available or the trial ends. Eligible patients will follow the dose escalation scheme described in Section 6.3 at the beginning of the treatment with open-label setmelanotide. Additional visits may be scheduled at the discretion of the Investigator or the Sponsor.

- Patients who complete treatment and do not enroll into the LTE trial will have the End of Study (EOS) visit conducted via telephone at [redacted]. 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 [redacted].
- Patients who have withdrawn or discontinued trial treatment after at least [redacted] of treatment in the current trial, regardless of randomized treatment assignment in this current trial, may be eligible to enroll in the LTE trial (or Bridging Visits if LTE is not available) at [redacted] from the date of their randomization in the current trial. Patients who transfer to the LTE (or Bridging visits before LTE availability) at [redacted] from their randomization date are not required to complete a separate EOS visit.
- Eligible patients who have withdrawn or discontinued trial treatment after at least [redacted] of treatment in the current trial but who do not wish to participate in the LTE will have an EOS visit at [redacted]
- Patients who withdraw or discontinue treatment prior to completing at least [redacted] of treatment in the current trial are not eligible to participate in the LTE trial. Patients who discontinue prior to [redacted] will have an in-person EOS visit at [redacted]. For these patients, a virtual EOS visit is permissible if they cannot attend in-person.

4.2. Scientific Rationale for Trial Design

Recent data from the Phase 2 RM-493-014 trial indicate that setmelanotide is effective in promoting clinically meaningful weight loss and reducing hunger in individuals who carry 1 gene variant (heterozygous) in the *POMC/PCSK1, LEPR*, *SH2B1*, or *NCOA1 (SRC1)* genes, revealing an opportunity to investigate setmelanotide as a treatment for patients beyond the biallelic population currently approved per the setmelanotide (IMCIVREE) prescribing information (USPI 2022, EU SmPC 2021, MHRA SmPC 2021).

Given the similarities across the multiple sub-studies with respect to experimental design, eligibility, and statistical analysis, a single protocol was chosen in lieu of separate protocols.

Each sub-study will have its own placebo arm stratified by age and by ACMG classification (ACMG classification only for Sub-study 035a, Sub-study 035b, and Sub-study 035d) to compare patients with variants in the same gene who are randomized to setmelanotide and minimize interindividual variability due to different gene variants.

Within each gene, ACMG variant classification guidelines are the accepted approach to integrate diverse lines of evidence for pathogenicity according to scoring rules with defined thresholds corresponding to 5 principal categories, Pathogenic (P), Likely Pathogenic (LP), VUS, Likely Benign (LB) and Benign (B) (Richards et al, 2015). Pathogenic variants are recognized as causative of disease. Likely pathogenic variants are considered to have a greater than 90% certainty of being disease causing. "Variants of Uncertain Significance" (VUS) represents the largest and most heterogenous ACMG category and includes a hierarchy of variants that span from those that are suspected to be pathogenic to those that are suspected to be benign. Although not typically reported, VUS variants can be further sub-categorized by specification according to their likelihood of pathogenicity. These laboratory-classified variants can be used to support clinical decision making in combination with disease evidence.

PreventionGenetics, the Sponsor's genetic testing partner, subclassifies VUS into the following 3 subcategories: Suspected Pathogenic (VUS-SP), Uncertain, and Suspected Benign based on the combined weight of evidence for each variant. VUS-SP currently accounts for less than 5% of all VUS variants. They are predicted to be protein damaging but are currently not directly implicated in disease.

Based on the mechanism of action of setmelanotide as an MC4R agonist, patients with variants more likely to be pathogenic are potentially also more likely to respond to setmelanotide. This trial will evaluate the potential for setmelanotide to benefit patients who carry POMC, PCSK1, or VUS LEPR Suspected Pathogenic (VUS-SP) variants in addition to patients who carry P or LP variants of these genes. The final patient classification of variants is referenced in Appendix 1 and Appendix 2.

