CLINICAL TRIAL PROTOCOL

Protocol RM-493-022

Long-Term Extension Trial of Setmelanotide (RM-493) for Patients Who Have Completed a Trial of Setmelanotide for the Treatment of Obesity Associated with Genetic Defects Upstream of the MC4 Receptor in the Leptin-Melanocortin Pathway

This extension trial applies to patients with rare genetic, syndromic, or acquired diseases of obesity and obesity potentially related to other abnormalities in the MC4 receptor pathway.

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

IND No.: [redacted]

EudraCT No.: 2017-005006-35

Trial Sponsor: Rhythm Pharmaceuticals, Inc.
[redacted]

Document Date (Version): 19 June 2023 (8.1)

[redacted]

SUMMARY OF CHANGES TO THE PROTOCOL

[redacted]

Key changes to the current version 8.1 (19 June 2023) of the protocol from version 8.0 (12 May 2023) are summarized below.

[redacted]

Key changes to version 8.0 of the protocol apply to changes from both version [redacted] except where noted and are summarized below.

Typographical and administrative changes were also made to improve the clarity of the document.

APPROVAL SIGNATURE PAGE

Protocol Title:	Long-Term Extension Trial of Setmelanotide (RM-493) for Patients Who Have Completed a Trial of Setmelanotide for the Treatment of Obesity Associated with Genetic Defects Upstream of the MC4 Receptor in the Leptin-Melanocortin Pathway ***This extension trial applies to patients with rare genetic, syndromic, or acquired diseases of obesity and obesity potentially related to other abnormalities in the MC4 receptor pathway.***
Protocol Number:	RM-493-022
Document Version:	Version 8.1
Document Date:	19 June 2023

REVIEWED/APPROVED BY:

[redacted]

[redacted]
Rhythm Pharmaceuticals, Inc.

Signature

Date

INVESTIGATOR STATEMENT

Protocol Title:	Long-Term Extension Trial of Setmelanotide (RM-493) for Patients Who Have Completed a Trial of Setmelanotide for the Treatment of Obesity Associated with Genetic Defects Upstream of the MC4 Receptor in the Leptin-Melanocortin Pathway ***This extension trial applies to patients with rare genetic, syndromic, or acquired diseases of obesity and obesity potentially related to other abnormalities in the MC4 receptor pathway.***
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I understand that all documentation provided to me by Rhythm Pharmaceuticals, Inc. (Rhythm; the sponsor) or its designated representative(s) concerning this trial that has not been published previously will be kept in the strictest confidence. This documentation includes the trial protocol, Investigator 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/Independent Ethics Committee. No changes will be made to the trial protocol without the prior written approval of the sponsor and the Institutional Review Board/Independent Ethics Committee, 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	Investigator Signature	Date

Investigational site or name of institution and location (printed)

CLINICAL TRIAL SYNOPSIS

Sponsor	Rhythm Pharmaceuticals, Inc.
Investigational Drug Product	Setmelanotide (RM-493)
Protocol Number	RM-493-022
Protocol Title	Long-Term Extension Trial of Setmelanotide (RM-493) for Patients Who Have Completed a Trial of Setmelanotide for the Treatment of Obesity Associated with Genetic Defects Upstream of the MC4 Receptor in the Leptin-Melanocortin Pathway ***This extension trial applies to patients with rare genetic, syndromic, or acquired diseases of obesity and obesity potentially related to other abnormalities in the MC4 receptor pathway.***
Clinical Phase/Trial Type	Open-label active treatment extension trial (Phase 2/3)
Treatment Indication	Treatment of obesity associated with genetic defects upstream of the MC4 receptor (MC4R) in the leptin-melanocortin pathway and with obesity related to other abnormalities in the MC4R pathway.
Objective(s)	<u>Primary</u> • To characterize safety and tolerability of setmelanotide in patients who have completed a previous trial on treatment with setmelanotide for obesity associated with genetic defects upstream of the MC4R in the leptin-melanocortin pathway and with obesity related to other abnormalities in the MC4R pathway. [redacted]
Trial Design	This is a long-term (treatment for up to 7 years) extension trial designed to evaluate the safety and tolerability of continued

	setmelanotide treatment in patients who have completed a previous clinical trial on treatment with setmelanotide for rare genetic, syndromic, or acquired diseases of obesity upstream of the MC4R in the melanocortin-leptin pathway and other abnormalities of the MC4R pathway. Patients who complete treatment in a previous trial (index trial) of setmelanotide and wish to continue with setmelanotide treatment will be considered for eligibility to enter this extension trial. Patients (or their legal guardians) will provide informed consent/assent to participate in this extension trial, and eligibility will be confirmed prior to completion of their index trial. Visit 1 of this trial will coincide with the final visit of the index trial; see Table 1 for details. Generally, there should be no gaps in treatment during the transition from the index trial to this extension trial. A gap in treatment between the index trial and extension trial may be allowed for individual patients, with approval by the sponsor. Patients will begin this extension trial on the same dose of setmelanotide that they were taking when they completed their index trial. Patients who received double-blind study drug in a placebo-controlled index trial will start open-label setmelanotide in this trial, with the starting dose from the index trial. The dose titration should follow the scheme in the index trial and in consultation with the sponsor. Patients will be evaluated approximately every 3 months at the trial site for adverse events (AEs), concomitant medications, [redacted] height (in children), [redacted] Additional tests will be completed at longer trial visit intervals.
Trial Population	Male and female patients who have completed all critical trial evaluations in a previous setmelanotide trial and would benefit from continued setmelanotide treatment.
Number of Patients & Trial Centers	It is anticipated that any patient receiving active therapy from a setmelanotide clinical trial and experiencing improvements in weight-related parameters could be a candidate for enrollment in this extension trial. Based on the number of patients currently enrolled or planned for enrolment in current or future setmelanotide clinical trials, it is anticipated that up to 500 patients may be enrolled in this trial; however, expansion in enrollment may occur if additional patients with obesity due to monogenic, syndromic or acquired disorders affecting the MC4R pathway are enrolled in Phase 2 or Phase 3 clinical trials evaluating setmelanotide. It is anticipated that up to 100 centers located worldwide will participate in this trial. In the event additional patients are to be enrolled, additional sites may be added, as necessary.

Inclusion Criteria	1. Patients aged 2 or older (or aged >2 years as per local regulations; only patients aged 12 years or older may be enrolled in the trial in Greece; only patients 6 years or older may be enrolled in the trial in Germany) who have completed participation in a previous setmelanotide clinical trial. 2. If patient received setmelanotide on an open-label basis in a previous setmelanotide clinical trial, patient demonstrated adequate safety and meaningful clinical benefit (efficacy) in the previous setmelanotide trial. Meaningful clinical benefit is defined as follows: • Patients 18 years of age or younger that have completed participation on active drug and demonstrated adequate safety and at least 3% BMI reduction or reduction in BMI Z-score of 0.2 compared to baseline. • Patients over 18 years of age should show reduction of 3% BMI compared to baseline. If the patient participated on a double-blind basis in the previous placebo-controlled clinical trial, patient tolerated blinded study drug. 3. Patient and/or parent or guardian is able to communicate well with the investigator, to understand and comply with the requirements of the trial, and to understand and sign the written informed consent/assent. The patient must consent/assent to participate in the trial. 4. Patient must meet one of the following requirements regarding contraception: • If a female of childbearing potential, defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), must use a highly effective form of contraception as outlined in Section 6.2.1. • If a female of non-childbearing potential, defined as permanently sterile (status post hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or post-menopausal for at least 12 months (and confirmed with a screening follicle-stimulating hormone (FSH) level in

	the post-menopausal laboratory range), contraception is not required during the trial. – Younger female patients who have not reached menarche upon trial entry will be assessed for Tanner staging and at first menarche will be required to comply with contraception requirements and pregnancy testing as outlined in the protocol. • If a male with female partner(s) of childbearing potential, must agree to a double barrier method if they become sexually active during the trial. Furthermore, male patients must not donate sperm during and for 90 days following their participation in the trial.
Exclusion Criteria	1. Pregnant and/or breastfeeding women. 2. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a screening comprehensive skin evaluation performed by a qualified dermatologist. Any concerning lesions identified during the screening period 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. 3. Patient is, in the opinion of the investigator, not suitable to participate in the trial. 4. Current, clinically significant disease, if severe enough to interfere with the trial and/or would confound the results. Any such patients should be discussed with the sponsor prior to enrollment in the trial. 5. Diagnosis of schizophrenia, bipolar disorder or other psychiatric disorder that the investigator believes will interfere significantly with trial compliance. 6. A Patient Health Questionnaire-9 (PHQ-9) score of ≥15. 7. Any suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS). Any lifetime history of a suicide attempt, or any suicidal behavior since the last visit in the index trial. *Note:* Patients who are unable to complete the C-SSRS due to significant neurocognitive defects may be enrolled in the trial, as long as in the opinion of the investigator there are no clinical signs or symptoms of suicidal behavior. 8. History of significant liver disease or liver injury, or a current liver assessment due to abnormal liver tests (as indicated by abnormal liver function tests, alanine transaminase [ALT],

	aspartate transaminase [AST], alkaline phosphatase, or serum bilirubin >1.5× the upper limit of normal [ULN] for any of these tests) for an etiology other than non-alcoholic fatty liver disease (NAFLD). Thus, any underlying etiology besides NAFLD, including diagnosed non-alcoholic steatohepatitis (NASH), other causes of hepatitis, or history of hepatic cirrhosis is exclusionary, but the presence of NAFLD is not exclusionary. 9. Severe renal dysfunction defined by a glomerular filtration rate (GFR) <30 mL/min/1.73 m^2 in patients <12 years of age or end stage renal disease (GFR <15 mL min/1.73 m^2 (see Appendix 11.4 for GFR calculation). 10. History or close family history (parents or siblings) of skin cancer or melanoma (not including non-invasive/infiltrative basal or squamous cell lesion), or patient history of ocular-cutaneous albinism.
Trial Procedures	The safety and tolerability of setmelanotide will be assessed by the frequency and severity of AEs as well as changes in physical examinations, electrocardiograms (ECGs), vital signs, laboratory evaluations, and injection site reactions. [redacted]
Study Drug and Administration	All study drugs are for investigational use only and are to be used only within the context of this protocol. Setmelanotide will be supplied by the sponsor. [redacted] Setmelanotide will be administered as a subcutaneous (SC) injection once daily. Setmelanotide doses and titration steps will follow the index trial scheme (Section 5.2).
Statistical Considerations	A detailed Statistical Analysis Plan will describe all analyses for this extension trial. A by-patient AE data listing including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided.

