STATISTICAL ANALYSIS PLAN

PROTOCOL RM-493-014

Setmelanotide (RM-493) Phase 2 Treatment Trial in Patients with Rare Genetic Disorders of Obesity

Protocol Number: RM-493-014

Protocol Version and Date: Amendment 10: 20 Feb 2020

[redacted]

Name of Test Drug: Setmelanotide (RM-493)

Phase: Phase 2

Methodology: Uncontrolled, open label pilot-study

Sponsor: Rhythm Pharmaceuticals, Inc.
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Boston, MA 02116, USA
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Analysis Plan Date: 21 Sep 2021

Analysis Plan Version: Version 3.0

APPROVAL SIGNATURE PAGE

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Veristat, LLC. Author:

John Morcos

Biostatistician II
Veristat, LLC.

Signature:_____

Date:_____

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

Guojun Yuan, PhD

VP, Biostatistics and DM
Rhythm Pharmaceuticals, Inc.

Signature:_____

Date:_____

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse Event
BMI	Body Mass Index
BP	Blood Pressure
CRF	Case Report Form
CS	Completer's Set
CSR	Clinical Study Report
[redacted]	[redacted]
ECG	Electrocardiogram
[redacted]	[redacted]
FAS	Full Analysis Set
[redacted]	[redacted]
HR	Heart Rate
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of Patients
[redacted]	[redacted]
PI	Primary Investigator
[redacted]	[redacted]
PP	Per-Protocol
PWS-FPD	Prader-Willi Syndrome Food Problem Diary
PWS-SEQ	Prader-Willi Syndrome Significant Event Questionnaire
P95	Percent of 95th Percentile (P95)
RGDO	Rare Genetic Disorders of Obesity
SA	Safety Analysis
SAP	Statistical Analysis Plan
SD	Standard Deviation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SOA	Schedule of Assessments
TEAE	Treatment-Emergent Adverse Event

Abbreviation	Definition
VAS	Visual Analog Scale
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

This document presents the statistical analysis plan (SAP) for Study RM-493-014, Setmelanotide (RM-493) Phase 2 Treatment Trial in Patients with Rare Genetic Disorders of Obesity. This SAP is based upon protocol amendment 10 dated 20 February 2020.

This SAP is designed to outline the methods to be used in the analysis of study data in order to answer the study objectives. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this study.

The SAP may modify the plans outlined in the study protocol. If changes are made to the plans outlined in the protocol, the SAP will supersede the relevant contents of the protocol. If, after the study has completed, changes are made to the SAP, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the CSR for the study, as appropriate.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study is to explore the impact of setmelanotide on obesity in patients with various specific rare genetic mutations.

1.2.2. Secondary Objectives

The secondary objectives of the study are to assess the effects of setmelanotide on:

- Safety and tolerability
- Hunger
- Waist circumference

[redacted]

1.3. Study Design

1.3.1. Synopsis of Study Design

This is a Phase 2, proof-of-concept study to assess initial safety and efficacy of setmelanotide within each identified subtype of rare genetic disorders of obesity (RGDO) and on suspected genetic mutations associated with obesity. All these conditions are: homozygous or compound heterozygous LEPR mutations, heterozygous POMC mutations, POMC hypermethylation variants, Bardet-Biedl syndrome or Alström syndrome, Smith-Magenis syndrome, SH2B1 haploinsufficiency, carboxypeptidase E deficiency, SRC1 mutations, leptin deficiency obesity,

MC4R deficiency obesity, PCSK1 deficiency obesity, chromosomal rearrangement of the 16p11.2 locus causing obesity, and potential additional RGDO cohorts provided they are collected in the database.

The study design is dependent upon time of enrollment, with a new study design being implemented for patients enrolling under amendment 9 and thereafter. Patients enrolled prior to amendment 9 will eventually transition to amendment 9 schedule of events.

For pre-amendment 9 patients, the treatment phase of the study will begin with an initial period of dose titration in 0.5 mg increments and lasting between 2 and 12 weeks. The dosing will range from as brief as a single dose step at either 1.0 mg for adults or 0.5 mg for adolescent (ages 12 – 18 years) patients, to as many as 5 (adults) or 6 (adolescents) dose steps to reach 3.0 mg once-daily. The highest potential dose allowed in dose titration, however, is expected to be 2.5 mg, with the option to progress further to 3.0 mg if there is a lack of response at 2.5 mg. Thus, each patient will have his/her dose individualized depending on the number of dosing increments administered, where each individual patient's therapeutic dose will be established by upwards dose titration in 2-week intervals. Thereafter, patients will continue on active treatment at their optimal therapeutic dose for an additional 10 weeks, for a total combined dosing duration of 12 weeks at the individual patient's established therapeutic dose [i.e., the last 2 weeks during dose titration plus 10 weeks of open label treatment]. Patients will complete all procedures as described Table 1-1, Table 1-2, Table 1-3. Patients who demonstrate at least 5 kg weight loss at the end of the Open Label Treatment Period (or 5% weight loss for patients with baseline body weight < 100 kg) will continue onto the long-term (1 year) extension period. It is planned that the individual patient's therapeutic dose, established during the initial period of dose titration, will continue throughout the study. In consenting patients, a 2- to 4-week period of active treatment withdrawal will be included during the 1-year extension.

Thus, pre-amendment patients will progress sequentially through the study as depicted in Figure 1.

For post-amendment 9 patients, upon providing informed consent, patients will enter the Screening Period. During the Screening Period, patients will be assessed for eligibility and complete all screening procedures as described in Table 2. Each patient's genetic information will be reviewed by the Sponsor to confirm the patient is eligible for the study. During the Screening Period, each patient will be instructed to complete a hunger questionnaire on a daily basis and will be required to have completed at least four days of the questionnaire prior to first dose.

Eligible patients will return to the clinic within 2 – 8 weeks of completing the Screening Visit for the Baseline Visit (Visit 2) and first dose of setmelanotide. Dose levels for all patients will escalate to a final dose of 3.0 mg/day during an initial dose-titration phase, but the starting dose will depend on patient age. Patients 6 up to 16 years old will initially be dosed at 1.0 mg/day for 2 weeks, beginning at the Baseline Visit on Study Day 1. Starting on Day 15, the dose will escalate to 2.0 mg/day and remain at that level for 2 weeks, until the patient returns to clinic for Visit 3 on Day 29. At Visit 3, the dose will be escalated to 3.0 mg/day; the patient will continue dosing at 3.0 mg/day for 12 weeks. Patients ≥16 years old will initiate dosing at 2.0 mg/day at the Baseline Visit, and continue dosing at that level for 2 weeks. The dose will be escalated to 3.0 mg/day beginning on Study Day 15, and the patient will continue that dose for 14 weeks. Study site staff will call all patients at their homes after the first 2 weeks of treatment to ensure the escalation occurred as planned and collect any adverse events (AEs).