4.3. [redacted]

[redacted]

- [redacted]

- [redacted]

[redacted]

- [redacted]

- [redacted]

4.4. End of Study Definition

The End of Study is defined as the date of the last scheduled visit (or contact) of the last patient.

The last visit or contact for each patient may be an unscheduled visit, the ET visit, the EOT visit, a scheduled Bridging Visit, or the EOS visit.

4.5. Trial, Site, or Cohort Termination or Suspension

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

4.6. Should the trial be closed prematurely, all trial materials must be returned to the Sponsor or designee. Trial Conduct During the COVID-19 Pandemic

The 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 patients become potentially exposed to or infected with COVID-19. To assure the safety of trial patients, 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 8.

5. TRIAL POPULATION

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

5.1. Patient Inclusion Criteria

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

1. Patients must have a pre-identified:
   - Heterozygous gene variant in the *POMC* gene or *PCSK1* gene (Sub-study 035a),
   - Heterozygous gene variant in the *LEPR* gene (Sub-study 035b),
   - Homozygous, heterozygous, or compound heterozygous variant in the *NCOA1 (SRC1)* gene (Sub-study 035c),
   - Homozygous, heterozygous, or compound heterozygous variant in the *SH2B1* gene, or chromosomal 16p11.2 deletion encompassing the *SH2B1* gene (Sub-study 035d),

   For *POMC*, *PCSK1*, *LEPR*, *NCOA1 (SRC1)*, and *SH2B1* gene variants, to be considered for inclusion, the variant must either:

   - Be categorized by a Clinical Laboratory Improvement Amendments (CLIA)/College of American Pathologists (CAP)/International Organisation for Standardization (ISO) 15189 – certified laboratory using ACMG criteria as:
     a) Pathogenic (P); or
     b) Likely pathogenic (LP); or
     c) VUS; or
     d) For *POMC*, *PCSK1*, and *LEPR,* in addition to P/LP, only the sub-category of VUS variants that are suspected to be pathogenic (VUS-SP) will be eligible for inclusion.

   If a patient has 2 or more variants eligible for the trial, she/he will be assigned to a sub-study according to the following 2 rules:

   1) To the highest ACMG pathogenicity category according to the following hierarchy: P > LP > VUS-SP > VUS (see Appendix 1 for further examples).
      – For example, if a patient carries both a *POMC* Pathogenic (P) variant and a *LEPR* VUS-SP variant, the patient will be assigned as a *POMC* Pathogenic (P) patient (Sub-study 035a).
   2) If the 2 variants have the same ACMG classification, the patient will be assigned to the sub-study with lower overall frequency of gene variants according to the

following hierarchy (least frequent to most frequent): *LEPR* > *POMC/PCSK1* > *NCOA1 (SRC1)* > *SH2B1* (see Appendix 2 for further examples).

- For example, if a patient carries both a *LEPR* Pathogenic (P) variant and a *SH2B1* Pathogenic (P) variant, the patient will be assigned as a *LEPR* Pathogenic (P) patient (Sub-study 035b).

[redacted]

2. Between 6 and 65 years of age at the time of provision of informed consent/assent.
3. Obesity, with reported onset in childhood, and body mass index (BMI) ≥30 kg/m^2 for patients ≥18 years of age or BMI ≥95th percentile for age and gender for patients 6 up to 17 years of age, based on the US Centers for Disease Control and Prevention (CDC) criteria at screening.
4. Patient and/or parent or guardian is able to communicate well with the Investigator, understand and comply with the requirements of the trial (including 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 into the trial.
3. Patient and/or parent or guardian reports that the patient experienced childhood obesity, defined as the patient and/or parent or guardian reporting that the patient had obesity or was significantly overweight prior to the age of 6 years old.
4. 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 7.2.6:

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

   Female participants of non-childbearing potential, defined as: permanently sterile (status post hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or post-

menopausal for at least 12 months (and confirmed with a screening follicle-stimulating hormone level in the post-menopausal lab range) do not require contraception during the trial.

