[redacted]

STATISTICAL ANALYSIS PLAN

STUDY SPONSOR:	Rhythm Pharmaceuticals, Inc. [redacted] Tel: [redacted]
SPONSOR REPRESENTATIVE:	[redacted]
PROTOCOL NUMBER & TITLE:	A Phase 3, Randomized, Double-Blind Trial of Two Formulations of Setmelanotide (Daily and Weekly) with a Crossover to Open-Label Once Weekly Setmelanotide in Patients with Specific Gene Defects in the Melanocortin-4 Receptor Pathway Who Are Currently on a Stable Dose of the Once Daily Formulation
PROTOCOL NUMBER:	RM-493-037
PROTOCOL VERSION AND DATE:	Version 3.0 (Amendment 2): 21 March 2022 Version 2.0 (Amendment 1): 10 December 2021 Version 1.0 (Original): 14 July 2021
NAME OF TEST DRUG:	Setmelanotide
PHASE:	Phase 3
METHODOLOGY:	Randomized, Double-Blind (Period 1), Open-Label (Period 2)
ANALYSIS PLAN DATE:	24 July 2023
ANALYSIS PLAN VERSION:	Final Version 2.0
AUTHOR:	[redacted]

APPROVAL SIGNATURE PAGE

Protocol Title:	A Phase 3, Randomized, Double-Blind Trial of Two Formulations of Setmelanotide (Daily and Weekly) with a Crossover to Open-Label Once Weekly Setmelanotide in Patients with Specific Gene Defects in the Melanocortin-4 Receptor Pathway Who Are Currently on a Stable Dose of the Once Daily Formulation
Sponsor:	Rhythm Pharmaceuticals, Inc. [redacted]
Protocol Number:	RM-493-037
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[redacted]	[redacted]

Approval Signature	Job Title
[redacted]	[redacted]

Sponsor Signatory: [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.

Approval Signature	Job Title
[redacted]	[redacted]

TABLE OF CONTENTS

Section **Page**

TABLES INCLUDED IN THE TEXT

Page

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ATC	Anatomic therapeutic class
BBS	Bardet-Biedl syndrome
[redacted]	[redacted]
CI	Confidence interval
cm	Centimeter
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
FAS	Full Analysis Set
FDA	Food and Drug Administration
[redacted]	[redacted]
HR	Heart rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	interactive response technology
ISR	Injection site reaction
kg	Kilogram
LEPR	Leptin receptor
LTE	Long-term extension
m^2	Meters squared
MC4R	Melanocortin-4 receptor
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MSH	Melanocyte-stimulating hormone
N	Number
NCI	National Cancer Institute
nM	Nanometer
%	Percent
PCSK1	Proprotein convertase subtilisin/kexin type 1
PK	Pharmacokinetic
POMC	Pro-opiomelanocortin

Abbreviation	Definition
PPL	POMC (pro-opiomelanocortin), PCSK1 (proprotein convertase subtilisin/kexin type 1), LEPR (leptin receptor)
PPS	Per Protocol Set
PR	PR interval
PT	Preferred term
QD	Once daily Setmelanotide
QRS	Interval between Q, R, and S waves
QT	Interval between Q and T waves
QW	Once weekly Setmelanotide
Rel Day	Relative study day
RGDO	Rare genetic disorder of obesity
RM-493	Setmelanotide
SA	Safety analysis set
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SI	International System of Units
SoA	Schedule of Assessments
SOC	System organ class
TEAE	Treatment-emergent adverse event
US	United States
VC	Vital capacity
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

This statistical analysis plan (SAP) summarizes the planned [redacted], safety and pharmacokinetic (PK) analyses for study RTHM-493-037, which is a Phase 3, double-blind, randomized, crossover to open label, multicenter trial to examine the effects of a combinatory once daily (QD) and once weekly (QW) formulation of setmelanotide. A sterile solution of [redacted] will be used for daily administration and a [redacted] will be used for weekly administration. The [redacted] technology transforms the injected drug into a gel which releases drug slowly by diffusion from the subcutaneous (SC) depot. The purpose of this study is to compare the QD and QW formulations of setmelanotide in patients with the following rare genetic disorders of obesity (RGDO): biallelic PPL (POMC [pro-opiomelanocortin], PCSK1 [proprotein convertase subtilisin/kexin Type 1], LEPR [leptin receptor]), heterozygous PPL, and patients with BBS (Bardet-Biedl syndrome).

Obesity is a multifactorial disease caused by various environmental, neurobehavioral, immunological, endocrine, medical, and genetic/epigenetic factors or a complex interplay between 2 or more of these factors (Maes 1997; Schousboe 2003; Silventoinen 2010; Hall 2012; Pigeyre 2016; Sheikh 2017; Thaker 2017). In a subset of individuals with obesity, rare genetic variants may result in severe obesity. The identification of key genetic determinants of the neuronal pathways and signaling molecules (e.g., leptin) regulating appetite and body weight has led to the discovery of multiple RGDO (van der Klaauw 2015). A key neuronal pathway, the central melanocortin and melanocortin-4 receptor (MC4R) pathway, plays an important role in appetite, hunger, and energy utilization. The melanocortins are a family of peptide hormones (including adrenocorticotropic hormone, α-melanocyte-stimulating hormone [MSH], β-MSH, and γ-MSH) derived from the common precursor, POMC. Originating in the hypothalamus, the MC4R pathway concertedly modulates appetite (feelings of hunger and satiety), energy intake (as caloric consumption), and energy expenditure (basal metabolism, thermogenesis, and physical activity) to define long-term body weight.

