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STATISTICAL ANALYSIS PLAN

PROTOCOL RM-493-022

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

Protocol Number:	RM-493-022
Protocol Version and Date:	Amendment 7: 12 May 2023 Amendment 6: 09 November 2022 Amendment 5: 05 August 2021 Amendment 4: 16 October 2019 Amendment 3: 15 October 2018 Amendment 2: 14 May 2018 Amendment 1: 12 April 2018 Original: 09 January 2018
Name of Test Drug:	Setmelanotide (RM-493, Melanocortin-4 Receptor Agonist)
Phase:	Open-label Active Treatment Extension Trial
Methodology:	Long-term extension trial
Sponsor:	Rhythm Pharmaceuticals, Inc. 500 Boylston Street Boston, MA 02116, USA Tel: (857) 264-4282 Fax: (857) 264-4299
Sponsor Representative:	[redacted] [redacted] Rhythm Pharmaceuticals, Inc. [redacted]
Analysis Plan Date:	28 June 2024
Analysis Plan Version:	Version 2.0

[redacted]

APPROVAL SIGNATURE PAGE

Protocol Title: Long Term Extension Trial of Setmelanotide (RM-493) for Patients who have Completed a Trial of Setmelanotide for the Treatment of Obesity Associated with Genetic Defects Upstream of the MC4 Receptor in the Leptin-melanocortin Pathway

Sponsor: Rhythm Pharmaceuticals, Inc.
[redacted]

Protocol Number: RM-493-022

Document Date / Version: 28 June 2024 / Version 2.0

[redacted] **Author:**
[redacted]

Signature: DocuSigned by: [redacted]

Date: 01 Jul [redacted]

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 guidances 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.

Rhythm Pharmaceuticals, Inc

Sponsor Signatory:
[redacted]
Rhythm Pharmaceuticals, Inc.
[redacted]

Signature: DocuSigned by: [redacted]

Date: 01 July [redacted]

TABLE OF CONTENTS

TABLES INCLUDED IN THE TEXT

Section **Page**

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
[redacted]	
BP	Blood pressure
CO_2	Carbon dioxide
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	
ECG	Electrocardiogram
[redacted]	
HbA1c	glycated hemoglobin
HR	Heart rate
[redacted]	
IWQOL-Lite	Impact of Weight on Quality of Life-Lite Questionnaire
LDH	Lactic dehydrogenase
LEPR	Leptin Receptor
MC	Melanocortins
MedDRA	Medical Dictionary for Regulatory Activities
MHP	Mental health provider
PedsQL	Pediatric quality of life
PHQ-9	Patient Health Questionnaire 9
[redacted]	
POMC	Pro-opiomelanocortin
PT	Preferred term
[redacted]	
SAE	Serious adverse event
SAP	Statistical analysis plan
[redacted]	
SF-36	36-item Short Form health survey
SOA	Schedule of assessments
SOC	System organ class

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction

This document presents the statistical analysis plan (SAP) for Study RM-493-022, Long Term Extension Trial of Setmelanotide (RM-493) for Patients Who Have Completed a Trial of Setmelanotide for the Treatment of Obesity Associated with Genetic Defects Upstream of the MC4 Receptor in the Leptin-Melanocortin Pathway. The SAP is based upon protocol version 8.0, dated 12 May 2023.

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 trial.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study is to characterize safety and tolerability of setmelanotide in subjects who have completed a previous trial on treatment with setmelanotide for obesity associated with genetic defects upstream of the MC4R in the leptin-melanocortin pathway or with obesity related to other abnormalities in the MC4R pathway.

1.2.2. Exploratory Objectives

1.3. Study Design

1.3.1. Synopsis of Study Design

This is a long-term extension study of up to an additional 7 years duration beyond the index trial for patients who have completed a previous study on treatment with setmelanotide for rare

genetic, syndromic, or acquired diseases of obesity upstream of the MC4R in the melanocortin-leptin pathway and other abnormalities of the MC4R pathway.

Since continued assessments of the safety and efficacy of setmelanotide are the same in this extension protocol regardless of the index protocol, all patients can be followed consistently in this single extension protocol. The index trials relevant to this study are identified in Table 1-1.Eligible and consenting patients start in the extension trial immediately on the completion of their index protocol (ideally, Visit 1 of this trial will coincide with the final visit of the index trial) in order to limit gaps in treatment.

Patients are assessed approximately every 3 months for adverse events (AEs), concomitant medications, [redacted] height (in children), [redacted]

Patients enrolled in this extension trial may exit the trial to participate in other setmelanotide clinical trials. At the conclusion of the other setmelanotide trial, the patient may transition back into this extension trial. In such cases, the patient resumes the extension trial at the time point/visit at which he or she was at prior to transition to the other trial. Furthermore, after transition back into this extension trial, the patient receives setmelanotide at the same dose as they had received prior to transition to the other trial, unless the dose needs to be reduced due to tolerability reasons or in cases where a dose increase is required for potential additional efficacy needs at the investigator's discretion.

