SETMELANOTIDE

RM-493-033

A Phase 3 Multi-Center, One-Year, Open-Label Study of Setmelanotide in Pediatric Patients Aged 2 to <6 Years of Age with Rare Genetic Causes of Obesity

This study 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 Number: 2021-004167-27

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

Document Date (Version): 22 June 2023 (V5.0)

SUMMARY OF CHANGES TO THE PROTOCOL

The protocol history is below:

Version and Date of Protocol	Comments
Version 1.0, 01 March 2021	Original version
Version 1.1, 16 June 2021	Global
Version 1.2, 17 November 2021	Netherlands only
Version 2.0, 24 January 2022	Global
Version 3.0, 10 March 2022	Global
Version 4.0, 05 December 2022	Global
Version 5.0, 22 June 2023	Current version

Key changes in the current version (5.0) of the protocol are summarized below.

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

APPROVAL SIGNATURE PAGE

A Phase 3 Multi-Center, One-Year, Open-Label Study of Setmelanotide in Pediatric Patients Aged 2 to <6 Years of Age with Rare Genetic Causes of Obesity

Protocol Number:	RM-493-033
Document Version:	Version 5.0
Document Date:	22 June 2023

REVIEWED/APPROVED BY:

[redacted]	[redacted] Electronically signed by: [redacted] Reason: I have reviewed and approve his document. Date: Jun 23, 2023 10:45 EDT	23-Jun-2023
[redacted] Rhythm Pharmaceuticals, Inc.	Signature	Date

INVESTIGATOR STATEMENT

A Phase 3 Multi-Center, One-Year, Open-Label Study of Setmelanotide in Pediatric Patients Aged 2 to <6 Years of Age with Rare Genetic Causes of Obesity

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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 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 or Ethics Committee. No changes will be made to the trial protocol without the prior written approval of Rhythm and the Institutional Review Board, except where necessary to eliminate an immediate hazard to the patient.

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

Investigator Name	Signature of Investigator	Date

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

1. SYNOPSIS

Name of Sponsor/Company: Rhythm Pharmaceuticals, Inc.	
Name of Investigational Product: Setmelanotide	
Title of Study: A Phase 3 Multi-Center, One-Year, Open-Label Study of Setmelanotide in Pediatric Patients Aged 2 to <6 Years of Age with Rare Genetic Causes of Obesity	
Trial center(s): Approximately 5 to 8 centers in North America, Europe and/or Asia Pacific	
Studied period (years): One year Estimated date first patient enrolled: February 2022 Estimated date last patient completed: September 2023	**Phase of development:** 3

Trial Objectives:

Primary:

The primary objective of the trial is:

To evaluate the effect of setmelanotide on weight-related parameters in pediatric patients aged 2 to <6 years with obesity due to either (1) biallelic variants of the *POMC*, *PCSK1,* or *LEPR* genes or (2) Bardet- Biedl Syndrome (BBS).

Secondary:

The secondary objectives of the trial are**:**

To evaluate the effect of Setmelanotide on additional weight-related parameters, as well as safety and tolerability in pediatric patients aged 2 to <6 years with obesity due to either (1) biallelic variants of the *POMC, PCSK1,* or *LEPR* genes or (2) BBS.

[redacted]

Methodology:

This is a 1-year, open-label trial.

Screening

The Screening Period begins with obtaining informed consent from the parent or guardian and will last between 1 and 8 weeks. During the Screening Period, patients will undergo all procedures as outlined in the Schedule of Assessments (SoA; Table 1) to determine if they meet all of the Inclusion and none of the Exclusion criteria of the trial.

During the Screening Period, patients will undergo medical evaluation; and caregivers will receive training on injection of trial drug and other trial procedures.

Enrollment and trial procedures

At the enrollment visit, patients will undergo all procedures as outlined in the SoA (Table 1) and it will be reconfirmed that the patient continues to meet all of the Inclusion and none of the Exclusion criteria of the trial.

At the enrollment visit, the patient will have height and body weight recorded. This will be the baseline height and weight. To be eligible for the trial, a patient's baseline weight must be at least 15 kg. Height and weight will be monitored closely during the trial.

During the enrollment visit, the caregiver will administer the patient's first dose of setmelanotide via subcutaneous (SC) injection under the supervision of the trial staff. Patients' caregivers will be issued and instructed on the use of an electronic diary to capture daily compliance with injections.

All patients will begin treatment with setmelanotide at a dose of 0.5 mg per day. Patients will then increase their dose by 0.5 mg increments, every 2 weeks, as described in the SoA (Table 1). The maximum dose level of setmelanotide used in this trial will be based on the weight bands for the 2- to <6-year-old patients to support an exposure similar to that observed for adults dosed at 2 to 3 mg setmelanotide once daily (QD). The maximum dose level in this trial for patients who weigh <20 kg, [redacted] will be 0.5 mg, 1.0 mg, 1.5 mg and 2.0 mg QD, respectively.

If a patient's weight decreases to below 15 kg during the trial, the Investigator and Sponsor will discuss the patient's status and will jointly determine if a patient should continue the current dose, decrease the dose or discontinue treatment with setmelanotide temporarily or permanently. A dose reduction to 0.25 mg QD can be considered in such scenarios or in case of safety or tolerability concerns. These dose adjustments are considered adequate to help attain and maintain appropriate body weight in growing pediatric patients.

At the discretion of the Investigator, the dose escalation may be paused for a patient at any step prior to reaching their final maintenance dose, for safety or tolerability reasons, or due to achieving adequate weight loss. The dose may continue to be evaluated and adjusted, at the discretion of the Investigator, as long as the daily dose is kept between 0.25 mg and 2.0 mg QD, according to their respective weight. Patients will have trial visits approximately every 4 weeks through Week 20 and then approximately every 8 weeks through Week 52, and assessments will be performed as per the SoA (Table 1). Due to the young age of the patients, it may not be possible to perform all planned assessments at each visit. Thus, as described in the SoA (Table 1), the Investigator may adjust the planned assessments and blood draws as appropriate for the optimal medical care of the patients.

In specific, individual cases, dose escalation may be delayed compared to the originally planned schedule at enrollment, in order to mitigate potential tolerability issues (e.g., in case of gastrointestinal adverse events). If the escalation to the next dose level is delayed, the escalation period will be extended for that patient and the subsequent available site visits will then become "dose escalation" visits, where the appropriate and specific assessments related to the escalation visits will take place.

End of Treatment

The End of Treatment (EOT) will occur as an in-person clinic visit on Trial Week 52, which is the final day of treatment with setmelanotide. At the EOT, patients who are considered likely to benefit from continued setmelanotide treatment and who have completed this trial may be eligible to enter an open-label long-term extension (LTE) trial with setmelanotide. Patients and or caregivers/guardians must meet the eligibility criteria and should discuss eligibility with the Investigator. Eligible patients may participate in Bridging visits (every 12 weeks) (Table 1) if the LTE is not yet active.

All patients who discontinue treatment prematurely should attend an Early Termination of Treatment visit (ETT) as soon as possible after the last dose of trial treatment. Patients who discontinue treatment but remain enrolled in the trial should continue to complete all assessments (as Retained Dropouts). These patients will be required to complete the End of Study visit (EOS) as applicable following the

ETT (Section 5.1.5). Patients who discontinue treatment prematurely but remain enrolled and complete assessments through Week 52 are eligible to enroll in the optional LTE trial.

Patients who discontinue prematurely and withdraw from the trial will not be required to complete the EOS following the ETT. If the ETT visit occurs 4 weeks or later following the last dose of Setmelanotide, then the ETT visit will replace the EOS if no AEs are being monitored.

End of Study

A final End of Study (EOS) visit will occur on Week 56 and may be conducted via telephone for patients who are not being monitored for an AE. The EOS visit is not required for patients who enroll in the LTE (or transition to Bridging visits prior to LTE).

At the Investigator's discretion and in consultation with the Sponsor, patients who have well tolerated setmelanotide, who are considered likely to benefit from continued treatment, and who have completed assessments through Week 52 may be offered continued setmelanotide treatment via:

- Enrollment in a separate LTE trial.
- Bridging visits until LTE availability (if the LTE trial is not active by the time of patient completion of this trial). See Table 1.
- Commercial use of Setmelanotide QD, if applicable, according to the approved indication in their country, and in consultation with their prescribing physician

Completion of trial participation for an individual patient is defined as 1 of the following:

- For patients who complete trial treatment and enroll in the LTE: the in-person EOT visit at Week 52.
- For patients who complete treatment and do not enroll in the LTE: a Week 56 visit conducted via telephone.
- For patients who discontinue trial treatment prematurely and complete all assessments, but do not withdraw consent (and assent, as applicable): the latest of the Week 52 visit, the ETT visit, or EOS (if required).
- For patients who discontinue early and withdraw consent or assent: the ETT visit.

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

Number of patients (planned):

The trial plans to enroll approximately 10-15 pediatric patients (approximately 5 or more with biallelic mutations of the *POMC*, *PCSK1*, or *LEPR* genes and approximately 5 or more with BBS) in a pivotal cohort. At the discretion of the Sponsor, if additional potential patients are identified, a supplemental cohort may be added to gain additional experience in this pediatric patient population.