	Safety data including laboratory evaluations and vital signs assessments will be summarized by time of collection. In addition, change from baseline to any post-dose values will be summarized for vital signs and clinical laboratory results. Frequency of patients with abnormal safety laboratory results will be tabulated. [redacted] This protocol includes a variety of patient populations with very rare genetic, syndromic or acquired diseases of obesity. Each population may be analyzed separately as long as ≥2 patients are enrolled and complete at least 6 additional months of treatment. Safety and efficacy data from both the index and extension trials can be combined to evaluate long-term safety and efficacy outcomes on a patient specific and population basis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug (i.e., setmelanotide) antibody
AE	Adverse event
ALT	Alanine transaminase
ARC	Arcuate nucleus of the hypothalamus
AS	Alström syndrome
AST	Aspartate transaminase
[redacted]	
BBS	Bardet-Biedl syndrome
BBSx	Bardet-Biedl syndrome-associated genes
[redacted]	
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
[redacted]	
CMHL	Combined medial hypothalamic lesion
CO_2	Carbon dioxide
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRA	Clinical research associate
CRF	Case report form
CRO	Contract research organization

Abbreviation	Definition
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	
DSM-III	Diagnostic and Statistical Manual of Mental Disorders Third Edition
[redacted]	
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Early termination
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
[redacted]	
HbA1c	Glycated hemoglobin
HO	Hypothalamic obesity
HR	Heart rate
[redacted]	
IB	Investigator Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	Intrauterine device
[redacted]	[redacted]
Ki	Inhibitory constant
LDH	Lactate dehydrogenase
LEP	Leptin hormone
LEPR	Leptin receptor
MC4R	Melanocortin-4 receptor
MedDRA	Medical Dictionary for Regulatory Activities
MHP	Mental health professional

Abbreviation	Definition
MSH	Melanocyte stimulating hormone
MTII	Melanotan II
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NDA	New Drug Application
NHLBI	National Heart, Lung, and Blood Institute
[redacted]	
PCSK1	Proprotein Convertase Subtilisin/Kexin Type 1
[redacted]	
POMC	Pro-opiomelanocortin
PPL	POMC/PCSK1/LEPR
[redacted]	
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SF-10	10-Item Short Form Health Survey for Children
SH2B1	SH2B Adaptor Protein 1
SMS	Smith-Magenis syndrome
SOA	Schedule of assessments
SRC1	Steroid receptor coactivator-1
[redacted]	
T4	Thyroxine
[redacted]	
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
VMN	Ventromedial nucleus of the hypothalamus

Abbreviation	Definition
[redacted]	
WOCBP	Woman of childbearing potential
[redacted]	

1. INTRODUCTION

Rhythm (the sponsor) is focusing the development of setmelanotide as a treatment for patients with rare genetic, syndromic, or acquired diseases of obesity due to specific genetic defects that impact the functioning of the melanocortin-4 receptor (MC4R) pathway, a highly conserved hypothalamic pathway critical for regulation of appetite, energy expenditure, and body weight. The MC4R pathway is the key pathway regulating body weight and appetite. Genetic or acquired defects in the MC4R pathway and other abnormalities of the MC4R pathway cause hyperphagia, an insatiable hunger, leading to severe and early-onset obesity.

The focus of setmelanotide development is on hyperphagia and obesity arising from lack of activation of MC4Rs and lack of "downstream signaling" due to genetic variants or other impairments "upstream" of the MC4R. By activating the MC4R with setmelanotide (a MC4R agonist), signaling occurs in the "downstream" portion of the pathway, and thereby setmelanotide is hypothesized to provide compelling and persistent efficacy on the regulation of appetite and body weight.

Human genetics studies have identified several diseases that are the result of genetic defects affecting the MC4R pathway, for example, syndromes or variants of the following genes:

- Pro-opiomelanocortin (POMC)
- Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1)
- Leptin receptor (LEPR)/leptin hormone (LEP)
- Bardet-Biedl syndrome (BBS)
- Alström syndrome (AS)
- Smith-Magenis syndrome (SMS)
- SH2B Adaptor Protein 1 (SH2B1), including 16p11.2 deletion
- Nuclear receptor coactivator-1 (NCOA1), also referred to as steroid receptor coactivator 1 (SRC1)
- MC4R

Central melanocortin signaling is the central element of energy homeostasis (Holland 2019). Somewhat similar to patients with genetic variants in the MC4R pathway, in patients with hypothalamic lesions, leptin signaling is often disturbed and as a result melanocortin signaling is reduced (Enriori 2016; Roth 1998; Roth 2010; Patel 2002; Shaikh 2008). Imaging studies in humans and rodent models show that lesions of the ventromedial nucleus of the hypothalamus (VMN) and the region of the arcuate nucleus (ARC), are more often associated with hyperphagia and excessive weight gain (Ahmet 2006; DeVile 1996; Roth 2011; Daousi 2005; Holmer 2010; Elfers 2011).

Hypothalamic obesity (HO) is a form of severe obesity that arises from mechanical hypothalamic lesions/insults (e.g., tumors, tumor resections, radiotherapy treatment). Lesions of the hypothalamus can derive from various types of tumors (craniopharyngiomas, gliomas, pituitary adenomas, hamartomas) as well as from the surgeries and radiotherapies for the treatment of the tumor itself. Patients with HO display a higher degree of hyperleptinemia and hyperinsulinemia

when compared to individuals with normal body mass indexes (BMIs). Alpha-melanocortin stimulating hormone (α-MSH) can be detectable in blood, and its levels can change depending on different energy states (Enriori 2016); however, in patients with craniopharyngioma or post-surgical treatment for it, α-MSH levels are significantly reduced (Roth 2010; Roth 2011). Reduced serum α-MSH levels suggest melanocortin pathway deficiency, which might explain lower energy expenditure in peripheral tissues due to reduced fat and muscle fatty acid oxidation (Roth 2010; Roth 2011; An 2007).

In a rat model of "combined medial hypothalamic lesion" (CMHL rat model) for HO (Roth 2011), Roth et al found that the characteristic metabolic changes of human HO were recapitulated when the lesion included the rat ARC. In this rat model, α-MSH levels are reduced (Roth 2011), similar to patients with craniopharyngioma (Roth 2010).

Additionally, an MC3/4 receptor agonist, melanotan II (MTII) 1 mg/kg/day administered intraperitoneally over a period of 14 days, resulted in a robust reduction of weight gain in CMHL rats without rebound/tachyphylaxia (Roth 2012). Preclinical and clinical findings offer a rationale for a novel melanocortin treatment also in patients with HO to compensate for and potentiate defective leptin signaling.

Overall, nonclinical and clinical data demonstrate that setmelanotide restores normal hunger, satiety, and energy expenditure regulation, leading to profound reduction of excess weight, in essence as a form of "replacement therapy". Setmelanotide is authorized for marketing in the United States (US), Great Britain (GB), Israel, the European Union (EU),and Canada in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1, or LEPR (PPL) deficiency (USPI 2022; EU SmPC 2022; MHRA SmPC 2021; Israel PPI 2022; Product Monograph 2023). Additionally, setmelanotide is also approved in the US, EU, and Canada to treat chronic weight management in adult and pediatric patients 6 years of age or older with monogenic or syndromic obesity due to BBS (USPI 2022, SmPC 2022, Product Monograph 2023). The clinical testing and regulatory approval of setmelanotide in certain countries have established its therapeutic value. This trial will continue to explore the long-term safety and tolerability of setmelanotide in patients who have successfully completed a prior index trial of setmelanotide. Trial participation may continue for up to 7 years or until setmelanotide is otherwise available through authorized use, or unless there is not a clinically meaningful treatment effect.

Patients may enter this trial immediately upon completion of their index trial such that dosing of setmelanotide continues without gaps in therapy, if possible. Patients may also enter this trial from the extension phases of any prior index trial. Efforts should be made to have the last visit of a prior index trial or an index trial extension phase and the initial visit of this long-term extension trial occur on the same day, if possible.

An index trial is defined as any setmelanotide trial in which a patient participated prior to enrollment in this extension trial.

1.1. Setmelanotide Background and Clinical Experience

Setmelanotide is an 8-amino acid, cyclic peptide that binds with high affinity (inhibitory constant [Ki] = 2.1 nM) to the human MC4R and is efficient in activating MC4R (50% effective concentration [EC_{50}] = 0.27 nM).

1.1.1. Clinical Background and Benefit–Risk Assessment

Nonclinical and clinical data generated to date with setmelanotide described in the Investigator Brochure (IB) provide meaningful information to support the benefit–risk assessment for the proposed use of setmelanotide in the current trial, a long-term extension trial for clinical evaluation of long-term treatment of obesity associated with genetic defects in the leptin-melanocortin pathway upstream of the MC4R and other abnormalities of the MC4R pathway.

The current clinical development program for setmelanotide is focused on rare monogenic forms of early-onset, severe obesity, including POMC deficiency obesity, LEPR deficiency obesity, and other genetic forms of early-onset, severe obesity with involvement of the leptin-MC4R pathway in their pathogenesis, including epigenetic obesity, PPL heterozygous obesity, and potentially other genetic and/or syndromic forms of obesity, and other abnormalities of the MC4R pathway, such as HO.

Informative clinical data from the initial phases of these trials in patients with early-onset severe obesity due to rare bi-allelic mutations in the *POMC* and *LEPR* genes, as well as BBS, are available and were published or presented at scientific meetings. The evolving profile of weight-related and hunger symptom reduction demonstrated with chronic setmelanotide treatment is important to consider, as these findings inform the overall benefit–risk consideration of setmelanotide.

In adult patients who tolerate the 3 mg QD dose level, if additional effect on [redacted] is desired in the current trial, a higher QD dose can be administered at the investigator's discretion and in consultation with the sponsor. The dose can be increased up to 4 mg QD, in patients with an absolute weight of >50 kg, and up to 5 mg QD in adult patients with an absolute weight of >60 kg. These dose levels have been investigated previously in trial RM-493-026. Adult patients exposed to these higher dose levels should be monitored closely via additional unscheduled visits or telephone calls to assess safety and tolerability. For patients who escalate to 4 or 5 mg QD, the dose level should be reduced to 3 mg and 4 mg if their absolute weight decreases to ≤50 kg and ≤60 kg, respectively. The maximum dose of setmelanotide is limited by absolute body weight (kg) in order to maintain exposure to excipients in the setmelanotide formulation at a lower level than those currently approved for other commercially available medicinal products (see Section 3.2 for further details).

Overall, the expected benefit–risk assessment supports continued evaluation of setmelanotide in these rare patient populations with high unmet medical needs.

Refer to the Investigator Brochure for data regarding setmelanotide administration at doses up to 5 mg.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1. Trial Objectives

2.1.1. Primary Objective

- To characterize safety and tolerability of setmelanotide in patients who have completed a previous trial on treatment with setmelanotide for obesity associated with

genetic defects upstream of the MC4R in the leptin-melanocortin pathway or with obesity related to other abnormalities in the MC4R pathway.

2.1.2. Exploratory Objectives

[redacted]