In humans and animal models, genetic defects in the MC4R pathway, such as POMC deficiency, result in severe forms of early-onset obesity and hyperphagia (Farooqi 2008). Patients with rare genetic variants in LEPR and patients with BBS, a rare pleiotropic autosomal recessive disorder caused by mutations in as many as 24 different genes, also present with unremitting hunger and severe obesity caused in part by a lack of activation of the MC4R pathway. As a result of hyperphagia, individuals with RGDO have increased calorie intake leading to early-onset, severe obesity, and obesity-related comorbidities such as type 2 diabetes. The Sponsor is developing setmelanotide (also known as RM-493), an MC4R agonist, as a treatment for patients with RGDO. Setmelanotide bypasses upstream signaling defects to directly activate MC4R. Setmelanotide binds with high affinity (inhibitory constant = 2.1 nM) to the human MC4R and is efficient in activating MC4R (50% effective concentration = 0.78 nM).

Thus, setmelanotide has the potential to restore reduced activity in the MC4R pathway in patients with these and other genetic defects, thereby serving as a form of "replacement" therapy to re-establish weight and appetite control in patients with these disorders.

1.1.2. Study Objectives

This SAP is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). 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.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

The study objectives are the following (per protocol):

Primary:

- To compare the pharmacokinetics (PK) of the once daily (QD) and once weekly (QW) formulations of setmelanotide

Secondary:

- To assess the safety of the QW formulation of setmelanotide with up to 6 months (26 months) of drug administration

[redacted]

1.2. Study Design

1.2.1. Synopsis of Study Design

This study is designed to compare the safety, PK, and [redacted] of QD and QW formulations of setmelanotide, as well as to evaluate the safety and [redacted] of up to 6 months of QW setmelanotide administration in patients with BBS, biallelic PPL, or heterozygous PPL.

Eligible patients are those who have taken QD setmelanotide in Study RM-493-022 (referred to as the long-term extension [LTE] study) for at least 6 months with acceptable safety and tolerability, and who wish to continue with setmelanotide treatment. Such patients otherwise meet all inclusion and exclusion criteria. Approximately 30 patients will be targeted in 3 age groups as follows: approximately 20 patients ≥18 years old; approximately 6 patients ≥12 to <18 years old; and approximately 4 patients ≥6 to <12 years old at the time of study entry.

The study consists of a Screening Period for transition from the LTE study, a Run-in Period of up to 1 week of continuation on the patient's current dose level of QD setmelanotide (2, 2.5, or 3 mg), a 13-week double-blind phase in which the patients will be randomized to either QD or QW setmelanotide, a 13-week non-randomized open-label phase where all patients will receive open-label QW setmelanotide, and a 3-week follow-up period in which all patients will return to their run-in dose level of QD setmelanotide to prepare for re-enrollment into Study RM-493-022 or to resume the QD formulation in some other way.

Once informed consent is provided, patients will enter the Screening Period, during which they will be assessed for eligibility and complete all screening procedures as described in the Schedule of Assessments (SoA) (Table 1). During the Screening Period, patients will undergo medical evaluation and other study procedures, [redacted] To ensure continuity of treatment, informed consent for this study will be obtained and eligibility of the patient will be confirmed before the patient is withdrawn from the LTE study.

The patient will have a Run-in Period of 1 day to 1 week on QD setmelanotide at the dose they received in the LTE study. The first day of the Run-in Period (Visit 2) should coincide with the patient's last visit in the LTE study to avoid an interruption of treatment. The first dose of QD setmelanotide as part of the RM-493-037 study will occur in clinic on the first day of the Run-in Period. On the first day of the Run-in Period, patients will have serial blood samples taken for measurement of setmelanotide concentrations (QD formulation) and 24-hour PK profiles (including optional timepoint at 12 hours after dosing) will be performed.

On Day 1 (Visit 3) patients will be randomized 1:1 to receive either QD or QW setmelanotide. Patients who received QD setmelanotide at a dose of 2 mg at the time of study entry will be

randomized to receive either QD setmelanotide 2 mg or QW setmelanotide at a dose of 20 mg, whereas patients who were on QD setmelanotide at a dose of 2.5 mg will be randomized to receive either QD setmelanotide 2.5 or QW setmelanotide at a dose of 25 mg, and finally patients who were on QD setmelanotide at a dose of 3 mg will be randomized to receive either QD setmelanotide 3 mg or QW setmelanotide at a dose of 30 mg. Study medication will be administered in a double-dummy fashion in order to maintain the double blind. Patients will receive the first QW dose on Day 1 of the randomized treatment period (Visit 3). The randomization will be stratified by age group.