Diagnosis and criteria for inclusion and exclusion:

Inclusion Criteria

1. Patients must have obesity due to either:
   a. POMC, PCSK1, or LEPR deficiency, confirmed by genetic testing demonstrating biallelic variants that are interpreted as pathogenic, likely pathogenic, or of undetermined significance (VUS) by the American College of Medical Genetics and Genomics (ACMG) criteria, **or**
   b. BBS as defined by both (1) the Beales Criteria, 1999 (Beales 1999; Appendix 1) AND (2) genetic confirmation of homozygous or compound heterozygous loss-of-function mutation in BBS genes.
2. Age between 2 to <6 years at the time of informed consent.

3. Obesity, defined as body mass index (BMI) ≥97th percentile for age and gender AND body weight of at least 15 kg at the time of enrollment.
4. Symptoms or behaviors of hyperphagia at any time during the patient's life, as determined by the Investigator at screening.
5. Parent or guardian of patient is able to communicate well with the Investigator, to 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 consent.

Exclusion Criteria:

1. HbA1c >9.0% at screening
2. History of significant liver disease other than non-alcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH).
3. Glomerular filtration rate (GFR) <60 mL/min/1.73 m^2.
4. History or close family history (parents or siblings) of melanoma, or patient history of oculocutaneous albinism.
5. 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.
6. Patient is, in the opinion of the Investigator, not suitable to participate in the trial.
7. Participation in any clinical trial with an investigational drug/device within 3 months prior to the first day of dosing.
8. Previously enrolled in a clinical trial involving setmelanotide or any previous exposure to setmelanotide.
9. Significant hypersensitivity to any excipient in the trial drug.
10. Abnormal hepatic function as evidenced by elevated Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) values >5x upper limit of normal (ULN).
11. Any other uncontrolled endocrine, metabolic or medical condition(s) known to impact body weight that could potentially interfere with interpretation of trial results.

Investigational product, dosage and mode of administration:

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

Dosage: Between 0.5 and 2.0 mg/day (if a dose of 0.5 mg/day is not tolerated or if weight decreases to below [redacted]

Mode of administration: SC injection

Duration of treatment: Total treatment with setmelanotide will be 52 weeks. Total participation in the trial will last up to 64 weeks, including the Screening Period and the EOS visit.

Criteria for Evaluation:

Primary Endpoints:

- The proportion of patients demonstrating response to setmelanotide, defined as a decrease from baseline to 52 weeks in the patient's body mass index (BMI) z-score of ≥0.2.
- Mean percent change in BMI from baseline to Week 52.

Secondary Endpoints:

- The following endpoints will be summarized and reported as change from baseline to 52 weeks:
  - Mean absolute change in BMI z-score per age and gender
  - Mean change in percent of the 95th percentile of BMI per age and gender
  - The mean change in vital signs and laboratory evaluations
  - The mean change in bone age
  - Mean change in Ages & Stages Questionnaires, Third Edition (ASQ®-3)
- Frequency and severity of AEs will also be summarized and reported during trial conduct.

[redacted]

Statistical methods:

Details of all statistical analyses will be described in a separate statistical analysis plan (SAP). The trial plans to enroll approximately 10-15 pediatric patients (approximately 5 or more patients with biallelic mutations of the POMC, PCSK1 or LEPR genes and approximately 5 or more patients with BBS). The sample size is not driven by statistical power considerations, but is primarily driven by clinical and practical considerations.

The primary objective is to evaluate the effect of setmelanotide on weight-related parameters, measured in terms of the response rate to setmelanotide. Due to the small sample size of the trial, no statistical hypothesis testing is planned, and efficacy will be reported using descriptive statistics. The safety population, including all patients who receive at least 1 dose of setmelanotide, will be used as the primary analysis population for all the analyses.

AEs will be coded by preferred term (PT) and system organ class (SOC) using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). All AE data will be presented in a data listing. Treatment-emergent AEs will be summarized by severity and relationship to trial drug. Serious AEs and AEs leading to early discontinuation will also be presented in data listings.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements etc., will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results. Clinical laboratory test results, vital sign measurements etc., will be presented in data listings.

The secondary objectives are to evaluate the efficacy of setmelanotide on weight-related parameters, as well as the safety and tolerability of setmelanotide. [redacted] No statistical hypothesis was made. The collected parameters will be summarized with appropriate descriptive statistics.

Due to the small sample size, summary statistics by genotype may be provided as appropriate.

2. SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

Assessment	Screening	Enrollment Visit (Baseline)	Dose Escalation Visits[1]	Trial Visits[2]	EOT	EOS[3]	ETT	Bridging Visits
Trial Week	**-8 to -1**		**2, 4, 6**	**8, 12, 16, 20, 28, 36, 44[2]**	**52**	**56**		**Q12 Weeks (If needed, In Person)**
Trial Day	**-56 to -1**	**1**	**15, 29, 43**	**57, 85, 113, 141, 197, 253, 309**	**365**	**393**		
Window			**±3**	**±5**	**±5**	**±3**		**±5**
Informed Consent	X							
Inclusion/ Exclusion	X	X						
Medical History	X	X						
Physical Examination[4]	X	X*	X	X	X		X	X
Fitzpatrick classification scale		X			X		X	
Comprehensive Skin Examination[5]	X	X		X	X		X	X
Weight[6]	X	X	X	X	X		X	X
Height[7]	X	X	X	X	X		X	X
[redacted]								
Vital Signs[9]	X	X	X	X	X		X	X
ECG[10]	X	X	X	X (W8 and 44)	X		X	X
Daily drug compliance[11]		X	X	X	X		X	
Genetic Sample[12, 20]		X						
Safety Lab Tests[12]	X	X	X	X	X		X	X

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Assessment	Screening	Enrollment Visit (Baseline)	Dose Escalation Visits[1]	Trial Visits[2]	EOT	EOS[3]	ETT	Bridging Visits
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Trial Day	**-56 to -1**	**1**	**15, 29, 43**	**57, 85, 113, 141, 197, 253, 309**	**365**	**393**		
Window			**±3**	**±5**	**±5**	**±3**		**±5**
[redacted]								
Anti-Drug Antibodies[12]	X			X	X		X	X
[redacted]								
Adverse events	X	X	X	X	X	X	X	X
Injection site inspection		X	X	X	X		X	X
Concomitant medication Review	X	X	X	X	X	X	X	X
Optional Nutritional Counseling[17]		X	X	X	X			X
Bone Age[18]		X			X			

Table 1: Schedule of Assessments

Assessment	Screening	Enrollment Visit (Baseline)	Dose Escalation Visits[1]	Trial Visits[2]	EOT	EOS[3]	ETT	Bridging Visits
Trial Week	**-8 to -1**		**2, 4, 6**	**8, 12, 16, 20, 28, 36, 44[2]**	**52**	**56**		**Q12 Weeks (If needed, In Person)**
Trial Day	**-56 to -1**	**1**	**15, 29, 43**	**57, 85, 113, 141, 197, 253, 309**	**365**	**393**		
Window			**±3**	**±5**	**±5**	**±3**		**±5**
Ages & Stages Questionnaires, Third Edition (ASQ-3)[19]		X		X	X			X
Dispense Trial Drug		X	X	X	X**			X
Return Trial Drug			X	X	X		X	X

Abbreviations: ECG=electrocardiogram; EOS=End of Study; EOT=end of treatment; ETT=Early Termination of Treatment; [redacted]; LTE=Long –term extension; [redacted]

*Note: If there are <2 weeks between screening and enrollment, the enrollment visit physical examination may be waived.

**Drug is dispensed at the EOT only for patients who continue to the Bridging visits.

[1] Patients should attend dose-escalation visits as appropriate per their respective escalation regimen, which is dictated by their weight, until achieving maximum dose level. See Section 7.3 for details.

[2] The dose may continue to be evaluated and adjusted, at the discretion of the Investigator, in 0.5 mg increments, so long as the daily dose is kept between 0.5 mg and the weight-based maximum for the patient (see Table 3).

[3] EOS visit should occur within 4 weeks of the last dose of study drug for patients who either discontinue prematurely or for patients who are being monitored for an adverse event (AE) after the EOT. This visit is not required for patients who complete the Week 52 visit and either enroll in the LTE or transition to Bridging visits.

[4] A complete physical examination will be conducted at screening and at the EOT visit. At other timepoints, an abbreviated examination will be performed. The abbreviated examination should focus on heart, lungs, skin, neurologic exam, and any areas of previous abnormal findings, noting any changes from baseline. Tanner staging should be performed at Screening and at the EOT (Week 52) visit. It may be done at additional visits, at the discretion of the Investigator

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

[6] Weight (kg) is to be measured at the clinic using the same scale throughout the trial or at home (during virtual visits or visiting nurse visits) using the same scale provided to the patient as part of the clinical trial. Weight should be measured after patients have attempted to empty their bladders and after fasting for

at least 8 hours. Patients are to wear light clothing or underwear and no shoes, with empty pockets, and will be weighed at approximately the same time of day. All measurements will be recorded to the nearest tenth kg if reported with a digital scale, or half kg with a mechanical scale.