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

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

5. Reported history of lifestyle intervention of diet and exercise.
6. Symptoms or behaviors of hyperphagia persistent during the patient's life, including manifestations in childhood, as determined by the Investigator at screening.

5.2. Patient Exclusion Criteria

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

1. 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.
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. 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.
4. 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, or any suicidal behavior in the last month, or a Patient Health Questionnaire-9 (PHQ-9) score of ≥15 during screening.
5. 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.

6. HbA1c >10% at screening.
7. 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.)
8. 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 to calculate eGFR (see Section 7.2.5).
9. History or close family history (parents or siblings) of melanoma, or patient history of oculocutaneous albinism.
10. 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. 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.
11. Patient is, in the opinion of the Investigator, not suitable to participate in the trial.
12. 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.
13. Previously enrolled in a clinical trial involving setmelanotide or any previous exposure to setmelanotide.
14. Hypersensitivity to the active substance or to any of the excipients of the investigational medicinal products (active and placebo).
15. Females who are pregnant or breastfeeding, or planning or desiring to become pregnant during the duration of the trial.
16. Patients with the following gene variants: [redacted] (and/or clinical diagnosis of [redacted], or any [redacted] [redacted].
17. Legally protected persons per local regulations (e.g., those that fall under the L1121-6 article of the Public Health code in France) or other applicable local laws.

5.3. Screen Failures

A patient who does not meet one or more inclusion criteria or who does meet one or more exclusion criteria will be considered a screen failure. It is expected that patients who are not eligible to continue in the trial will return the e-diary.

5.4. Lifestyle Considerations

5.4.1. Physical Activity

During the trial, patients will receive physical activity counseling and training by qualified site personnel and will be strongly encouraged to perform aerobic physical activity for a duration of at least 150 minutes per week, maintaining an average target heart rate of 70% of their maximum heart rate. Aerobic physical activity includes repetitive motions of large muscle groups, such as brisk walking, swimming, mowing the lawn, running, dancing, etc. Maximum heart rate is calculated as 220 bpm minus patient's age in years.

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

Each patient will be provided with an electronic tracker to monitor heart rate 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.

5.4.2. Dietary Restrictions

During the trial, patients will receive dietary counseling and training by qualified site personnel and will be strongly encouraged to follow a diet with a reduction of 500-750 kilocalories (Kcal) per day (Apovian 2015) as advised by the ACC, AHA, TOS Guidelines 2013. At each visit (virtual and in-person) patients will be counselled on diet, and compliance will be assessed by site personnel.

6. TRIAL INTERVENTION AND CONCOMITANT THERAPY

6.1. [redacted]

[redacted]

6.2.

6.2.1.

6.2.2.

[redacted]

6.3. [redacted]

[redacted]

6.4. Treatment Compliance

Accountability for the trial drug at the trial site is the responsibility of the Investigator. The Investigator will ensure that the trial drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the delivery date to the site, inventory at the site, use by each patient, return of all used trial drug 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 to dosing will be monitored throughout the trial by having the patient/caregiver complete a daily dosing log, and by accounting for trial drug dispensed and returned (used and partially used).

6.5. Preparation/Handling/Storage/Accountability

Only patients enrolled in the trial may receive trial drug and only authorized site staff may supply or administer trial drug. All trial drug 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 drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

All unopened trial drug 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 drug 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 drug must be stored in the patient's refrigerator. Opened trial drug may be stored at room temperature for up to 30 days.

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

6.6. Concomitant Medications

Medication that is considered necessary for the patient's safety and wellbeing may be given during the trial at 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 a change in the patient's condition.

As GLP-1 treatments may cause nausea and vomiting, they should not be started simultaneously with trial drug. However, trial drug can be started in patients who are on stable doses of GLP-1 treatments for at least 3 months prior to randomization, or GLP-1 treatments at doses indicated for the management of diabetes can be added if needed for patients who have been on trial drug for more than 12 weeks.