Table 1-1 Index Studies Currently Included in RM-493-022

Study Identifier	Study Phase	Number of Subjects who participated in Extension Trial	Diagnosis of Subjects
011	2	9	Genetic disorder of obesity
012	3	13	Early Onset POMC/PCSK1 Deficiency Obesity
014	2	119	Genetic disorder of obesity
015	3	12	LEPR Deficiency Obesity
023	3	38	BBS and AS
030	2	14	Hypothalamic Obesity
034	2	1	Genetic disorder of obesity

Abbreviations: AS=Alstrom Syndrome; BBS= Bardet-Biedl Syndrome; LEPR = Leptin Receptor; POMC = Pro-opiomelanocortin.

Note: Patients in RM-493-037 were previously enrolled in one of the index studies and RM-493-022 prior to entering the RM-493-037; patients were eligible to reenroll in RM-493-022 after participation in the RM-493-037. These patients are analyzed according to their index trial.

1.3.2. Stopping Rules and Unblinding

This study is open label so there is no blinding. All blinded index trials have been completed and are unblinded for analysis of RM-493-022.

A specific gene cohort or the whole trial may be 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 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 subjects
- Failure to enter subjects at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the study drug
- Lack of clinical efficacy

1.3.3. Randomization Methodology

As this is a single arm, open-label study, there will be no randomization in this trial.

1.4. Study Procedures

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

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

Table 1-2: Schedule of Assessments

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

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

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

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

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

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

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

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

[5] A complete physical examination will be conducted yearly. Tanner Staging for assessment of pubertal development will be conducted as part of this yearly examination, with the exception of females approaching childbearing potential. Whenever possible, the same trained health care professional will conduct the examination and Tanner Staging. Abbreviated physical examinations may be conducted at all other time points. Height (cm) will be measured at V1 only for those patients ≥21 years of age. Height will be

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

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

[8] Prior to study drug administration.

[10] Study drug is administered by patients/caregivers beginning the morning of Day 1 and for the duration of dosing. (If the index study drug is administered on the last day of the index trial/Day 1 of the current trial, then study drug administration in the current trial will begin on Day 2.) Patients/caregivers will draw up and self-administer/administer the drug QD in the morning. On days with clinic visits, the patients/caregivers will administer the drug in the clinic in the presence of the clinical staff to ensure proper technique. Patients/caregivers will return all used vials to the clinic when they visit (the number recorded) and both clinic administered study drug, as well as outpatient study drug administration will be recorded in a trial diary. In patients aged ≥18 years who tolerate the 3 mg QD dose level for at least 6 months, if additional effect on [redacted] is desired per the patient individual needs, a higher QD dose can be administered at the investigator's discretion and in consultation with the sponsor; the dose can be escalated to 3.5 mg and, if tolerated, it can be escalated by an additional 0.5 mg every second week, until reaching the maximum dose of 5 mg QD in adult patients with on absolute body weigh >60 kg. The maximum dose level is 4 mg in patients with an absolute weight of >50 kg. These dose levels have been investigated previously in trial RM-493-026. Patients exposed to these dose levels should be monitored closely via additional unscheduled visits or telephone calls to assess safety and tolerability. For patients who escalated to 4 or 5 mg QD, the dose level should be reduced to 3 mg and 4 mg if their absolute weight decreases to ≤50 kg and ≤60 kg, respectively. This is due to the excipients content in the setmelanotide formulation (see study protocol for details).

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

[12] All vital signs are to be obtained in the sitting position following at least 5 minutes of rest. All measurements, except body temperature, will be taken in triplicate, approximately 2 minutes apart. When possible, BP should be taken in the non-dominant arm throughout the trial, using the same methodology (automated or manual). Vital signs should be obtained prior to blood draws whenever possible.

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

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

[redacted]

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

[redacted]

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

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

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

[redacted]

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

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

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

1.4.1. Primary Endpoint

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

1.4.2. [redacted]

[redacted]

2. SUBJECT POPULATIONS

2.1. Population Definitions

- Safety Analysis Population (SAS) – The SAS includes all subjects who received at least one dose of treatment in RM-493-022. The safety population will be used for all analyses.

2.2. Protocol Violations

All protocol deviations will be presented in a data listing; major deviations will be indicated.

Categorization of protocol deviations will be determined by a review of the protocol deviation data collected on the case report form (CRF). Determination of major/minor and categorization of each protocol deviation type will be made prior to database lock.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

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

Given the rarity of these genetic and acquired diseases of the MC4R pathway, estimated power for exploratory endpoints such as expected weight-related improvements and change in hunger will not be provided, and efficacy will be only summarized.

