SETMELANOTIDE

RM-493-030

A Phase 2, Open-Label 20-Week Study to Evaluate the Safety and Efficacy of Setmelanotide in Subjects with Hypothalamic Obesity

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

IND No. [redacted]

Short Title: Open-Label Study of Setmelanotide in Hypothalamic Obesity

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

Document Date (Version): 09 September 2021 (V2.0; Amendment 1)

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CONFIDENTIALITY NOTE

APPROVAL SIGNATURE PAGE

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REVIEWED/APPROVED BY:

[Please see e-signature page appended to this protocol]

[redacted]

[redacted]
Rhythm Pharmaceuticals, Inc.

Signature

Date

INVESTIGATOR STATEMENT

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I understand that all documentation provided to me by Rhythm Pharmaceuticals, Inc. (Rhythm) or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, Investigator Brochure (IB), case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board. No changes will be made to the study protocol without the prior written approval of Rhythm and the Institutional Review Board, except where necessary to eliminate an immediate hazard to the subject.

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)

1. SYNOPSIS

Name of Sponsor/Company:
Rhythm Pharmaceuticals, Inc.

Name of Investigational Product:
Setmelanotide

Name of Active Ingredient:
Setmelanotide (RM-493; Melanocortin-4 Receptor Agonist)

Title of Study:
A Phase 2, Open-Label 20-Week Study to Evaluate the Safety and Efficacy of Setmelanotide in Subjects with Hypothalamic Obesity

Study center(s):
Approximately 3-5 clinical sites in the United States (US)

Principal Investigator:
Dr. Chris Roth

Studied period (years):	**Phase of development:**
Estimated date first patient enrolled: 26Feb2021 Estimated date last patient completed: 31Mar2022	2

Objectives:

***Primary*:** The primary objective of this study is to evaluate the change in body weight in response to setmelanotide administered subcutaneously (SC) daily in patients with hypothalamic obesity (HO).

***Secondary*:** The secondary objectives of this study are to evaluate changes in parameters of body weight, body mass index (BMI), waist circumference, and hunger in response to setmelanotide in patients with HO and to evaluate the safety and tolerability of setmelanotide in patients with HO.

[redacted]

Methodology:

This is a Phase 2, multicenter, open-label, proof of concept study designed to assess the effect of setmelanotide on weight loss on a population affected by HO. Approximately 15 patients aged 6 to 40 years, inclusive, are planned to be enrolled across approximately 3-5 clinical sites in the US.

Screening Period

Upon providing informed consent, patients will enter the Screening Period, during which they will be assessed for eligibility and complete all screening procedures as described in the Schedule of Activities (SoA).

Treatment Period

Patients who are determined to be eligible, based on Screening assessments, will return to the clinic for the Baseline Visit (Visit 2) and receive the first setmelanotide dose. The starting setmelanotide dose is dependent on patient age; however, for all patients, the setmelanotide dose will be titrated to a final dose of 3.0 mg/day (initial titration phase), as follows:

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Patients aged 6 to <16 years, inclusive • Starting at Baseline (Day 1; Visit 2) through approximately Day 14, patients will receive setmelanotide 1.0 mg/day. • Starting at approximately Day 15 through 28, patients will receive setmelanotide 2.0 mg/day. Patients/caregivers will be contacted by study center personnel on Day 15 to ensure dose titration has occurred and to document any adverse events (AEs). • Starting on approximately Day 29 (Visit 3), patients will receive setmelanotide 3.0 mg/day; patients will continue to receive setmelanotide 3.0 mg/day for 12 weeks. The dose of setmelanotide should be titrated as explained in the SoA. ***Patients aged ≥16 years, inclusive*** • Starting at Baseline (Day 1; Visit 2) through approximately Day 14, patients will receive setmelanotide 2.0 mg/day. • Starting at approximately Day 15, patients will receive setmelanotide 3.0 mg/day; patients will continue to receive setmelanotide 3.0 mg/day for 14 weeks. The dose of setmelanotide should be titrated as explained in the SoA. Patients will return to the study center for Visits 3, 4, and 5 (Weeks 4, 8, and 12, respectively), with each of these visits conducted approximately 4 weeks apart. All patients will return to the study center at Week 16 (Visit 6) and receive the last setmelanotide injection. Study endpoints are analyzed at Visit 6. After completion of Visit 6, participation in the current study will then conclude in one of the following 2 ways: • Patients meeting the primary endpoint may be eligible to be enrolled in a separate extension study, Rhythm Study RM-493-022, under which auspices the patient will continue to receive setmelanotide. • Patients who do not meet the primary endpoint or elect not to continue setmelanotide are to discontinue setmelanotide at Visit 6 and return for an End-of-Study Visit (Visit 7) 4 weeks thereafter for a final safety review under the auspices of the current study.
Number of patients (planned): Approximately 15 patients are planned to be enrolled.

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Diagnosis and main criteria for inclusion:

Inclusion Criteria

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

1. Patient has documented evidence of HO, including:
   a. Recent (within the previous 8 months before Screening) evidence of hypothalamic injury on magnetic resonance imaging (MRI); AND
   b. Diagnosis of craniopharyngioma or other non-malignant brain tumor affecting the hypothalamic region; AND
   c. Has undergone surgery, or chemotherapy, or radiation ≥6 months and ≤15 years before Screening.
2. Patient has either unilateral hypothalamic lesions (at least 6 patients) or bilateral hypothalamic lesions (at least 7 patients), as assessed by MRI.

   Note: Although the intention of the study is to enroll at least 6 patients with unilateral hypothalamic lesions, the Sponsor may decrease the required number during the course of the study.
3. Aged 6 to 40 years, inclusive, at time of enrollment. (A maximum of 10 patients between the ages of 6 and 12 will be enrolled in the study.)
4. Obesity, documented by a BMI ≥35 kg/m^2 for patients ≥18 years of age or BMI ≥95th percentile for age and gender for patients 6 to <18 years of age based on the US Centers for Disease Control and Prevention criteria.
5. Documented increase in BMI (change from pre-surgery baseline in BMI Z-score ≥0.2 for patients <18 years of age or BMI >5% for patients ≥18 years of age) either during the first 6 months following surgery or within 1 year before surgery AND still present at Screening.
6. More than 6 months after the end of post-tumor treatment, including chemotherapy, surgery, or radiation.
7. Patient must meet one of the following contraception requirements:
   - 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 9.19.5.
   - 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 study.
   - Younger female patients who have not reached menarche upon study 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.

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- If a male with female partner(s) of childbearing potential, must agree to a double barrier method if they become sexually active during the study. Furthermore, male patients must not donate sperm during and for 90 days following their participation in the study.

8. Ability to communicate well with the Investigator, understand and comply with the requirements of the study, and understand and sign the written informed consent, or, for patients aged <18 years, a parent/legal guardian that can sign.
9. If receiving hormone replacement therapy (ie, thyroid hormones, glucocorticoids, growth hormone or other medications known to affect metabolism or weight/body composition), the dose of such therapy has remained stable for at least 2 months prior to Screening. (Changes in dose of ≤15% may be permissible, with the Sponsor's approval.)

Exclusion Criteria

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

1. Weight gain >5% in the previous 3 months.
2. Weight loss ≥2% in the previous 3 months.

   NOTE: Dietary and/or exercise regimens, with or without the use of medications, supplements or herbal treatments associated with weight loss (eg, orlistat, lorcaserin, phentermine, topiramate, naltrexone, bupropion, glucagon-like peptide-1 [GLP-1] receptor agonists, etc.) are allowed if:

   - the regimen and/or dose has been stable for at least 3 months prior to randomization
   - the patient has not experienced weight loss ≥2% during the previous 3 months, AND
   - the patient intends to keep the regimen and/or dose stable throughout the course of the study.
3. Bariatric surgery or procedure (eg, gastric bypass/band/sleeve, duodenal switch, gastric balloon, intestinal barrier, etc) within the last 6 months. All patients with a history of bariatric surgery or procedures must be discussed with and receive approval from the Sponsor prior to enrollment.
4. Diagnosis of severe psychiatric disorders (eg, schizophrenia, bipolar disorder, personality disorder), or Major Depressive Disorder (MDD) within the previous 2 years, or Screening Patient Health Questionnaire (PHQ)-9/PHQ-A score ≥15, or any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) during Screening, or lifetime history of suicide attempts, or any suicidal behavior in the last month.
5. Glycated hemoglobin (HbA1c) >10.0% at Screening.
6. Current, clinically significant pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor to determine eligibility.
7. Glomerular filtration rate (GFR) <30 mL/min/1.73 m^2 during Screening.
8. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a comprehensive