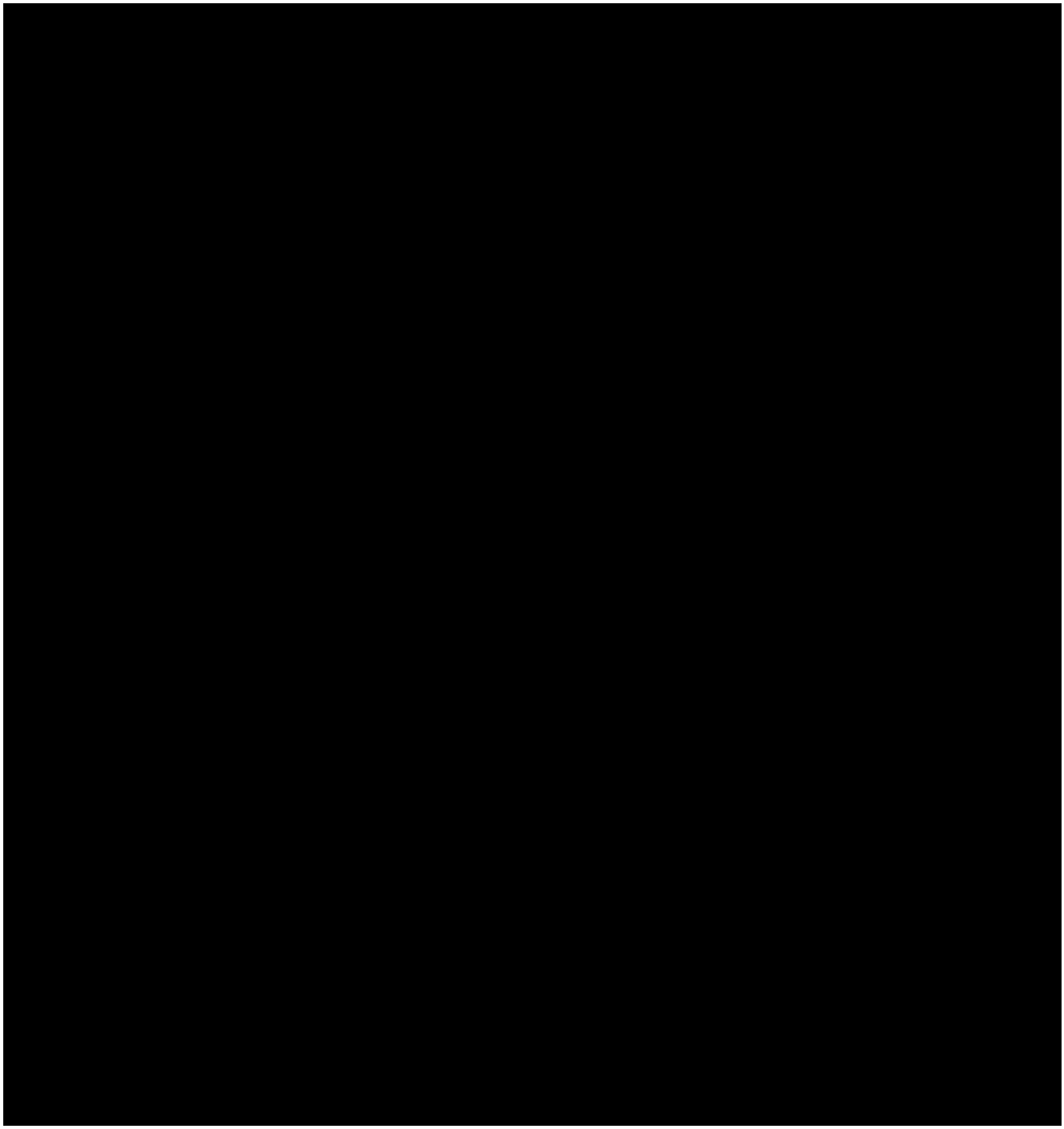
2.2. Trial Endpoints

2.2.1. Primary Endpoint

The safety and tolerability of setmelanotide, as assessed by the frequency and severity of AEs, as well as changes in physical examinations, vital signs, laboratory evaluations, and injection site reactions.

2.2.2. [redacted]

[redacted]



3. INVESTIGATIONAL PLAN

3.1. Overall Design and Plan of the Trial

This is an extension trial of up to an additional 7 years duration for patients who have completed a previous trial of setmelanotide for rare genetic, syndromic, or acquired diseases of obesity upstream of the MC4R in the melanocortin-leptin pathway and other abnormalities of the MC4R pathway. Since continued assessments of the safety and efficacy of setmelanotide are the same in this extension trial regardless of the disease studied in the index trial, all patients can be followed

in this single extension trial. Nevertheless, the analysis of each sub-population will be performed separately with the ability to combine data from the original index trial and this extension trial on a disease-specific basis.

For patients who qualify and provide consent, the trial will start immediately on the completion of their index protocol such that there are no gaps in treatment, if possible. Efforts should be made to have the last visit of a prior index trial or an index trial extension phase and the initial visit of this long-term extension trial to occur on the same day, if possible.

Patients will be assessed in the clinic approximately every 3 months for vital signs, AEs, concomitant medications, [redacted] height (in children), [redacted] Safety laboratory samples will be collected at each visit and additional assessments will be done on a yearly basis. In general assessments will be less frequent and burdensome than was required in their index protocol.

Unscheduled clinic and/or telephone visits may be added at the discretion of the investigator to follow any changes in dose or adverse event, as required.

3.2. Justification of the Trial Design

Setmelanotide may be administered chronically; therefore, it is important to evaluate its long-term safety and efficacy.

Assessments of vital signs, AEs, [redacted], height (in children), [redacted] conducted approximately every 3 months along with selected less frequent assessments should be adequate to achieve these goals. Since eligibility and trial assessments in this extension trial are the same regardless of which index protocol the patient completed, the objective of long-term follow-up for each sub-population cohort can be achieved within this single extension protocol. When desired, data from individual index protocols can be combined with data obtained in this extension protocol to evaluate the safety and efficacy of the entire setmelanotide exposure of a single patient or group of patients with a specific disease within the MC4R pathway.

The trial has been designed for continued administration of setmelanotide in patients who have demonstrated benefits from receiving setmelanotide in a previous index trial. Patients who received setmelanotide on an open-label basis in the index trial will begin this extension trial on the same dose of setmelanotide they were taking when they completed their index trial, unless tolerability or safety reasons justify a dose decrease, or if additional potential clinical effect is desired on [redacted] a dose increase is justified; setmelanotide doses >5 mg are not permitted. Patients who participated in a placebo-controlled index trial will start open-label setmelanotide in this trial with the starting dose from the index trial, based on the patient's age and weight. Dose titration should follow the scheme in the index trial and in consultation with the sponsor.

3.2.1. Rationale for Setmelanotide Administration at Doses Up to 5 mg

While the target dose of setmelanotide is 3 mg QD, nonclinical and clinical data support dose escalation up to 5 mg QD in adult patients in this trial. For additional information, see Section 5.2.1 and the IB.

[redacted]

Refer to the IB for additional information.

3.3. Patient, Cohort or Trial Termination

A specific gene cohort (or gene variants or subset of variants) or the whole trial may be terminated, if in the opinion of the investigator (at a participating site) or the sponsor there is sufficiently reasonable cause. The terminating party will provide written notification. documenting the reason for trial termination to either the investigator or the sponsor.

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

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

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

3.4. Transition into Another Rhythm Trial

Patients enrolled in this extension trial may exit the trial to participate in other setmelanotide clinical trials with the patient's (or legal guardian's) written informed consent, at the discretion of the investigator and sponsor. The patient is to complete the extension Transition Visit prior to commencing treatment in the other setmelanotide clinical trial; applicable data from this visit will serve as Screening data for the other trial. After completion of the Transition Visit, the patient will not need to complete the Early Termination (ET) visit in the extension trial prior to transition to the other trial.

At the conclusion of the other setmelanotide trial, the patient may transition back into this extension trial, again with the patient's written informed consent, at the discretion of the investigator and sponsor, if continuation of setmelanotide treatment is considered beneficial and the patient continues to be eligible for the extension trial. In such cases, the patient will resume the extension trial at the time point/visit at which he or she was at prior to transition to the other trial. Furthermore, after transition back into this extension trial, the patient is to receive setmelanotide at the same dose as they had received prior to transition to the other trial, unless the dose needs to be reduced due to tolerability reasons or in case a dose increased is required for potential additional efficacy needs, at the investigator's discretion. If at the time the patient completes the other setmelanotide trial, setmelanotide becomes commercially available for an indication for which that patient qualifies, the patient will not be eligible to re-enter this extension trial.

If a patient transitions to another setmelanotide clinical trial before completing the ET visit in this extension trial, but does not transition back into this extension trial, the patient will not complete the ET visit or follow-up in the extension trial.

If feasible, patients are to have no interruption in setmelanotide treatment between this extension trial and the other setmelanotide trial. If an interruption in treatment is necessary due to administrative reasons, every effort is to be made to minimize the duration of the interruption and interruptions >21 days are not permissible without prior approval from the sponsor.

If a patient in this extension trial elects to transition to another setmelanotide clinical trial, then any screening assessments performed as part of the Screening visit in the other setmelanotide clinical trial within 30 days of the Transition Visit in this extension trial need not be repeated.

4. TRIAL POPULATION

4.1. Number of Patients

It is anticipated that any patient participating in a setmelanotide clinical trial could be a candidate for enrollment in this extension trial. Based on the number of patients currently enrolled or planned for enrolment in setmelanotide clinical trials, it is anticipated that up to 500 patients may be enrolled in this trial; however, expansion in enrollment may occur if additional patients with obesity due to monogenic, syndromic or acquired disorders affecting the MC4R pathway are enrolled in Phase 2 or Phase 3 clinical trials evaluating setmelanotide. It is anticipated that up to 100 centers located worldwide will participate in this trial. In the event additional patients are to be enrolled, additional sites may be added, as necessary.

4.2. Patient Selection Criteria

The specific inclusion and exclusion criteria for enrolling patients in this trial are presented in the section below. As these patients are ultra-rare, any criteria not fulfilled will be reviewed with the sponsor. Assuming no severe health concerns, a joint determination will be made regarding the acceptability of enrolling patients not fulfilling all criteria on a case-by-case basis. Any exceptions to the inclusion and exclusion criteria will be documented in writing and approved by responsible sponsor medical personnel prior to dosing the patient.

4.2.1. Inclusion Criteria

1. Patients aged 2 or older (or aged >2 years as per local regulations; ; only patients aged 12 years or older may be enrolled in the trial in Greece; only patients 6 years or older may be enrolled in the trial in Germany) who have completed participation in a previous setmelanotide clinical trial.
2. If patient received setmelanotide on an open-label basis in a previous setmelanotide clinical trial, patient demonstrated adequate safety and meaningful clinical benefit (efficacy) in the previous setmelanotide trial. Meaningful clinical benefit is defined as follows:

   - Patients 18 years of age or younger that have completed participation on active drug and demonstrated adequate safety and at least 3% BMI reduction or reduction in BMI Z-score of 0.2 compared to baseline.
   - Patients over 18 years of age should show reduction of 3% BMI compared to baseline.

   If the patient participated in a double-blind basis in the previous placebo-controlled clinical trial, patient tolerated blinded study drug.
3. Patient and/or parent or guardian is able to communicate well with the investigator, to understand and comply with the requirements of the trial, and to understand and sign the written informed consent/assent. The patient must consent/assent to participate in the trial.
4. Patient must meet one of the following requirements regarding contraception:

   - If a female of childbearing potential, defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), must use a highly effective form of contraception as outlined in Section 6.2.1.
   - If a female of non-childbearing potential, defined as permanently sterile (status post hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or post-menopausal for at least 12 months (and confirmed with a screening follicle-stimulating hormone (FSH) level in the post-menopausal laboratory range), contraception is not required during the trial.
     - Younger female patients who have not reached menarche upon trial entry will be assessed for Tanner staging and at first menarche will be required to comply with contraception requirements and pregnancy testing as outlined in the protocol.
   - If a male with female partner(s) of childbearing potential, must agree to a double barrier method if they become sexually active during the trial. Furthermore, male patients must not donate sperm during and for 90 days following their participation in the trial.

4.2.2. Exclusion Criteria

1. Pregnant and/or breastfeeding women.
2. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a screening comprehensive skin evaluation performed by a qualified dermatologist. Any concerning lesions identified during the screening period 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.
3. Patient is, in the opinion of the investigator, not suitable to participate in the trial.
4. Current, clinically significant disease, if severe enough to interfere with the trial and/or would confound the results. Any such patients should be discussed with the sponsor prior to enrollment in the trial.
5. Diagnosis of schizophrenia, bipolar disorder, personality disorder or other Diagnostic and Statistical Manual of Mental Disorders (DSM-III) disorders that the investigator believes will interfere significantly with trial compliance.
6. A Patient Health Questionnaire-9 (PHQ-9) score of ≥15.
7. Any suicidal ideation of type 4 or 5 on the C-SSRS. Any lifetime history of a suicide attempt, or any suicidal behavior since the last visit in the index trial.

   Note: Patients who are unable to complete the C-SSRS due to significant neurocognitive defects may be enrolled in the trial, as long as in the opinion of the investigator there are no clinical signs or symptoms of suicidal behavior.
8. History of significant liver disease or liver injury, or a current liver assessment due to abnormal liver tests (as indicated by abnormal liver function tests, alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase, or serum bilirubin >1.5× the upper limit of normal [ULN] for any of these tests) for an etiology other than non-alcoholic fatty liver disease (NAFLD). Thus, any underlying etiology besides NAFLD, including diagnosed non-alcoholic steatohepatitis (NASH), other causes of hepatitis, or history of hepatic cirrhosis is exclusionary, but the presence of NAFLD is not exclusionary.
9. Severe renal dysfunction defined by a glomerular filtration rate (GFR) <30 mL/min/1.73 m^2 in patients <12 years of age or end stage renal disease (GFR <15 mL min/1.73 m^2 (see Appendix 11.4 for GFR calculation).
10. History or close family history (parents or siblings) of skin cancer or melanoma (not including non-invasive/infiltrative basal or squamous cell lesion), or patient history of ocular-cutaneous albinism.