At present, there is little evidence that setmelanotide will result in drug interactions, but data are limited.

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

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

6.6.1. Concomitant Obesity Medications

Medications that are approved to treat obesity (e.g., orlistat, phentermine-topiramate, naltrexone-bupropion, GLP-1, etc.) are permitted if the patient has had <2% weight loss in the previous

3 months, the dose has been stable for at least 3 months prior to randomization, and the patient intends to continue the same dose throughout the trial.

6.7. Treatment Discontinuation, Withdrawal from the Trial, and Participation in the Long-term Extension Trial

Given these rare patient populations, 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 patients and caregivers 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.

Eligibility for participation in the LTE and post-treatment follow-up visits and assessments are provided in Section 4.1.5 and in the SoA Table 1.

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. Patients should be reminded that at their initial consent they agreed to third party follow-up.

If a patient withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the Investigator must document the request and the date of destruction the 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 discontinue trial treatment or withdraw patients from the trial for reasons such as:

- AEs, which in opinion of the Investigator justifies trial drug or treatment discontinuation, or trial withdrawal. For specific predefined events, additional monitoring and guidance for the Investigator is provided in Appendix 7.
- Non-adherence to trial drug regimen or protocol requirements.
- Non-compliance with instructions or failure to return for follow-up.

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), even if they are no longer receiving trial drug.

6.8. 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 documented contact attempts to follow-up should be made, including at least 1 in relation to the final visit on Day 364. The patient should only be permanently recorded as lost to follow-up if they did not respond to any contact attempts by Day 364. These contact attempts should be documented in the patient's medical records.

- Patients who are lost to follow-up are not eligible to participate in the LTE trial.

7. [redacted]

[redacted]

7.1. Efficacy Assessments

Efficacy will be assessed as described in the following subsections.

7.1.1. Weight

Weight (kg) will be recorded at the time points designated in the SoA (Table 1). 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 10^{th} of a kg if reported with a digital scale, or half kg with a mechanical scale.

Whenever possible, the same scale should be used throughout the trial at trial visits, including the screening visit, and should be calibrated on a regular basis per manufacturer's specifications.

7.1.2. Waist Circumference

Waist circumference (cm) will be measured according to the National Heart, Lung, and Blood Institute (NHLBI) criteria [NHLBI 2000] during the trial at the time points designated in the SoA (Table 1). All measurements will be done in triplicate at each time point and recorded to the nearest half centimeter. Whenever possible, the same trial staff member should perform the measurement for a given patient to minimize variability. Waist circumference should be measured when patients are fasted for at least 8 hours and at approximately the same time at each

visit. Patients should be in standing position, in light clothing and have attempted to empty their bladder.

7.1.3. Height

[redacted] years of age, height should be measured at screening only. For patients aged <21 years, height is to be measured at the time points designated in the SoA (Table 1).

Height (cm) will be measured, without shoes, socks, or hats, using a wall-mounted stadiometer. The stadiometer should be calibrated by site personnel on a daily basis prior to height assessment. All measurements will be done in triplicate at each time point and recorded to the nearest half centimeter.

[redacted]

[redacted]

Patients ≥12 [redacted]

[redacted]

[redacted]

[

[redacted]

[redacted]

[redacted]

examination. At other time points, as designated in the SoA (Table 1), 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 examination 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 electronic case report form (eCRF).

7.2.3. Comprehensive Skin Examination

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

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 significant 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.

7.2.4. Electrocardiogram

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

7.2.5. Clinical Safety and Metabolic Laboratory Assessments

Blood and urine samples for clinical laboratory tests are to be collected at the time points designated in the SoA (Table 1). 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 (including [redacted] and fasting lipid panel), coagulation studies, as well as urine analysis, are identified in the SoA (Table 1).

eGFR will be calculated in patients ≥18 years of age using the MDRD Equation: eGFR = 175 x (creatinine in mg/dL)-1.154 x (age in years)-0.203 x (0.742 if female) x (1.210 if African American). eGFR will be calculated in patients <18 years of age using the Bedside Schwartz Equation: eGFR (mL/min/1.73 m^2) = (0.41 x height in centimeters)/creatinine in mg/dL).