Patients will continue dosing at 3.0 mg/day and return to the clinic every four weeks (Visits 3-5) to complete the assessments in Table 2. After 16 weeks in the study, patients will return to the clinic for Visit 6. At Visit 6, the patient will receive the last setmelanotide injection. Participation in the study will then conclude in one of the following two ways:

- Complete Visit 6 and enroll in a separate extension study, Rhythm Study RM-493-022. If RM-493-022 is not yet open at the clinic site, the patient will continue daily setmelanotide injections and other activities per the current study, as presented in the Schedule of Assessments (SOA) (Table 2). The patient will return to the clinic for Bridging Visits every 12 weeks for up to one year, until the extension study opens at the site. Additional clinic visits may be scheduled at the discretion of the primary investigator (PI).
- Decide not to participate in the extension study and proceed to the final study visit (Visit 7) in 4 weeks.

Patients on study prior to amendment 9 should transition to dose escalation as outlined in protocol amendment 9 in the manner outlined below:

- Patients who are in the dose titration phase and are not currently at a dose of 3.0 mg/day will be assessed by the PI and the Sponsor, to determine if an increase in the dose to 3.0 mg/day is appropriate.
- Patients who have completed dose titration and are assigned to a dose of less than 3.0 mg/day will be assessed by the PI to determine if an increase in the dose to 3.0 mg/day is appropriate.
- Patients who are post 16 weeks may roll into the separate extension study (RM-493-022) directly or via Bridging Visits, or proceed to the final study Visit 7 and finish the study.

Thus, post-amendment 9 patients will progress sequentially through the study as depicted in Figure 2.

Figure 1 Study Design Schematic – Pre-Amendment 9

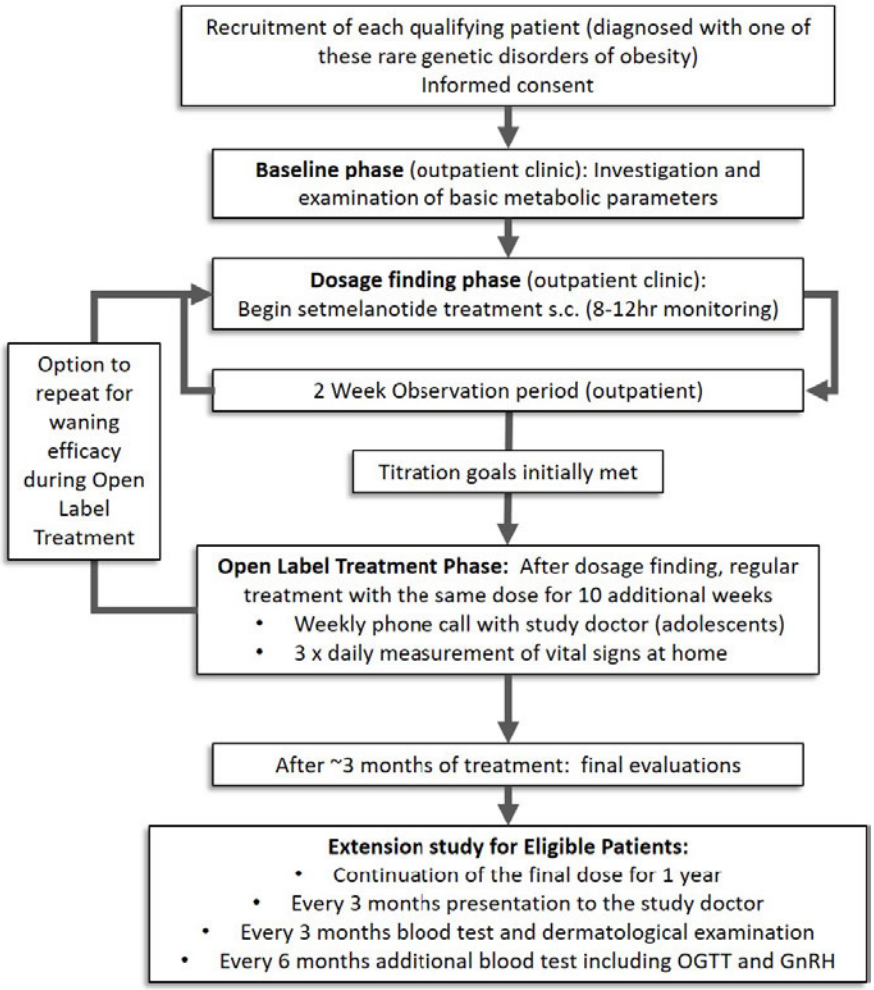
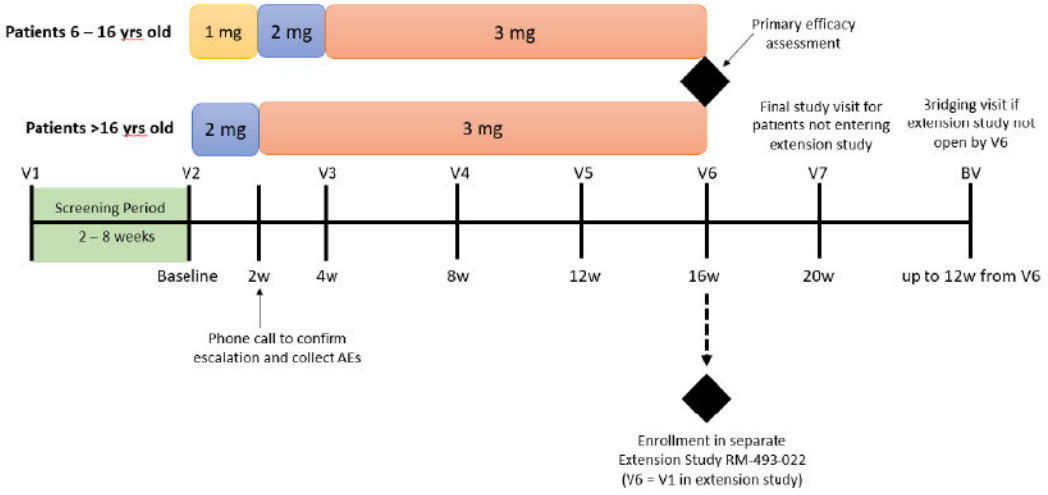


Figure 2 Study Design Schematic – Post-Amendment 9



1.3.2. Randomization Methodology

There will be no randomization in this trial.

1.3.3. Stopping Rules and Unblinding

This study may be prematurely terminated if, in the opinion of the Investigator (at a participating site) or Rhythm (for the whole study), there is sufficiently reasonable cause. The terminating party will provide written notification documenting the reason for study termination to either the Investigator or Rhythm.