4.3. Patient Identification and Registration

Patients who complete treatment in a previous trial of setmelanotide (i.e., index trial) and wish to continue with setmelanotide treatment will be considered for eligibility to enter this extension trial. Patients who are candidates for enrollment into the trial will be evaluated for eligibility by

the investigator to ensure that the inclusion and exclusion criteria have been satisfied and that the patient is eligible for participation in this clinical trial.

All patients enrolled in the trial will be assigned a unique 9-digit number which will be a combination of the last 2-digits of the current protocol number (RM-493-022), the last 2-digits of the index protocol number (RM-493-XXX), the 2-digit site number, and a sequential 3-digit patient number, which will be used to identify patients throughout their participation in the trial. Patient numbers will be assigned sequentially starting at 001 (i.e., the first patient enrolled from index Protocol RM-493-012 at Site 10 would be assigned Number 22-12-10-001). Once a patient number has been assigned, it cannot be reused.

Note that patient numbers may be modified to identify those patients who transition from this extension trial into another setmelanotide clinical trial and, as applicable, transition back into the extension trial. However, the patient number will enable tracking the patient across both clinical trials.

4.4. Withdrawal of Patients

Patients will be informed that they have the right to withdraw from the trial at any time for any reason, without prejudice to their medical care. Patients withdrawn from the trial should discontinue trial treatment and complete the ET visit assessments as per the SOA (Table 1).

Per Section 3.3, the sponsor has elected to terminate the investigation of the MC4R gene cohort; therefore, patients with MC4R gene variants should be withdrawn from the trial. Exceptions will be made to allow patients that have displayed reductions from baseline of their index trial in [redacted] These patients can continue to receive setmelanotide treatment and participate in trial assessments provided they continue to demonstrate this threshold of clinical response at every visit thereafter.

To be eligible for continued treatment after one year on setmelanotide, all other patients have to display evidence of meaningful clinical benefit via [redacted] treatment effect or other assessments. The length of setmelanotide treatment will be calculated by adding the time the patient received setmelanotide treatment in the index trial plus the time that the patient received setmelanotide in the current extension trial.

The below criteria for withdrawal of setmelanotide treatment apply to all patients, with the exception of those identified as having meaningful clinical benefit–risk ratio at the investigator's discretion:

Withdrawal Criteria:

- AEs, which justify treatment or trial withdrawal. For specific predefined events, additional monitoring and guidance for the investigator is provided in Section 7.5 and Appendices 11.2 and 11.3.
- Non-adherence to study drug regimen or protocol requirements.
- Non-compliance with instructions or failure to return for follow-up.
- IMCIVREE is available through authorized use for the patient's indication.
- The patient becomes pregnant during the trial.

The sponsor may choose to discontinue investigation of a particular indication or genetic cohort/variants at any time; therefore, continued participation of patients for that indication or genetic cohort/variants will be addressed at that time.

If a patient is withdrawn or discontinued from the trial, the primary reason for withdrawal or discontinuation from the trial is to be recorded in the source documents/case report form (CRF).

All patients withdrawn prior to completing the treatment period should be strongly encouraged to complete the ET visit as outlined in the Schedule of Assessments (SOA) (Table 1 in Section 6), even if they are no longer receiving study drug. (Refer to Section 3.4 for information regarding completion of the Termination Visit for patients who transition into another setmelanotide clinical trial.)

In case of discontinuation, all AEs should be followed as described in Section 7.4; any skin AEs should continue to be followed, if at all feasible, for up to ~90 days to confirm near, or complete resolution (as has been shown in previous trials).

The sponsor will provide support for patient and caregiver travel, will make available visiting home health care professionals, and other necessary logistical support to ease the burden on the patient and to facilitate compliance with the trial procedures.

4.5. Patients' Re-entry from Other Trials

Patients that have left the current trial to enter other setmelanotide trials might re-enter the current trial upon discussion with the sponsor.

If a patient decides to withdraw consent from another setmelanotide trial, they might not be able to re-enter the current trial unless the reason for ET was due to a tolerability issue with a different setmelanotide formulation. All the other circumstances will be discussed with the sponsor on a case-by-case basis and supporting documentation justifying re-entry should be provided by the investigator.

5. TRIAL TREATMENTS

5.1. Study Drugs

All study drugs are for investigational use only and are to be used only within the context of this protocol. Setmelanotide will be supplied by the sponsor.

[redacted]

Setmelanotide is a clear, colorless to slightly opalescent solution essentially free of visible particulates. Setmelanotide will be administered as a subcutaneous (SC) injection once daily.

All unopened study drug must be kept in a secure, limited-access storage area at a temperature between 2°C to 8°C. Setmelanotide is stable at room temperature for a short time period that will allow patients to transport study drug home; ice packs and cooler bags will be provided for patients and caregivers who will travel long distances from the clinic. Patients will be encouraged to proceed directly home after clinic visits in which study drug is dispensed in order to minimize the amount of time the study drug is exposed to potentially elevated temperatures. Once at home, the unopened study drug must be stored in the patient's refrigerator. Opened study drug may be stored at room temperature for up to 30 days.

A separate pharmacy manual with specific instructions for the management of study drug will be provided to the investigative site.

5.2. Study Drug Dose and Administration and Dose Adjustments

Study Drug Dose at Trial Entry: Patients who received setmelanotide on an open-label basis in the index trial will begin this extension trial on the same dose of setmelanotide they were taking when they completed their index trial, unless tolerability or safety reasons justify a dose decrease. Patients who received double-blind study drug in a placebo-controlled index trial will start open-label setmelanotide in this trial with the starting dose from the index trial. The dose titration should follow the scheme in the index trial and in consultation with the sponsor.

Study Drug Administration: Trial patients will receive open-label setmelanotide by SC injection once daily (administered in the morning). Patients and/or their caregivers (including home health practitioners) will be responsible for all procedures associated with study drug administration at all times, i.e., drawing up, and self-administering the study drug once daily. Patients should be

instructed to rotate injection sites as per the dosing instructions and to avoid tight fitting clothing near the injection site to potentially reduce any injection site reactions.

Study drug is administered by patients/caregivers beginning the morning of Day 1 and for the duration of dosing. (If the index study drug is administered on the last day of the index trial/Day 1 of the current trial, then study drug administration in the current trial will begin on Day 2.) Patients/caregivers will draw up and self-administer/administer the drug once on a daily basis in the morning. On days with clinic visits, the patients/caregivers will administer the drug in the clinic in the presence of the clinical staff to ensure proper technique. Patients/caregivers will return all used vials to the clinic when they visit (the number recorded) and both clinic administration of study drug, as well as outpatient study drug administration will be recorded in a trial diary.

Study Drug Administration in Patients with Severe Renal Impairment

In Patients ≥12 years of age with severe renal impairment (eGFR 15 to 29 mL min/1.73 m^2), the starting dose of setmelanotide is 0.5 mg (0.5 mL) injected subcutaneously QD for 2 weeks. The dose may be increased by 0.5 mg QD every 2 weeks, if tolerated, to a maximum of 1.5 mg QD. If the starting dose is not tolerated, treatment should be discontinued.

The use of setmelanotide in patients <12 years of age with severe renal impairment is not permitted in this trial.

5.2.1. Dose Adjustments

The patient will continue the same dose of setmelanotide as taken at the end of the index trial. However, dose changes may be considered for safety/tolerability or efficacy reasons after discussion with the sponsor. For patients entering from a double-blind index trial, the starting dose will be the initial dose from the index trial. Dosing steps will also mirror the titration scheme from the index trial. During the course of the trial, if the patient attains a BMI or BMI Z-score within the normal range, per local guidelines, the investigator can reduce the dose of setmelanotide to the appropriate dose level, in order to maintain normal BMI or BMI Z-score and appetite, at their discretion. This should be discussed with the sponsor prior to initiating dose reduction.

[redacted]

5.3. Blinding, Packaging, and Labeling

5.3.1. Blinding

This trial is open-label so there is no blinding.

5.3.2. Packaging and Labeling

Open-label setmelanotide will be supplied by the sponsor.

Packaging and labeling will be prepared to meet all regulatory requirements.

5.4. Duration of Patient Participation

The duration of patient participation in this extension trial is up to 7 years. Patients may continue setmelanotide treatment under this protocol until they become eligible for commercially available setmelanotide, until any applicable trial cohorts are stopped, or if any AEs require treatment discontinuation. The end of the trial will be defined as the last patient's last visit. Patients may be offered the opportunity to participate in other setmelanotide clinical trials (see Section 3.4).

5.4.1. Commercial Availability of Setmelanotide

Patient participation in this long-term extension trial will conclude once setmelanotide receives marketing authorization indicated for the patient's condition and is available for commercial use in the region. The sponsor will notify a clinical site once commercial product is available for any applicable patient.

Once this occurs and the patient has access to authorized setmelanotide, the patient will complete an ET visit in person as soon as possible. This will be considered the final trial visit for this patient. The assessments outlined in the SOA for the ET visit should be performed and the patient will return all remaining study drug to the site. A follow-up telephone call may be conducted to follow-up on any new or ongoing AEs from this final visit. This telephone call will mark the end of participation in the trial for this patient.

In the event that a patient has opted to access commercial setmelanotide treatment and is due for another trial visit prior to assuring commercial drug access, then the patient should be discussed with the sponsor. With sponsor approval, the next planned trial visit may occur as per the SOA to minimize gaps in treatment if needed.

5.5. Assessment of Treatment Compliance

In order to evaluate the safety, tolerability, and efficacy of the study drug, it is critical that patients receive study drug as directed. All used study drug vials will be collected to assess compliance with the protocol.

Patients and/or caregivers will record any missed doses in the trial diary.

If a patient does not receive the entire dose of study drug, the amount administered will be recorded in the study diary. In addition, the reason(s) for the altered dose is to be recorded in source documents and the CRF.

5.6. Study Drug Accountability

The investigator is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records) at the trial site. The investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual at the trial site. Drug accountability records indicating the delivery date to the site, inventory at the site, use by each patient, return of all used study drug to the trial site, and return to the sponsor (or disposal of the drug, if approved by the sponsor) will be maintained by the trial site. These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all study drug received at the trial site from the sponsor. Reasons for departure from the expected dispensing regimen must also be recorded. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers. The sponsor or its designee will review drug accountability records at the trial site during monitoring visits.

All unused and used study drug will be returned by patients and retained at the trial site until inventoried by the monitor. All used, unused or expired study drug will be returned to the sponsor or designee or if authorized, disposed of at the trial site and documented.

5.7. Prior and Concomitant Treatment

5.7.1. Prohibited Medication and Substances

Unless concomitant medications are likely to present a strong potential safety concern, the general goal of this protocol is to allow as many as possible patients with these ultra-rare conditions to participate in the trial without prohibition of concomitant medications.

Patients who enter this trial from an index trial may continue all current medications as prescribed.

All concomitant medications should be kept at a stable dose throughout the course of the trial, unless a dose change is necessary to treat an AE. If any new medication for weight loss or a [redacted] agonist is started prior to or during the extension trial, the sponsor should be informed.

5.7.2. Concomitant Procedures

Concomitant procedures conducted during the trial, including those used to treat AEs, are to be reported on the CRF.

6. TRIAL ASSESSMENTS

6.1. Overview of Schedule of Assessments

The SOA to be conducted is depicted in Table 1.

Any patient withdrawing from the trial will complete the ET visit, if possible.