In addition, blood samples for measurement of anti-drug antibodies (ADA) will be collected according to the SOA (Table 1). A positive ADA will be followed every 3 months after the ADA sample analysis until resolution of the ADA.

7.2.6. Pregnancy and Contraception

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

Women of childbearing potential (WOCBP), 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. With the exception of virtual visits, at all other time points designated in the SoA (Table 1), serum pregnancy testing will also be performed; however, setmelanotide dosing may continue with results pending. At sites where pregnancy tests are required for virtual visits, WOCBP will be given urine pregnancy kits for use at each of the virtual visits at V1. For WOCBP potential, a highly effective form of contraception (as defined in the Inclusion Criteria, Section 5.1) 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, implantable, or injectable)
- 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.

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 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 first 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 for SAEs outlined in Appendix 7.

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.

7.2.7. Injection Site Examination

Injection sites will be carefully inspected, evaluated and scored at the time points outlined in the SoA Table 1 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. [redacted].

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

7.2.8. Suicidal Ideation and Behavior Risk Monitoring

Suicidal ideation and risk will be assessed using the C-SSRS scale (Section 7.2.8.1) and depression will be assessed using the PHQ-9 (Section 7.2.8.2) or the Children's Depressive Inventory-2 (CDI-2) (Section 7.2.8.3).

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

- Any suicidal behavior
- Any suicidal ideation of type 4 or 5 on the C-SSRS
- A PHQ-9 score ≥10
- 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 disorder can be adequately treated with psycho- and/or pharmacotherapy, then the patient, at the discretion of the MHP, should be continued in the trial.

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

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

Any deviation from the intended use of an instrument should be documented by the Investigator, along with the reason for the deviation. If the C-SSRS and PHQ-9 are not administered, the Investigator should document that the issue of suicidality and depression were assessed clinically (e.g., discussion with caregivers).

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

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 an MPH) that can be completed in patients ≥6 years of age. There are 2 versions of the C-SSRS that will be administered according to the SoA (Table 1):

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

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

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

7.2.8.2. 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. The PHQ-9 will be used for patients ≥12 years of age. After the patient has completed the PHQ-9 questionnaire, it is scored by the trial staff. Any patient with a PHQ-9 score ≥10 will be referred to an MHP. The PHQ-9 will be administered according to the SoA (Table 1).

7.2.8.3. 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.

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

7.2.9. Overdose

One accidental overdose has been previously reported in the setmelanotide clinical development program in a pediatric patient receiving a 5-mg dose instead of a 0.5-mg dose. The patient had mild symptoms (i.e., nausea vomiting and headache) 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 Medical Monitor based on the clinical evaluation of the patient.

7.3. Adverse Events 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 6.7).

Details on recording AEs and SAEs, including definitions, are provided in Appendix 7.

7.3.1. 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). Adverse events reported after dosing on Day 1 will be considered treatment-emergent AEs (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 and not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee without undue delay but no later than within 24 hours, as indicated in Appendix 7. 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 in patients who have completed trial participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the trial, and he/she considers the event to be reasonably related to the trial treatment or trial participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 7.

7.3.2. 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.

7.3.3. 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 7.

7.3.4. Stopping Criteria for Safety Considerations

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 Monitoring Plan provides for detailed instructions.

7.3.5. 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, IRB, IEC, and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and the 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.4. Informed Consent/Assent

A complete description of the trial is to be presented to each potential patient or parent/legal guardian 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.

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 in distress in patients younger than 18 years of age are included in the protocol (Appendix 4).