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

- Determination of unexpected, significant, or unacceptable risk to patients.
- Failure to enter patients at an acceptable rate. This is particularly important, as the number of patients hoped to enroll in this study represents a substantial portion of all already identified patients worldwide.
- Insufficient adherence to protocol requirements.
- Insufficient complete and/or evaluable data.
- Plans to modify, suspend, or discontinue the development of the study drug.
- Termination of an individual population for a specific disorder of obesity if data from at least two, and possibly up to five, patients in that disorder fail to show substantial weight loss (e.g., no patients meet the threshold for continuation into extensions).

In addition, it is still unclear how many patients will be required to assess the safety and efficacy of setmelanotide in each of these rare conditions before it is appropriate to transition to pivotal trials. Therefore, this study (or enrollment of any individual population within the study) may be terminated when Rhythm, in consultation with regulatory authorities, determines that there are sufficient patient data in Phase 2 to support initiation of pivotal and safety studies.

This study is open label so there is no blinding.

1.3.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, are provided in Table 1-1, Table 1-2, Table 1-3, and Table 2.

Table 1-1 Schedule of Assessments: Screening and Dose Titration – Pre-Amendment 9

Study Period	Screening	Open Label Dose Titration[6] 1st Visit	Open Label Dose Titration[6] Subsequent Visits
Procedure **Visit Number (V)**	**V1**	**V2a[6]**	**V2b, 2c, 2d, etc.[6]**
Start of Dose Titration Week (Dose Titration Study Day ± 3 days)	**-4 to 0 (-28 to -1)**	**1 (1)**	**3, 5, 7 etc. 14, 28, 42, etc.**
Informed consent/Assent	X		
Inclusion/Exclusion review	X	X[5]	
Medical history review	X	X[5]	
Pregnancy test	X	X[4, 5]	X[4,5]
Physical examination[1]	X		
Height[1]	X		
Comprehensive skin exam[2]	X		
Fitzpatrick scale	X		
Open label placebo practice	X		
Dose Titration Decision[24]		X[5]	X[5]
[redacted]			
Weight/waist circumference[11]	X	X[5]	X[5]
Archive sample for storage[12]	X		
Therapeutic Dose Established			X[7]
Study treatment administration[13]		X	X
Injection site inspection[14]		X	X
Vital signs[8,15]	X	X[5,8,16]	X[5,8,16]
ECG (12-lead)[17]	X	X[5, 17]	
Safety laboratory tests[19]	X	X[5]	X[5]
OGTT[28]	X		
[redacted]			
Hunger Questionnaire[20]	X	X[5]	X[5]
[redacted]			
Anti-RM-493 antibody samples	X	X[5, 26, 31]	X[5, 26, 31]
Adverse Event assessment[25]	X	X	X
Concomitant meds review	X	X	X
Telephone contact		X	X
Genotyping[32]	X		
Global Hunger Questions	X[33]		
Optional Sub-Studies			
[redacted]			

Table 1-2 Schedule of Assessments: 10 Week Active Treatment – Pre-Amendment 9

Study Period	Open Label		
	Active Treatment[7]		
Procedure / **Visit Number (V)** / **End of Week** / **(Approximate Study Day)**	**V4*** **4** **(29)**	**V5** **8** **(57)**	**V6[35]** **12** **(85)**
Pregnancy test	X[4,5]	X[4,5]	X[4,5]
Physical examination[1]			X
Height[1]			X
Comprehensive skin exam[2]			
[redacted]			
Weight/waist circumference[11]	X[5]	X[5]	X[5]
Archive sample for storage[12]			X[5]
Therapeutic Dose Established			
Study treatment administration[13]	X	X	X
Injection site inspection[14]	X	X	X
Vital signs[8,15]	X[5,8]	X[5,8]	X[5,8]
ECG (12-lead)[17]			X[5]
Safety laboratory tests[18]	X[5]		X[5]
OGTT[28]			X[5]
[redacted]			
Hunger Questionnaire[20]	X[5]	X[5]	X[5]
[redacted]			
Anti-RM-493 antibody samples	X[5, 26]		X[5, 26]
Adverse Event assessment[25]	X	X	X
Concomitant meds review	X	X	X
Telephone contact	X	X	X
[redacted]			

Optional Sub-Studies

[redacted]

Table 1-3 Schedule of Assessments: Additional 52 Week Open Label Extension – Pre-Amendment 9

Study Period		Open Label Active Treatment[8]								Early Termination Visit[9]
Procedure	**Visit Number (V) End of Week (Approximate Study Day)**	**V7[35] 20 (141)**	**V8[35] 26 (183)**	**V9* 32 (225)**	**V10 38 (267)**	**V11* 44 (309)**	**V12 52 (365)**	**V13* 58 (407)**	**V14 64 (449**	
Pregnancy test		X[4, 5]	X[4,5]	X[4,5]	X[4, 5]	X[4,5]	X[4, 5]	X[4,5]	X[4, 5]	X
Physical examination[1]			X				X			X
Height[1]			X		X		X		X	
Comprehensive skin exam[2]					X		X		X	X
[redacted]										
Weight/waist circumference[11]		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
Archive sample for storage[12]							X[3]			
Study treatment administration[13]		X	X	X	X	X	X	X	X	
Injection site inspection[14]		X	X	X	X	X	X	X	X	X
Vital signs[15]		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
ECG (12-lead)[17]			X[5]				X[5]			
Safety laboratory tests[10]			X[5]		X[5]		X[5]		X[5]	X
OGTT[28]							X[5]			
[redacted]										
Hunger Questionnaire[20]		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
[redacted]										
Anti-RM-493 antibody samples			X[5, 26]		X[5, 26]		X[5, 26]		X[5, 26]	X[5, 26]
Adverse Event assessment[23]		X	X	X	X	X	X	X	X	X
Concomitant meds review		X	X	X	X	X	X	X	X	X
Telephone contact		X	X	X	X	X	X	X	X	X
[redacted]										

Optional Sub-Studies

[redacted]

1 A complete physical examination will be conducted at screening and at the end of study. [redacted] for assessment of pubertal development will be conducted according to the SOA for those patients who have yet to reach [redacted] Whenever possible, the same trained health care professional will conduct the exam and [redacted]. Height will be measured during the Screening Period only for those patients ≥18 years of age. Height will be measured according to the SOA for those patients <18 years of age.

2 A comprehensive skin evaluation will be performed by a dermatologist. Any concerning lesions identified during the screening period will be biopsied and results known to be benign prior to first dose of setmelanotide. If the pre-treatment biopsy results are of concern, the patient will be excluded from the study.

3 [redacted]

4 Urine pregnancy test may be performed in order to expedite availability of results prior to dosing on Dose Titration Day 1. All other pregnancy tests will be serum; dosing may continue with results pending.