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skin evaluation performed by the Investigator during Screening. Any concerning lesions identified during Screening will be biopsied and results known to be benign prior to enrollment. If the pre-treatment biopsy results are of significant concern, the patient is not eligible for study participation. 9. History or close family history (parents or siblings) of skin cancer or melanoma (not including noninvasive, infiltrative basal or squamous cell lesion), or patient history of ocular-cutaneous albinism. 10. Participation in any clinical study with an investigational drug/device within 3 months or 5 half-lives, whichever is longer, prior to the first setmelanotide dose. 11. Previously enrolled in a clinical study involving setmelanotide or any previous exposure to setmelanotide. 12. Inability to comply with once daily (QD) injection regimen. 13. Pregnant and/or breastfeeding, or desiring to become pregnant during this trial. 14. Cognitive impairment that, in the Investigator's opinion, precludes participation to the study and completions of study procedures or questionnaires. 15. Patient is, in Investigator's opinion, otherwise not suitable to participate in the study.
Investigational product, dosage, and mode of administration: **Investigational product**: Setmelanotide, 10 mg/mL in a sterile solution for injection. **Dosage**: 1.0, 2.0, 3.0 mg QD for patients 6 to <16 years of age, and 2.0 to 3.0 mg QD for patients ≥16 years of age. **Mode of administration**: SC injection
Duration of treatment: All patients will receive study treatment for 16 weeks. Total study participation will last between 22 and 28 weeks, based on the variable length of the Screening Period.
Reference therapy, dosage, and mode of administration: NA

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Criteria for evaluation:

Primary endpoints:

- Proportion of patients with ≥5% reduction from baseline in BMI after 16 weeks of setmelanotide treatment compared to a historic control of <5% in this patient population.

Key Secondary Endpoints:

- Composite proportion of patients aged ≥6 to <18 years with ≥0.2 reduction of BMI Z-score and patients aged ≥18 years with 5% reduction of body weight from baseline after 16 weeks of setmelanotide
- Proportion of patients aged ≥6 to <18 years with ≥0.2 reduction of BMI Z-score from baseline after 16 weeks of setmelanotide
- Proportion of patients aged ≥18 years with ≥5% reduction of body weight from baseline after 16 weeks of setmelanotide

Other Secondary Endpoints:

- Change from baseline in waist circumference in patients aged ≥18 years after 16 weeks of setmelanotide treatment.
- Change in hunger in response to 16 weeks of setmelanotide treatment as measured by change from baseline in daily and global hunger scores.
- Safety and tolerability assessed by the frequency and severity of AEs, vital signs, and laboratory evaluations.

[redacted]

Statistical methods:

The study is a Phase 2, Proof-of-Concept study. The objective of this study is to evaluate safety and preliminary efficacy on weight loss in patients with HO. The primary endpoint is the proportion of patients who achieve at least 5% reduction from baseline in BMI at ~16 weeks of treatment with setmelanotide. Given the exploratory nature of the study, the sample size is primarily driven by clinical considerations, with the consideration of statistical testing. It is planned to enroll ~5 to 10 patients aged ≥12 years, and up to 10 patients between 6 and <12 years. With 10 patients aged ≥12 years and up to

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10 patients aged 6 to <12 years, at 1-sided 0.05 significance level, the study provides ~90% power to reject the null hypothesis that the true response rate is less than 5%, assuming a 40% target response rate in setmelanotide.

2. SCHEDULE OF ACTIVITIES

The schedule of activities (SoA) is presented in Table 1.

Table 1: Schedule of Activities

Study Period/Procedure	**Screening**	**Study Treatment**						**EOS Visit**	**Treatment Discontinuation Visit**
Clinic Visit Number	**V1**	**V2**	**-**	**V3 [1]**	**V4**	**V5**	**V6 [2]**	**V7 [2]**	
Study Day	-56 to -14	1	15	29	57	85	113	141	
Visit Window (days)	-	-	+3d	**±4 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**
Informed consent/assent [3]	X								
Inclusion/exclusion criteria review	X	X							
Medical history review	X								
Physical examination [4]	X	X		X	X	X	X	X	X
Comprehensive skin examination [5]	X						X		X
Fitzpatrick classification scale	X						X	X	X
Weight [6]	X	X		X	X	X	X	X	X
Waist circumference [7]	X	X		X	X	X	X	X	X
Height [8]	X			X	X	X	X	X	X
Body composition assessment by DXA [9]	X						X		X
Vital signs [10]	X	X		X	X	X	X	X	X
ECG (12-lead) [11]	X	X [11]		X [11]			X [11]		X
Pregnancy test [12]	X	X[13]		X	X[13]	X[13]	X[13]		X
Daily hunger questionnaires [14, 15]	X	Daily							X
Global hunger assessment [15]		X[13]		X[13]	X[13]	X[13]	X[13]	X	X
PHQ-A or PHQ-9 [16, 17]	X	X[13]		X[13]	X[13]	X[13]	X[13]	X	X
C-SSRS [18]	X	X[13]		X[13]	X[13]	X[13]	X[13]	X	X
SF-12 or SF-10 [19]	X	X[13]		X[13]			X[13]		X
IWQOL-Lite-CT [20]	X	X[13]		X[13]			X[13]		X

Study Period/Procedure	**Screening**	**Study Treatment**						**EOS Visit**	**Treatment Discontinuation Visit**
Clinic Visit Number	**V1**	**V2**	**-**	**V3 [1]**	**V4**	**V5**	**V6 [2]**	**V7 [2]**	
Study Day	-56 to -14	1	15	29	57	85	113	141	
Visit Window (days)	-	-	+3d	**±4 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**
EQ-5D-5L or Y [21]	X	X[13]		X[13]			X[13]		X
Safety laboratory tests [22]	X	X		X[13]	X[13]	X[13]	X[13]	X	X
FSH*	X								
[redacted]									
Injection site inspection [24]		X		X	X	X	X		X
Telephone call [25]			X						
Review lesion type on MRI [26]	X								
Study drug administration [27]		Daily dosing							
Dispense/Return study drug [28]		X		X	X	X	X		
Adverse event assessment [29]	X	X	X	X	X	X	X	X	X
Concomitant medications review	X	X	X	X	X	X	X	X	X

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; D = Days; DXA = Dual-energy X-ray absorptiometry; ECG = electrocardiogram; EOS = End of Study; EQ-5D = EuroQol-5 Dimension; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical Trials version; FSH = follicle-stimulating hormone; [redacted] MRI = magnetic resonance imaging; PHQ = Patient Health Questionnaire; SF= Short Form; V = Study Visit Number.

1. Patients who are <16 years of age will receive first daily dose of 3.0 mg at V3, at the clinic.
2. Study endpoints are analyzed at V6. After completing V6. Patients meeting the primary endpoint may be eligible to be enrolled in a separate extension study, Rhythm Study RM-493-022, under which auspices the patient will continue to receive setmelanotide. Patients who do not meet the primary endpoint or elect not to continue setmelanotide are to discontinue setmelanotide at Visit 6 and return for an End-of-Study Visit (Visit 7) 4 weeks thereafter for a final safety review under the auspices of the current study.
3. Although the study procedures and assessments required per protocol are classified as "No or Minimal Risk" (with the exception of DXA which may be classified as "Minor Increase over Minimal Risk") according to the 2008 Guidance Document "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population," considerations for reducing pain in distress in patients younger than 18 years of age are included in Appendix 2.

4. A complete physical examination will be conducted at Screening and at the EOS V7. At other time points, an abbreviated examination will be performed. The abbreviated examination should focus on heart, lungs, skin, neurologic exam, and any areas of previous abnormal findings, noting any changes from baseline. In addition, Tanner Staging for assessment of pubertal development will be conducted for those patients who have yet to reach Tanner Stage V. Whenever possible, the same trained health care professional will conduct the exam and Tanner Staging.
5. A comprehensive skin examination will be performed by the Investigator. The skin examination should include a full body (head-to-toe skin examination). If any concerning lesions are identified during Screening, the patient should be referred to a dermatologist. Any concerning lesions will be biopsied by the dermatologist and results must be benign prior to the first dose of setmelanotide. If the pre-treatment biopsy results are of concern, the patient will be excluded from the study. Additionally, any concerning lesion or change in an existing lesion during the course of the study must be evaluated by the dermatologist and biopsied, if clinically indicated in the opinion of the dermatologist.
6. Weight (kg) is to be measured at the clinic using the same scale throughout the study, including the Screening Visit, after patients have emptied their bladders and pockets and after fasting for at least 8 hours. Patients are to wear light clothing or underwear and no shoes, and will be weighed at approximately the same time of day. Weight should be recorded to the nearest tenth of a decimal place if reported by a digital scale or to the nearest half of a kg if reported by a mechanical scale.
7. Waist circumference (cm) will be done in triplicate and recorded to the nearest half cm. Waist circumference should be measured after patients have fasted for at least 8 hours and at approximately the same time at each visit. Patients should be standing and in light clothing and have emptied their bladder. Whenever possible, the same study staff member should perform the measurement for a given patient to minimize variability.
8. For patients ≥18 years of age, height needs to be measured at Screening only. Height (cm) will be measured, without shoes, socks, or hats, using a wall-mounted stadiometer. All measurements will be done in triplicate at each time point and recorded to the nearest half cm.
9. Body composition assessment will be performed using DXA. If DXA is not available at the clinic, this procedure may be skipped, with prior approval of the Sponsor.
10. All blood pressure (BP) and heart rate (HR) measurements are to be obtained with the patient in the sitting position following at least 5 minutes of rest. All measurements will be taken in triplicate, approximately 2 minutes apart. When possible, BP should be taken in the non-dominant arm throughout the study, using the same methodology (automated or manual). Body temperature (°C) and respiration rate (breaths/minute) will be obtained in the sitting position following at least 5 minutes of rest.
11. A single 12-lead ECG will be performed in the supine position following a period of at least 10 minutes of rest. At V2, the ECG will be performed before and 4 hours after dosing, and at V3 and V6, the ECG is to be performed at 4 hours after dosing.
12. A urine pregnancy test may be performed to expedite availability of results prior to dosing on Day 1. All other pregnancy tests will be serum tests; dosing may continue with results pending.
13. Collected prior to study drug administration.
14. Daily hunger questionnaire scores will be recorded prior to the patient's morning meal. During Screening, the patient must complete the daily hunger questionnaire in the electronic diary at least 4 of the 7 days prior to V2, paper version can be used if required. Patients who do not meet this requirement should not be enrolled into the study. V2 may be rescheduled if needed to fulfill this requirement with Sponsor approval.