Discussion of this trial with the patient should occur prior to completion of their index trial and attempts should be made to minimize gaps/discontinuation of setmelanotide during transition from their index trial to this extension trial. Visit 1 of this trial will coincide with the final visit from the index trial, if possible. Visit procedures from the last visit of the index trial and the first visit of the extension trial are not intended to be duplicated. Thus, any repeat assessments do not need to be conducted and data from the last visit of the index trial will be used as V1 data in this trial as applicable. Patients will begin this extension trial on the same dose of setmelanotide that they were taking when they completed their index trial.

In order to provide flexibility to the patient and trial staff for the number of clinic visits, the actual scheduling of clinic visits can allow flexibility in timing of visits.

The actual scheduling and timing of clinic visits is flexible to accommodate the patient and trial staff. The SOA depicts the weeks visits are to be scheduled and in some cases, multiple visits are to be scheduled within a range of weeks.

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 (Appendix 11.5). Due to the age of the children, it may not be possible to collect blood samples for all laboratory tests at every trial visit. After enrollment, if blood sample collection for all laboratory tests is not possible, then the samples should be collected in the following descending order of priority:

1. safety laboratory tests,
2. anti-setmelanotide antibodies (ADA),
3. [redacted]
4. glycated hemoglobin (HbA1c),
5. [redacted],
6. [redacted]
7. laboratory assessments indicative of nutritional status (e.g., albumin).

If it is not possible to collect the safety laboratory samples on 2 consecutive visits, the patient should be discussed with the sponsor. Refer to the Laboratory Manual for the volumes of blood to be collected.

Table 1: Schedule of Assessments

Trial Period	Open-label Active Treatment[8]																ET[2]	Follow Up[26]
Visit Number	V1	V2-V4	V5	V6-V8	V9	V10-V12	V13	V14-V16	V17	V18-V20	V21	V22-V24	V25	V26-V28	V29 (EOT)	Trans-ition Visit[1] (if applies)		
Start of Week	1	13, 25, 37	53	65, 77 89	104	116, 128, 140	156	168 180, 192	208	220, 232, 244	260	272, 284, 296	308	320 332, 344	356			
Informed consent/assent	X																	
Pregnancy test[3]	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion Review/ Brief Medical History	X[4]																	
Physical examination	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tanner Staging[5]		X		X			X		X		X		X		X			
Height[5]	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive skin examination[6]	X[4,5,6]		X[6]		X[6]		X[6]		X[6]		X[6]		X[6]		X[6]	X[6]	X[6]	X[6]
[redacted]																		
Study drug dispensation/ administration[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Injection site inspection[11]	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[12]	X[4]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X	X	X

Trial Period	Open-label Active Treatment[8]															Trans-ition Visit[1] (if applies)	ET[2]	Follow Up[26]
Visit Number	V1	V2-V4	V5	V6-V8	V9	V10-V12	V13	V14-V16	V17	V18-V20	V21	V22-V24	V25	V26-V28	V29 (EOT)			
Start of Week	1	13, 25, 37	53	65, 77 89	104	116, 128, 140	156	168 180, 192	208	220, 232, 244	260	272, 284, 296	308	320 332, 344	356			
ECG (12-lead)[13]	X[4]		X		X		X		X		X		X		X	X	X	X
Safety laboratory tests[14]	X[4,8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]
[redacted]																		
Bone Age Assessment[18]	X[4]		X		X		X		X		X		X[6]		X[6]	X	X	
[redacted]																		
Anti-setmelanotide antibody samples[21]	X[4]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]
Adverse Event assessment[22]	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant meds review	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Nutritional Counseling and Monitoring[23]	X[4]	X	X	X	X	X	X	X	X	X	X		X		X	X	X	
[redacted]																		

Trial Period	Open-label Active Treatment[8]															Transition Visit[1] (if applies)	ET[2]	Follow Up[26]
Visit Number	V1	V2-V4	V5	V6-V8	V9	V10-V12	V13	V14-V16	V17	V18-V20	V21	V22-V24	V25	V26-V28	V29 (EOT)			
Start of Week	1	13, 25, 37	53	65, 77 89	104	116, 128, 140	156	168 180, 192	208	220, 232, 244	260	272, 284, 296	308	320 332, 344	356			
Chart Review substudy (optional)[27]	X																	
Patient Survey substudy (optional)[28]	X																	

Table 1: **Schedule of Assessments Footnotes**

Abbreviations: ADA = anti-setmelanotide antibody; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BIA = bioelectrical impedance; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood cell count; CPK = creatine phosphokinase; [redacted] ECG = electrocardiogram; EOT = end of treatment; ET = early termination; GGT = gamma glutamyl transpeptidase; [redacted] HbA1c = glycated hemoglobin; HR = heart rate; [redacted] LDH = lactate dehydrogenase; MHP = mental health provider; [redacted] QD=once daily; [redacted]

[1] Patients currently enrolled in this trial may exit the trial to participate in other setmelanotide clinical trials with the patient's (or legal guardian's) written informed consent/assent, at the discretion of the investigator and sponsor. The patient is to complete the Transition Visit prior to commencing treatment in the other setmelanotide clinical trial; applicable data (as indicated by shading) from this visit will serve as Screening data for the other trial. Note that if a patient in the current trial elects to transition to another setmelanotide clinical trial, then any screening laboratory tests performed as part of the Screening visit in the other setmelanotide clinical trial within 30 days of the Transition Visit in the current trial need not be repeated.

[2] ET: For those patients who withdraw consent, are withdrawn from the trial and not willing to complete the remaining trial visits, or for patients who transition to commercial setmelanotide, the ET visit assessments should be performed, when possible. Additionally, patients who withdraw and are not willing to return for the remaining clinic visits can be contacted via telephone, if amenable, to collect self-reported patient data [redacted] AEs, etc.). Patients who transition into another setmelanotide clinical trial before completing the ET visit need not complete the ET visit prior to transition to the other trial. If the patient does not transition back into the extension trial, then the ET visit and any follow-up will not be completed for that patient.

[3] A urine or serum pregnancy test must be performed for female patients of childbearing potential; dosing may continue with results pending.

[4] If a procedure is conducted at the last visit of the index trial, it is not intended that the procedure be duplicated at the first visit in the current trial if performed within the previous 30 days. However, the procedure should be conducted if it was not conducted as part of the index trial.

[5] A complete physical examination will be conducted yearly. Tanner Staging for assessment of pubertal development will be conducted as part of this yearly examination, with the exception of females approaching childbearing potential. Whenever possible, the same trained health care professional will conduct the examination and Tanner Staging. Abbreviated physical examinations may be conducted at all other time points.

Height (cm) will be measured at V1 only for those patients ≥21 years of age. Height will be measured at each visit for patients <21 years of age. Height will be measured, without shoes, socks or hats using a wall-mounted stadiometer. All measurements will be done in triplicate at each timepoint and recorded to the nearest half cm. The stadiometer should be calibrated by site personnel on a daily basis prior to height assessment.

[6] A comprehensive skin evaluation will be performed yearly by a dermatologist. As part of the physical examination at each visit, the investigator will note any significant skin abnormalities and refer the patient to the dermatologist if necessary.

[redacted]

[8] Prior to study drug administration.

[redacted]

[10] Study drug is administered by patients/caregivers beginning the morning of Day 1 and for the duration of dosing. (If the index study drug is administered on the last day of the index trial/Day 1 of the current trial, then study drug administration in the current trial will begin on Day 2.) Patients/caregivers will draw up and self-administer/administer the drug QD in the morning. On days with clinic visits, the patients/caregivers will administer the drug in the clinic in the presence of the clinical staff to ensure proper technique. Patients/caregivers will return all used vials to the clinic when they visit (the number recorded) and both clinic administered study drug, as well as outpatient study drug administration will be recorded in a trial diary. [redacted]

[11] Injection site evaluations and scoring (by the clinical staff) will include identification and measurement of areas of erythema, edema and induration, as well as the presence of localized pain, tenderness and itching. Additional unscheduled evaluations may also be recorded as warranted by clinical conditions, including in the interval between scheduled visits.

[12] All vital signs are to be obtained in the sitting position following at least 5 minutes of rest. All measurements, except body temperature, 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). Vital signs should be obtained prior to blood draws whenever possible.

[13] A single 12-lead ECG will be performed in the supine position following a period of at least 5 minutes of rest.

[14] Safety laboratory tests will include: CBC with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, CO_2, albumin, total protein, glucose, BUN, creatinine, uric acid, AST, ALT, GGT, CPK, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, calcium, phosphorus), urinalysis (pH, glucose, protein, ketones, bilirubin, blood, urobilinogen, specific gravity, nitrite, and leukocytes) with microscopic analysis if positive findings on dipsticks warrant further examination. Fasting samples (8-hour minimum) are required at all timepoints where feasible. Fasting lipid panel and HbA1c will also be included.

[redacted]

[redacted]

[18] If bone age was assessed in the index trial, bone age X-rays of the hand with magnified views will be continued in this trial for continued monitoring of pediatric patients through sexual maturation to adulthood, or until bone epiphyseal plate fusion and maturation are complete, as per routine pediatric evaluation for growth and bone development in patients with underlying endocrine disorders.

[redacted]

[21] Any patient with a positive ADA will be followed ~every 3 months after detection until titers resolve or return to baseline. Note that in pediatric patients, samples for ADA as well as [redacted] should be collected as feasible/permissible by local regulations.

[22] Adverse events will be recorded from the time a patient provides informed consent/assent. AEs occurring after dosing on Day 1 will be considered treatment-emergent AEs in the current trial.

[23] For pediatric (age 2-11 years) patients only, Nutritional Counseling and Monitoring may be performed by an appropriate dietician or nutritionist (or equivalent), at the investigator's discretion, to ensure that pediatric patients have adequate nutritional/dietary intake to maintain proper growth and development. Additional laboratory assessments indicative of nutritional status may be monitored, as appropriate (e.g., albumin).

[redacted]

[26] In the event that a patient is completing this trial but continuing treatment with setmelanotide, then this follow-up visit may be converted to a telephone call. In that case, the site should document any new AEs and follow-up on any ongoing AEs; remaining study drug should be returned to site, no other activities are required (see Section 5.4.1).

[27] Investigators may be asked by the sponsor to perform a chart review and a detailed analysis and collection of the clinical history of certain patient populations (e.g., selected based on indication, genetics, age group, duration of participation in the current trial [e.g., at least 6 months]). Patients or their legal guardians must provide written informed consent/assent to participate in this substudy. Refer to Section 6.4.1 for details.

[28] Certain patient populations (e.g., selected based on indication, genetics, age group, duration of participation in the current trial [e.g., at least 6 months]), may be offered the opportunity to participate in a substudy involving a patient/caregiver survey. Patients or their legal guardians will be required to provide written informed consent/assent to participate in this substudy. Refer to Section 6.4.1 for details.

6.2. Patient Requirements

6.2.1. Contraception and Pregnancy Testing

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

Female patients of childbearing potential must not be pregnant and must have a negative pregnancy test result at each visit.

Furthermore, it is imperative that all trial patients adhere to the contraception requirements as outlined below.

Women of childbearing potential (WOCBP), defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), must use a highly effective form of contraception throughout the trial and for 90 days following the trial. Highly effective forms of contraception include:

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

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

Younger female patients who are not sexually mature at trial entry will be assessed for Tanner staging and required to comply with contraception and pregnancy testing requirements at first menarche.

Male patients with female partner(s) of childbearing potential must agree to use contraception (e.g., if they have not had a vasectomy then should either (a) abstain from reproductive sexual intercourse or (b) use a single barrier method in combination with a female partner using a highly reliable method (i.e., hormonal or IUD) if they become sexually active during the trial and for 90 days following the trial. Male patients must not donate sperm for 90 days following their participation in the trial.

If a pregnancy should occur while a male or female patient is on study drug, the pregnancy will be followed up on to determine birth and neonatal outcomes.