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. The last day of study medication is designated with an "L" (e.g., Day 14L). Post-treatment study days are numbered relative to the last dose and are designated as Day 1P, Day 2P, etc.

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

Tabulations will be produced for appropriate demographic, baseline, efficacy, pharmacokinetic, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented. . For the reporting of descriptive statistics, the mean and median will be reported to 1 decimal place more than the source data; the minimum and the maximum values will be presented to the same precision as the source data, and SD will be reported to 2 decimal places more than the source data.

3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.4 (SAS Institute Inc., Cary, NC, USA), unless otherwise noted. Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or later. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version September 2023 or later.

3.4. Baseline Definitions

To assess the temporal dynamics of setmelanotide on weight, BMI, BMI z-score, percent of BMI 95th percentile, waist circumference, body composition, two baseline definitions will be utilized:

- Extension study baseline will be defined as the last value obtained in the index study prior to the first dose of active treatment in the extension study. For subjects with a >1 day gap in Setmelanotide treatment between the index study and the extension study, the last value obtained prior to first active treatment dose in the extension study will be used as the baseline

- Index study baseline will be defined as the last value obtained prior to the first dose of active treatment in the index study.

For all other parameters, baseline will use the extension study baseline as defined above.

3.5. Methods of Pooling Data

For safety-related analyses, data will be pooled across index studies and rare genetic disorders of obesity and summarized together. For non-safety-related analyses, data will be pooled by rare genetic disorder of obesity within study, as applicable, and data will therefore be summarized by index study.

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

No subpopulations have been defined.

3.9. Data from Index Studies

In general, data from index studies will only be used for identifying index study baseline and the extension study baseline, as applicable. Index study data will additionally be used to summarize demographic and disease characteristics at time of entry into index study such as age at enrollment in index study, country of investigational site, sex, race, ethnicity, gene type, height, weight, BMI, and waist circumference.

3.10. Withdrawals, Dropouts, Loss to Follow-up

Subjects will be followed for the duration of the study, except where:

- Informed consent is withdrawn and the subject or guardian refuses further follow-up (subjects have the right to withdraw consent and discontinue from the study at any time, for any reason.)

- The subject is unable to comply with protocol-defined requirements (non-adherence/compliance to dosing regimens or visits).

- Investigator decision to withdraw subject

The subject's reason for, and date of, withdrawal from the study is to be recorded in the CRF. Any subject withdrawing from the study will complete the Early Termination Visit, if possible.

3.11. Missing, Unused, and Spurious Data

In general, no missing data will be imputed for this extension study and analyses will be carried out on all available data. Imputation of missing questionnaire data will be applied for the derivation of summary scores, dependent on the questionnaire and imputation rules of the questionnaire. Questionnaire-specific imputation rules will be outlined in the sections below, as applicable.

3.12. Visit Windows

It is expected that all visits should occur according to the protocol schedule. 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. All available data will be listed for each subject.

3.13. Interim Analyses

No formal interim analyses are planned; however, various data cuts may occur in support of regulatory submission such as NDA. The timing of these data cuts and the number of subjects included in each analysis will take into account specific requests from regulatory agencies and applicable regulatory guidance. The rationale for each analysis will be documented.

3.14. Final Analyses

A final analysis will be performed when all subjects complete the study, defined as last subject last visit.

4. STUDY ANALYSES

4.1. Subject Disposition

A tabulation of the disposition of subjects will be presented, including the number enrolled, the total time followed since index study baseline and since extension study baseline, the number of subjects completing the extension study, the number of subjects discontinuing from the study, and the reasons for any subject who discontinued. Disposition will be summarized by index study and overall.

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

4.2. Demographics and Disease Characteristics

Demographics and disease characteristics will be summarized and presented overall and by index study. Age at index study enrollment, country of investigational site, height, weight, BMI, and waist circumference will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum). The number and percentage of subjects in each sex, gene type, ethnicity and race category will also be presented.

Medical history prior to enrollment in index trial and brief medical history collected prior to enrollment into extension study will be included in a by-subject listing, with extension study medical history flagged in the listing.

4.3. Exploratory Evaluations

4.3.1. [redacted]

[redacted]

4.3.2. [redacted]

[redacted]

Change and percent change from the index trial baseline as well as change and percent change from the extension study baseline (as defined in Section 3.4). will be summarized for all patients and separately for patients > 18 years of age .

A by-subject listing be provided for all subjects.

4.3.3.

4.3.4.

4.3.5. [redacted]

[redacted]

4.3.6. [redacted]

[redacted]

4.3.7. [redacted] and HbA1c

[redacted] and HbA1c will be collected according to the SOA (Table 1-2) and will consist of [redacted] and HbA1c. Descriptive statistic summaries of the extension study raw, change and percent change from extension study baselines will be presented for each measure. By-subject results will be presented in a listing.