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

[8] [redacted]

[9] All blood pressure (BP) and heart rate (HR) measurements are to be obtained in a sitting position following at least 5 minutes of rest. All measurements will be taken in triplicate, approximately 2 minutes apart. When possible, BP should be taken in the non-dominant arm using the same methodology (automated or manual) throughout the trial.

[10] A single 12-lead ECG will be performed. If an ECG is not practical in a young patient, it may be replaced by a rhythm strip and HR and PR interval should be documented.

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

[12] Safety laboratory tests will include CBC with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, CO2, albumin, total protein, glucose, BUN, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), creatine phosphokinase (CPK), alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), calcium, phosphorus), thyroid- stimulating hormone (TSH) and urinalysis with microscopic analysis if positive findings on dipsticks warrant further examination. Due to the age of the children, it may not be possible to collect samples (including urine samples) for all laboratory tests at every study visit. Screening may be performed over multiple days, to complete the required assessments. After enrollment, if all laboratory tests are not possible, then the tests should be collected in the following descending order of priority: safety, anti-drug antibodies, [redacted], [redacted] and then [redacted]. If it is not possible to collect the safety laboratory tests on two consecutive visits, the patient should be discussed with the Sponsor. If there is a marginal value close to the exclusion range, it is suggested to repeat the laboratory analyses at Investigator's discretion. To allow for pre- and post-dose sampling, patients will attend the site visit having fasted for an 8-hour time period without injecting the trial product. On the day of the site visit, dosing will be conducted on site. The Investigator's will adhere to the site-specific blood volume limits for safety laboratory and [redacted] to ensure minimal distress to the pediatric patients. If the genetic sample cannot be collected at the enrollment visit, it may be collected during a later trial visit. Anti-drug antibody samples (Section 8.5) are to be collected prior to dosing with setmelanotide. [redacted]

[13] [redacted]

[14] [redacted]

[15] [redacted]

[16] [redacted]

[17] [redacted]

[18] Bone age may be read locally initially, but the Sponsor may request central reading of images. A standard bone age measurement (of the hand/wrist area) will be obtained at the beginning and the end of the trial to monitor for growth related safety concerns.

[19] The ASQ-3 is intended for use at six-month intervals for patients between 6 months and 3 years of age, and then at 1-year intervals through age 5. Thus, for patients who enter the trial at ages between 2 years and 3 years, the ASQ-3 should be administered at the Baseline visit, Week 28 visit and EOT visit. For patients who enter the trial between the ages of 3 and 6 years old, the ASQ-3 should only be administered at the Baseline visit and EOT visit.

[20] A blood sample will be obtained at baseline to confirm a genetic diagnosis. However, patients may be entered into the trial with documentation of previously obtained genetic results.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
ACMG	American College of Medical Genetics and Genomics criteria
ADA	Anti-drug antibodies
AE	Adverse Event
ALT	Alanine Aminotransferase
ASQ-3	Ages & Stages Questionnaires, Third Edition
AST	Aspartate Aminotransferase
AUC	Area Under Curve
BMI	Body Mass Index
BP	Blood Pressure
BBS	Bardet-Biedl Syndrome
BUN	Blood Urea Nitrogen
[redacted]	[redacted]
COVID-19	Coronavirus Disease 2019
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
ETT	Early Termination of Treatment visit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-glutamyl transferase
HbA1c	Glycated hemoglobin
HR	Heart Rate
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase

Abbreviation or Specialist Term	Explanation
LEPR	Leptin Receptor
LTE	Long-term Extension
MC4R	Melanocortin 4 Receptor
mg	Milligram
mL	Milliliter
mPEG/DSPE	N-[Carbonyl-methoxypolyethylene glycol 2000]-1,2-distearoyl- glycero-3-phosphoethanolamine sodium salt
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Nonalcoholic Steatohepatitis
NOAEL	No Observed Adverse Effect Level
PCSK1	Proprotein Convertase Subtilisin/kexin Type 1
POMC	Pro-opiomelanocortin
[redacted]	[redacted]
PT	Preferred Term
QD	Once Daily
rIMV	Remote Interim Monitoring Visit
rSDM	Remote Source Data Monitoring
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneously
SoA	Schedule of Assessments
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
VUS	Variant of Undetermined Significance

3. INTRODUCTION

3.1. Trial Rationale

Human genetic trials have identified several diseases that are the result of genetic variants affecting the melanocortin-4 receptor (MC4R) pathway, including, but not limited to, pro-opiomelanocortin (POMC) deficiency obesity due to mutations in the *POMC* gene; heterozygous proprotein convertase subtilisin/kexin type 1 (PCSK1) deficiency due to mutations in the *PCSK1* gene, leading to a hormone processing defect that also causes POMC deficiency obesity; and leptin receptor (LEPR) deficiency obesity due to mutations in the *LEPR* gene. These MC4R pathway mutations cause rare genetic diseases of obesity that start early in childhood, progress over time, and can become life-threatening in severity.

Setmelanotide, an MC4R agonist, has the potential to restore reduced activity in MC4Rs in patients with these genetic defects in MC4R pathway. Consequently, the effect of setmelanotide may serve as a form of "replacement" therapy to re-establish weight and appetite control in patients with these disorders.

Previous clinical trials have shown evidence that setmelanotide can help manage weight and reduce hunger in children with these genetic variants (Haws 2020; Clément 2020). The daily formulation (QD) of setmelanotide is authorized for commercial use in the United States (US) the European Union (EU), and Canada in adult and pediatric patients 6 years of age and older with obesity due to Bardet-Biedl Syndrome (BBS) (USPI 2022, EU SmPC 2022, Product Monograph 2023). Setmelanotide is also authorized for commercial use in the US, Great Britain (GB), the EU, Israel, and Canada in adult and pediatric patients 6 years of age and older with obesity due to pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency (collectively PPL deficiency obesity (USPI 2022, EU SmPC 2022, MHRA SmPC 2022, Israel PPI 2022; Product Monograph 2023)

In this study, the safety, tolerability, and efficacy of setmelanotide will be studied in pediatric patients aged 2 to <6 years with variants in *POMC*, *PCSK1* or *LEPR* genes or with Bardet-Biedl Syndrome (BBS).

3.2. Setmelanotide

Setmelanotide is a synthetic, cyclic octapeptide (8-amino acid-containing peptide) that functions as a potent MC4R agonist. Setmelanotide binds with high affinity (inhibitory constant = 2.1 nM) to the human MC4R and is efficient in activating MC4R (50% effective concentration = 0.27 nM). While not an analog, it retains the specificity and functionality of the naturally occurring POMC-derived neuropeptide, α-MSH, which is the endogenous ligand for the MC4R. Setmelanotide is more potent and has a much longer half-life (~10-12 hours in humans) than the short-lived α-MSH ligand.

The setmelanotide peptide was initially selected for clinical development based on its acceptable circulating half-life as a saline formulation (2.8 - 3.5 hours in non-human primates) and the ability to decrease body weight gain and suppress food intake in normal rats. Pre-clinical studies demonstrated the efficacy of setmelanotide in suppressing food intake and body weight gain in diet-induced obese mice, rats, dogs, and monkeys, as well as in genetic models of obesity, including leptin-deficient ob/ob mice and leptin receptor deficient obese Zucker rats. Later

studies in obese monkeys showed that setmelanotide did not increase blood pressure (BP) or heart rate (HR), a potential concern observed with other MC4R agonist compounds.

To support clinical trials, the toxicological profile of setmelanotide formulations has been evaluated in repeat-dose continuous SC infusion toxicity studies up to 13 weeks in duration in rats and monkeys. The formulation used in almost all of these studies, including the pivotal 28-day and 13-week toxicology studies, was setmelanotide in 0.9% sodium chloride for injection (setmelanotide-saline formulation), tested over a range of concentrations. An International Council for Harmonisation (ICH)-compliant battery of in vitro and in vivo genetic toxicity studies that included a bacterial mutation assay, a chromosomal aberration assay in cultured human peripheral blood lymphocytes and a rat micronucleus study has been completed with this formulation. Finally, chronic, reproductive, and juvenile toxicology studies using the RM-493-mPEG-DSPE formulation have been completed.

Setmelanotide has been well tolerated by patients who have received it in clinical trials. Regardless of formulation, setmelanotide has demonstrated a mostly similar set of adverse events (AEs) in both short-term and long-term clinical trials.

3.3. Benefit/Risk Assessment

Current development of setmelanotide is focused on assessing the risks and benefits in several genetic diseases of early-onset severe obesity that result from rare genetic mutations that impair the hypothalamic leptin-POMC-melanocortin pathway upstream from the MC4R. Setmelanotide, an MC4R agonist, may restore the impaired signaling of this pathway. Data obtained to date in the setmelanotide clinical development program demonstrate robust reduction in weight and hunger in patients with rare genetic diseases of obesity.

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

4. TRIAL OBJECTIVES AND ENDPOINTS

The trial objectives and the corresponding endpoints are summarized in Table 2 below.