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 (Table 1).

7.5. Inclusion/Exclusion Review

Inclusion and exclusion criteria (see Section 5) are to be reviewed per the SoA (Table 1) to ensure the patient is eligible for the trial.

7.6. 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 from patient report and medical records where available (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 drug, 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.

7.7. Fitzpatrick Scale

Each patient is to be categorized for skin type according to the Fitzpatrick scale. The Fitzpatrick Scale is presented in Appendix 5.

7.8. Pharmacokinetic Assessments

Blood samples for determination of setmelanotide levels in plasma will be collected as indicated in the SoA in Table 1. For all blood samples for pharmacokinetic (PK) analysis, the actual (clock) time each PK blood sample is collected will be recorded in the source documents and 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, percent coefficient of variation (% CV) based on dose and visit.

7.9. Biomarkers

Blood samples will be collected at baseline, EOT visit, and at the Early Termination visit for metabolic, inflammation, metabolomic and/or proteomic biomarker analysis. These samples might not be analyzed. All samples are sent to a central laboratory. Additional details are described in the laboratory manual.

7.10. Nutrition and Physical Activity Counseling and Follow-Up

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

8. DATA SAFETY 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 (i.e., 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. Details of the DSMB's composition and operations will be in the DSMB charter.

9. STATISTICAL CONSIDERATIONS

For each sub-study, details of the statistical methodology for summaries and statistical analyses will be provided in separate statistical analysis plans (SAPs), which will be maintained by the Sponsor. The SAPs 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 in the clinical trial report for the sub-study, along with an explanation as to why they occurred.

9.1. Statistical Hypotheses

9.1.1. Multiplicity Adjustment

No multiplicity adjustments for testing the primary efficacy endpoint are required because each sub-study has only 1 primary efficacy endpoint, and each sub-study will be analyzed separately. This approach controls the overall alpha at 0.025, one-sided for each sub-study.

For each sub-study, there are multiple key secondary efficacy endpoints planned in the trial. The key secondary endpoints are presented according to the Sponsor-specified hierarchical order in Table 2 of Section 3. If the primary efficacy endpoint is statistically significant, a step-down procedure of a hierarchical order of testing for the key secondary efficacy endpoints will be applied to control Type-1 error, if needed for any purpose.

9.2. Analysis Set

For each sub-study, there are 3 analysis populations defined in the protocol:

- Intention-to-treat (ITT) Set: All randomized patients regardless of treatment adherence and availability of baseline data.
- Per-Protocol (PP) Set: All patients in ITT set without any major protocol deviations that will result in exclusion of the patients from the primary efficacy analyses. This analysis will only include patients whose gene variants and respective sub-study cohort assignment are confirmed based on the PreventionGenetics (PG) Uncovering Rare Obesity (URO) 3.0 genetic panel.
- Safety Analysis Set: All patients who received at least 1 dose of trial drug (placebo or setmelanotide).

9.3. Statistical Analyses

For each sub-study, a separate SAP will be developed, which will include a more technical and detailed description of the statistical analyses described in this section, as well as a description of the approaches to be taken for summarizing other trial information, such as patient disposition, demographics, baseline characteristics, treatment exposure, and prior and concomitant medications.

For each sub-study, the SAP will be finalized prior to the database lock to preserve the integrity of the statistical analysis and trial conclusions.

9.3.1. [redacted]

[redacted]

9.3.2. [redacted]

[redacted]

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

[redacted]

9.3.3. [redacted]

[redacted]

9.3.3.1. Analysis of Dichotomous Endpoints with Proportion of Patients

For the key secondary efficacy endpoints at [redacted], the Cochran-Mantel-Haenszel test (raw mean score difference) will be conducted at 1-sided 0.025 level on comparison of setmelanotide arm versus placebo arm controlling for stratification variables. The 2-sided 95% CI for the proportion of patients at [redacted] will be provided using the exact Clopper-Pearson method for each group, and the strata-adjusted proportion difference between the groups will be also provided.