5 Prior to study drug administration.

6 The Dose Titration phase will be a variable schedule lasting a minimum of 2 weeks in which patients will return to the clinic approximately every 2 weeks in order to establish the individual patient's therapeutic dose according to Protocol. Given the variable number of dose titration steps in the Dose Titration Phase, each Dose Titration Visit Number (V) will remain V2 with an alphabetized suffix added to each titration visit (i.e.; first dose titration at start of Week 1 = V2a, second dose titration at start of Week 3 = V2b, etc.). This will allow for the Visits to be appropriately tracked. Additionally, each dose titration visit will have the same pre and post dose assessments as outlined in the SOA (with the exception of Anti-Rm-493 antibodies, metabolic and hormonal assays, ECG, Inclusion/Exclusion review and Medical History Review).

7 Once the patient's individual therapeutic dose is established the patient will enter the Open Label Active Treatment phase for 10 additional weeks, for a combined total of 12 weeks of dosing at the therapeutic dose. During this time, the study calendar will be reset, starting when the therapeutic dose was initiated (i.e. the last 2 weeks of dose titration when the therapeutic dose was established). Therefore, the Open Label Active Treatment phase starts at the beginning of Week 3 (V2x – final dose titration visit). Patients losing 5 kg of weight (or 5% if baseline weight is <100 kg) at the end of the Open Label Treatment phase will be eligible to enter the one-year extension.

8 During the titration period and the 10-week Open Label Treatment Period, patients (and/or parents/guardians) will measure blood pressure and heart rate at home once daily prior to dosing in the morning, and record the values. The measurements should be taken in triplicate and all 3 readings recorded. If needed, Rhythm will supply a blood pressure machine for these readings.

9 Early Termination: For those patients who withdraw consent or are withdrawn and not willing to complete the remaining study visits, the early termination visit assessments should be performed, when possible. Final Visit: For patients who complete the study but do not wish to enroll into the future long-term extension study (as noted in Protocol Section 5.5), patients will be required to return for a Final Visit ~30 days after the last dose of setmelanotide, for a final follow-up safety assessment. Any ongoing AEs reported at this visit should be monitored as outlined in Protocol Section 7.4. For patients who enroll into the long-term extension study, this visit is not required. Additionally, patients who are not willing to return for the remaining clinic visits/Final Visit, assessments by home health care professionals can be arranged, or at a minimum, patients can be contacted via phone if amenable, to collect self-reported patient data (i.e.: weight, hunger, AEs, etc.).

10 [redacted]

11 Weight is to be measured at the clinic using the same scale after patients have emptied their bladder and while fasting. Patients are to wear light clothing or underwear, no shoes, and will be weighed at approximately the same time of day. Weight measurements are to be done in triplicate; waist circumference will be single measures.

12 Extra retain samples will consist of 2 serum and 2 plasma (K2EDTA) vacutainer tubes.

13 Study drug is administered by patients/caretakers beginning the morning of Day 1 and for the duration of dosing. Patients/caretakers will draw up and self-administer/administer the drug once on a daily basis in the morning. 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. Patients/caretakers will return all used vials to the clinic when they visit (the number recorded) and both clinic administered study drug, as well as outpatient study drug administration will be recorded in a study diary.

14 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 where there are injection site reactions even if not a timepoint for formal assessment.

15 All BP and HR measurements are to be obtained in the sitting position following at least 5 minutes of rest. All measurements will be taken in triplicate, approximately 2 minutes apart. When possible, BP should be taken in the non-dominant arm throughout the study, using the same methodology (automated or manual) according to Protocol. Body temperature (°C) and respiration rate (breaths/minute) will be obtained in the sitting position following at least 5 minutes of rest.

16 During Day 1 and for any dose titration, vitals will be collected prior to dosing and then approximately hourly post-dose for up to 8 hours.

17 A single 12-lead ECG will be performed in the supine position following a period of at least 10 minutes of rest. On days in which dose titration occurs, measures will be obtained prior to dosing and approximately 8 hours post-dose

18 Safety laboratories will include: CBC with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, CO2, albumin, total protein, glucose, BUN, creatinine, uric acid, AST, ALT, GGT, CPK, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, calcium, phosphorus), urinalysis with microscopic analysis if positive findings on dipsticks warrant further examination. Safety laboratories should also include a coagulation profile (prothrombin time [PT] or international normalized ratio [INR], and partial thromboplastin time [PTT], also referred to as activated partial thromboplastin time [aPTT]. Fasting samples (8-hour minimum) are required at all timepoints where feasible. [redacted] also be included.

[redacted]

[redacted]

23 Body composition may be performed using an appropriate method available at sites (e.g. BIA, [redacted], etc.) Refer to Protocol regarding appropriate methodology for assessing this patient population.

24 Once all the pre-dose assessments have been performed, the decision to dose titrate will be made. If the patient's therapeutic dose has been established, the patient will transition into the 10-week Open Label Active Treatment Phase, receive their therapeutic dose, and complete the post-dose assessments as defined in the SOA. If the patient's therapeutic dose has not been established according to Protocol, the patient will be administered study drug, complete the dose titration post-dose assessments as defined in the V2 SOA, and return to the clinic in ~2 weeks for the next sequential Visit 2 (i.e.; V2b, V2c, etc.).

25 Adverse events will be recorded from the time a patient provides informed consent. AEs reported after dosing on Day 1 will be considered treatment-emergent AEs.

26 Any patients with positive anti-drug antibodies will be followed ~every 3 months until titers resolve or return to baseline.

27 Telephone contact by site on a monthly basis, or more frequently, if needed.

28 Following collection of pre-meal (time 0) blood samples, patients will be given a standard oral glucose tolerance test. The following blood samples will be obtained during each OGTT: Blood glucose and insulin at approximately 30, 60 90 and 120 minutes after meal start. OGTT will not be performed for patients with a diagnosis of Type 1 or Type 2 diabetes.

[redacted]

31 To be collected on the first two, two-week dose titration visits (V2a and V2b).

32 A blood sample will be obtained at Screening from all patients for genotyping for mechanisms considered to be possibly related to the safety or efficacy response to the study medication (e.g., other obesity related genes; drug metabolism). A portion of this sample may be used, under informed consent, for patients who do not have a diagnosis confirmed by genetic test to confirm diagnosis of one of the studied mutations prior to study participation.

33 Global Hunger Questions will be administered in clinic as follows: Question 1 will be asked at screening, and Questions 1 and 2 will then be asked at Visit 6 (start of 52-week Open Label Extension), additional withdrawal Visits A, B, and C (see footnote 35), Visit 7, Visit 8 (~6 months) and Visit 14 (end of 1 year).