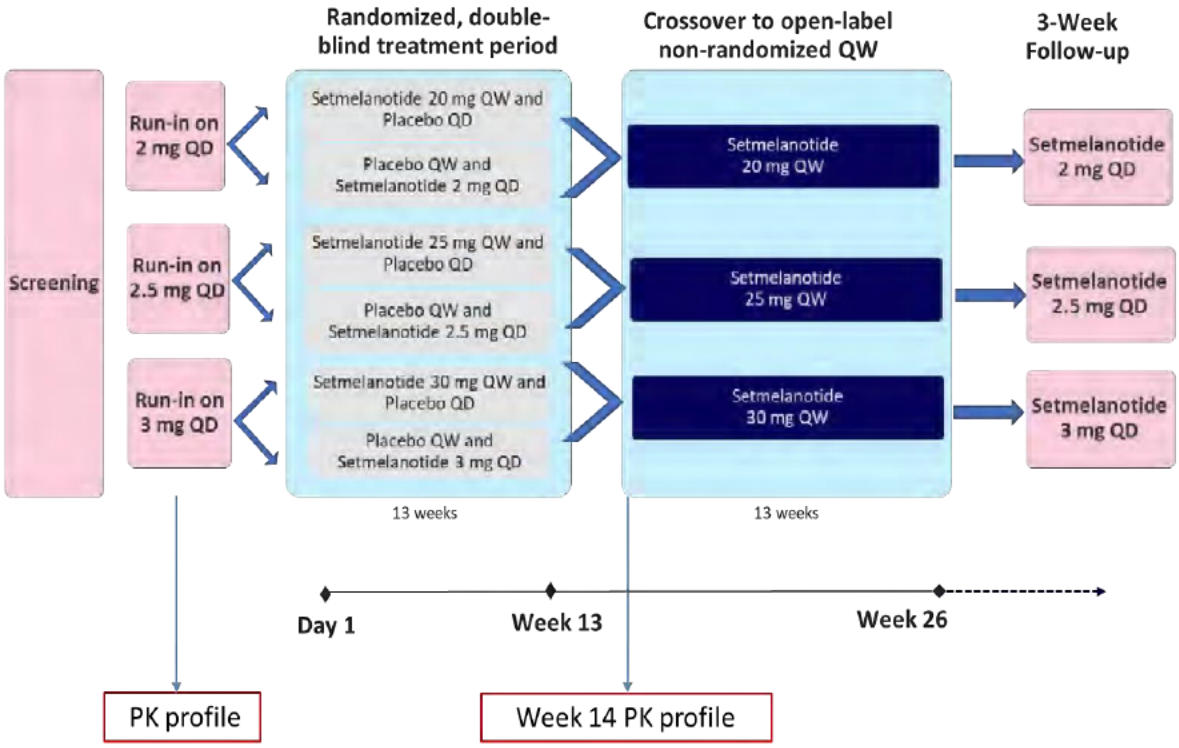
- Patients randomized to QW setmelanotide will receive blinded QW setmelanotide and QD placebo injections until the Week 14 visit (i.e., completion of 13 weeks of blinded dose administration). Starting with Week 14, patients will continue with open-label QW injections of setmelanotide during the 13-week non-randomized phase of the study.

- Patients randomized to QD setmelanotide will receive blinded QD setmelanotide and QW placebo injections until the Week 14 visit (i.e., completion of 13 weeks of blinded dose administration). Starting with Week 14, patients will continue with open-label QW injections of setmelanotide during the 13-week non-randomized phase of the study.

For the 3-week Follow-up Period, all patients will return to their allocated run-in medication of QD setmelanotide to prepare for re-enrollment into Study RM-493-022 or to resume the QD formulation in some other way.

The study design is depicted graphically in Figure 1.

Figure 1 Study Design Schematic



1.2.2. Randomization Methodology

Patients will be randomized 1:1 on Day 1 (Visit 3) to treatment with either QD or QW setmelanotide, stratified by age group (≥18 years old; ≥12 to <18 years old; ≥6 to <12 years old). The study staff will use an interactive response technology (IRT) system to obtain the randomization number for each patient. To maintain the blind during the 13-week randomized treatment period, all patients will receive placebo injections [redacted] from the QD formulation or [redacted] from the QW formulation) in addition to the setmelanotide injections in a double-dummy fashion. Randomization numbers will not be re-used once assigned. Please refer to the official randomization plan for more details. No randomization or blinding will be done for the 13-week open-label phase or for the 3-week QD follow-up phase.

1.2.3. Stopping Rules and Unblinding

Emergency unblinding for adverse events (AEs) may be performed through the IRT system. The IRT system will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's intervention assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor before unblinding a patient's intervention assignment unless this could delay emergency treatment for the

patient. The date and reason for the unblinding by the Investigator must be recorded. If a patient's intervention assignment is unblinded, the Sponsor must be notified by the Investigator within 24 hours that an unblinding occurrence. The Investigator should not reveal to the Sponsor the patient's treatment allocation unless the Sponsor requests this information for safety purposes.