6.2.2. Protection from Sun

Skin hyperpigmentation, or tanning, was observed in the cynomolgus monkey toxicology trials, and the human trials. These events were reversible upon cessation of study 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.

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

6.3. Efficacy Measurements

6.3.1. [redacted]

[redacted]

6.3.2. [redacted]

[redacted]

6.3.3. [redacted]

[redacted]

[redacted]

6.4. Clinical Procedures and Safety Assessments

6.4.1. Informed Consent/Assent

A complete description of the trial is to be presented to each potential patient or parent/legal guardian and signed and dated informed consent/assent is to be obtained before any trial specific procedures are performed.

6.4.2. Demographics and Medical History

A brief recent medical history will be obtained on Day 1 (Visit 1) prior to first dose of drug to assess continued trial eligibility and adherence to inclusion/exclusion criteria.

Information relating to demographics and a detailed medical history will be available and should be cited and cross-referenced from the original (index) clinical trial for each patient. Thus, a complete medical history along with demographic data will not be required for patients at V1. Key data to be recorded in the source document and CRF include the patient's identification number from the prior setmelanotide trial, gender, race, age and year of birth and concomitant medication use.

6.4.3. [redacted]

[redacted]

6.4.4. [redacted]

[redacted]

[redacted]

6.4.5. [redacted]

[redacted]

6.4.6. Physical Examination/Tanner Staging, Height, and Comprehensive Skin Examination

Physical Examinations

A complete physical examination will be conducted yearly. A complete physical examination will include review of peripheral lymph nodes, head, eyes (including conjunctiva), ears, nose, mouth and oropharynx, neck, heart, lungs, abdomen, musculoskeletal including back, extremities, neurologic examination, and a skin examination. If unexpected clinically significant skin abnormalities are noted the patient should be referred to the dermatologist. Abbreviated physical examinations may be conducted at all other time points.

All physical examinations are to be conducted in adequate light.

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

Tanner Staging for assessment of pubertal development will be conducted as part of this examination yearly, with the exception of females approaching childbearing potential. according to the SOA (Table 1). Whenever possible, the same trained health care professional will conduct the physical examination and Tanner Staging.

Height

Height (cm) will be measured, without shoes, socks, or hats, according to the SOA (Table 1) using a wall-mounted stadiometer. Height will be measured at each visit for patients <21 years of age and only at V1 for patients ≥21 years of age. All measurements will be done in triplicate at each timepoint and recorded to the nearest half cm.

The stadiometer should be calibrated by site personnel on a daily basis and prior to any height assessments.

Comprehensive Skin Examination

Each patient will receive a complete, comprehensive skin examination yearly by a dermatologist (Table 1).

The investigator will identify a dermatologist to serve as a consultant for the investigative site.

Any atypical lesions identified during the index trial should continue to be monitored as clinically indicated. The dermatologist will continue to monitor each patient, performing comprehensive skin examinations as outlined in the SOA (Table 1).

In the event a patient experiences changes to skin or skin lesions that are unresolved (or have not significantly improved or are close to resolution) at the ET Visit, the patient may be asked to return for additional follow-up assessments to document progress towards resolution.

6.4.7. Bone Age Assessment

If bone age was assessed in the index trial, bone age X-rays of the hand with magnified views will be continued in this extension trial for continued monitoring of pediatric patients through sexual maturation to adulthood, or until when bone epiphyseal plate fusion and maturation is complete, as per routine pediatric evaluation for growth and bone development in patients with underlying endocrine disorders. X-rays will be assessed for bone age at the site by an appropriate individual, and scans maintained for transmission to a central reading facility, if deemed necessary. Bone age assessments will be performed via X-ray according to the SOA (Table 1).

6.4.8. Concomitant Medication Review

A review of concomitant medications will be conducted at V1 and at every trial visit. Any medications taken by trial patients will be recorded in source documents and on the appropriate CRF.

6.4.9. Vital Signs

Vital signs include BP (mmHg), HR (bpm), respiratory rate (RR, in breaths/minute) and body temperature (°C). All vital signs will be obtained in the sitting position following at least 5 minutes of rest each time they are measured according to the SOA (Table 1). Vital signs should be obtained prior to blood draws whenever possible. All measurements, except body temperature, will be taken in triplicate, approximately 2 minutes apart.

BP and HR will be performed using the same methodology throughout the trial (manual or automated) and should be taken in the non-dominant arm throughout the trial. Special attention should be paid to ensure the appropriate cuff size is used in this patient population.

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

To allow for a BP reading at the time of [redacted] sampling, the patient should be instructed not to take the study drug on trial days when vital signs are to be measured in the clinic.

6.4.10. 12-Lead Electrocardiogram

Single 12-lead ECGs will be performed following a period of at least 5 minutes of rest in the supine position according to the SOA (Table 1). The investigator will read and interpret the ECG. In the case of an abnormal ECG, the investigator might contact a cardiologist as a consultant at his/her local institution.

6.4.11. Clinical Laboratory Tests

Clinical safety laboratory tests are to be performed by the local laboratory until central laboratory services become available. Patients are to be fasting for at least 8 hours and labs are to be drawn prior to dosing, but after measurement of vital signs.

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

In certain situations, it may not be feasible to complete all blood draws scheduled for a specific visit (e.g., a younger patient, or difficulty with phlebotomy). In this situation, the investigator may use his/her discretion to determine which laboratory tests are completed. Laboratory tests should be prioritized in the following manner:

1. safety laboratory tests,
2. anti-drug antibodies (ADA),
3. [redacted],
4. glycated hemoglobin (HbA1c),
5. [redacted]
6. [redacted]
7. laboratory assessments indicative of nutritional status (e.g., albumin).

Any patient who does not complete all blood draws as described in the SOA (Table 1) on 2 consecutive visits should be discussed with the sponsor.

Specific tests are described below.

6.4.11.1. Hematology, Clinical Chemistry and Urinalysis

Hematology:

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

Chemistry:

Sodium, potassium, chloride, CO_2, albumin, total protein, glucose, blood urea nitrogen (BUN), creatinine, uric acid, AST, ALT, gamma-glutamyltranspeptidase (GGT), creatine phosphokinase (CPK), alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), calcium, and phosphorus will be obtained.

[redacted] *and HbA1c*

[redacted] HbA1c will also be collected. Blood samples will need to be collected when the patient is in the fasted state.

Urinalysis:

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

6.4.12. [redacted]

[redacted]

[redacted]

6.4.13. Pediatric Nutritional Assay

For pediatric patients (age 2 to 11 years) only, Nutritional Counseling and Monitoring may be performed by a qualified dietician or nutritionist (or equivalent) to ensure that pediatric patients have adequate nutritional/dietary intake to maintain proper growth and development. Additional laboratory assessments indicative of nutritional status may be performed, at the investigator's discretion, in case of rapid and conspicuous weight loss (e.g., albumin) (Bharadwaj 2016). In this occurrence, the investigator should inform the sponsor who may request additional assessments.

6.4.14. [redacted]

[redacted]

6.4.15. Injection Site Evaluation and Scoring

Injection sites will be carefully inspected, evaluated and scored during the trial period. The injection site evaluation will include identification and measurement of areas of erythema,

edema, and induration, as well as the presence of localized pain, tenderness and itching. A sample injection site evaluation form is included in Appendix 11.1.

In addition, unscheduled evaluations may also be recorded as warranted by clinical conditions, including in the interval between scheduled visits.

6.4.16. Anti-Setmelanotide Antibody (ADA) Measurements

Blood samples for measurement of anti-setmelanotide antibodies will be collected at each visit. Any patient with a positive titer will be followed ~ every 3 months after detection until resolution or return to baseline.

6.4.17. [redacted]

6.4.17.1. [redacted]

[redacted]

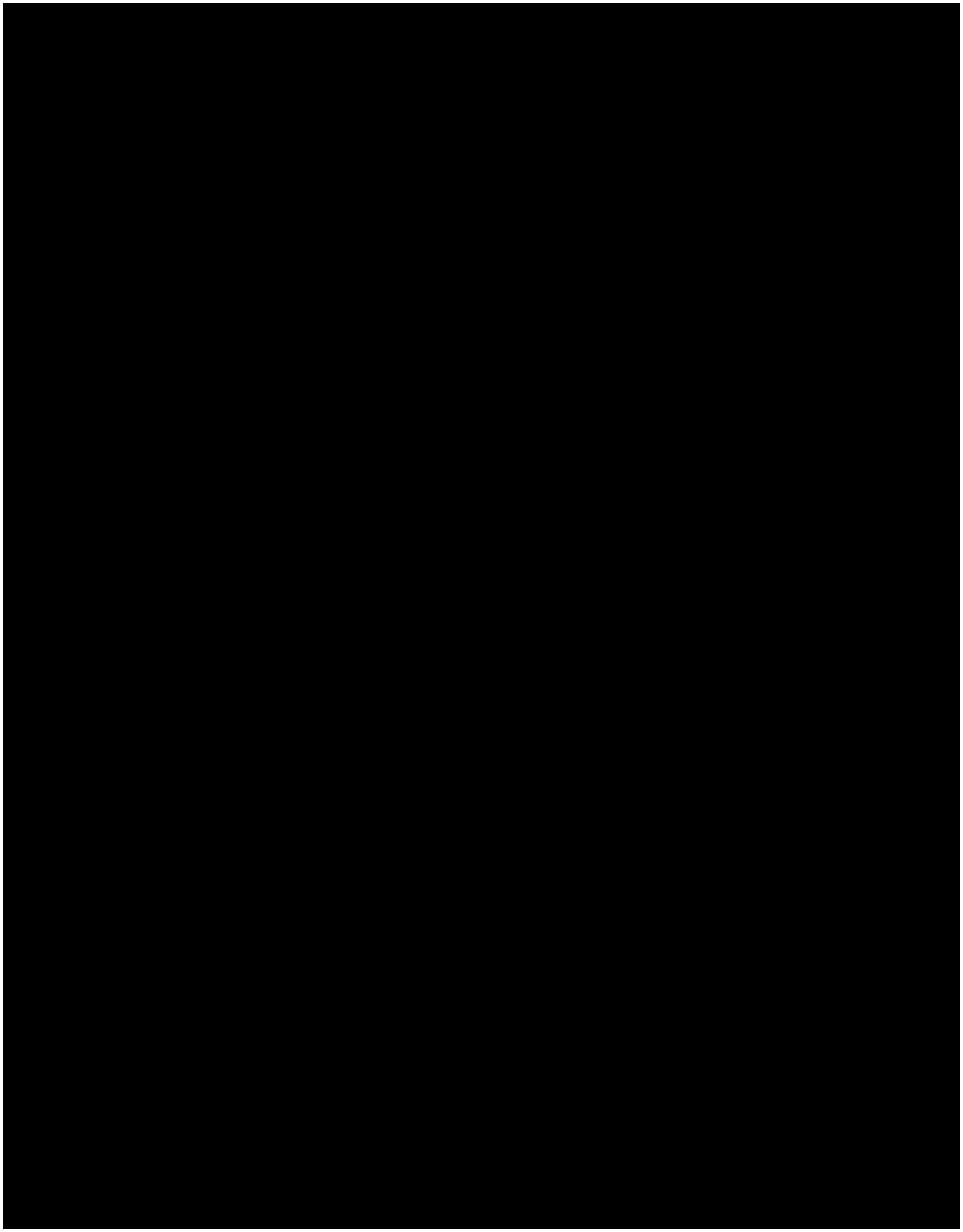
6.4.17.2. [redacted]

[redacted]

[redacted]

6.4.17.3. [redacted]

[redacted]



6.4.18. Diet and Nutritional Counseling

For adolescent and adult patients, no special dietary counseling will be part of this trial, but patients will be counseled to adhere to a calorie reduced diet, at the discretion of the investigator.