Table 2: Trial Objectives and Endpoints

Objective	Endpoint
Primary: To evaluate the effect of setmelanotide on weight-related parameters in pediatric patients aged 2 to <6 years with obesity due to either (1) biallelic variants of the *POMC, PCSK1* or *LEPR* genes or (2) BBS	• The proportion of patients demonstrating response to setmelanotide, defined as a decrease from baseline to 52 weeks in the patient's body mass index (BMI) z-score of ≥0.2. • Mean percent change in BMI from baseline to Week 52.
Secondary: To evaluate the effect of setmelanotide on additional weight-related parameters, as well as safety and tolerability in pediatric patients aged 2 to <6 years with obesity due to either (1) biallelic variants of the *POMC*, *PCSK1* or *LEPR* genes or (2) BBS	**Secondary**: • The following endpoints will be summarized and reported as change from baseline to 52 weeks: – Mean absolute change in BMI z-score per age and gender – Mean change in percent of the 95th percentile of BMI per age and gender – The mean change in vital signs and laboratory evaluations – The mean change in bone age – Mean change in Ages & Stages Questionnaires, Third Edition (ASQ®-3) • Frequency and severity of AEs will also be summarized and reported during trial conduct.
[redacted]	

Abbreviations: AEs=adverse events; BBS=Bardet-Biedl Syndrome; BMI=body mass index; LEPR=leptin receptor; PCSK1=proprotein convertase subtilisin/kexin type 1; POMC=pro-opiomelanocortin; [redacted].

5. INVESTIGATIONAL PLAN

5.1. Overall Trial Design

This is a Phase 3 multi-center, open-label trial of setmelanotide in pediatric patients aged 2 to <6 years with rare genetic causes of obesity. The trial is designed to evaluate safety and tolerability of setmelanotide as well as its efficacy on weight-related parameters in pediatric patients.

5.1.1. Trial Population

The trial plans to enroll pediatric patients with biallelic mutations of the *POMC*, *PCSK1* or *LEPR* genes and pediatric patients with BBS.

5.1.2. Screening Period

The Screening Period begins with obtaining informed consent from the parent or guardian and will last between 1 and 8 weeks. During the Screening Period, patients will undergo all procedures as outlined in the Schedule of Assessments (SoA; Table 1) to determine if they meet all of the Inclusion (Section 6.1) and none of the Exclusion criteria (Section 6.2) for trial eligibility. A patient who does not meet one or more of the eligibility criteria will be considered a screen failure. Any patient that is rescreened is required to have a new ICF signed by the parent or guardian.

During the Screening Period, patients will undergo medical evaluation; and caregivers will receive training on injection of trial drug and other trial procedures.

5.1.3. Enrollment and trial procedures

At the enrollment visit, patients will undergo all procedures as outlined in the SoA (Table 1) and it will be reconfirmed that the patient continues to meet all of the Inclusion and none of the Exclusion criteria of the trial.

At the enrollment visit, the patient will have height and body weight recorded. This will be the baseline height and weight. To be eligible for the trial, a patient's baseline weight must be at least 15 kg. Height and weight will be monitored closely during the trial.

During the enrollment visit, the caregiver will administer the patient's first dose of setmelanotide via subcutaneous (SC) injection under the supervision of the trial staff. Patients' caregivers will be issued an electronic diary to capture daily compliance with injections.

All patients will begin treatment with setmelanotide at a dose of 0.5 mg per day. Patients will then increase their dose by 0.5 mg increments, every 2 weeks, as described in the SoA (Table 1). The maximum dose level of setmelanotide used in this trial will be based on the weight bands for the 2- to <6-year-old patients to support an exposure similar to that observed for adults dosed at 2 to 3 mg setmelanotide QD. The maximum dose level in this trial for patients who weigh [redacted] ill be 0.5 mg, 1.0 mg, 1.5 mg and 2.0 mg QD, respectively.

If a patient's weight decreases to below 15 kg during the trial, the Investigator and Rhythm Pharmaceuticals, Inc. (henceforth Sponsor) will discuss the patient's status and will jointly

determine if a patient should continue the current dose, decrease the dose or discontinue treatment with setmelanotide temporarily or permanently. A dose reduction to 0.25 mg QD can be considered in such scenarios or in case of tolerability concerns, including for example, the occurrence of severe renal impairment. These dose adjustments are considered adequate for the pediatric patients to grow in height at a normal rate and support attaining and maintaining an appropriate body weight.

At the discretion of the Investigator, the dose escalation for a patient may be temporarily paused at any step prior to reaching their final maintenance dose, for safety or tolerability reasons, or due to achieving adequate weight loss. The dose may continue to be evaluated and adjusted, at the discretion of the Investigator, so long as the daily dose is kept between 0.25 mg and 2.0 mg QD, according to their respective weight.

Patients will have trial visits approximately every 4 weeks through Week 20 and then approximately every 8 weeks through Week 52 and assessments will be performed as per the SoA (Table 1). Due to the young age of the patients, it may not be possible to perform all planned assessments at each visit. Thus, as described in the SoA (Table 1), the Investigator may adjust the planned assessments and blood draws as appropriate for the optimal medical care of the patients.

In specific, individual cases, dose escalation may be delayed compared to the originally planned schedule at enrollment, in order to mitigate potential tolerability issues (e.g., in case of gastrointestinal adverse events). If the escalation to the next dose level is delayed, the escalation period will be extended for that patient and the subsequent available site visits will then become "dose escalation" visits, where the appropriate and specific assessments related to the escalation visits will take place.

5.1.4. End of Treatment

The End of Treatment (EOT) will occur as an in-person clinic visit on Trial Week 52, which is the final day of treatment with setmelanotide. At the EOT, patients who are considered likely to benefit from continued setmelanotide treatment and who have completed this trial may be eligible to enter an open-label long-term extension (LTE) trial with setmelanotide. Patients must meet the eligibility criteria and should discuss eligibility with the Investigator. Eligible patients may participate in Bridging visits (every 12 weeks) (Table 1) if the LTE is not yet active.

All patients who discontinue treatment prematurely should attend an Early Termination of Treatment visit (ETT) as soon as possible after the last dose of trial treatment. Patients who discontinue treatment but remain enrolled in the trial should continue to complete all assessments (as Retained Dropouts). These patients will be required to complete the End of Study (EOS) as applicable following the ETT (Section 5.1.5). Patients who discontinue treatment prematurely but remain enrolled and complete assessments through Week 52 are eligible to enroll in the optional LTE trial.

Patients who discontinue prematurely and withdraw from the trial will not be required to complete the EOS visit following the ETT. If the ETT visit occurs 4 weeks or later following the last dose of Setmelanotide, then the ETT visit will replace the EOS visit if no AEs are being monitored.

5.1.5. End of Study Visit

A final EOS visit will occur on Week 56 and may be conducted via telephone for patients who are not being monitored for an AE. The EOS visit is not required for patients who enroll in the LTE (or transition to Bridging visits prior to enrollment in the LTE).

At the Investigator's discretion and in consultation with the Sponsor, patients who have well tolerated setmelanotide, who are considered likely to benefit from continued treatment, and who have completed assessments through Week 52 may be offered continued setmelanotide treatment via:

- Enrollment in a separate LTE trial.
- Bridging visits until LTE availability (if the LTE trial is not active by the time of patient completion of this trial). See Table 1.
- Commercial use of setmelanotide QD, if applicable, according to the approved indication in their country, and in consultation with their prescribing physician.

5.1.6. Completion of Trial Participation

Completion of trial participation for an individual patient is defined as 1 of the following:

- For patients who complete trial treatment and enroll in the LTE: the in-person EOT visit at Week 52.
- For patients who complete treatment and do not enroll in the LTE: a Week 56 visit conducted via telephone.
- For patients who discontinue trial treatment prematurely and complete all assessments, but do not withdraw consent (and assent, as applicable): the latest of the Week 52 visit, the ETT visit, or EOS visit (if required).
- For patients who discontinue early and withdraw consent or assent: the ETT visit.

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

5.2. Site Closure and Study Termination

5.2.1. 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 enrolled earlier than expected.

5.2.2. Criteria for Trial Termination or Suspension

This trial may be prematurely terminated or suspended, if in the opinion of the Sponsor, there is sufficiently reasonable cause. The Sponsor will provide written notification documenting the reason for trial or site termination.

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

- Determination of unexpected, significant, or unacceptable risk to patients.
- Failure to enroll patients into the trial.
- Insufficient adherence to protocol requirements.
- Insufficient complete and/or evaluable data.
- Plans to modify, suspend, or discontinue the development of the trial drug.

If the trial is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the Independent Ethics Committees (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 patients and should assure appropriate patient therapy and/or follow-up. Should the trial be closed prematurely, all trial materials must be returned to the Sponsor or designee.