For any unexpected serious adverse event (SAE) that is treatment-related (e.g., possibly or probably related), the blind will be lifted by the Sponsor only for that specific patient. The blind will be maintained for persons responsible for the ongoing conduct of the study (such as the monitors, investigators, etc.) and those responsible for data analysis and interpretation of results at the conclusion of the study (such as biometrics personnel). Unblinded information will only be accessible to those who need to be involved in the safety reporting to Health Authorities, Ethics Committees, and/or Institutional Review Boards (IRBs). Investigators will receive only blinded information unless unblinded information is judged necessary for safety reasons.

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:

- Discontinuation of further study intervention development
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of patients by the Investigator
- Total number of patients enrolled earlier than expected

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

Every attempt will be made to maintain the blind through the end of the study. Breaking the blind for a patient should be done only in the event of a medical emergency where the identity of study drug is necessary to appropriately treat the patient. As noted above, the Primary Investigator will be provided with access to the IRT system to unblind their patients, but, if possible, the decision to break the blind should first be discussed with the Sponsor. If the blind is broken, the reason, when, and how the blind was broken will be documented.

1.2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in **Error! Reference source not found.**.

Table 1 Schedule of Assessments

Study Period	Screening* (up to 21 days)	Run-In$^{\Delta}$ (up to 1 week)	Randomized, Double-Blind Treatment (QD and QW)													Open-Label Non-Randomized QW Administration				Restart QD	Follow - up on QD (EoS)	Early Ter-mi-nation
Visit (V) Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	
Study Week	-4	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	16	18	22	27	30	
Study Day ± Visit Window	-28 to -8	-7 to -1	1	8 ± 1	15 ± 1	22 ± 1	29 ± 3	36 ± 1	43 ± 1	50 ± 1	57 ± 3	64 ± 1	71 ± 1	78 ± 1	85 ± 1	92 ± 0	106 ± 1	120 ± 3	148 ± 3	183 ± 3	204 ± 3	(n/a)
In Person Visit	X	X	X				X				X					X		X	X	X	X	X
Telehealth Visit[1]				X	X	X		X	X	X		X	X	X	X		X					
Informed consent/assent	X																					
Inclusion/exclusion review	X		X																			
Medical history & prior medication review	X		X																			
Fitzpatrick scale	X																					
Comprehensive skin exam[2]	X																			X	X	X
Randomization			X																			
Pregnancy test[3]	X	X	X†				X†				X†					X†		X†	X†	X†	X†	X†
Study drug: administer[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study drug dispense[4]		X	X				X				X					X		X	X	X		
[redacted]																						
Height[6]	X		X													X				X		X

Study Period	Screening* (up to 21 days)	Run-In$^{\Delta}$ (up to 1 week)	Randomized, Double-Blind Treatment (QD and QW)													Open-Label Non-Randomized QW Administration				Restart QD	Follow-up on QD (EoS)	Early Termination
Visit (V) Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	
Study Week	**-4**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**16**	**18**	**22**	**27**	**30**	
Study Day ± Visit Window	**-28 to -8**	**-7 to -1**	**1**	**8 ± 1**	**15 ± 1**	**22 ± 1**	**29 ± 3**	**36 ± 1**	**43 ± 1**	**50 ± 1**	**57 ± 3**	**64 ± 1**	**71 ± 1**	**78 ± 1**	**85 ± 1**	**92 ± 0**	**106 ± 1**	**120 ± 3**	**148 ± 3**	**183 ± 3**	**204 ± 3**	**(n/a)**
In Person Visit	**X**	**X**	**X**				**X**				**X**					**X**		**X**	**X**	**X**	**X**	**X**
Telehealth Visit[1]				**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**	**X**		**X**					
[redacted]																						
C-SSRS[10]	X	X†	X†				X†				X†					X†		X†	X†	X†	X†	X†
PHQ-9[21]	X	X†	X†				X†				X†					X†		X†	X†	X†	X†	X†
Dosing Diary [11]		X	For each dose administered (QW or QD)																			
[redacted]																						
PK blood sampling (trough)[13]			X†				X†				X†					X†		X†	X†	X†		
PK profile[14]		X														X†						
Injection site inspection[15]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests[16]	X		X								X					X				X	X	X

Study Period	Screening* (up to 21 days)	Run-In$^{\Delta}$ (up to 1 week)	Randomized, Double-Blind Treatment (QD and QW)													Open-Label Non-Randomized QW Administration				Restart QD	Follow-up on QD (EoS)	Early Termination
Visit (V) Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	
Study Week	**-4**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**16**	**18**	**22**	**27**	**30**	
Study Day ± Visit Window	**-28 to -8**	**-7 to -1**	**1**	**8 ± 1**	**15 ± 1**	**22 ± 1**	**29 ± 3**	**36 ± 1**	**43 ± 1**	**50 ± 1**	**57 ± 3**	**64 ± 1**	**71 ± 1**	**78 ± 1**	**85 ± 1**	**92 ± 0**	**106 ± 1**	**120 ± 3**	**148 ± 3**	**183 ± 3**	**204 ± 3**	**(n/a)**
In Person Visit	**X**	**X**	**X**				**X**				**X**					**X**		**X**	**X**	**X**	**X**	**X**
Telehealth Visit[1]				**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**	**X**		**X**					
Anti-drug antibodies[17]			X								X					X				X		X
[redacted]																						
Vital signs[18]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG (12-lead)[19]	X		X								X					X				X	X	X
Physical examination[20]	X		X				X				X					X		X		X	X	X
Activity Sensor Sub-Study (optional)	X	Daily from Screening through the end of the double-blind period																				
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EoS = End of Study; [redacted] HR = heart rate; min = minute; n/a = not applicable; LTE = long-term extension; PHQ-9=Patient Health Questionnaire – 9; PK = pharmacokinetic; QD = once daily; QW = once weekly; V = visit.