For pediatric patients (age 2-11 years), nutritional counseling and monitoring may be performed by a qualified dietician or nutritionist (or equivalent), at the investigator's discretion, according to the SOA (Table 1), to ensure that pediatric patients have adequate nutritional/dietary intake to maintain proper growth and development. Additional laboratory assessments indicative of nutritional status may be monitored as appropriate (e.g., albumin).

6.4.19. Adverse Events

Each patient must be carefully monitored for the development of any AEs throughout the trial from V1 through the patient's last visit. This information should be obtained in the form of non-leading questions (e.g., "How are you feeling?"), and from signs and symptoms detected during each examination, from laboratory evaluation, observations of trial personnel, and spontaneous reports from patients.

All AEs, including injection site reactions and potential systemic reactions will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grading system.

Complete details on AE monitoring are provided in Section 7.

6.4.20. Order of Assessments

When scheduled at the same timepoint, the order of procedures should be as follows: obtain vital signs, perform 12-lead ECG, followed by blood draws (at the specified time point, if applicable). Adjustments may be made depending upon specific circumstances. Questionnaires are to be completed before the morning meal and study drug administration; they may be performed before or after blood draws and/or 12-lead ECGs.

7. ADVERSE EVENTS

Monitoring of adverse events (AEs) will be conducted throughout the trial. AEs will be recorded in the CRFs from V1 through the patient's last visit, as indicated in Table 1. AEs that occur after the start of study drug administration will be considered treatment-emergent adverse events. Any AEs that are reported as ongoing at the time of the subject's final visit in their index trial, will be recorded as pre-existing condition on the trial AE logs. Serious adverse events (SAEs) will be recorded through the patient's last 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).

7.1. Definitions, Documentation, and Reporting

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can

arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

An AE or suspected adverse reaction is considered serious (SAE) if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death.
- Life-threatening. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction, which hypothetically might have caused death had it occurred in a more severe form.
- In-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the trial period, but planned prior to trial entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. 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 in-patient hospitalization, or the development of drug dependency or drug abuse.

7.2. Procedures for AE and SAE Reporting

Each patient must be carefully monitored for the development of any AEs. This information should be obtained in the form of non-leading questions (e.g., “How are you feeling?”) and from signs and symptoms detected during each examination, observations of trial personnel, and spontaneous reports from patients.

All AEs (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from trial personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate CRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the appropriate CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

All SAEs that occur during the course of the trial must be reported by the investigator to the sponsor or designee **within 24 hours** from the point in time when the investigator becomes aware of the SAE. All SAEs must be reported whether or not considered causally related to the study drug. An SAE Report Form will be completed and sent to the sponsor within 24 hours. The information collected will include patient number, a narrative description of the event, and an

assessment by the investigator as to the severity of the event and relatedness to study drug. All SAEs must also be entered into the CRFs. Follow-up information on the SAE may be requested by the sponsor or its designee.

Sites will submit all SAE Report Forms within 24 hours via email or fax to the address below:

[redacted]

If there are serious, unexpected adverse drug reactions associated with the use of the study drug, the sponsor or designee will notify the appropriate regulatory agency/agencies and all participating investigators on an expedited basis. It is the responsibility of the investigator to promptly notify the IRB/IEC where required of the IRB/IEC of all unexpected serious adverse drug reactions involving risk to human patients.

7.2.1. Assessment of Severity, Relationship to Study Drug, and Expectedness

For both serious and non-serious AEs, the investigator must determine both the severity of the event and the relationship of the event to study drug administration. Only those injection site reactions and laboratory abnormalities considered clinically significant by the investigator will be recorded as AEs. Expectedness will be evaluated by the sponsor.

7.2.1.1. Assessment of Severity

Intensity of AEs including clinically significant treatment-emergent laboratory abnormalities, injection site reactions and potential systemic reactions will be graded according to the CTCAE Version 4.0. The CTCAE grade refers to the severity of the AE and ranges from Grade 1 (mild AE), Grade 2 (moderate AE), Grade 3 (severe AE), and Grade 4 (life-threatening or disabling AE) to Grade 5 (death related to AE).

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

- **Mild**: discomfort noticed but no disruption of normal daily activity.
- **Moderate:** discomfort sufficient to reduce or affect daily activity.
- **Severe:** inability to work or perform normal daily activity.
- **Life threatening**: represents an immediate threat to life.

7.2.1.2. Assessment of Relationship

Relationship to of an AE to study drug administration will be determined by the investigator according to the following criteria:

- **None:** No relationship between the event and the administration of study drug. The event is related to other etiologies, such as concomitant medications or patient's clinical state.
- **Unlikely:** The current state of knowledge indicates that a relationship to study drug is unlikely or the temporal relationship is such that study drug would not have had any reasonable association with the observed event.

- **Possible:** A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction might have been produced by the patient's clinical state or other modes of therapy administered to the patient.
- **Probable:** A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction cannot be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient.

For the purpose of safety analyses, all AEs that are classified as possible or probable will be considered treatment-related events.

7.2.1.3. Assessment of Expectedness

The reference safety information (RSI) for this trial will be within the current IB. The sponsor will be responsible for assessment of expectedness for all AEs to determine regulatory reporting requirements. An unexpected AE is one that is not listed within the RSI of the IB.

7.3. Adverse Events and Risks

Overall, setmelanotide has been generally well-tolerated in previous trials. The most common adverse reactions have been injection site reactions, skin hyperpigmentation, nausea, headache, diarrhea, abdominal pain, back pain, fatigue, vomiting, depression, upper respiratory tract infection, and spontaneous penile erection. The investigator (or a covering clinician) will be available at all times to trial participants in the event of a clinical emergency. This availability and how to reach the investigators in an emergency will be clearly communicated orally and in writing to trial participants. All trial interventions will be provided free of cost.

Please refer to the current IB for a comprehensive summary of the AEs reported to date.

7.3.1. Medical Monitoring

The medical monitoring for the trial may be delegated to a medical monitor supplied by the Contract Research Organization (CRO) managing the operational conduct of this trial. The investigator has overall responsibility for the integrity of the trial and participant safety at their site. This information, as well as any other unanticipated problems involving risks to patients or others, will also be reported to the applicable regulatory authorities in accordance with regulatory requirements.

7.4. Monitoring of Adverse Events and Period of Observation

AEs will be recorded on the CRFs starting from V1 up to and including the patient's last visit. SAEs and deaths will be recorded on the CRFs starting from the time the ICF is signed and continuing through the patient's last 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).

Any SAE that occurs at any time after completion of the trial, which the investigator considers to be related to study drug, must be reported to the sponsor or designee.

7.5. Guidelines for Additional Monitoring and Suspension of Dosing for a Patient

Patients will be monitored carefully during the treatment period during onsite clinic visits as well as periodic telephone calls made to the patients by the trial staff. In the event a patient is withdrawn from treatment due to an AE, the patient should be encouraged to complete the ET Visit in order to monitor the event to resolution and obtain additional protocol defined safety assessments.

Specific guidelines for dermatological events and penile erections are provided in the Appendices (Section 11, Appendix 11.2, and Appendix 11.3). At all times, this guidance is subject to the clinical judgment of the investigator and trial consultants (if applicable).

The investigator will notify the Medical Monitor in the event any trial participant fulfills any of the criteria defined in the appendices noted above, or undergoes additional monitoring for any of the events defined herein.

Male and female sexual function and hyperpigmentation will be monitored throughout the trial using specific CRF pages.

7.5.1. Depression or Suicidality

A patient should be referred to a mental health provider (MHP) if he/she has:

- [redacted]
- Any suicidal behavior.
- [redacted]

A referral to an MHP should also be made if in the opinion of the investigator it is necessary for the safety of the patient. Any event necessitating referral to an MHP is to be reported as an AE. If a patient's psychiatric disorder can be adequately treated with psychotherapy and/or pharmacotherapy, then the patient, at the discretion of the MHP, should be continued in the trial.

Any elevation in [redacted] should be evaluated to determine whether it meets the criteria for reporting as an AE.

8. STATISTICAL PROCEDURES

This section describes the plans for analysis. Details of the statistical analysis will be described in the Statistical Analysis Plan (SAP) and the final clinical trial report.

8.1. Sample Size Estimation

The primary objective of this trial is to evaluate long-term safety and tolerability in patients with various rare genetic, syndromic, or acquired forms of obesity impacting the MC4R pathway after completing planned setmelanotide treatment in a previously completed index protocol. All patients who complete an index protocol and meet eligibility criteria can enroll in this trial. Thus, sample size estimation and power analyses are not relevant.

Given the rarity of these genetic and acquired diseases of the MC4R pathway, estimated power for exploratory endpoints such as expected [redacted] will not be provided, and efficacy will be only summarized.

8.2. Hypotheses

Setmelanotide continues to be safe and well tolerated throughout this extension protocol.

Setmelanotide leads to a clinically relevant reduction of body [redacted] endpoints and long-term maintenance of weight-related improvements in each population of patients with rare genetic, syndromic, or acquired diseases of obesity (each population analyzed separately).

8.3. Definition of Population(s) for Analysis

This protocol includes a variety of patient populations who are included as a matter of administrative convenience (each population is so rare this protocol anticipates a small number of patients in each population). Each sub-population may be analyzed separately as ≥2 patients are enrolled, and complete at least 6 additional months of treatment.

8.4. Statistical Methods

Statistical methods, populations and approaches to missing data will be outlined in the SAP.

As these patient populations are extremely rare, efforts will be made to keep all patients in the trial, and all data collected, even if outside of visit windows, will be included in all analyses of endpoints. No missing data will be imputed, analyses will be carried out on all available data.

With respect to the exploratory endpoints, no adjustment for multiplicity will be included for the many patient populations in this trial as these different populations are included in this trial only for administrative convenience.

AEs will be coded by using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and preferred term for the number and percent of AEs reported, the number of patients reporting each AE, and the number of patients with any AE.

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as any AE with onset after the administration of study drug through the end of the trial, specifically, 30 days after the last dose of setmelanotide, or any event that was present at baseline but worsened in severity or was subsequently considered drug-related by the investigator through the end of the trial.

A by-patient AE data listing including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided.

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

[redacted]

Safety and efficacy data from both the index and extension trial may be combined to evaluate long-term safety and efficacy outcomes on a patient specific and population basis.

It is planned that analyses may be completed once all patients within each sub-population/cohort have completed at least 1 year of this extension protocol, data have been cleaned and finalized, and the database is locked for assessments in this first year. Additional supplemental analyses will be conducted on a yearly basis for patients who continue in the trial (for up to 7 years).

8.5. Statistical Analysis Plan

The full SAP for this trial will provide more detailed statistical procedures prior to any planned analysis.

9. ADMINISTRATIVE REQUIREMENTS

9.1. Good Clinical Practice

The trial will be conducted in accordance with the International Council for Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and IB. Essential clinical documents will be maintained to demonstrate the validity of the trial and the integrity of the data collected. Master files should be established at the beginning of the trial, maintained for the duration of the trial and retained according to the appropriate regulations.

9.2. Ethical Considerations

The trial will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. For Germany the version of the Declaration of Helsinki from 1996 applies. The IRB/IEC will review all appropriate trial documentation in order to safeguard the rights, safety, and well-being of the patients. The trial will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator.

9.3. Patient Information and Informed Consent/Assent

After the trial has been fully explained, written informed consent/assent will be obtained from either the patient him/herself for adult patients (age 18 and greater) or his/her guardian or legal representative for minor patients, prior to trial participation. The method of obtaining and documenting the informed consent/assent and the contents of the consent/assent will comply with ICH-GCP and all applicable regulatory requirement(s).

A copy of the signed informed consent/assent form will be provided to the patient or his/her guardian or legal representative.

The patient or his/her guardian or legal representative must provide written informed consent/assent any time the informed consent form/assent form is updated during the course of the trial. Patients must be informed of and provide consent/assent to the most current version of the informed consent form(s) (ICFs) during their participation in the trial, and a copy of the ICF(s) must be provided to the patient or their legally authorized representative.