As supportive analyses, by-visit analysis will be performed. The proportion of patients at each visit including the EOT visit will be provided with 2-sided 95% CI using the exact Clopper-Pearson method for each group.

For the assessment of hunger in patients ≥12 years old, in addition to evaluation of the continuous endpoint based on change in peak (most) hunger, a responder analysis comparing treatment groups will also be conducted.

[redacted]

9.4. Interim Analysis

There are no planned interim analyses for any of the sub-studies.

9.5.

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10. LIST OF REFERENCES

Apovian CM, Aronne LJ. The 2013 American Heart Association/American College of Cardiology/The Obesity Society guideline for the management of overweight and obesity in adults: what is new about diet, drugs, and surgery for obesity? Circulation. 2015;132(16):1586-91.

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 Esthet. 1975;2:33034.

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.

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.

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 06 September 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 06 September 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 06 September 2022.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-24.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

APPENDIX 1. FINAL CATEGORIZATION IF PATIENT HAS TWO OR MORE ELIGIBLE VARIANTS

The final sub-study assignment will follow this hierarchy:

Pathogenic (P) > Likely Pathogenic (LP) > Variant of Uncertain Significance sub-category Suspected Pathogenic (VUS-SP) > Variant of Uncertain Significance (VUS).

See examples below for sub-study assignment of patients who may have 2 eligible variants.

Patient Variant 1	**Patient Variant 2**	**Patient Final Categorization (Sub-study Assignment)**
*PCSK1*Pathogenic (P)	*LEPR* VUS-SP	*POMC/PCSK1* Sub-study 035a stratified as P/LP
SH2B1 Likely Pathogenic (LP)	*NCOA1 (SRC1)* VUS	*SH2B1* Sub-study 035d stratified as P/LP
LEPR VUS-SP	*SH2B1* VUS	*LEPR* Sub-study 035b stratified as VUS-SP
POMC Likely Pathogenic (LP)	*LEPR* VUS-SP	*POMC/PCSK1* Sub-study 035a stratified as P/LP
LEPR Pathogenic (P)	*POMC* Likely Pathogenic (LP)	*LEPR* Sub-study 035b stratified as P/LP

Abbreviations: LEPR = leptin receptor; *NCOA1* = nuclear receptor coactivator 1; *PCSK1* = proprotein convertase subtilisin/kexin type 1; *POMC* = pro-opiomelanocortin; SH2B1 = SRC homology 2 B adapter protein 1; SRC1 = steroid receptor coactivator-1; VUS = variant of uncertain significance; VUS-SP = VUS suspected pathogenic.

APPENDIX 2. FINAL CATEGORIZATION IF PATIENT HAS 2 VARIANTS WITH THE SAME ACMG CLASSIFICATION

If a patient has 2 or more variants with 2 or more of the same American College of Medical Genetics (ACMG) classification, adjudication will be assigned following this hierarchy based on predicted prevalence:

LEPR > *POMC/PCSK1* > *NCOA1 (SRC1)* > *SH2B1*; see examples below.

Patient Variant 1	**Patient Variant 2**	**Patient Final Categorization (Sub-Study Assignment)**
PCSK1 VUS-SP	*LEPR* VUS-SP	*LEPR* Sub-study 035b stratified as VUS-SP
SH2B1 Pathogenic (P)	*PCSK1* Pathogenic (P)	*POMC/PCSK1* Sub-study 035a stratified as P/LP
NCOA1 (SRC1) VUS	*SH2B1* VUS	*NCOA1 (SRC1)* Sub-study (035c)

Abbreviations: *LEPR* = leptin receptor; NCOA1 = nuclear receptor coactivator 1; *PCSK1* = proprotein convertase subtilisin/kexin type 1; *POMC* = pro-opiomelanocortin; *SH2B1* = SRC homology 2 B adapter protein 1; *SRC1* = steroid receptor coactivator-1; VUS = variant of uncertain significance; VUS-SP = VUS suspected pathogenic.