* Due to the rarity of these patients and difficulty associated with travel to the study site, the Screening Period may be extended beyond 3 weeks, if necessary, after discussion with the Sponsor.

Δ The patient will have a Run-in Period of 1 day to 1 week on QD setmelanotide at the dose they were on in the LTE study. The first day of the Run-in Period (V2) should coincide with the patient's last visit in the LTE study to avoid an interruption of treatment.

† Assessment/sample should be performed/obtained prior to administration of study drug.

[1] Any telehealth visit may optionally be converted to an in-person visit.

[2] A comprehensive skin evaluation will be performed by the Investigator. Any concerning lesions identified during the Screening Period will be biopsied and results known to be benign prior to study entry. If the pretreatment biopsy results are of concern, the patient will be excluded from the study.

[3] A urine pregnancy test may be performed in order to expedite availability of results prior to the first dose at Run-in (V2). All other pregnancy tests will be serum; dosing may continue with results pending.

[4] For the QD doses of study drug, patients/caretakers will draw up and self-administer/administer the study drug each morning beginning with the first dose of Run-in (V2) and for the duration of the 13-week double-blind period. In addition, once each week the QW dose of study drug will be prepared and administered at the study center or self-administered/administered by the patient/caretaker in between visits. A home healthcare provider can optionally be made available at the patient's home to administer or supervise administration of the QW dose. The patient will receive the first QW dose on Day 1 (V3) at the study center. On the days of in-person clinic visits, the patients/caretakers will self-administer/administer the QD dose of study drug in the clinic in the presence of the clinical staff to assure proper technique. For accountability, patients/caretakers will return all used vials to the clinic when they visit; the study staff will record the number returned; and both study drug administration at the clinic, as well as outpatient study drug administration will be recorded in a study diary.

[redacted]

[6] For patients ≥21 years of age, height will be measured only during the Screening Period. For patients aged <21 years, height is to be measured at the time points listed in the SoA. 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 halfcm. The stadiometer should be calibrated on a daily basis prior to height assessment.

[redacted]

[redacted]

[10] The Baseline/Screening version of the C-SSRS should only be administered to patients who have never completed an initial C-SSRS assessment prior to entering this trial; however, this version is expected to have been completed in the index study for all patients prior to entry into this study. The Screening version of the C-SSRS is to be completed at the Screening visit. At all subsequent visits, the Since Last Version is to be completed. If at any time during the study a patient has suicidal ideation of type 4 or 5, or any suicidal behavior, the patient should be referred to a mental health professional.

[11] The dosing diary will be completed for all QD and QW dose administration.

[redacted]

[13] Prior to the QW dose of study drug, a blood sample for trough plasma levels of setmelanotide will be drawn within 10 minutes prior to dosing. On the days when 24-hour PK profiles (including optional timepoint at 12 hours after dosing) are done, the predose (trough) PK sample will be drawn within 5 minutes prior to study drug administration. The trough sample to be drawn at Week 14 (V16) will be used as the 168-hour postdose sample for the purpose of the PK profile, therefore no visit window is allowed for
Week 14, which must occur exactly 7 days after the last dose of double-blind QW study drug. Patients/caretakers will be reminded that there should be NO study drug administration at home on the day of clinic visits; the drug will be administered in the clinic AFTER the PK sample is obtained. For the PK sample, the actual collection (clock) time will be recorded, as well as the time of the previous day's study drug injection as reported by the patient/caretaker.

[14] Patients will undergo serial blood samples taken for measurement of steady-state setmelanotide concentrations (both QD and QW) and 24-hour PK profiles (including optional timepoint at 12 hours after dosing) will be performed. On the first day of the Run-in Period, blood samples for the QD PK profile will be drawn within 5 minutes prior to dose administration and at 0.5, 1, and 2 hours (±5 min) postdose and at 3, 4, 6, and 8 hours (±10 min) postdose. At Week 14, blood samples for the PK profiles will be drawn within
5 minutes prior to dose administration and at 0.5, 1, and 2 hours (±5 min) postdose and at 3, 4, 6, and 8 hours (±10 min) postdose and at 24 hours postdose. When possible, additional optional blood draws will be done at 48, 72, 96, 120, and 148 hours. Patients/caretakers will be reminded that there should be NO study drug administration at home on the day of clinic visits and that the predose (trough) blood draw must occur PRIOR to study drug administration. The blood draws for the Week 14 PK sampling must occur exactly 7 days after the prior visit.