9.4. Patient Confidentiality

In order to maintain patient privacy, all source documents/CRFs, study drug accountability records, trial reports and communications will identify the patient by the assigned patient number. The investigator will grant monitor(s) and auditor(s) from the sponsor or its designee and regulatory authority/authorities access to the patient's original medical records for verification of data gathered on the source documents/CRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

9.5. Protocol Compliance

The investigator will conduct the trial in compliance with the protocol provided by the sponsor, and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority/authorities. Modifications to the protocol should not be made without agreement of both the investigator and the sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority/authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing trials that have the approval /favorable opinion of the IRB/IEC. The sponsor or designee will submit all protocol modifications to the regulatory authority/authorities in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the investigator will contact the sponsor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documents/CRF.

9.6. Trial Conduct During the COVID-19 (Coronavirus) 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 trial participants become potentially exposed to or infected with COVID-19. To assure the safety of trial participants, 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 11.6.

9.7. Data Management

9.7.1. Data Handling

Data will be recorded at the site on source documents and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRA will verify data recorded in the electronic CRF (eCRF) system with source documents. All corrections or changes made to any trial data must be appropriately tracked in an audit trail in the eCRF system. Electronic CRFs will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

9.7.2. Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

9.7.3. Data Entry

Data must be recorded using the eCRF system as the trial is in progress. All trial site personnel must log into the system using their secure user name and password in order to enter, review, or correct trial data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11). All passwords will be strictly confidential.

9.7.4. Medical Information Coding

For medical information, the following thesauri will be used:

- MedDRA for AEs
- WHO Drug for concomitant medications

9.7.5. Data Validation

Validation checks programmed within the eCRF system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

Electronic CRFs must be reviewed and electronically signed by an investigator who signed the protocol.

9.8. Direct Access to Source Data

The trial will be monitored by the sponsor or its designee. Monitoring will be performed by a representative of the sponsor (site monitor) and will include review of the source documents/CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, and fax).

All unused study drug and other trial materials are to be returned to the sponsor or designee after the clinical phase of the trial has been completed (see Section 5.6).

Regulatory authorities, the IRB/IEC, and/or the sponsor's clinical quality assurance group or designee may request access to all source documents, CRFs, and other trial documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

9.9. Source Document/Case Report Form Completion

Source documents/CRFs will be completed for each trial patient. It is the investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's source document/CRF. The source document/CRFs should indicate the patient's participation in the trial and should document the dates and details of trial procedures, AEs, and patient status.

The investigator, or designated representative, should complete the source document/CRFs as soon as possible after information is collected, preferably on the same day that a trial patient is seen for an examination, treatment, or any other trial procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The investigator must sign and date the investigator's Statement at the end of the source document/CRFs to endorse the recorded data.

9.10. Record Retention

The investigator will maintain all trial records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained 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 in writing if a custodial change occurs.

9.11. Liability Insurance

The sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

9.12. Publication of Trial Findings and Use of Information

All information regarding setmelanotide supplied by the sponsor to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the trial and will not use it for other purposes without consent from the sponsor. It is understood that there is an obligation to provide the sponsor with complete data obtained during the trial. The information obtained from the clinical trial will be used towards the development of setmelanotide and may be disclosed to regulatory authority/authorities, other investigators, corporate partners, or consultants as required.

It is the intention of the sponsor and the academic investigators to publish the results of this trial in a peer-reviewed journal upon completion. For this purpose, a publication committee of the key investigators will likely be identified and initiated during the course of this trial.

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11. APPENDICES

11.1. Injection Site Evaluations

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

An example assessment form is shown below:

Local Skin Tolerability Assessment

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

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

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

Initials: _____

11.2. Guidance for Monitoring Potential Treatment-Related Dermatological Changes and Suggested Criteria for Discontinuation of Dosing

In clinical trials conducted with setmelanotide, skin hyperpigmentation (tanning), primarily noted on sun exposed areas, was reported during the first 7-14 days of treatment at clinical doses. In Phase 1/2 clinical studies, hyperpigmentation appeared uniform, and in most instances, returned to baseline within 30 days of discontinuing study drug. Some patients also noted changes in hair color as well. Facial hyperpigmentation on the muzzle and periorbital region was seen in the 14-day, 28-day, and 13-week toxicology studies in cynomolgus monkeys, with improvement or resolution seen by the end of the recovery period.

The investigator will identify a dermatologist to serve as a consultant for the investigative site. The dermatologist will receive training in trial procedures and the effects of setmelanotide prior to evaluating patients.

Each patient will receive a complete, comprehensive dermatology examination during V1, prior to any setmelanotide treatment. Photographs of any specific lesions at baseline are suggested, and any worrisome lesions should be considered for biopsy prior to trial start. The dermatologist will continue to monitor each patient, performing comprehensive skin examinations as outlined in the SOA. The findings of the dermatological examinations will be captured as part of the trial information for each patient. Photographs of lesion progression using standard dermatological procedures, or even if captured by a hand-held camera, should be considered, to record changes in skin condition.

While standard dermatological photographs do not robustly capture changes in skin color or hue (which require very carefully controlled standard conditions and lighting), sites that may have such equipment should discuss this with the sponsor to determine if their equipment meets the rigorous standards for following patients over time. If the sponsor and investigator both agree that such testing can be performed, sites are encouraged to do so with the careful monitoring by the sponsor. It is expected that few sites (and patients) will have the necessary facilities.

The dermatologist will also serve as a consultant for the investigative site in the event a patient reports changes to their skin, including skin tanning, or darkening of existing, or the appearance of new, pigmented skin lesions. These events are expected, and were observed in other setmelanotide clinical studies, but may require dermatological evaluation outside of the SOA.

In the event of skin tanning, the patient should generally remain on treatment, with continued monitoring, or at more frequent intervals as deemed appropriate by the investigator and/or dermatologist.

In the event of darkening skin lesions, or the presence of a new pigmented skin lesion, the investigator can refer the patient to the dermatologist for an evaluation. If clinically indicated, the lesion may be biopsied, otherwise careful monitoring is recommended and the patient should remain on study drug.

Any biopsies must be evaluated by a trained dermatopathologist, and biopsy reports must be part of the trial information for each patient.

While it is not expected that patients will discontinue drug as a result of skin or lesion darkening, in some cases it is possible this course will be indicated in some circumstances. If so, experience in the clinical trials demonstrates the changes in lesions reverse upon cessation of study drug, so if a lesion continues to darken or change after study drug has been discontinued, careful consideration should be given for further dermatological evaluation or biopsy. If drug is discontinued, all patients with clinically indicated lesions are to be followed by the dermatologist until progress towards resolution of the event (up to ~60-90 days after last dosing, if needed).

11.3. Guidance for Monitoring Potential Treatment-Related Penile Erections and Suggested Criteria for Discontinuation of Dosing

Male patients will be instructed to immediately report any non-erotic erections lasting for more than 30 minutes, or a painful erection of any duration, to the investigator.

As previously noted, penile erections in males are effects associated with MC4R agonism, and have been seen in setmelanotide clinical studies. However, occurrence of these events does not appear to correlate with dose and duration of dosing, as the number of events did not increase with dose or duration of dosing. These events have been intermittent usually lasting less than 20 minutes, painless, and resolved without intervention. Some patients have had a series of such erections over a multi-hour interval, with intermittent flaccidity. If a patient reports a painless, non-erotic continuous erection of more than 1-hour duration, they will be instructed to urgently contact the investigator, and based on investigator judgment, study drug injection is to be immediately discontinued. If after study drug discontinuation the event does not resolve, further treatment may be provided as clinically indicated.

Erections lasting more than 4 hours or painful erections of shorter duration are of serious concern, especially since the presence of pain may connote localized penile ischemia. No painful or prolonged erections have been reported in setmelanotide clinical studies, however, in the event one is reported, study drug injection is to be stopped immediately and an examination of the patient performed by the investigator; alternatively, the patient should be instructed to seek emergent medical care.

11.4. Assessment of Renal Function

11.4.1. Modification of Diet in Renal Disease (MDRD) Equation

In patients, ≥18 years of age, the Modification of Diet in Renal Disease (MDRD) Equation should be used as follows:

GFR = 175 x (creatinine in mg/dL)$^{-1.154}$ x (age in years)$^{-0.203}$ x (0.742 if female) x (1.210 if African American)

11.4.2. Bedside Schwartz Equation

In patients, <18 years of age, the Bedside Schwartz Equation should be used as follows:

GFR (mL/min/1.73 m²) = (0.41 × height in centimeters) / creatinine in mg/dL

11.5. Considerations for Reducing Pain and Distress in the Pediatric Population

Although the study procedures and assessments required per protocol are classified as “No or Minimal Risk” (with the exception of DXA, which is classified as “Minor Increase over Minimal Risk”) according to the 2008 Guidance Document “Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population”, considerations for reducing pain in distress in participants younger than 18 years of age are suggested below.

- The clinical trial may only be conducted if it subjects the person concerned to as little burden and other foreseeable risks as possible.

- Physical and emotional pain should be prevented as much as possible, and effectively treated when unavoidable.
- In order to minimize pain, distress, and fear, facilities should be appropriate to childcare, and the personnel should be trained to look after children and supervised by experienced health care professionals. Staff should be trained to communicate with both parents (or legal representative) and children. Generally, this would assume non-adult patients are being studied at experienced pediatric centers.
- For most procedures, the child should always be accompanied by a trial-related staff member who could provide reassurance. At the sign of distress and/or dissent the procedure should be stopped; a short pause to allow the child to feel in control, further explanation and an assessment of the situation may be needed to reassure the child, or to decide to definitely abandon the procedure at the discretion of the investigator.
- In all situations, investigations/interventions should be limited to the minimum required for obtaining valid data and performed using size-/age-appropriate material and devices, including limiting in advance the number of attempts for sampling.
- Study drug injections should only be performed by parents (or home health care professionals), unless the child is of suitable age and competency, and desires the ability to do so.
- Although almost all study procedures are classified as low risk (with the exception of DXA, which is classified as “minor increase over minimal risk”), risk should be continuously monitored and assessed by appropriate personnel.
- For assessments in which there is a psychological component measures should be taken to minimize distress. For example, Tanner Staging assessments could utilize a diagram for the child to point to and indicate what stage they currently are, vs. having to have an examination without clothes.

A comment on benefit–risk: risk is very low, from procedures and/or known safety profile of the drug (both clinically and toxicologically, where large margins and preliminary data from juvenile tox studies have not identified any new or concerning safety concerns), and based on treatment experience in several forms of rare genetic, syndromic, or acquired diseases of obesity impacting the MC4R pathway, there is the possibility of major benefit.

11.6. Guidance on Study Conduct During the COVID-19 (Coronavirus) Pandemic

Coronavirus disease 2019 (COVID-19) could impact the conduct of this clinical study for several reasons, including: self-isolation/quarantine by patients and study-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 study conduct in the event of disruption of the study. 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, study intervention will be discontinued, and study follow-up will be conducted.

If COVID restrictions are imposed on or by the study 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 study-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, electrocardiograms (ECGs), recording of adverse events (AEs), collection of blood and urine samples. Most efficacy assessments could potentially be done off site. investigators should use their clinical judgment to determine whether a patient can continue study treatment in the absence of on-site clinic visits, or consider alternatives such as temporary treatment interruption or study discontinuation.
- All protocol-required assessments missed due to COVID restrictions should be documented in detail within the patients' source documents and should be clearly designated as "COVID-19 RELATED". It must be documented if a site visit is instead conducted remotely. Source documentation should detail how each assessment was collected (e.g., remote vs. on-site, central vs. local laboratory, vital signs taken at home by caregiver vs. delegated in-home nursing).
- If applicable, discontinuations of study interventions and withdrawal from the study due to disruption of study conduct by the pandemic should be documented with the prefix "COVID-19 RELATED" in the case report form (CRF).

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

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