4.3.8. [redacted]

4.3.8.1. [redacted]

[redacted]

4.3.8.2. [redacted]

[redacted]

[redacted]

4.3.8.3. [redacted]

[redacted]

4.3.9. [redacted]

[redacted]

4.3.10. [redacted]

[redacted]

4.3.11. [redacted]

[redacted]

4.4. [redacted]

[redacted]

4.5. Safety Evaluations

4.5.1. Study Drug Exposure

The duration of exposure in days will be reported for the for both the index + extension studies as wells the extension study only. The duration of exposure for the extension study will be calculated as the extension study last dose date minus the extension first dose date + 1.; the duration of exposure for the index + extension studies will be calculated as the sum of the extension period duration (as described above) plus the duration of exposure for the index study (last dose date – first dose date +1 from index study) .Data will be summarized and listed.

4.5.2. Adverse Events

All AEs will be coded using the MedDRA coding system (version 25.0 or higher) and displayed in tables and in data listings using system organ class (SOC) and preferred term (PT). AE Grade assessment will be based on Investigator reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], version 4.03.

Summarization will focus on incidence of drug product related AEs, treatment-emergent SAEs by SOC and PT,

A by-subject listing for the following AEs that occurred on extension study will also be provided: drug product-related AEs, treatment-emergent SAEs, drug product-related SAEs, deaths, AEs leading to study withdrawal, and subject deaths. Adverse event listings will be sorted by index study.

4.5.3. Injection Site Evaluations

Injection site evaluations will be measured as shown in the SOA (Table 1-2) 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 subjects reporting more than one occurrence of the same type of reaction, the most severe reaction will be used for the summary.

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

4.5.4. Laboratory Data

Clinical laboratory values will be expressed using the International System of Units (SI). Values will be summarized using raw, change and percent change from extension study baseline for

each clinical laboratory parameter. Clinical laboratory parameters include hematology, chemistry, and urinalysis.

Shift tables, which will indicate abnormally high or abnormally low changes in laboratory parameter grade based on CTCAE criteria from extension study baseline through extension study follow-up, will be performed by visit.

By-subject listings will be provided for all laboratory data collected, including hematology, chemistry, urinalysis, and pregnancy tests.

4.5.5. Concomitant Medications and Procedures

Prior and concomitant medications will be coded using the WHO Drug Dictionary. Concomitant medications are those which were ongoing or began after the patient began participating in the extension trial.

The use of concomitant medications during the extension study will be included in a summary table. Prior and concomitant procedures will be included in a by-subject data listing.

Concomitant procedures will be included in a by-subject data listing.

4.5.6. 12-Lead Electrocardiogram

Electrocardiogram results will be summarized in a by-visit shift table, including the number and percentage of subjects with normal, abnormal, and clinically significant abnormal results at extension study baseline and shift to each extension study visit.

Electrocardiogram data for each subject, including heart rate, PR interval, QRS interval, QT interval, and QTcF interval, as well as the overall interpretation, will be provided in a summary table and a data listing.

4.5.7. Quantitative Skin Color Measurement

Quantitative skin color measurement data will be provided in a by-patient listing.

4.5.8. Bone Age Assessment

Bone age assessment will be measured as shown in the SOA (Table 1-2) if done in the index study. A by-subject listing, including the date of the assessment and result, will be provided as available.

4.5.9. [redacted]

[redacted]

[redacted]

4.5.10. Vital Signs

Vital signs will be measured as shown in the SOA (Table 1-2). Aside from those used in exploratory evaluation, the raw, change and percent change from extension study baseline of additional vital signs of temperature, heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate will be summarized descriptively by visit. A by-subject listing of all vital signs will be provided.

4.5.11. Physical Exam and Comprehensive Skin Examination

Physical exams will be measured as shown in the SOA (Table 1-2). Results from each component of the physical exam will be provided in shift tables, summarizing the shift from extension study baseline by visit. A by-subject listing of all physical exam findings will be provided; results of the comprehensive skin examination will be provided in the listing.

Tanner Staging will be presented in a by-subject listing.

4.5.12. Anti-RM Antibody

Anti-RM Antibody will be measured as shown in the SOA (Table 1-2). A by-subject listing, including the date of the assessment and result, will be provided.

5. CHANGES TO PLANNED ANALYSES

6. REFERENCES

NHLBI. The practical guide identification, evaluation, and treatment of overweight and obese in adults. NIH Publication No. 00-4084, October 2000.

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

Vami, JW. (2017). Scaling and Scoring of the Pediatric Quality of Life Inventory PedsQL. Lyon, France: Mapi Research Trust.

7. APPENDIX