[15] Injection site evaluations and scoring (by the clinical staff) will include identification of areas of erythema, edema, and induration, as well as the presence of localized pain, tenderness, and itching. At in-person study visits, the clinical staff will also record measurements of areas of erythema, edema, and induration if possible. Unscheduled evaluations may also be recorded as warranted by clinical conditions.

[16] Safety laboratory tests will include: complete blood count with platelet count and standard indices, chemistry panel, coagulation, and urinalysis with microscopic analysis (if positive findings on dipsticks warrant further examination).

[17] Any patient with a positive ADA at the end of study or early termination will be followed every 3 months after the sample analysis until resolution (ie, no measurable ADA response).

[18] 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.

[19] A single 12-lead ECG will be performed with the patient in the supine position following a period of at least 10 minutes of rest.

[20] A complete physical examination will be conducted at Screening and at the end of study (Week 30). At other time points, an abbreviated examination, noting any changes from baseline will be performed. In addition, Tanner Staging for assessment of pubertal development will be conducted for those patients who have yet to reach Tanner Stage V. Whenever possible, the same trained health care professional will conduct the examination and Tanner Staging.

[21] If at any time during the study an individual patient's PHQ9 score is ≥10, the patient should be referred to a Mental Health Professional.

[redacted]

1.2.5.2. Pharmacokinetic Parameters

The primary [redacted] endpoint is the comparison of steady-state PK parameters (C_{max}, T_{max}, C_{trough}, $AUC_{0\text{-}tau}$) for QW compared with QD setmelanotide.

1.2.5.3. Safety Parameters

The safety endpoints include AEs, SAEs, and injection site reactions (ISRs), and laboratory parameters (including pregnancy testing), vital signs, ECG recordings, physical examination findings, skin examination, and the Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire results.

2. PATIENT POPULATION

2.1. Population Definitions

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

- Pharmacokinetic Analysis Set (PKAS): All patients who receive at least 1 dose of setmelanotide and who have a sufficient number of measurable plasma concentrations to permit assessment of noncompartmental parameters.
- Full Analysis Set (FAS): All patients who receive at least 1 dose of setmelanotide after the randomization. Patients will be analyzed according to their randomly assigned treatment.
- Per Protocol Set (PPS): All patients in the FAS without any major protocol violations that would result in exclusion of the patients from the analysis. Patients will be analyzed according to their randomly assigned treatment.
- Safety Analysis (SA) Set: All patients who receive at least 1 dose of protocol-specified study drug. Patients will be analyzed according to the treatment they actually received.

The FAS is the primary population for the analysis of [redacted] parameters. A subset of [redacted] parameters will be evaluated for the PPS (see Section 4.3). The SA set is the primary population for the analysis of safety endpoints.

2.2. Protocol Violations

At the discretion of the Sponsor, major protocol violations, as determined by a review of the data prior to unblinding of the study results and the conduct of statistical analyses, may result in the removal of a patient's data from the PPS. Any type of dose adjustment will be captured as a protocol violation. The Sponsor or designee will be responsible for producing the final protocol violation file (formatted as a Microsoft Excel file), in collaboration with [redacted] 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 PPS. This file will be finalized prior to hard database lock.

All protocol violations will be presented in a data listing.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

The sample size is based on availability of the patients enrolled in the LTE study and is not driven by formal statistical hypothesis testing on non-inferiority/similarity.

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 vaccine 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 incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, 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, [redacted] PK, and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of patients, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Summarizations will be created for the groups of setmelanotide, genetic subgroups, and age groups.

This study is primarily descriptive in nature; therefore, there are no formal statistical hypothesis tests planned. Data will be presented by patient and summarized by QD/QW as well as genetic subgroup or by age group depending on the analysis. Summary statistics will be presented, as well as confidence intervals (CIs) on selected parameters, as described in the sections below.

3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.4, unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or later. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version March 1, 2021 or later.

3.4. Baseline Definitions

For all [redacted] analyses, baseline will be defined as the following: the last value prior to randomization in the 13-week double-blind period.

For safety parameters including key laboratory (e.g., hematology and chemistry) data, the last value obtained prior to the first dose of setmelanotide or placebo in RM-493-037 will be used as the baseline. For the C-SSRS analysis, the baseline assessment that was collected at the beginning of the index study [redacted] should continue to be used as the baseline for this study.

3.5. Methods of Pooling Data

There will be two groups pooled to categorize the setmelanotide treatments so that differences between QD/QW can be easily seen: QW and QD. The QD group includes those patients who were randomized to QD setmelanotide in the randomized double-blind treatment period (Period 1) and QW setmelanotide in the open-label period (Period 2). The QW group includes those patients randomized to QW setmelanotide in the randomized double-blind treatment period (Period 1) and in the open-label period (Period 2).

Summary tabulations may be pooled across genetic obesity disorder populations as available.

In certain cases, tabulations will be stratified by age group (≥6 to <12 years old, ≥12 to <18 years old, ≥18 years old). All of these patients must have participated in the extension study, RM-493-022.

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

For purposes of the summary tabulations, data may be stratified by age group (≥6 to <12 years old, ≥12 to <18 years old, ≥18 years old).