34 Metabolic and Hormonal Assays: Assays will be collected and analyzed on an ongoing basis during or post study, including LH, FSH, TSH, free T4, ACTH (screening visit only)[36], IGF-1, and IGFBP-3, Serum procollagen type 1 N-propeptide, COOH-terminal telopeptide of type 1 collagen, N-terminal telopeptide of type 1 collagen, Bone-specific alkaline phosphatase, osteocalcin. Other assays (including testosterone, estradiol, GH, aldosterone, renin, cortisol and anti-inflammatory markers) will be measured on an as needed basis and would be assayed only if clinical signs or symptoms require further evaluation (e.g., renin and aldosterone would be measured only if BP increases are noted).

35 Optional Withdrawal Visits A (start of withdrawal), B (after 2 weeks of withdrawal), and C (end of withdrawal). If it is determined a patient will participate in the optional withdrawal period, the 2 to 4 weeks off study drug will occur between visits 6 and 7 or between Visits 7 and 8 (first 13 weeks of 52-week extension). The following study assessments should be completed at these visits: Pregnancy test[4], [redacted], Weight/Waist circumference[11], Injection site inspection[14], Vital signs[15], [redacted], [34] (both local and storage), [redacted], Adverse Event Assessment[25], Concomitant Meds Review, Telephone Contact, Serial Photographs[3]. If the patient only participates for 2 weeks, Visit C will not be completed and Visit B becomes the end of withdrawal visit.

36 A sample for ACTH should be collected only at the Screening Visit and between 8 AM and 10 AM prior to study drug administration.

Once a patient's therapeutic dose has been established according to Protocol, no further dose titrations will occur, and patients will transition directly into the 10 week Open Label Active Treatment phase.

* For patients that reside a considerable distance from the clinic, these visits are optional clinic visits, and may be performed by home health care professionals.

Table 2 Schedule of Assessments: Post-Amendment 9

Study Period/Procedure	Screening	Study Treatment						EOS Visit	Bridging Visit(s) [31] + up to 12 weeks from V6 (up to one year from V6)	Treatment Discontinuation Visit
Clinic Visit Number	V1	V2	-	V3 [29]	V4	V5	V6 [30]	V7		
Start of Week X	-8 to -2	0	2	4	8	12	16	20		
Study Day (± 3 days)	-56 to -14	1	15	29	57	85	113	141		
Sponsor review of patient genetics/Genetic Testing [1]	X									
Informed consent/Assent [33]	X									
Inclusion/Exclusion review	X	X								
Medical history review	X									
Physical examination [2]	X	X		X	X	X	X	X	X	X
Comprehensive skin exam [3]	X						X			X
Fitzpatrick classification scale	X						X	X		X
Hepatic imaging [35]	X									
Weight [4]	X	X		X	X	X	X	X	X	X
Waist circumference [5]	X	X		X	X	X	X	X	X	X
Height [6]	X			X	X	X	X	X	X	X
[redacted]										
Vitals [8]	X	X		X	X	X	X	X	X	X
ECG (12-lead) [9]	X	X[36]		X			X		X	X
Pregnancy test [10]	X	X [32]		X	X[32]	X[32]	X[32]		X[32]	X[32]
Daily hunger questionnaires [11]	X	Daily [32]								X[32]
Global hunger assessment [12]		X[32]		X[32]	X[32]	X[32]	X[32]	X	X[32]	X[32]
[redacted]										

Study Period/Procedure	Screening	Study Treatment						EOS Visit	Bridging Visit(s) [31] + up to 12 weeks from V6 (up to one year from V6)	Treatment Discontinuation Visit
Clinic Visit Number	V1	V2	-	V3 [29]	V4	V5	V6 [30]	V7		
Start of Week X	-8 to -2	0	2	4	8	12	16	20		
Study Day (± 3 days)	56 to 14	1	15	29	57	85	113	141		
[redacted]										
Safety laboratory tests [19]	X	X		X[32]	X[32]	X[32]	X[32]	X	X[32]	X[32]
[redacted]										
Anti-drug antibody samples	X	X		X			X	X	X	X
[redacted]										
Injection site inspection [24]		X		X	X	X	X		X	X
Telephone call [25]			X							
Study drug administration [26]		Daily dosing							X	
Dispense/Return study drug [27]		X		X	X	X	X		X	
Adverse event assessment [28]	X	X	X	X	X	X	X	X	X	X

Study Period/Procedure	Screening	Study Treatment						EOS Visit	Bridging Visit(s) [31] + up to 12 weeks from V6 (up to one year from V6)	Treatment Discontinuation Visit
Clinic Visit Number	V1	V2	-	V3 [29]	V4	V5	V6 [30]	V7		
Start of Week X	-8 to -2	0	2	4	8	12	16	20		
Study Day (± 3 days)	56 to 14	1	15	29	57	85	113	141		
Concomitant medications review	X	X	X	X	X	X	X	X	X	X
[redacted]										

V, Study Visit Number; EOS, End of Study; PK, Pharmacokinetics.

1. Prior to conducting any screening assessments, Sponsor will review and approve the specific genotype to ensure it meets the criteria for the patient populations included in the study (Protocol Section 11.1).
2. A complete physical examination will be conducted at Screening and at the EOS V7. At other timepoints, an abbreviated examination will be performed. The abbreviated examination should focus on heart, lungs, skin, neurologic exam, and any areas of previous abnormal findings, noting any changes from baseline. In addition, [redacted] for assessment of pubertal development will be conducted for those patients who have yet to reach [redacted] Whenever possible, the same trained health care professional will conduct the exam and [redacted] (Protocol Section 11.5).
3. A comprehensive skin evaluation will be performed by a dermatologist. The skin exam should include a full body skin exam (head-to-toe skin examination) from a trained and licensed dermatologist. Any concerning lesions identified during the Screening Period will be biopsied and results known to be benign prior to first dose of setmelanotide. If the pre-treatment biopsy results are of concern, the patient will be excluded from the study. Additionally, any 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. Any biopsies must be evaluated by a trained dermatopathologist, and biopsy reports must be part of the study information for each patient (Protocol Section 11.6).
4. Weight (kg) is to be measured at the clinic using the same scale throughout the study, after patients have emptied their bladders and bowels 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 measurements are to be done in triplicate (Protocol Section 11.8).
5. Waist circumference (cm) will be single measures (Protocol Section 11.9).
6. For patients ≥18 years of age, height needs to be measured at the screening visit 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 timepoint and recorded to the nearest 10th of a decimal place (Protocol Section 11.10).
7. Body composition assessment may be performed using an appropriate method available at sites (e.g., BIA [redacted]). Refer to Protocol Section 11.11 for details.
8. All BP and HR measurements are to be obtained in the sitting position following at least 5 minutes of rest. All measurements will be taken in triplicate, approximately 2 minutes apart. When possible, 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 (Protocol Section 11.13).

9. A single 12-lead ECG will be performed in the supine position following a period of at least 10 minutes of rest (Protocol Section 11.14). At visit 2 the ECG will be performed before and 8 hours after dosing.
10. 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 (Protocol Section 11.15); dosing may continue with results pending.