6. SELECTION AND WITHDRAWAL OF PATIENTS

6.1. Inclusion Criteria

1. Patients must have obesity due to either:
   a. POMC, PCSK1, or LEPR deficiency, confirmed by genetic testing demonstrating biallelic variants that are interpreted as pathogenic, likely pathogenic, or of undetermined significance (VUS) by the American College of Medical Genetics and Genomics criteria (ACMG), **or**
   b. BBS as defined by both (1) the Beales Criteria, 1999 (Beales 1999, [Appendix 1]) AND (2) genetic confirmation of homozygous or compound heterozygous loss-of-function mutation in BBS genes.
2. Age between 2 to <6 years at the time of informed consent.
3. Obesity, defined as BMI ≥97th percentile for age and gender AND body weight of at least 15 kg at the time of enrollment.
4. Symptoms or behaviors of hyperphagia at any time during the patient's life, as determined by the Investigator at screening.
5. Parent or guardian of patient is able to communicate well with the Investigator, to understand and comply with the requirements of the trial (including the once daily [QD] injection regimen and all other trial procedures) and is able to understand and sign the written consent.

6.2. Exclusion Criteria

1. HbA1c >9.0% at screening.
2. History of significant liver disease other than non-alcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH).
3. Glomerular filtration rate (GFR) <60 mL/min/1.73 m^2.
4. History or close family history (parents or siblings) of melanoma, or patient history of oculocutaneous albinism.
5. 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.
6. Patient is, in the opinion of the investigator, not suitable to participate in the trial.
7. Participation in any clinical trial with an investigational drug/device within 3 months prior to the first day of dosing.
8. Previously enrolled in a clinical trial involving setmelanotide or any previous exposure to setmelanotide.

9. Significant hypersensitivity to any excipient in the trial drug.
10. Inadequate hepatic function as evidenced by elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values >5x upper limit of normal (ULN).
11. Any other uncontrolled endocrine, metabolic or medical condition(s) known to impact body weight that could potentially interfere with interpretation of trial results.

6.3. Treatment Discontinuation and Patient Withdrawal Criteria

Given this rare patient population, every effort will be made to encourage and keep patients enrolled in the trial until completion, regardless of premature treatment discontinuation. In the case of treatment discontinuation, efforts should be made to keep the patient in the trial, attending at a minimum the key trial visits, e.g., the EOT (and EOS as necessary) visit, for safety evaluations.

The Sponsor will provide assistance for patient and caregiver travel and will provide other necessary logistical support to ease the burden on the patient in order to facilitate compliance.

Patients can withdraw their consent to participate in the trial at any time. If the parent or their legal guardian(s) withdraw consent/assent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient and/or their legal guardian(s) withdraw from the trial, they may request destruction of any samples taken and not tested, and the Investigator must document this in the site trial records.

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

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

7. TREATMENT OF PATIENTS

7.1. Description of Trial Drug

Setmelanotide will be supplied by the Sponsor. Setmelanotide drug product (RM-493-mPEG-DSPE formulation) is a sterile solution for injection. The product is manufactured at a concentration of 10.0 mg/mL.

7.2. Treatment Dose Selection

The dose of setmelanotide was chosen for this trial based on effective doses in other clinical trials, a review of the amount of benzyl alcohol in the formulation and the pharmacokinetic (PK) results in previous clinical trials.

7.2.1. Benzyl Alcohol Dose

The amount of benzyl alcohol in the formulation was compared with the amount delivered by Increlex (Increlex Product SmPC), an approved product containing phenol and benzyl alcohol. Each mL of Increlex contains 10 mg/mL mecasermin and 9 mg/mL benzyl alcohol.

Based on Posology, the recommended starting dose of mecasermin is 0.04 mg/kg of body weight twice daily by an SC injection. If no significant adverse reactions occur for at least one week, the dose may be raised in increments of 0.04 mg/kg to the maximum dose of 0.12 mg/kg given twice daily. Doses greater than 0.12 mg/kg BID should not be exceeded. [redacted]

[redacted] is well within these already approved dose ranges given to small children for Increlex.

7.2.2. Setmelanotide Dose

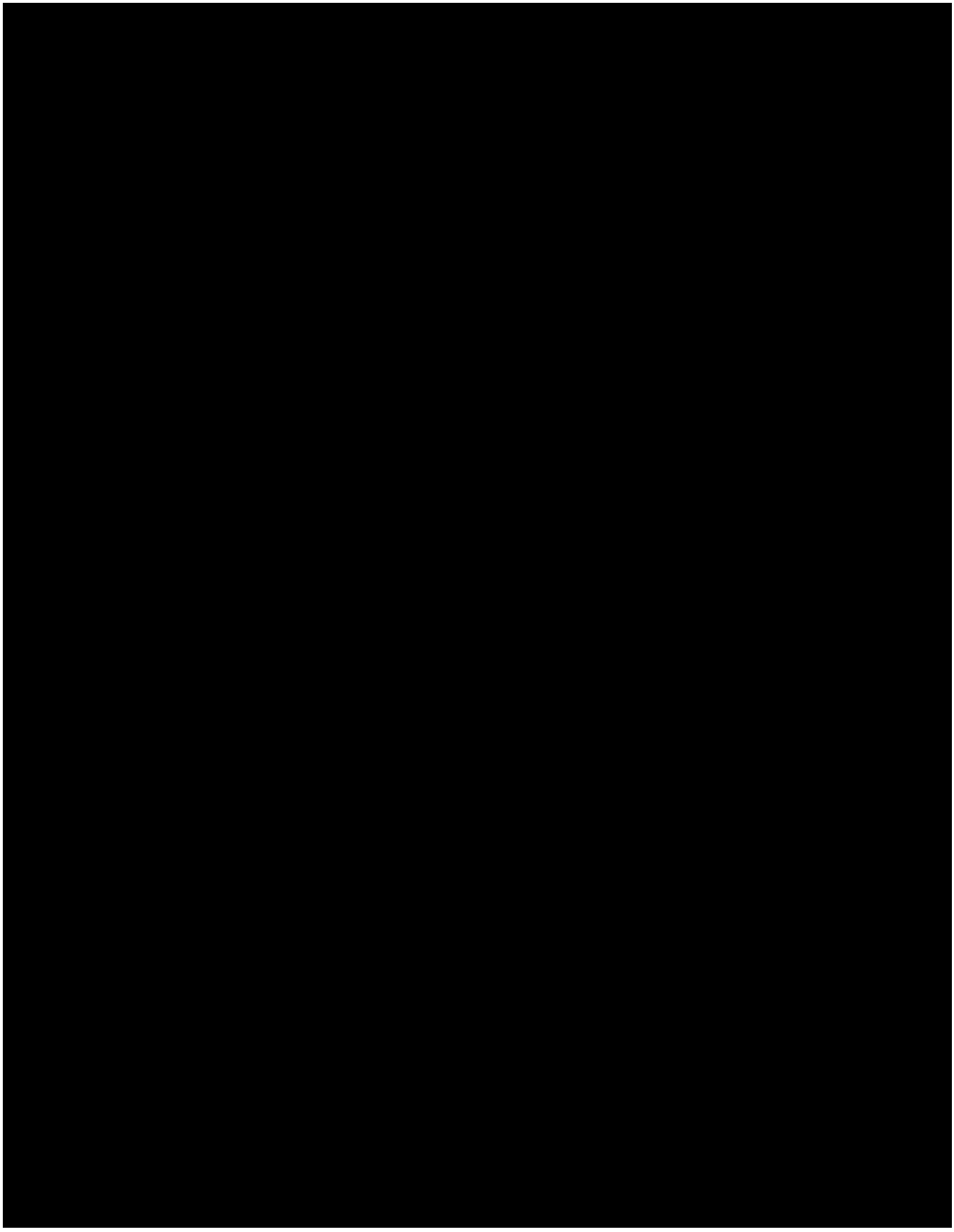
The dose level of setmelanotide used in this trial will be based on the weight bands for the 2- to <6- year-old patients (Table 3) to ensure the exposure is similar to that observed for adults dosed at 2 to 3 mg setmelanotide QD. [redacted]