Additionally, data may be stratified by genetic obesity disorder.

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 for reasons such as:

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

The patient's reason for and date of withdrawal from the study are to be recorded in the case report form (CRF). Any patient withdrawing from the study will complete the Early Termination Visit, if possible.

3.10. Missing, Unused, and Spurious Data

In general, no missing data will be imputed for this 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. [redacted]

When tabulating AE data, partial dates will be handled as follows:

- If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment.
- If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent.
- A missing onset date will be coded as the day of treatment.

For prior and concomitant medications (as defined in Section 4.4.7), partial start dates will not be imputed, as stop dates determine prior versus concomitant. Partial stop dates will be assumed to be the latest possible date consistent with the partial date.

All data recorded on the CRF will be included in data listings that are placed in the CSR appendices.

If any data is missing at the two key timepoints of Week 14 or Week 26 for any [redacted] analysis, the last observation carried forward method will be used to impute observations at those two visits. Any observation carried forward to these visits must have originated in their respective study period (Period 1 for Week 14, Period 2 for Week 26).

3.11. 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 within 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 patient.

3.12. Interim Analyses

No unblinded interim analysis is planned. Blinded interim analyses may be conducted during the course of the trial to facilitate scientific monitoring and business needs.

4. STUDY ANALYSES

4.1. Patient Disposition

Patient disposition will be tabulated and include the number of patients screened, randomized, treated in total, in the QD setmelanotide group, in the QW setmelanotide group (see Section 3.5), in each patient population for analysis, who discontinued prior to completing the study and reason(s) for early study discontinuation, who discontinued prior to completing the treatment and reason(s) for early treatment discontinuation, and the number of patients that have completed the study

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

4.2. Demographics, Baseline Characteristics, and Medical History

Demographics and baseline characteristics information will be summarized by QD/QW setmelanotide group for the FAS using the [redacted] baseline as well as for the SA set using the safety baseline. No formal statistical comparisons will be performed. Age at baseline as well as baseline height, [redacted]
The number and percentage of patients in each age category (≥6 to <12 years old, ≥12 to <18 years old, ≥18 years old), sex, ethnicity, race, and genetically defined deficiency categories will also be presented. Skin type as measured by the Fitzpatrick Classification Scale, which is defined below, will also be summarized:

Table 2 Fitzpatrick Classification Scale

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

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

Demographic and baseline data for each patient will be provided in data listings.

The patient's history of childhood obesity and previous weight loss efforts will be collected. This medical history will be summarized in a table by System Organ Class (SOC) and Preferred Term (PT) frequencies for the SA set. This data will also be provided in a data listing.

[redacted]

[redacted]

[redacted]

4.4. Pharmacokinetic Evaluations

Primary [redacted] analysis will be conducted using the PKAS.

4.4.1. Primary [redacted] Analysis

For the primary [redacted] endpoint, the PK profile of the 2 formulations of setmelanotide will be characterized and the steady-state PK parameters (C_{max}, T_{max}, C_{trough}, $AUC_{0\text{-}tau}$) will be summarized by dose level and prior treatment regimen (QW or QD) during the double-blind phase of the study using descriptive statistics including n, mean, standard deviation,

geometric mean, minimum, median, maximum, % coefficient of variation (CV), geometric mean CV, and 95% confidence intervals (CIs).

A separate tabulation will be created for the same analysis by subgroup (age category and genetic subgroup).

4.5. Safety Analyses

Safety analyses will be conducted using the SA Set.

4.5.1. Drug Exposure

Drug exposure will be summarized by QD/QW treatment group across the entire length of the study. The number of doses administered, total dose received in mg, treatment duration in weeks, and percentage of dosing compliance will be summarized using descriptive statistics (N, mean, SD, median, minimum, maximum, and 95% confidence intervals). Treatment duration will be defined in weeks as (date of last dose – date of first dose + 1) / 7. Dosing compliance percentage will be defined as ([number of doses administered] / [duration of treatment in days]) * 100 for QD treatment and ([number of doses administered * 7] / [duration of treatment in days]) * 100 for QW treatment. A by-patient listing for dosing will be created.

4.5.2. Adverse Events

All AEs will be coded using the MedDRA coding system (Version 24.0 or later) and displayed in tables and data listings by SOC and PT. Adverse events will also be graded using the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) on a scale of Grades 1 to 5 in which Grade 1 is a mild AE, Grade 2 a moderate AE, Grade 3 a severe AE, Grade 4 a life-threatening or disabling AE, and Grade 5 a fatal AE). Those not listed by CTCAE will be graded as either mild, moderate, or severe.

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as any AE with onset after the administration of randomized study medication at the start of the Run-in period through the end of the study *(*at the end of the 3-week follow-up period), any event that was present at baseline (beginning of Run-in period) but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study, or any event deemed to be related to study drug exposure.

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, any serious related TEAE, with any TEAE resulting in study drug withdrawal, with any TEAE leading to death will be summarized by QD/QW treatment group and overall. All TEAE analyses will have separate tabulations for two time frames: the beginning of the randomized, double-blind period (Day 1) to Week 14 and the beginning of the Run-in period through the end of the 3-week follow-up period (end of study). Since visits are not collected for AEs, the dates that each patient started and ended treatment at

each of these periods will be used to compare to the AE start and end dates for each patient in order to subset on the AEs specific to the randomized, double-blind period.