[redacted]

16. In order to be eligible for the study, an individual patient's PHQ-A or PHQ-9 score must be <15 at Screening. If at any time during the study an individual patient's PHQ-A or PHQ-9 score is ≥10, the patient should be referred to a Mental Health Professional (MHP).
17. The PHQ-A will be administered to patients 11-17 years old and the PHQ-9 will be administered to patients ≥18.
18. In order to be eligible for the study, a patient at Screening cannot have a suicidal ideation of type 4 or 5, any lifetime history of a suicide attempt, or any suicidal behavior in the last month. If at any time during the study a patient has a suicidal ideation of type 4 or 5, or any suicidal behavior, the patient should be referred to an MHP.
19. The SF-12 will be administered to patients ≥18 years of age and the SF-10 will be administered to the parents/caregivers of patients <18 years of age.

20. IWQOL-Lite-CT will be administered to patients ≥18 years of age.
21. The EQ-5D-5L will be administered to patients ≥16 years of age. The EQ-5D-Y will be administered to patients >8 up to <16 years of age. In patients under the age of 8 years of age will not complete the EQ-measures.
22. Safety laboratory tests will include: complete blood count with differential (platelet count, red blood cell [RBC] count, hemoglobin, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, basophils) and standard indices (mean corpuscular volume, mean corpuscular hemoglobin, %reticulocytes), 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), and urinalysis with microscopic analysis if positive findings on dipsticks warrant further examination.
23. Blood samples will be collected prior to dose administration in the fasting state for total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides.
24. 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 evaluation data can be collected at any visit in which there are injection site reactions, even if not a time point for formal assessment.
25. Site personnel will call the patient on Day 15 to confirm the proper dose escalation has occurred and to collect AEs.
26. All patients must have evidence of hypothalamic injury on MRI completed within 8 months of Screening. If no MRI is available, then it may be repeated during the Screening Period.
27. Patients/caretakers will draw up and self-administer/administer the drug once daily in the morning beginning the morning of Day 1 and for the duration of dosing. On days with clinic visits, the patients/caretakers will administer the drug in the clinic in the presence of the clinical staff to assure proper technique.
28. Patients/caretakers will return all (the number recorded) used vials to the clinic when they visit, and both clinic-administered study drug as well as outpatient study drug administration will be recorded in a study diary.
29. AEs will be recorded from the time a patient provides informed consent. AEs reported after dosing on Day 1 will be considered TEAEs.

* FSH should be measured in women who have been post-menopausal >12 months and should be in post-menopausal range.

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3. INTRODUCTION

3.1. Rationale for the Study

Central melanocortin signaling is the central element of energy homeostasis [Holland 2019]. In patients with hypothalamic lesions, leptin signaling is often disturbed and as a result melanocortin signalling is reduced [Enriori 2016; Roth 2010; Roth 1998; Patel 2002; Shaikh 2008]. Imaging studies in humans and rodents 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 severe obesity that arises from mechanical hypothalamic insults (eg, tumors, tumor resections, radiotherapy treatment). Lesions of hypothalamus can derive from various types of tumors (craniopharyngiomas, gliomas, pituitary adenomas, hamartomas) and surgeries and radiotherapies for the treatments of the tumor itself. Literature reports that patients with craniopharyngioma are less physically active than controls with comparable body mass indices (BMIs) [Harz 2003]. Moreover, they display higher degree of hyperleptinemia and hyperinsulinemia when compared to individuals with normal 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" or 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, MTII 1mg/kg/d intraperitoneally over a period of 14 days, resulted in a robust reduction of weight gain in CMHL rats without rebound/tachyphylaxia (-17.2% vs. saline injected controls) [Roth 2012]. Taken together, these preclinical and clinical findings offer a rationale for a novel melanocortin treatment in patients with HO to compensate for potentiate the defective leptin signaling.

Setmelanotide, a potent agonist of the human melanocortin 4 receptor (MC4R) [Sharma 2019], has been studied in relevant genetic models of obesity, and in clinical studies. In mice, leptin-receptor deficient Zucker fa/fa rats (a rodent model of genetic obesity impacting the MC4R pathway) and Magel2-null mice (a mouse model for Prader-Willi syndrome), treatment with a melanocortin receptor agonist reduced both body weight and food intake [Bischof 2016; Hwa 2001]. These data demonstrate that setmelanotide is effective in these models of monogenic and syndromic obesity. In humans, homozygous mutations of the proopiomelanocortin (POMC) and leptin receptor (LEPR) obesity were successfully treated by setmelanotide [Kuhnen 2016; Clement 2018]. 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".

Putting together these results, MC4Rs expressed in the paraventricular nucleus (PVN) of the hypothalamus play a paramount role for body-weight regulation and for the leptin–melanocortin weight regulatory pathway of the hypothalamus [Kuhnen 2019]. Although setmelanotide has not been tested in a model of HO, given its role in restoring POMC pathway in POMC/LEPR deficient patients and the reported damage of the POMC pathway in the HO syndrome, this proposed study will investigate whether setmelanotide can be employed to recover melanocortin signaling and reduce body weight and/or hunger in patients with HO.

3.2. Setmelanotide

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

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

To support clinical studies, the toxicological profile of setmelanotide formulations has been evaluated in repeated-dose continuous SC infusion toxicity studies up to 13 weeks in duration in rats and monkeys. The formulation used in almost all of these studies, including the pivotal 28-day and 13-week toxicology studies, was setmelanotide in 0.9% sodium chloride for injection (setmelanotide-saline formulation), tested over a range of concentrations. An International Council for Harmonisation (ICH)-compliant battery of in vitro and in vivo genetic toxicity studies that included a bacterial mutation assay, a chromosomal aberration assay in cultured human peripheral blood lymphocytes and a rat micronucleus study has been completed with this formulation. In addition, a 7-day repeat dose local tolerability bridging study was conducted with the current clinical formulation, setmelanotide-mPEG/DSPE (N-[Carbonyl-methoxypolyethylene glycol 2000]-1,2-distearoyl- glycero-3-phosphoethanolamine sodium salt) in rodents.

Finally, chronic toxicology, reproductive, and juvenile toxicology studies using the RM-493-mPEG/DSPE formulation are completed and reports are in preparation.

The most significant potential safety issue for MC4R agonist compounds is the concern about potential mechanism-based increases in HR and BP. An MC4R agonist, LY2112688 (Eli Lilly and Company), had been studied in the clinic and caused HR and BP increases at all doses (eg, up to a mean 9.4 mm Hg increase in systolic BP [SBP] at the highest dose) [Greenfield 2009, Kievit et al 2013]. While the increases were not an immediate safety concern for the healthy volunteers in the Lilly study, similar but chronic increases in a patient population with obesity would have been problematic.

Setmelanotide was developed in nonclinical studies to analyze and obviate these cardiovascular (CV) effects. A large number of nonclinical studies were performed to demonstrate that setmelanotide did not cause similar CV effects as LY2112688, while still delivering equal or greater efficacy in animal models. The underlying premise of the development program was that setmelanotide in humans would deliver efficacy on weight loss without unacceptable CV effects.

A review of the clinical effects of setmelanotide revealed little if any evidence of BP or HR change from baseline versus placebo in any study, nor evidence of a pharmacokinetic/pharmacodynamic relationship [Gottesdiener 2015].

Other potential safety and/or tolerability issues that have been reported from published literature for some MC4R agonists in clinical and animal studies have included nausea and vomiting, male penile erections, increases in female sexual arousal, and off-target activity at the closely related MC1R (which mediates melanin deposition in the skin, producing tanning). In addition to careful CV monitoring, the setmelanotide program was designed to include careful monitoring for these potential mechanism-based effects in the initial clinical studies.