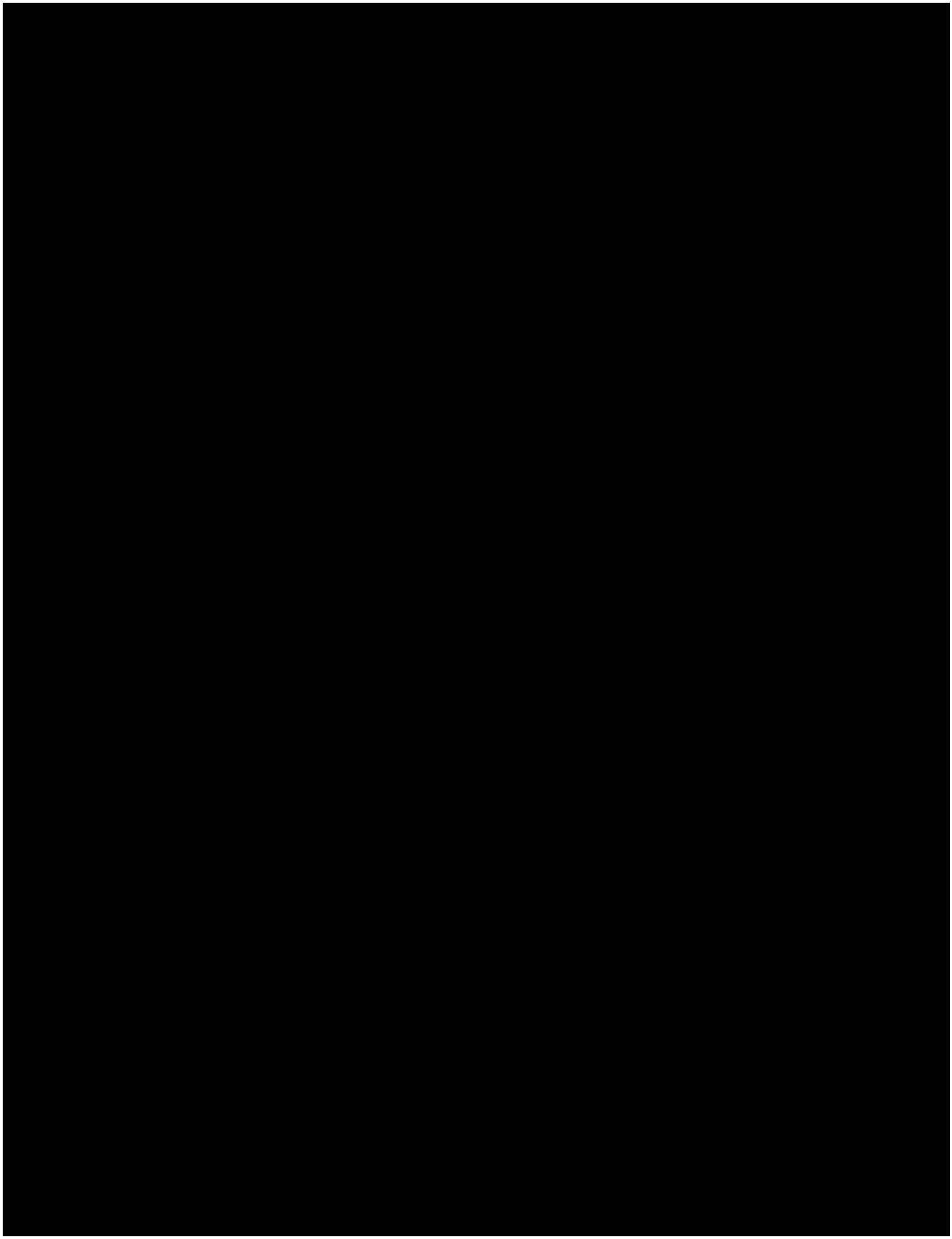
Table 3: Dosing Schedule for Patients 2- to <6 Years Old

[redacted]	**Maximum Dose**
	0.5 mg/day
	1.0 mg/day*
	1.5 mg/day
	2.0 mg/day

* [redacted]

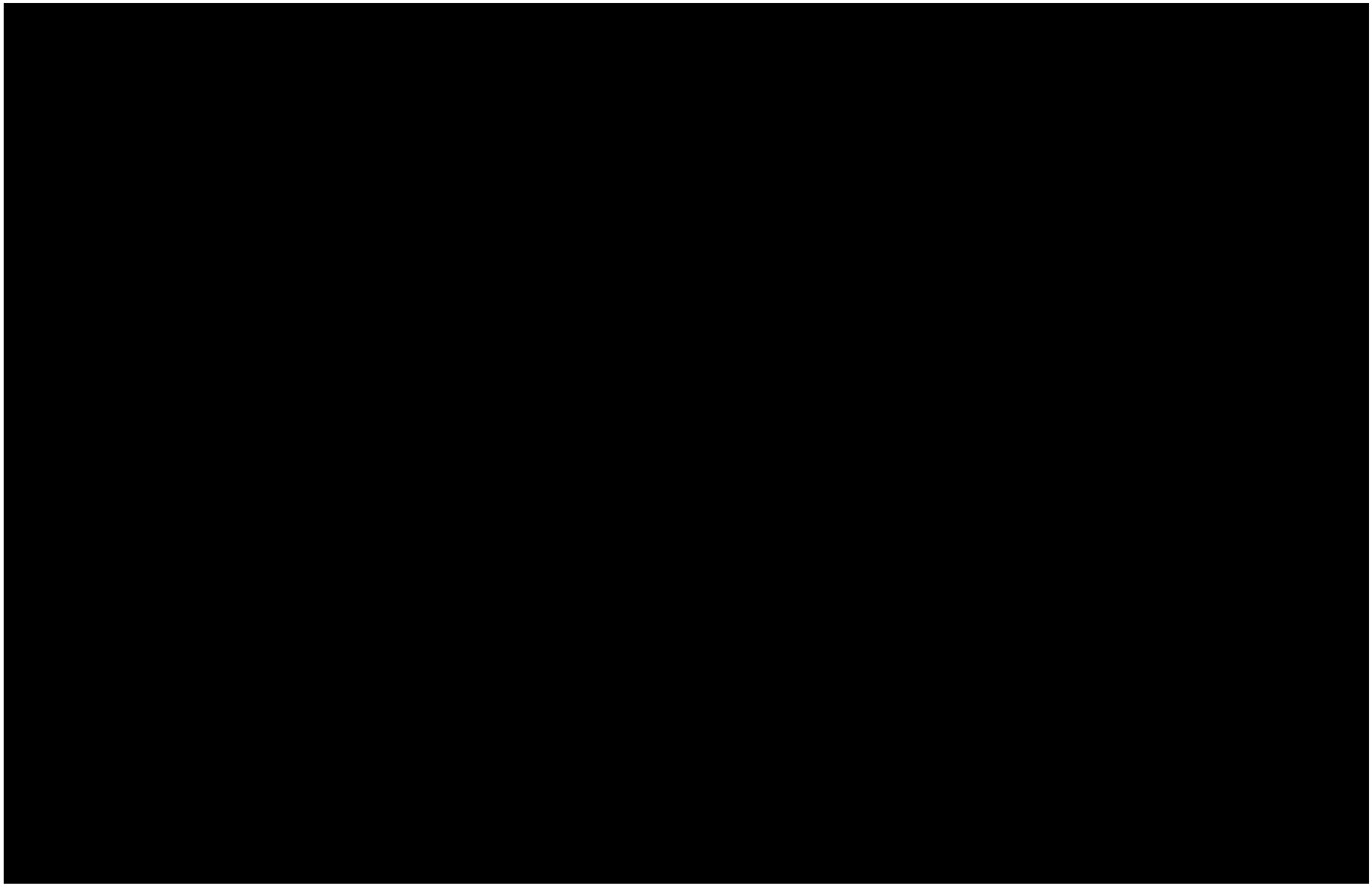
[redacted]





[redacted] Refer to the IB for additional information on the toxicology of setmelanotide in mPEG-DSPE.

[redacted]



[redacted]

7.3. Treatment Administration

Setmelanotide will be administered as a SC injection. All patients will begin treatment at a dose of 0.5 mg of setmelanotide per day. Patients will then increase their dose by 0.5 mg increments, every 2 weeks, as described in the SoA (Table 1). The maximum dose level of setmelanotide used in this trial will be based on the weight bands for the 2- to <6-year-old patients to support an exposure similar to that observed for adults dosed at 2 to 3 mg setmelanotide QD. The maximum dose level in this trial for patients who weigh [redacted] will be 0.5 mg, 1.0 mg, 1.5 mg and 2.0 mg QD, respectively.

If a patient's weight decreases to below 15 kg during the trial, the Investigator and Sponsor will discuss the patient's status and will jointly determine if a patient should continue the current dose, decrease the dose or discontinue treatment with setmelanotide temporarily or permanently. A dose reduction to 0.25 mg can be considered in such scenarios or in case of safety or tolerability concerns. These dose adjustments are considered adequate to help attain and maintain appropriate body weight in growing pediatric patients.

At the discretion of the Investigator, a patient may temporarily pause the dose escalation at any step prior to reaching their final maintenance dose, for safety or tolerability reasons, or due to achieving adequate weight loss. The dose may continue to be evaluated and adjusted, at the

discretion of the Investigator, as [redacted] and 2.0 mg QD, according to their respective weight.

During the Dose Escalation visits (Weeks 2, 4 and 6 in SoA), the dose is to be increased as appropriate for the individual patient's weight at enrollment. At each visit, the decision to escalate the dose is to be based on patients' tolerability and health status. If a patient has already achieved their final maintenance dose prior to Week 4 or 6, the subsequent visits will not be considered "dose escalation" visits, but rather standard visits.

It is recommended to maintain a 2-week interval between the dose escalations, although the dose may be escalated at a longer interval (i.e., within 4 weeks), depending on patient weight and tolerability.

If it is not possible to achieve the final maintenance dose by Week 6 due to tolerability concerns (e.g., severe gastrointestinal adverse events) or due to potential effects on weight or hunger levels, the dose may be escalated over the next visit(s) (Week 8, etc.), with trial visits continued as per protocol. There is no need to perform an Unscheduled Visit 2 weeks after escalation of the dose unless it is required for patient safety.

7.4. Concomitant Medications

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

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

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

The dose of concomitant medications used during the trial should not be changed and new concomitant medications should not be started during the trial, unless necessary to treat an AE.