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.

No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs occurring on study will be listed in patient data listings. By-patient listings also will be provided for the following: patient deaths, serious TEAEs, serious related TEAEs, TEAEs leading to withdrawal, TEAEs related to the drug, and TEAEs of CTCAE Grade 3 or higher.

4.5.3. Injection Site Evaluations

Injection site evaluations will be summarized for all visits over time by QD/QW treatment received 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 included in the summary.

A by-patient 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 in the International System of Units.

The actual value and change from baseline to each on-study evaluation will be summarized for each continuous clinical laboratory parameter by visit and QD/QW treatment received. Categorical results will be summarized by counts and percentages of patients in each category. In the event of repeat values, the last non-missing value per study day/time will be used. Clinical laboratory parameters include:

Hematology

Complete blood count with platelet count and standard indices

Chemistry

Sodium, potassium, chloride, carbon dioxide, albumin, total protein, glucose, blood urea nitrogen, creatinine, uric acid, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, creatine phosphokinase, alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase, calcium, and phosphorus.

Coagulation Profile

Prothrombin time or international normalized ratio, and partial thromboplastin time, also referred to as activated partial thromboplastin time.

Urinalysis

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

The frequency of patients with abnormal safety laboratory results will be tabulated by treatment received.

Shift tables of change in CTCAE grade of laboratory parameters from baseline to worst on-study values will be presented for hematology and clinical chemistry by QD/QW treatment received, if applicable. Shift tables of urinalysis results will be provided.

All laboratory data, including pregnancy test results, will be provided in data listings. A subset listing will be presented for all clinically significant laboratory values.

4.5.5. Vital Signs

Vital signs will be measured according to the SoA (Table 1). Aside from those used in [redacted] evaluations, the actual value and change and percent change from baseline of temperature, HR, systolic blood pressure, diastolic blood pressure, and respiratory rate will be summarized descriptively by visit and QD/QW treatment received. Abnormal evaluations will be summarized in a table by QD/QW treatment received. A by-patient listing of all vital signs will be provided.

4.5.6. Physical Examination and Comprehensive Skin Examination

Skin examination findings will be presented in a shift table, summarizing the shift from baseline to each visit for a given region by QD/QW treatment received. A by-patient listing of all skin examination findings will be provided.

Results from each component of the physical examination will be provided in shift tables, summarizing the shift from baseline to most abnormal result during follow-up. All physical examination findings will be presented in a data listing, including whether post-baseline findings were significant.

4.5.7. Electrocardiogram

Electrocardiogram (ECG) results will be measured as shown in Table 1 and overall interpretation will be summarized in a by-visit shift table by QD/QW treatment.

Continuous ECG data for each patient, including HR, PR interval, QRS duration, QT interval, and QT interval corrected with Fridericia's method will be provided in a summary table by treatment received and a by-patient data listing.

4.5.8. Prior and Concomitant Medications

A prior medication is defined as any medication that was used and stopped before the start of the trial (Day -1 or before). A concomitant medication is defined as any medication with a stop date that is on or after the date of first dose of study drug.

Prior and concomitant medications will be coded using the WHO Drug Dictionary, version March 1, 2021, or later. Results will be tabulated by anatomic therapeutic class (ATC) and PT.

Prior and concomitant medications over the full study will be tabulated by QD/QW treatment group as well as by ATC level and PT in frequency tables. Patients with more than 1 medication at a given ATC level and PT will be counted only once in that category. If an end date is missing or the medication is ongoing, the medication will be included. Medications starting after the treatment withdrawal date will be listed but will not be classified or summarized. Partial dates will not be imputed.

The use of prior and/or concomitant medications will be included in a by-patient data listing.

4.5.9. Columbia Suicide Severity Rating Scale

The C-SSRS will be measured as shown in the SoA (Table 1) according to the age of the patient (child <12 or adult ≥12). Results of the C-SSRS will be provided in a shift table assessing shifts from the baseline most severe ideation to most severe ideation during follow-up. A by-patient listing including the ideation, intensity of ideation, behavior, and number of attempts will be provided.

4.5.10. Patient Health Questionnaire-9

The Patient Health Questionnaire-9 will be measured as shown in the SoA (Table 1). The actual values, change, and percent change from baseline of the total scores will be summarized with descriptive statistics by visit. A by-patient listing of the results of the individual 9 questions will be provided.

4.5.11. Anti-RM Antibody

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

5. CHANGES TO PLANNED ANALYSES

All changes from procedures outlined in the protocol and procedures outlined in this SAP will be summarized in the CSR. Decisions to deviate from planned analyses will be documented at the time they are made.

If any modifications in the experimental design, dosages, parameters, patient selection, or any other sections of the protocol are indicated or required, the Investigator will consult with the Sponsor before such changes are instituted. Modifications will be accomplished through formal amendments to this protocol by the Sponsor and approval from the appropriate IRB or IEC.

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