Overall, ~600 subjects have been exposed to setmelanotide or matching placebo at doses ranging from 0.0025 to 0.1 mg/kg/24 hours (0.12-9.12 mg total daily dose) in the setmelanotide clinical development program. (The exact number is not known, due to ongoing double-blinded clinical studies.) Overall, setmelanotide has been well tolerated by subjects who have received it in clinical studies. Regardless of formulation, setmelanotide has demonstrated a mostly similar set of adverse events (AEs) in both short-term and long-term clinical studies. Treatment-emergent adverse events (TEAEs) associated with setmelanotide include injection site reactions, intermittent and short-duration gastrointestinal AEs (mostly mild in grade, including reduced appetite, nausea, diarrhea, and vomiting), gradual and reversible increases in skin and nevi pigmentation, and short duration, intermittent male penile erections.

Data obtained to date in the setmelanotide clinical program demonstrate robust weight reduction and hunger suppression efficacy in obesity disorders impacting the leptin-melanocortin pathway, with proof-of-concept established for obesity associated with POMC deficiency, LEPR deficiency, Bardet-Biedl syndrome, and Alström syndrome. By restoring impaired signaling in this pathway, setmelanotide can serve as an indirect form of replacement therapy for patients with hypothalamic deficiencies leading to extreme obesity, with the potential for dramatic improvements in body weight and appetite control.

3.3. Benefit/Risk Assessment

Setmelanotide has not been investigated previously in patients with HO, a population of patients with no effective long-term therapeutic options [Abuzzahab 2019]. However, in patients with rare genetic forms of obesity, setmelanotide has been associated with clinically meaningful reductions in weight and improvement in hunger. In particular, in patients with POMC or LEPR deficiency obesity, who are characterized by early onset obesity, severe hunger and progressive weight gain, setmelanotide has demonstrated clinically meaningful and statistically significant weight reduction, often bringing patients with very high morbid obesity BMI (>40 kg/m^2) to BMI ranges in the overweight or normal range (<30 kg/m^2). In addition to weight loss, setmelanotide has demonstrated clinically meaningful and statistically significant decreases in hunger. Both the decreased hunger and the weight loss continue over 52 weeks of treatment and are maintained with continued setmelanotide treatment. Furthermore, following the significant

weight loss with setmelanotide treatment, there were improvements in glycated hemoglobin (HbA1c), glucose and lipids, as well as body composition with decreased fat mass and decreased waist circumference. These weight loss changes were accompanied by improvements in quality of life.

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

Overall, the substantial weight loss, reduction of hunger, and improvement in cardiometabolic parameters, as well as quality of life, represents a clinically significant benefit with minimal safety risk to patients with rare forms of obesity treated with setmelanotide.

In conclusion, it is considered that setmelanotide will have a positive benefit-risk profile in patients with HO who have no long-term successful therapeutic options.

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

4. OBJECTIVES AND ENDPOINTS

The objectives and endpoints are summarized in Table 2.

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary	
• The primary objective of this study is to evaluate the change in body weight in response to setmelanotide administered subcutaneously (SC) daily in patients with HO.	• Proportion of patients with ≥5% reduction from baseline in BMI after 16 weeks of setmelanotide treatment compared to a historic control of <5% in this patient population.
Secondary	
• The secondary objectives of this study are to evaluate changes in parameters of body weight, body mass index (BMI), waist circumference, and hunger in response to setmelanotide in patients with HO and to evaluate the safety and tolerability of setmelanotide in patients with HO.	*Key Secondary* • Composite proportion of patients aged ≥6 to <18 years with ≥0.2 reduction of BMI Z-score and patients aged ≥18 years with 5% reduction of body weight from baseline after 16 weeks of setmelanotide • Proportion of patients aged ≥6 to <18 years with ≥0.2 reduction of BMI Z-score from baseline after 16 weeks of setmelanotide • Proportion of patients aged ≥18 years with ≥5% reduction of body weight from baseline after 16 weeks of setmelanotide *Other Secondary* • Change from baseline in waist circumference in patients aged ≥18 years after 16 weeks setmelanotide treatment. • Change in hunger in response to 16 weeks of setmelanotide treatment as measured by change from baseline in daily and global hunger scores. • Safety and tolerability assessed by the frequency and severity of AEs, vital signs, and laboratory evaluations.

Objectives	Endpoints
[redacted]	[redacted]

5. STUDY DESIGN

5.1. Overall Design

This is a Phase 2, multicenter, open-label, proof of concept study designed to assess the effect of setmelanotide on weight loss on a population affected by HO. Approximately 15 patients aged 6 to 40 years, inclusive, are planned to be enrolled across approximately 3-5 clinical sites in the United States (US).

Screening Period

Upon providing informed consent, patients will enter the Screening Period, during which they will be assessed for eligibility and complete all screening procedures as described in the Schedule of Activities (SoA) (Table 1).

Treatment Period

Patients who are determined to be eligible, based on Screening assessments, will return to the clinic for the Baseline Visit (Visit 2) and receive the first setmelanotide dose. The starting setmelanotide dose is dependent on patient age; however, for all patients, the setmelanotide dose will be titrated to a final dose of 3.0 mg/day (initial titration phase), as follows:

Patients aged 6 to <16 years, inclusive

- Starting at Baseline (Day 1; Visit 2) through approximately Day 14, patients will receive setmelanotide 1.0 mg/day.
- Starting at approximately Day 15 through 28, patients will receive setmelanotide 2.0 mg/day.

  Patients/caregivers will be contacted by study center personnel on Day 15 to ensure dose titration has occurred and to document any AEs.
- Starting on approximately Day 29 (Visit 3), patients will receive setmelanotide 3.0 mg/day; patients will continue to receive setmelanotide 3.0 mg/day for 12 weeks.

The dose of setmelanotide should be titrated as explained in the SoA.

Patients aged ≥16 years, inclusive

- Starting at Baseline (Day 1; Visit 2) through approximately Day 14, patients will receive setmelanotide 2.0 mg/day.
- Starting at approximately Day 15, patients will receive setmelanotide 3.0 mg/day; patients will continue to receive setmelanotide 3.0 mg/day for 14 weeks.

  Patients/caregivers will be contacted by study center personnel on Day 15 to ensure dose titration has occurred and to document any AEs.

The dose of setmelanotide should be titrated as explained in the SoA.

Patients will return to the study center for Visits 3, 4, and 5 (Weeks 4, 8, and 12, respectively), with each of these visits conducted approximately 4 weeks apart. All patients will return to the study center at Week 16 (Visit 6) and receive the last setmelanotide injection. Study endpoints are analyzed at Visit 6. After completion of Visit 6, participation in the current study will then conclude in one of the following 2 ways:

- Patients meeting the primary endpoint may be eligible to be enrolled in a separate extension study, Rhythm Study RM-493-022, under which auspices the patient will continue to receive setmelanotide.
- Patients who do not meet the primary endpoint or elect not to continue setmelanotide are to discontinue setmelanotide at Visit 6 and return for an End-of-Study (EOS) Visit (Visit 7) 4 weeks thereafter for a final safety review under the auspices of the current study.

5.2. Patient and Study Completion

The study is planned to enroll ~15 patients, with ~5 to 10 patients aged >12 years, and up to 10 patients between 6 and 12 years.

A patient is considered to have completed the study if he/she has either:

- Receives the last planned setmelanotide dose at Week 16 (Visit 6), meets the primary endpoint, and elects to enroll in a separate extension study, Rhythm Study RM-493-022, under which auspices the patient will continue to receive setmelanotide.

- Receives the last planned setmelanotide dose at Week 16 (Week 6) and completes the EOS Visit (Visit 7) for a final safety review under the auspices of the current study.

Patients who discontinue before completing the 16-week treatment period are to attend a Treatment Discontinuation visit within 7 days (±4 days) after the last setmelanotide dose for final study assessments.

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

5.3. Scientific Rationale for Study Design

Setmelanotide is being evaluated as a potential treatment for obesity in rare mechanistically induced populations with hypothalamic injury and subsequent obesity.

Given the rarity of the condition under study, no placebo control group is planned. Placebo comparisons with so few patients with HO existing, all of whom are expected to demonstrate a very high need for therapy, are not considered feasible.

[redacted]

5.4. Justification for Dose

Based on the results of previous studies in patients with rare genetic forms of obesity, the recommended setmelanotide dose for adults is a starting dose of 2 mg once daily (QD), with, if tolerated for 2 weeks, an increase to 3 mg QD, aiming to achieve a normal BMI.

For adolescents 12 to 15 years of age and pediatric patients 6 to 11 years of age, the recommended starting setmelanotide dose is 1 mg QD, with, if tolerated for 2 weeks, an increase to 2 mg, aiming to achieve a healthy weight 50-90th centile per charts/guidelines. A further escalation to 3 mg QD is required at the end of Week 4 (Day 28). There are 2 main factors supporting this regimen.