APPENDIX 3.

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

Although the trial procedures and assessments required per protocol are classified as "No or Minimal Risk", which may be classified as "Minor Increase over Minimal Risk") according to the 2008 Guidance Document "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population", considerations for reducing pain and distress in patients <18 years of age are suggested below.

- The clinical trial may only be conducted if it exposes the person concerned to as little burden and other foreseeable risks as possible.
- Physical and emotional pain should be prevented as much as possible, and effectively treated when unavoidable.
- 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 drug injections should only be performed by parents (or home health care professionals), unless the child is of suitable age and competency, and desires the ability to do so.
- Although almost all trial procedures are classified as low risk, risk should be continuously monitored and assessed by appropriate personnel.
- For assessments in which there is a psychological component, measures should be taken to minimize distress. For example, Tanner Staging assessments could utilize a diagram for the child to point to and indicate what stage they currently are, vs. having to have an exam without clothes.

A comment on benefit risk: Risk is very low, from procedures and/or known safety profile of the drug (both clinically and toxicologically, where large margins and preliminary data from juvenile toxicology studies have not identified any new or concerning safety concerns) and based on 1 representative example of rare genetic disease of obesity impacting the MC4R pathway, there is the possibility of major benefit.

APPENDIX 5. 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 1975.

APPENDIX 6. [redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	☐	☐	☐	☐	
[redacted]	☐	☐	☐	☐	
[redacted]	☐	☐	☐	☐	
[redacted]	☐	☐	☐	☐	
[redacted]	☐	☐	☐	☐	
[redacted] _____	☐	☐	☐	☐	

[redacted]

- In the event of severe erythema, defined as ≥10 [redacted] injection area of the size of ≥10 [redacted] and in the presence of fever defined as ≥38°C, or based on the Investigator's clinical judgement, the Investigator [redacted].

[redacted]

APPENDIX 7. 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 trial, death due to progression of disease).

An 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

An 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 drug, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

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

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

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

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 drug).

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the trial or during a recognized follow-up period, the Investigator will provide a copy of any 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 to 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 8. GUIDANCE ON TRIAL CONDUCT DURING THE COVID-19 (CORONAVIRUS) PANDEMIC

Coronavirus disease 2019 (COVID-19) 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 Events via a home visit, including but not limited to collection of 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).
- 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 directly to the patient.

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

There is currently no available data suggesting that patients treated with setmelanotide should have treatment interrupted during the COVID-19 pandemic. If a patient develops symptoms associated with coronavirus infection, it is recommended to confirm the diagnosis using locally approved laboratory kits and report it to the local health authorities, as required. Patients with positive test results for SARS-COV-2 should have this recorded as an AE, and if hospitalized, this should be reported as a serious adverse event (SAE).

APPENDIX 9. TRIAL GOVERNANCE CONSIDERATIONS

Regulatory and Ethical Considerations

- This trial will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB) or 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/IEC 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.

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 form (eCRF) unless transmitted to the Sponsor electronically (e.g., e-diary). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

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

The Investigator must permit trial-related monitoring, audits, IRB/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 (e.g., due to COVID-19), the Clinical Research Associate (CRA) will perform routine scheduled remote interim monitoring visits (rIMV) for active sites. The aim of the remote activities is to ensure adequate ongoing oversight of trial activities to identify and eliminate any immediate risk to the safety and integrity of the patients. Each individual RMV should be approved by the Sponsor on a case-by-case basis.

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

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

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

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

Source Documents

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

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

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

Trial and Site Closure

The Sponsor or designee reserves the right to close the trial 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:

- Discontinuation of further trial intervention development.

For site termination:

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

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

- Total number of patients included earlier than expected.

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

Publication Policy

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

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

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

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

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

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

APPENDIX 10. 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 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. 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 electronic case report form (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.