[redacted]

19. Safety laboratory tests will include: CBC with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, CO2, albumin, total protein, glucose, BUN, creatinine, uric acid, 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. Safety laboratories will also include a coagulation profile (PT or INR, and PTT also referred to as aPTT).

[redacted]

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 timepoint for formal assessment (Appendix A).
25. Site should call the patient to confirm the proper dose escalation has occurred, and to collect AEs.

26. 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.
27. 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.
28. Adverse events will be recorded from the time a patient provides informed consent. AEs reported after dosing on Day 1 will be considered treatment-emergent AEs.
29. Patients who are <16 years of age will receive first daily dose of 3.0 mg at V3, at clinic site.
30. Study endpoints are analyzed at V6. After completing V6, patient enters a separate extension study (Protocol RM-493-022), does not enter the extension study and returns for the final study Visit 7 in 4 weeks, or completes Bridging Visits for up to one year or until the extension study is initiated.
31. Bridging Visits only needed if separate extension study RM-493-022 is not initiated at site at the time of V6.
32. Collected prior to study drug administration.
33. Although the study procedures and assessments required per protocol are classified as "No or Minimal Risk" (with the exception of [redacted] 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 participants younger than 18 years of age are included in Appendix J.

[redacted]

35. Only applicable to SCR1 patients.
36. During visit 2 ECG will be collected prior to dosing and ~8 hours post-dose.

1.3.5. Efficacy, Pharmacokinetic, and Safety Parameters

Unless specified otherwise, all the efficacy endpoints will be defined and analyzed per RGDO cohort.

The primary endpoint is the proportion of patients in each subgroup of RGDO who achieve at least 5% body weight reduction from baseline at ~3 months treatment with setmelanotide.

The following 4 endpoints have been identified as secondary endpoints:

- Safety and tolerability of setmelanotide injection, assessed by the frequency and severity of AEs, vital signs, and laboratory evaluations.
- Change and percentage change from baseline in body weight.
- Change from baseline in Daily and Global Hunger Scores.
- Change from baseline in waist circumference.

[redacted]

2. ANALYSIS POPULATION

2.1. Population Definitions

The following analysis populations will be evaluated and used for presentation and analysis of the data:

- Safety Analysis (SA) Set: All patients who received at least 1 dose of study drug, excluding patients from Axis Sites #22 through #27 inclusive.
- Full Analysis Set (FAS): All patients who received at least 1 dose of study drug and have baseline weight data, excluding patients from Axis Sites #22 through #27 inclusive.
- Completer's Set (CS): All patients in the FAS who have non-missing weight data collected at least once between 60 days and 120 days on therapeutic dose, inclusive.
    - For patients enrolled prior to amendment 9, therapeutic dose will be considered the maximum dose received during the dose escalation phase (identified by Clinical Visit 2X). For patients enrolled post-amendment 9, the therapeutic dose will be considered the dose received at Visit 3.
    - The first date that this dose was received will be considered the date of the first therapeutic dose (this will be the date of Visit 3 for post-amendment 9 patients). If a patient has a visit falling within 60 to 120 days after first therapeutic dose and was still on treatment, this visit should be considered for analysis as ~3 months of treatment. If a patient has two visits falling within this window, the visit closest to Day 90 in which the patient was still on treatment should be considered. If a patient has two visits falling within this window that are equidistant from Day 90, the later visit should be considered. For post-amendment 9 patients, if the patient's last visit during the study is Study Visit 5 and the patient is still on treatment, then that date should be used for this analysis, even if it does not fall within 60 to 120 days after first therapeutic dose. If a patient has no visit falling within this window, this patient will be treated as missing for completer's analysis purposes. If a patient has no visit falling within this window and no observation prior to the window, this patient will be treated as missing for analysis purposes, as well.
- Per-Protocol (PP) Set: All patients in the FAS without any major protocol violations.

The FAS is the primary population for the analysis of efficacy parameters. Sensitivity analyses of efficacy parameters may be conducted on the CS population, if appropriate. A subset of efficacy parameters may be evaluated for the PP Set if the population in PP is over 20% different from the FAS population. The SA Set is the primary population for the analysis of PK parameters and safety endpoints.

2.2. Protocol Violations

At the discretion of the Sponsor, major protocol violations, as determined by a review of the data may result in the removal of a patient's data from the PP Set. The Sponsor or designee will be responsible for producing the final protocol violation file (formatted as a Microsoft Excel file), in collaboration with Veristat and the data monitoring group as applicable; this file will include a description of the protocol violation and clearly identify whether or not this violation warrants exclusion from the PP Set. This file will be finalized prior to database

lock.

All protocol violations will be presented in a data listing.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

It is estimated that at least 5 patients within each subgroup of RGDO will be recruited. Given the rarity of these disorders, the sample size is not driven by statistical considerations, but primarily driven by clinical considerations. Therefore, estimated power for expected weight change will not be provided, and efficacy will be only summarized. P-values and confidence intervals may be provided wherever is appropriate, but these should be considered for estimation and clinical scrutiny purpose, instead of formal statistical hypothesis testing purpose.

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

All output will be sorted and labeled according to the International Conference on Harmonisation recommendations and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category of the parameter will be presented. For continuous variables, the number of patients (N), mean, median, standard deviation (SD), minimum, and maximum values will be presented.

Data that was collected prior to amendment 9 that will no longer be collected under amendment 9 or thereafter, will be provided in by-patient listings. Summary tables may be provided as appropriate.

3.3. Computing Environment

Unless otherwise noted, all descriptive statistical analyses will be performed using SAS® statistical software Version 9.4 (SAS Institute Inc., Cary, NC, USA) or higher. Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary.

3.4. Baseline Definitions

The last value (or last week of values for weekly average hunger scores) obtained prior to the first dose of study drug will be considered the baseline for all endpoints. If there is insufficient hunger score data prior to first dose of study drug, Week -1 or Day 1 will serve as baseline; hunger score data prior to Week -1 will not be considered for baseline.

3.5. Methods of Pooling Data

The data from this study may be pooled with other studies based on genetic/disease indication as appropriate. If the appropriate pooling will be needed, the analysis strategy will be addressed in the pivotal study SAP.

3.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned.

3.7. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a descriptive interpretation.

3.8. Subpopulations

All primary, secondary, and exploratory endpoints will be examined separately for each specific subgroup of RGDO.

In addition, data cuts looking at sub-populations within each subgroup of RGDO may be further examined. Examples may include:

- Age
  - >=18 years old/<18 years old
  - >=18 years old/12 – <18 years old/<12 years old
- Sex (male, female), body mass index (BMI) or other demographic factors
- Type or pathogenicity of genetic variants

3.9. Withdrawals, Dropouts, Loss to Follow-up

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 if it is medically appropriate in the opinion of the investigator.