[redacted]

[redacted]

5.5. Study Conduct During the COVID-19 (Coronavirus) Pandemic

The worldwide Coronavirus Disease 2019 (COVID-19) pandemic may impact the conduct of clinical studies due to the challenges from quarantines, site closures, travel limitations, and other considerations if site personnel or study participants become potentially exposed to or infected with COVID-19. To assure the safety of study participants, maintain compliance with Good Clinical Practice (GCP), and minimize risks to study integrity, if necessary, in consultation with the Sponsor, the method of assessment may be changed (eg, 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 study conduct during the COVID-19 pandemic is provided in Appendix 8.

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

1. Patient has documented evidence of HO, including:
   a. Recent (within the previous 8 months before Screening) evidence of hypothalamic injury on magnetic resonance imaging (MRI); AND
   b. Diagnosis of craniopharyngioma or other non-malignant brain tumor affecting the hypothalamic region; AND
   c. Has undergone surgery, or chemotherapy, or radiation ≥6 months and ≤15 years before Screening.
2. Patient has either unilateral hypothalamic lesions (at least 6 patients) or bilateral hypothalamic lesions (at least 7 patients), as assessed by MRI.

   Note: Although the intention of the study is to enroll at least 6 patients with unilateral hypothalamic lesions, the Sponsor may decrease the required number during the course of the study.
3. Aged 6 to 40 years, inclusive, at time of enrollment. (A maximum of 10 patients between the ages of 6 and 12 will be enrolled in the study.)

4. Obesity, documented by a BMI ≥35 kg/m^2 for patients ≥18 years of age or BMI ≥95th percentile for age and gender for patients 6 to <18 years of age based on the US Centers for Disease Control and Prevention criteria.
5. Documented increase in BMI (change from pre-surgery baseline in BMI Z-score ≥0.2 for patients <18 years of age or BMI >5% for patients ≥18 years of age) either during the first 6 months following surgery or within 1 year before surgery AND still present at Screening.
6. More than 6 months after the end of post-tumor treatment, including chemotherapy, surgery, or radiation.
7. Patient must meet one of the following contraception requirements:
   - 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 9.19.5.
   - 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 study.
   - Younger female patients who have not reached menarche upon study 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 study. Furthermore, male patients must not donate sperm during and for 90 days following their participation in the study.
8. Ability to communicate well with the Investigator, understand and comply with the requirements of the study, and understand and sign the written informed consent, or, for patients aged <18 years, a parent/legal guardian that can sign.
9. If receiving hormone replacement therapy (ie, thyroid hormones, glucocorticoids, growth hormone or other medications known to affect metabolism or weight/body composition), the dose of such therapy has remained stable for at least 2 months prior to Screening. (Changes in dose of ≤15% may be permissible, with the Sponsor's approval.)

6.2. Exclusion Criteria

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

1. Weight gain >5% in the previous 3 months.
2. Weight loss ≥2% in the previous 3 months.

   NOTE: Dietary and/or exercise regimens, with or without the use of medications, supplements or herbal treatments associated with weight loss (eg, orlistat, lorcaserin,

phentermine, topiramate, naltrexone, bupropion, glucagon-like peptide-1 [GLP-1] receptor agonists, etc.) are allowed if:

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

3. Bariatric surgery or procedure (eg, gastric bypass/band/sleeve, duodenal switch, gastric balloon, intestinal barrier, etc.) within the last 6 months. All patients with a history of bariatric surgery or procedures must be discussed with, and receive approval from, the Sponsor prior to enrollment.
4. Diagnosis of severe psychiatric disorders (eg, schizophrenia, bipolar disorder, personality disorder), or Major Depressive Disorder (MDD) within the previous 2 years, or Screening Patient Health Questionnaire (PHQ)-9/PHQ-A score ≥15, or any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) during Screening, or lifetime history of suicide attempts, or any suicidal behavior in the last month.
5. HbA1c >10.0% at Screening.
6. Current, clinically significant pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor to determine eligibility.
7. Glomerular filtration rate (GFR) <30 mL/min/1.73 m^2 during Screening.
8. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a comprehensive skin evaluation performed by the Investigator during Screening. Any concerning lesions identified during Screening will be biopsied and results known to be benign prior to enrollment. If the pre-treatment biopsy results are of significant concern, the patient is not eligible for study participation.
9. History or close family history (parents or siblings) of skin cancer or melanoma (not including noninvasive, infiltrative basal or squamous cell lesion), or patient history of ocular-cutaneous albinism.
10. Participation in any clinical study with an investigational drug/device within 3 months or 5 half-lives, whichever is longer, prior to the first setmelanotide dose.
11. Previously enrolled in a clinical study involving setmelanotide or any previous exposure to setmelanotide.
12. Inability to comply with QD injection regimen.
13. Pregnant and/or breastfeeding, or desiring to become pregnant during this trial.
14. Cognitive impairment that, in the Investigator's opinion, precludes participation to the study and completions of study procedures or questionnaires.
15. Patient is, in Investigator's opinion, otherwise not suitable to participate in the study.

6.3. Lifestyle Restrictions

There are no lifestyle restrictions during study participation.

6.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be eligible for rescreening at a later date, depending on the reason for the initial screen failure and provided enrollment is still open. Rescreening of a patient must be approved by the Sponsor prior to rescreening. If a patient is approved for rescreening by the Sponsor, the rescreened patients should be assigned the same Screening number as for the initial screening. Up to 3 screenings per patient are allowed (2 screening failures).

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the study protocol.

7.1. Treatments Administered

All patients will receive open-label setmelanotide in this study.

Setmelanotide will be supplied by Rhythm.

Setmelanotide drug product is a preserved, multidose solution for injection to be administered SC, QD. It is formulated as a 10 mg/mL sterile, preserved, clear to slightly opalescent, colorless to slightly colored solution, practically free of visible particles. The drug product solution (1 mL) is presented in a clear 2R glass vial with a rubber stopper.

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

Setmelanotide will be administered as SC injection QD.

7.2. Method of Treatment Assignment

All patients will receive setmelanotide in this study. The starting setmelanotide dose is dependent on patient age at the time of Visit 2 (Day 1); however, for all patients, the setmelanotide dose will be titrated to a final dose of 3.0 mg/day (initial titration phase), as follows:

Patients aged 6 to <16 years

- Starting at Baseline (Day 1; Visit 2) through approximately Day 14, patients will receive setmelanotide 1.0 mg/day.

- Starting at approximately Day 15 through 28, patients will receive setmelanotide 2.0 mg/day.
- Patients/caregivers will be contacted by study center personnel on Day 15 to ensure dose titration has occurred and to document any AEs.
- Starting on approximately Day 29 (Visit 3), patients will receive setmelanotide 3.0 mg/day; patients will continue to receive setmelanotide 3.0 mg/day for 12 weeks.

The dose of setmelanotide should be titrated as explained in the SoA.

Patients aged ≥16 years

- Starting at Baseline (Day 1; Visit 2) through approximately Day 14, patients will receive setmelanotide 2.0 mg/day.
- Starting at approximately Day 15, patients will receive setmelanotide 3.0 mg/day; patients will continue to receive setmelanotide 3.0 mg/day for 14 weeks.

The dose of setmelanotide should be titrated as explained in the SoA.

7.3. Dose Modification

The intention of the study is for all patients to reach a dose of 3.0 mg per day. If a patient experiences tolerability or safety issues during the dose titration phase, a lower maintenance dose may be used during the trial, with approval by the Sponsor. Additionally, after titration to a dose of 3.0 mg is complete, the setmelanotide dose should not be lowered unless discussed and approved by the Sponsor. No dose greater than 3.0 mg per day will be used in this study.

7.4. Blinding

This is an open-label study; no blinding methods will be employed.

7.5. Preparation/Handling/Storage/Accountability

Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

All 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 caretakers who will travel long distances from the clinic. Once home, the un-opened study drug must be stored in the patient's refrigerator. Opened study drug may be stored at room temperature for up to 30 days.

There will be extensive training of patients in drug administration including educational materials. Study specific training materials will be provided to both the investigative staff and study patients and caregivers.

7.6. Assessment of Treatment Compliance and Study Drug Accountability

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

Compliance to dosing will be monitored throughout the study by having the patient complete a daily dosing log that records daily dosing information, including whether the dose was administered, and if not administered, the rationale for why it was not administered. If a patient is non-compliant with the dosing schedule, the Sponsor may implement steps to ensure compliance, eg, sending a nurse to the patient's home for retraining or having a nurse administer the study drug.

7.7. Concomitant Therapy

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

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

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

7.7.1. Prohibited Medications

Unless concomitant medications are likely to present a strong potential safety concern, the general goal of this protocol is to allow as many patients with this rare condition to participate in the study as possible.