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

7.5. Treatment Compliance

Treatment compliance will be recorded by the pediatric patient's caregiver. A daily question querying whether the patient completed their daily injection will be asked via electronic diary. With Sponsor approval, paper versions can be used, if required.

7.6. Randomization and Blinding

This is an open-label trial with a single treatment arm, therefore there is no randomization and the treatment is unblinded.

8. ASSESSMENTS

Trial procedures and their timing are summarized in the SoA (Table 1). Adherence to the trial design requirements, including those specified in the SoA, is essential and required for trial conduct.

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

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

A visiting home nurse may assist with injections at home if requested by families, provided that a caregiver needs or desires assistance, and this is acceptable to the investigative site.

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

8.1. General Trial Assessments

8.1.1. Informed Consent/Assent

A complete description of the trial is to be presented to the parent/legal guardian(s) of each potential patient and signed and dated. Informed consent/assent is to be obtained before any study- specific procedures are performed. In the event of an amendment to the informed consent, reconsent by the patient or parent/legal guardian is necessary.

A copy of the informed consent/assent must be provided to the patient or the parent/legal guardian.

8.1.2. Demographic/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.

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.

Additionally, weight-related history including growth charts since birth should be obtained and reported.

8.1.3. Genetic Sample

A blood sample will be obtained at baseline to confirm a genetic diagnosis. However, patients may be entered into the trial with documentation of previously obtained genetic results.

8.1.4. Physical Examination

A complete physical examination will be conducted at Screening and at the EOT visit. At other timepoints, an abbreviated examination will be performed. The abbreviated examination should focus on heart, lungs, skin, neurologic examination, and any areas of previous abnormal findings, noting any changes from baseline. Tanner staging should be performed at Screening and at the EOT visit (Week 52) visit. It may be done at additional visits, at the discretion of the Investigator.

8.1.5. Electrocardiogram (ECG)

A single 12-lead ECG will be performed at the time points designated in the SoA (Table 1). If an ECG is not practical in a young patient, it may be replaced by a rhythm strip and HR and pulse rate interval should be documented. The ECG (or HR and pulse rate) results will be interpreted locally by the investigator or qualified designee and documented in the patient's medical records.

8.1.6. Comprehensive Skin Evaluation

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

Protection from Sun

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

8.1.7. Fitzpatrick Scale

Each patient is to be categorized for skin type according to the Fitzpatrick scale (Fitzpatrick1975) at timepoints listed in the SoA. The Fitzpatrick Scale is presented Appendix 3.

8.2. Efficacy Assessments

8.2.1. Weight and Height

Weight (kg) and height (cm) will be recorded at the time points designated in the SoA (Table 1). All measurements will be done in triplicate at each time point.

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 decimal place if reported with a digital scale, or half kg with a mechanical scale.

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

Patient's weight will be monitored closely during the trial. If a patient's weight decreases to below 15 kg, the Investigator and Sponsor will discuss the patient's status and will jointly determine if that patient should continue the current dose, decrease the dose or discontinue treatment with setmelanotide temporarily or permanently. A dose reduction to 0.25 mg QD can be considered in such scenarios or in case of tolerability concerns. These dose adjustments are considered adequate to help attain and maintain appropriate body weight in growing pediatric patients

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. Both weight and height measurements will be used to determine BMI and BMI-related assessments (i.e., Z-score and percentiles).

[redacted]

8.2.3. Trial questionnaires

[redacted]

8.2.3.2. Ages & Stages Questionnaires®, Third Edition (ASQ®-3)

The ASQ-3 is a developmental screening tool that assesses developmental progress in children between one month to 5 ½ years (). The ASQ-3 is intended for use at six-month intervals between 6 months and 3 years of age, and then at one-year intervals through age 5.

For patients who enter the study at ages between 2 years and 3 years, the ASQ-3 will be administered at the Baseline visit, Week 28 visit and EOT Visit. For patients who enter the trial between the ages of 3 and 6 years old, the ASQ-3 will only be administered at the Baseline visit and EOT visit.

Timepoints are as depicted in the SOA (Table 1).

8.3. Safety Assessments

8.3.1. Vital Signs

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

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

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

8.3.2. Laboratory Assessments

Safety laboratory test parameters to be evaluated are listed in Table 7.

The Investigators will adhere to the site-specific blood volume limits for safety laboratory and [redacted] analyses to ensure minimal distress to the pediatric patients. Due to the age of the children, it may not be possible to collect all labs at every trial visit. Screening may be completed over multiple days, to complete the required assessments. After enrollment, if all laboratory tests are not possible, then the tests should be collected in the following order: safety, anti-drug antibodies, [redacted]. If it is not possible to collect the safety laboratory tests on two consecutive visits, the patient should be discussed with the Sponsor. To allow for pre- and post-dose sampling, patients will attend the site visit having fasted for an 8-hour time period without injecting the trial product. On the day of the site visit, dosing will be conducted on site.

Table 7: Safety Laboratory Tests

Hematology	
• Complete Blood Count with Differential: – Hematocrit – Hemoglobin – White Blood Cells with differential – Red Blood Cells – Platelet Count	
Serum Chemistry	
• Sodium • Potassium • Chloride • Carbon dioxide • Creatinine • Blood urea nitrogen • Glucose • Calcium • Phosphorus • Thyroid stimulating hormone	• Alkaline phosphatase • Aspartate aminotransferase • Alanine aminotransferase • Gamma glutamyl transferase • Creatine phosphokinase • Total and direct bilirubin • Lactate dehydrogenase • Albumin • Total protein • Uric acid
Urinalysis	
• Color • Appearance • Specific Gravity • pH • Blood • Ketones	

[redacted]

8.5. Anti-Drug Antibodies

Blood samples for analysis of ADAs will be collected at the time points specified in the SoA. All samples should be collected before trial treatment administration on the day of collection. Any patient with a positive ADA will be followed every 3 months after the ADA sample analysis until resolution of the ADA (ie, no measurable ADA response).

8.6. Adverse and Serious Adverse Events

Adverse events (AEs) will be monitored throughout the trial. AEs will be recorded in the eCRFs from Screening through the EOS visit. AEs that occur after the start of trial drug administration will be considered treatment-emergent adverse events (TEAEs). Serious AEs (SAEs) will be recorded through to the EOS visit. All AEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

All trial sites will be provided with the contact information of key trial personnel to be contacted in case of emergencies.

8.6.1. Definition of Adverse Events

8.6.1.1. Adverse Event (AE)

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug related. Patients/caregivers will be instructed to contact the Investigator at any time after a patient has been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, if any symptoms develop.

A TEAE is defined as any event not present before exposure to trial drug or any event already present that worsens in intensity or frequency after exposure.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the trial drug caused the AE. For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the trial drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

An adverse reaction is any AE caused by a trial drug. Adverse reactions belong to a subset of all suspected adverse reactions and indicate that there are reasons to conclude that the trial drug caused the event.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Reference Safety Information section of the Investigator brochure or if it occurs with specificity or severity that has not been previously observed with the trial drug being tested; or, if an Investigator brochure is not required or available, the AE or suspected adverse reaction is not consistent with the risk information described in the general investigational plan or elsewhere in

the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

All AEs that occur after any patient has been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the trial, must be recorded on forms provided by the Sponsor.

8.6.1.2. Serious Adverse Event (SAE)

An SAE is an AE occurring during any trial phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

- Results in death
- It is immediately life-threatening
- Note: "Life-threatening" refers to a situation in which the subject was at risk of death at the time of the event; it does not refer to an event which might have caused death if it were more severe.
- It requires in-patient hospitalization or prolongation of existing hospitalization
- Note: AEs requiring hospital admissions that are less than 24 hours in duration do not meet this criterion. A scheduled hospitalization for a pre-existing condition that has not worsened during participation in the trial does not meet this criterion. Pre-planned hospitalizations for an elective medical/surgical procedure or routine check-ups do not meet this criterion.
- It results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- It is a congenital anomaly/birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

  Note: Important medical events are those that may not result in death, be life threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

All SAEs that occur after any patient has been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the trial, must be recorded on forms provided by the Sponsor.

8.6.2. Relationship to Trial Drug

A medically-qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product, 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 drug exposure and onset of the AE
- Whether the manifestations of the AE are consistent with known actions or toxicity of the investigational product
- Dechallenge: The AE resolved or improved with decreasing the dose or stopping use of the investigational product. Judgment should be used if multiple products are discontinued at the same time
- Rechallenge: The AE recurred or worsened upon re-exposure to the investigational product.

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

Not Related: An AE is not associated with trial drug if:

- 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); or
- Dechallenge was either not clinically indicated or did not result in clinical improvement; or
- AE did not reoccur upon rechallenge (if applicable).

Related: An AE is attributed to the trial drug if:

- There is a positive temporal relationship (e.g., the event occurred within a reasonable time frame following administration of trial drug); and
- 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 investigational product), or the event improved on dechallenge and/or re-occurred upon rechallenge (if applicable).