3.10. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the case report form (CRF) will be included in data listings that will accompany the CSR.

When tabulating AE data, partial dates will be handled to more accurately determine whether an event was treatment-emergent.

AE start dates that are missing or incomplete will be handled as follows:

(1) Missing Day Only

- If the month and year are the same as the month and year of the first dose date, the first dose date will be used.
- If the month and year are before the month and year of the first dose date, the last day of the month will be assigned to the missing day.
- If the month and year are after the month and year of the first dose date, the first day of the month will be assigned to the missing day.

(2) Missing Day and Month

- If the year is the same as the year of the first dose date, the first dose date will be used.

- If the year is prior to the year of the first dose date, December 31 will be assigned to the missing fields.
- If the year is after the year of first dose date, January 1 will be assigned to the missing fields.

(3) Missing Day, Month, and Year

- The first dose date will be used.

If the stop date is non-missing and the imputed start date is after the stop date, the stop date will be used as the start date. If the stop date is missing and the imputed start date is after a patient's date of discontinuation, the date of discontinuation will be used.

AE stop dates that are missing or incomplete will be handled as follows:

(1) Missing Day Only

- The last day of the month will be assigned as the missing day.

(2) Missing Day and Month

- December 31 will be assigned to missing fields.

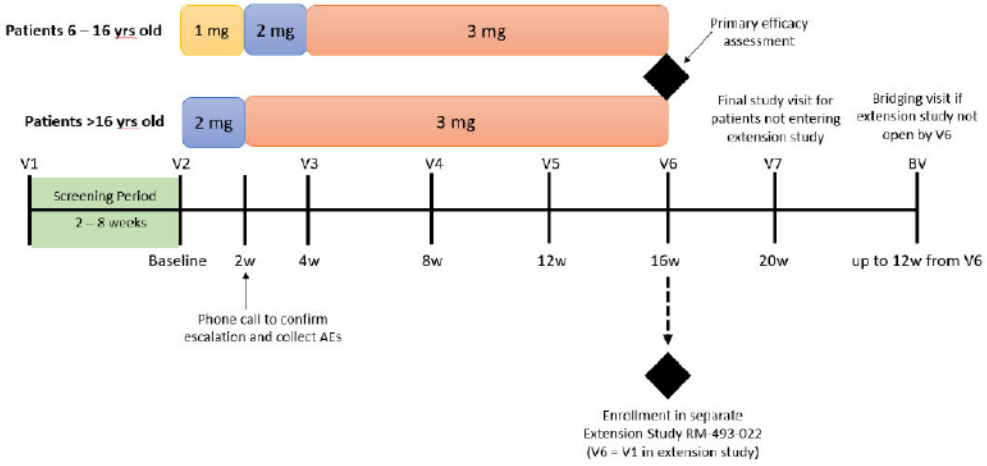
(3) Missing Day, Month, and Year

- The event will be regarded as ongoing.

If the start date is non-missing and the imputed stop date is before the start date, the start date will be used. If the death date is available and the imputed stop date is after the death date, the death date will be used.

3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. For patients enrolled prior to amendment 9, visits should start to transition towards the post-amendment 9 SOA as outlined in Section 1.3.1. All data will be tabulated per the evaluation visit as recorded on the CRF even if the assessment is outside of the visit window. If the evaluation visit is missing in the database but there are data from an unscheduled or additional visit that is inside the visit window, the data from the unscheduled or additional visit will be used in data summaries. If a patient discontinues or completes the study prior to having their visits updated to align with the post-amendment 9 schedule of assessments, then the patient's visits will be mapped in accordance with the amendment 9 schedule of assessments as outlined in a separate document. All available data will be listed for each patient.



3.12. Interim Analyses

No formal interim analysis is currently planned for this study; however, given the exploratory nature of the study, various data cuts may occur in support of business decision making or regulatory submission such as a New Drug Application. The timing of these data cuts and the number of patients included in each analysis will take into account specific requests from regulatory agencies and applicable regulatory guidance.

Additionally, various data cuts may occur once a pre-specified number of patients in each subgroup of RGDO have completed ~3 months of treatment with setmelanotide. The number of patients may depend on the prevalence of each subgroup of RGDO.

After enrollment of a subgroup of RGDO patients has been completed and all patients in that subgroup have completed the study, their data may be finalized, and an interim analysis of their final data may be performed.

4. STUDY ANALYSES

4.1. Patient Disposition

Patient disposition will be tabulated and include the number screened, the number enrolled, the number enrolled prior to amendment 9, the number enrolled post-amendment 9, the number treated, the number in each patient population for analysis, and the number who withdrew prior to completing the study and reason(s) for withdrawal.

A by-patient data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented. Patient disposition will be for all screened patients.

4.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized and presented by subgroup of RGDO and overall. Age at enrollment, height at baseline, weight at baseline, waist circumference at baseline, and BMI at baseline will be summarized using descriptive statistics (N, mean, SD, 90% CI of the mean, median, minimum, and maximum). The number and percentage of patients in each sex, ethnicity, race, baseline Fitzpatrick classification, and genetic deficiency categories will be presented. The number and percentage of patients with cognitive impairment will also be presented. No formal statistical comparisons will be performed. Patient demographics will include patients in the FAS.

4.3. All Medical History events will be coded using the MedDRA coding system and displayed in tables by RGDO and overall, and in data listings using system organ class and preferred term. Efficacy Analyses

4.3.1. Primary Analysis

The primary analysis on the primary endpoint will be based on the FAS.

The primary endpoint is the proportion of patients in each subgroup of RGDO who achieve at least 5% reduction from baseline in body weight (i.e., are 'responders') after ~3 months of treatment with setmelanotide.

The visit designated for analysis at ~3 months of treatment will be identified as follows: A patient's therapeutic dose will first be established. For patients enrolled prior to amendment 9, therapeutic dose will be considered the max dose received during the dose escalation phase (identified by Clinical Visit 2X). For patients enrolled post-amendment 9, the therapeutic dose will be considered the dose received at Visit 3. The first date that this dose was received will be considered the date of the first therapeutic dose (this will be the date of Visit 3 for post-amendment 9 patients). If a patient has a visit falling within 60 to 120 days after first therapeutic dose, this visit should be considered for analysis as ~3 months of treatment. If a patient has two visits falling within this window, the visit closest to Day 90 should be considered. If a patient has two visits falling within this window that are equidistant from Day 90, the later visit should be considered. If a patient has no visit falling within this window, the last observation before the window will be used for analysis purposes. If a patient has no visit falling within this window and no observation prior to the window, this patient will be treated as missing for analysis purposes.