However, patients are not permitted to enter the study if they have had weight gain >5% during the previous 3 months or >2% weight loss during the prior 3 months. It should be noted that dietary and/or exercise regimens, with or without the use of medications, supplements or herbal treatments associated with weight loss (eg, orlistat, lorcaserin, phentermine, topiramate, naltrexone, bupropion, glucagon-like peptide1 [GLP1] receptor agonists, etc.) are allowed if:

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

- the patient intends to keep the regimen and/or dose stable throughout the course of the study.

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

Other medications that may cause weight loss (eg, stimulants) are allowed as long as the patient (1) has used a stable dose for at least 3 months prior to enrollment, (2) has not lost weight during the previous 3 months, and (3) intends to keep the dose of the medication stable through the course of the study.

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

7.8. Treatment after the End of the Study

After the EOS Visit, no further treatment is planned under the auspices of this protocol. Patients who meet the primary endpoint of this study may be eligible to enroll in a separate long-term extension study under which auspices the patient would continue to receive setmelanotide.

8. DISCONTINUATION/WITHDRAWAL CRITERIA

Given this rare patient population, every effort will be made to encourage and keep patients enrolled in the study until completion, unless there are any safety concerns necessitating withdrawal of the patient. Rhythm will provide assistance for any patient and caregiver travel, will make available visiting home health care professionals, and any other necessary logistical support to ease the burden on the patient in order to facilitate compliance.

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

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

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

- AEs, which justify treatment or study withdrawal. For specific predefined events, additional monitoring and guidance for the Investigator is provided in Appendix 6.
- Non-adherence to study drug regimen or protocol requirements.
- Non-compliance with instructions or failure to return for follow-up.

9. PATIENT ASSESSMENTS

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

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

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

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

9.1. Informed Consent/Assent

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

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the informed consent form (ICF) may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

9.2. Inclusion/Exclusion Review

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

9.3. Demographics, Concomitant Medications and Medical History Review

Medical history and demographic data including the patient's gender, race, date of birth, and concomitant medication use will be obtained for all patients during the Screening Period (Table 1).

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

9.4. Type of Lesions on Magnetic Resonance Imaging

All patients must have evidence of hypothalamic injury on MRI completed within 8 months of Screening. If no MRI is available, then it may be repeated during the Screening Period.

Hypothalamic Lesion score [Roth 2015] will be noted and collected for each patient when possible.

9.5. Height

For patients ≥18 years of age, height needs to be measured at Screening only. For patients aged <18 years, height is to be measured at the time points designated in the SoA (Table 1).

Height (cm) will be measured, without shoes, socks, or hats, using a wall-mounted stadiometer. All measurements will be done in triplicate at each time point and recorded to the nearest half cm.

9.6. Weight

Weight (kg) will be recorded at the time points designated in the SoA (Table 1). Weight (kg) is to be measured at the clinic using the same scale throughout the study, including the Screening Visit, after patients have emptied their bladders and pockets and after fasting for at least 8 hours. Patients are to wear light clothing or underwear and no shoes, and will be weighed at approximately the same time of day. Weight should be recorded to the nearest tenth of a decimal place if reported by a digital scale or to the nearest half of a kg if reported by a mechanical scale.

The scale should be calibrated on a regular basis per the manufacturer's specifications.

9.7. Waist Circumference

Waist circumference (cm) will be measured according to the National Heart, Lung, and Blood Institute (NHLBI) criteria [NHLBI 2000] during the study at the time points designated in the SoA (Table 1). All measurements will be done in triplicate at each time point and recorded to the nearest half cm.

Waist circumference should be measured after patients have fasted for at least 8 hours and at approximately the same time at each visit. Patients should be standing and in light clothing and have emptied their bladder. Whenever possible, the same study staff member should perform the measurement for a given patient to minimize variability.

9.8. Body Composition Assessment by DXA

Patients will have body composition measurements performed by dual-energy X-ray absorptiometry (DXA) at the time points designated in the SoA (Table 1). If DXA is not available at the clinic, this procedure may be skipped, with prior approval of the Sponsor.

For DXA methodology, which uses low dose x-rays to non-invasively assess skeletal and soft tissue density, half-body scans may be performed for patients that extend beyond the scanning area. The risk associated with exposure to ionizing radiation is minimal and further minimized through the exclusion of pregnant women. If patients have severe obesity and cannot be measured in the DXA scanner available due to practical limitations (size of DXA machine), then this assessment can be skipped. If DXA is available but patients are too large to enter at Screening, DXA should be added to assessments (in addition to the methods used at study entry) at a time when patients may have lost enough weight to do adequate DXA measurements (as

DXA may provide additional information above BIA, for example). If DXA is begun in the middle of the study, it will be considered supplemental to the methodology used at Baseline.

9.9. Physical Examination and Comprehensive Skin Examination

9.9.1. Physical Examinations

A complete physical examination will be conducted at Screening and at the EOS visit (Visit 7). At other time points, as designated in the SoA, an abbreviated examination will be performed (Table 1).

- A complete physical examination will include review of peripheral lymph nodes, head, eyes (including conjunctiva), ears, nose, mouth and oropharynx, neck, heart, lungs, abdomen, musculoskeletal including back, extremities and neurologic.
- The abbreviated examination should focus on heart, lungs, skin, neurologic examination, and any areas of previous abnormal findings, noting any changes from baseline.
- Tanner Staging for assessment of pubertal development will be conducted for those patients who have yet to reach Tanner Stage V.

Whenever possible, the same trained health care professional will conduct the exam and Tanner Staging.

All physical examinations are to be conducted in adequate light.

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

9.9.2. Comprehensive Skin Examinations

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

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

9.10. Fitzpatrick Classification Scale

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

9.11. Vital Signs

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

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

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

9.12. Electrocardiograms

A single 12-lead ECG will be performed at the time points designated in the SoA (Table 1). ECGs are to be performed with the patient in the supine position following a period of at least 10 minutes of rest. At Visit 2, the ECG will be performed before and 4 hours after dosing, and at Visit 3 and Visit 6, the ECG will be performed at 4 hours after dosing.

9.13. Clinical Laboratory Tests

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

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

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

9.13.1. Pregnancy Testing

Pregnancy testing is to be performed for female patients of childbearing potential, as defined in Section 9.19.5.

A urine pregnancy test may be performed to expedite availability of results prior to dosing on Day 1. At all other time points designated in the SoA (Table 1), serum pregnancy tests may be performed; setmelanotide dosing may continue with results pending.

9.14. Injection Site Examination

Injection sites will be carefully inspected, evaluated, and scored during the study 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 5.

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

9.15. Patient Questionnaires

The patient questionnaires will be answered by the patient and/or caretaker after careful training.

9.15.1. Hunger Scores

Hunger will be assessed as shown in the SoA (Table 1).

[redacted]

For all patients, the daily hunger questionnaire will be completed prior to the morning meal (fasted) and prior to dosing each day in the morning.

The Global Hunger Questions and Daily Hunger Questionnaire are described in Appendix 4. The Global Hunger Questions will be completed during specified study visits at the clinic and the Daily Hunger Questionnaire will be recorded each day directly into an electronic data capture device (paper version can be used if needed).

9.15.2. Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT)

The Impact of Weight on Quality of Life-Lite Clinical Trials (IWQOL-Lite-CT) is a validated 20-item self-report measure of obesity-specific quality of life questionnaire [Kolotkin 2019]. The IWQOL-Lite-CT yields a Total score and 3 composite scores: Physical (7 items), including Physical Function (5 items) and Psychosocial (13 items). The IWQOL-Lite will be conducted in patients 18 years of age and older at the time points designated in the SoA (Table 1).

9.15.3. Patient Health Questionnaire-9 (PHQ-9 or PHQ-A)

The PHQ-9 is a 9-item depression scale of the Patient Health Questionnaire. The PHQ-9 is a tool for assisting clinicians in diagnosing depression as well as selecting and monitoring treatment. The PHQ-A is a modification of the PHQ-9 for adolescents. After the patient has completed the PHQ-9 or PHQ-A questionnaire, it is scored by the study staff.

The PHQ-A will be administered to patients 11-17 years of age and the PHQ-9 will be administered to patients ≥18 years of age.

The PHQ-9 or PHQ-A will be implemented at the time points designated in the SoA at the time points designated in the SoA (Table 1).

In order to be eligible for the study, the patient must have a Screening PHQ-9/PHQ-A score <15.

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

The C-SSRS is a tool used not only to predict suicide attempts but to assess the full range of evidence-based ideation and behavior items, with criteria for next steps (eg, referral to an MPH). There are 2 versions of the C-SSRS that will be administered according to the SoA (Table 1):

1. The Baseline/Screening version of the scale combines the Baseline and Screening forms to assess suicidality in a patient's lifetime and during a predefined time. This version can assess a patient's lifetime suicidality for data collection purposes as well as eligibility based on inclusion/exclusion criteria.
2. The Since Last Visit version of the scale assesses suicidality since the patient's last visit. This version is meant to assess patients who have completed at least 1 initial C-SSRS assessment and should be used in every subsequent visit. The 'Since Last Visit' version of the C-SSRS is asking about any suicidal thoughts or behaviors the patient/participant may have had since the last time the C-SSRS was administered.