8.6.3. Overdose

An overdose is a significant variation from the recommended/scheduled dosage for a product. For this trial, an overdose of setmelanotide is considered a dose higher than:

- 2 mg in any patient
- 1.5 mg in patients with body weight [redacted]
- 1.0 mg in patients with body weight [redacted]
- 0.5 mg in patients with body weight [redacted]

8.6.4. Recording Adverse Events

AEs spontaneously reported by the patient/caregiver and/or in response to an open question from the trial personnel or revealed by observation will be recorded during the trial at the investigational site.

Clinically significant changes in laboratory values, BP, and pulse need not be reported as AEs. However, abnormal values that constitute an SAE or lead to discontinuation of administration of trial drug must be reported and recorded as an AE.

AEs will be recorded from obtaining consent until the end of the trial. SAE information will be collected from obtaining consent until EOS. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the trial.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. A severe AE may not be considered serious.

8.6.5. Reporting Adverse Events

All AEs reported or observed during the trial will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, type of event, time of onset, dosage, Investigator-specified assessment of severity and relationship to trial drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Any AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved, stable, or judged by the Investigator to be not clinically significant. The MedDRA will be used to code all AEs. Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the trial, it should be recorded as an AE.

A referral to a mental health practitioner should be issued to the patient for any instance of reported AEs indicative of a change in mental health status.

8.6.6. Reporting of Expedited Safety Observations by the Investigator

Any occurrence of the following events or outcomes in a subject in the trial must be reported expeditiously by the Investigator or qualified designee to the Sponsor via an SAE form:

- SAE
- Death of a subject
- Overdose
- Cancer

The Investigator is to report any of the items in the list above within24 hours of becoming aware of the event. Any observation reported to The Sponsor that is also an AE, is to be recorded in the eCRF, as well as in the subject's source documentation along with any actions taken. If not all information is available at the time of the initial report, follow-up SAE reports will be completed and submitted. The Investigator is required to follow SAEs until resolution regardless of whether the patients are still participating in the trial. Resolution is defined as follows:

- Resolved with or without residual effects
- A return to baseline for a pre-existing condition
- The Investigator does not expect any further improvement or worsening of the event
- Fatal outcome -If an autopsy is performed on a deceased subject, the autopsy report must be provided to the Sponsor as soon as it is available.

9. STATISTICS

Details of all statistical analyses will be described in a separate Statistical Analysis Plan (SAP).

9.1. Sample Size Determination

No formal sample size determination was made based on statistical inference. The sample size is not driven by statistical power considerations but is primarily driven by clinical and practical considerations. Given the rare patient population, the trial plans to enroll approximately 10-15 patients (approximately 5 or more pediatric patients with biallelic mutations of the *POMC*, *PCSK1* or *LEPR* genes and approximately 5 or more pediatric patients with BBS).

9.2. Statistical Analyses

The primary objective is to evaluate the effect of setmelanotide on weight-related parameters measured in terms of the response rate to setmelanotide. Due to the small sample size of the trial, no statistical hypothesis testing is planned, and efficacy will be reported using descriptive statistics. The safety population, including all patients who receive at least 1 dose of setmelanotide, will be used as the primary analysis population for all the analyses.

AEs will be coded by preferred term (PT) and system organ class (SOC) using the latest version of MedDRA and summarized. All AE data will be presented in a data listing. TEAEs will be summarized, including by severity and relationship to trial drug. Serious AEs and AEs leading to early discontinuation will also be presented in data listings.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements etc. will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results. Clinical laboratory test results, vital sign measurements etc. will be presented in data listings.

The secondary objectives are to evaluate the effect of setmelanotide on additional weight-related parameters, as well as safety and tolerability. [redacted] No statistical hypothesis was made. The collected parameters will be summarized with appropriate descriptive statistics.

Due to the small sample size, summary statistics by genotype may be provided as appropriate.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

10.1. Trial Monitoring

During the trial, a monitor from The Sponsor or designee will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s) and site staff
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the trial. This will require direct access to all original records for each patient (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to The Sponsor
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to The Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between monitoring visits if the Investigator(s) or other staff needs information or advice.

10.1.1. Trial Conduct During the COVID-19 Pandemic

The worldwide Coronavirus Disease 2019 (COVID-19) pandemic may impact the conduct of clinical trials due to the challenges from quarantines, site closures, travel limitations, and other considerations if site personnel or patients become potentially exposed to or infected with COVID-19. To assure the safety of patients, maintain compliance with 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 2.

10.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IRB or IEC may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Council for Harmonisation (ICH), and any applicable regulatory requirements. The

Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

10.3. Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

The Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this trial including the written consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

10.4. 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 of 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.

11. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, The Sponsor may conduct a quality assurance audit.

12. ETHICS

12.1. Ethics Review

The final trial protocol, including the final version of the written consent, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enroll any patient into the trial.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the trial. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other trial conducted with the investigational product. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

12.2. Ethical Conduct of the Trial

The trial will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policy on Bioethics.

12.3. Written Informed Consent

The Investigator(s) at each site will ensure that the patient and their legal guardian are given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the trial. Patients and their legal guardian(s) must also be notified that they are free to discontinue from the trial at any time. The patients and their legal guardian(s) should be given the opportunity to ask questions and allowed time to consider the information provided.

The parent/legal guardian(s) signed and dated consent must be obtained before conducting any trial procedures.

The Investigator(s) must maintain the original, signed consent. A signed copy of the consent must be given to the parent/legal guardian(s).

13. DATA HANDLING AND RECORDKEEPING

13.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigate facilities for monitoring any aspect of the trial. The Investigator agrees to allow the monitor to inspect the drug storage area, trial drug stocks, drug accountability records, patient charts and trial source documents, and other records relative to trial conduct.

13.2. Retention of Records

The Investigator must maintain all documentation relating to the trial for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the trial, the Investigator must permit access to such records.

13.3. Data Protection

Any patient records or data sets transferred to the Sponsor will contain the trial 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 or IEC members, and by inspectors from regulatory authorities.

13.4. Data Quality Assurance

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

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

The Investigator must permit trial-related monitoring, audits, IRB 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 rIMV should be approved by the Sponsor on a case-by-case basis.

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

- Remote Source Data Monitoring (rSDM) visits: The CRA will verify data remotely, off site if unable to be at the site. The Site coordinator will show the CRA source data via Zoom or alternate teleconference portal.
- Remote Data Verification visits: The CRA will verify source data remotely, off-site if unable to be at the site.
- Audio Data Verification visits: An alternative approach for remote data verification of critical patient data, when Monitor asks an Investigator site staff member to read patient source documents during a telephone call while reviewing the eCRF to verify patient safety is protected and the data reported by Investigator (e.g., in the eCRF) is accurate and complete.
- Video Source Data Monitoring visits: Process for conducting rSDM 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 visits: the CRA will attend the site to review the investigator site file (ISF), investigative product (IP) supply, etc.

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

Records and documents, including signed informed consent forms, 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.

14. PUBLICATION POLICY

All information regarding setmelanotide supplied by the Sponsor to the Investigator or generated as a result of any clinical trials is privileged and confidential information belonging to the Sponsor. The Investigator agrees to use the Sponsor 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 trials 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.

15. LIST OF REFERENCES

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[redacted]

APPENDICES

APPENDIX 1. BEALES CRITERIA

BBS clinical diagnosis as per Beales 1999 (with either 4 primary features or 3 primary and 2 secondary features from table below):

Bardet-Biedl Syndrome	
Primary Diagnostic Criteria	
• Rod cone dystrophy	• Learning disabilities
• Polydactyly	• Hypogonadism in males
• Obesity	• Renal anomalies
Secondary Diagnostic Criteria	
• Speech disorder/delay	• Mild spasticity (especially lower limbs)
• Strabismus/cataracts/astigmatism	• Diabetes mellitus
• Brachydactyly/syndactyly	• Dental crowding/hypodontia/small roots/high arched palate
• Developmental delay	• Left ventricular hypertrophy/congenital heart disease
• Polyuria/polydipsia (nephrogenic diabetes insipidus)	• Hepatic fibrosis
• Ataxia/poor coordination	

APPENDIX 2. GUIDANCE ON TRIAL CONDUCT DURING THE COVID-19 PANDEMIC

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

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

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

- Where possible, every effort should be made to complete all protocol-required assessments. In place of a required site visit, a qualified healthcare provider could perform trial-related procedures as per the SoA (Table 1) via a home visit, including but not limited to collection of body weight, vital signs, physical examinations, ECGs, recording of 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-19 restrictions should be documented in detail within the patients' source documents and should be clearly designated as "COVID-19 RELATED". It must be documented if a site visit is instead conducted remotely. Source documentation should detail how each assessment was collected (e.g., remote vs. on-site, central vs. local laboratory, vital signs taken at home by caretaker vs. delegated in-home nursing, etc.).
- If applicable, discontinuations of trial interventions and withdrawal from the trial due to disruption of trial conduct by the pandemic should be documented with the prefix "COVID-19 RELATED" in the CRF.

COVID-19 Infection in Trial Patients:

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

APPENDIX 3. FITZPATRICK SCALE

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

Fitzpatrick 1975.