The summary of the primary endpoint and the associated two-sided 90% Clopper-Pearson

confidence interval will be provided. Descriptive statistics for the actual, change, and percent change from baseline in body weight (kg) at the ~3 month analysis endpoint will be presented for patients of the FAS by RGDO.

Body weight (kg) will be recorded as shown in the SOA (Table 1-1, Table 1-2, Table 1-3, and Table 2). Weight is repeated in triplicate and the mean weight is calculated per study visit. Mean weight will be utilized for analysis purposes.

4.3.2. Secondary Analyses

Body Weight (kg):

Descriptive statistics for the actual, change and percent change from baseline in body weight (kg) will be presented for patients of the FAS for all visits by subgroup of RGDO and overall.

Daily Hunger Scores:

Descriptive statistics for the actual and change from baseline in the weekly average of the daily hunger score for non-cognitively impaired patients in the FAS will be provided for all weeks by subgroup of RGDO. Descriptive statistics for the actual and change from baseline in the weekly average of the daily hunger score for patients in the FAS will be provided for the ~3 month analysis endpoint (identified as per handling approach of primary efficacy endpoint) by RGDO for exploratory purposes.

Prior to summarization, daily hunger scores for each of the 3 hunger assessments for patients >=12 years of age will be averaged separately by week. For patients <12 years of age, there is only one daily hunger assessment to be averaged by week. For a week of hunger scores to be considered evaluable, scores need to be recorded and available for analysis on at least 1 of 7 days to provide sufficient data to determine mean values. If sufficient data is not available to determine mean values, mean hunger score for that week will be considered missing.

Descriptive statistics for the actual and change from baseline in the weekly average of the daily hunger score for patients in the FAS will also be provided for all weeks by subgroup of RGDO and where scores need to be recorded and available for analysis on at least 3 of 7 days. If sufficient data is not available to determine mean values, mean hunger score for that week will be considered missing.

Global Hunger Scores:

Global Hunger Scores will be summarized by visit by subgroup of RGDO. Shift from baseline in global hunger score for patients in the FAS will be provided by subgroup of RGDO by visit.

Waist Circumference (cm):

Descriptive statistics for the actual and change from baseline in waist circumference (cm) for patients in the FAS will be provided for all visits by subgroup of RGDO.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.6. Safety Analyses

Safety analyses will be conducted using the SA Set.

4.6.1 Adverse Events

All AEs will be coded using the MedDRA coding system and displayed in tables by treatment received and in data listings using system organ class and preferred term. AE grade assessment will be based on investigator reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events.

Analyses of AEs will focus on those events that are considered treatment-emergent, where treatment-emergent is defined as any AE with onset the day of or after the administration of study medication through the end of the study (28 days after last dose administered), or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study.

The number and percentage of patients with any treatment-emergent adverse event (TEAE), with any TEAE assessed by the Investigator as related to treatment (definite, probable, or possible relationship), with any serious TEAE, with any related serious TEAE, with any TEAE leading to study drug withdrawal, or with any TEAE leading to death will be summarized.

In these tabulations, each patient will contribute only once (i.e., the most related occurrence

or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

All AEs occurring on-study will be listed in patient data listings. Listings will also be provided for the following: drug product related TEAEs, Serious TEAEs, drug product related serious TEAEs, TEAEs leading to study drug withdrawal, and deaths.

4.6.1 Events of Special Interest

Events of special interest include recognized events within the categories of skin hyperpigmentation and sexual events (male or female). The number and percentage of subjects with events of special interest will be summarized by visit.

In these tabulations, each subject will contribute only once per visit to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

4.6.2 Injection Site Evaluations

Injection site evaluations will be performed according to the SOA (Table 1-1, Table 1-2, Table 1-3, and Table 2) and will be summarized by visit according to severity (none, mild, moderate, severe) and type of reaction (erythema, edema, induration, itching, pain or tenderness, or other reaction). For patients reporting more than one occurrence of the same type of reaction, the most severe reaction will be used for the summary.

A by-patient listing will be provided for all injection site evaluations and will also include measurement (if applicable).

4.6.3 Laboratory Data

Clinical laboratory values will be using the International System of Units (SI).

The actual value and change from baseline to each on-study evaluation will be summarized for each clinical laboratory parameter by visit.

In the event of repeat values, the last non-missing value per study day/time will be used.

The frequency of patients with abnormal safety laboratory results will be tabulated. Shift tables of change in CTCAE grade of laboratory parameters from baseline by visit will be presented for hematology and clinical chemistry by RGDO and overall, if applicable.

All laboratory data, including pregnancy test results, will be provided in data listings.

4.6.4 Vital Signs

Vital signs will be measured according to the SOA (Table 1-1, Table 1-2, Table 1-3, and Table 2). Aside from those used in efficacy evaluations, the actual value and change from baseline of additional vital signs of temperature, heart rate (HR), mean systolic blood pressure (BP), mean diastolic BP, and respiratory rate will be summarized descriptively by visit. A by-patient listing of all vital signs will be provided.

4.6.5 Physical Examination and Comprehensive Skin Examination

Physical exams will be performed according to the SOA (Table 1-1, Table 1-2, Table 1-3, and Table 2). A by-patient listing of all physical exam findings will be provided; results of the comprehensive skin examination will be provided in a listing.

Fitzpatrick classification data will be provided in a by-patient listing as available.

4.6.6 12-Lead Electrocardiogram

Electrocardiogram (ECG) results will be measured as shown in the SOA (Table 1-1, Table 1-2, Table 1-3, and Table 2) and will be summarized with descriptive statistics and in a by-visit shift table, including the number and percentage of patients with normal results, non-clinically significant abnormal results, and clinically significant abnormal results at baseline and shift to each study visit.

ECG data for each patient, including HR, PR interval, QRS duration, QT interval, and QT interval corrected with Fridericia's method, as well as the overall interpretation will be provided in a data listing.

[redacted]

[redacted]

4.6.9 Prior and Concomitant Medications

Prior and concomitant medications will be assessed according to the schedule in Table 1-1, Table 1-2, Table 1-3, and Table 2 and coded using the WHO Drug Dictionary. The use of prior and concomitant medications will be included in separate summary tables by subgroup of RGDO and overall. Medications will be tabulated by Anatomical Therapeutic Chemical class and Preferred Term. Prior and concomitant medications will also be included in a by-patient data listing.

4.6.10 Anti-RM-493 Antibody Measurements

Blood samples for Anti-RM-493 antibody assessment will be collected as shown in the SOA (Table 1-1, Table 1-2, Table 1-3, and Table 2). Results will be provided in a by-patient listing, including the date of the assessment and result, based on the availability of ADA data.

[redacted]

6. REFERENCES

Saris-Baglama R, Dewey C, Chisholm G, et al. (2011). *QualityMetric Health Outcomes Scoring Software 4.5 User's Guide*. Lincoln, RI: QualityMetric Incorporated.