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

Significantly cognitively impaired patients may not be able to complete the PHQ-9 or C-SSRS as intended. If in the clinical opinion of the Primary Investigator a specific patient cannot complete either or both of these instruments, the following strategies may be employed:

- Regardless of the patient's actual age, the site staff may administer the pediatric version of the C-SSRS, which may be more appropriate to the cognitive age of the patient.
- Site staff may administer the questions directly to the patient or may ask for the information from a third party, such as a caregiver or family members, as appropriate.
- The Primary Investigator may use his/her clinical judgment to skip any questionnaires that he/she feels are not appropriate for a specific patient.

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

9.15.5. Short Form-12/Short Form-10 (SF-12/SF-10)

The Short Form-12 (SF-12) is a self-reported outcome measure assessing the impact of health on an individual's everyday life that is often used as a quality of life measure. It is a 12-item shortened form of the 36-item SF-36 that can be completed by the patient or through interview. The SF-10 is a modified 10-item questionnaire that is to be completed by caregivers rather than the patient. The scoring method yields 2 summary measures: a physical summary score and a psychosocial summary score.

The SF-12 will be administered to patients ≥18 years of age and the SF-10 will be administered to the parents/caregivers of patients <18 years of age. The SF-12 or SF-10 is to be conducted at the time points designated in the SoA (Table 1).

9.15.6. EuroQol-Five Dimension

Patients will complete either the EuroQol-5 Dimension (EQ-5D)-5L or the EQ-5D-Y.

- EQ-5D-5L

Used for patients ≥16 years of age, the EQ-5D-5L is a standardized instrument to measure health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D-5L consists of a descriptive system and the EQ VAS. The EQ-5D instrument will be administered according to the SoA (Table 1).

- EQ-5D-Y

Used for patients 8 to 16 years of age, the EQ-5D-Y is a standardized instrument to measure health-related quality of life that can be used in a wide range of health conditions and treatments. It is the child-friendly version of the EQ-5D. The EQ-5D-Y consists of a descriptive system and the EQ VAS. The EQ-5D-Y instrument will be administered according to the SoA (Table 1).

Patients between 6 and 8 years of age will not complete this questionnaire.

9.16. Telephone Call

The site will call a patient's home on Day 15 to assess AEs and ensure the patient escalated to the appropriate dose, depending on age, as outlined in the SoA (Table 1).

9.17. Study Drug Administration

Study drug will be administered daily as outlined in the SoA (Table 1).

9.18. Dispensing/Return of Study Drug

Study drug will be dispensed as outlined in the SoA (Table 1) and Section 7.5. Any unused drug will be returned to the clinic site and the Sponsor as described in Section 7.6.

9.19. Adverse Events

The definitions of an AE or SAE can be found in Appendix 6.

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

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the patient to discontinue study treatment (see Section 8).

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

All AEs, including SAEs, will be collected from the provision of informed consent until the EOS visit (Visit 7) at the time points designated in the SoA (Table 1). AEs reported after dosing on Day 1 will be considered TEAEs.

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

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 6. The Investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 6.

9.19.2. Method of Detecting AEs and SAEs

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

9.19.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up. Further information on follow-up procedures is given in Appendix 6.

9.19.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the sponsor of a SAE is essential so that regulatory obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

9.19.5. Pregnancy and Contraception

Setmelanotide has not been completely evaluated in any preclinical Developmental and Reproductive Toxicology Studies to date, therefore, the effects of setmelanotide on embryo-fetal development are unknown at this time.

Females must not be pregnant and must have a negative pregnancy test result at each visit.

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

Female patients 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 throughout the study and for 90 days following the study. 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 woman of childbearing potential (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

Females of non-childbearing potential, defined as permanently sterile (status post hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or post-menopausal for at least 12 months (and confirmed with a screening FSH level in the post-menopausal range) do not require contraception during the study. Younger female patients who are not sexually mature at study 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 (eg, 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 (ie, hormonal or IUD) if they become sexually active during the study and for

90 days following the study. Male patients must not donate sperm for 90 days following their participation in the study.

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

9.19.6. Overdose

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

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

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

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

9.19.7. Depression or Suicidality

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

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

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

9.20. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

9.21. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.22. Genetics

Genetics are not evaluated in this study.

9.23. Biomarkers

Biomarkers are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

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

10.1. Sample Size Determination

The study is a Phase 2, Proof-of-Concept study. The objective of this study is to evaluate safety and preliminary efficacy on weight loss in patients with HO. The primary endpoint is the proportion of patients who achieve at least 5% reduction from baseline in BMI at ~16 weeks of treatment with setmelanotide. Given the exploratory nature of the study, the sample size is primarily driven by clinical considerations, with the considerations of statistical testing. It is planned to enroll ~5 to 10 patients aged >12 years, and up to 10 patients between 6 and 12 years. With 10 patients aged >12 years and up to 10 patients aged 6 to 12 years, at 1-sided 0.05 significance level, the study provides ~90% power to reject the null hypothesis that the true response rate is less than 5%, assuming a 40% target response rate in setmelanotide.

10.2. Populations for Analyses

There are 3 analysis population defined in the protocol:

- Full Analysis Set: All patients who received at least 1 dose of setmelanotide and have baseline data.
- Per-Protocol Set: All patients in FAS without any major protocol violations that will result in exclusion of the patients from the analysis
- Safety Analysis Set: All patients who received at least 1 dose of study drug.

10.3. Statistical Analyses

A separate statistical analysis plan will be developed, which will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and other endpoints

The primary endpoint is defined as the proportion of patients who achieve at least 5% BMI reduction from baseline, at ~16 weeks of treatment with setmelanotide. The primary statistical hypothesis will be tested with an exact binomial test at 1-sided 0.05 significant level, compared to a historical control rate of 5%. The 2-sided 90% Clopper-Pearson confidence interval will be provided.

For the primary endpoint, and all other endpoints, the last value obtained prior to the first dose of active treatment will be considered the baseline value for statistical analyses.

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

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 and by treatment group. 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 by treatment.

10.3.1. Interim Analyses

There is no planned interim analysis for the purposes of modifying the study.

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12. APPENDICES

APPENDIX 1. ABBREVIATIONS AND TRADEMARKS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ARC	Arcuate nucleus
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CMHL	Combined medial hypothalamic lesion
COVID-19	Coronavirus Disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End-of-Study
EQ-5D	EuroQol-5 Dimension
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GLP-1	Glucagon-like peptide-1
[redacted]	
HDL	High-density lipoprotein
HO	Hypothalamic obesity
HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IUD	Intrauterine device
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite Clinical Trials Version
[redacted]	

Abbreviation	Definition
LEPR	Leptin receptor
MC4R	Melanocortin 4 receptor
MDD	Major Depressive Disorder
MHP	Mental health professional
mPEG/DSPE	N-[Carbonyl-methoxypolyethylene glycol 2000]-1,2-distearoyl-glycero-3-phosphoethanolamine sodium salt
MRI	Magnetic resonance imaging
MSH	Melanocortin stimulating hormone
NHLBI	National Heart, Lung, and Blood Institute
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PHQ	Patient Health Questionnaire
POMC	Proopiomelanocortin
PVN	Paraventricular nucleus
QD	Once daily
RBC	Red blood cell
RR	Respiration rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SF	Short Form
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
US	United States
VMN	Ventromedial nucleus of the hypothalamus
WOCBP	Woman of childbearing potential

APPENDIX 2. 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 may be classified as "Minor Increase over Minimal Risk") according to the 2008 Guidance Document "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population", considerations for reducing pain in distress in participants <18 years of age are suggested below.

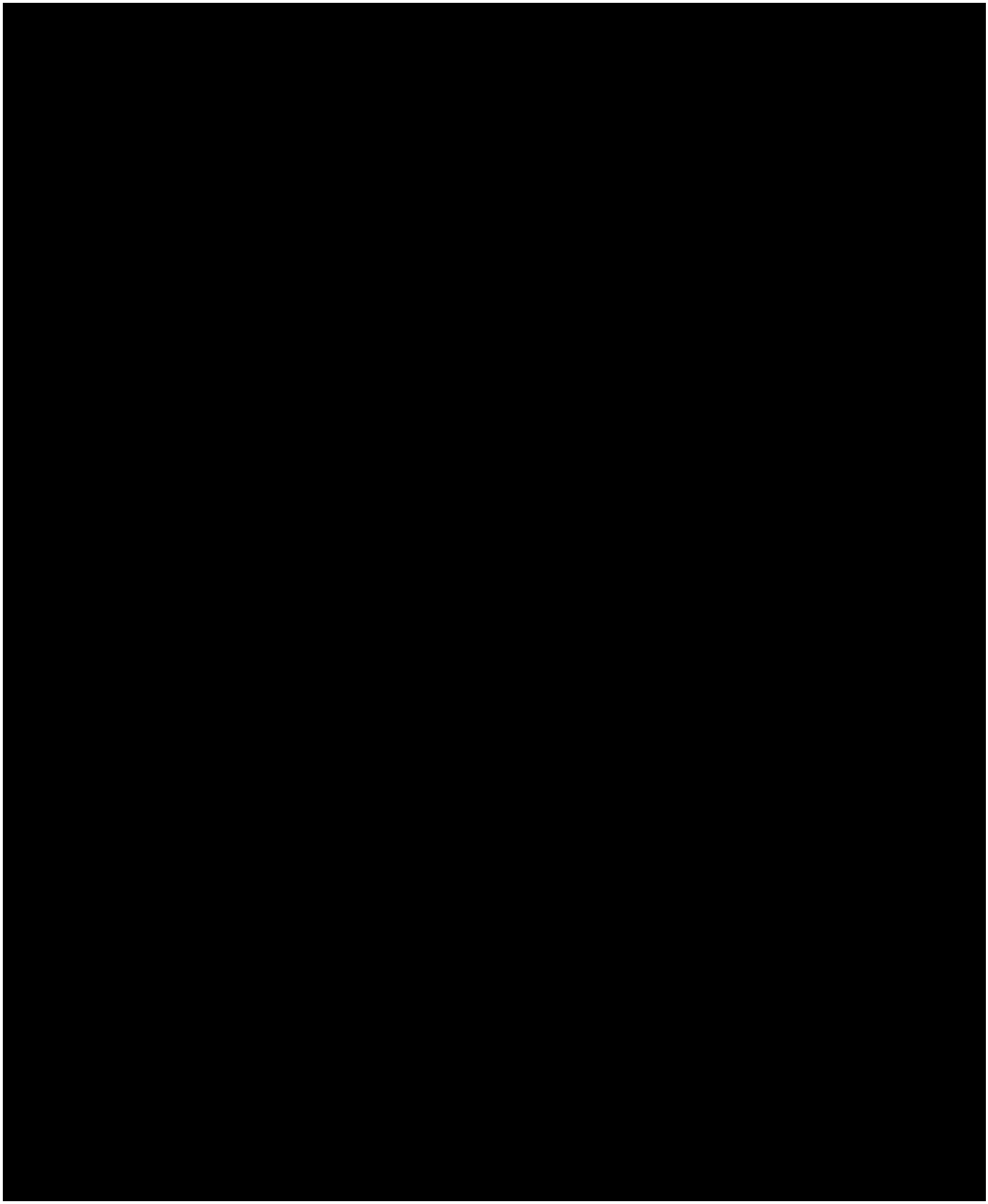
- The clinical trial may only be conducted if it patients the person concerned to as little burden and other foreseeable risks as possible.
- Physical and emotional pain should be prevented as much as possible, and effectively treated when unavoidable.
- In order to minimize pain, distress, and fear, 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 may be 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 exam without clothes.

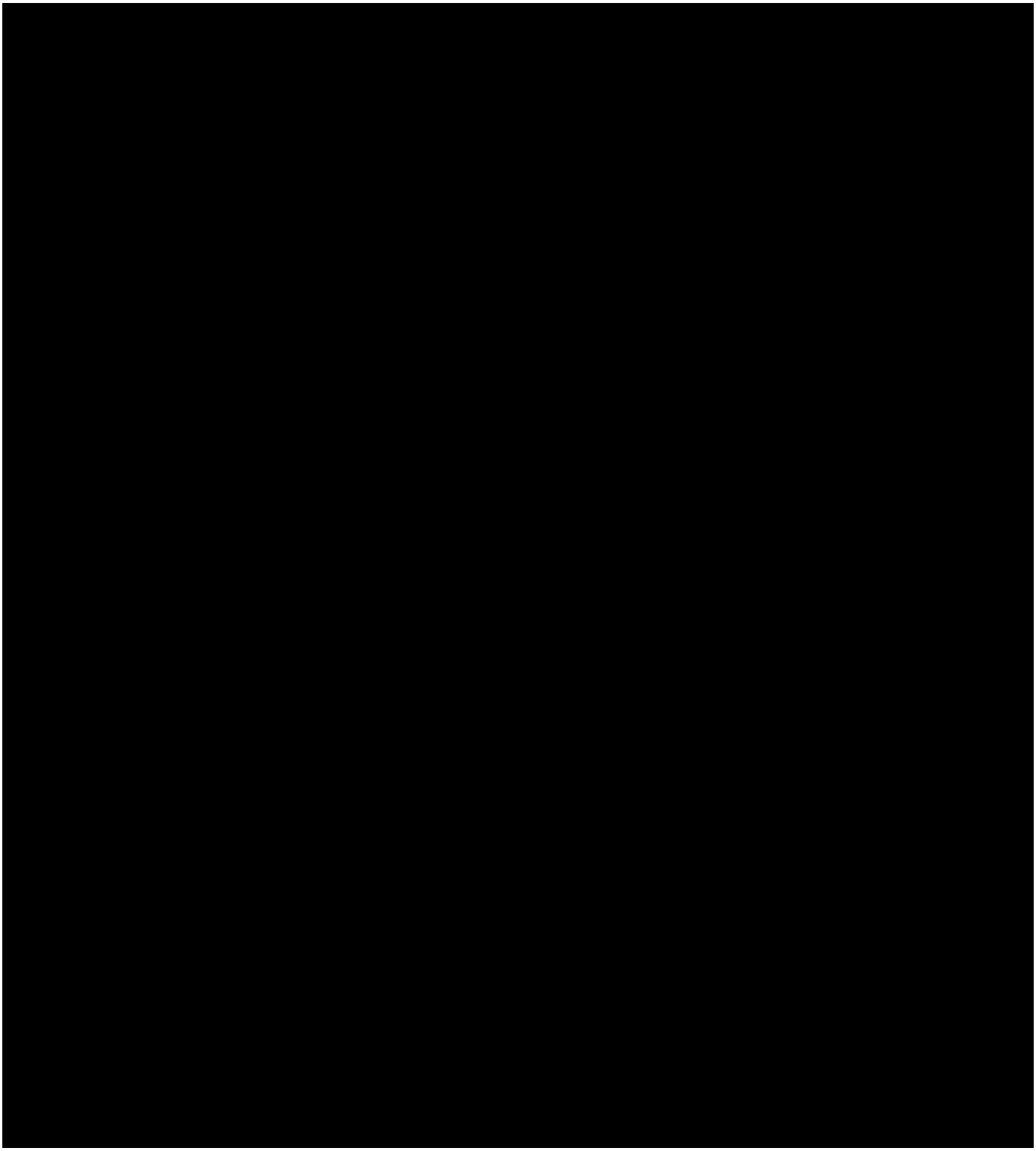
A comment on benefit risk: Risk is very low, from procedures and/or known safety profile of the drug (both clinically and toxicologically, where large margins and preliminary data from juvenile toxicology studies have not identified any new or concerning safety concerns), and based on one representative example of rare genetic disorder of obesity impacting the MC4 pathway, there is the possibility of major benefit.

APPENDIX 3. FITZPATRICK SCALE

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

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





APPENDIX 5. INJECTION SITE EVALUATIONS

Injection sites will be assessed using a form similar to the depiction below at the time points outlined in the SoA, and in the setting of any injection site reaction adverse experience.

Local Skin Tolerability Assessment

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

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

Initials: _____

APPENDIX 6. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of Adverse Event (AE)

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

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

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

Definition of Serious Adverse Event (SAE)

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

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

Recording and AE and/or SAE

AE and SAE Recording

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

Assessment of Intensity

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

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

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

Assessment of Causality

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data**.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

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

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

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

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

Reporting of SAEs

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

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

APPENDIX 7. STUDY GOVERNANCE CONSIDERATIONS

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

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

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

- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

Patients who are rescreened are required to sign a new ICF.

Data Protection

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

Data Quality Assurance

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

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

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

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

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

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

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

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

Source Documents

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

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

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

Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

For study termination:

- Discontinuation of further study intervention development.

For site termination:

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

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

- Total number of participants included earlier than expected.

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

Publication Policy

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

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

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

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

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

APPENDIX 8. GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 (CORONAVIRUS) PANDEMIC

The Coronavirus Disease 2019 (COVID-19) pandemic 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 Schedule of Events 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 (eg, remote vs. on-site, central vs. local laboratory, vital signs taken at home by caretaker vs. delegated in-home nursing, etc).
- If applicable, discontinuations of 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).

COVID-19 Infection in Study Patients:

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

APPROVAL SIGNATURE PAGE

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Protocol Number:	RM-493-030
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REVIEWED/APPROVED BY:

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Signature

Sep 13, 2021

Date

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